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Novel route to 5-position vinyl derivatives of thiolactomycin: olefination versus deformylation

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Abstract—Vinyl and diene derivatives of thiolactomycin have been prepared via Horner–Wadsworth–Emmons olefination from protected 5-formyl-3,5-dimethylthiotetronic acid. Several 4-position protecting groups and a variety of phosphonates were evaluated, with MOM protection and β-ketophosphonates yielding the highest ratio of the desired product to deformylated product.

Thiolactomycin (TLM, Fig. 1) is an antibacterial natural product with broad-spectrum activity originally isolated from a species of *Nocardia*.[1] The thiotetronic acid core structure and 5-position isoprene side chain of TLM are found in several other natural products including thiotetromycin, U68204, and 834-B1.[2] Thiotetronic acids inhibit fatty acid biosynthesis in both prokaryotes and eukaryotes and may have multiple therapeutic applications.[2,3i] Thus, significant synthetic efforts have been directed at TLM and its derivatives.[3] The antibiotic activity of TLM is the result of inhibition of important fatty acid biosynthetic enzymes, the β-ketoacyl ACP synthases.[4] These enzymes catalyze a Claisen condensation between malonyl-ACP and an acyl-CoA or acyl-ACP primer, elongating the growing fatty acyl chain by two carbon atoms. We have explored the SAR of the 5-position of TLM against condensing enzymes from both *Escherichia coli* (FabB) and *Mycobacterium tuberculosis* (KasA/B) and found that the double bonds of the TLM isoprene side chain play a critical role in determining the biological activity of this molecule.[3k] We therefore sought a facile synthetic route to diverse 5-vinyl derivatives of TLM.

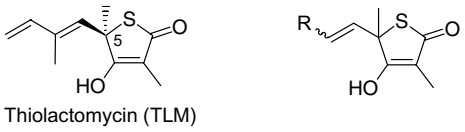

Figure 1. Structures of thiolactomycin and vinyl derivatives of 3,5-dimethylthiotetronic acid.

Previous methods of preparing 5-vinyl derivatives of TLM relied upon formation of the thiotetronic acid ring after generation of one or both double bonds of the isoprenoid chain.[3e,i,5] These linear routes offer limited potential for synthesis of large numbers of 5-vinyl TLM derivatives. Wang and Salvino prepared a 5-methacrolein derivative from **1** via a tandem aldol-type reaction followed by dehydration.[3a] This strategy led to the synthesis of racemic TLM but was very low yielding and allowed only limited diversity. We have focused on the discovery of novel synthetic routes for TLM derivatives that conserve the double bond closest to the thiolactone ring with the opportunity for preparation of small libraries of related compounds (Fig. 1). Herein, we report new routes to 5-vinyl and 5-diene derivatives of TLM starting from 3,5-dimethylthiotetronic acid (**1**).

Initially, we attempted to generate 5-vinyl derivatives using an aldol-type reaction of **1**[3a] with a variety of aldehydes, followed by dehydration (Scheme 1). The dianion of **1**, generated with LiHMDS, was reacted with selected aldehydes to obtain secondary alcohols at the 5-position in moderate to good yield. However, attempted dehydration of the resulting alcohols under a variety of conditions failed to give the corresponding 5-vinyl products. Instead, only the retroaldol-type reaction was observed, regenerating starting material **1**.

Keywords: Thiolactomycin; Olefination; Deformylation.
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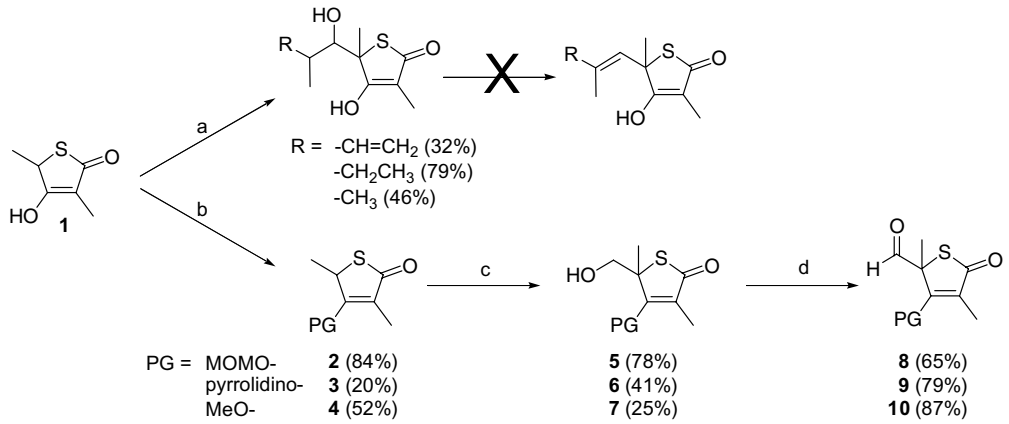


Scheme 1. Synthesis of protected aldehydes of 3,5-dimethylthiotetronic acid. Reagents and conditions: (a) LiHMDS (2.2 equiv), $RCH(CH_3)CHO$; (b) **2**: MOMCl, DIPEA, CH_2Cl_2, rt, 2 h; **3**: pyrrolidine, toluene, reflux, overnight; **4**: (i) nBu$_4$NOH (aq), rt, 1 h; (ii) Me_2SO_4, CH_2Cl_2, rt, 1 h; (c) (i) LiHMDS (1.1 equiv), THF, 0 °C, 30 min; (ii) paraformaldehyde, 0 °C→rt, 1 h; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h.

These results led us to prepare 5-formyl derivatives envisioning an olefination strategy that did not rely upon this problematic dehydration (Scheme 1). Neither direct formylation of **1** nor oxidation of the corresponding 5-hydroxymethyl compound were successful (not shown).[3k] Oxidation of primary alcohols at the 5-position of tetronic or thiotetronic acids has been previously reported to have been unsuccessful without first protecting the hydroxyl group at the 4-position.[3b,6] We explored three strategies for protecting the hydroxyl group of **1**. MOMCl and DIPEA were used to obtain **2**,[3k,7] pyrrolidine under reflux to obtain **3**,[8] and Me_2SO_4 with nBu$_4$NOH to obtain **4**.[3g,6] Hydroxymethylation of **2**–**4** using LiHMDS and paraformaldehyde successfully generated **5**–**7**.[8b] Oxidation of **5**–**7** with Dess–Martin periodinane gave protected aldehydes **8**–**10**.[9]

A variety of reaction conditions using aldehydes **8**–**10** were explored to generate the 5-position double bond. Simple Wittig[10] and Tebbe[11] reactions with **8** failed to give 5-vinyl products, and olefination attempts from **8** using phosphoranylidenes also did not afford the desired compounds, despite literature precedent for the latter reaction from the corresponding tetronic acid.[6] Treatment of compound **8** or **10** with simple alkylphosphonates and nBuLi/HMPA, failed to produce the desired products (Table 1, entries 1 and 2). Similar results were found using α-branched alkylphosphonates (not shown). The only products resulting from the above reactions were the deformylated products **2** and **4**.

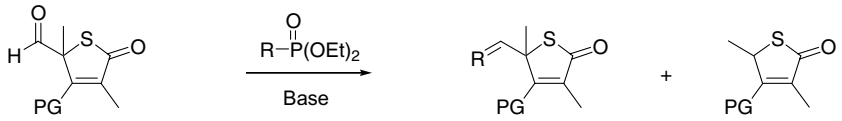
Horner–Wadsworth–Emmons (HWE) reactions using allylphosphonates were successful in generating the desired olefins but only in the case of pyrrolidine-protected aldehyde **9** (Table 1, entries 4 and 5).[12] Using diethyl allylphosphonate, *trans*-diene **11**[13] was formed in 31% yield whereas the deformylated product **3** was formed in 45% yield (entry 4). The yield for the reaction with the corresponding α-methyl phosphonate was dramatically lower (4%, entry 5), and the deformylated product **3** was the major product. Likewise, aldehydes **8** and **10** yielded only the undesired deformylated product (entry 3 and others not shown).

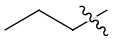
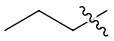
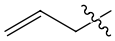
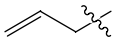
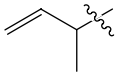
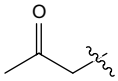
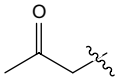
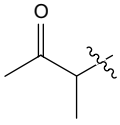
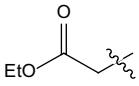
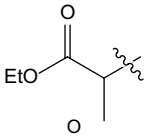
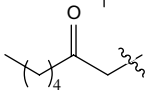
Both MOM- and pyrrolidino-protected aldehydes **8** and **9** gave the desired olefins with trans geometry using stabilized β-ketophosphonates and DIPEA/LiCl (Table 1, entries 6, 7, 9, and 11[14]). Unexpectedly, these products were the major ones formed in these reactions. The best results were obtained using MOM-protected aldehyde **8** with either diethyl (2-oxopropyl)phosphonate to give conjugated ketone **14** or dimethyl (2-oxoheptyl)phosphonate to give **16**. α-Branched-β-ketophosphonates,[15] unfortunately, yielded only deformylation product **2** when reacted with aldehyde **8** (entries 8 and 10).

The observation that olefination preferentially occurred using stabilized phosphonates led us to propose a mechanism for deformylation (Fig. 2). Production of the β-alkoxyphosphonate intermediate can result in two potential outcomes: formation of an oxygen–phosphorus bond leading to the desired olefin product (path a), or regeneration of the carbonyl bond giving rise to a retro-aldol-type reaction (path b). The latter pathway would be predicted to result in the release of an α-formylphosphonate and protected-3,5-dimethylthiotetronic acid. In the case of diethyl allylphosphonate, molecular ions for **3** and α-formylallylphosphonate were detected by LC/MS, and compound **3** was confirmed by NMR. For either phosphonate, we would expect generation of the aromatic thiophenoxide anion to contribute to the driving force for this side reaction.[16] Alternatively, allylic migration of the diethyl allylphosphonate anion would also lead to the deformylated product.

To demonstrate the utility of this chemistry in generating derivatives of TLM with a diene at the 5-position, we investigated the possibility of methylenation of HWE product **14** (Scheme 2). Wittig and Tebbe reaction conditions gave the desired products, while Nysted[17] and Peterson[18] methylenations did not. The Wittig reaction condition afforded a slightly lower yield than the Tebbe condition to generate compound **17**. The Tebbe reaction condition also gave the desired product **18**[19] from conjugated ketone **16**. Conjugated ester **15** did not generate the diene product under the Tebbe reagent condition. MOM deprotection of diene compounds **17**

Table 1. Products and yields from HWE reactions: olefination versus deformylation



Entry	R	Aldehyde (PG)	Base	Desired product (% yield)	Deformylation product (% yield)
1		**8** (MOMO-)	*n*BuLi/HMPA	—	**2** (only product)
2		**10** (CH_3O-)	*n*BuLi/HMPA	—	**4** (only product)
3		**8** (MOMO-)	*n*BuLi/HMPA	—	**2** (only product)
4		**9** (pyrrolidino-)	*n*BuLi/HMPA	**11** (31%)	**3** (45%)
5		**9** (pyrrolidino-)	*n*BuLi/HMPA	**12** (4%)	**3** (46%)
6		**9** (pyrrolidino-)	DIPEA/LiCl	**13** (19%)	**3** (10%)
7		**8** (MOMO-)	DIPEA/LiCl	**14** (48%)	**2** (18%)
8		**8** (MOMO-)	DIPEA/LiCl	—	**2** (only product)
9		**8** (MOMO-)	DIPEA/LiCl	**15** (30%)	**2** (21%)
10		**8** (MOMO-)	DIPEA/LiCl	—	**2** (only product)
11[a]		**8** (MOMO-)	DIPEA/LiCl	**16** (48%)	**2** (12%)

[a] Dimethyl (2-oxoheptyl)phosphonate was used.

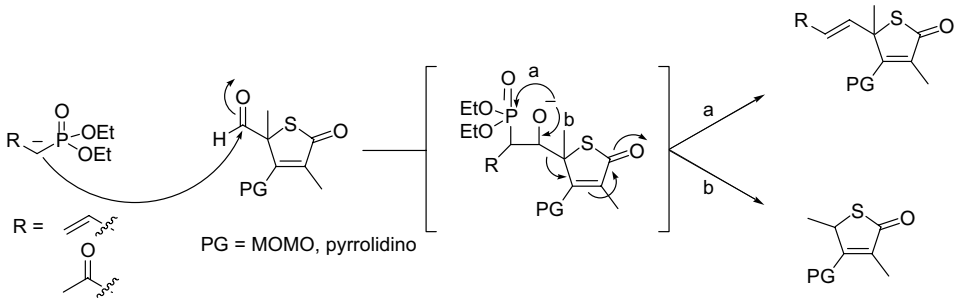
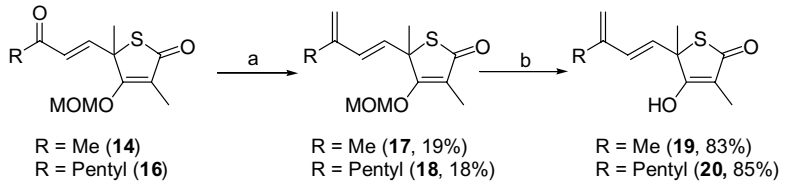


Figure 2. Proposed mechanism for olefination versus deformylation.

and **18** was accomplished using polymer-bound TsOH and silica gel in MeOH[3k] to afford diene compounds **19** and **20**.[20]

In summary, 5-vinyl derivatives of TLM were prepared via HWE olefination of MOM- and pyrrolidino-protected aldehydes (**8** and **9**) with stabilized phosphonates. Due to the pro-aromatic nature of these aldehydes, deformylation was always observed as the major competing side reaction. Deformylation was minimized using β-ketophosphonates in the presence of a mild base. 5-Position dienes were synthesized via methylena-



Scheme 2. Terminal double bond synthesis of TLM diene derivatives. Reagents and conditions: (a) Tebbe reagent, THF, −10 °C→0 °C, 3 h; (b) silica gel, polymer-bound TsOH, MeOH, rt, overnight.

tion of conjugated ketones, demonstrating the utility of this method in generating novel thiotetronic acid analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.058.

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13. 5-(Buta-1,3-dienyl)-3,5-dimethyl-4-(pyrrolidin-1-yl)-5*H*-thiophen-2-one (**11**): At −78 °C and under an argon atmosphere, 1.6 M *n*BuLi in hexanes (0.20 mL, 0.32 mmol) was added to a solution of diethyl allylphosphonate (57 mg, 0.32 mmol) in THF (0.5 mL). After stirring for 15 min, a solution of **9** (60 mg, 0.27 mmol) in THF and HMPA (1.3 mL; THF/HMPA = 10:1) was added. The reaction mixture was allowed to warm to rt, stirred overnight, quenched with H_2O, and extracted with EtOAc (2×). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Column chromatography using silica gel (EtOAc/hexanes = 1:7) afforded the title compound as a colorless oil (21 mg, 0.084 mmol, 31%)

as well as **3** (24 mg, 0.12 mmol, 45%). Compound **11**: ^{1}H NMR ($CDCl_3$) δ 1.76–1.98 (m, 4H), 1.91 (s, 3H), 1.99 (s, 3H), 3.48–3.74 (m, 4H), 5.09–5.13 (m, 1H), 5.19–5.24 (m, 1H), 5.93 (d, $J = 15.3$ Hz, 1H), 6.18 (dd, $J = 15.3$, 10.2 Hz, 1H), 6.35 (dt, $J = 16.8$, 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.3, 25.1, 25.5, 51.5, 56.5, 106.9, 118.0, 129.6, 135.4, 136.2, 169.9, 193.4; LC/MS: 250.1 ($M+H^+$), 272.0 ($M+Na^+$), 521.2 ($2M+Na^+$).

14. 3,5-Dimethyl-4-methoxymethoxy-5-((*E*)-3-oxooct-1-enyl)-5*H*-thiophen-2-one (**16**): To a solution of LiCl (120 mg, 2.8 mmol) in CH_3CN (4 mL) was added dimethyl (2-oxoheptyl)phosphonate (0.64 mL, 2.6 mmol) and DIPEA (0.40 mL, 2.2 mmol) at rt. To this mixture was added a solution of **8** (399 mg, 1.85 mmol) in CH_3CN (4 mL). The reaction mixture was stirred for 2 h at rt, quenched with H_2O, and extracted with EtOAc (2×). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Column chromatography using silica gel (EtOAc/hexanes = 1:20–1:10) afforded the title compound as a colorless oil (276 mg, 0.88 mmol, 48%) as well as **2** (43 mg, 0.23 mmol, 12%). Compound **16**: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, $J = 6.9$ Hz, 3H), 1.15–1.35 (m, 4H), 1.56 (quint, $J = 7.5$ Hz, 2H), 1.77 (s, 3H), 1.90 (s, 3H), 2.51 (t, $J = 7.5$ Hz, 2H), 3.45 (s, 3H), 5.23 (dd, $J = 7.5$, 6.3 Hz, 2H), 6.23 (d, $J = 15.6$ Hz, 1H), 6.75 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.0, 22.5, 23.5, 23.7, 31.4, 40.8, 56.1, 57.4, 96.1, 113.7, 129.1, 145.2, 175.3, 194.1, 200.1; HRMS (ESMS) calcd for $C_{16}H_{24}O_4S$ [$M+H^+$] 313.1474, found 313.1464.
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19. 3,5-Dimethyl-4-methoxymethoxy-5-(3-pentylbuta-1,3-dienyl)-5*H*-thiophene-2-one (**18**): At −10 °C and under an argon atmosphere, 0.5 M Tebbe reagent (0.50 mL, 0.25 mmol) in toluene was added to a solution of **16** (68 mg, 0.22 mmol) in THF (5 mL). The reaction mixture was allowed to warm to 0 °C, stirred for 3 h, quenched with 0.3 M NaOH (aq) at 0 °C, and extracted with EtOAc (3×). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Chromatography on preparative TLC (EtOAc/hexanes = 1:3) afforded the title compound as a slightly yellow oil (12 mg, 0.039 mmol, 18%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.26–1.28 (m, 4H), 1.42–1.51 (m, 2H), 1.81 (s, 3H), 1.94 (s, 3H), 2.14–2.19 (m, 2H), 3.49 (s, 3H), 5.00 (s, 1H), 5.03 (s, 1H), 5.25 (s, 2H), 5.75 (d, $J = 15.9$ Hz, 1H), 6.29 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.2, 22.7, 24.2, 27.9, 31.9, 32.1, 57.2, 57.3, 96.1, 113.5, 116.5, 129.5, 132.8, 145.5, 176.8, 195.6; HRMS (ESMS) calcd for $C_{17}H_{26}O_3S$ [$M+H^+$] 311.1681, found 311.1682.
20. 3,5-Dimethyl-5-(3-pentylbuta-1,3-dienyl)-5*H*-thiophene-2-one (**20**): To a solution of **18** (14 mg, 0.044 mmol) in MeOH (2 mL) was added silica gel (58 mg) and polymer-bound TsOH (28 mg, 0.056 mmol). The reaction mixture was allowed to stir at rt overnight, then was filtered and concentrated to give the title compound as a slightly yellow oil (10 mg, 0.038 mmol, 85%). ^{1}H NMR (MeOH-d_4) δ 0.91 (t, $J = 6.9$ Hz, 3H), 1.22–1.56 (m, 6H), 1.70 (s, 3H), 1.79 (s, 3H), 2.21 (td, $J = 7.8$, 0.9 Hz, 2H), 5.03 (m, 2H), 5.78 (d, $J = 15.6$ Hz, 1H), 6.31 (d, $J = 15.6$ Hz, 1H); HRMS (ESMS) calcd for $C_{15}H_{22}O_2S$ [$M+H^+$] 267.1419, found 267.1420.