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L-Ascorbic acid in organic synthesis: DBU-catalysed one-pot synthesis of tetramic acid derivatives from 5,6-*O*-isopropylidene ascorbic acid☆

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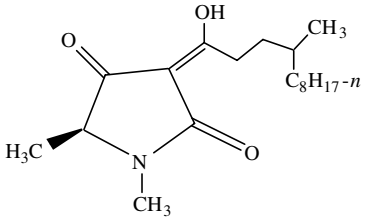
Abstract—Reaction of 5,6-*O*-isopropylidene-2,3-bis-*O*-alkyl ascorbic acid with different amines in the presence of DBU at ambient temperature resulted in the formation of 3,4-bis-*O*-alkyl-1-alkyl-5-(2-hydroxy ethyl)-5-hydroxy-1,5-dihydropyrrol-2-ones in moderate yields.

Tetramic acid derivatives are the key structural core found in a variety of natural products including many antibiotics such as melophilin B, reutericyclin, tirandamycin, BU2313A, blasticidin A and vancoresmycin.[1–5] The wide spectrum of biological activities in this class of molecule include potent antiviral, antibiotic and antifungal properties as well as cytotoxicities and antitumour action.[6–8] These compounds have also been designed as glycine site *N*-methyl-D-asparatate (NMDA) antagonists for the treatment of neurological disorders.[6] One such prominent molecule, melophilin B, is depicted in Figure 1.



Melophilin B

Figure 1.

Recently a number of solution- and solid-phase syntheses of tetramic acids have been reported.[9–13] Ascorbic acid has been used in organic synthesis for the preparation of many intermediates and biologically active molecules. Our interest in ascorbic acid chemistry arose from our quest for new drugs against tuberculosis. Thiolactomycins and thiotetronic acid derivatives, which show antitubercular activity via mycobacterial FAS-II inhibition[14a,b] and many 5-hydroxymethyl tetronic acid analogues exhibit HIV protease inhibitory activity.[14c] We were interested in the synthesis of compounds where the ring oxygen of ascorbic acid is replaced with nitrogen and the resulting core, a tetramate, might serve as a good pharmacophore. Ascorbic acid as a synthon has been used in the synthesis of pyrano[3,4-*b*]indoles and a variety of other heterocycles by Preobrzhenskaya's group.[15] Very recently Dallacker's group[16] and Khan et al.[17] reported the reaction of liquid ammonia and amines with ascorbic acid derivatives to give lactams. Encouraged by their reports we decided to synthesise tetramic acid derivatives from a suitably protected ascorbic acid.

The reaction of 2,3-*O*-bis-allyloxy-5,6-*O*-isopropylidene ascorbic acid **2a**, prepared by the slightly modified method reported earlier,[18] with *n*-butylamine in THF at 0–40 °C did not result in any product as was evident from TLC. However, addition of DBU as catalyst led to the formation of several products (TLC) and compound **2a** was totally consumed within 10 h at ambient temperature. Column (SiO_2) chromatography of the

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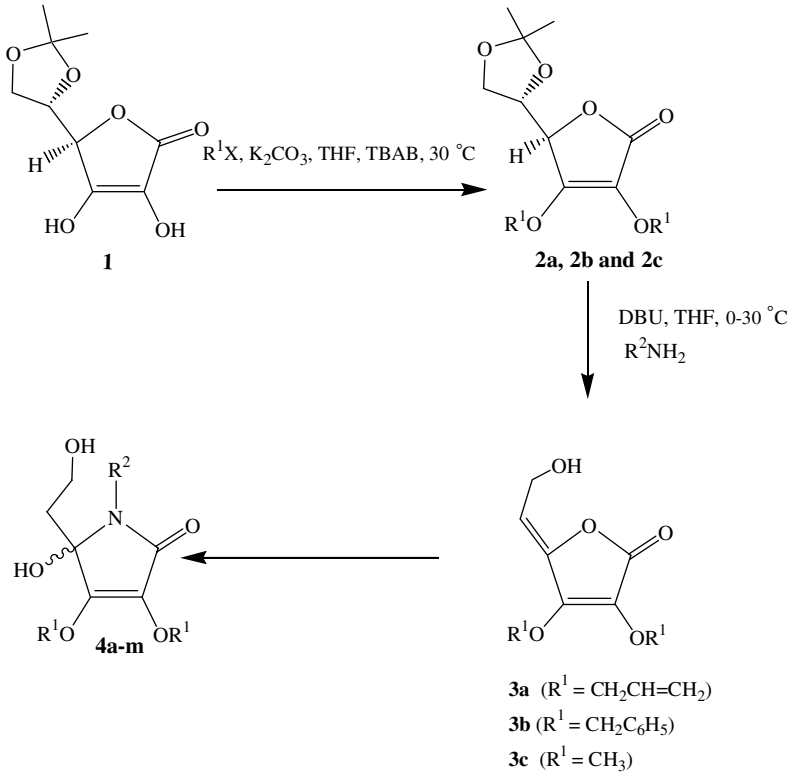
crude reaction mixture led to the isolation of only two compounds as major and minor products. Other compounds (in very minute amounts) could not be isolated in pure forms. The major compound isolated was found to be 3,4-bis-allyloxy-1-propyl-5-hydroxy-5-(2-hydroxyethyl)-1,5-dihydropyrrol-2-one **4a** in 50% yield. The structure was confirmed from spectroscopic data and analysis.[19] The minor product was characterised as 3,4-bis-allyloxy-5-(2-hydroxyethylidene)-5*H*-furan-2-one **3a** in 10% yield. The *Z* geometry of the double bond in this compound was apparent from its PMR spectrum and its structure was also evidenced on the basis of spectroscopic data. Careful monitoring of the reaction by TLC showed that **2a** was formed first and with the passage of time it was converted into **4a**. We reacted **3a** under similar conditions with *n*-butylamine to give **4b** in good yield. Similarly, reaction of 2,3-allyloxy-5,6-*O*-isopropylidene ascorbic acid with other amines in the presence of DBU at ambient temperature led to the formation of the respective 1-alkyl tetramates (**4c**–**4h**) in good yields along with the 5-hydroxyethylidene products in minor amounts (Table 1).

To see the effect of 2,3-alkoxy substitutents on this reaction we carried out the reaction of 2,3-bis-benzyloxy-5,6-*O*-isopropylidene ascorbic acid **2b** and 2,3-bis-methoxy-5,6-*O*-isopropylidene ascorbic acid **2c**, which were reacted with *n*-butylamine separately. The products obtained were the respective 1-alkyl tetramates **4j** and **4k** in moderate yields along with the intermediate ethylidene derivatives (**3b** and **3c**) in $\leqslant$15% yields. There was no major improvement in the yield of the isolated

Table 1. Synthesis of 2,3-O-substituted-1-alkyltetramates (**4a**–**m**)

Entry	R^1	R^2	Reaction time (h)	% Yield[a] of (**4a**–**m**)	% Yield[a] of (**3a**–**c**)
4a	$-CH_2CH{=}CH_2$	*n*-Propyl	15	50	10
4b	$-CH_2CH{=}CH_2$	*n*-Butyl	16	50	10
4c	$-CH_2CH{=}CH_2$	*n*-Hexyl	14	60	8
4d	$-CH_2CH{=}CH_2$	*n*-Octyl	15	60	10
4e	$-CH_2CH{=}CH_2$	*n*-Dodecyl	10	55	10
4f	$-CH_2CH{=}CH_2$	Benzyl	8	60	15
4g	$-CH_2CH{=}CH_2$	$-(CH_2)_5-$	15	45	10
4h	$-CH_2CH{=}CH_2$	Adamantyl	20	25	15
4i	$-CH_2C_6H_5$	*n*-Propyl	12	60	10
4j	$-CH_2C_6H_5$	*n*-Butyl	7	50	15
4k	$-CH_3$	*n*-Butyl	9	50	10
4l	$-CH_3$	*n*-Octyl	8	55	10
4m	$-CH_3$	Benzyl	8	35	15

[a] After column chromatography.



Scheme 1.