Regioselective Ring Opening of Malic Acid Anhydrides by Carbon Nucleophiles. Application in the Synthesis of Chiral Tetronic Acids

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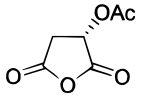
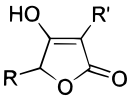
S-Malic acid is an important chiral building block which has found wide application in the enantioselective synthesis of chiral compounds.[1] Manipulation of this polyfunctional synthon requires the selective protection of the different functionalities and the distinction of the two carboxyl groups present. The O-protected hydroxysuccinic anhydrides (**I**) derived from malic acid offer a unique way to achieve both these tasks. These anhydrides react regioselectively at the C-2 site with oxygen and nitrogen nucleophiles providing malic acid monoesters[2] and monoamides,[3] respectively. However, no report has appeared concerning similar behavior toward carbon nucleophiles.



I



II

In the course of our studies on the synthesis of heterocyclic systems comprising a β-dicarbonyl moiety[4] we required a facile route to tetronic acid derivatives (**II**). The appreciable number of tetronic acids found in nature[5] and the antibiotic activity displayed by many of them[6] has attracted the interest of many research groups on the synthesis of this class of heterocyclic compounds. Among the natural occurring tetronic acids a number of compounds bearing a 5-carboxymethyl substituent have been isolated as fungal metabolites, namely carlosic, carlic,[7] and viridicatic acid.[8] Although, several procedures for the preparation of these compounds have appeared in the literature, they require not readily available starting materials, as β-ketothioesters[6] and 1,3-dioxin-4-ones,[9] and comprise a final hydrolysis step in order to afford the free carboxyl functionality.

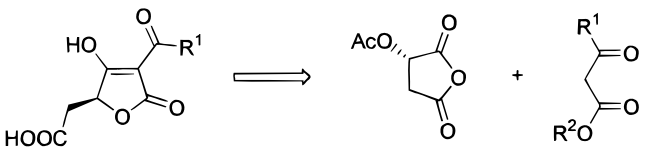
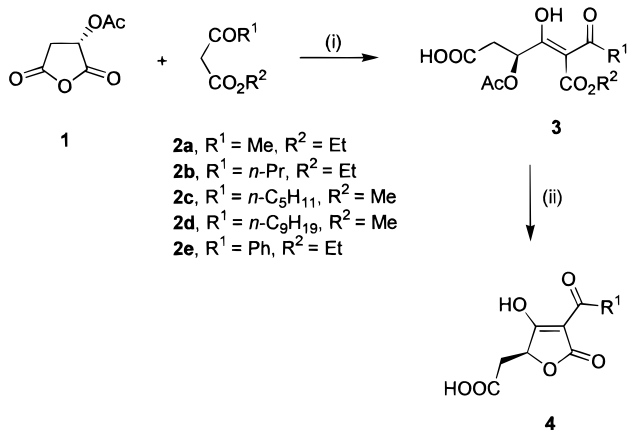


Figure 1.

Scheme 1[a]



[a] Key: (i) NaH, THF; (ii) NaOH, H_2O, MeOH.

The use of malic acid anhydride as starting material for the preparation of 5-carboxymethyl substituted tetronic acids would overcome the time-consuming hydrolysis step. The basic framework of a 3-acyl-5-carboxymethyltetronic acid can be constructed through a regioselective ring opening of malic acid anhydride by the anion of an appropriate β-ketoester, as outlined in Figure 1.

To exploit this approach, at first we attempted the synthesis of racemic tetronic acids of this type. The requisite *RS*-malic acid anhydride (*RS*-**1**) was easily prepared from *RS*-malic acid upon heating at reflux with 3.5 equiv of acetyl chloride. This anhydride was found to react regioselectively at the C-2 site with anions of β-ketoesters (**2a**−**e**) to afford β-hydroxy-γ-acetoxybutenoates of type **3** (Scheme 1). The protocol used requires the reaction of **1** with 2 equiv of the anion of the appropriate β-ketoester, generated with sodium hydride. After acidification with 10% hydrochloric acid, intermediates **3** were obtained in an oily form containing small amounts of the corresponding β-ketoester, as evidenced from the ^{1}H NMR spectra. Deacetylation and subsequent cyclization of **3** was effected under basic hydrolytic conditions to provide the desired 3-acyl-5-carboxymethyltetronic acids (**4**, R = Me, *n*-Pr, *n*-C_9H_{19}, Ph) in good overall yields (51−79% from *RS*-**1**).

Application of this methodology in the synthesis of 5-(*S*)-carboxymethyltetronic acids is straightforward utilizing *S*-malic acid anhydride (*S*-**1**).[10] Thus, *S*-carlosic acid (*S*-**4b**) was obtained from *S*-**1** and ethyl butyryl acetate (**2b**) in 70% yield (2 steps), $[\alpha]^{21}_D$ −125 (*c* 0.28, H_2O) [lit.[6] $[\alpha]^{21}_D$ −138 (*c* 0.28, H_2O)]. Similarly, *S*-viridicatic acid (*S*-**4c**) was obtained from *S*-**1** and methyl hexanoyl acetate (**2c**) in 62% yield: $[\alpha]^{21}_{546}$ −101 (*c* 1,

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Table 1. Tetronic Acids Obtained with the Proposed Methodology

product	R^1	β-ketoester	yield (%)
RS-**4a**	Me	**2a**	75
S-**4a**	Me	**2a**	62
RS-**4b**	*n*-Pr	**2b**	72
S-**4b**	*n*-Pr	**2b**	70
S-**4c**	*n*-C_5H_{11}	**2c**	62
RS-**4d**	*n*-C_9H_{19}	**2d**	51
RS-**4e**	Ph	**2e**	79

EtOH) [lit.[9] $[\alpha]^{21}_{546}$ −105 (*c* 1, EtOH)]. Tetronic acids synthesized with the above methodology are summarized in Table 1.

In conclusion, the regioselectivity of the reaction of O-acetylmalic acid anhydride (**1**) with carbanions has been established. This anhydride represents a versatile derivative of malic acid where the selective activation and protection of the carboxyl groups are simultaneously achieved. The reaction of **1** with the anions of β-ketoesters leads to β-hydroxy-γ-acetoxybutenoates of type **3**, which are useful intermediates for the synthesis of certain tetronic acid natural products.

Experimental Section

General Methods. All the commercial available starting materials were used without further purification. The β-ketoesters used were either purchased from Fluka or prepared by a literature procedure.[11] Commercially available THF and dichloromethane were dried prior to use by refluxing over sodium and phosphorus pentoxide, respectively. Melting points are uncorrected. Chemical shifts are quoted in ppm (t = triplet, dd = doublet of doublets, m = multiplet, br = broad).

General Procedure for the Preparation of 3-Acyl-5-carboxymethyltetronic Acids. To a suspension of sodium hydride (10 mmol) in anhydrous THF (30 mL), chilled at 0 °C, is added dropwise the appropriate **2** (10 mmol) and, after stirring at 0 °C for 30 min, a clear solution results. A solution of **1** (5.0 mmol) in anhydrous THF (5 mL) is added at once. The mixture is stirred at 0 °C for 30 min, and after the addition of water (10 mL), the mixture is concentrated in a rotary evaporator. The aquatic residue is washed with ether (5 mL) and then acidified with 10% hydrochloric acid under cooling in an ice−water bath. The acidified mixture is extracted with dichloromethane, and the combined extracts dried over sodium sulfate and evaporated to afford the crude β-hydroxy-γ-acetoxybutenoate **3** in an oily form. A solution of crude **3** (∼4 mmol) in methanol (2 mL) is chilled at 0 °C, and a 2 N NaOH solution (6 mL) is added dropwise. The solution is stirred at room temperature for 2−3 h and then acidified with 10% hydrochloric acid under cooling in an ice−water bath. The product **4** is either filtered off or extracted with ethyl acetate.

3-Acetyl-5-carboxymethyltetronic Acid (*RS*-4a). Starting from *RS*-**1** (5.0 mmol, 0.79 g), the title compound was obtained as a white solid (0.75 g, 75%). Mp: 172−174 °C (lit.[12] mp 178−180 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15 (3H, s), 2.20 (1H, dd, J = 16, 9.2 Hz), 2.70 (1H, dd, J = 16, 3.4 Hz), 4.40 (1H, dd, J = 9.2, 3.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0, 37.4, 76.2, 95.3, 172.1, 174.7, 192.0, 194.5.

3-Acetyl-5-(*S*)-carboxymethyltetronic Acid (*S*-4a). Starting from *S*-**1** (5.0 mmol, 0.79 g), the title compound was obtained as a pale yellow solid (0.62 g, 62%). Mp: 183−184 °C (lit.[13] mp 182−184 °C). $[\alpha]^{21}_D$: −107 (*c* 3.58, acetone) [lit.[6] $[\alpha]_D$ −36.4 (*c* 3.58, acetone)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.36 (3H, s), 2.53 (1H, dd, J = 17, 7.3 Hz), 2.79 (1H, dd, J = 17, 3.4 Hz), 4.77 (1H, dd, J = 7.3, 3.4 Hz), 9.57 (2H, br).

3-Butanoyl-5-carboxymethyltetronic Acid (*RS*-Carlosic Acid) (*RS*-4b). Starting from *RS*-**1** (5.0 mmol, 0.79 g), the title compound was obtained as a beige solid (0.82 g, 72%). Mp: 177−178 °C (lit.[13] mp 178−179 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (3H, t, J = 7.1 Hz), 1.44−1.60 (2H, m), 2.54 (1H, dd, J = 17, 7.6 Hz), 2.68−2.75 (2H, m), 2.83 (1H, dd, J = 17, 3.8 Hz), 4.82 (1H, dd, J = 7.6, 3.8 Hz), 9.62 (2H, br). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7, 18.2, 36.2, 38.9, 76.0, 98.3, 170.9, 171.0, 192.7.

3-Butanoyl-5-(*S*)-carboxymethyltetronic Acid (*S*-Carlosic Acid) (*S*-4b). Starting from *S*-**1** (2.3 mmol, 0.36 g), *S*-carlosic acid (*S*-**4b**) was obtained as a white solid (0.36 g, 70%). Mp: 176−177 °C (lit.[9] mp 176.5−177.5 °C). $[\alpha]^{21}_D$: −125 (*c* 0.28, H_2O) [lit.[6] $[\alpha]^{21}_D$ −138 (*c* 0.28, H_2O)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (3H, t, J = 7.3 Hz), 1.44−1.58 (2H, m), 2.50 (1H, dd, J = 17, 7.8 Hz), 2.66−2.74 (2H, m), 2.81 (1H, dd, J = 17, 3.9 Hz), 4.77 (1H, dd, J = 7.8, 3.9 Hz), 7.72 (2H, br).

5-(*S*)-Carboxymethyl-3-hexanoyltetronic Acid (*S*-Viridicatic Acid) (*S*-4c). Starting from *S*-**1** (10 mmol, 1.59 g), *S*-viridicatic acid was obtained as a pale yellow solid (1.58 g, 62%). Mp: 173−174 °C (lit.[9] mp 172−173 °C). $[\alpha]^{21}_{546}$ −101 (*c* 1, EtOH) [lit.[8] $[\alpha]^{21}_{546}$ −105 (*c* 1, EtOH)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (3H, t, J = 6.8 Hz), 1.18−1.32 (4H, m), 1.44−1.56 (2H, m), 2.57 (1H, dd, J = 17, 7.3 Hz), 2.70−2.77 (2H, m), 2.82 (1H, dd, J = 17, 3.9 Hz), 4.85 (1H, dd, J = 7.3, 3.9 Hz), 7.21 (2H, br). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8, 21.8, 24.5, 30.9, 36.1, 36.5, 76.0, 98.5, 170.5, 171.0, 192.6, 192.7.

5-Carboxymethyl-3-decanoyltetronic Acid (*RS*-4d). Starting from *RS*-**1** (2.0 mmol, 0.32 g), the title compound was obtained as a pale yellow solid (0.32 g, 51%). Mp: 151−153 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (3H, t, J = 6.8 Hz), 1.22 (12H, br), 1.45 (2H, m), 2.42 (1H, dd, J = 17, 8.3 Hz), 2.67 (2H, t, J = 7.3 Hz), 2.76 (1H, dd, J = 17, 3.9 Hz), 4.66 (1H, dd, J = 8.3, 3.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 22.1, 24.8, 28.7, 28.8, 28.85, 28.9, 31.3, 36.3, 37.0, 76.0, 97.9, 171.2, 171.3, 192.9, 193.1. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.42; H, 7.76.

3-Benzoyl-5-carboxymethyltetronic Acid (*RS*-4e). Starting from *RS*-**1** (10 mmol, 1.59 g), the title compound was obtained as a beige solid (2.08 g, 79%). Mp: 165−167 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.61 (1H, dd, J = 17, 7.6 Hz), 2.89 (1H, dd, J = 17, 3.5 Hz), 4.97 (1H, dd, J = 7.6, 3.5 Hz), 7.38−7.76 (5H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.4, 74.9, 98.6, 128.1, 129.2, 132.3, 137.9, 171.0, 171.1, 187.4, 187.8. Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.51; H, 3.90.

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