Synthesis of Tetronic Acid Derivatives from Novel Active Esters of α-Hydroxyacids

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Received May 7, 2002

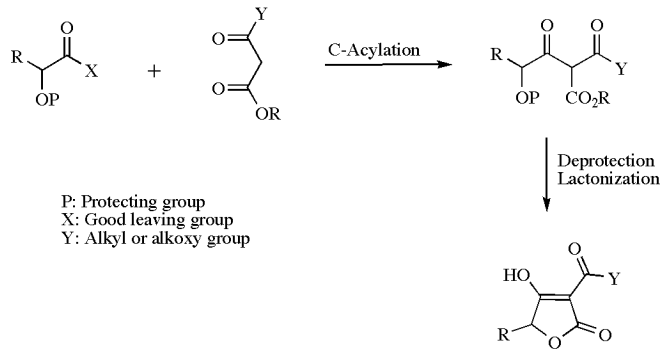
Active esters, produced by condensation of *O*-acetyl protected α-hydroxyacids with *N*-hydroxysuccinimide, react with anions of active methylene compounds to afford β,β'-tricarbonyl derivatives which upon deprotection undergo cyclization to 3-alkoxycarbonyl and 3-acyl tetronic acids. Incorporation of (*S*)-2-acetoxyphenylacetic acid in this reaction sequence enables the synthesis of optically active 5-phenyltetronic acid derivatives.

J. Heterocyclic Chem., **39**, 1201(2002).

The 3-acyltetronic unit, a structural feature known for many years to be present in mold metabolic products [1], has been found during the last two decades in many natural products exhibiting remarkable biological activities. The antitumor antibiotics tetrocarcins [2], the antiviral antibiotic MM46115 [3] and kijanimicin, which displays activity against a broad range of microorganisms [4], contain an acylspirotetronic moiety [5]. The quartromicins, a family of antibiotics with excellent antiviral activity against herpes virus type 1, influenza virus type A and HIV, possess a unique structure comprising four tetronic acid subunits [6]. Tetronasin (ICI M139603) is an acyltetronic acid ionophore of great interest due to its antibiotic, antiparasitic and growth promoting properties [7]. Some recently isolated 3-alkanoyl-5-hydroxymethyltetronic acids display inhibitory effect on HIV-1 protease [8] among other interesting biological activities [9]. The wide range of biological properties and the potency for pharmaceutical applications has attracted considerable interest on the development of general methods for the synthesis of this group of heterocyclic compounds [10].

An efficient route to 3-acyl and 3-alkoxycarbonyltetronic acids, illustrated in Scheme 1, comprises the *C*-acylation reaction of β-keto and malonic esters with activated derivatives of *O*-acetyl protected α-hydroxyacids as the critical step. Deprotection of the β,β'-tricarbonyl intermediates is accompanied by spontaneous cyclization to 3-acyl and 3-alkoxycarbonyltetronic acids. This approach was introduced by Anchütz, who used α-acetoxyacid chlorides as acylating agents of active methylene compounds [11], and has been applied in the synthesis of various 5-substituted tetronic acids, though its application in the synthesis of nonracemic products has been limited [12].

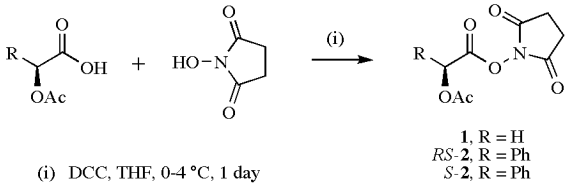
Scheme 1



In order to improve this route, targeting the synthesis of optically active products, we have considered the application of alternative activation methods instead of the previously utilized acid chlorides. Derivatization of α-aminoacids by way of the corresponding *N*-succinimidyl (2,5-dioxopyrrolidin-1-yl) esters is a well-known activation method, being applied mainly in the synthesis of peptides [13]. Prompted by the observation that related active esters of anthranilic acids constitute efficient acylating agents of β-keto esters for the production of quinolone derivatives [14], we have investigated the application of this activation method in the synthesis of 3-acyl and 3-alkoxycarbonyltetronic acids.

The requisite *N*-succinimidyl esters of α-acetoxyacids were prepared by a standard protocol involving condensation of equimolar quantities of the *O*-acetyl protected α-hydroxyacid and *N*-hydroxysuccinimide in the presence of 1 equivalent of *N*,*N'*-dicyclohexylcarbodiimide (Scheme 2). The desired active esters **1**, *RS*-**2** and *S*-**2** were isolated in very good yields, as pure stable solids, and used in the next step without further purification.

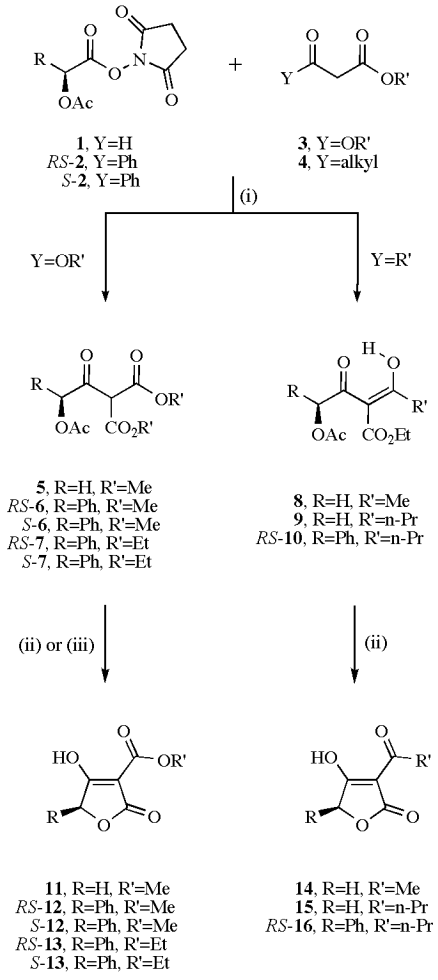
Scheme 2



Subsequently, the efficiency of these novel active esters as acylating agents of active methylene compounds was examined (Scheme 3). The reaction protocol involved the addition of 1 equivalent of the solid active ester **1** or **2** to a dispersion of 2 equivalents of the anion of a malonic ester **3** (or

a β-keto ester **4**), generated by the action of sodium hydride, in anhydrous benzene. The reaction mixture was stirred at room temperature for 2-5 hours and the *C*-acylation product extracted with water and isolated after acidification of the aqueous extracts with 10% hydrochloric acid. The crude *C*-acylation products were obtained in oily form containing small amounts of the corresponding active methylene compound and were used in the next step without purification. The identity of compounds **5-10** was confirmed by the ^{1}H nmr spectral data (Table 1). The presence of a singlet resonance in the region 5-6 ppm, attributable to the methine proton of a β,β'-tricarbonyl moiety, indicates that the acylated malonates **5-7** possess the keto form in deuterochloroform solutions. On the contrary, the acylated β-keto esters **8-10** exist in an enol tautomeric form, as indicated by the presence of a low-field resonance at approximately 17.6 ppm, prominently assigned to the proton of an enol.

Scheme 3



(i) *N*-succinimidyl ester (1 equiv.), NaH (2 equiv.), active methylene compound (2 equiv.), benzene, rt, 2-5 h; (ii) Method A: KOH, R'OH, rt, 3-4 h; (iii) Method B: HCl, R'OH, H_2O, rt, 1 day.

Table 1

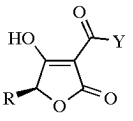
^{1}H nmr Data of Compounds **5-9** (deuteriochloroform solutions)

Product	δ (ppm)
5	2.14 (3H, s, $OCOCH_3$), 3.81 (6H, s, CO_2CH_3), 4.85 (2H, s, CH_2OAc), 5.01 (1H, s, CHCO)
6	2.19 (3H, s, $OCOCH_3$), 3.77 (3H, s, CO_2CH_3), 3.79 (3H, s, CO_2CH_3), 5.93 (1H, s, CHCO), 6.32 (1H, s, PhCH), 7.3-7.5 (5H, m, Ph)
7	1.26 (6H, t, J=7Hz, $CO_2CH_2CH_3$), 2.20 (3H, s, $OCOCH_3$), 4.1-4.3 (4H, m, $CO_2CH_2CH_3$), 5.92 (1H, s, CHCO), 6.33 (1H, s, PhCH), 7.3-7.5 (5H, m, Ph)
8	1.35 (3H, t, J=7Hz, $CO_2CH_2CH_3$), 2.18 (3H, s, $OCOCH_3$), 2.45 (3H, s, $CCOCH_3$), 4.27 (2H, q, J=7Hz, $CO_2CH_2CH_3$), 5.13 (2H, s, CH_2OAc), 17.68 (1H, s, OH)
9	0.97 (3H, t, J=7Hz, $CH_2CH_2CH_3$), 1.34 (3H, t, J=7Hz, $CO_2CH_2CH_3$), 1.6-1.8 (2H, m, $CH_2CH_2CH_3$), 2.17 (3H, s, $OCOCH_3$), 2.73 (2H, t, J=7Hz, $CH_2CH_2CH_3$), 4.26 (2H, q, J=7Hz, $CO_2CH_2CH_3$), 5.10 (2H, s, CH_2OAc), 17.6 (1H, s, OH)
10	0.97 (3H, t, J=7Hz, $CH_2CH_2CH_3$), 1.35 (3H, t, J=7Hz, $CO_2CH_2CH_3$), 1.6-1.8 (2H, m, $CH_2CH_2CH_3$), 2.19 (3H, s, $OCOCH_3$), 2.76 (2H, t, J=7Hz, $CH_2CH_2CH_3$), 4.26 (2H, q, J=7Hz, $CO_2CH_2CH_3$), 6.39 (1H, s, PhCH), 7.3-7.6 (5H, m, Ph)

Deprotection of the hydroxyl group was expected to induce cyclization of compounds **5-10** to the desired tetronic acid derivatives. Removal of the *O*-acetyl group was attempted under basic (KOH, MeOH or EtOH, method A) or acidic conditions (HCl, MeOH or EtOH, H_2O, method B). Actually, deprotection was accomplished under both reaction protocols to provide, after spontaneous lactonization, 3-alkoxycarbonyl and 3-acyltetronic acids (**11-13** and **14-16**, respectively), in moderate overall yields (Table 2).

Table 2

Tetronic Acids Synthesized from Active Esters **1** and **2**



Product	R	Y	Cyclization Method	Overall Yield (%)
11	H	OMe	A	32
			B	41
RS-**12**	Ph	OMe	A	34
			B	55
S-**12**	Ph	OMe	A	21
RS-**13**	Ph	Oet	A	26
			B	45
S-**13**	Ph	Oet	A	29
14	H	Me	A	37
15	H	*n*-Pr	A	53
RS-**16**	Ph	n-Pr	A	33

Production of enantiomerically pure tetronic acids would be feasible by the implementation of optically pure

α-hydroxyacids as starting materials in this reaction sequence. Thus, the *N*-succinimidyl ester of 2*S*-acetoxyphenylacetic acid (*O*-acetyl-*S*-mandelic acid) was prepared by the same procedure and utilized as acylating agent of malonic esters. The crude products *S*-**6** and *S*-**7**, which were isolated by the usual procedure, displayed optical activity, indicating that during this step only partial, if any, racemization occurred. Cyclization of *S*-**6** and *S*-**7** was effected using method A (KOH, MeOH or EtOH) to afford 3-alkoxycarbonyl 5*S*-phenyltetronic acids *S*-**12** and *S*-**13**, which displayed specific rotations +107 and +126, respectively (c 0.5 in acetone). Although, the optical purity of these novel products needs to be evaluated, these preliminary results support the importance of this methodology for the synthesis of 5-substituted tetronic acids in non-racemic form.

Tetronic acid derivatives are presented in Scheme 3 with the 4-hydroxyfuran-2-one tautomeric form, consistent with the structure of the parent compound. In the case of the 3-alkoxycarbonyl substituted products **11**, **12** and **13**, nmr spectroscopic data support the existence of an enol tautomeric form in deuteriochloroform solutions, as indicated by the presence of only one set of signals in both ^{1}H and ^{13}C nmr spectra. The absence of the methine proton resonance in the range 5-6 ppm, characteristic of the β,β'-tricarbonyl moiety, establishes the enol structure of these compounds.

Table 3

^{1}H nmr Spectral Data of 3-Acyltetronic Acids **14-16** [a]

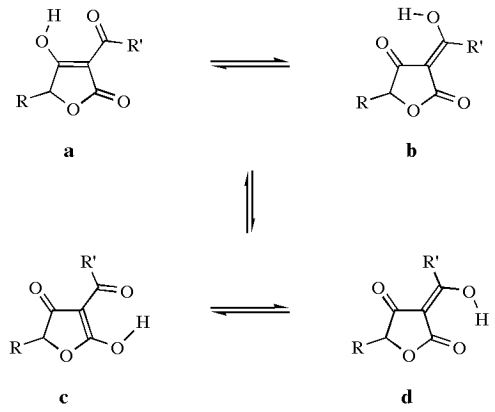
Product	δ (ppm)	**ab**:**cd**
14	2.55 (1.8H, s, CH_3, **ab**), 2.56 (1.2H, s, CH_3, **cd**), 4.56 (0.8H, s, CH_2, **cd**), 4.67 (1.2H, s, CH_2, **ab**), 10.51 (1H, br, OH)	60:40
15	1.01 (m, CH_3), 1.75 (m, CH_2Me), 2.91 (m, $COCH_2$), 4.56 (0.8H, s, CH_2, **cd**), 4.67 (1.2H, s, CH_2, **ab**)	61:39
16	1.02 (m, CH_3), 1.74 (m, CH_2Me), 2.94 (m, $COCH_2$), 5.57 (0.8H, s, CH_2, **cd**), 5.69 (1.2H, s, CH_2, **ab**), 7.39 (5H, br, Ph), 11.00 (1H, br, OH)	60:40

[a] In deuteriochloroform solutions.

In the case of compounds **14**, **15** and **16**, bearing an acyl substituent at position 3, the β,β'-tricarbonyl keto form is also excluded, as indicated by the ^{1}H nmr spectra in deuterochloroform solutions (Table 3). However, the presence of two signals for the methylene group of 5-unsubstituted compounds **14** and **15** reveals the existence of two different enol forms in unequal proportions. The same conclusion is derived for the 5-substituted compound **16**, showing two signals for the methine proton at position 5. The coexistence of two tautomeric forms is proved by the ^{13}C nmr spectra, exhibiting two signals for all carbons of **14** and **15** (Table 4). The relative proportions of these two tautomers, estimated by the integration of the proton signal of methylene or methine at position 5, is about 3:2 for all three compounds.

Establishment of equilibrium, favoring one of the two forms, is the most prominent interpretation of these results. The enol tautomers of 3-acyltetronic acids and the possible equilibria between them are presented in Scheme 4.

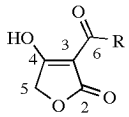
Scheme 4



All four enol tautomers are stabilized through hydrogen bonding of the enol to the adjacent carbonyl. Interconversions **a** to **b** and **c** to **d** involving displacement

Table 4

^{13}C nmr Spectral Data of 3-Acyltetronic Acids **14-15** [a]



Product	Tautomer	C-2	C-3	C-4	C-5	C-6	R'
14	**ab**	168.4	100.7	198.1	68.8	194.2	22.0
	cd	176.6	97.8	192.5	73.7	188.4	19.6
15	**ab**	168.3	100.2	198.2	68.7	197.7	36.7 (CH_2), 18.3 (CH_2), 13.5 (CH_3)
	cd	176.9	97.2	192.3	73.5	192.2	34.4 (CH_2), 19.3 (CH_2), 13.5 (CH_3)

[a] In deuteriochloroform solutions.

of the enolic proton along the hydrogen bond are presumed to be fast on the nmr time scale to be observed [15]. On the contrary, intercorversion **ab** to **cd** is expected to be slow enough to give discrete sets of signals in the nmr spectra. In accordance with these considerations, the two sets of signals are observed in the nmr spectra of compounds **14**, **15** and **16**. These may be attributed to a weighted average of interconversions between **a** to **b** and **c** to **d**. Form **ab** is assigned as the dominant form, in agreement with previous spectroscopic studies [16].

In conclusion, reaction of novel *N*-hydroxysuccinimidyl esters of α-hydroxyacids with active methylene compounds offers an efficient route to tetronic acid derivatives bearing electron withdrawing substituents at position 3. Preparation of nonracemic 5-substituted tetronic acids is feasible through the utilization of suitable optically active α-hydroxyacids as starting materials.

EXPERIMENTAL

Melting points were determined on a Gallenkamp MFB-595 apparatus and are uncorrected. The nmr spectra were recorded on a Varian Gemini-2000 300 MHz spectrometer. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiple, br = broad); J values are given in Hz.

Acetoxyacetic Acid 2,5-Dioxopyrrolidin-1-yl Ester (**1**).

A solution of *N*,*N'*-dicyclohexylcarbodiimide (72 mmol, 14.86 g) in anhydrous tetrahydrofuran (50 ml) was added dropwise over a period of 1 hour to a solution of acetoxyacetic acid (72 mmol, 8.51 g) and *N*-hydroxysuccinimide (72 mmol, 8.29 g) in anhydrous tetrahydrofuran (120 ml) under cooling in an ice-water bath. The mixture was stirred at 0 °C for 1 hour, then at room temperature for 4 hours, and left standing at 4 °C for 2 days. The precipitated solid was filtered off and the filtrate evaporated *in vacuo*. The solid residue was treated with diethyl ether, collected by filtration and washed with diethyl ether to afford compound **1** as a white solid (14.12 g, 91%), mp 86-88 °C; ^{1}H nmr (deuteriochloroform): δ 2.17 (3H, s, CH_3), 2.85 [4H, s, $(CH_2)_2$], 4.94 (2H, s, CH_2OAc); ^{13}C nmr (deuteriochloroform): δ 20.1 (CH_3), 25.4 [$(CH_2)_2$], 58.3 (CH_2OAc), 163.8 (COON), 168.6 (CON), 169.8 (OCOMe).

Anal. Calcd for $C_8H_9NO_6$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.52; H, 4.28; N, 6.37.

(*RS*)-2-Acetoxyphenylacetic Acid 2,5-Dioxopyrrolidin-1-yl Ester ((*RS*)-**2**).

A solution of *N*,*N*'-dicyclohexylcarbodiimide (50 mmol, 10.32 g) in anhydrous tetrahydrofuran (20 ml) was added dropwise over a period of 1.5 hours to a solution of *RS*-2-acetoxyphenylacetic acid (50 mmol, 8.85 g) and *N*-hydroxysuccinimide (50 mmol, 5.75 g) in anhydrous tetrahydrofuran (50 ml) under cooling in an ice-water bath. The mixture was stirred at room temperature for 6 hours and left standing overnight at 4 °C. The precipitated solid was filtered off and the filtrate evaporated *in vacuo*. The solid residue was treated with diethyl ether, collected by filtration and washed with diethyl ether to afford compound (*RS*)-**2** as a white solid (12.10 g, 83%), mp 122-125 °C; ^{1}H nmr (deuteriochloroform): δ 2.19 (3H, s, CH_3), 2.78 [4H, s, $(CH_2)_2$], 6.31 (1H, s, CHOAc), 7.4-7.6 (5H, m, Ph); ^{13}C nmr (deuteriochloroform): δ 20.3 (CH_3), 25.4 [$(CH_2)_2$], 72.4 (CHOAc), 128.2 (C-3'), 129.1 (C-2'), 130.1 (C-4'), 132.2 (C-1'), 164.9 (COON), 168.5 (CON), 169.8 (OCOMe).

Anal. Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81. Found: C, 57.81; H, 4.43; N, 4.69.

(*S*)-2-Acetoxyphenylacetic Acid 2,5-Dioxopyrrolidin-1-yl Ester ((*S*)-**2**).

Following the same procedure as above, active ester (*S*)-**2** was obtained as a white solid (5.15 g, 93%), mp 125-126 °C; $[\alpha]^{20}_D$ +55.8 (c 2 in acetone); ^{1}H nmr (deuteriochloroform): δ 2.19 (3H, s, CH_3), 2.78 [4H, s, $(CH_2)_2$], 6.31 (1H, s, CHOAc), 7.4-7.6 (5H, m, Ph); ^{13}C nmr (deuteriochloroform): δ 20.3 (CH_3), 25.4 [$(CH_2)_2$], 72.4 (CHOAc), 128.2 (C-3'), 129.1 (C-2'), 130.1 (C-4'), 132.2 (C-1'), 164.9 (COON), 168.5 (CON), 169.8 (OCOMe).

General Procedure for the Preparation of Compounds **5-10**.

The appropriate active methylene compound **3** (or **4**) (5.0 mmol) was added dropwise to a dispersion of sodium hydride (60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (25 mL) and the thick slurry thus formed was stirred at room temperature for 1 hour. The active ester **1** (or **2**) (2.5 mmol) was added and the mixture stirred at room temperature for 2-5 hours. The reaction mixture was extracted with water (2×5 mL) and the combined aqueous extracts acidified with 10% hydrochloric acid under cooling in an ice-water bath. The acidified solution was extracted with dichloromethane (5×10 mL) and the combined extracts dried over sodium sulfate and evaporated *in vacuo* to afford the *C*-acylation product in an oily form. Crude products **5-10** derived with this procedure were used for the production of tetronic acids without further purification.

General Procedures for the Synthesis of Tetronic Acids **11-16**.

(i) Method A. A solution of potassium hydroxide (5.0 mmol, 0.3 g) in the minimum required volume of methanol (or absolute ethanol) was added to a solution of the crude *C*-acylation product in methanol (or absolute ethanol) (5 mL) under cooling in an ice-water bath and the mixture was stirred at room temperature for 3-4 h. The reaction mixture was acidified with 10% hydrochloric acid under cooling in an ice-water bath. The final product was either precipitated and collected by filtration, or extracted with dichloromethane (5×10 mL) and isolated in solid form after drying over sodium sulfate and evaporation *in vacuo* of the combined extracts.

(ii) Method B. Hydrochloric acid (10%, 10 mL) was added to a solution of the crude *C*–acylation product in methanol (or absolute ethanol) (5 mL) under cooling in an ice-water bath and the mixture was stirred at room temperature for 1 day. The final product was either precipitated and collected by filtration, or extracted with dichloromethane (5×10 mL) and isolated in solid form after drying over sodium sulfate and evaporation *in vacuo* of the combined extracts.

3-Methoxycarbonyltetronic Acid (**11**).

Following methods A and B compound **11** was isolated in 32 and 41% overall yields, respectively, as a white solid, mp 128-129 °C; ^{1}H nmr (deuteriochloroform): δ 3.96 (3H, s, CH_3), 4.80 (2H, s, CH_2); ^{13}C nmr (deuteriochloroform): δ 50.9 (CH_3), 66.2 (C-5), 93.1 (C-3), 162.0 (C-2), 169.3 (CO_2Me), 185.6 (C-4).

Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.82. Found: C, 45.81; H, 3.94.

(*RS*)-3-Methoxycarbonyl-5-phenyltetronic Acid ((*RS*)-**12**).

Following methods A and B compound (*RS*)-**12** was isolated in 34 and 55% overall yields, respectively, as a white solid, mp 141-142 °C; ^{1}H nmr (deuteriochloroform): δ 3.97 (3H, s, CH_3), 5.85 (1H, s, CH), 7.3-7.5 (5H, m, Ph); ^{13}C nmr (deuteriochloroform): δ 52.7 (CH_3), 78.6 (C-5), 94.1 (C-3), 126.5-129.2-130.0-132.2 (5-Ph), 166.4 (CO_2Me), 166.8 (C-2), 190.3 (C-4).

Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.34; H, 4.21.

(*S*)-3-Methoxycarbonyl-5-phenyltetronic Acid ((*S*)-**12**).

Following method A compound (*S*)-**12** was isolated in 21% overall yield as a white solid, mp 139-140 °C; $[a]^{20}_D$ +107 (c 0.5 in acetone); ^{1}H nmr (deuteriochloroform): δ 3.97 (3H, s, CH_3), 5.85 (1H, s, CH), 7.3-7.5 (5H, m, Ph); ^{13}C nmr (deuteriochloroform): δ 52.7 (CH_3), 78.6 (C-5), 94.1 (C-3), 126.5-129.2-130.0-132.2 (5-Ph), 166.4 (CO_2Me), 166.8 (C-2), 190.3 (C-4).

(*RS*)-3-Ethoxycarbonyl-5-phenyltetronic Acid ((*RS*)-**13**).

Following methods A and B compound (*RS*)-**13** was isolated in 26 and 45% overall yields, respectively, as a white solid, mp 141-143 °C (lit [17] mp 139-141 °C); ^{1}H nmr (deuteriochloroform): δ 1.41 (3H, t, J=7.1, CH_3), 4.43 (2H, q, J=7.1, CH_2), 5.83 (1H, s, CH), 7.3-7.5 (5H, m, Ph); ^{13}C nmr (deuteriochloroform): δ 14.0 (CH_3), 62.2 (CH_2), 78.5 (C-5), 94.2 (C-3), 126.5-129.2-129.9-132.4 (5-Ph), 166.3 (CO_2Me), 166.6 (C-2), 190.3 (C-4).

(*S*)-3-Ethoxycarbonyl-5-phenyltetronic Acid ((*S*)-**13**).

Following method A compound (*S*)-**13** was isolated in 29% overall yield as a white solid, mp 143-144 °C; $[a]^{20}_D$ +126 (c 0.5 in acetone); ^{1}H nmr (deuteriochloroform): δ 1.42 (3H, t, J=7.1, CH_3), 4.43 (2H, q, J=7.1, CH_2), 5.83 (1H, s, CH), 7.3-7.5 (5H, m, Ph); ^{13}C nmr (deuteriochloroform): δ 14.0 (CH_3), 62.2 (CH_2), 78.5 (C-5), 94.2 (C-3), 126.5-129.2-129.9-132.4 (5-Ph), 166.3 (CO_2Me), 166.6 (C-2), 190.3 (C-4).

3-Acetyltetronic Acid (**14**).

Following method A compound **14** was isolated in 37% overall yield as a white solid, mp 77-78 °C (diethyl ether-light petroleum ether); (lit [18] mp 78-80 °C, [19] mp 77-79 °C); ^{1}H and ^{13}C nmr spectral data, see Tables 3 and 4.

3-Butanoyltetronic Acid (**15**).

Following method A compound **15** was isolated in 53% overall yield as a white solid, mp 75-78 °C (light petroleum ether); (lit [20] mp 78-80 °C); ^{1}H and ^{13}C nmr spectral data, see Tables 3 and 4.

(*RS*)-3-Butanoyl-5-phenyltetronic Acid ((*RS*)-**16**).

Following method A compound (*RS*)-**16** was isolated in 33% overall yield as a white solid, mp 106-107 °C (dichloromethane-light petroleum ether); ^{1}H and ^{13}C nmr spectral data, see Tables 3 and 4.

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.42; H, 5.61.

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