3-O and 2-C Alkylation of L-ascorbates with benzyl halides and N-substituted indolemethanol derivatives

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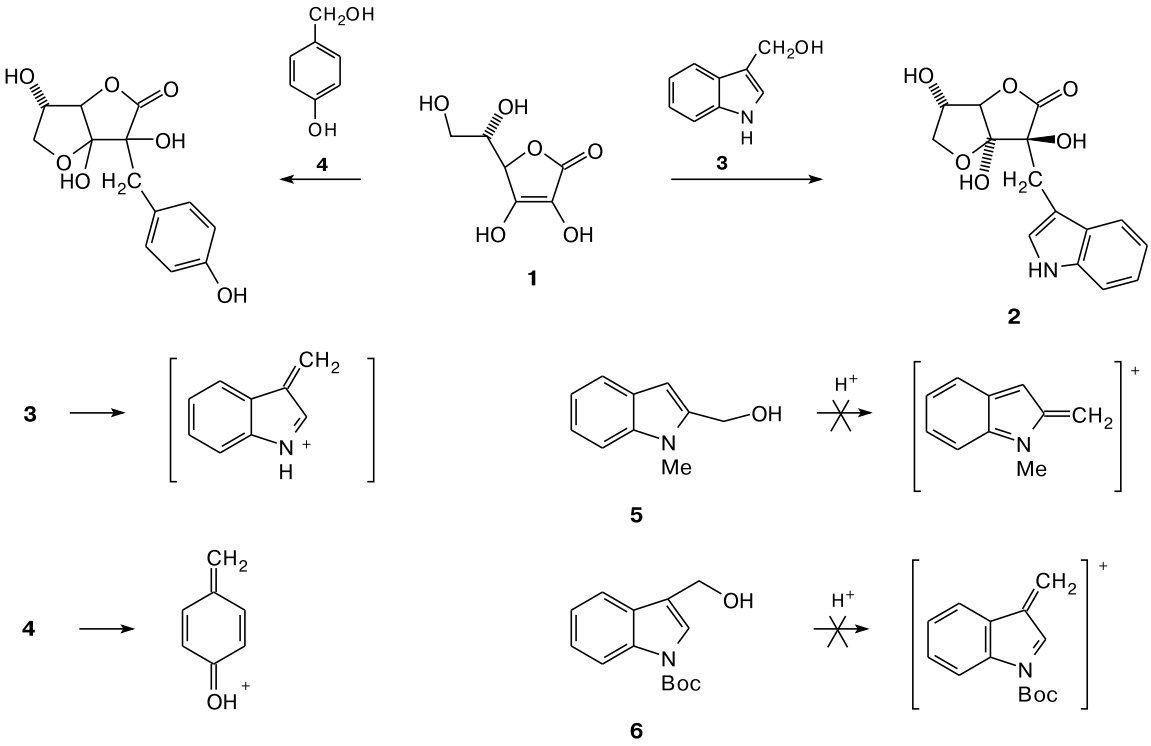
Coupling of alkali metal ascorbates with benzyl halides and 2- and 3-hydroxymethylindole methanesulfonates resulted in L-ascorbic acid 3-*O*- and 2-*C*-derivatives. In contrast to 3-*O*-benzyl L-ascorbate, its indole analogs are unstable compounds, which underwent decomposition or rearrangement during isolation to give thermodynamically stable 2-*C*-isomers.

Key words: ascorbigen, L-ascorbic acid, 3-O- and 2-C-alkylation, regioselectivity.

Derivatives of L-ascorbic acid (**1**) substituted at the positions O(3), O(5), and O(6) are well known, some of them are commercially available products.[1,2] Derivatives of **1** substituted at the position C(2) are also of interest. The most well-known is ascorbigen, 2-*C*-[(indol-3-yl)-methyl]-α-L-*xylo*-hex-3-ulofuranosono-1,4-lactone (**2**), a very active immunomodulator, which is formed in the reaction of **1** with 3-hydroxymethylindole (**3**) (Scheme 1). Ascorbigen (**2**) was also isolated from Brassicacae.[3] A large range of 2-*C*-derivatives of **1** are known. Some of them possess valuable biological properties.[4] They were isolated from natural sources or synthesized on the base of unsaturated aldehydes, ketones, and some alkyl aromatic alcohols, for example, 4-hydroxybenzyl alcohol (**4**) and its analogs.

A characteristic feature of the 2-C alkylation of **1** in acidic media is the involvement of stable intermediate cat-

Scheme 1



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ions, which can be generated by two pathways.[3] Protonation of the compounds bearing electron-withdrawing groups (formyl, keto, nitro, or cyano groups), which are conjugated with unsaturated radicals affords electrophilic species. The latter undergo 1,4-conjugate addition of the Michael type or aldol condensation giving 2-*C*-derivatives of **1**. Protonation and dehydration of a molecule of an alkyl aromatic alcohol of type **3** or **4** leads to stable electrophilic species such as quinonemethides, for example, 3-methylideneindoleninium cation or *p*-hydroxybenzyl cation. Under weakly acidic conditions (pH 4—5), such cations stereospecifically and regioselectively alkylate **1** following an S_{E1} mechanism affording exclusively 2-*C*-derivatives (Scheme 1). However, under these conditions, no reactions of **1** with electrophilic reagents that cannot produce stable cations were observed. Thus no formation of structural analogs of ascorbigen was observed from 2-hydroxymethyl-1-methylindole[5] (**5**) and 1-(*tert*-butoxycarbonyl)-3-hydroxymethylindole (**6**). Low reactivity of alcohols **5** and **6** can apparently be explained by instability of the corresponding carbocations due to violation of the aromatic stabilization or a decrease in the ability of the nitrogen atom for positive charge delocalization.[6,7]

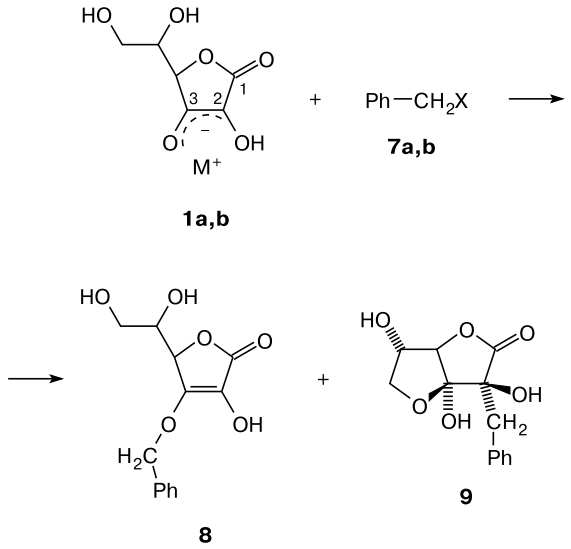
Like ethyl acetoacetate, L-ascorbic acid gives an ambident anion under basic conditions, which is an electrophilic O- and C-alkylation agent. The position C(2) of compound **1** is more nucleophilic as compared with the position O(3) and, as a result, 2-*C*-derivatives are more thermodynamically stable. However, the ratio of the O- and C-structural isomers depends on the reaction conditions, the nature of the electrophilic agents, and their structural features.[3]

The aim of the present work was the study of the reactions of ascorbates **1a,b** with benzyl halides and indolemethanol derivatives that do not form stable carbocations. It has previously been shown[8] that alkylation of sodium ascorbate (**1a**) with benzyl chloride (**7a**) in aqueous-organic solutions led to 3-*O*-benzylascorbic acid (**8**) along with the 2-C alkylation product, 2-*C*-benzyl-α-L-*xylo*-hex-3-ulofuranosono-1,4-lactone (**9**). In the present work, this reaction was studied in detail, the resulting products were isolated and characterized; other O- and C-alkylation reaction of sodium and potassium ascorbates were studied as well.

Results and Discussion

In alkylation of ascorbates **1a,b** with benzyl halides **7a,b** (Scheme 2), the product ratio depended on the reaction conditions. 3-*O*-Alkylation proceeded mainly in aprotic polar solvents (acetone, DMSO). Mixtures of 3-*O*- and 2-*C*-derivatives **8** and **9** were obtained in water—organic media containing acetone, THF, or DMSO. No noticeable influence of the aprotic solvent content in the mixture on the ratio of the resulting structural isomers was found. Thus the ratio of the 2-C and 3-O alkylation products is 1 : 2 and remained practically unchanged with a decrease in the DMSO content in the solvent mixture from 50% to 10%. The nature of benzyl halide also affected the product ratio insignificantly, although benzyl bromide (**7b**) accelerated the reaction considerably. No noticeable increase in the yields of the final products **8** and **9** was found with the increase in the reaction time and temperature. The ratios of the 3-O and 2-C alkylation products were determined by ^{1}H NMR spectroscopy, since great difference in their molar extinction did not allow the use of HPLC with UV detection.

Scheme 2

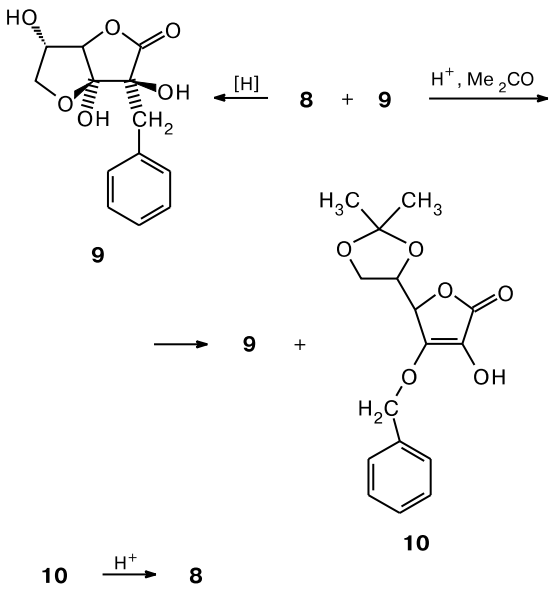


X = Cl (**a**), Br (**b**);
M = Na (**a**), K (**b**)

Isolation of structural isomers **8** and **9** by chromatography (TLC or HPLC) failed. For the isolation of these compounds in the individual state, other methods were developed (Scheme 3). Hydrogenolysis of the product mixture in the presence of Pd/C led to decomposition of 3-*O*-benzyl ether **8**, and lactone **9** was isolated in 30% yield. Treatment of the product mixture with acetone in the presence of TsOH resulted in the conversion of 3-*O*-benzyl ether **8** into isopropylidene derivative **10**, while compound **9** remaines virtually unaffected. Chromatography of the resulting mixture afforded ketal **10** in 66% yield. Subsequent removal of the isopropylidene protecting group by acid hydrolysis furnished 3-*O*-benzyl-L-ascorbic acid (**8**).

2-Hydroxymethyl-1-methylindole (**5**), which was obtained by reduction of ethyl 1-methylindole-2-carboxylate (**11**) in the presence of $LiAlH_4$ in 70% yield, was converted in methane sulfonate (**12**) (Scheme 4). The reaction of **12** with sodium ascorbate (**1a**) in DMSO resulted in (1-methylindol-2-yl)methyl derivatives **13** and **14**. Pre-

Scheme 3



parative TLC on silica gel was used for the isolation of the individual compounds. During chromatography, 3-*O*-[(indol-2-yl)methyl]-L-ascorbic acid (**14**), which is apparently a kinetic reaction product, converted partially into 2-C isomer (**13**). The latter is a structural isomer and homolog of ascorbigen (**2**) (see Scheme 4).

To date, only one example of such isomerization has been known: upon refluxing in toluene, 3-*O*-allyl-5,6-*O*-isopropylidene-L-ascorbic acid converted into the 2-C isomer by a mechanism of pericyclic [3,3]-sigmatropic rearrangement.[9]

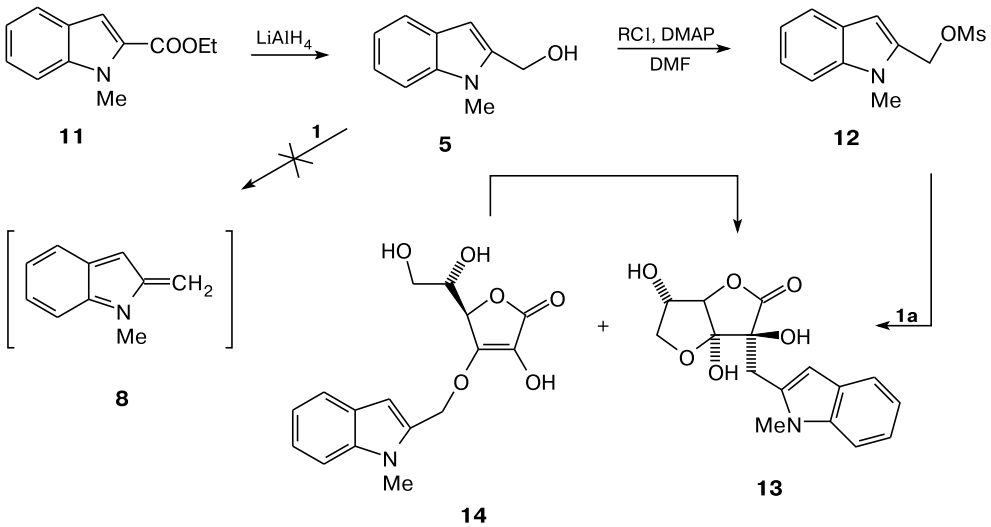
The alkylating reagent (1-Boc-indol-3-yl)methyl methanesulfonate (**15**), which is an analog of compound **12**, was synthesized by acylation of 3-formylindole with subsequent reduction with $NaBH_4$ and sulfonylation (Scheme 5). The reaction of methanesulfonate **15** with ascorbate **1a** resulted mainly in 2-*C*-derivative of **1**, *viz.* *N*-Boc-ascorbigen (**16**). Treatment with trifluoroacetic acid led to cleavage of the Boc-protecting group and elimination of the skatole moiety furnishing a mixture of di(indol-3-yl)methane (**17**) and ascorbigen (**2**).

The ^{1}H NMR spectra of carbohydrate fragments of derivatives **9**, **13**, and **16** are similar to those of indole-containing bicyclic ascorbigens.[10] A characteristic feature of the ^{1}H NMR spectra of the carbohydrate moieties of the ascorbigen analogs is the spin-spin coupling constant $J_{4,5}$ = 0 Hz. Thus, the signal for the H(4) proton is a singlet, and the signals for the H(5), H_a(6), and H_b(6) protons are doublets with characteristic coupling constants (geminal coupling constant $J_{6a,6b}$ = 9.7 Hz, *trans*-vicinal coupling constant $J_{5,6a}$ =5.9 Hz and *cis*-vicinal coupling constant $J_{5,6b}$ = 3.3 Hz), giving the three-spin systems AMX. The spectral parameters of the carbohydrate moiety of 3-*O*-derivative **14** were established by comparing them with those for benzyl ether **8**.[11]

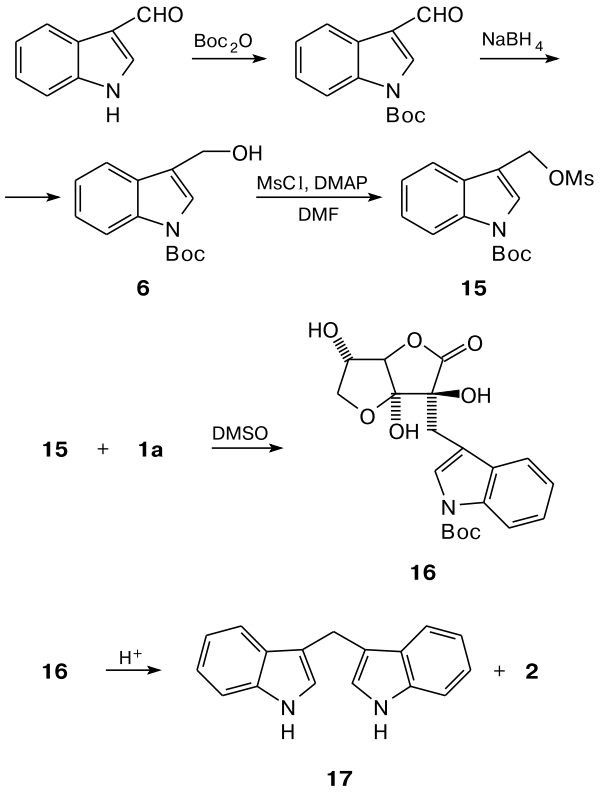
The mass spectra (ESI) of compounds **8—10**, **13**, **14**, and **16** revealed the peaks of low abundances (20—50%) that were attributed to the molecular ion ($[M]^+$) and fragment ions ($[M - CO_2]^+$, $[M - CO_2 - H_2O]^+$, $[M - CO]^+$, and $[M - Bu^t - CO]^+$), as well as the ion peaks of the benzyl and skatyl radicals. Furthermore, the mass spectra of all ascorbic acid derivatives exhibited characteristic ion fragment peaks of ascorbic acid (m/z = 77, 55). High-resolution mass spectra revealed the peaks corresponding to the lactone molecular ions $[M]^+$, $[M + Na]^+$, and $[M + K]^+$.

The IR spectra of compounds **8—10**, **13**, and **16** contained the absorption bands characteristic of the lactone fragment in the range of 1790 cm^{-1}.

Scheme 4



Scheme 5



Similar to ascorbigen (**2**),[10] the electrophilic addition of benzyl halides **7a,b** and 2- and 3-hydroxymethylindole methanesulfonates **12** and **15** proceeded from the side that is opposite that where the chain is involved in ring closure to hemiketal. Therefore, the chiral C(2) atom has the *S*-configuration, which is confirmed by the positive optical rotation of compounds **9**, **13**, and **16**.

Analysis of the reaction products demonstrated the influence of the structural factors on regioselectivity of alkylation of ascorbates with benzyl halides and hydroxymethylindole sulfonates, as well as on the stability of the resulting 3-*O*- and 2-*C*-ascorbic acid derivatives.

Experimental

Indolemethanols **5** and **6** were synthesized from the commercially available compounds, ethyl indole-2-carboxylate (Aldrich) and 3-formylindole (Fluka). Compound **11** was obtained by the known procedure.[5]

The ^{1}H and ^{13}C NMR spectra were recorded on a VXR-400 instrument at 400 MHz in $CDCl_3$ or CD_3OD. Chemical shifts are given in the δ scale relative to the residual solvent signals ($CDCl_3$, δ_H 7.25, δ_C 77.00; CD_3OD, δ_H 3.32, δ_C 49.00). Analytical TLC was performed on precoated silica gel F_{254} plates (0.2 mm, Merck), preparative TLC was carried out on the plates (20×20 cm×0.5 mm) with silica gel 60 F_{254} (Merck), silica gel 60 (Merck) was used for column chromatography. The indole-containing compounds were visualized in the UV light and by spraying with the Ehrlich reagent (2% 4-dimethylaminobenzaldehyde in EtOH—HCl) or the van Urk reagent (2% 4-dimethylaminobenzaldehyde in EtOH : 50% H_2SO_4, 1 : 1). The mass spectra (EI) were obtained on a Finnigan SAQ 710 spectrometer (70 eV, direct inlet, the ion source temperature 150 °C). The high-resolution mass spectra (ESI) were recorded on a Finnigan MAT 900S spectrometer. Analytical HPLC was performed on a Shimadzu LC10 vp instrument equipped with a Kromasil-100 C18 column (4×250 mm, 5 μm, Knauer, Germany). The injection volume is 20 μL. The UV detection was performed at 254 nm (λ_{max} of ascorbigen). The column was eluted with a MeCN — 0.01 *M* H_3PO_4 mixture, pH 2.6, in a gradient mode, where the percentage of MeCN increased from 20 to 22% within 15 min, then to 90% within 15 min at a flow rate 1 mL min^{-1}. The optical rotation was measured on a Perkin—Elmer 241 polarimeter. The IR spectra were obtained on a Nicolet-iS10 Fourier transform IR spectrometer (DTGS detector, splitter — KBr) with a Smart Performer module equipped with a ZnSe-crystal. The spectra were run in the range of 3000—650 cm^{-1} with a resolution of 4 cm^{-1}. The spectra were processed using the OMNIC-7.0 program package.

Alkylation of alkali metal ascorbates with benzyl halides (general procedure). To a solution of **1** (5.6 g, 0.035 mol) in water (30 mL) equimolar amount of NaOH or KOH was added. After short stirring, to the resulting solution of ascorbate (pH~7.0), a solution of benzyl halide **7a,b** in acetone or DMSO (30 mL) was added. The mixture was stirred until complete consumption of **7** (TLC monitoring), diluted with water, the aqueous layer was saturated with NaCl, and the mixture was extracted with EtOAc. The combined organics was washed with water, dried with Na_2SO_4, and the solvent was removed *in vacuo*. Flash column chromatography of the residue (eluent — $CHCl_3$, $CHCl_3$—MeOH, 50 : 1→10 : 1) afforded several fractions containing benzyl derivatives of the ascorbic acid (**1**). The fraction with R_f 0.45 ($CHCl_3$—MeOH, 5 : 1) contained a mixture of 3-*O* and 2-*C*-derivatives **8** and **9**. This mixture was subjected to hydrogenolysis in EtOAc with 5% Pd/C. After 30 min, the catalyst was filtered off, the solvent was removed *in vacuo*, and 2-*C*-derivative **9** was isolated by column chromatography, eluent — $CHCl_3$—MeOH, 10 : 1.

2-*C*-Benzyl-α-L-*xylo*-hex-3-ulofuranosono-1,4-lactone (9) was obtained by the reaction of sodium ascorbate (**1a**) (0.035 mol) with benzyl chloride (**7a**) (2.2 g, 2 mL, 0.017 mol) or with benzyl bromide (**7b**) (2.88 g, 2 mL, 0.017 mol) in a yield of ~1.1 g (24%), colorless crystals, R_f 0.52 ($CHCl_3$—MeOH, 7 : 1), R_t = = 8.48 min (98.2%, sample concentration 1—2 mg mL^{-1}), m.p. 190—196 °C (decomp.), $[\alpha]_D^{20}$ +8 (*c* 0.05, MeOH). IR (powder), ν/cm^{-1}: 1781 (CO lactone). ^{1}H NMR (CD_3OD), δ: 3.22 (d, 1 H, PhC$\underline{H}_2$, *J* = 13.0 Hz); 3.27 (d, 1 H, PhC$\underline{H}_2$, *J* = 13.0 Hz); 3.75 (s, 1 H, H(4)); 4.05 (dd, 1 H, H(6a), *J* = 9.7 Hz, *J* = 3.4 Hz); 4.14 (d, 1 H, H(6b), *J* = 5.7 Hz); 4.25 (m, 1 H, H(5)); 6.27 (s, 1 H, H (3′)); 6.88 (t, 1 H, H(6′), *J* = 7.1 Hz); 7.09 (t, 1 H, H(5′), *J* = 7.1 Hz); 7.22—7.33 (m, 5 H, Ph). ^{13}C NMR (CD_3OD), δ: 41.94; 75.50; 75.74; 81.23; 88.09; 108.45; 128.19; 129.03; 131.94; 135.32; 177.58. MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 266 [M]$^+$ (39). Found: *m*/*z* 289.0670 [M + Na]$^+$. $C_{13}H_{14}O_6Na$. Calculated: M = 289.0688.

3-*O*-Benzyl-5,6-*O*-isopropylidene-L-ascorbic acid (10). To a solution of the mixture of **8** and **9** (500 mg, 1.56 mmol) in dry acetone (10 mL), TsOH (10 mg) was added. The mixture was

stirred for 40 min, diluted with 10% $NaHCO_3$ (100 mL), extracted with EtOAc (2×30 mL), the combined organics was dried with Na_2SO_4, and the solvent was removed *in vacuo*. Purification by column chromatography afforded compound **9** (150 mg) and 3-*O*-benzyl derivative **10** (250 mg), yellowish oil, R_f 0.34 (petroleum ether—EtOAc, 3 : 1). ^{1}H NMR($CDCl_3$), δ: 1.47 (s, 3 H, C—Me); 1.50 (s, 3 H, C—Me); 4.22—4.10 (m, 2 H, H_a(6), H_b(6)); 4.36 (m, 1 H, H(5)); 4.67 (s, 1 H, H(4)); 5.62 (d, 1 H, PhC$\underline{H}_2$, J = 11.9 Hz); 5.67 (d, 1 H, PhC$\underline{H}_2$, J = 11.9 Hz) 7.55—7.35 (m, 5 H, Ph). ^{13}C NMR (CD_3OD), δ: 14.0; 22.55; 61.59; 65.14; 73.33; 73.96; 78.49; 121.40; 127.50; 128.55; 128.56; 135.35; 155.22; 172.75. MS (EI, 70 eV), m/z (I_{rel} (%)): 306 $[M]^+$ (40). Found: m/z 329.0992 $[M + Na]^+$. $C_{16}H_{18}O_6Na$. Calculated: M = 329.1001.

3-*O*-Benzyl-L-ascorbic acid (8). A solution of isopropylidene derivative **10** (0.1 g, 0.32 mmol) in a mixture of 1 *M* HCl and THF (1 : 1) was stirred until complete consumption of the starting compound. The reaction mixture was neutralized with 10% $NaHCO_3$ and extracted with BuOH (2×20 mL). The combined organics was washed with water and the solvent was removed *in vacuo*. Purification of the residue by column chromatography (eluent — CH_2Cl_2—MeOH, 20 : 1) afforded compound **8** in a yield of 0.07 g (80%), R_t = 12.84 min (sample concentration 0.1—0.4 mg mL^{-1}). IR (powder), ν/cm^{-1}: 1781 (CO lactone). ^{1}H NMR (CD_3OD), δ): 3.64—3.68 (m, 2 H, H_a(6), H_b(6)); 3.88 (m, 1 H, H(5)); 4.90 (s, 1 H, H(4)); 5.50 (d, 1 H, PhC$\underline{H}_2$, J = 11.9 Hz); 5.57 (d, 1 H, PhC$\underline{H}_2$, J = 11.9 Hz); 7.46—7.32 (m, 5 H, Ph). ^{13}C NMR (CD_3OD), δ: 61.59; 70.60; 73.96; 78.49; 121.40; 129.12; 129.55; 129.78; 137.86; 150.90; 172.75. MS (EI, 70 eV), m/z (I_{rel} (%)): Found: m/z 289.0684 $[M + Na]^+$. $C_{13}H_{14}O_6Na$. Calculated: M = 289.0688.

2-Hydroxymethyl-1-methylindole (5). To a suspension of $LiAlH_4$ (0.2 g, 0.005 mmol) in diethyl ether (10 mL), ethyl 1-methylindole-2-carboxylate (**11**) (1.0 g, 0.005 mol) was added and the reaction mixture was stirred for 30 min until complete consumption of the starting ester. The excess of $LiAlH_4$ was decomposed by addition of aqueous MeOH, the product was extracted with Et_2O, the combined organics was washed with water (3×50 mL), and dried with Na_2SO_4. Removal of the solvent *in vacuo* furnished alcohol **5** in a yield of 0.55 g (70%), dark-brown powder, R_f = 0.20 (petroleum ether—EtOAc, 3 : 1). ^{1}H NMR ($CDCl_3$), δ): 3.73 (s, 3 H, Me); 4.72 (s, 2 H, $\underline{CH}_2$OH); 7.09 (t, 1 H, H(6′), J = 7.1 Hz); 7.22 (t, 1 H, H(5′), J = 7.21 Hz); 7.29 (d, 1 H, H(7′), J = 7.3 Hz); 7.57 (d, 1 H, H(4′), J = 7.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 29.62; 57.26; 101.16; 109.06; 119.35; 120.49; 121.34; 126.97; 137.92; 138.47. Found (%): C, 74.45; H, 6.95; N, 8.79. $C_{10}H_{11}NO$. Calculated (%): C, 74.51; H, 6.88; N, 8.69.

2-*C*-[(1-Methylindol-2-yl)methyl]-α-L-*xylo*-hex-3-ulofuranosono-1,4-lactone (13) and 3-*O*-(1-methylindol-2-yl)methyl-L-ascorbic acid (14). To a solution of alcohol **5** (0.5 g, 0.003 mol) in THF (5 mL), a solution of the MsCl—DMAP complex (prepared from MsCl (0.43 g, 0.29 mL, 0.003 mol) and DMAP (0.46 g, 0.0038 mol)) in DMF (10 mL) was slowly added. The reaction mixture was stirred for 16 h, the volatiles were removed *in vacuo*, and the residue was diluted with DMSO. In a separate flask, sodium ascorbate (**1a**) was prepared from L-ascorbic acid (1.5 g, 0.0085 mol) and NaOH (0.34 g, 0.0085 mol) in a DMSO—H_2O (4 : 1) mixture, then the above solution was slowly added. The resulting clear solution was stirred until complete consumption of the starting mesylate. The reaction mixture was diluted with saturated aqueous NaCl (30 mL), extracted with ethyl acetate (2×30 mL), the combined organics was washed with aqueous NaCl, dried with Na_2SO_4, and the solvent was removed *in vacuo*. Purification of the residue (350 mg) by flash column chromatography and preparative TLC (silica gel, eluents — petroleum ether—EtOAc, 3 : 1; $CHCl_3$—MeOH, 10 : 1) afforded compound **13** (100 mg, 20%), pale pink amorphous powder, R_f = 0.36 ($CHCl_3$—MeOH, 7 : 1) and ether **14** (50 mg, ~10%), R_f = 0.24 ($CHCl_3$—MeOH, 7 : 1).

Compound **13**, R_t = 23.60 min (96.8%, sample concentration 0.1—0.4 mg·mL^{-1}), $[\alpha]_D^{20}$ +12 (*c* 0.05, MeOH). IR (powder), ν/cm^{-1}: 1781 (CO lactone). ^{1}H NMR (DMSO-d_6), δ: 3.21 (d, 1 H, C$\underline{H}_2$-Ind, J = 15.0 Hz); 3.24 (d, 1 H, CH_2-Ind, J = = 15.0 Hz); 3.69 (s, 3 H, N—Me); 3.88 (dd, 1 H, H(6b), J_1 = J_2 = = 5.7 Hz); 4.15 (dd, 1 H, H(6a), J = 9.7, J = 3.4 Hz); 4.24 (s, 1 H, 4-H); 4.22 (m, 1 H, H(5)); 6.27 (c, 1 H, H(3′)); 6.88 (t, 1 H, H(6′), J = 7.1 Hz); 7.09 (t, 1 H, H(5′), J = 7.1 Hz); 7.38 (d, 1 H, H(7′), J = 8.1 Hz); 7.46 (d, 1 H, H(4′), J = 8.1 Hz). ^{13}C NMR (DMSO-d_6), δ: 29.40; 31.85; 75.53; 75.54; 80.90; 88.32; 103.50; 108.67; 110.10; 119.40; 120.25; 121.50; 126.59; 137.53; 138.49; 178.75. MS (EI, 70 eV), m/z (I_{rel} (%)): 319 $[M]^+$ (48). Found: m/z 342.0946 $[M + Na]^+$. $C_{16}H_{17}NO_6Na$. Calculated: M = 342.0954. Found: m/z 358.0686 $[M + K]^+$. $C_{16}H_{17}NO_6K$. Calculated: M = 358.0693.

3-*O*-(1-Methylindol-2-yl)methyl-L-ascorbic acid (14). IR (powder), ν/cm^{-1}: 1756 (CO lactone). ^{1}H NMR (DMSO-d_6), δ: 3.65 (s, 3 H, N—Me); 3.78—3.83 (m, 2 H, H_a(6), H_b(6)); 4.10 (m, 1 H, H(5)); 4.80 (s, 1 H, H(4)); 5.62 (d, 2 H, C$\underline{H}_2$-Ind, J = 15.0 Hz); 5.69 (d, 2 H, C$\underline{H}_2$-Ind, J = 15.0 Hz); 6.64 (s, 1 H, H(3′)); 7.08 (t, 1 H, H(6′), J = 7.1 Hz); 7.20 (t, 1 H, H(5′), J = 7.1 Hz); 7.48 (d, 1 H, H(7′), J = 8.1 Hz); 7.56 (d, 1 H, H(4′), J = 8.1 Hz). ^{13}C NMR (CD_3OD), δ: 29.62; 61.59; 63.26; 70.60; 73.96; 101.16; 108.68; 109.06; 119.35; 120.49; 121.40; 126.97; 137.40; 137.92; 138.47; 171.15. MS (EI, 70 eV), m/z (I_{rel} (%)): 319 $[M]^+$ (43). Found: m/z 320.1126 $[M + H]^+$. $C_{16}H_{18}NO_6$. Calculated: M = 320.1134.

1-(*tert*-Butoxycarbonyl)-3-formylindole. To a cooled to 0 °C suspension of NaH (1.44 g, 0.025 mol) in anhydrous DMF (50 mL), a solution of 3-formylindole (3.6 g, 0.025 mol) in DMF (30 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 30 min, and a solution of Boc_2O (5.75 g, 0.025 mol) in THF (10 mL) was added. Then the reaction mixture was acidified with a solution of 1 *M* HCl in THF to pH 9.0, diluted with petroleum ether (30 mL) and with water (pH 3.0, 30 mL). The organic layer was separated, washed with water (pH 3.0, 3×50 mL), 5% $NaHCO_3$ (3×50 mL), and brine until neutral. The organic layer was dried with Na_2SO_4, the solvent was removed *in vacuo* to give 1-Boc-3-formylindole in a yield of 7.2 g (85%), light-brown powder, R_f = 0.89 ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR ($CDCl_3$), δ: 1.87 (s, 9 H, Boc); 7.26 (t, 1 H, H(6), J = 7.1 Hz); 7.34 (t, 1 H, H(5), J = 7.1 Hz); 7.64 (d, 1 H, H(7), J = 8.0 Hz); 7.72 (s, 1 H, H(2)); 8.37 (d, 1 H, H(4), J = 8.1 Hz); 10.61 (s, 1 H, 3-CHO). MS (EI, 70 eV), m/z (I_{rel} (%)): 245 $[M]^+$ (80). Found (%): C, 68.50; H, 6.09; N, 5.62. $C_{14}H_{15}NO_3$. Calculated (%): C, 68.55; H, 6.16; N, 5.71.

1-(*tert*-Butoxycarbonyl)-3-hydroxymethylindole (6). To a solution of 1-Boc-3-formylindole (2.0 g, 0.008 mol) in EtOH, $NaBH_4$ (0.16 g, 0.004 mol) was added and the reaction mixture was stirred for 30 min until complete consumption of the starting aldehyde. The reaction mixture was diluted with water, extracted with Et_2O (30 mL), the combined organics was washed with water (3×50 mL), and dried with Na_2SO_4. Removal of the sol-

vent *in vacuo* furnished compound **6** (1.7 g, 85%), light-brown powder, $R_f = 0.73$ ($CHCl_3$—MeOH, 10 : 1). ^{1}H NMR ($CDCl_3$), δ: 1.66 (s, 9 H, Boc); 4.83 (s, 2 H, $\underline{CH_2}$OH); 7.26 (t, 1 H, H(6′), J = 7.1 Hz); 7.34 (t, 1 H, H(5′), J = 7.1 Hz); 7.57 (s, 1 H, H(2′)); 7.64 (d, 1 H, H(7′), J = 8.0 Hz); 8.15 (d, 1 H, H(4′), J = 8.1 Hz). Found (%): C, 67.82; H, 6.68; N, 5.49. $C_{14}H_{17}NO_3$. Calculated (%): C, 67.70; H, 6.93; N, 5.67.

2-*C*-(1-Boc-Indol-3-yl)methyl-α-L-*xylo*-hex-3-ulfuranosono-1,4-lactone (16). To a solution of 3-hydroxymethylindole (**6**) (0.6 g, 0.0024 mol) in THF (5 mL), a solution of the MsCl—DMAP complex (prepared from MsCl (0.35 g, 0.24 mL, 0.003 mol) and DMAP (0.42 g, 0.0034 mol)) in DMF (10 mL) was slowly added. The resulting suspension was stirred for 16 h, the volatiles were removed *in vacuo*, the residue containing mesylate **15** was diluted with DMSO (5 mL). In a separate flask, sodium ascorbate (**1a**) was prepared from L-ascorbic acid (0.86 g, 0.0049 mol) and NaOH (0.19 g, 0.0048 mol) in a DMSO—H_2O (4 : 1) mixture, then the above solution of mesylate **15** was slowly added. The resulting clear solution was stirred until complete consumption of mesylate **15**. The reaction mixture was diluted with brine (30 mL), extracted with ethyl acetate (2×30 mL), the combined organics was washed brine, dried with Na_2SO_4, and the solvent was removed *in vacuo*. Purification of the residue (350 mg) by flash column chromatography (silica gel, eluents — $CHCl_3$; $CHCl_3$—MeOH, 10 : 1, 7 : 1) afforded compound **16** (250 mg, 25%), pale pink amorphous powder, $R_f = 0.48$ ($CHCl_3$—MeOH, 7 : 1), R_t = 27.41 min (96.8%, sample concentration 0.1—0.2 mg mL^{-1}). IR (powder), ν/cm^{-1}: 1792 (CO lactone); $[\alpha]_D^{20}$ +13 (*c* 0.05, MeOH). ^{1}H NMR (CD_3OD), δ: 1.67 (s, 9 H, Boc); 3.20 (d, 1 H, C$\underline{H_2}$-Ind, J = 15.0 Hz); 3.26 (d, 1 H, C$\underline{H_2}$-Ind, J = 15.0 Hz); 4.03 (dd, 1 H, H(6b), $J_1 = J_2 = 5.7$ Hz); 4.15 (s, 1 H, H(4)); 4.18 (dd, 1 H, H(6a), J = 9.7 Hz, J = 3.4 Hz); 4.29 (m, 1 H, H(5)); 7.18 (t, 1 H, H(6′), J = 7.1 Hz); 7.26 (t, 1 H, H(5′), J = 7.1 Hz); 7.57 (s, 1 H, H(2′)); 7.62 (d, 1 H, H(7′), J = 8.1 Hz); 8.07 (d, 1 H, H(4′), J = 8.1 Hz). ^{13}C (CD_3OD), δ: 27.65; 29.40; 75.60; 76.05; 81.90; 88.05; 106.06; 108.50; 112.10; 119.99; 121.25; 122.40; 123.50; 131.09; 137.59; 142.53; 152.2; 178.75. MS (EI, 70 eV), m/z (I_{rel} (%)): 405 $[M]^+$ (53). Found: m/z 428.1323 $[M + Na]^+$. $C_{20}H_{23}NO_8Na$. Calculated: M = 428.1321.

Ascorbigen (2) and di(indol-3-yl)methane (17). A solution of compound **16** (0.05 g, 0.12 mmol) in $CHCl_3$ (2 mL) was acidified with trifluoroacetic acid (0.1 mL) and stirred for 10 min. The reaction mixture was poured onto ice, extracted with $CHCl_3$, the extracts was washed with water until neutral, dried with Na_2SO_4. Removal of the solvent *in vacuo* afforded a mixture of compounds **2** and **17** identified by HPLC with the known samples with R_t = 9.86 and R_t = 7.21 min, respectively.

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