Regio- and Chemoselective One-Step 3-O-Alkylenation of Unprotected Ascorbic Acid Using ω-Iodoalkanols

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Abstract: A regio- and chemoselective alkylenation employing unprotected ascorbic acid and a series of unprotected iodoalkanols in the presence of sodium hydrogen carbonate in dimethyl sulfoxide is described. This atom economic high yielding procedure delivers the corresponding 3-*O*-alkylene ethers in a single step without prior protection. Specific 3-O-etherification was also observed with unprotected 16-iodohexadecanoic acid and with 2-(10-iododecyl)isoindole-1,3-dione. Furthermore, an 2-*O*-alkylene derivative was obtained when 3-*O*-benzyl ascorbic acid was reacted with unprotected 10-iododecanol under slightly modified conditions. Finally, the antioxidative activity of all compounds was determined and compared to vitamin C and E.

Key words: ascorbic acid, regioselective, chemoselective, 3-O-alkylenation, ω-iodoalkanols

For some time now, our respective groups have been involved in the synthesis and biological evaluation of hybrid compounds combining an antioxidant moiety with a ω-alkanol side chain for the treatment of neurodegenerative and neuroinflammatory diseases.[1] This has resulted in different lead structures, namely cyclohexenon-,[2] tocopherol-,[3] quinol-[4] and lately resveratrol-[5] fatty alcohols having interesting pharmacological properties. Here we report on preliminary results concerning the antioxidative activity of a new series of hybrid compounds merging the nucleus of vitamin C at position 3 with different iodoalkylene side chains.

Ascorbic acid or vitamin C is one of Nature's most potent water-soluble antioxidants which protects cells and tissues against oxidative damage. Besides, vitamin C is known to play an important role in the prevention of several chronic diseases.[6] Although its high hydrosolubility facilitates oral uptake, it seriously limits its application in certain domains, e.g. as lipid peroxidation inhibiting agent.[7] As a consequence, numerous efforts have been made to enhance its lipophilicity, mostly by adding alkyl side chains. The majority of the literature references on this subject focus on the preparation of 2- or 3-*O*-alkyl ascorbic acids.[8–13]

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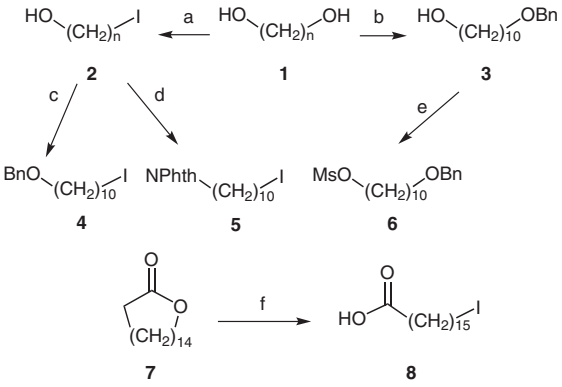
Various protocols use 5,6-isopropylidene-L-ascorbic acid as starting material and deliver a mixture of 2- and 3-alkylation products.[8] In some cases however, regio- and chemoselective 3-O-alkylation is observed.[9] Selective 2-O-alkylation can be achieved after protection of the more acidic position 3.

In addition to these procedures, several groups have developed methods to address 3-alkyl ethers without the need for prior protection. Unprotected L-ascorbic acid can, for example, be regio- and chemoselectively alkylated at position 3 under Mitsunobu conditions in good yields.[10]



Scheme 1 Syntheses of the different chains. *Reagents and conditions*: (a) n = 10, 12, 14, 16: aq HI (57%), toluene, 90 °C, 6 h (61–78%); (b) n = 10: NaH, BnBr, NBu_4Br, THF, reflux, 12 h (49%); (c) n = 10: NaH, BnBr, THF, reflux, 12 h (95%); (d) n = 10: phthalimide, DEAD, Ph_3P, CH_2Cl_2, 0 °C to r.t., 24 h (93%); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 18 h (quant); (f) aq HI (57%), AcOH, 60 °C, 6 h (96%).

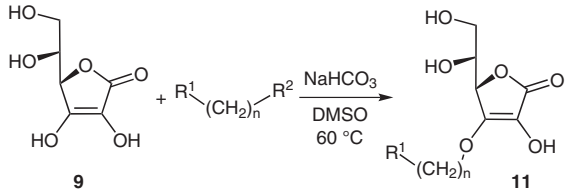
Regioselective one-pot 3-O-alkylation of unprotected ascorbic acid has also been achieved using alkyl mesylates in the presence of sodium hydrogen carbonate in DMSO[11] or by refluxing alkyl mesylates or sulfonates with triethylamine in alcohols.[12] O-Alkylenation reactions of vitamin C are much rarer though[13] and to the best of our knowledge, there is no example to date of a one-pot synthesis of such a compound.

Here we present an efficient one-pot synthesis for 3-*O*-alkylene ethers of vitamin C without need for protecting groups which is based on a slight modification of a known

chemo- and regioselective approch.[11] These compounds are very interesting as potent amphiphilic antioxidants. In addition to the corresponding alkyl ethers of vitamin C, already used in this context, our compounds with their terminal functionalization offer the possibility for further derivatization.

In order to access the different 3-*O*-alkylene ethers, we first had to prepare the different alkylene chains (Scheme 1). Diols **1** were monoiodinated using a 57% aqueous solution of hydroiodic acid in toluene.[3a] Compound **5** was obtained as single product via a Mitsunobu reaction of iodoalcohol **2a** and phthalimide.[14] Benzylation of **2a** in the presence of sodium hydride gave [(10-iododecyloxy)methyl]benzene (**4**). Monobenzylation of decan-1,10-diol (**1a**) afforded 10-(benzyloxy)decan-1-ol (**3**)[3b] which was further converted into mesylate **6**.[11] 16-Iodohexadecanoic acid (**8**) was obtained by reacting lactone **7** in glacial acetic acid in the presence of hydroiodic acid.[15]

With all the different alkylene chains in hand, we started investigating the regioselective etherification of vitamin C. We began to explore the procedure developed by Beifuss et al. reacting unprotected ascorbic acid with mesylates and sodium hydrogen carbonate in DMSO (Scheme 2, Table 1).[11]



Scheme 2 3-O-Alkylenation attempts of unprotected ascorbic acid

Table 1 Specific 3-O-Alkylenation of Ascorbic Acid

Entry	Reactant	R^1	R^2	n	Time (h)	Product (yield, %)
1	**6**	OBn	OMs	10	24	**11a** (42)
2	**4**	OBn	I	10	19	**11a** (68)
3	**2a**	OH	I	10	3	**11b**[a] (80)
4	**2b**	OH	I	12	3	**11c**[a] (71)
5	**2c**	OH	I	14	3	**11d**[a] (74)
6	**2d**	OH	I	16	3	**11e**[a] (78)
7	**10a**	Me	I	9	3	**11f**[a] (84)
8	**10b**	Me	I	11	3	**11g**[a] (79)
9	**10c**	Me	I	15	3	**11h**[a] (80)
10	**10d**	Me	I	17	3	**11i**[a] (42)
11	**5**	NPhth	I	16	3	**11j**[a] (79)
12	**8**	CO_2H	I	10	3	**11k**[a] (65)

[a] Reaction workup was performed under non-acidic conditions.

Using crude mesylate **6**, the corresponding 3-*O*-ether **11a** was obtained in only 42% yield after 24 hours at 60 °C (Table 1, entry 1). We consequently looked for other leaving groups and turned towards the corresponding iodide **4**. We were pleased to note that the corresponding ether **11a** was obtained in 68% yield in 19 hours (entry 2). Next, we tried reacting directly unprotected 10-iododecan-1-ol (**2a**) which resulted in decomposition of the starting materials during the acidic workup.[11b] Performing the workup in neutral conditions led to the desired 3-*O*-alkylene ascorbic acid **11b** in 80% yield in only three hours (entry 3).[16] All attempts to use another solvent (acetone, toluene, methanol) in order to avoid the distillation under reduced pressure of DMSO, only led to recovery of the starting materials. Using the thus adapted method allowed to obtain 3-*O*-ethers **11c–e** with even longer alkanol chains (entries 4–6) as well as the corresponding 3-alkyl ethers **11f–i** (entries 7–10) in high yields. It was only when very long alkyl chains were reacted that the yield started to drop (entry 10). Finally, we tried to regioselectively 3-*O*-alkylenate vitamin C using 2-(10-iododecyl)isoindole-1,3-dione (**5**; entry 11) and unprotected 16-iodohexadecanoic acid (**8**; entry 12). As before, the resulting compounds **11j**,**k** were obtained as single product in good yields.

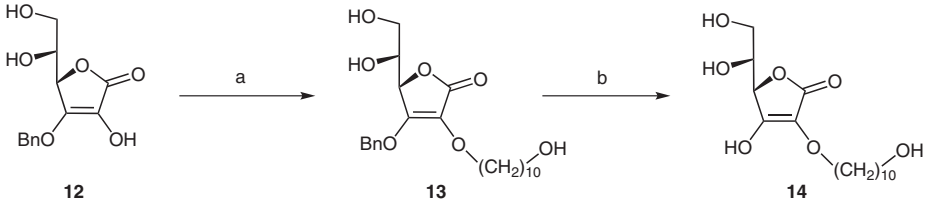
We next adapted our method based on a slightly modified procedure[11] to the synthesis of 2-*O*-alkylene ascorbic acids. Starting from 3-*O*-benzyl ascorbic acid (**12**)[10a] and unprotected 10-iododecan-1-ol (**2a**), 2,3-*O*,*O*-dialkyl ether **13** was obtained in good yield using only a slightly stronger base (K_2CO_3) as before (Scheme 3). 2-*O*-Alkylene ascorbic acid **14** was finally obtained by hydrogenation over Pd/C in excellent yield.

Finally, we evaluated the antioxidative capacity of all ascorbic acid derivatives. Their free radical scavenging activity was determined by the corresponding IC_{50} using the DPPH [2,2′-di(4-*tert*-octylphenyl)-1-picrylhydrazyl] test (Table 2).[13]

Table 2 Results of the DPPH Antioxidative Test

Entry	Compound	IC_{50} (μM)	Error
1	α-tocopherol	900	± 60
2	Trolox®	80	± 30
3	vitamin C	80	± 20
4	**11b**	730	± 60
5	**11f**	860	± 40
6	**11j**	790	± 50
7	**11k**	–[a]	–
8	**13**	–[a]	–
9	**14**	130	± 20

[a] No effect was detected.



12 13 14

Scheme 3 2-O-Alkylenation attempts of 3-*O*-benzyl ascorbic acid. *Reagents and conditions*: (a) 10-iododecanol, K_2CO_3, DMSO, 60 °C, 3 h (77%); (b) H_2, 5% Pd/C, EtOH, r.t., 2 h (96%).

Vitamin E (α-tocopherol), Trolox®, a water-soluble derivative of the latter, and vitamin C were used as control compounds (entries 1–3). Trolox® has generally a better antioxidative activity than vitamin E due to its increased solubility in ethanol. The IC_{50}s of a given series, e.g. **11b–e** and **11f–i** were not affected by the different chain lengths (data not shown). 3-*O*-Alkanol ascorbic acid **11b** (entry 4) has a slightly better antioxidative activity than the corresponding 3-*O*-alkyl ether **11f** (entry 5) which might again be explained by a better solubility of **11b** in ethanol owing to an additional alcohol function. Both compounds do however not compete with vitamin C which has a significantly lower IC_{50}. These findings are in contradiction with the results of Kato et al. who found comparable reducing activities for all three types of compounds.[13] Derivative **11j** showed reducing activity in the range of compounds **11b** and **11f** (entry 6). Carboxylic acid **11k** as well as compound **13** completely lost their antioxidative activity (entries 7 and 8). These results are in accordance with those of Kato et al. who also observed complete loss of reducing activity for ascorbic acid derivatives bearing specific functional groups as well as for 2,3-*O*,*O*-disubstitued compounds.[13] Finally, 2-*O*-alkylene ether **14** exhibited an almost identical reductive ability as vitamin C (entries 3 and 9) which is again in agreement with the findings of Kato et al.[13]

In conclusion we have developed a regioselective 3-O-alkylation reaction of vitamin C with a series of different unprotected iodoalkylene derivatives. These amphiphilic products offer the possibility of further derivatization. Moreover, this optimized procedure allows for the straightforward synthesis of 2-*O*-alkylene ether derivatives using the same readily available iodides. The determination of the antioxidative capacity of the different compounds showed that there appears to be a difference between 2-*O*- and 3-*O*-monoalkylene derivatives although further 2-*O*-alkylene ethers will have to be prepared and tested to confirm this result. Furthermore, the functionalization of the attached chain can strongly influence on the reducing activity of given compounds.

There are ongoing studies in our respective groups on the synthesis of additional 2-*O*-alkylene ascorbic acids and on biological screening reactions to determine potent candidates for the treatment of neurological diseases.

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(16) **Typical Experimental Procedure; Preparation of (*R*)-5-[(*S*)-1,2-Dihydroxyethyl)]-3-hydroxy-4-(10-hydroxydecyloxy)furan-2 (5*H*)-one (11b)**: Ascorbic acid (3.20 g, 18.20 mmol, 2.5 equiv) and $NaHCO_3$ (1.83 g, 21.85 mmol, 3 equiv) were added to a solution of 10-iododecanol (2.07 g, 7.28 mmol, 1 equiv) in anhyd DMSO (18 mL) and the resulting mixture was heated at 60 °C. After 3 h, DMSO was evaporated under reduced pressure and the residue was suspended in ethanol (12 mL) and brine (12 mL). EtOAc (200 mL) was added to the suspension which was then dried over $MgSO_4$, filtered and evaporated under reduced

pressure. The crude was purified via silica gel column chromatography (CH_2Cl_2–MeOH, 9:1) and was recrystallized (EtOAc–hexane) to give a white solid (80%). R_f = 0.30 (EtOAc); mp 71–73 °C. IR ($CHCl_3$): 3396 (OH), 1748 (CyO), 1693 (CyO) cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 1.31 (br s, 12 H, H-3′ to H-8′), 1.51 (m, 2 H, H-9′), 1.72 (m, 2 H, H-2′), 3.52 (t, *J* = 6.6 Hz, 2 H, H-10′), 3.64 (m, 2 H, CH_2OH), 3.82 (m, 1 H, CHOH), 4.48 (m, 2 H, H-1′), 4.75 (d, *J* = 1.8 Hz, 1 H, CH). ^{13}C NMR (75 MHz, CD_3OD): δ = 25.2, 25.5 (C-2′, C-3′), 28.2–29.2 (C-4′ to C-8′), 32.2 (C-9′), 61.6 (CH_2OH), 70.0 (CHOH), 70.5 (C-10′), 72.4 (C-1′), 75.2 (CH), 119.0 (=COH), 150.8 (=CO-alkyl), 171.8 (C=O).