Novel Short-Step Synthesis of Optically Active Tetronic Acids from Chiral α-Hydroxy Acids Mediated by 1-Hydroxybenzotriazole

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Abstract: A novel method for the synthesis of functionalized γ-hydroxy acids and optically active tetronic acids is reported. The synthesis is simple and the compounds are produced in good yields (45–81%). Measurements of their optical rotations show that the reaction proceeds without or with partial racemization of the starting materials.

Key words: tetronic acids, γ-hydroxy acids, 1-hydroxybenzotriazole, natural products

The appreciable number of tetronic acids (Figure 1) found in nature[1] and the antibiotic activity displayed by many of them[2] has attracted the interest of many research groups on the synthesis of this class of heterocyclic compounds. For example, six homologues of sodium salt of 3-alkanoyl-5-hydroxymethyl tetronic acid have been isolated from sponges and act as HIV-1 protease inhibitors.[3] In addition, isolation of smenotronic acid[4] and two new sesterterpene tetronic acids[5] from marine sponges have been reported lately. Finally, carlosic, carlic[6] and viridicatic acid[7] are well known as fungal metabolites and (+)-blastomycinine[8] as an antibiotic.

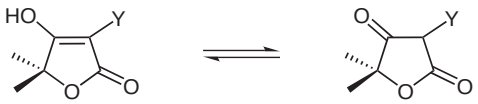

Figure 1

While there are a number of reliable methods for the construction of tetronic acid derivatives, the development of new methods, particularly one applicable to enantioselective synthesis, still presents a timely challenge. Several methodologies include Dieckmann cyclization,[2] cycloaddition,[9] oxidation,[3] Wittig–Claisen,[10] lactonization[11a] and enzymatic reactions.[11b] Recently, the synthesis of 3-acyl-5-methoxycarbonyl tetronic acids has been reported from our laboratory.[12]

Also, we recently proposed a novel one-step methodology for the synthesis of 3-substituted tetramic acids[13] and functionalized 4-amino-3-hydroxybutenoates.[14] As a logical extension of this chemistry we decided to investigate the condensation reaction of *N*-hydroxybenzotriazole esters of O-protected α-hydroxy acids and active methylene compounds bearing appropriate substituents suitable for preparing highly functionalized γ-hydroxy esters and tetronic acid derivatives with pharmacological interest. In this paper we describe a general short-step methodology for producing chiral 3-substituted tetronic acids via a C-acylation reaction between the *N*-hydroxybenzotriazole ester of an appropriate O-protected α-hydroxy acid and the desired active methylene compound (Scheme 1).

The proposed strategy comprises a C-acylation reaction between an active methylene compound **3** and the *N*-hydroxybenzotriazole ester of the appropriate O-protected α-hydroxy acid **1**. In cases where the main product of the C-acylation reaction was the functionalized 4-acetoxy-3-hydroxybutenoates **7**–**14**, we have used these γ-hydroxy esters for the preparation of the corresponding chiral tetronic acid derivatives **15**, **16**, **18**–**21** under acidic conditions (MeOH, 10% HCl). The lactonization of the β-hydroxybutenoates proceeded without racemization. One first remark in our proposed synthetic route is that only the *O*-acetyl-glycolic acid **1a** gave the corresponding tetronic acids **4**–**6** via one-step reaction. In contrast, (*S*)-mandelic acid **1b**, α-hydroxyisobutyric acid **1c**, L-α-hydroxyisovaleric acid **1d** and L-α-hydroxyisocaproic acid **1e** gave the corresponding γ-acetoxy-β-hydroxybutenoates **7**–**14** as oily products. These intermediates were treated with 10% HCl in MeOH at room temperature for 24 or 48 hours to afford the corresponding tetronic acids **15**–**21**. An obvious notice is that the presence of an electron donor group (Me, *i*-Pr, *i*-butyl) at the stereogenic carbon atom instead of an electron withdrawing (Ph) plays an important role in the lactonization reaction. Nevertheless, the cyclization of these intermediates **9**–**14** to the corresponding tetronic acids **17**–**21** was achieved under the same reaction conditions for 48 hours.[15] Additionaly, the tetronic acids **15**, **16**, **18**–**21** have been found to be optically active as shown by their optical rotations. This observation is in full accordance with the results obtained in the synthesis of tetramic acids[13] and γ-amino-α-cyano-β-hydroxybutenoates.[14]

The structures of the C-acylation compounds **9**–**14** and tetronic acids **4**–**6** and **15**–**21** have been elucidated by NMR and FT-IR Spectroscopy.[16] One very interesting remark on the ^{1}H NMR spectra of the γ-hydroxy acids **9**–**14**

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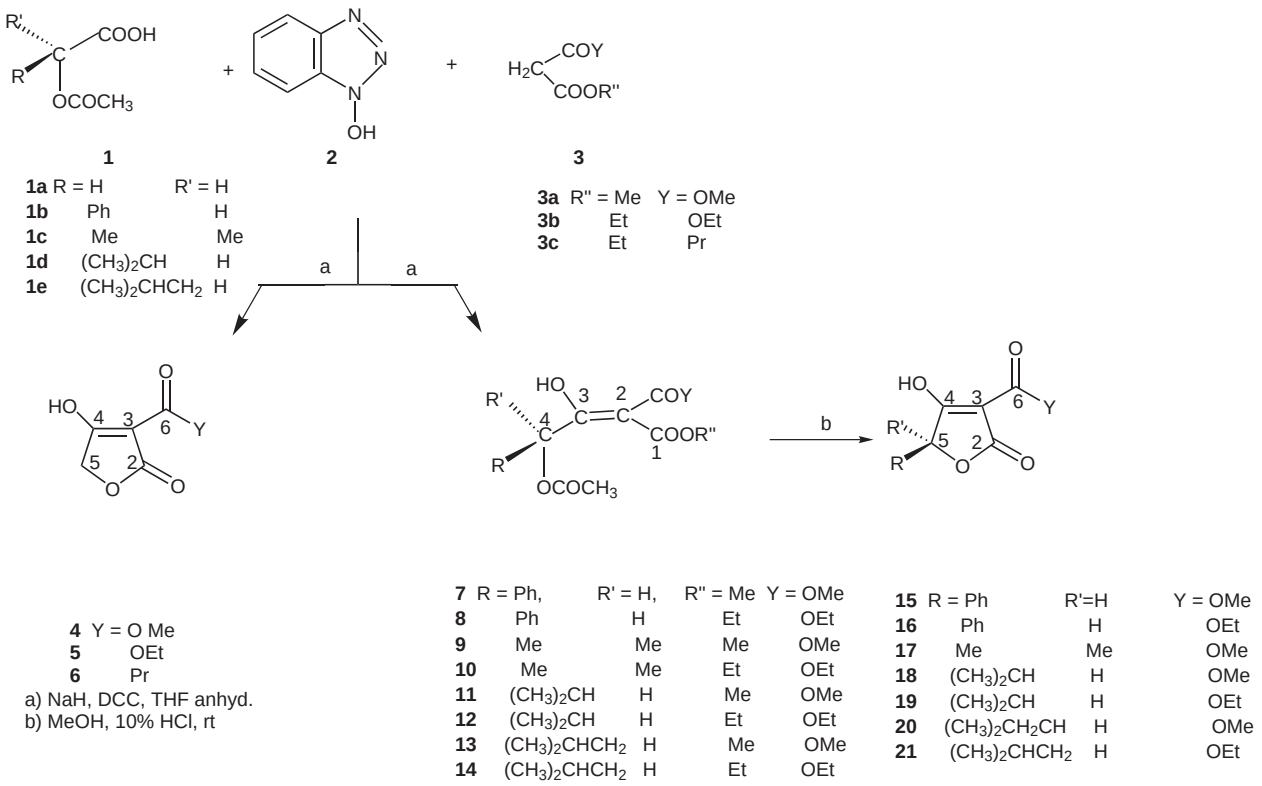

Scheme 1

is the signal at δ = 4.65–4.85 ppm for the methine proton (keto form **B**, Figure 2). This proton is not integrated as one since the product is found as a mixture of the enolic **A** and the keto form **B**.

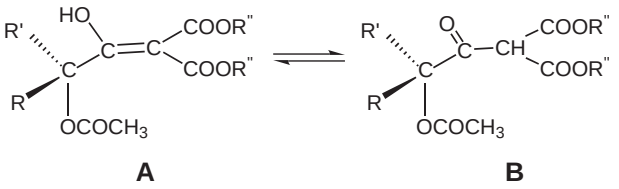

Figure 2

The ^{1}H and ^{13}C NMR spectra of 3-alkanoyl tetronic acids **4**, **5** and **15**–**21** show one set of signals in $CDCl_3$. On the other hand, two sets of signals can be observed in the ^{1}H and ^{13}C NMR spectra of the 3-butanoyl tetronic acid **6** in $CDCl_3$, indicating the existence of the 'external' tautomers **CD** and **EF** (Figure 3). In the ^{1}H NMR spectrum, the 5-methylene signal was split into two parts **CD** and **EF**, indicating that the dominant form should be the 'external' tautomer **CD** with an intensity ratio of **CD**/**EF** = 1/0.67, whereas for the equivalent *NH*-tetramic acid the dominant form should be the 'external' tautomer **EF**.

The ^{13}C NMR assignments of the 3-butanoyltetronic acid **6** are based on the off-resonance decoupling and the signals of the carbon atoms have been assigned by comparison with the established values of these carbon atoms reported for the corresponding 3-acyl tetramic acid derivatives.[17,18]

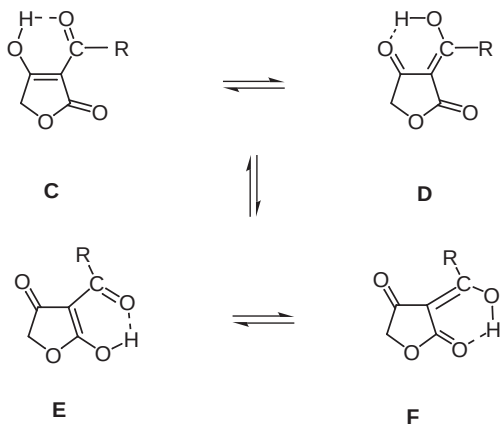

Figure 3

In conclusion, we have successfully synthesized a series of functionalized γ-hydroxy esters and chiral tetronic acids using a short-step methodology. The reaction gives high yields, proceeds without or with partial racemization

of the starting optically active materials and a short reaction time is required in contrast to previous methodologies.[11] Work currently in progress includes application of the proposed methodology on the preparation of highly functionalized tetronic acid derivatives with known biological activity. Also, the γ-hydroxy esters may serve as attractive potential intermediates for synthesizing more complex biologically important molecules. Additionally, the catalytic asymmetric hydrogenation reaction of the functionalized γ-hydroxy esters and tetronic acid derivatives is under investigation.

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(15) **General Procedure for the Synthesis of Compounds 4–21:**
In a typical reaction, 10 mmol of the appropriate *O*-acetyl hydroxy acid **1a–e** was treated with 10 mmol of 1-hydroxybenzotriazole **2** and 10 mmol DCC in anhyd THF (40 mL) at 0 °C for 1 h. The resulting suspension was refrigerated overnight at 3–5 °C. The precipitated solid (DCCU) was filtered off and discarded, the THF filtrate was added to a solution of 20 mmol NaH and 10 mmol of dimethyl malonate **3a**, diethyl malonate **3b** or butyryl acetate **3c** in anhyd THF. The resulting mixture was stirred at r.t. for 2.5 h and then concd in vacuo. The obtained gummy solid was diluted with water and washed with diethyl ether. The aq extract was acidified with 10% HCl in an ice water bath to afford a white solid (1-hydroxybenzotriazole) which was filtered off. The aq filtrate was extracted with DCM (3 ×) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford either 3-substituted tetronic acids **4–6** as white solids or the C-acylation compounds **7–14** as oils. The oily products **7–14** were dissolved in methanol and treated with 10% HCl for 24 h (**7** and **8**) or 48 h (**9–14**) at r.t. to afford the corresponding tetronic acids **15–21** as white solids. The solid products were filtered off, washed with light petrol and dried in vacuo.
(16) **Spectroscopic and Analytical Data of Selected Compounds:**
3-Methoxycarbonyl Tetronic Acid (**4**). 59% Yield, mp: 166–167 °C. IR (KBr): 1720/1703 (C=O), 1605 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, $COOCH_3$), 4.81 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.3 ($COO\mathit{C}H_3$), 66.0 (C-5), 100.2 (C-3), 167.0 (C-6), 169.4 (C-2), 189.4 (C-4) ppm. Anal. Calcd for $C_6H_6O_5$: C, 45.57; H, 3.80. Found: C, 45.49; H, 3.86.
4-Acetoxy-3-hydroxy-2-methoxycarbonyl-4-methyl-2-pentenoate (**9**). 78% Yield. IR (KBr): 1743/1739/1735/1732/1728/1724 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 (s, 6 H, 2 × CH_3), 2.05/2.06 (two s, 3 H, $OCOCH_3$), 3.77 (s, 6 H, 2 × $COOCH_3$), 4.96 (s, 0.5 H, O=C-C*H*), 13.38 (s, 0.5 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_3), 24.4 (CH_3), 41.1 (O=C-*C*H), 53.2 ($COO\mathit{C}H_3$), 59.5 ($OCO\mathit{C}H_3$), 77.8 (C-4), 84.7 (C-2), 164.5 ($O\mathit{C}OCH_3$), 170.1 (C-1), 197.7 (C-3) ppm.
3-Methoxycarbonyl-5-phenyl Tetronic Acid (**15**). 81% Yield, mp: 188–189 °C. $[\alpha]_D^{21}$: +86.6 (c1, MeOH). IR (KBr): 1759/1716 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, $COOCH_3$), 5.84 (s, 1 H, *H*CPh), 7.39–7.44 (m, 5 H, PhH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): (ppm) 52.7 ($COO\mathit{C}H_3$), 78.6 (C-5), 94.2 (C-3), 126.5/129.2/130.0/132.3 (phenyl carbons), 166.3 (C-6), 166.9 (C-2), 190.3 (C-4). Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.27. Found: C, 61.60; H, 4.21.
3-Ethoxycarbonyl-5-phenyl Tetronic Acid (**16**). 80% Yield, mp: 156–157 °C. $[\alpha]_D^{21}$: +71.1 (c1, MeOH). IR (KBr): 1758/1714 (C=O), 1607 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.5 Hz, 3 H, $COOCH_2C\mathit{H}_3$), 4.43 (q, *J* = 6.6 Hz, 2 H, $COOC\mathit{H}_2CH_3$), 5.83 (s, 1 H, *H*CPh), 7.39–7.44 (m, 5 H, PhH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 ($COOCH_2\mathit{C}H_3$), 62.2 ($COO\mathit{C}H_2CH_3$), 78.5 (C-5), 94.2 (C-3), 126.5/129.2/129.9/132.4/(phenyl carbons), 166.3 (C-6), 166.6 (C-2), 190.3 (C-4) ppm. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.84. Found: C, 62.98; H, 4.94.
3-Methoxycarbonyl-5-dimethyl Tetronic Acid (**17**). 50% Yield, mp: 118–120 °C. IR (KBr): 1748/1721 (C=O), 1625 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 6 H, 2 × CH_3), 3.78/3.94 (two s, 3 H, $COOCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (CH_3), 52.6 ($COO\mathit{C}H_3$), 80.9 (C-5), 99.9 (C-3), 165.5 (C-6), 167.0 (C-2), 194.6 (C-4) ppm. Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.38. Found: C, 51.79; H, 5.48.
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