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Reaction of Vanilmandelic Acid and 4-Hydroxybenzyl Alcohol Derivatives with L-Ascorbic Acid

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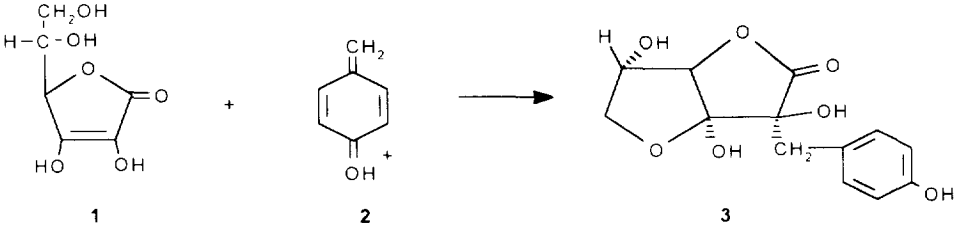
Abstract: The interaction between vanilmandelic and L-ascorbic acids led to a cyclopent-2-en-one derivative, whereas the reaction of methyl vanilmandelate with L-ascorbic acid yielded 2-furancarboxylic acid as the major product. The model 3-substituted 4-hydroxybenzyl alcohols and L-ascorbic acid produced ascorbigen-type structures, which easily decarboxylated to give mixtures of the corresponding 1-aryl-1-deoxyketoses. © 1997 Elsevier Science Ltd.

Introduction. L-Ascorbic acid can be easily 2-C-substituted by 3-hydroxymethylindole or 4-hydroxybenzyl alcohol and their derivatives to produce ascorbigens, 2-C-arylmethyl-3-ketohexulosono-1,4-lactones stabilised by the hemiketal formation with the participation of 6-CH_2OH and 3-CO groups of ascorbic acid moiety[1]. For 4-hydroxybenzyl alcohol the reaction proceeds through the addition of L-ascorbic acid **(1)** to the quinone methide **(2)** derived from the alcohol[2] (Scheme 1).

Scheme 1

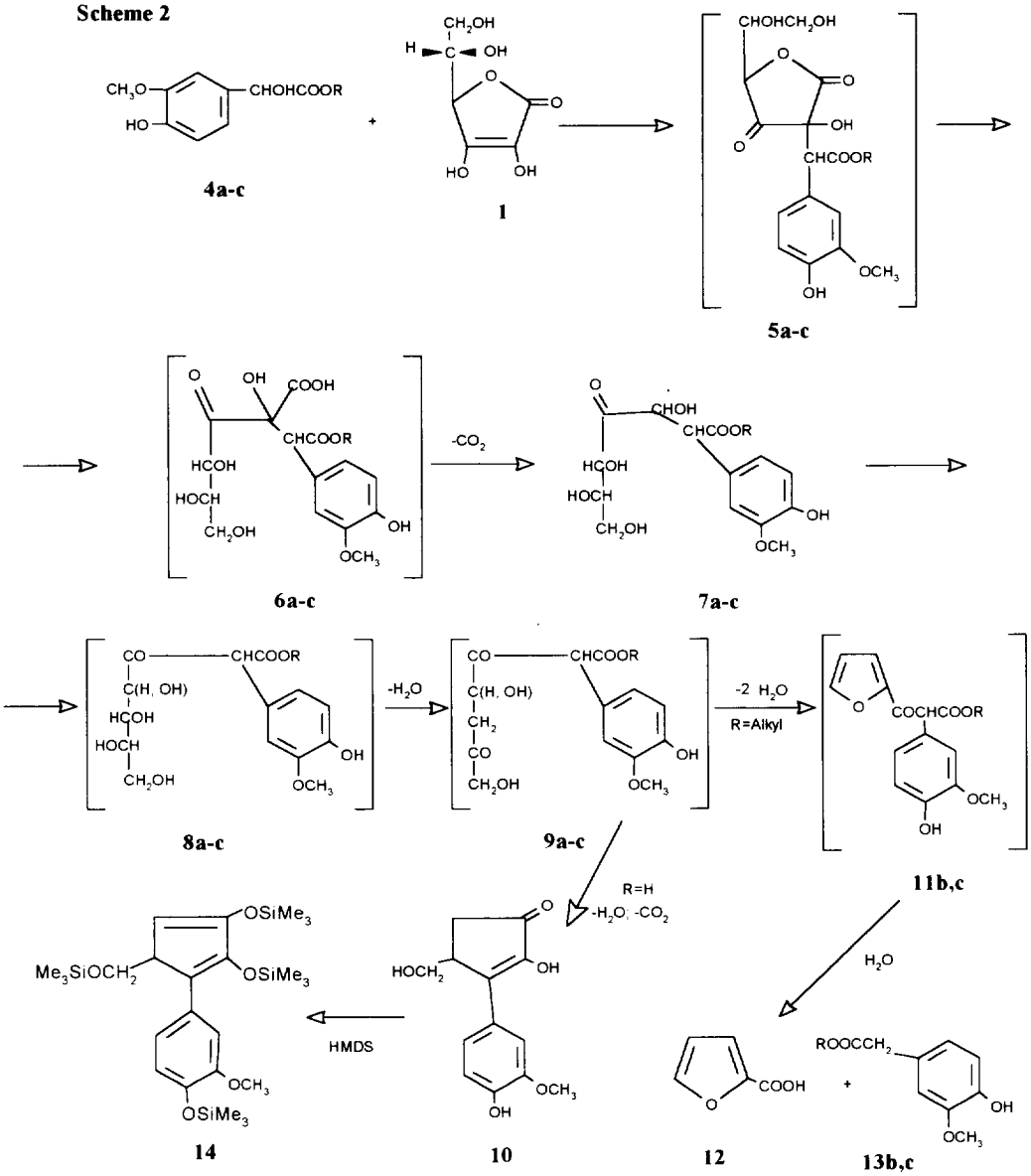


1 **2** **3**

Whereas indole-derived ascorbigens are important components of vegetable diet and represent sources of a plethora of biologically active compounds[1,3], 4-hydroxyphenyl derived ascorbigens were studied mainly in connection with the chemistry of natural phenolic derivatives from marine algae belonging to *Delesseriaceae* family[2] or heartwood of the *Chamaecyparis pisifera* tree[4,5]. As 4-hydroxybenzyl alcohol moiety is present in the structures of adrenaline and noradrenaline and their metabolites, it suggests that protonated quinone methides generated from these compounds in acidic media can add to L-ascorbic acid. Adrenaline and noradrenaline are produced in adrenal glands of humans and animals, where the concentration of L-ascorbic acid is very high. Hence, the investigation of the interaction of adrenaline, noradrenaline or their metabolites with ascorbic acid is of great biological importance and can provide information about new pathways of biotransformations of these compounds..

Results and Discussion. Our research was focused on the addition of ascorbic acid to the major metabolite of adrenaline - vanilmandelic acid and its esters[6] in comparison with the products of interaction of 4-hydroxybenzyl alcohols with L-ascorbic acid.

Scheme 2

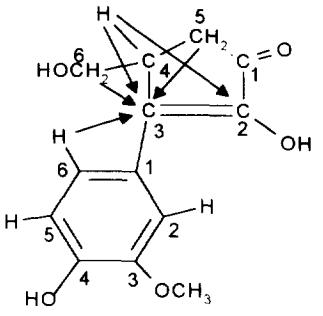


R = H (a), Et (b), Me (c)

The incubation of vanilmandelic acid (**4a**) and L-ascorbic acid (**1**) in diluted HCl (pH 1) at 50-60°C for 5 days led to 2-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-4-hydroxymethylcyclopent-2-en-one (**10**) in 10% yield, about 20% of vanillin and traces of 2-furancarboxylic acid (**12**) were also isolated (Scheme 2). The same reagents in 75% aqueous ethanol at pH 1 produced 41% of ethyl vanillylmandelate (**4b**) and about 58% of **12**. Under the same conditions methyl vanilmandelate (**4c**) and **1** gave **12** as the main product and traces of **10** and vanillin. The structures of **10** and **12** were confirmed by ^{1}H and ^{13}C NMR spectroscopy as well as EI and FAB mass spectra, and by EI mass spectrum of tetra-O-trimethylsilyl derivative **14** obtained by the action of

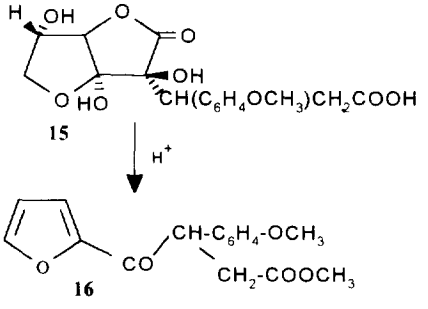
HMDS on **10**. The sequence of compound **10** structural determination using 1D and 2D ^{1}H and ^{13}C NMR spectroscopy was the following: in addition to signals of the vanillyl moiety, the signals of carbonyl and C=C groups were observed in the low-field area of the ^{13}C NMR spectrum and signals of the CH_2-CH-CH_2 fragment in the aliphatic part of the ^{1}H and ^{13}C NMR spectra. Carbon framework of this part of the molecule was unambiguously identified by selective INEPT experiments (Scheme 3). The presence of hydroxyl groups was confirmed by recording the ^{1}H NMR spectra in DMSO-d_6. A broad 2H singlet and broad triplet belong to 2-OH and 4'-OH and CH_2OH respectively.

Scheme 3



→ ^{1}H,^{13}C-connectivity from selective INEPT experiments

Scheme 4

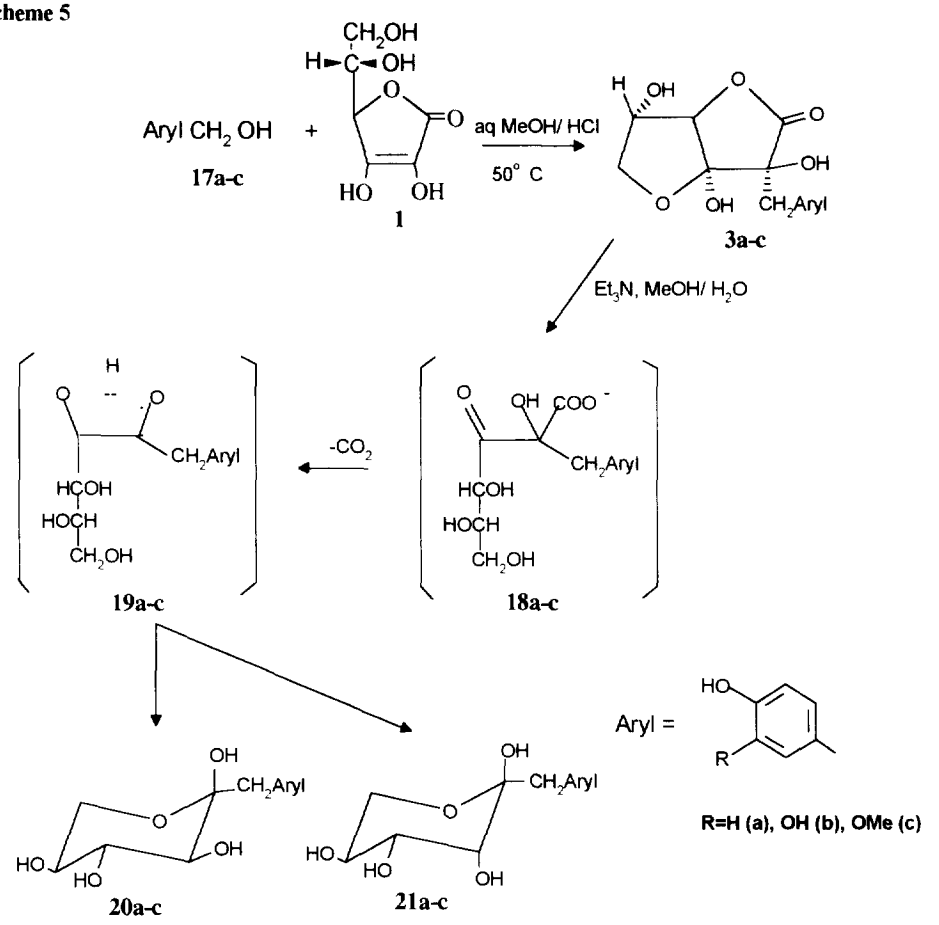


The retrosynthetic analysis suggests that 2-C-(carboxy)(4-hydroxy-3-methoxyphenyl)methylation of the L-ascorbic acid moiety in the presence of an acid first should give the desired framework **5a** similar to those described for the interaction of L-ascorbic acid with 4-hydroxyphenyl alcohol or methyl ß-hydroxy-ß-(4-hydroxyphenyl)propionate[2]. In the case of **4a** this framework **5a** appears to be unstable and opens the lactone ring to give β-keto acid **6a**, which easily decarboxylates yielding a ketone intermediate **8a** and, after dehydration, the γ-diketone **9a**, which produces 2-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-4-hydroxymethyl-cyclopent-2-en-one **(10)** after cyclization and decarboxylation. β-Keto ester **9b** or **c** resulted from the interaction of **1** with the ester **4b or 4c**[6] undergoes dehydrative cyclyzation and, *via* ß-keto ester **11**, yields 2-furancarboxylic acid (**12**) and, supposedly, an alkyl 4-hydroxy-3-methoxyphenyl acetate **13**[7]. The homologue of **11**, γ-keto ester derivative **16**, was described previously[2] as a stable product of the acidic transformation of compound **15**[2] (Scheme 4).

Substituted 4-hydroxybenzyl alcohols **17a-c** are decarboxy analogues of vanilmandelic acid and represent the simplest models for studying interaction of adrenaline and its derivatives with L-ascorbic acid and clarifying the role of carboxyl group of vanilmandelic acid in this reaction. We have synthesised 2-C-(4-hydroxybenzyl)- **(3a)** , 2-C-(3,4-dihydroxybenzyl)- **(3b)** and 2-C-(4-hydroxy-3-methoxybenzyl)-3-ketohexulo-furanosono-1,4-lactones **(3c)** by the interaction of **1** with the corresponding substitituted benzylic alcohols in acidic media[8]. The structures of the compounds obtained were confirmed by mass and NMR spectra (Table). No compounds of type **10** or **12** were isolated in this reaction, which demonstrates that the presence of an α-carboxyl group in the substituted benzyl alcohol is essential for the formation of **10** or **12** . Incubation of **3a** and **b** in a methanolic HCl solution led to the corresponding 3-O-methyl derivatives **(22a, and b)** respectively (Table). Similarly to indole-derived ascorbigens[9] , **3a-c** in slightly alkaline media were transformed into mixtures of the corresponding 1-deoxy-1-aryl-α-L-sorbopyranoses **(20a-c)** and 1-deoxy-1-aryl-α-L-tagatopyranoses **(21a-c)** through the cleavage of the lactone and hemiketal cycles, formation of the ß-keto acid anion **18** and subsequent decarboxylation into **19** (Scheme 5). 1-Deoxy-1-aryl-α-L-sorbopyranoses **(20 a-c)** are major products and 1-deoxy-1-aryl-α-L-tagatopyranoses **(21 a-c)** are minor products of decarboxylation. Pattern of NMR spectra of **20** and **21** are similar to those of the corresponding indole-containing ketoses[9]. The ratios **20a:21a, 20b:21b, and 20c:21c,** were 82:16, 64:29, and 70:20, respectively as shown by HPLC. ^{1}H

NMR data for compounds **20a-c** and **21b** are presented in the Table[10].

Scheme 5



Experimental

General. NMR spectra were measured on a Varian VXR-400 instrument operated at 400 MHz for ^1H and 100.6 MHz for ^{13}C using CD_3OD as a solvent. EI and FAB mass-spectra were obtained on an SSQ 710 Finnegun instrument. IR spectra (in KBr pellets) were measured on an SP-1100 spectrometer (Pye Unicam, England). HPLC was performed on a Shimadzu liquid chromatograph with a Zorbax C8 column in a linear gradient of acetonitrile in 0.01 M H_3PO_4 (7 → 12%). Analytical TLC was performed on Merck Kiesegel F_{254} plates in the chloroform-methanol 5:1 (A), or 15:1 (B) systems. PreparativeTLC was performed on glass plates (20x20 cm; 0.5 mm) with Kieselgel 60 F_{254} (Merck) in the same systems.

2-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-4-hydroxymethyl-cyclopent-2-en-one (9)[11]. A solution of 100 mg (0.5 mmol) vanilmandelic acid **(4a)** and 200 mg (1.1 mmol) **1** in 7 ml of water and 0.1 ml of 12 N HCl was stirred for 5 days at 60°C, then extracted with 50 ml of EtOAc and the extract was evaporated *in vacuo* to the volume of ~ 150 ml, then chromatographed on Kieselgel 60 (Merck) in the system B. The fraction enriched with **7** (Merck plates, Rf 0.54, A; light blue spot under UV_{254}) was purified by TLC (Rf 0.74, A) to yield 12 mg (10%) of **9**. M.p. 184-185°C (dec.); IR: ν_{max} 1669 cm^{-1}; ^1H NMR (δ, ppm; J, Hz): 8.11 (2'-H, $J_{2'6'}$ 1.9), 7.79 (6'-H, $J_{5'6'}$ 8.3), 7.30 (5'-H), 4.24 and 3.93 (6-CH_2, J_{AB} 18.4, $J_{4,6a}$ 1.0, $J_{4,6b}$ 6.5), 3.83 (OCH_3), 3.67 (4-H, $J_{4,5a}$ 3.2, $J_{4,5b}$ 6.2), 2.93 and 2.76 (5-CH_2, J_{AB} 10.7); ^{13}C NMR (δ, ppm): 202.51(1-C), 150.95(2-C), 149.04(4'-C), 148.52(3'-C), 139.33(3-C), 126.54(1'-C), 122.33(6'-C), 116.51(5'-C), 64.82(6-C),

55.93(OCH_3), 38.95(C-4), 37.24(C-5); EI-or FAB-Ms, *m/z* 250 $(M)^+$. Anal. calcd. for $C_{13}H_{14}O_5$: C, 62.39; H 5.64. Found: C, 62. 18; H 5.74. EI-Ms of **14,** obtained by boiling **10** with HMDS, *m/z*: 538 $[C_{13}H_{13}O_7(SiMe_3)_4]^+$, 466 $[C_{13}H_{12}O_7(SiMe_3)_3]^+$, 394 $[C_{13}H_{11}O_7(SiMe_3)_2]^+$.

Table 1. ^1H NMR data for the carbohydrate moieties of compounds **4a-c** , **20 a-c** and **21b** in methanol - d_4 Chemical shifts (ppm) and coupling constants (Hz).

Compounds	H-1	H-3	H-4	H-5	H-6ax	H-6eq
4a	2.93 3.12 J_{AB} 13.4	-	3.72 $J_{4,5}$ 0	4.30 $J_{5,6a}$ 5.8	4.14 J_{6a6b} 9.7	4.00 $J_{5,6b}$ 3.3
4b	2.87 3.07 J_{AB} 13.4	-	3.75 $J_{4,5}$ 0	4.26 $J_{5,6a}$ 5.9	4.14 J_{6a6b} 9.6	4.00 $J_{5,6b}$ 3.2
4c	2.93 3.11 J_{AB} 13.4	-	3.72 $J_{4,5}$ 0	4.24 $J_{5,6a}$ 5.8	4.13 J_{6a6b} 9.7	3.98 $J_{5,6b}$ 3.3
20a	2.80 2.98 J_{AB} 13.5	3.02 $J_{3,4}$ 9.2	3.55 $J_{4,5}$ 9.2	3.23 $J_{5,6a}$ 10.8	3.62 $J_{6a,6b}$ 10.8	3.50 $J_{5,6b}$ 5.8
20b	2.75 2.92 J_{AB} 13.4	3.06 $J_{3,4}$ 9.4	3.55 $J_{4,5}$ 9.4	~ 3.3 $J_{5,6a}$ 10.0	3.62 $J_{6a,6b}$ 10.0	3.50 $J_{5,6b}$ 5.7
20c	2.84 2.90 J_{AB} 13.5	3.08 $J_{3,4}$ 9.2	3.58 $J_{4,5}$ 9.2	~ 3.3 $J_{5,6a}$ 10.8	3.65 $J_{6a,6b}$ 10.8	3.55 $J_{5,6b}$ 5.8
21b	2.69 2.96 J_{AB} 13.9	3.48 $J_{3,4}$ 2.9	3.55 $J_{4,5}$ 9.2	~ 3.3 $J_{5,6a}$ 10.8	3.62 $J_{6a,6b}$ 10.8	3.80 $J_{5,6b}$ 7.5
22a*	2.95 3.11 J_{AB} 13.6	-	3.75 $J_{4,5}$ 0	4.26 $J_{5,6a}$ 5.9	4.28 J_{6a6b} 9.7	3.86 $J_{5,6b}$ 3.3
22b**	2.89 3.06 J_{AB} 13.5	-	3.76 $J_{4,5}$ 0	4.26 $J_{5,6a}$ 5.9	4.28 J_{6a6b} 9.7	3.86 $J_{5,6b}$ 3.3

* δ OCH_3 3.57 ppm **δ OCH_3 3.58 ppm

2-Furancarboxylic acid. A solution of **4a**[12] and **1** in 4 ml of 75% aqueous ethanol acidified with 12 N HCl to pH 1 was stirred for 8 h. at 60° C, evaporated to 1 ml, diluted with 10 ml of water and extracted with 20 ml of EtOAc. Evaporation of the extract *in vacuo* gave 40 mg of a residue, which was purified by TLC to yield 10 mg of **12** (58%) (Rf 0.16, A) and 14 mg of **4b** (41%) (Rf 0.69, A). **12:** m.p.[13] 139°C , ^1H NMR spectrum : 7.54 (d, $J_{3,4}$ 1.7, 3-H), 6.68 (d, $J_{4,5}$ 3.4, 5-H) and 6.47 (dd, 4-H). EI-Ms, *m/z:* 112 $[M^+]$. **14:** ^{13}C NMR ($CDCl_3$): 173.83, 146.62, 145.82, 130.36, 119.92, 114.34, 108.81, 72.71, 62.16, 55.94, 14.04. EI-Ms, *m/z:* 226 $[M]^+$.

2-C-(4-Hydroxybenzyl)-α-L-xylo-3-ketohexulofuranosono-1,4-lactone (3a) A stirred solution of 200 mg (1.64 mmol) 4-hydroxybenzaldehyde in 10 ml of ethanol was hydrogenated over Raney nickel. After 1 h the catalyst was removed and the solution of 4-hydroxybenzyl alcohol obtained was added dropwise to 1.1g (6.5 mmol) of ascorbic acid in 11 ml of water[14], acidified to pH 1 by 12 N HCl and stirred for 6 h. at 50°C. The reaction mixture was evaporated *in vacuo* by half, saturated with NaCl, washed with $CHCl_3$ (5 ml) and extracted with EtOAc (5x20 ml). The extract after evaporation yielded 140 mg of a residue, which was purified by TLC (Rf 0.32, A) to give 76 mg of **3a** (16%). $[\alpha]^{20}_D$ +6.02°(c 1.0, MeOH); IR. ν_{max} 1790 cm^{-1};

EI-Ms, *m/z:* 282 $[M]^+$, 107 $[CH_2C_6H_4OH]^+$. Anal. calcd. for $C_{13}H_{14}O_7$: C, 55.32; H 5.00. Found: C, 55.10; H 5.24.

2-C-(3,4-Dihydroxybenzyl)-α-L-xylo-3-ketohexulofuranosono-1,4-lactone (3b) was obtained similarly from 3,4-dihydroxybenzaldehyde and L-ascorbic acid in 51% yield. $[\alpha]^{20}_D$ +3.50° (c 1.0, MeOH); IR: ν_{max} 1790 cm^{-1}; EI-Ms, *m/z:* 298 $[M]^+$, 123 $[CH_2C_6H_3(OH)_2]^+$. Anal. calcd. for $C_{13}H_{14}O_8$: C, 55.35; H 4.73. Found: C, 55.10; H 4.95.

2-C-(4-Hydroxy-3-methoxybenzyl)-α-L-xylo-3-ketohexulofuranosono-1,4-lactone (3c) was obtained in 25% yield. $[\alpha]^{20}_D$ +6.0° (c 1.0, MeOH); IR: ν_{max} 1790 cm^{-1}; EI-Ms, *m/z:* 312 $[M]^+$, 137 $[CH_2C_6H_3(OH)OCH_3]^+$. Anal. calcd. for $C_{14}H_{16}O_8$: C, 53.85; H 5.16. Found: C, 53.65; H 5.24.

1-Deoxy-1-(4-hydroxyphenyl)-α-L-sorbopyranose (20a) and 1-deoxy-1-(4-hydroxyphenyl)-α-L-tagatopyranose (21a). A solution of 30 mg (0.1 mmol) of **3a** in 6 ml of methanol, 1 ml of water and 32 µl of Et_3N (0.2 mmol) was stirred at 40-60° C for 1 h. After evaporation *in vacuo* the reaction mixture was purified by TLC (Rf 0.30, A) to yield 10 mg (35%) of a mixture of **20a** and **21a**. HPLC: **20a** Rt 6.50 min (82%), **21a** Rt 4.61 min (16%). EI-Ms, *m/z:* 256 $[M]^+$, 107 $[CH_2C_6H_4OH]^+$. Anal. calcd. for $C_{12}H_{16}O_6$: C, 56.25; H 6.29. Found: C, 56.00; H 6.30.

1-Deoxy-1-(3,4-dihydroxyphenyl)-α-L-sorbopyranose (20b) and 1-deoxy-1-(3,4-dihydroxyphenyl)-α-L-tagatopyranose (21b) were obtained similarly from **3b** in 37% yield. HPLC: **20b** Rt 4.76 min (64%), **21b** Rt 3.88 min (29%). EI-Ms, *m/z:* 272 $[M]^+$, 123 $[CH_2C_6H_4(OH)_2]^+$. Anal. calcd. for $C_{12}H_{16}O_7$: C, 52.94; H 5.92. Found: C, 52.72; H 5.70.

1-Deoxy-1-(4-hydroxy-3-methoxyphenyl)-α-L-sorbopyranose (20c) and 1-deoxy-1-(4-hydroxy-3-methoxyphenyl)-α-L-tagatopyranose (21c) were obtained similarly in 40% yield. HPLC: **20c** Rt 8.06 min (70%), **21c** Rt 5.99 min (20%). EI-Ms, *m/z:* 286 $[M]^+$, 137 $[CH_2C_6H_4(OH)OCH_3]^+$. Anal. calcd. for $C_{13}H_{18}O_7$: C, 54.54 H 6.34. Found: C, 54.29; H 6.20.

3-O-Methyl-2-C-(4-hydroxybenzyl)-3-ketohexulofuranosonolactone (22a). A solution of 40 mg (0.13 mmol) of **3a** in 1.7 ml of dry methanol and 1.5 N methanolic HCl was stirred for 3 weeks. After evaporation *in vacuo* the reaction mixture was purified chromatographically (Rf 0.57, B) to yield 27 mg (63%) of **22a.** $[\alpha]^{20}_D$ +14.65 (c 1.0, MeOH); EI-Ms, *m/z:* 296 $[M]^+$, 107 $[CH_2C_6H_4OH]^+$. Anal. calcd. for $C_{14}H_{16}O_7$: C, 56.76; H 5.44. Found: C, 56.66, H 5.24.

3-O-Methyl-2-C-(3,4-dihydroxybenzyl)-3-ketohexulofuranosonolactone (22b) was obtained similarly from **3b** in 65% yield. $[\alpha]^{20}_D$ +6.12 (c 1.0, MeOH); EI-Ms, *m/z:* 312 $[M]^+$, 123 $[CH_2C_6H_3(OH)_2]^+$. Anal. calcd. for $C_{14}H_{16}O_8$: C, 53.85; H 5.16. Found: C, 53.80; H 5.24.

References and Notes

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6. RS-Vanilmandelic (2-hydroxy-4-methoxymandelic acid) (**4a**) was purchased from Merck. Esters **4b,c** can be easily obtained by the incubation of **4a** in the corresponding alcohol even in the presence of water.
7. We could not find **13** among minor products of this reaction.
8. **3a** was previously described[2], but no characteristics were given.
9. Preobrazhenskaya, M.; Lazhko, E.; Korolev, A.; Reznikova, M.I.; Rozhkov, I.I. *Tetrahedron Asymmetry,* **1996,** *7,* 461.
10. NMR data for minor components **21a,c** were not obtained because of their low content.
11. Under the atmosphere of argon the yield of **10** did not increase.
12. 2-Furancarboxylic acid can also be obtained from **1** and **4c** under similar conditions.
13. M.p. 133-134°. The Merck Index. 9th Ed.Merck & Co, Inc. Rahway, N.J. USA. 1976. p. 555.
14. The reaction was carried out in the argon atmosphere

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