Tetrahedron 65 (2009) 3711–3716

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective ring opening of thiomalic acid anhydrides by carbon nucleophiles. Synthesis and X-ray structure elucidation of novel thiophenone derivatives

Stefanos Kikionis [a], Vickie McKee [b], John Markopoulos [c], Olga Igglessi-Markopoulou [a,*]

[a] National Technical University of Athens, School of Chemical Engineering, Laboratory of Organic Chemistry, Zografou Campus, Athens 15773, Greece
[b] University of Loughborough, Chemistry Department, Leicestershire LE113TU, UK
[c] University of Athens, Department of Chemistry, Laboratory of Inorganic Chemistry, Panepistimiopolis, Zografou, Athens 15771, Greece

ARTICLE INFO

Article history:
Received 23 October 2008
Received in revised form 2 February 2009
Accepted 23 February 2009
Available online 6 March 2009

Keywords:
Thiomalic anhydride
Mercaptosuccinic anhydride
Thiotetronic
Thiophenone
Thiolactone
Thiolactomycin

ABSTRACT

Novel and promising thiophenone derivatives were synthesised by regioselective ring opening of activated thiomalic acid anhydrides, with a variety of active methylene nucleophiles via a C-acylation/cyclisation process involving an S–C bond formation. This regioselective approach could be moreover established by X-ray diffraction structure analysis. The thiolactone ring can act as valuable synthetic scaffold for the preparation of natural and synthetic compounds with important biological and pharmacological activities.

1. Introduction

Thiophenone derivatives found in a substantial number of bioactive compounds possessing the common thiotetronic acid ring system (Fig. 1) are structurally related to the natural antibiotics thiolactomycin and thiotetramycin (Fig. 2).

Thiolactomycin is one of the most important biologically active thiophenone-based natural products. It has been isolated from the actinomycete *Nocardia* sp.[1,2] and exhibits antibiotic activity against many species of pathogens including gram-positive and gram-negative bacteria,[3] mycobacterium tuberculosis[4] and malaria parasite *Plasmodium falciparum*.[5] Thiolactomycin also exhibits inhibitory activity against fatty acid synthase FAS I and FAS II systems.[6–9]

To generate the thiolactone core required for the synthesis of the thiotetronic acid nucleus a number of methods involving formation of a C(3)–C(4) bond or S–C(2) bond were employed.

The first synthetic approach for the construction of 3-substituted thioteronic acids was reported by Benary[10] in which thiolactic acid chlorides were used as acylating agents. A similar method has been applied for the synthesis of various thiotetronic acids.[11,12]

Figure 1. Thiotetronic acid ring system.

The first synthetic method for the racemic TLM analogues was developed by Salvino and Wang[2] starting from α-propionylpropionate as precursor by a three-step procedure. Significant studies have been made by Thomas and Chambers[13] who described an asymmetric synthesis of (5*S*)-thiolactomycin. Townsend et al.[14] synthesised (5*R*)-thiolactomycin from (2*R*)-alanine. Moreover,

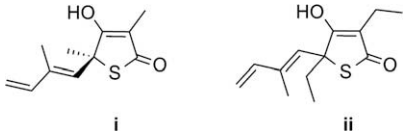


Figure 2. Thiolactomycin (i) and thiotetramycin (ii).

* Corresponding author. Tel.: +30 210 772 3 079; fax: +30 210 772 3 072.
E-mail address: ojmark@orfeas.chemeng.ntua.gr (O. Igglessi-Markopoulou).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.02.081

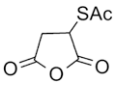


Figure 3. *S*-Acetylthiomalic acid anhydride (*S*-acetylmercaptosuccinic anhydride).

Gilbert et al.[15] have synthesised a number of TLM analogues and undertook a complete structure–activity relationships (SAR) study. Recently, Ohata and Terashima,[16] synthesised (5*R*)-thiolactomycin from D-alanine and Brückner and Dormann[17] proposed a short asymmetric synthesis of the natural products, (+)-thiolactomycin, thiotetramycin and 834-B1. Also, synthesis and spectroscopic studies of 2- and 4- alkoxythiotetronic acids have been described.[18]

During the course of our research program on the synthesis of nitrogen,[19] oxygen[20,21] and sulfur heterocycles[22,23] containing the β,β′-dicarbonyl system, we required the construction and structure elucidation of thiophenone nucleus containing 'polar functionalities' from simple building blocks.

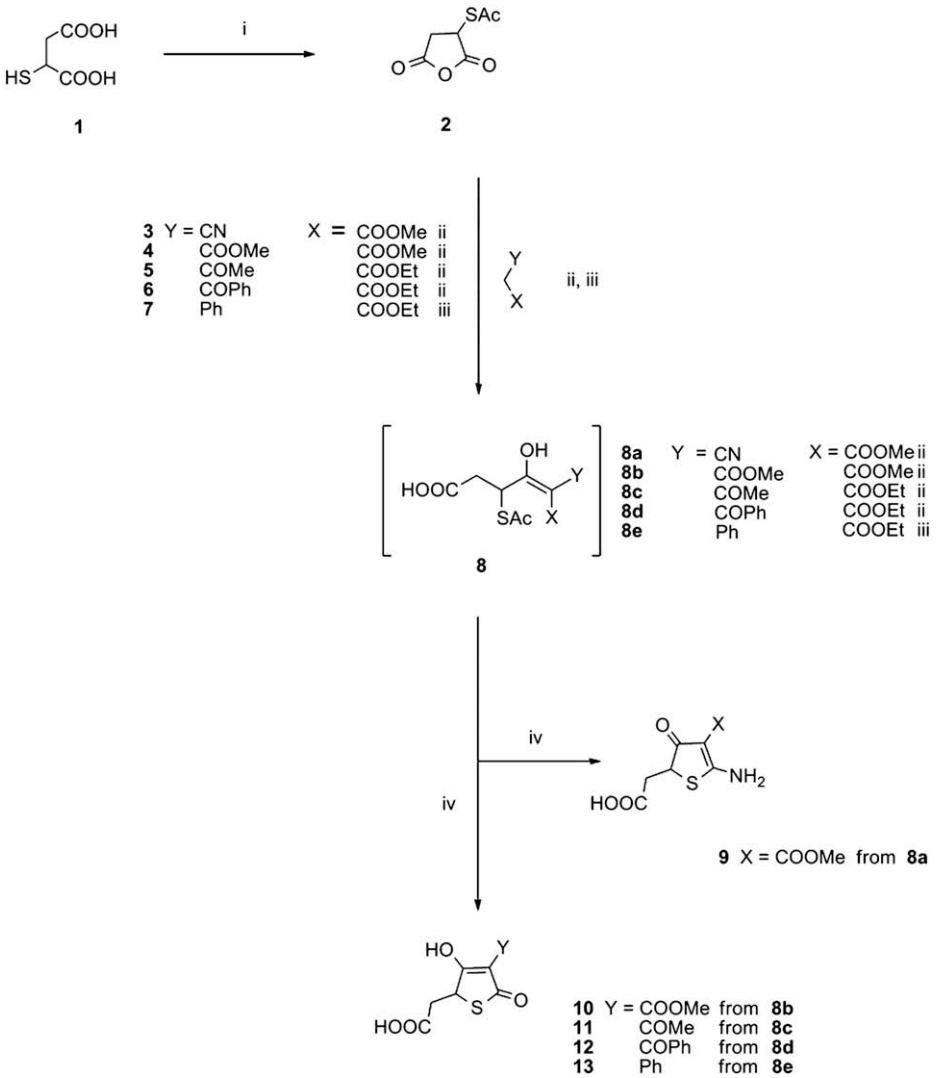
We now wish to report a useful methodology, which allows an approach to the synthesis of novel heterocycles, containing the thiolactone nucleus starting from a new scaffold, the *S*-acetylthiomalic acid anhydride (*S*-acetylmercaptosuccinic anhydride) (Fig. 3).

The proposed protocol involves (a) deprotonation of an active methylene compound, (b) nucleophilic attack at the 2-carbonyl of thiomalic anhydride (c) in situ intramolecular cyclisation of the intermediate precursor, affording substituted thiophenones with flexible substituted patterns, for example, a polar group (CH_2COOH) at C-5 and acyl, alcoxycarbonyl or phenyl group at C-3 position.

The 'key control element' for the preparation of 4-hydroxy thiophenone ring system,[5] containing the 5-carboxymethyl group, **9**–**13**, was the polyfunctional synthon derived from thiomalic acid (mercaptosuccinic acid) (**1**), the *S*-protected mercaptosuccinic anhydride **2**, possessing carbonyl groups activated towards nucleophilic attack (Scheme 1).

The *S*-acetylthiomalic acid anhydride (**2**) is found to react regioselectively at the more reactive electro-deficient carbonyl at the C-2 site with carbon nucleophiles for a subsequent coupling reaction. The observed high regioselectivity of the nucleophilic attack to the more hindered carbonyl could be attributed to the electron withdrawing effect of the *S*-acetyl group. In this way, the use of this anhydride serves as a potential precursor for the protection, activation and deprotection of carboxylates.

We discovered that the regioselectivity of this reaction is applicable for a series of active methylene compounds **3**–**7** with good yields (52–81%). Now we herein report a highly regioselective ring opening of *S*-acetylthiomalic acid anhydride with the enolate of an



Scheme 1. Reagents and conditions: (i) CH_3COCl, reflux; (ii) NaH, THF; (iii) LDA, THF −78 °C; (iv) MeOH, 2 M NaOH.

Table 1
Bond lengths [Å] and angles [°] for **11**

S(1)–C(1)	1.791(4)	C(3)–C(4)	1.489(5)
S(1)–C(6)	1.821(3)	C(5)–O(3)	1.309(4)
C(1)–O(1)	1.210(4)	C(5)–C(6)	1.489(5)
C(1)–C(2)	1.459(5)	C(6)–C(7)	1.516(4)
C(2)–C(5)	1.379(5)	C(7)–C(8)	1.496(5)
C(2)–C(3)	1.442(5)	C(8)–O(5)	1.227(4)
C(3)–O(2)	1.260(4)	C(8)–O(4)	1.302(4)
C(1)–S(1)–C(6)	93.95(16)	O(3)–C(5)–C(2)	126.3(3)
O(1)–C(1)–C(2)	128.6(3)	O(3)–C(5)–C(6)	116.0(3)
O(1)–C(1)–S(1)	121.5(3)	C(2)–C(5)–C(6)	117.7(3)
C(2)–C(1)–S(1)	109.9(2)	C(5)–C(6)–C(7)	112.2(3)
C(5)–C(2)–C(3)	120.6(3)	C(5)–C(6)–S(1)	105.4(2)
C(5)–C(2)–C(1)	113.0(3)	C(7)–C(6)–S(1)	112.6(2)
C(3)–C(2)–C(1)	126.4(3)	C(8)–C(7)–C(6)	114.1(3)
O(2)–C(3)–C(2)	118.5(3)	O(5)–C(8)–O(4)	124.5(3)
O(2)–C(3)–C(4)	120.7(3)	O(5)–C(8)–C(7)	122.9(3)
C(2)–C(3)–C(4)	120.8(3)	O(4)–C(8)–C(7)	112.5(3)

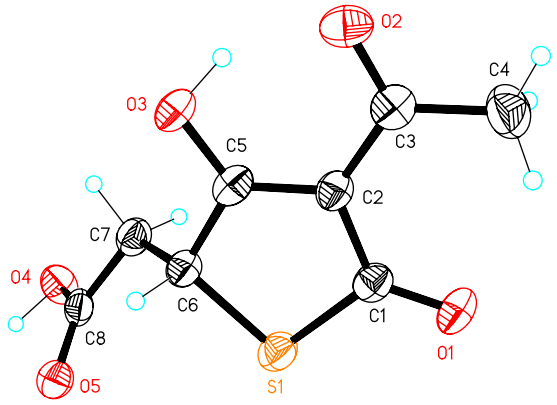
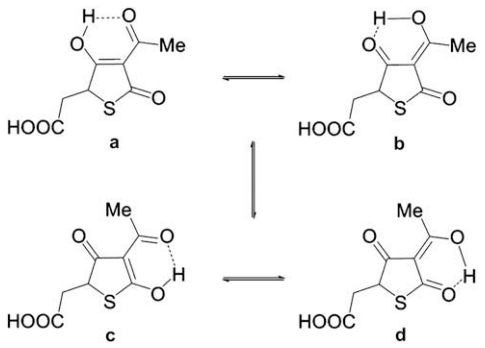


Figure 4. Molecular structure of **11**, the dashed line represents a hydrogen bond. Thermal ellipsoids drawn at the 50% probability level.

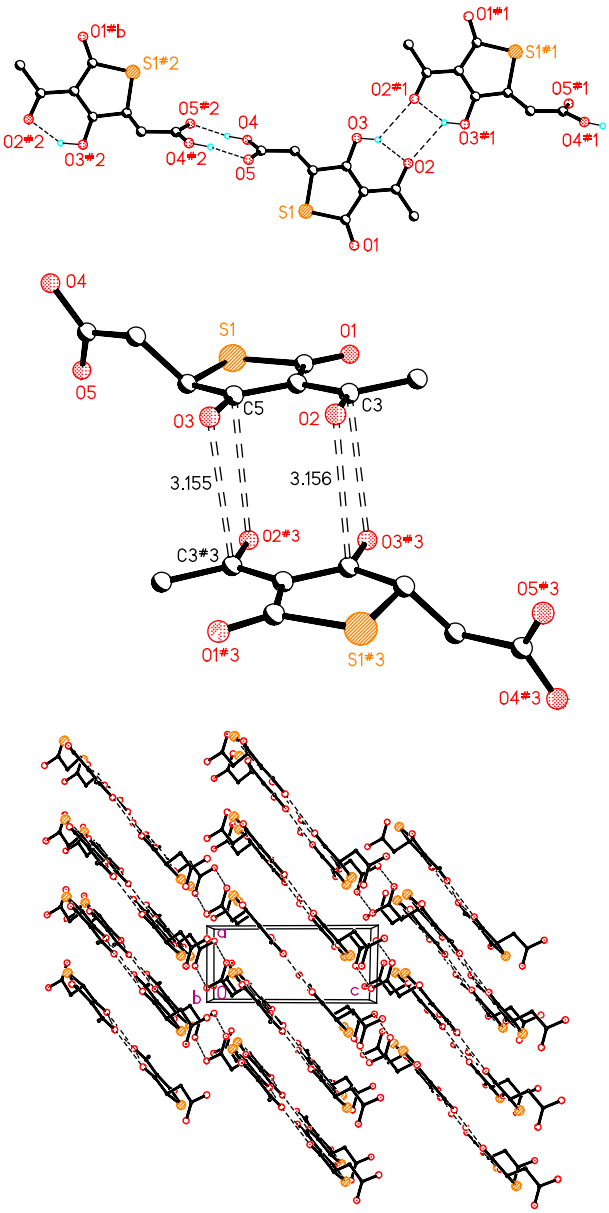
active methylene compound and subsequent intramolecular cyclisation of the 'C-acylation intermediates' **8** to a stable five-membered thiolactone ring system.

2. Results and discussion

Thiomalic acid (mercaptosuccinic acid) (**1**) on treatment with acetyl chloride furnished the corresponding *S*-acetylthiomalic acid anhydride (*S*-acetylmercaptosuccinic anhydride) (**2**) isolated in 91% yield (Scheme 1) as a white solid, which was used in the C-acylation reaction without further purification. Subsequently, the efficiency of compound **2** as acylating agent of active methylene compounds



Scheme 2. Enol–enol equilibrium of the 3-acetyl-5-carboxymethylthiotetronic acid (**11**).



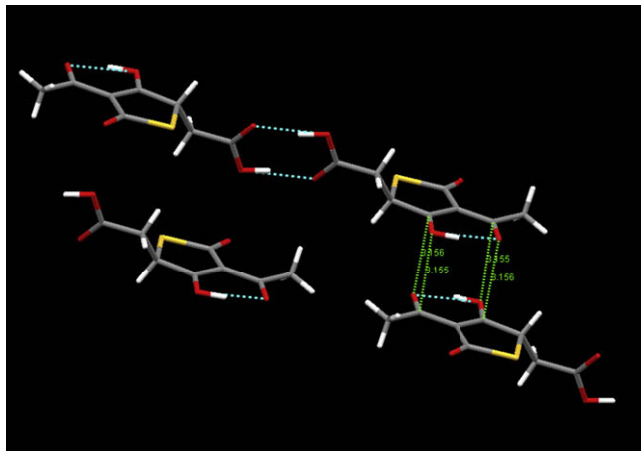


Figure 5. Intermolecular interactions in **11**: hydrogen-bonded chain with dashed lines representing hydrogen bonds (top) and π-stacking interactions (bottom). Symmetry transformations used to generate equivalent atoms: #1 −*x*−1,−*y*, −*z*+1; #2 −*x*+1, −*y*−1, −*z*; #3 −*x*, −*y*, −*z*+1.

Table 2
Hydrogen bonds in **11** [Å and °]

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
O(3)–H(3O)···O(2)	0.97	1.71	2.574(3)	146.8
O(3)–H(3O)···O(2)#1	0.97	2.40	3.076(4)	126.2
O(4)–H(4O)···O(5)#2	0.97	1.73	2.674(3)	164.7

Symmetry transformations used to generate equivalent atoms: #1 $-x-1$, $-y$, $-z+1$; #2 $-x+1$, $-y-1$, $-z$.

was examined. The reaction protocol involved the addition of 1 equiv of **2** to a dispersion of 2 equiv of the anion of active methylene compounds **3**–**6** generated by the action of sodium hydride in anhydrous tetrahydrofuran. The reaction mixture was stirred at 0 °C for 30 min and the C-acylation intermediate **8** extracted with water and isolated after acidification of the aqueous extracts with 10% aqueous hydrochloric acid. We noted that the C-acylation intermediate products were obtained in a mixture with the corresponding cyclised compounds as determined on the basis of NMR spectroscopic data. Ring closure of the intermediates **8a**–**8d** was achieved under basic conditions, by treating them with 2 M NaOH in MeOH at room temperature for 2–3 h.

The cyclisation of **8** by intramolecular nucleophilic attack of the sulfur lone pair on the ester carbonyl group would produce structures such as **10**–**12** whereas the intermediate **8** possessing the CN group produces the structure of amino thiophenone ring (compound **9**, 3-alkoxycarbonyl-2-amino-5-carboxymethylthiophenone) by an intramolecular interaction of the electron-deficient carbon atom with the nucleophilic sulfur in the cyclisation process.[22]

Having established the feasibility of this approach to the synthesis of 3-alkoxycarbonyl and 3-acylthiotetronic acids, we extended our methodology to the synthesis of the thiotetronic acid bearing phenyl group at C-3 position. The nucleophilic ring opening of *S*-acetylmercaptosuccinic anhydride (**2**) by the anion of ethyl phenylacetate, generated with LDA in THF at −78 °C resulted the C-acylation synthon **8e** as an oily product, which could be easily transformed to 5-carboxymethyl-3-phenylthiotetronic acid (**13**), using basic conditions by treating with 2 M NaOH in MeOH at room temperature for 2 h.

The structures of the above mentioned functionalised thiophen-4-ones were proved by the combination of ^{1}H and ^{13}C NMR, FTIR and mass spectroscopy (ESI-MS) (see Experimental).

An X-ray structure determination of 3-acetyl-5-carboxymethylthiotetronic acid (**11**) was carried out to confirm the structure in the solid state (Table 1). The molecular structure and numbering scheme are shown in Figure 4. The structure resembles that of tautomer **a** (Scheme 2) with a double bond character in the C(2)–C(5) bond (1.379 Å) and the O(3)–C(5) bond is distinctly longer that the conventional carbonyl distance for O(1)–C(1) (1.379 and 1.210 Å, respectively). There is a short intramolecular hydrogen bond between the enol and the carbonyl oxygen atoms (O(2)–O(3), 2.574 Å). Figure 5 shows the intermolecular interactions. Hydrogen bonds link the molecules into chains (Fig. 5) via a conventional carboxylic acid H-bond interaction, and also an unsymmetric bifurcated H-bond involving the OH group (Table 2). The molecules show π-stacking principally involving the partially conjugated carbonyl and C=C portion of the molecule.

3. Conclusions

In summary, a new and promising synthetic methodology has been established for the synthesis of the thiotetronic acid family of thiolactomycin antibiotics. The key step involved the regioselective ring opening of *S*-acetylthiomalic acid anhydride with active methylene nucleophiles under basic conditions. The new synthetic protocol allow us to introduce the CH_2COOH functionality at C-5 position of the thiolactone ring. These compounds bear structural similarities to thiolactomycin antibiotics and the proposed strategy paves the way for the synthesis of a variety of thiophenone derivatives with a potential of structural diversity. Detailed bioevaluation of these compounds for different activities will be reported in due course.

4. Experimental section

4.1. General

Mps were determined on a Gallenkanp MFB-595 melting point apparatus and are uncorrected. FTIR spectra were recorded on a FTIR Jasco 4200 instrument. Mass spectra were obtained on a TSQ 7000 Finnigan MAT (ESI) instrument. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Varian Gemini-2000 300 MHz spectrometer; chemical shifts are quoted in parts per million (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad); *J* values are given in hertz. Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyzer. Petroleum ether refers to the fraction with bp 40–60 °C. All commercially available starting materials were used without further purification. Commercially available THF was dried prior to use by refluxing over Na. All other solvents (puriss quality) were used without further purification.

4.2. Synthesis

*4.2.1. Synthesis of S-acetylmercaptosuccinic anhydride (**2**)*

A mixture of mercaptosuccinic acid (**1**) (50 mmol, 7.5 g) and acetyl chloride (170 mmol, 12 mL) was heated under reflux for 3 h. The clear solution that formed was concentrated under reduced pressure at 60 °C and dried in vacuo to afford a crude solid, which was washed with diethyl ether and filtered off to afford the *S*-acetylmercaptosuccinic anhydride (**2**) as white solid.

*4.2.1.1. S-Acetylmercaptosuccinic anhydride (**2**).* The title compound was obtained as white solid. Yield: 7.9 g, 91%; mp 84–86 °C (lit.[24] 83–86 °C). IR (ATR): 1867, 1793, 1733, 1718, 1678, 1558, 1540, 1508, 1468, 1418 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.39 (s, 3H, CH_3), 2.97 (dd, *J*=18.6, 6.6, 1H, CH_2), 3.43 (dd, *J*=18.6, 10.2, 1H, CH_2), 4.76 (dd, *J*=10.2, 6.6, 1H CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ=29.6 ($COCH_3$), 36.0 (C-4), 40.1 (C-3), 170.0 ($COCH_3$), 171.7 (C-5), 195.5 (C-2). Anal. Calcd for $C_6H_6O_4S$: C, 41.37; H, 3.47; S, 18.41. Found: C, 41.51; H, 3.29; S, 18.26.

4.2.2. General procedure for the preparation of 3-substituted-5-carboxymethylthiotetronic acids

To a suspension of sodium hydride (10 mmol, 0.4 g) in anhydrous THF (30 mL), chilled at 0 °C, was added dropwise the appropriate active methylene compound (methyl cyanoacetate, malononitrile, dimethyl malonate, ethyl acetoacetate and ethyl benzoylacetate) (10 mmol) and after stirring at 0 °C for 30 min, a clear solution resulted. A solution of **2** (5 mmol, 0.87 g) in anhydrous THF (5 mL) was added at once. The reaction mixture was stirred at 0 °C for 30 min, and after the addition of water (10 mL), the mixture was concentrated under reduced pressure. The aqueous residue was washed with diethyl ether (5 mL) and then acidified with aqueous hydrochloric acid (10%) under cooling in an ice–H_2O bath. The acidified mixture was extracted with dichloromethane (3×15 mL), and the combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and dried in vacuo to afford the crude (non isolated) C-acylation intermediate **8** in an oily form. A solution of crude **8** (~4 mmol) in methanol (2 mL) was chilled at 0 °C, and a 2 M NaOH solution (6 mL) was added dropwise. The solution was stirred at room temperature for 2–3 h and then acidified with aqueous hydrochloric acid (10%)

under cooling in an ice–H_2O bath. The products **9**–**12** were either filtered off or extracted with ethyl acetate.

*4.2.2.1. 2-Amino-5-carboxymethyl-3-methoxycarbonylthiophenone (**9**).* Using methyl cyanoacetate as the active methylene compound, the title compound was obtained as a pale yellow solid. Yield: 0.68 g, 59%; mp 246–248 °C. MS (ESI) m/z=230.0 ($[M-H]^+$). IR (ATR): 2388, 2348, 1748, 1716, 1669, 1607, 1558, 1487 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=2.53 (dd, J=17.7, 11.1, 1H, CH_2), 3.04 (dd, J=17.7, 3.9, 1H, CH_2), 3.63 (s, 3H, CH_3), 3.96 (dd, J=11.1, 3.9, 1H, CH), 8.92 (s, 1H, NH_2), 9.41 (s, 1H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ=37.4 ($COOCH_3$), 48.1 (CH_2), 50.3 (C-5), 95.0 (C-3), 164.9 (C-2), 172.6 (COOH), 182.5 ($COOCH_3$), 191.4 (C-4). Anal. Calcd for $C_8H_9O_5NS$: C, 41.55; H, 3.92; N, 6.06; S, 13.87. Found: C, 41.68; H, 3.80; N, 5.92; S, 13.71.

*4.2.2.2. 5-Carboxymethyl-3-methoxycarbonylthiotetronic acid (**10**).* Using dimethyl malonate as the active methylene compound, the title compound was obtained as a white solid. Yield: 0.81 g, 70%; mp 159–161 °C. MS (ESI) m/z=231.0 ($[M-H]^+$). IR (ATR): 1710, 1653, 1591, 1460 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=2.62 (dd, J=17.1, 10.2, 1H, CH_2), 3.21 (dd, J=17.1, 3.3, 1H, CH_2), 4.45 (dd, J=10.2, 3.3, 1H, CH), 9.31 (br s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ=38.1 ($COOCH_3$), 44.6 (CH2), 51.1 (C-5), 104.1 (C-3), 163.4 ($COOCH_3$), 171.9 (COOH), 189.5 (C-2), 190.3 (C-4). Anal. Calcd for $C_8H_8O_6S$: C, 41.38; H, 3.47; S, 13.81. Found: C, 41.51; H, 3.32; S, 13.68.

*4.2.2.3. 3-Acetyl-5-carboxymethylthiotetronic acid (**11**).* Using ethyl acetoacetate as the active methylene compound, the title compound was obtained as a pale yellow solid. Yield: 0.85 g, 81%; mp 136–138 °C. MS (ESI) m/z=215.0 ($[M-H]^+$). IR (ATR): 1715, 1558, 1508, 1418 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=2.47 (s, 3H, CH_3), 2.82 (dd, J=17.1, 9.3, 1H, CH_2), 3.12 (dd, J=17.1, 3.6, 1H, CH_2), 4.6 (dd, J=9.3, 3.6, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ=23.4 ($COCH_3$), 36.8 (CH_2), 46.8 (C-5), 109.5 (C-3), 171.6 (COOH), 192.5 ($COCH_3$), 192.6 (C-2), 199.0 (C-4). Anal. Calcd for $C_8H_8O_5S$: C, 44.44; H, 3.73; S, 14.83. Found: C, 44.59; H, 3.85; S, 14.93.

*4.2.2.4. 3-Benzoyl-5-carboxymethylthiotetronic acid (**12**).* Using ethyl benzoylacetate as the active methylene compound, the title compound was obtained as a pale yellow solid. Yield: 0.73 g, 52%; mp 158–160 °C. MS (ESI) m/z=277.1 ($[M-H]^+$). IR (ATR): 1703, 1581, 1540, 1508, 1488, 1434 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=2.84 (dd, J=17.1, 9.9, 1H, CH_2), 3.25 (dd, J=17.1, 3.3, 1H, CH_2), 4.62 (dd, J=9.9, 3.6, 1H, CH), 7.45–7.79 (m. 5H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=37.7 (CH_2), 45.5 (C-5), 113.0 (C-3), 128.4, 129.3, 133.2, 136.7 (C_6H_5), 172.0 (COOH), 187.5 (COC_6H_5), 189.7 (C-2), 191.3 (C-3). Anal. Calcd for $C_{13}H_{10}O_5S$: C, 56.11; H, 3.62; S, 11.52. Found: C, 56.23; H, 3.74; S, 11.41.

*4.2.3. Synthesis of 5-carboxymethyl-3-phenylthiotetronic acid (**13**)*

A solution of the ethyl phenylacetate (6 mmol, 0.98 g) in anhydrous THF (8 mL) was added dropwise, under argon, to a solution of LDA (2.0 M solution in THF/hexane/ethylbenzene, 6 mmol) in anhydrous THF (20 mL) at −78 °C. The addition was completed in 15 min and the mixture was stirred at −78 °C for 45 min. A solution of *S*-acetylmercaptosuccinic anhydride (3 mmol, 0.52 g) in anhydrous THF (5 mL) was added dropwise over 15 min and the mixture was allowed to stir at −78 °C for 1 h. After stirring for an additional hour to room temperature, the reaction quenched with 10 mL of water and the mixture was concentrated under reduced pressure. The aqueous residue was washed with diethyl ether (20 mL) and then acidified with aqueous hydrochloric acid (10%) under cooling in an ice–H_2O bath. The acidified mixture was extracted with ethyl acetate (3×15 mL), and the combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and dried in vacuo to afford the crude (non-isolated) C-acylation intermediate **8e** in an oily form. A solution of crude **8e** (~4 mmol) in methanol (2 mL) was chilled at 0 °C, and a 2 M NaOH solution (6 mL) was added dropwise. The solution was stirred at room temperature for 2 h and then acidified with aqueous hydrochloric acid (10%) under cooling in an ice–H_2O bath. The product **13** was extracted with ethyl acetate.

*4.2.3.1. 5-Carboxymethyl-3-phenylthiotetronic acid (**13**).* Using ethyl phenylacetate as the active methylene compound, the title compound was obtained as a white solid. Yield: 0.57 g, 76%; mp 171–173 °C. MS (ESI) m/z=249.1 ($[M-H]^+$). IR (ATR): 1704, 1579, 1557, 1540, 1508, 1403 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=2.62 (dd, J=17.4, 11.4, 1H, CH_2), 3.39 (dd, J=17.4, 3.3, 1H, CH_2), 4.53 (dd, J=11.4, 3.3, 1H, CH), 7.23–7.52 (m, 5H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=38.7 (C-6), 43.4 (C-5), 113.4 (C-3), 126.8, 127.8, 128.7, 131.1, 134.0 (C_6H_5), 172.1 (C-7), 179.1 (C-2), 193.1 (C-4). Anal. Calcd for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03; S, 12.81. Found: C, 57.71; H, 4.18; S, 12.93.

*4.2.4. Crystal structure determination of **11***

Compound **11**: $C_8H_8O_5S$, triclinic, $P\bar{1}$, a=5.057(2), b=8.028(4), c=11.167(5) Å, α=81.017(6), β=87.832(6), γ=80.515(6)°, V=441.6(3) $Å^3$, T=150(2) K, λ=0.71073 Å, Z=2, 3306 reflections measured, 1539 unique (R_{int}=0.037), $wR2$=0.1413 (all data), $R1$=0.0513 ($I>2\sigma(I)$). Data were collected on a Bruker ApexII CCD diffractometer. Structure was solved by direct methods and refined on F^2 using all the reflections.[25] All the non-hydrogen atoms were refined using anisotropic ADPs and hydrogen atoms bonded to carbon were inserted at calculated positions. Hydrogen atoms involved in H-bonding were located from difference maps and not refined. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 716355. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The author S.K. would like to thank the National Technical University of Athens, Chemical Engineering Department for financial support. The author J.M. would like to thank the National and Kapodistrian University of Athens for financial support (special account for research grant no. 70/4/3337).

References and notes

1. Oishi, H.; Noto, T.; Sasaki, H.; Suzuki, K.; Hayashi, T.; Okazaki, H.; Ando, K.; Sawada, M. *J. Antibiot.* **1982**, *35*, 391.
2. Wang, C.-L. J.; Salvino, J. M. *Tetrahedron Lett.* **1984**, *25*, 5243.
3. Noto, T.; Miyakawa, S.; Oishi, H.; Endo, H.; Okazaki, H. *J. Antibiot.* **1982**, *35*, 401.
4. (a) Kremer, L.; Douglas, J. D.; Baulard, A. R.; Morehouse, C.; Guy, M. R.; Alland, D.; Dover, L. G.; Lakey, J. H.; Jacobs, W. R.; Brennan, P. J.; Minnikin, D. E.; Besra, G. S. *J. Biol. Chem.* **2000**, *275*, 16857; (b) Slayden, R. A.; Lee, R. E.; Armour, J. W.; Cooper, A. M.; Orme, I. M.; Brennan, P. J.; Besra, G. S. *Antimicrob. Agents Chemother.* **1996**, *40*, 2813; (c) Kim, P.; Zhang, Y.-M.; Shenoy, G.; Nguyen, Q.-A.; Boshoff, H. I.; Manjunatha, U. H.; Goodwin, M. B.; Lonsdale, J.; Price, A. C.; Miller, D. J.; Duncan, K.; White, S. W.; Rock, C. O.; Barry, C. E., III; Dowd, C. S. *J. Med. Chem.* **2006**, *49*, 159.
5. Ohata, K.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4070.
6. Price, A. C.; Choi, K.-H.; Heath, R. J.; Li, Z.; White, S. W.; Rock, C. O. *J. Biol. Chem.* **2001**, *276*, 6551.
7. (a) Bhowruth, V.; Brown, A. K.; Senior, S. J.; Snaith, J. S.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5643; (b) Bhowruth, V.; Dover, L. G.; Besra, G. S. In *Progress in Medicinal Chemistry*; King, F. D., Lawton, G., Eds.; Elsevier: Amsterdam, 2007; Vol. 45, pp 169–203.
8. Johanson, P.; Wiltschi, B.; Kumari, P.; Kessler, B.; Vonrhein, C.; Vonck, J.; Oesterhelt, D.; Grininger, M. *PNAS* **2008**, *105*, 12803–12808.
9. McFadden, J. M.; Medghalchi, S. M.; Thupari, J. N.; Pinn, M. L.; Vadlamudi, A.; Miller, K. I.; Kuhajda, F. P.; Townsend, C. A. *J. Med. Chem.* **2005**, *48*, 946.
10. (a) Benary, E. *Ber.* **1910**, *43*, 1943; (b) Benary, E. *Ber.* **1913**, *46*, 2103.
11. O' Mant, D. M. *J. Chem. Soc., Perkin Trans. 1* **1968**, 1501.
12. Budnikova, M. V.; Rubinov, D. B. *Russ. J. Org. Chem.* **2001**, *37*, 1478.
13. Chambers, M. S.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 417.

14. Mc Fadden, J. M.; Frehywot, G. L.; Townsend, C. A. *Org. Lett.* **2002**, *4*, 3859.
15. Jones, S. M.; Urch, J. E.; Kaiser, M.; Brun, R.; Harwood, J. L.; Berry, C.; Gilbert, I. H. *J. Med. Chem.* **2005**, *48*, 5932.
16. (a) Ohata, K.; Terashima, S. *Tetrahedron Lett.* **2006**, *47*, 2787; (b) Ohata, K.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5598.
17. Dormann, K. L.; Brückner, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1160.
18. Shenoy, G.; Kim, P.; Goodwin, M.; Nguyen, Q.-A.; Barry, C. E.; Dowd, C. S. *Heterocycles* **2004**, *63*, 519.
19. Petroliagi, M.; Igglessi-Markopoulou, O. *Tetrahedron: Asymmetry* **1999**, *10*, 1873.
20. Mitsos, C.; Zografos, A.; Igglessi-Markopoulou, O. *J. Org. Chem.* **2000**, *65*, 5852.
21. Athanasellis, G.; Igglessi-Markopoulou, O.; Markopoulos, J. *Synlett* **2002**, 1736.
22. Kikionis, S.; Prousis, K. C.; Detsi, A.; Igglessi-Markopoulou, O. *ARKIVOC* **2006**, 28.
23. Kikionis, S.; McKee, V.; Markopoulos, J.; Igglessi-Markopoulou, O. *Tetrahedron* **2008**, *64*, 5454.
24. *Fluka Catalogue*; Buchs SG, 2008.
25. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.