HETEROCYCLES, Vol. 63, No. 3, 2004, pp. 519 - 527
Received, 4th November, 2003, Accepted, 25th December, 2003, Published online, 9th January, 2004

# SYNTHESIS AND SPECTROSCOPIC DIFFERENTIATION OF 2- AND 4-ALKOXYTHIOTETRONIC ACIDS

**Gautham Shenoy, Pilho Kim, Michael Goodwin, Quynh-Anh Nguyen, Clifton E. Barry, 3rd, and Cynthia S. Dowd***

Tuberculosis Research Section, National Institute of Allergy and Infectious Diseases, Rockville, MD 20852 USA; Email: cdowd@niaid.nih.gov

**Abstract** – *O*-Alkylation of thiotetronic acids gives a mixture of 2- and 4-position enol ether products. Comparison of the physical data revealed that UV spectroscopy was the most reliable method of distinguishing between these related ethers. We have determined that 4-position ethers have a distinct absorption between 235-240 nm, while 2-position ethers have two absorbance peaks, one between 205-220 nm and the other between 305-310 nm. This report describes the synthesis and unambiguous characterization of 2- and 4-methoxy-3,5-dimethylthiotetronic acids. The UV absorption properties of several other pairs of thiotetronic acid ethers confirm that these differences are general features that provide a simple method for distinguishing between 2- and 4-substituted isomers.

## INTRODUCTION

The thiotetronic acid ring structure (**1**), closely related to that of tetronic acid (**2**), is found within several antibacterial natural products (Figure 1).[1-4] Thiolactomycin (**3**) and thiotetramycin (**4**), for example, are

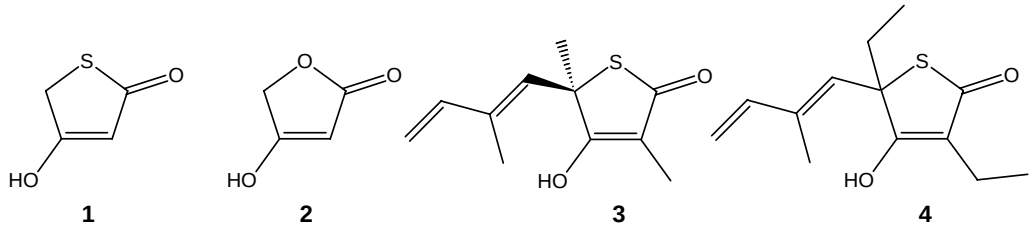



**Figure 1.** Structures of thiotetronic acid (**1**), tetronic acid (**2**), thiolactomycin (**3**), and thiotetramycin (**4**).

produced by soil microbes and have broad-spectrum antibacterial activity. Thiotetronic acids, such as thiolactomycin,[5] are thought to inhibit bacterial fatty acid synthesis through structural mimicry of a key condensation intermediate by the enolized thiolactone. To define the role of the potential keto-enol tautomers (Figure 2) in the activities of these molecules, we attempted to trap the two enolic forms by preparation of the 2- and the 4-ethers of 3,5-dimethylthiotetronic acid.[†]

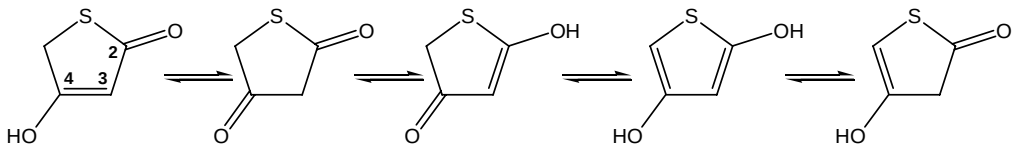



**Figure 2.** Tautomers of thiotetronic acid.

There are very few examples in the literature that describe the general synthesis of substituted thiotetronic acids. A few of these discuss the synthesis of 4-substituted ethers from the corresponding thiophene.[6-8] However, there are no reports that describe a completely regioselective preparation of a 2- or 4-alkoxythiotetronic acid directly from the corresponding thiotetronic acid. Schachtner *et al.* described the 4-alkylation of a substituted thiotetronic acid, but no mention of separation of the two resulting isomers was made.[9] Indeed, the same method of alkylation (diazomethane) was used in a more recent study by Budnikova and Rubinov, and a mixture of products was observed.[10]

In contrast, several methods of preparing 2- and 4-alkoxytetronic acids are reported.[11-13] Two examples describe regioselective alkylation of tetronic acids that gives exclusively 4-substituted products. Wengel *et al.* used tetrabutylammonium hydroxide (TBAH) to first generate the enolate, and then added the appropriate dialkyl sulfate.[14] Schobert and Siegfried described a second regioselective 4-alkylation *via* a substituted isourea.[15]

Because no work has described the regioselective alkylation of thiotetronic acids, we applied the tetronic acid methods described above to the synthesis of 2- and 4-ethers of thiotetronic acid. During the course of this work, however, it became necessary to find a reliable means of differentiating between these regioisomeric products.

## RESULTS AND DISCUSSION

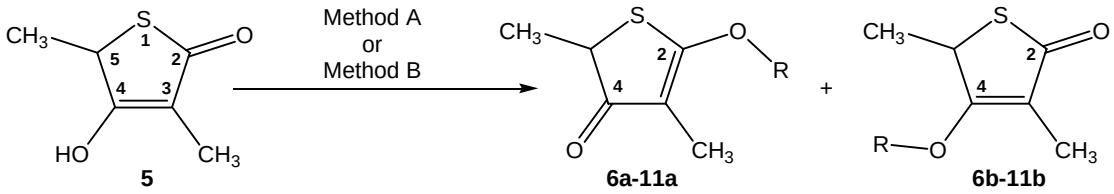
2- And 4-alkoxy-3,5-dimethylthiotetronic acids were made using literature methods for the corresponding tetronic acid ethers (Table 1).[14,15] In Method A, the tetrabutylammonium salt of 3,5-dimethylthiotetronic acid (**5**)[16] was alkylated with dimethyl sulfate (or an alkyl halide) in

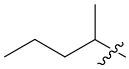
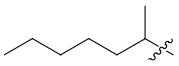
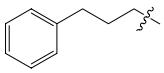
[†] The IUPAC name of 3,5-dimethylthiotetronic acid is 4-hydroxy-3,5-dimethyl-5*H*-thiophen-2-one. Upon alkylation of the C-2 oxygen atom, the numbering of the thiophenone ring changes so that the IUPAC name for 2-methoxy-3,5-dimethylthiotetronic acid is 5-methoxy-2,4-dimethyl-2*H*-thiophen-3-one. Because of this changing nomenclature, compounds are referred to simply as 2- or 4-derivatives of thiotetronic acid.

dichloromethane or THF, while in Method B, the appropriately substituted 1,3-dicyclohexylisourea was reacted with compound (**5**). In the case of the methoxy compounds, both routes of synthesis generated a mixture of the 2- and 4-methoxy isomers (compounds **6a** and **6b**, respectively). Method A yielded the isomers in a 1:6.4 ratio, while Method B yielded a 1:2.3 ratio. Since we were primarily interested in obtaining the 4-alkoxy derivatives, the remaining compounds of the series (**7-11**) were made using Method A. This method was utilized with over twenty different alkylating agents, and the 4-alkoxy isomer was always the major product.

From the results in Table 1, it is apparent that neither of these methods are completely regioselective for *O*-alkylation of thiotetronic acids. As a consequence, we sought a reliable means of differentiating between the 2- and the 4-isomeric products. Unfortunately, the $^{1}H$ and $^{13}C$ NMR spectral data for compounds (**6a**) and (**6b**) were very similar. These values were so similar, in fact, that the structure of each isomer could not be confidently assigned based solely on these data. Indeed, other authors have employed NOE NMR spectral experiments to differentiate between these isomers without success.[10]

**Table 1. Synthesis and UV absorption data of 2- and 4-alkoxy-3,5-dimethylthiotetronic acids**




| R | Method | Ratio of 2- : 4-isomer | 2-alkoxy $\lambda_{max}$ (ε) | 4-alkoxy $\lambda_{max}$ (ε) |
|---|---|---|---|---|
| | | | **6a:** | **6b:** |
| $CH_3$- | A | 1 : 6.4 | 209 nm (6400)<br>308 nm (7500) | 237 nm (10,900)<br>267 nm (4800) |
| $CH_3$- | B | 1 : 2.3 | — | — |
|  | A | 1 : 5.3 | **7a:**<br>212 nm (9100)<br>308 nm (9800) | **7b:**<br>239 nm (11,300)<br>267 nm (5300) |
|  | A | 1 : 9.7 | **8a:**<br>215 nm (5800)<br>306 nm (4600) | **8b:**<br>239 nm (12,900)<br>267 nm (6000) |
|  | A | 1 : 4.3 | **9a:**<br>216 nm (9400)<br>309 nm (10,200) | **9b:**<br>239 nm (11,500)<br>267 nm (5300) |
|  | A | 1 : 4.4 | **10a:**<br>216 nm (8800)<br>308 nm (9600) | **10b:**<br>239 nm (13,600)<br>268 nm (6300) |
|  | A | 1 : 9.3 | **11a:**<br>206 nm (15,100)<br>309 nm (7900) | **11b:**<br>237 nm (13,300)<br>267 nm (6500) |

We found, however, major differences in the UV absorption spectra of these compounds. Compound (**6b**) had a $\lambda_{max}$ value of 237 nm (ε 10,900) with a minor absorption at 267 nm (ε 4800) (Figure 3). In contrast, compound (**6a**) had a $\lambda_{max}$ value of 209 nm (ε 6400) and a second $\lambda_{max}$ at 308 nm (ε 7500).

To confirm our structural assignment, we compared the $^{1}$H NMR spectral values of **6b** with those reported for 4-methoxy-3,5-dimethylthiotetronic acid. Cruz-Almanza *et al.* prepared the 4-methoxy isomer using an unrelated and unambiguous synthetic route (*via* thiophene hydroxylation).[6] While, this synthetic path was not convenient for preparing diverse thiotetronic acid analogues, the reported $^{1}$H-NMR

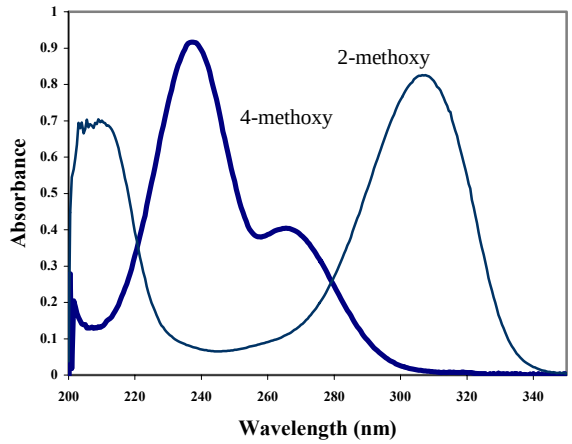



**Figure 3.** UV spectra of 2-methoxy- (**6a**, thin line) and 4-methoxy- (**6b**, thick line) 3,5-dimethylthiotetronic acid, recorded in MeOH at 25 °C.

spectral values confirmed the structure of **6b** as the 4-methoxy isomer. Therefore, the remaining compound (**6a**) was likely the 2-methoxy isomer. The structure of compound (**6a**) as the 2-methoxy isomer was verified by single crystal X-Ray analysis (Figure 4).[17]

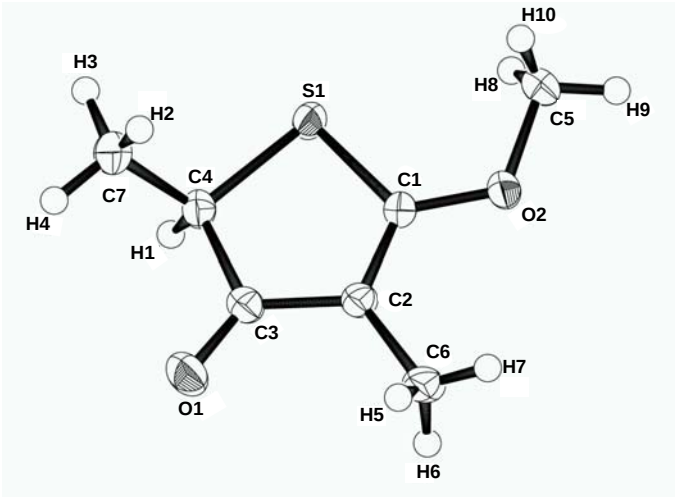



**Figure 4.** ORTEP drawing of compound (**6a**).[17]

Small differences in the NMR spectra of 2- versus 4-alkoxy compounds were also observed. These differences were occasionally useful during separation and structure validation, but were not general or large enough to confidently assign the structures of each isomer. In the $^{1}$H NMR spectrum, an allylic coupling ($J$ = 1.2 Hz) was observed in the spectra of 4-alkoxythiotetronic acids, but not in the corresponding 2-alkoxy compounds. This coupling does not occur in 5,5-disubstituted 4-alkoxy compounds, limiting its utility in assigning structure for those derivatives. The slightly greater ketone character of the C-4 carbon atom in **6a** was also apparent in the $^{13}$C NMR spectra. For example, C-4 in **6a** showed a slightly higher chemical shift (200.6 ppm) than C-2 in **6b** (196.0 ppm). The chemical shift of C-5 in **6a** was also higher (49.6 ppm) than that of C-5 in **6b** (41.9 ppm).

The $\lambda_{max}$ differences observed in **6a** and **6b** remained consistent throughout a series of 2- and 4-alkoxy-3,5-thiotetronic acid derivatives (Table 1). The 4-alkoxy isomers uniformly showed one distinct absorption between 235-240 nm, while the 2-alkoxy isomers had two absorbance peaks, one between 205-220 nm and the other between 305-310 nm. Examples found in the literature corroborate these absorption trends.[1-3,8,18] From these data, the 2- and 4-alkoxythiotetronic acids can therefore be distinguished easily and reliably based solely on their UV absorbance patterns.

The longer wavelength absorbance of the 2-alkoxy isomers could be due to the contribution of the sulfur atom to the resonance forms of these molecules. In the 2-alkoxy compounds, the lone pair electrons of the sulfur atom are conjugated with the α,β-unsaturated carbonyl system, effectively delocalizing these electrons through the five atoms of this structure (Figure 5). In contrast, the lone pair electrons of the sulfur atom in the 4-alkoxy compounds are cross-conjugated with the α,β-unsaturated system, delocalizing these electrons only through the adjacent carbonyl.

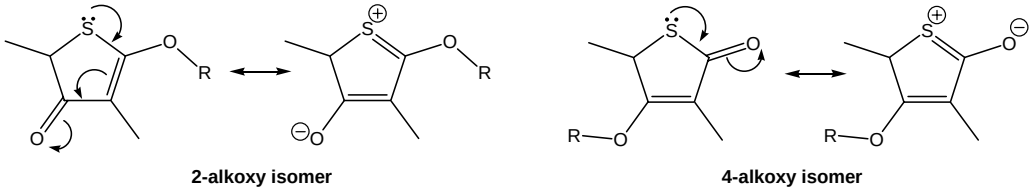



**Figure 5.** Resonance structures of 2- versus 4-alkoxy-3,5-dimethylthiotetronic acid.

Interestingly, 2- versus 4-alkoxy*tetronic* acids do not show this same dramatic difference in UV absorbance. For example, the $\lambda_{max}$ of 2-methoxy and 4-methoxy-3,5-dimethyltetronic acid are 256 nm (ε 100,000) and 229 nm (ε 12,880), respectively.[11] Similar values have been reported for other pairs of alkoxytetronic acids.[19-21]

## CONCLUSIONS

The UV absorption properties appear to be a general characteristic for distinguishing 2- from 4-alkoxythiotetronic acids. Thus, this work describes a reliable means of differentiating between these compounds. Because regioselective methods for their synthesis have yet to be developed, such a method of differentiation should facilitate the synthesis and biological evaluation of diverse 2- and 4-alkoxythiotetronic acids.

## EXPERIMENTAL

NMR spectra were recorded on a Mercury NMR spectrometer ($^{1}$H: 300 MHz, $^{13}$C: 75 MHz) using Varian VNMR 6.1c software. Deuterated chloroform was used as the solvent with TMS as an internal standard. The melting points were determined using an Electrothermal 9100 melting point apparatus and were uncorrected. Column chromatography was performed using silica gel 60 (Aldrich). MS were collected on a Hewlett Packard 5890A gas chromatograph with in-line MSD (HP 5972A) and a Hewlett Packard electrospray LC-MS 1100 with single quad detection. UV spectra were collected on a Beckman DU 640 spectrophotometer. Elemental analysis was performed by Atlantic Microlab (Norcross, GA USA). X-Ray structure determination was done using a Rigaku Saturn 70 area detector with graphite monochromated Mo-K$\alpha$ radiation.

Compound (**5**) was synthesized as described in the literature.[16] The NMR data of compounds (**7a, 7b**, **9a, 9b**, **10a**, and **10b**) reflect the presence of diastereomers. No attempt was made to separate diastereomeric mixtures.

### Procedures for synthesis of 6a and 6b.

Method A: A solution of 3,5-dimethylthiotetronic acid (**5**, 1.0 g, 6.9 mmol) in 40% tetrabutylammonium hydroxide in water (4.5 mL, 6.9 mmol) was stirred at rt for 1 h. The solvent was evaporated under reduced pressure. Recrystallization of the crude mixture from EtOAc gave the tetrabutylammonium (TBA) salt of **5** as a white powder in quantitative yield. The salt was dissolved in dichloromethane (30 mL), and dimethyl sulfate (0.83 mL, 8.7 mmol) was added dropwise at rt. The reaction mixture was stirred at rt for 1 h, and then the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (1x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (10% EtOAc in hexanes) afforded the products.

Method B: To a solution of 3,5-dimethylthiotetronic acid (**5,** 1.5 g, 10 mmol) in anhydrous THF (25 mL) was added the 1,3-dicyclohexyl-2-methylisourea (2.5 g, 10 mmol). The reaction mixture was heated at reflux for 18 h. The precipitated urea was filtered, and the solvent was removed under reduced

pressure to give the crude product. The product was purified by column chromatography (petroleum ether: EtOAc, 10:1.4) to give the products.

**2-Methoxy-3,5-dimethylthiotetronic acid (6a):** Yield from Method A: 0.12 g (11%); yield from Method B: 0.32 g (13%). White solid. mp = 59.0-59.7 ºC (from hexanes); $^{1}$H NMR δ 1.57 (d, *J* = 7.2 Hz, 3H), 1.69 (s, 3H), 3.82 (q, *J* = 7.2 Hz, 1H), 4.06 (s, 3H); $^{13}$C NMR δ 8.0 (C-3 Me or C-5 Me), 18.0 (C-3 Me or C-5 Me), 49.6 (C-5), 58.9 ($OCH_3$), 108.2 (C-3), 185.9 (C-2), 200.6 (C-4); GC-MS m/z 83 (100), 158 ($M^+$). Anal. Calcd for $C_7H_{10}O_2S$: C, 53.14; H, 6.37. Found: C, 53.29; H, 6.45.

**4-Methoxy-3,5-dimethylthiotetronic acid (6b):** Yield from Method A: 0.76 g (70%); yield from Method B: 0.73 g (30%). Slightly yellow oil. $^{1}$H-NMR δ 1.56 (d, *J* = 6.9 Hz, 3H), 1.84 (d, *J* = 1.2 Hz, 3H), 4.02 (s, 3H), 4.15, (qq, *J* = 6.9, 1.2 Hz, 1H); $^{13}$C-NMR δ 9.1 (C-3 Me or C-5 Me), 19.9 (C-3 Me or C-5 Me), 41.9 (C-5), 58.8 ($OCH_3$), 113.9 (C-3), 178.8 (C-4), 196.0 (C-2); GC-MS m/z 158 (100, $M^+$).

**General Procedure for the preparation of compounds (7-11).**

The appropriate alkyl halide was added to a solution of the TBA salt of **5** in THF (21 mL) and heated at reflux for 20 h. The solvent was removed *in vacuo*, and the residue was diluted with EtOAc. The solution was washed with 5% HCl and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (pet. ether/ EtOAc, 10:1.4) to give the two products.

***sec*-Butoxy:** 1.24 g (3.22 mmol) of the TBA salt of **5** and 0.35 mL (3.2 mmol) of 2-bromobutane. **2-*sec*-Butoxy-3,5-dimethylthiotetronic acid (7a).** Oil. Yield: 37 mg (5.8%). $^{1}$H NMR δ 0.987 (t, *J* = 7.8 Hz, 1.5H), 0.993 (t, *J* = 7.8 Hz, 1.5H), 1.40 (dd, *J* = 6.0, 2.1 Hz, 3H), 1.58 (d, *J* = 7.2 Hz, 3H), 1.64-1.84 (m, 2H), 1.70 (d, *J* = 0.9 Hz, 3H), 3.82 (q, *J* = 7.2 Hz, 1H), 4.49 (sextet, *J* = 6.0 Hz, 1H); GC-MS m/z 83 (100), 200 ($M^+$). **4-*sec*-Butoxy-3,5-dimethylthiotetronic acid (7b).** Oil. Yield: 0.19 g (31%). $^{1}$H NMR δ 0.94 (t, *J* = 7.5 Hz, 1.5H), 1.02 (t, *J* = 7.5 Hz, 1.5H), 1.23 (d, *J* = 5.7 Hz, 1.5H), 1.36 (d, *J* = 6.3 Hz, 1.5H), 1.56 (d, *J* = 6.3 Hz, 1.5H), 1.57 (d, *J* = 6.9 Hz, 1.5H), 1.60-1.77 (m, 2H), 1.79 (d, *J* = 1.5 Hz, 1.5H), 1.81 (d, *J* = 1.5 Hz, 1.5H), 4.10-4.20 (m, 1H), 4.42-4.59 (m, 1H); GC-MS m/z 145 (100), 200 ($M^+$).

**Isobutoxy:** 1.13 g (2.93 mmol) of the TBA salt of **5** and 0.37 mL (3.1 mmol) of 1-iodo-2-methylpropane. **2-Isobutoxy-3,5-dimethylthiotetronic acid (8a).** Oil. Yield: 14 mg (2.4%). $^{1}$H NMR δ 1.03, (d, *J* = 6.9 Hz, 6H), 1.57 (d, *J* = 7.5 Hz, 3H), 1.71 (s, 3H), 2.06-2.20 (m, 1H), 3.81 (q, *J* = 7.5 Hz, 1H), 4.02 (d, *J* = 6.6 Hz, 2H); GC-MS m/z 83 (100), 200($M^+$). **4-Isobutoxy-3,5-dimethylthiotetronic acid (8b).** Oil. Yield: 0.14 g (23%). $^{1}$H NMR δ 1.010 (d, *J* = 6.6

Hz, 3H), 1.014 (d, *J* = 6.9 Hz, 3H), 1.59 (d, *J* = 6.9 Hz, 3H), 1.85 (d, *J* = 0.9 Hz, 3H), 1.96-2.09 (m, 1H), 3.93 (d, *J* = 6.3 Hz, 0.5H), 3.95 (d, *J* = 6.3 Hz, 0.5H), 4.05 (d, *J* = 6.6 Hz, 0.5H), 4.08 (d, *J* = 6.3 Hz, 0.5H), 4.13-4.22 (m, 1H); GC-MS m/z 57 (100), 200 ($M^+$).

**1-Methylbutoxy:** 1.24 g (3.22 mmol) of the TBA salt of **5** and 0.397 mL (3.05 mmol) of 2-bromopentane. **2-(1-Methylbutoxy)-3,5-dimethylthiotetronic acid (9a).** Oil. Yield: 45 mg (6.8%). $^1$H NMR δ 0.957 (t, *J* = 7.2 Hz, 1.5H), 0.961 (t, *J* = 7.2 Hz, 1.5H), 1.38 (d, *J* = 2.4 Hz, 1.5H), 1.41 (d, *J* = 2.4 Hz, 1.5H), 1.42-1.86 (m, 4H), 1.57 (d, *J* = 7.5 Hz, 3H), 1.69 (s, 3H), 3.82 (q, *J* = 7.5 Hz, 1H), 4.55 (sextet, *J* = 6.0 Hz, 1H); LC-MS m/z 215 (M+1). **4-(1-Methylbutoxy)-3,5-dimethylthiotetronic acid (9b).** Oil. Yield: 0.19 g (29%). $^1$H NMR δ 0.93 (t, *J* = 6.9 Hz, 1.5H), 0.97 (t, *J* = 7.2 Hz, 1.5H), 1.23 (d, *J* = 6.0 Hz, 1.5H), 1.37 (d, *J* = 6.0 Hz, 1.5H), 1.42-1.80 (m, 4H), 1.56 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.80 (dd, *J* = 5.1, 1.2 Hz, 3H), 4.12-4.16 (m, 1H), 4.51-4.62 (m, 1H); LC-MS m/z 215 (M+1).

**1-Methylhexyloxy:** 1.24 g (3.22 mmol) of the TBA salt of **5** and 0.50 mL (3.2 mmol) of 2-bromoheptane. **2-(1-Methylhexyloxy)-3,5-dimethylthiotetronic acid (10a).** Oil. Yield: 51 mg (6.5%). $^1$H NMR δ 0.87-0.96 (m, 3H), 1.22-1.37 (m, 6H), 1.38 (d, *J* = 2.1 Hz, 1.5H), 1.40 (d, *J* = 2.1 Hz, 1.5H), 1.57 (d, *J* = 7.5 Hz, 3H), 1.68 (s, 3H), 1.71-1.82 (m, 2H), 3.81 (q, *J* = 7.5 Hz, 1H), 4.48-4.58 (m, 1H); GC-MS m/z 144 (100), 242 ($M^+$). **4-(1-Methylhexyloxy)-3,5-dimethylthiotetronic acid (10b).** Oil. Yield: 0.22 g (28%). $^1$H NMR δ 0.84-0.92 (m, 3H), 1.21 (d, *J* = 6.0 Hz, 1.5H), 1.24-1.76 (m, 8H), 1.34 (d, *J* = 6.0 Hz, 1.5H), 1.54 (dd, *J* = 6.9, 1.2 Hz, 3H), 1.77 (dd, *J* = 4.5, 0.6 Hz, 3H), 4.08-4.17 (m, 1H), 4.46-4.61 (m, 1H); GC-MS m/z 57 (100), 242 ($M^+$).

**3-Phenylpropoxy:** 1.24 g (3.22 mmol) of the TBA salt of **5** and 0.488 mL (3.15 mmol) of 1-bromo-3-phenylpropane. **2-(3-Phenylpropoxy)-3,5-dimethylthiotetronic acid (11a).** Oil. Yield: 46 mg (5.5%). $^1$H NMR δ 1.58 (d, *J* = 7.2 Hz, 3H), 1.72 (s, 3H), 2.10-2.20 (m, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 3.82 (q, *J* = 7.2 Hz, 1H), 4.27 (t, *J* = 6.3 Hz, 2H), 7.20-7.35 (m, 5H); GC-MS m/z 91 (100), 262 ($M^+$). **4-(3-Phenylpropoxy)-3,5-dimethylthiotetronic acid (11b).** Oil. Yield: 0.42 g (51%). $^1$H NMR δ 1.57 (d, *J* = 7.2 Hz, 3H), 1.84 (d, *J* = 1.2 Hz, 3H), 2.03-2.12 (m, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 4.10 (qq, *J* = 6.9, 1.2 Hz, 1H), 4.16 (dt, *J* = 9.6, 6.3 Hz, 1H), 4.30 (dt, *J* = 9.6, 6.0 Hz, 1H), 7.17-7.35 (m, 5H); GC-MS m/z 91 (100), 262 ($M^+$).

**ACKNOWLEDGEMENTS**

Lee Daniels of Rigaku/MSC (The Woodlands, TX USA) performed the X-Ray structure determination of compound (**6a**). This work was generously supported by GlaxoSmithKline.

**REFERENCES**


1. H. Sasaki, H. Oishi, T. Hayashi, I. Matsuura, K. Ando, and M. Sawada, *J. Antibiot.*, 1982, **35**, 396.
2. S. Omura, A. Nakagawa, R. Iwata, and A. Hatano, *J. Antibiot.*, 1983, **34**, 1781.
3. C. Rapp, G. Jung, C. Isselhorst-Scharr, and H. Zähner, *Liebigs Ann. Chem.*, 1988, 1043.
4. L. A. Dolak, T. M. Castle, S. E. Truesdell, and O. K. Sebek, *J. Antibiot.*, 1986, **39**, 26.
5. A. C. Price, K. –H. Choi, R. J. Heath, Z. Li, S. W. White, and C. O. Rock, *J. Biol. Chem.*, 2001, **276**, 6551.
6. R. Cruz-Almanza, T. Hernández-Quiroz, L. J. Breña-Valle, and F. Pérez-Flores, *Tetrahedron Lett.*, 1997, **38**, 183.
7. C. Corral and J. Lissavetzky, *J. Chem. Soc., Perkin Trans. I*, 1984, 2711.
8. R. Raap, *Can. J. Chem.*, 1968, **46**, 2255.
9. J. E. Schachtner, H. –D. Stachel, K. Polborn, and T. Anke, *Eur. J. Med. Chem.*, 1998, **33**, 309.
10. M. V. Budnikova and D. B. Rubinov, *Russ. J. Org. Chem.*, 2001, **37**, 1478.
11. R. Muntwyler and W. Keller-Schierlein, *Helv. Chim. Acta*, 1972, **55**, 2071.
12. H. Zimmer, A. Amer, C. Van Pham, and D. Grob Schmidt, *J. Org. Chem.*, 1988, **53**, 3368, and references therein.
13. F. Effenberger and J. Syed, *Tetrahedron: Asymmetry*, 1998, **9**, 817.
14. A. S. Wengel, T. Reffstrup, and P. M. Boll, *Tetrahedron*, 1979, **35**, 2181.
15. R. Schobert and S. Siegfried, *Synlett*, 2000, **5**, 686.
16. C. –L. J. Wang and J. M. Salvino, *Tetrahedron Lett.*, 1982, **25**, 5243.
17. Crystal data for compound (**6a**). $C_7H_{10}O_2S$, $M_w$ 158.21, triclinic, space group *P*-1 (#2); *Z*=4, *a*=7.8625(5), *b*=9.0901(7), *c*=11.9855(10) Å, α=81.749(7), β=75.796(7), γ=68.997(5)º; *V*=773.79(10) Å$^3$, *F*(000)=336.00; $D_x$=1.36 g/cm$^3$; $2\theta_{max}$=65.7° (Rigaku Saturn70 area detector with graphite monochromated Mo-Kα radiation), *R*=0.033 (2913 data with I>3σI, 261 parameters). The sample analyzed was a racemic mixture. Crystallographic data (excluding structure factors) for this structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC 217475). 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 email: deposit@ccdc.cam.ac.uk].
18. J. D. Schachtner, H. –D. Stachel, S. S. Chatterjee, H. Hauer, and K. Polborn, *Eur. J. Med. Chem.*, 1998, **33**, 665.
19. L. Trifonov, J. H. Bieri, R. Prewo, A. S. Dreiding, D. M. Rast, and L. Hoesch, *Tetrahedron*, 1982, **38**, 397.
20. W. Hofheinz and P. Schonhölzer, *Helv. Chim. Acta*, 1977, **60**, 1367.
21. G. Alfano, G. Cimino, and S. De Stefano, *Experientia*, 1979, **35**, 1136.