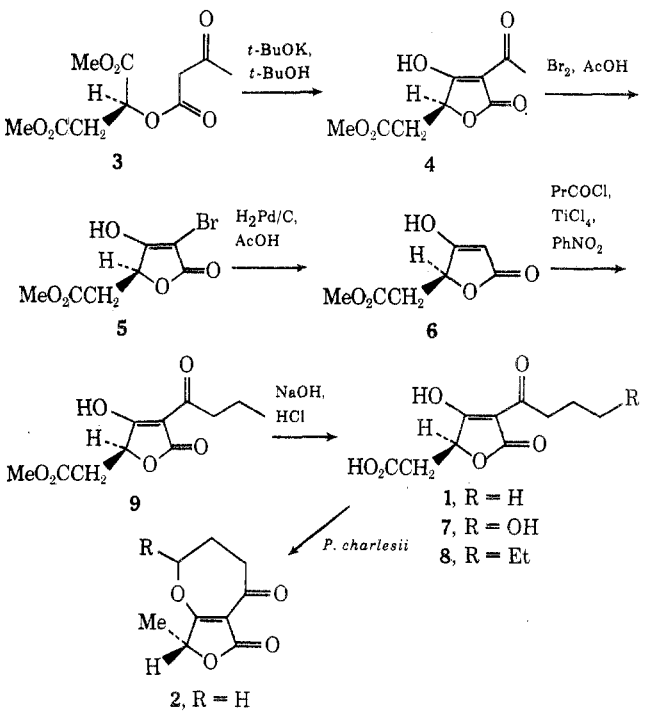
Total Synthesis of a γ-Carboxymethyltetronic Acid. (S)-Carlosic Acid

Summary: The first total synthesis of a naturally occurring mold tetronic acid with correct absolute configuration is described, as well as a possible biogenetic precursor for the entire family.

Sir: In recent biosynthetic studies,[1] we demonstrated that carlosic acid (**1**) was the major precursor of (*R*)-carolic acid (**2**) in *Penicillium charlesii*. We noted that no synthetic work had been done on any of the mold tetronic acids bearing the γ-carboxymethyl substituent. Furthermore, the reported total syntheses in the γ-methyl series, *viz.*, (±)-carolic acid[2] and (±)-carolinic acid,[3] were not applicable to either work with chiral compounds or isotopic labeling.[4] This communication describes the first example of a total synthesis of a mold tetronic acid in its correct absolute configuration and incorporates all of the desirable features described above.

The key step in the synthesis involved the cyclization of **3**, which was formed in 80% yield from dimethyl (*S*)-malate and diketene (Et_3N catalyst, PhH). The nmr spectrum of **3** was similar to the starting ester. In addition to the malate moiety [δ 3.67 (3 H, s, ester), 3.72 (3 H, s, ester), 2.90 (2 H, d, J = 6 Hz, methylene), and 5.47 (1 H, t, J = 6 Hz, methine)], new signals appeared at δ 2.25 (3 H, s, acetyl) and 3.50 (2 H, s, methylene) ($CDCl_3$) for the acetoacetyl group. Compound **3** was very thermolabile, and had to be purified by chromatographic means (alumina). The cyclization of **3** to **4** had to be carried out at a low temperature; otherwise mainly dimethyl fumarate was obtained (with concomitant loss of CO_2 and acetone). Treatment of **3** with *t*-BuOK in *t*-BuOH at the freezing point effected a 39% yield of **4** in which the acetoacetyl methylene signal and the ester signal at δ 3.72 were no longer present. In addition to nmr signals at δ 2.38 (3 H, s, acetyl), 3.67 (3 H, s, ester), 2.72 (2 H, m, methylene), and 4.57–4.75 (1 H, m, methine), a new signal appeared at δ 8.42 (1 H, s, enol) ($CDCl_3$). The bromination of **4** to **5** had to be carried out rapidly owing to the sensitivity of the ester function to HBr liberated by the reaction. Compound **5** had a similar nmr spectrum to **4** except for loss of the acetyl signal (δ 2.38) (DMSO-d_6). Its structure was confirmed by conversion to the free carboxylic acid which had been obtained from carlosic acid by degradation.[5] The catalytic reduction of **5** to **6** [which had a nmr similar to **5** except for the appearance of a new signal at δ 4.99 (1 H, s, vinylic) ($CDCl_3$ + 5% DMSO-d_6)] was carried out similarly to that for α-bromo-(*S*)-γ-methyltetronic acid.[6]



Excepting the cyclization, all synthetic yields were in the 70–80% range. Elementary analyses and spectral data for all of the above compounds were in agreement with the assigned structures.

Since our biosynthetic studies[1] seemed to indicate that *P. charlesii* contained a relatively nonspecific biological acylation system, the compound **6** represents a potential intermediate in both the biosynthesis (as the free acid) and synthesis of carlosic acid (**1**), carlic acid (**7**), and viridicatic acid (**8**). In the specific instance of carlosic acid (**1**), treatment of **6** with butyryl chloride, $TiCl_4$, and $PhNO_2$ gave the ester **9**, which was converted by gentle saponification to **1**. The **1** thus obtained was identical in all respects with the natural product. The application of intermediate **6** to the synthesis of **7** and especially **8** should be straightforward. Our present work allows specific isotopic labeling of **9** or **1** *via* use of PrC*OCl, which is available with either ^{14}C or ^{13}C label as shown.

A full account will be given of this work upon completion.

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Nucleic Acid Related Compounds. 9. The Synthesis of 6-Amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)-purine, the First 1′,2′-Unsaturated Purine Nucleoside[1,2]

Summary: Adenosine has been transformed into 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine (**4b**) by elimination of hydrogen iodide from a suitably blocked 2′-iodo derivative, and hydrogenation of **4b** completes the conversion to α- and β-2′-deoxyadenosines.

Sir: Access into unsaturated pentofuranosyl nucleosides including the 2′,3′,[3] 3′,4′,[4] and 4′,5′[5] olefinic systems has been reported. However, no authenticated 1′,2′-unsaturated purine nucleoside has been described, although the antibiotic augustmycin A (decoyinine)[6] was originally assigned this structural feature.[7] It has been considered that biological transformation of ribo nucleosides to their 2′-