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SYNTHESIS OF CARLOSIC ACID, VIRIDICATIC ACID AND CARLIC ACID METHYL ESTER

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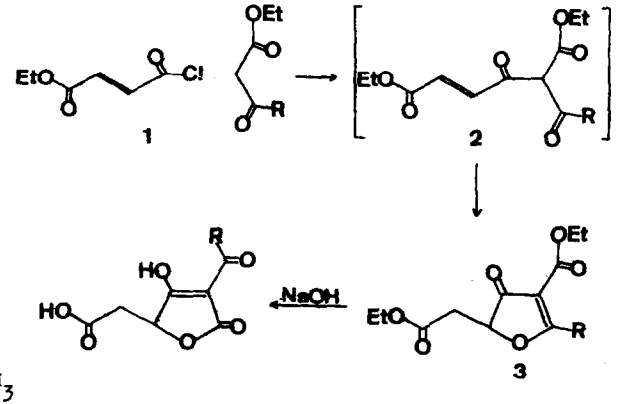
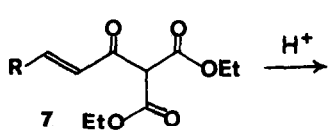
Prompted by a recent publication by Bloomer and Kappler[1] dealing with the synthesis of (S)-carlosic acid (5) via the tetronic acid synthon 11, which as the free acid may be considered as a possible biogenetic precursor for the entire family of mold tetronic acids, we present our results on the synthesis of carlosic acid (5), viridicatic acid (6), carlic acid methyl ester (13) and other 5-carboxymethyltetronic acids.

As a synthetic simplification for obtaining (±)-3-acyl-5-carboxymethyltetronic acids we have reacted trans-β-carbethoxyacrylyl chloride (1) with different β-keto esters using ethyl magnesium bromide in methylene chloride as the base of choice. The initially formed α-fumaroyl-β-keto esters (2) readily enolized via the keto group of the original β-keto ester and the enol group added to the double bond forming the keto lactones 3[2] (average yield 55-65 %). Action of dilute NaOH rearranged 3 to the desired tetronic acids 4 (m.p. 178-180°, lit.[3] m.p. 177-178°, 49 % yield), 5 (m.p. 160-163°, 35 % yield) and 6 (m.p. 158-160°, 24 % yield). Synthesis of carlic acid (14) along this route was unsuccessful so far.



4: R = CH_3
5: R = $(CH_2)_2CH_3$
6: R = $(CH_2)_4CH_3$

On the other hand acylation of 11[4] with 4-chlorobutyryl chloride afforded carlic acid methyl ester 13, m.p. 118-122°, NMR ($CDCl_3$): 2.29 (2 H, m, CH_2-$\underline{CH_2}$-CH_2), 2.62-3.25 (2 H, m, CO-$\underline{CH_2}$-$\underline{CH}$-O), 3.44 (2 H, t, CO-$\underline{CH_2}$-CH_2), 3.69 (3 H, s, $COO\underline{CH_3}$) 4.80 (2 H, t, CH_2-$\underline{CH_2}$-O), 4.65-4.94 (1 H, m, CH_2-$\underline{CH}$-C=O), 18 % yield). The NMR



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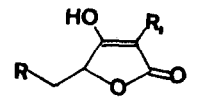
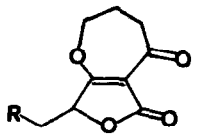


8: R = R_1 = COOEt
9: R = COOH R_1 = COOEt
10: R = COOH R_1 = H
11: R = $COOCH_3$ R_1 = H



12: R = H
13: R = $COOCH_3$
14: R = COOH

data are similar to those of carolic acid (12).[5] The absence of signals from deuterium exchangeable protons favours the presence of the indicated cyclic structure.

The synthesis of the synthon 10, which can be acylated[1,6] to different naturally occurring α-acyltetronic acids (exemplified in the synthesis of carlic acid methyl ester mentioned above), involves lactonization ofdiethylfumaroylmalonate (7, R= COOEt) with conc. H_2SO_4 to 8 (67 % yield). When 8 is hydrolyzed at room temperature with 0.2 M $Ba(OH)_2$ 9 is formed, whereas 5-carboxymethyltetronic acid 10 is formed, when 8 is hydrolyzed at room temperature with 1.4 M NaOH. An unambigous structure assignment of 10 was made by an independent synthesis of 10 from dimethyl kitipinate.

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