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Regioselective Synthesis of 3-*O*-Alkyl Ethers of Ascorbic Acid without Protecting Groups in a Single Step

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Abstract—The direct alkylation of L-ascorbic acid (vitamin C) with alkyl mesylates using sodium hydrogen carbonate as a base without protecting groups proceeds regioselectively and yields the corresponding 3-*O*-alkyl ethers of L-ascorbic acid exclusively.

Active oxygen species and free radicals which are constantly being formed in aerobic organisms are responsible for the oxidative damage to enzymes, lipid membranes and DNA in cells and tissues and are therefore involved in the development or exacerbation of various kinds of diseases. Under normal conditions they are removed by enzymatic and nonenzymatic antioxidant defense systems.[1] L-Ascorbic acid (**1**)[2] is one of the naturally occurring antioxidants and radical scavengers that protect cellular components against oxidative damage by free radicals and active oxygen species.[3] It is characterized by a 1-oxo-2-ene-2,3-diol (aci-reductone) structure element[4] which is responsible for the antioxidative effect of **1**. L-Ascorbic acid (**1**) also serves as a reductant in a number of important enzymatic transformations.[5] In addition, there is considerable evidence that vitamin C (**1**) is important in the prevention of a large number of chronic diseases such as cancer, cerebral apoplexy, diabetes, atopic dermatitis, myocardial infarction, and AIDS.[6]

Apart from its physiological and biochemical importance, L-ascorbic acid (**1**) has been widely employed as an antioxidant for the stabilization of nutrients.[7] However, the low lipophilicity of **1** and its susceptibility to thermal and oxidative degradation restricts its field of application and has raised considerable interest in the synthesis of ascorbic acid derivatives with increased lipophilicity and stability. The synthesis is not only of great interest for the development of new pharmaceuticals but also for the stabilization of nutrients, cosmetics, polymers and oil products, to name but a few potential applications. Naturally, the selective chemical modification of the hydroxyl groups of **1** is of particular interest.[8] So far, most studies have concentrated on the synthesis of derivatives like 6-*O*-monoesters,[9] 5,6-*O*,*O*-diesters[10] and 5,6-*O*,*O*-acetals[11] exhibiting a free 1-oxo-2-ene-2,3-diol (aci-reductone) structure element which is thought to be essential to the antioxidative properties of **1**. Recently it has been shown, though, that several 2-*O*- and 3-*O*-functionalized lipid soluble ascorbic acid derivatives also exhibit antioxidative properties.[12] 2-*O*- and 3-*O*-alkyl ethers of **1**, for example, have been found to protect lipid membranes against peroxidation.[12b,d–g] Of course, a better understanding of the chemistry and biochemistry of these compounds with a masked aci-reductone structure element is of importance not only for the development of new pharmaceuticals. The regioselective *O*-alkylation of L-ascorbic acid (**1**) and its derivatives itself is a long-standing problem in carbohydrate chemistry, and despite the interest in 3-*O*-ethers of **1**, no method for their direct preparation from **1** has been available so far.[12,13] As alkylation reactions of **1** are fairly sensitive to alkylation reagent, base, solvent and reaction conditions, the best way of preparing 3-*O*-alkylated ascorbic acids **3** was based on the regioselective alkylation of the 5,6-*O*,*O*-isopropylidene L-ascorbic acid with alkyl halides in the presence of different bases. Acetal cleavage finally yields the 3-*O*-alkyl derivatives **3**. Similar protocols have been developed for the preparation of the corresponding 2,3-di-*O*-alkyl-, 2,3-di-*O*-allyl- and 2,3-di-*O*-benzyl compounds.[13a,14] If, however, the acidity differences of the four hydroxyl groups in **1** are taken into account, regioselective 3-*O*-alkylation should be possible by employing appropriate reagents and reaction conditions (Scheme 1).

Here we give a full account on the first regioselective 3-*O*-alkylation of **1** without protecting groups, providing an efficient method for the preparation of 3-*O*-alkyl ethers **3**.[15] Initial studies revealed, that the reaction of L-ascorbic acid (**1**) with alkyl bromides in the presence of sodium hydrogen

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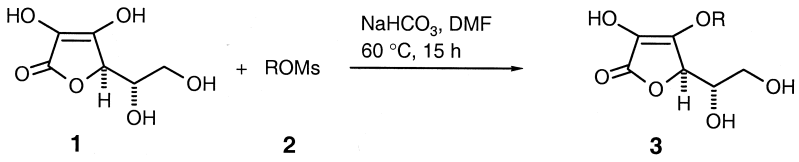

Scheme 1.

carbonate and dimethyl sulfoxide (DMSO) as solvent gave the desired 3-*O*-alkyl ethers **3**, though, in low yields. Changing solvents and bases as well as extending the reaction time and increasing the reaction temperature did not improve the yields of the alkyl ethers. After some experimentation it was found that the 3-*O*-alkylation of **1** without protection of *O*-5 and *O*-6 can easily be achieved, when alkyl mesylates **2** are employed as alkylation reagents instead. The alkyl mesylates **2a**–**l** were obtained from the corresponding alcohols with high yields following standard procedures. The reaction of 2.5 equiv. of L-ascorbic acid (**1**) with 1 equiv. alkyl mesylate **2** in the presence of 3.5 equiv. $NaHCO_3$ in DMSO at 60°C delivered the corresponding 3-*O*-alkyl ethers **3** as single products with yields ranging from 70 to 88% (Table 1). Under the reaction conditions given no regioisomers could be detected (^{1}H NMR spectroscopy) and isolated. After evaporation of the solvent at reduced pressure the crude products could easily be purified by column filtration followed by crystallization. The results compare favorably with those from the three-step procedure with respect to yield and purity.[12e]

The ^{13}C NMR spectra clearly revealed the structure of the 3-*O*-ethers **3**. As a representative example, the C-atoms of the aci-reductone moiety in **3a** resonate at δ=173.24 ppm (C-1), δ=120.41 ppm (C-2), and δ=152.23 ppm (C-3). The additional C-atoms of the basic ascorbic acid structure in **3a** show resonances at δ=76.62 ppm (C-4), δ=70.57 ppm (C-5) and δ=63.44 ppm (C-6).[16]

First investigations concerning the antioxidative potential using Differential Scanning Calorimetry show that even at higher temperatures the prepared 3-*O*-alkyl ethers exhibit antioxidative properties. The details of this study will be reported in due course.

To summarize, the regioselective 3-*O*-alkylation of L-ascorbic acid without using any protecting group is reported to provide the 3-*O*-alkyl ethers of ascorbic acid in a single step.

Table 1. The regioselective 3-*O*-alkylation of L-ascorbic acid (**1**)

Entry	Alkyl mesylate **2**	Product **3**	R	Yield **3** (%)
1	**a**	**a**	C_5H_{11}	73
2	**b**	**b**	C_6H_{13}	74
3	**c**	**c**	C_7H_{15}	75
4	**d**	**d**	C_8H_{17}	72
5	**e**	**e**	C_9H_{19}	70
6	**f**	**f**	$C_{10}H_{21}$	76
7	**g**	**g**	$C_{11}H_{23}$	77
8	**h**	**h**	$C_{12}H_{25}$	83
9	**i**	**i**	$C_{13}H_{27}$	88
10	**j**	**j**	$C_{14}H_{29}$	84
11	**k**	**k**	$C_{15}H_{31}$	70
12	**l**	**l**	$C_{16}H_{33}$	72

Experimental

Methods and materials

All solvents were distilled prior to use. DMSO was dried over CaH_2. Reagents and materials were either obtained from commercial suppliers and used without further purification or prepared by standard methods. Column filtration: silica gel 60, Merck. TLC: silica gel 60 F_{254} glass plates, Merck; compounds were visualized by conc. H_2SO_4 (180°C, 5 min). Melting points (uncorrected): Büchi 510. UV: Perkin Elmer Lambda 9. IR: Perkin Elmer Paragon 1000 FT IR-spectrometer or Bruker IFS 25 FTIR-spectrometer. Optical rotations: Perkin Elmer 241 polarimeter. ^{1}H and ^{13}C NMR: Jeol JNM-EX 270; δ in [ppm] calibrated to residual solvent signal with chemical shifts referred to TMS (0.00 ppm); *J* in [Hz]. MS: MAT 312 mass spectrometer. Combustion analyses: Microanalytical laboratory of the Institut für Organische Chemie der Universität Göttingen.

General procedure for the preparation of 3-*O*-alkyl ascorbic acids 3. 2.5 equiv. L-ascorbic acid (**1**) was dissolved in dry DMSO (1 mL/1.0 mmol **1**) under argon at room temperature. The solution was treated with 1.0 equiv. of the alkyl mesylate **2**. After addition of 3.5 equiv. $NaHCO_3$ the reaction mixture was stirred at 60°C for 15 h. The solvent was distilled off at 60–70°C under reduced pressure. The residue was dissolved in 2N HCl (1 mL/1.0 mmol $NaHCO_3$) and extracted five times with ethyl acetate (1 mL/1.0 mmol **1**). The collected organic phases were dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was purified by column filtration on silica gel followed by crystallization.

3-*O*-Pentyl-L-ascorbic acid (3a). Reaction of 8.81 g (50 mmol) of **1** with 3.32 g (20 mmol) pentyl mesylate (**2a**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from $CHCl_3$, 3.59 g (73%) of **3a** as colourless crystals. R_f=0.30 (cyclohexane/ethyl acetate=1:2). mp 81–83°C. $[\alpha]_D^{20}$=+41.5 (*c*=1.0 in methanol). IR (KBr): ν=1756 cm^{-1} (C=O), 1692 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.02). ^{1}H NMR (270 MHz, CD_3OD): δ=0.93 (m_c, 3 H, 5′-H_3), 1.30–1.45 (m, 4 H, 3′-H_2, 4′-H_2), 1.75 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, *J*=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.32 (C-5′), 23.40 (C-4′), 28.81 (C-3′), 30.54 (C-2′), 63.44 (C-6), 70.57 (C-5), 72.69 (C-1′), 76.62

(C-4), 120.41 (C-2), 152.23 (C-3), 173.24 (C-1). MS (70 eV); *m/z* (%): 246 (7) [M^+], 186 (4), 177 (2), 176 (3), 116 (100). Anal. Calcd. for $C_{11}H_{18}O_6$ (246.26): C, 53.65; H, 7.37. Found: C, 53.80; H, 7.36.

3-*O*-Hexyl-L-ascorbic acid (3b). Reaction of 8.81 g (50 mmol) of **1** with 3.61 g (20 mmol) hexyl mesylate (**2b**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration, 3.85 g (74%) of **3b** as colourless solid. R_f=0.30 (cyclohexane/ethyl acetate=1:2). mp 54–56°C. $[\alpha]_D^{20}$=+36.8 (*c*=1.0 in methanol). IR (KBr): ν=1758 cm^{-1} (C=O), 1684 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.00). ^1H NMR (270 MHz, CD_3OD): δ=0.91 (m_c, 3 H, 6′-H_3), 1.25–1.50 (m, 6 H, 3′-H_2 to 5′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.81 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, *J*=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.34 (C-6′), 23.59 (C-5′), 26.29 (C-3′), 30.81 (C-2′), 32.62 (C-4′), 63.44 (C-6), 70.58 (C-5), 72.70 (C-1′), 76.63 (C-4), 120.43 (C-2), 152.23 (C-3), 173.24 (C-1). MS (70 eV); *m/z* (%): 260 (9) [M^+], 200 (6), 177 (6), 176 (8), 116 (100). Anal. Calcd. for $C_{12}H_{20}O_6$ (260.28): C, 55.37; H, 7.74. Found: C, 55.20; H, 7.66.

3-*O*-Heptyl-L-ascorbic acid (3c). Reaction of 8.81 g (50 mmol) of **1** with 3.88 g (20 mmol) heptyl mesylate (**2c**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from $CHCl_3$, 4.11 g (75%) of **3c** as colourless crystals. R_f=0.41 (cyclohexane/ethyl acetate=1:2). mp 85–87°C. $[\alpha]_D^{20}$=+35.6 (*c*=1.0 in methanol). IR (KBr): ν=1755 cm^{-1} (C=O), 1698 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.01). ^1H NMR (270 MHz, CD_3OD): δ=0.90 (t, *J*=6.6 Hz, 3 H, 7′-H_3), 1.22–1.50 (m, 8 H, 3′-H_2 to 6′-H_2), 1.75 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.81 (m_c, M of ABMX, 1 H, 5-H), 4.50 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, *J*=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.41 (C-7′), 23.64 (C-6′), 26.59 (C-3′), 30.09 (C-4′), 30.86 (C-2′), 32.90 (C-5′), 63.44 (C-6), 70.59 (C-5), 72.72 (C-1′), 76.64 (C-4), 120.44 (C-2), 152.23 (C-3), 173.25 (C-1). MS (70 eV); *m/z* (%): 274 (7) [M^+], 214 (3), 177 (8), 176 (5), 116 (100). Anal. Calcd. for $C_{13}H_{22}O_6$ (274.31): C, 56.92; H, 8.08. Found: C, 57.06; H, 8.02.

3-*O*-Octyl-L-ascorbic acid (3d). Reaction of 8.81 g (50 mmol) of **1** with 4.17 g (20 mmol) octyl mesylate (**2d**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from ethyl acetate, 4.15 g (72%) of **3d** as a colourless solid. R_f=0.31 (cyclohexane/ethyl acetate=1:2). mp 70°C (Ref. 12e 58–60°C). $[\alpha]_D^{20}$=+32.2 (*c*=1.0 in methanol). IR (KBr): ν=1760 cm^{-1} (C=O), 1690, 1660 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (3.95). ^1H NMR (270 MHz, CD_3OD): δ=0.90 (m_c, 3 H, 8′-H_3), 1.20–1.50 (m, 10 H, 3′-H_2 to 7′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.49 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, *J*=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.42 (C-8′), 23.69 (C-7′), 26.63 (C-3′), 30.33 (C-5′), 30.37 (C-4′), 30.86 (C-2′), 32.95 (C-6′), 63.46 (C-6), 70.61 (C-5), 72.72 (C-1′), 76.65 (C-4), 120.45 (C-2), 152.26 (C-3), 173.26 (C-1). MS (70 eV); *m/z* (%): 288 (5) [M^+], 228 (3), 177 (9), 176 (5), 116 (100). Anal. Calcd. for $C_{14}H_{24}O_6$ (288.34): C, 58.32; H, 8.39.

3-*O*-Nonyl-L-ascorbic acid (3e). Reaction of 8.81 g (50 mmol) of **1** with 4.45 g (20 mmol) nonyl mesylate (**2e**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave after column filtration and recrystallization from cyclohexane/ethyl acetate (4:1) 4.23 g (70%) of **3e** as colourless crystals. R_f=0.32 (cyclohexane/ethyl acetate=1:2). mp 88–90°C. $[\alpha]_D^{20}$=+31.2 (*c*=1.0 in methanol). IR (KBr): ν=1755 cm^{-1} (C=O), 1699 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.03). ^1H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 9′-H_3), 1.18–1.50 (m, 12 H, 3′-H_2 to 8′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.63 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, *J*=1.6 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.43 (C-9′), 23.72 (C-8′), 26.66 (C-3′), 30.39, 30.44 and 30.65 (C-4′ to C-6′), 30.89 (C-2′), 33.04 (C-7′), 63.45 (C-6), 70.63 (C-5), 72.74 (C-1′), 76.67 (C-4), 120.48 (C-2), 152.27 (C-3), 173.27 (C-1). MS (70 eV); *m/z* (%): 302 (27) [M^+], 242 (9), 177 (52), 176 (38), 116 (100). Anal. Calcd. for $C_{15}H_{26}O_6$ (302.36): C, 59.59; H, 8.67. Found: C, 59.53; H, 8.65.

3-*O*-Decyl-L-ascorbic acid (3f). Reaction of 8.81 g (50 mmol) of **1** with 4.73 g (20 mmol) decyl mesylate (**2f**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from cyclohexane/ethyl acetate (4:1), 4.81 g (76%) of **3f** as colourless crystals. R_f=0.32 (cyclohexane/ethyl acetate=1:2). mp 81–84°C (Ref. 12e 73–75°C). $[\alpha]_D^{20}$=+31.7 (*c*=1.0 in methanol). IR (KBr): ν=1754 cm^{-1} (C=O), 1695, 1658 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.05). ^1H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 10′-H_3), 1.20–1.50 (m, 14 H, 3′-H_2 to 9′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, *J*=1.3 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.44 (C-10′), 23.71 (C-9′), 26.63 (C-3′), 30.42, 30.44 and 30.66 (C-4′ to C-7′), 30.86 (C-2′), 33.04 (C-8′), 63.44 (C-6), 70.59 (C-5), 72.71 (C-1′), 76.63 (C-4), 120.44 (C-2), 152.21 (C-3), 173.23 (C-1). MS (70 eV); *m/z* (%): 316 (6) [M^+], 256 (5), 177 (16), 176 (10), 115 (100). Anal. Calcd. for $C_{16}H_{28}O_6$ (316.39): C, 60.74; H, 8.92. Found: C, 60.55; H 8.77.

3-*O*-Undecyl-L-ascorbic acid (3g). Reaction of 8.81 g (50 mmol) of **1** with 5.00 g (20 mmol) undecyl mesylate (**2g**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from cyclohexane/ethyl acetate (4:1), 5.09 g (77%) of **3g** as colourless crystals. R_f=0.33 (cyclohexane/ethyl acetate=1:2). mp 95–96°C. $[\alpha]_D^{20}$=+30.0 (*c*=1.0 in methanol). IR (KBr): ν=1756 cm^{-1} (C=O), 1700 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.03). ^1H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 11′-H_3), 1.18–1.50 (m, 16 H, 3′-H_2 to

10′-H_2), 1.73 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, J=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.43 (C-11′), 23.73 (C-10′), 26.66 (C-3′), 30.44, 30.46, 30.68, 30.72 and 30.74 (C-4′ to C-8′), 30.89 (C-2′), 33.07 (C-9′), 63.47 (C-6), 70.62 (C-5), 72.74 (C-1′), 76.66 (C-4), 120.49 (C-2), 152.27 (C-3), 173.28 (C-1). MS (70 eV); m/z (%): 330 (8) [M^+], 270 (7), 177 (53), 176 (30), 116 (100). Anal. Calcd. for $C_{17}H_{30}O_6$ (330.42): C, 61.80; H, 9.15. Found: C, 61.80; H, 9.12.

3-*O*-Dodecyl-L-ascorbic acid (3h). Reaction of 8.81 g (50 mmol) of **1** with 5.29 g (20 mmol) dodecyl mesylate (**2h**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from $CHCl_3$, 5.72 g (83%) of **3h** as colourless crystals. R_f=0.32 (cyclohexane/ethyl acetate=1:2). mp 90–92°C (Ref. 12e 86–88°C). $[\alpha]_D^{20}$=+28.3 (c=1.0 in methanol). IR (KBr): ν=1760 cm^{-1} (C=O), 1696, 1658 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.03). ^{1}H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 12′-H_3), 1.19–1.50 (m, 18 H, 3′-H_2 to 11′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.82 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.75 (d, X of ABMX, J=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.44 (C-12′), 23.73 (C-11′), 26.66 (C-3′), 30.44, 30.48, 30.68, 30.72, 30.76 and 30.78 (C-4′ to C-9′), 30.89 (C-2′), 33.07 (C-10′), 63.46 (C-6), 70.62 (C-5), 72.74 (C-1′), 76.66 (C-4), 120.47 (C-2), 152.28 (C-3), 173.28 (C-1). MS (70 eV); m/z (%): 344 (10) [M^+], 284 (11), 177 (64), 176 (48), 116 (100). Anal. Calcd. for $C_{18}H_{32}O_6$ (344.44): C, 62.77; H, 9.36. Found: C, 62.49; H, 9.32.

3-*O*-Tridecyl-L-ascorbic acid (3i). Reaction of 8.81 g (50 mmol) of **1** with 5.57 g (20 mmol) tridecyl mesylate (**2i**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from cyclohexane/ethyl acetate (4:1), 6.31 g (88%) of **3i** as colourless crystals. R_f=0.34 (cyclohexane/ethyl acetate=1:2). mp 99–100°C. $[\alpha]_D^{20}$=+26.5 (c=1.0 in methanol). IR (KBr): ν=1757 cm^{-1} (C=O), 1702 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.01). ^{1}H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 13′-H_3), 1.19–1.50 (m, 20 H, 3′-H_2 to 12′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, J=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.45 (C-13′), 23.74 (C-12′), 26.66 (C-3′), 30.44, 30.48, 30.69, 30.73, 30.77, 30.78 and 30.80 (C-4′ to C-10′), 30.89 (C-2′), 33.07 (C-11′), 63.46 (C-6), 70.61 (C-5), 72.73 (C-1′), 76.65 (C-4), 120.47 (C-2), 152.23 (C-3), 173.26 (C-1). MS (70 eV); m/z (%): 358 (5) [M^+], 298 (10), 177 (57), 176 (16), 116 (100). Anal. Calcd. for $C_{19}H_{34}O_6$ (358.47): C 63.66, H 9.56, found C 63.68, H 9.31.

3-*O*-Tetradecyl-L-ascorbic acid (3j). Reaction of 8.81 g (50 mmol) of **1** with 5.85 g (20 mmol) tetradecyl mesylate (**2j**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from cyclohexane/ethyl acetate (4:1) 6.26 g (84%) of **3j** as colourless crystals. R_f=0.36 (cyclohexane/ethyl acetate=1:2). mp 86–88°C (Ref. 12e 68–69°C). $[\alpha]_D^{20}$=+23.2 (c=1.0 in methanol). IR (KBr): ν=1760 cm^{-1} (C=O), 1708 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (4.01). ^{1}H NMR (270 MHz, CD_3OD): δ=0.90 (m_c, 3 H, 14′-H_3), 1.19–1.50 (m, 22 H, 3′-H_2 to 13′-H_2), 1.73 (m_c, 2 H, 2′-H_2), 3.65 (m_c, AB of ABMX, 2 H, 6-H_2), 3.84 (m_c, M of ABMX, 1 H, 5-H), 4.49 (m_c, 2 H, 1′-H_2), 4.77 (d, X of ABMX, J=1.3 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.44 (C-14′), 23.73 (C-13′), 26.66 (C-3′), 30.44, 30.48, 30.68, 30.72, 30.78 and 30.80 (C-4′ to C-11′), 30.89 (C-2′), 33.07 (C-12′), 63.47 (C-6), 70.62 (C-5), 72.74 (C-1′), 76.66 (C-4), 120.47 (C-2), 152.27 (C-3), 173.27 (C-1). MS (70 eV); m/z (%): 372 (12) [M^+], 312 (13), 177 (69), 176 (55), 116 (100). Anal. Calcd. for $C_{20}H_{36}O_6$ (372.50): C, 64.49; H, 9.74. Found: C, 64.63; H, 9.79.

3-*O*-Pentadecyl-L-ascorbic acid (3k). Reaction of 8.81 g (50 mmol) of **1** with 6.13 g (20 mmol) pentadecyl mesylate (**2k**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from cyclohexane/ethyl acetate (4:1) 5.41 g (70%) of **3k** as colourless crystals. R_f=0.37 (cyclohexane/ethyl acetate=1:2). mp 102–104°C. $[\alpha]_D^{20}$=+24.7 (c=1.0 in methanol). IR (KBr): ν=1756 cm^{-1} (C=O), 1702 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (3.89). ^{1}H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 15′-H_3), 1.15–1.50 (m, 24 H, 3′-H_2 to 14′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.83 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (d, X of ABMX, J=1.65 Hz, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.45 (C-15′), 23.75 (C-14′), 26.67 (C-3′), 30.46, 30.48, 30.70, 30.74 and 30.80 (C-4′ to C-12′), 30.90 (C-2′), 33.09 (C-13′), 63.47 (C-6), 70.63 (C-5), 72.74 (C-1′), 76.67 (C-4), 120.49 (C-2), 152.25 (C-3), 173.26 (C-1). MS (70 eV); m/z (%): 386 (4) [M^+], 326 (5), 177 (53), 176 (18), 116 (100). Anal. Calcd. for $C_{21}H_{38}O_6$ (386.53): C, 65.26; H 9.91. Found: C, 64.98; H, 9.90.

3-*O*-Hexadecyl-L-ascorbic acid (3l). Reaction of 8.81 g (50 mmol) of **1** with 6.41 g (20 mmol) hexadecyl mesylate (**2l**) in the presence of 5.88 g (70 mmol) $NaHCO_3$ and 50 mL DMSO according to the *General Procedure* gave, after column filtration and recrystallization from $CHCl_3$, 5.77 g (72%) of **3l** as colourless crystals. R_f=0.38 (cyclohexane/ethyl acetate=1:2). mp 94–95°C (Ref. 12e 73–74°C). $[\alpha]_D^{20}$=+22.3 (c=1.0 in methanol). IR (KBr): ν=1761 cm^{-1} (C=O), 1704 (C=C). UV (CH_3CN): λ_{max} (log ϵ)=242.5 nm (3.92). ^{1}H NMR (270 MHz, CD_3OD): δ=0.89 (m_c, 3 H, 16′-H_3), 1.15–1.50 (m, 26 H, 3′-H_2 to 15′-H_2), 1.74 (m_c, 2 H, 2′-H_2), 3.64 (m_c, AB of ABMX, 2 H, 6-H_2), 3.84 (m_c, M of ABMX, 1 H, 5-H), 4.48 (m_c, 2 H, 1′-H_2), 4.76 (s_{br}, X of ABMX, 1 H, 4-H). ^{13}C NMR (67.8 MHz, CD_3OD): δ=14.45 (C-16′), 23.75 (C-15′), 26.68 (C-3′), 30.46, 30.49, 30.70, 30.74 and 30.81 (C-4′ to C-13′), 30.90 (C-2′), 33.09 (C-14′), 63.47 (C-6), 70.62 (C-5), 72.74 (C-1′), 76.65 (C-4), 120.48 (C-2), 152.25 (C-3), 173.28 (C-1). MS (70 eV); m/z (%): 400 (5) [M^+], 340 (7), 177 (56), 176 (18), 116 (100). Anal. Calcd. for $C_{22}H_{40}O_6$ (400.55): C, 65.96; H, 10.07. Found: C, 65.66; H, 9.83.

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