Study of the transformations of 2-*C*-(indol-3-yl)methyl-α-L-*xylo*-hex-3-ulofuranosonic acid (the open form of ascorbigen) in an acidic medium

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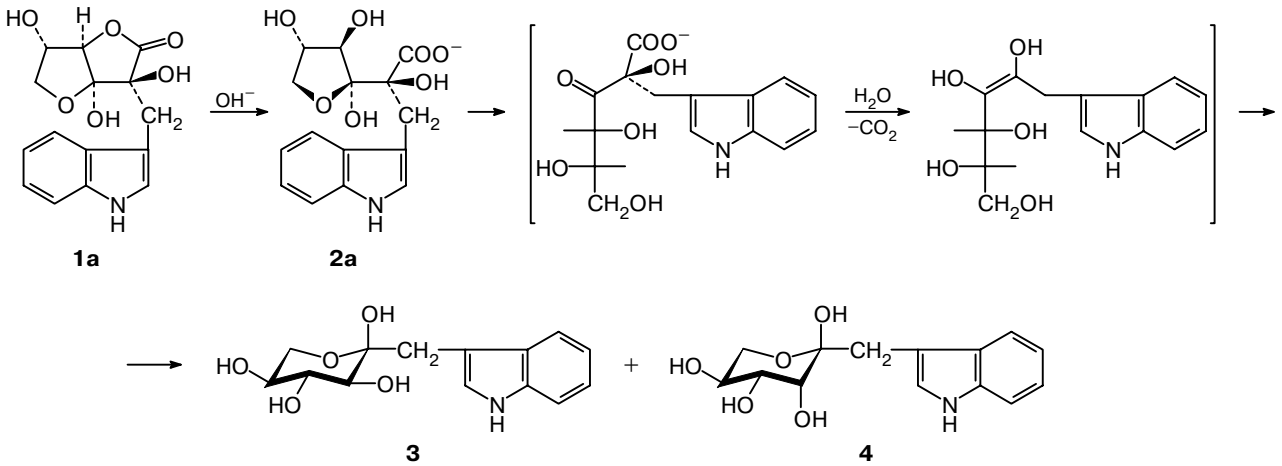
Transformation of ascorbigen in an acidic medium, which affects the carbohydrate moiety of the molecule and results in the formation of 2-hydroxy-4-hydroxymethyl-3-(indol-3-yl)cyclopent-2-enone, 5-hydroxymethyl-2-(indol-3-yl)methylidenetetrahydrofuran-3-one, and 2-(indol-3-yl)acetylfuran, was investigated. Isolation and identification of the intermediates allowed the elucidation of the mechanism of this domino-type reaction.

Key words: ascorbigen, L-ascorbic acid, 2-hydroxy-4-hydroxymethyl-3-(indol-3-yl)cyclopent-2-enone, 5-hydroxymethyl-2-(indol-3-yl)methylidenetetrahydrofuran-3-one, 2-(indol-3-yl)acetylfuran.

Ascorbigen, 2-*C*-(indol-3-yl)methyl-α-L-*xylo*-hex-3-ulofuranosono-1,4-lactone (**1a**) (an indole derivative), is derived from alkaloid glucobrassicin in plants belonging to the Cruciferae family. It is administered into the human organism with food and is thought to be responsible for the anticarcinogenic effect of a cruciferous-vegetable diet. It is easily obtained by condensation of 3-hydroxymethylindole with L-ascorbic acid, which is a rare example of *C*-alkylation of ascorbic acid under mild conditions. Ascorbigen is a highly labile compound, which undergoes rearrangements under mild conditions including physiological.[1—3] The study of the products of these transformations is necessary for the understanding of the biological role of ascorbigen. Ascorbigen can also be a source of a new type of compounds in organic synthesis.

The lactone ring of ascorbigen opens in weakly alkaline media (including blood) yielding a salt of acid **2a**. Subsequent furanose ring opening, decarboxylation, isomerization, and cyclization result in the formation of a mixture of 1-deoxy-(indol-3-yl)-α-L-sorbopyranose (**3**) and 1-deoxy-(indol-3-yl)-α-L-tagatopyranose (**4**), which are the main products of ascorbigen biotransformation observed in blood of mice fed with ascorbigen (Scheme 1).[4] Upon heating in an acidic medium, ascorbigen releases L-ascorbic acid, and 3-methylideneindolenine liberated is either captured by the other ascorbigen molecule to yield derivatives with two or even three indole residues, or produces methylideneindolenine oligomers and 5*H*,11*H*-indolo[3,2-*b*]carbazole, which are thought to be responsible for the anticarcinogenic properties of a cruciferous-vegetable diet.[5]

Scheme 1



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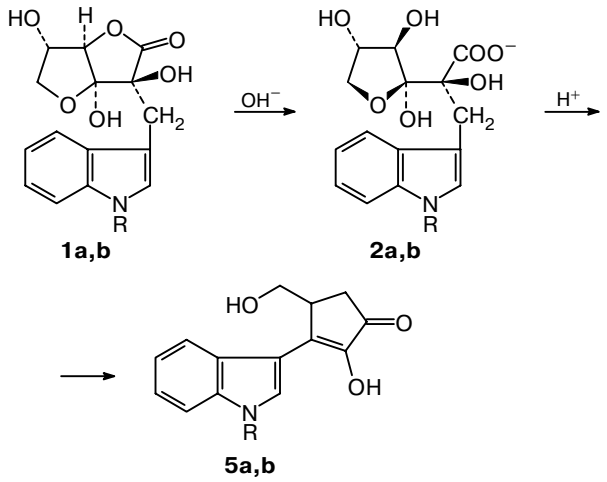
Previously, we have found yet another route of ascorbigen transformation in acidic media. Its heating in an aqueous solution of L-ascorbic acid results in the formation of 2-hydroxy-4-hydroxymethyl-3-(indol-3-yl)cyclopent-2-enone (**5a**), an indole derivative of a new type.[6] Analogous transformations upon heating with L-ascorbic acid solution have been performed for a series of *N*-alkyl- and *N*-alkoxyascorbigens to yield the corresponding cyclopentenone derivatives, *e.g.,* **5b** (Scheme 2).[6]

Scheme 2



R = H (**a**), Me (**b**)

Results and Discussion

In this study, we have shown that cyclopentenone **5a** can be obtained in higher yield from 2-*C*-(indol-3-yl)methyl-α-L-*xylo*-hex-3-ulofuranosonic acid (**2a**) as the open form of ascorbigen and have studied the mechanism of this transformation.

A solution of ascorbigen in aqueous methanol was alkalified with Et_3N until complete lactone ring opening (TLC and HPLC monitoring). Then the reaction mixture was acidified to pH 2—2.5 and heated at 50—65 °C for various periods of time (45 min, 2 h, 8 h, and 12 h) by monitoring the course of the reaction using HPLC every 30 min. This allowed us to establish the dynamics of generation of intermediate and final products of this reaction and, after their isolation and identification, to suggest a scheme of transformations occurring in a slightly acidic medium (Scheme 3).

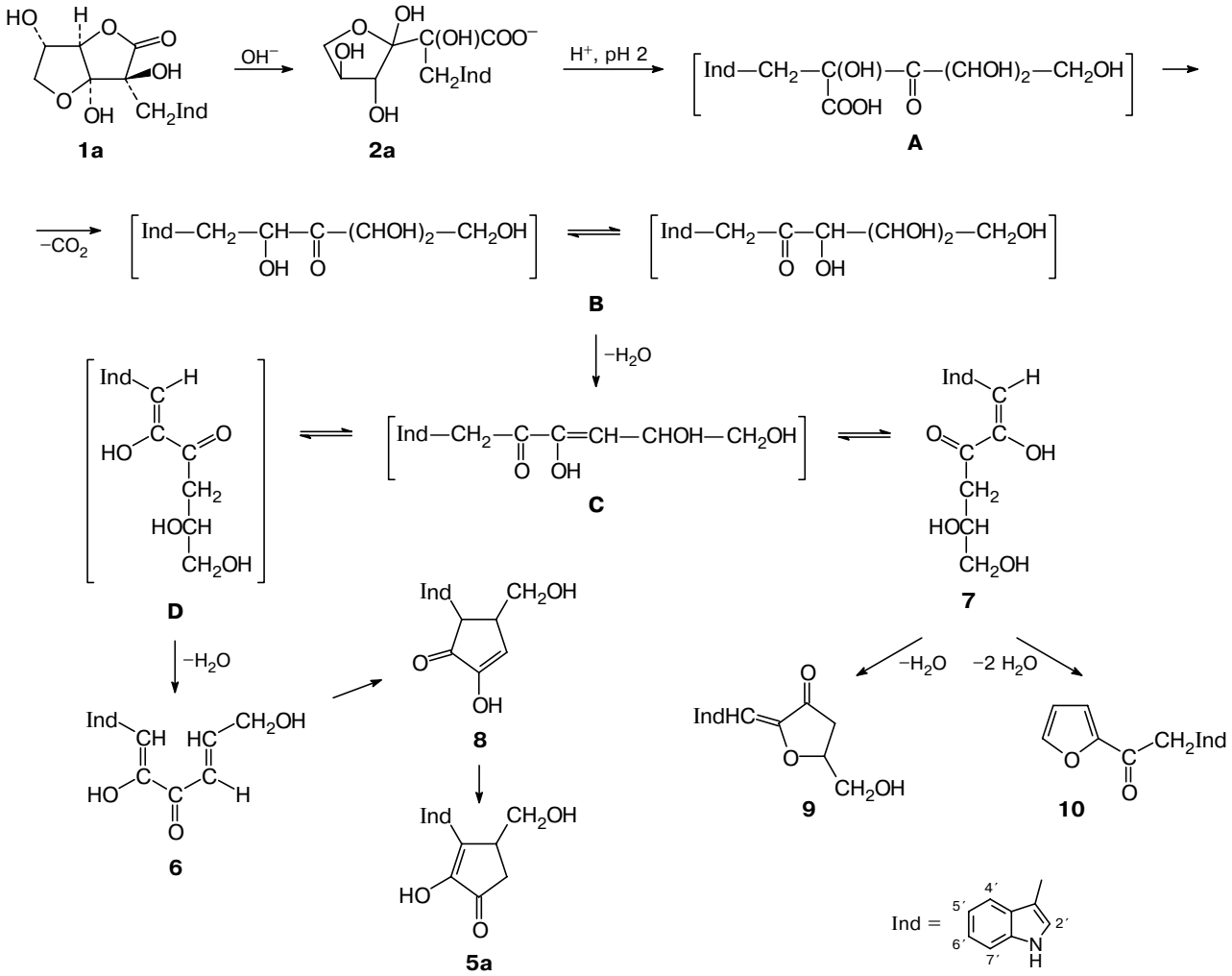
Thus heating of the reaction mixture for 45 min and subsequent gel chromatography on Sephadex LH-20 yield the following compounds: 2,6-dihydroxy-1-(indol-3-yl)hexa-1,4-dien-3-one (**6**), 20%; 2,5,6-trihydroxy-1-(indol-3-yl)hex-1-en-3-one (**7**), 16%; 2-hydroxy-4-hydroxymethyl-5-(indol-3-yl)cyclopent-2-enone (**8**), 8%; and 2-hydroxy-4-hydroxymethyl-3-(indol-3-yl)cyclopent-2-enone (**5a**), 15%. Heating for 2 h gave cyclopentenone **8** in 16% yield and cyclopentenone **5a** in 20% yield; 5-hydroxymethyl-2-(indol-3-yl)methylidenetetrahydrofuran-3-one (**9**) and 2-(indol-3-yl)acetylfuran (**10**) were also isolated in 7% and 15% yields, respectively. Heating of the reaction mixture for 12 h resulted in the disappearance of the starting and the intermediate compounds and in the formation of cyclopentenone **5a** in 45% yield; furans **9** (15%) and **10** (15%) were also formed, which are the final stable products of the transformation of acid **2a**. Analogously, 2-hydroxy-4-hydroxymethyl-3-(1-methylindol-3-yl)cyclopent-2-enone (**5b**) was isolated in 41% yield after heating of acid **2b** obtained from *N*-methylascorbigen **1b** for 12 h (see Scheme 2).

The structures of compounds **6—10** were confirmed by ^1H and ^{13}C NMR spectroscopic and mass spectrometry data. Cyclopentenones **5a** and **5b** were identical with compounds synthesized previously.[6] Comparison of the ^1H NMR spectra of compounds **6** and **7** allowed us to conclude that the indole ring and the carbonyl group in the former as well as the protons H(4) and H(5) are in the *trans*-position, whereas the indole ring and the carbonyl group in the latter are in the *cis*-orientation. The signal for C(5) (δ 79.4) in the ^{13}C NMR spectrum of **9** is shifted downfield compared with the analogous signal in the spectrum of triol **7** (δ 66.9), which suggests that compound **9** has a cyclic structure. This was confirmed by an INEPTL experiment. Selective irradiation of H(5) (δ 4.83) resulted in the appearance of the signal for C(2) (δ 146.6) indicating the presence of the $^3J_{H(5),C(2)}$ spin-spin coupling, which is impossible in an acyclic structure.

According to HPLC data, dienone **6** is generated immediately after acidification of the reaction mixture. This is rapidly accumulated and quickly disappears because of transformation to cyclopentenone **8** and then to cyclopentenone **5a**. Cyclopentenone **8** is also derived from individual dienone **6** upon storage or heating and, due to its lability, is completely transformed to cyclopentenone **5a** within 12 h. Triol **7** is formed in a noticeable amount (according to HPLC and TLC data) in *ca.* 1 h, and then starts to disappear due to transformation to furan derivatives **9** and **10**.

Chromatograms illustrating the dynamics of the formation of intermediate and final products of the transformation of acid **2a** are given in Fig. 1. The composition of the reaction mixture was monitored by recording spectra simultaneously at λ = 280 nm (spectra *Ia—c*) and at λ = 350 nm (spectra *IIa—c*). Two hours after the beginning of heating (spectra *Ia* and *IIa*), the reaction mixture was found to contain the peak of the starting acid **2a**, a small amount of ketoses **3** and **4**, which were likely generated during brief incubation of **2a** in the alkaline medium, cyclopentenones **8** and **5a**, triol **7**, dienone **6**, and furan **10**. At λ = 350 nm, only compounds **6** and **7** are registered. Six hours after the beginning of heating (spectra *Ib* and *IIb*), the peak of

Scheme 3



cyclopentenone **5a** increased, the amount of labile cyclopentenone **8** reduced, but the peak corresponding to dienone **6** still remained rather abundant, since this retention time is also the characteristic of furanone **9**. After 8 h of heating (spectra *Ic* and *IIc*), cyclopentenone **5a** and furan derivatives **9** and **10** were dominant in the reaction mixture. Triol **7** was also registered, as can clearly be seen in the spectrum *IIc*.

One can envision the following mechanism of the transformations of 2-*C*-(indol-3-yl)methyl-α-L-*xylo*-hex-3-ulofuranosonic acid (**2a**) obtained from ascorbigen **1a** by treatment with Et_3N (see Scheme 3). Presumably, the hemiketal ring of the oxo acid is retained under brief treatment with Et_3N. Acidification results in the furanose hemiketal ring opening in **2**, and the resulting acyclic acid **A** is decarboxylated yielding tautomeric 1-deoxy-1-(indol-3-yl)hex-3-ulose and 1-deoxy-1-(indol-3-yl)hex-2-ulose (**B**). Compounds **B** do not form pyranosides in the acidic medium, as it occurs at pH > 7 (which is proved by HPLC data), but are dehydrated to give anhydro ketoses **C** (compounds **A**, **B**, and **C** were not isolated). Tautomeric transformation of **C** results in the formation of two enols (**7** and **D**) with the *cis*- and *trans*-orientation of the indole ring relative to the CO group, respectively. Enol **7** was isolated and characterized. Enol **D** (we failed to isolate it) underwent dehydration to yield dienone **6** with the indole ring and the carbonyl group at C(3) remaining in the *trans*-position. We succeeded in isolation and characterization of this labile enol **6**, which gave cyclopentenone **8** upon storage for several hours or heating; the latter compound, in turn, is quickly transformed to stable cyclopentenone **5a**. Enol **7** was dehydrated upon storage or heating resulting in the formation of furanone **9** and furan **10**.

We also studied whether ketoses **3** and **4** transform to compounds **5a** and **8**. Heating of a mixture of 1-deoxy-1-(indol-3-yl)-α-L-sorbopyranose (**3**) and 1-deoxy-1-(indol-3-yl)-α-L-tagatopyranose (**4**) with *p*-toluenesulfonic acid resulted in furanone **9** together

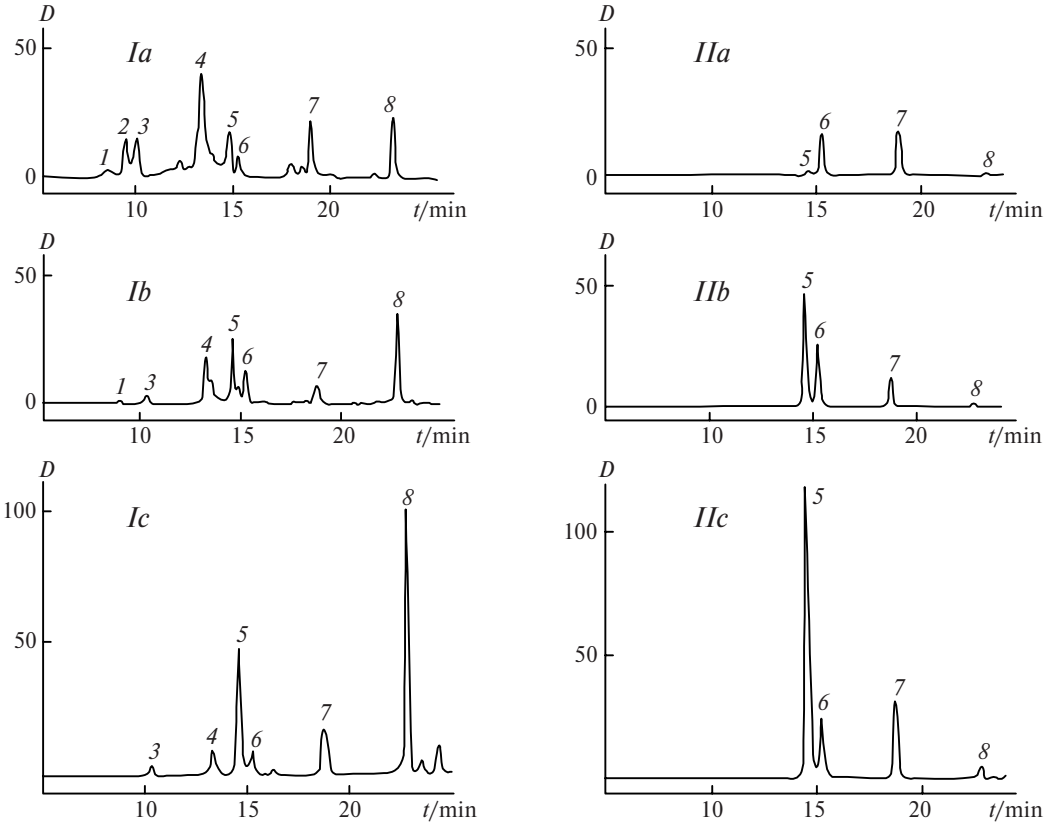


Fig. 1. Analysis of the progress of ascorbigen transformation by HPLC, UV detection at λ = 280 (*Ia—c)* and λ = 350 nm (*IIa—c*), incubation time is (*a*) 2, (*b*) 6, and (*c*) 8 h: (*1*) 1-deoxy-1-*C*-(indol-3-yl)-L-tagatopyranose **4**, (*2*) acid **2a**, (*3*) 1-deoxy-1-*C*-(indol-3-yl)-L-sorbopyranose **3**, (*4*) cyclopentenone **8**, (*5*) cyclopentenone **5a**, (*6*) triol **7**, (*7*) dienone **6** and furanone **9**, and (*8*) furan **10**.

with other unidentified products. Cyclopentenone **5a** was not however observed among these compounds.

Transformations of the open form of ascorbigen **2a** to indolylketoses **3** and **4** in the alkaline medium or to cyclopentenone **5a** and furan derivatives **9** and **10** under the treatment with acids consist in subsequent combinations of simple transformations, such as hydrolysis, decarboxylation, dehydration, and cyclization. These reactions occur spontaneously without any additional reagents and can be named domino-type reactions.

A number of biologically important compounds with a cyclopentenone fragment have been revealed recently.[7] The ascorbigen transformation under study is a new synthetic approach to this type of compounds.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a VXR-400 spectrometer with a working frequency of 400 and 100.6 MHz, respectively. Chemical shifts were measured in $CDCl_3$ or CD_3OD using these solvents as internal references ($CDCl_3$, δ_H of the residual proton is 7.25 and δ_C is 77.00; CD_3OD, δ_H of the residual proton is 3.32 and δ_C is 49.00). Analytical TLC was performed on aluminum plates precoated with an 0.2-mm layer of Silica gel F_{254} (Merck) in $CHCl_3$—MeOH (7 : 2). Preparative TLC was carried out on plates (20×20 cm) precoated with an 0.5-mm layer of Silica gel 60 F_{254} (Merck). Column chromatography was performed on Silica gel 60 (Merck) or Sephadex LH-20. Mass spectra (EI) were obtained on an SAQ 710 Finnigan instrument with the energy of ionizing electrons of 70 eV, direct inlet of a sample in the ion source, and the temperature of the ion source of 150 °C. High-resolution mass spectra were taken on a Finnigan MAT 8430 (Bremen, Germany) mass spectrometer with the SS-300 system for data processing with the acceleration voltage of 3 kV, the energy of ionizing electrons of 70 eV, the temperature of the ion source of 250 °C, and the temperature of sample vaporization of 70—240 °C using the direct inlet of a sample into the ionization chamber. The empirical formulas of the molecular ions were determined based on the high-resolution mass spectra by comparison of the mass for the ion measured with the exact value for the nearest perfluorokerosene reference ion (the analysis was performed at the Institute of Biochemistry and Physiology of Microorganisms, Russian Academy of Sciences, Pushchino). Analytical HPLC was performed on a Shimadzu LC10 instrument on columns with Diasorb C16 (7 μm) (Biokhimmak) with an injector loop volume of 10 μL and detection at λ = 280 and 350 nm. The eluent contained 0.01 *M* H_3PO_4 and acetonitrile; the concentration of acetonitrile varied sequentially from 10 to 45% in 17 min, from 45 to 63% in 4 min, and from 63 to 95% in 14 min at a flow rate of 1 mL min^{-1}.

Stepwise transformation of ascorbigen (1a). Triethylamine (0.27 mL, 0.2 mmol) was added to a solution of ascorbigen **1a** (305 mg, 0.1 mmol) in 9 mL of methanol—water (1 : 2). After the transformation of lactone **1a** to the salt of acid **2a** ($R_f \approx 0$ in $CHCl_3$—MeOH, 7 : 2), the reaction mixture was acidified with 1 *M* HCl to pH ~2 (according to a pH-paper), heated at 50 °C

for 45 min, diluted with water, and extracted sequentially with $CHCl_3$ (3×10 mL) and EtOAc. The extracts were washed several times with brine to pH 7.0, dried with Na_2SO_4, and concentrated *in vacuo*. The residues were chromatographed separately on Sephadex LH-20; the reaction products were eluted with methanol. Dienone **6** was isolated from the $CHCl_3$ extract and fractions containing **7** and **8** were obtained from the EtOAc extract.

To obtain compounds **5a**, **9,** and **10**, the reaction mixture was heated for 2 h, and the products were extracted with EtOAc and isolated by chromatography on Sephadex LH-20 as described above.

2,6-Dihydroxy-1-(indol-3-yl)hexa-1*Z*,4*E*-dien-3-one (6), amorphous, bright orange substance, R_f 0.70, R_t 18.90 min, yield 48.6 mg (20%), can be stored under argon at −17 °C. ^{1}H NMR (CD_3OD + $CDCl_3$), δ: 4.39 (dd, 2 H, H(6), $J_{6,4}$ = 2.1 Hz, $J_{6,5}$ = 4.0 Hz); 7.06 (dt, 1 H, H(5), $J_{5,4}$ = 15.4 Hz); 7.15 (t 1 H, H(5′), J = 8.1 Hz); 7.18 (s, 1 H, H(1)); 7.19 (t, 1 H, H(6′), J = 8.2 Hz); 7.30 (dt, 1 H, H(4), $J_{4,5}$ = 15.4 Hz, $J_{4,6}$ = 2.0 Hz); 7.41 (d, 1 H, H(7′), J = 8.0 Hz); 7.83 (d, 1 H, H(4′), J = 7.8 Hz); 8.04 (s, 1 H, H(2′)).^{13}C NMR (CD_3OD + $CDCl_3$), δ: 62.6 (C(6)); 110.1 (C(1)); 111.8 (C(3′)); 112.6 (C(7′)); 119.1 (C(4′)); 121.2 (C(5′)); 121.6 (C(6′)); 123.3 (C(5)); 128.3 (C(3′a)); 130.7 (C(2′)); 137.5 (C(7′a)); 146.7 (C(4)); 147.6 (C(2)); 185.6 (C(3)). MS (high resolution), found, *m/z*: 243.0880. $C_{14}H_{13}NO_3$. Calculated, *m/z*: 243.0895.

2,5,6-Trihydroxy-1-(indol-3-yl)hex-1*E*-en-3-one (7), amorphous, yellow substance, R_f 0.52, R_t 15.24 min, yield 40.7 mg (16%). ^{1}H NMR (CD_3OD), δ: 3.00 and 3.08 (both dd, each 2 H, H(4), $J_{4a,4b}$ = 15.4 Hz, $J_{4a,5}$ = 4.6 Hz, $J_{4b,5}$ = 7.7 Hz); 3.60 (d, 2 H, H(6), $J_{6,5}$ = 5.5 Hz); 4.21 (m, 1 H, H(5)); 7.08 (s, 1 H, H(1)); 7.14 (m, 1 H, H(6′)); 7.17 (m, 1 H, H(5′)); 7.40 (d, 1 H, H(7′), J = 7.9 Hz); 7.82 (d, 1 H, H(4′), J = 7.8 Hz); 8.70 (s, 1 H, H(2′)). ^{13}C NMR (CD_3OD), δ: 40.3 (C(4)); 66.9 (C(5)); 70.8 (C(6)); 109.8 (C(1)); 111.6 (C(3′)); 112.5 (C(7′)); 119.2 (C(4′)); 121.1 (C(5′)); 123.3 (C(6′)); 128.4 (C(3′a)); 130.2 (C(2′)); 137.5 (C(7′a)); 147.1 (C(2)); 195.7 (C(3)). MS (high resolution), found, *m/z*: 261.1020. $C_{14}H_{15}NO_4$. Calculated, *m/z*: 261.1001.

2-Hydroxy-4-hydroxymethyl-5-(indol-3-yl)cyclopent-2-enone (8), light yellow powder, R_f 0.42, R_t 13.34 min, yield 19.4 mg (8%). ^{1}H NMR (CD_3OD + $CDCl_3$), δ: 3.08 (m, 1 H, H(4)); 3.55 (d, 1 H, H(5), $J_{5,4}$ = 2.4 Hz); 3.66 (dd, 1 H, H(6a), $J_{6a,4}$ = 6.1 Hz, $J_{6a,6b}$ = 10.8 Hz); 3.79 (dd, 1 H, H(6b), $J_{6b,4}$ = 4.6 Hz); 6.62 (d, 1 H, H(3), $J_{3,4}$ = 2.7 Hz); 6.96 (t, 1 H, H(5′), $J_{5,4}$ = 8.1 Hz); 7.08 (m, 2 H, H(4′), H(7′)); 7.33 (t, 1 H, H(6′), J = 8.3 Hz); 8.14 (s, 1 H, H(2′)). MS (high resolution), found, *m/z*: 243.0876. $C_{14}H_{13}NO_3$. Calculated, *m/z*: 243.0895.

Cyclopentenone **8** was isolated in 16% yield after heating of the reaction mixture for 2 h and also after storage of compound **6** in a solution for ~16 h. Storage for several hours resulted in the transformation of cyclopentenone **8** into compound **5a**.

5-Hydroxy-2-(indol-3-yl)methylidenetetrahydrofuran-3-one (9), R_f 0.54, R_t 18.75 min, yield 25.0 mg (10%). ^{1}H NMR (CD_3OD + $CDCl_3$), δ: 2.65 (dd, 1 H, H(6b), CH_2OH, $J_{6a,6b}$ = 18.3 Hz, $J_{6b,5}$ = 6.5 Hz); 2.80 (dd, 1 H, H(6a), CH_2OH, $J_{6a,5}$ = 8.1 Hz); 3.74 (dd, 1 H, H(4b), $J_{4a,4b}$ = 12.2 Hz, $J_{4b,5}$ = 4.8 Hz); 3.91 (dd, 1 H, H(4a), $J_{4a,5}$ = 3.4 Hz); 4.81 (m, 1 H, H(5)); 6.74 (d, 1 H, IndC<u>H</u>=, J = 0.7 Hz); 7.10 (t, 1 H, H(5′), J = 7.8 Hz); 7.14 (t, 1 H, H(6′), J = 7.8 Hz); 7.40 (d, 1 H, H(7′), J = 8.0 Hz); 7.73 (d, 1 H, H(4′), J = 7.9 Hz); 8.00 (s, 1 H, H(2′)). ^{13}C NMR (CD_3OD), δ: 38.0 (C(4)); 65.0 (<u>C</u>H_2OH); 79.4 (C(5)); 99.5 (Ind<u>C</u>H=); 110.9 (C(3′)); 112.5 (C(7′)); 119.2 (C(4′)); 121.0 (C(5′)); 123.2 (C(6′)); 129.8 (C(2′)); 128.3 (C(3′a)); 137.6 (C(7′a)); 146.4 (C(2)); 200.0 (CO). MS (EI), *m/z* (I_{rel}(%)): 117 (100), 129 (39), 157 (39), 213 (14), 227 (7), 243 (57). MS (high resolution), found, *m/z*: 243.0886. $C_{14}H_{13}NO_3$. Calculated, *m/z*: 243.0895.

2-(Indol-3-yl)acetylfuran (10), R_f 0.81, R_t 22.77 min, yield 15.0 mg (6%). ^{1}H NMR ($CDCl_3$), δ: 4.25 (br.s, 2 H, CH_2); 6.50 (dd, 1 H, H(4′), $J_{4,3}$ = 1.8 Hz, $J_{4,5}$ = 3.6 Hz); 7.12 (t, 1 H, H(5′), J = 8.1 Hz); 7.18 (t, 1 H, H(6′), J = 8.2 Hz); 7.20 (s, 1 H, H(2′)); 7.22 (dd, 1 H, H(5′), $J_{5,3}$ = 0.7 Hz, $J_{5,4}$ = 3.5 Hz); 7.34 (d, 1 H, H(7′), J = 8.0 Hz); 7.55 (dd, 1 H, H(3′)); 7.63 (dd, 1 H, H(4′), $J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 0.6 Hz). MS (high resolution), found, *m/z*: 225.0780. $C_{14}H_{11}NO_2$. Calculated, *m/z*: 225.0790.

2-Hydroxy-4-hydroxymethyl-3-(indol-3-yl)cyclopent-2-enone (5a). Triethylamine (0.14 mL, 0.1 mmol) was added to a solution of ascorbigen **1a** (152 mg, 0.05 mmol) in 5 mL of methanol—water (1 : 1) and stirred for 15 min at ~20 °C. The reaction mixture was then acidified with 10 *M* HCl to pH 2 and heated for 12 h at 65 °C with HPLC monitoring. After the amount of cyclopentenone **5a** ceased to increase, the reaction mixture was twofold diluted with equal volume of water and extracted sequentially with $CHCl_3$ and EtOAc. The EtOAc extract was dried with Na_2SO_4, the solvent was removed *in vacuo*, and the residue was chromatographed on silica gel in $CHCl_3$—MeOH (20 : 1) to yield 54 mg (45%) of cyclopentenone **5a**, which was identical with the authentic compound according to NMR and HPLC data,[6] and also compounds **9** (18.1 mg, 15%) and **10** (28 mg, 25%) identical with those described above.

2-Hydroxy-4-hydroxymethyl-3-(1-methylindol-3-yl)cyclopent-2-enone (5b) was obtained from 0.16 g (0.5 mmol) of 1-methylascorbigen. The product was isolated by flash chromatography in $CHCl_3$—MeOH (20 : 0.5) to yield 50 mg (41%) of **5b**, which was identical with the authentic compound according to NMR and HPLC data,[6] R_t 14.60 min.

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