



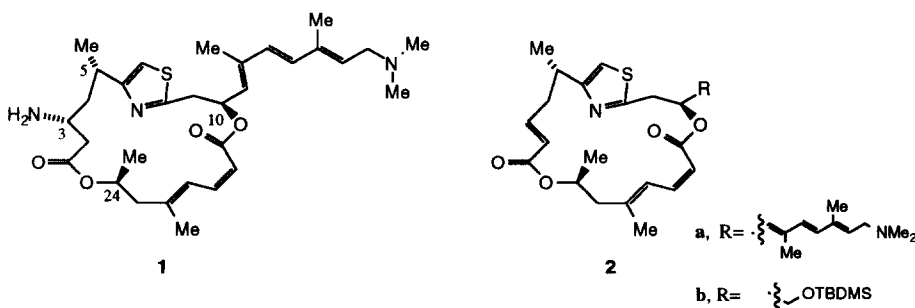
Synthetic Studies towards Pateamine, a Novel Thiazole-based 19-Membered Bis-lactone from *Mycale* sp

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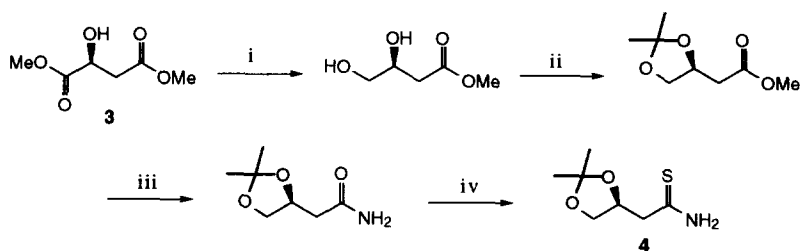
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Abstract: A concise synthesis of the 19-membered *bis*-lactone core **2b** present in pateamine **1** using chiral pool starting materials and featuring an intramolecular Stille coupling reaction as a key stratagem, is described. Copyright © 1996 Elsevier Science Ltd

Pateamine **1** is a strikingly unusual naturally occurring thiazole-based 19-membered *bis*-lactone structure which has been isolated from the marine sponge *Mycale* sp.¹ The compound has been found to possess potent *in vitro* antifungal activity as well as immunomodulatory properties. In addition to the novel *bis*-lactone functionality, the 19-membered ring in pateamine accommodates four asymmetric centres, an *E,Z*-1,3-diene unit, and is substituted by an unusual all-*E*-trienamine residue. Ammonia is easily lost from the natural product to reveal the Δ^2 -unsaturated pateamine **2a**.¹ A degradation study, complemented by synthetic work, has led to the assignment of the *S*-configuration at C24 in pateamine.² Furthermore, molecular modelling studies in association with 2-D nmr experiments³ have suggested that the most likely stereomodel for natural pateamine is that depicted in structure **1**, *ie* 3*R*, 5*S*, 10*S*, 24*S*. In this *Letter* we describe a concise synthesis of the 19-membered *bis*-lactone core **2b** found in pateamine, using chiral pool starting materials and featuring the intramolecular Stille coupling reaction as a key stratagem.

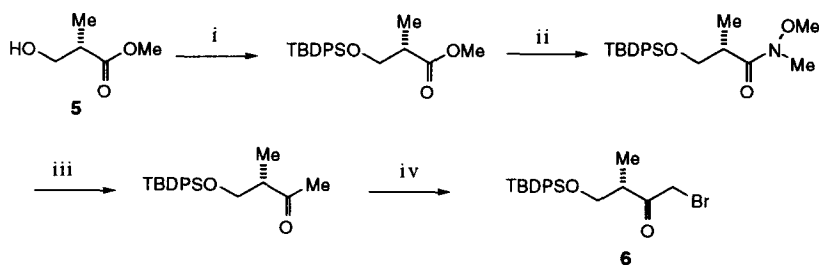


Thus, the 2,4-disubstituted thiazole **8** (Scheme 3) containing two of the chiral centres in the target molecule was first elaborated using a Hantzsch reaction between the thioamide **4** and the α -bromoketone **6**. In turn, the thioamide **4** was prepared from *S*-dimethyl malate **3**⁴ (Scheme 1), and the α -bromoketone **6** was prepared starting from commercially available *S*-methyl 3-hydroxy-2-methylpropanoate **5** (Scheme 2).



Reagents and Conditions: i, 1.1 eq. $\text{BH}_3\text{-SMe}_2$ complex, THF, r.t, 30 min, 5mol % NaBH_4 , $0^\circ\text{C}\rightarrow\text{r.t}$, 12 hr, 95%; ii, 2.0 eq. 2,2-dimethoxypropane, cat. pTsA. H_2O , CH_2Cl_2 , Δ , 2 hr, 69 %; iii, Excess conc. aqueous NH_3 solution, r.t, 24 hr, 96 %; iv. 0.55 eq. Lawesson's reagent, THF:benzene (1:1), Δ , 1 hr, 55 %.

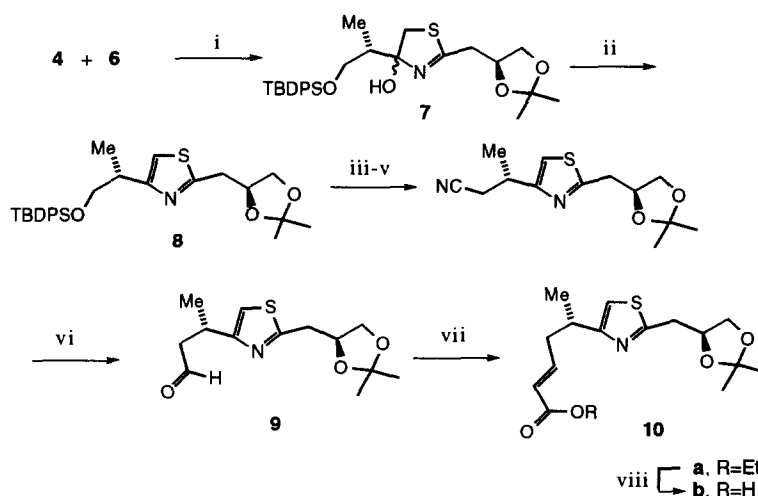
Scheme 1



Reagents and Conditions: i, 1.2 eq. TBDPS-Cl, 2.5 eq. imidazole, DMF, r.t, 12 hr, 96%; ii, 2.5 eq. AlMe_3 (2.0 M in toluene), 2.5 eq. *N*, *O*-dimethylhydroxylamine hydrochloride, CH_2Cl_2 , Δ , 4 hr, 60%; iii, 1.5 eq. MeMgBr , THF, 0°C , 1hr, 94%; iv, 1.5 eq. $\text{LiN}(\text{SiMe}_3)_2$, THF, -78°C , 1 hr, 3.0 eq. TMS-Cl , $-78^\circ\text{C}\rightarrow 0^\circ\text{C}\rightarrow 78^\circ\text{C}$, 2.0 eq. Br_2 , 30 min, 95% yield.

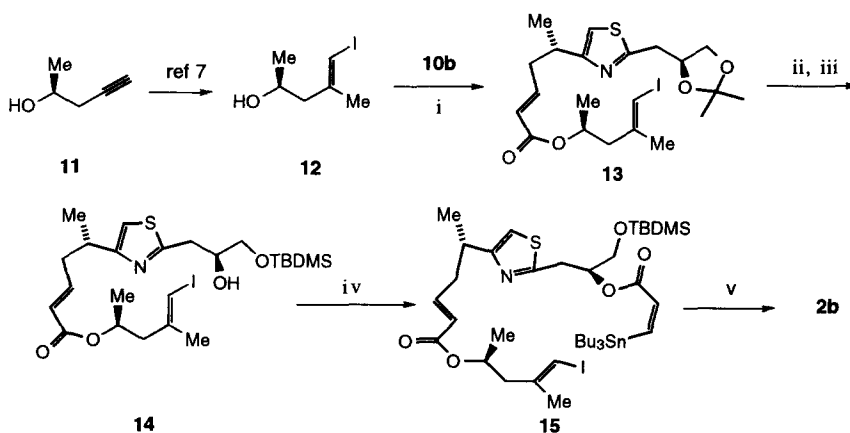
Scheme 2

The Hantzsch reaction⁵ between **4** and **6** then gave rise to the thiazole **8** (via **7**) which, following deprotection and one-carbon homologation, was next elaborated to the aldehyde **9**.⁶ A Wadsworth-Emmons condensation between **9** and triethyl phosphonoacetate then produced the *E*-unsaturated ester **10a** which was saponified to the corresponding carboxylic acid **10b** (Scheme 3) in readiness for coupling to the chiral alcohol **12**. The chiral alcohol **12** was readily obtained *via* a zirconium-catalysed carboalumination and iodination⁷ of the known alkyne **11**, using literature conditions.⁸ Esterification of the carboxylic acid **10b** with **12** under Steglich's conditions⁹ then led to **13** which, after manipulation of the protecting groups, was next converted into the secondary alcohol **14**. Esterification of *Z*-3-tributylstannylpropenoic acid¹⁰ with the alcohol **14**, under Yamaguchi conditions,¹¹ finally provided the vinyl stannane/vinyl iodide *bis*-ester precursor **15**⁶ for the projected intramolecular Stille coupling reaction leading to the pateamine core ring system **2b** (Scheme 4). Gratifying, when the stannane iodide **15** was treated with triphenylarsine and palladium(O) dibenzylideneacetone in DMF at 50°C for 2h (*ie* Farina conditions¹²) it underwent rapid $\text{sp}^2\text{-sp}^2$ coupling to produce the triene *bis*-lactone pateamine precursor **2b** in 72% yield,¹³ without any loss of stereochemical integrity about the double bonds participating in the macrocyclisation.¹⁴ Studies are now in hand to incorporate the C-3 β -amino unit and the (C10) triene amine side chain residue into **2b** and complete the total synthesis of pateamine **1**.



Reagents and Conditions: i, 8.0 eq. KHCO_3 , THF, r.t, 24 hr, 57%; ii, 1.1 eq. $(\text{CF}_3\text{CO})_2\text{O}$, 3.3 eq. pyridine, CH_2Cl_2 , 0°C , 5 min, 81%; iii, 1.1 eq. TBAF, THF, r.t, 14 hr; iv, 1.1 eq. methanesulfonyl chloride, 1.5 eq. triethylamine, CH_2Cl_2 , 0°C –r.t, 1 hr, 100%; v, 3.0 eq. NaCN, DMSO, 50°C , 3 hr, 88%; vi, 2.5 eq. DIBAL-H, PhCH_3 , -78°C – 0°C , 0°C , 2 hr, MeOH, H_2O , stirred with silica/EtOAc for 30 mins and then filtered, 92%; vii, 1.5 eq. triethyl phosphonoacetate, 1.5 eq. LiCl, 1.2 eq. DBU, acetonitrile, r.t, 15 min, 100%; viii, 1.5 eq. $\text{LiOH}\cdot\text{H}_2\text{O}$, THF:MeOH: H_2O (4:1:1), r.t, 4 hr, 100%.

Scheme 3



Reagents and Conditions: i, 1.2 eq. vinyl iodide **12**, 1.5 eq. DCC, 0.1 eq. DMAP, CH_2Cl_2 , 0°C to r.t, 12 hr, 56%; ii, 7.0 eq. 1,2-ethanedithiol, cat. pTsA. H_2O , CHCl_3 , Δ , 2 hr, 90%; iii, 3.0 eq. TBDMS-Cl, 12.0 eq. imidazole, DMF, r.t, 10 min, 81%; iv, 2.5 eq. 2,4,6-trichlorobenzoyl chloride, 2.6 eq. triethylamine, THF, r.t, then 1.0 eq. DMAP, toluene, 0°C to r.t, 3 hr, 63%; v, $\text{Pd}(0)$, Ph_3As , DMF, 50°C , 2 hr, 72%.

Scheme 4

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- All new compounds showed satisfactory spectroscopic data together with mass spectrometric data: Selected ^1H -nmr data: (a) Z- α,β -unsaturated ester **10a**: δH (CDCl_3 , 400MHz) 6.89 (1H, dm, $J=15.4$ Hz), 6.78 (1H, s), 5.82 (1H, d, $J=15.4$ Hz), 4.49 (1H, m), 4.17 (2H, q, $J=7.1$ Hz), 4.10 (1H, dd, $J=8.2$, 6.0 Hz), 3.76 (1H, dd, $J=8.2$, 6.4 Hz), 3.32 (1H, dd, $J=14.9$, 6.6 Hz), 3.11 (1H, m), 2.68 (1H, m), 2.45 (1H, m), 1.44 (3H, s), 1.38 (3H, s), 1.28 (3H, t, $J=7.1$ Hz). (b) vinyl stannane/vinyl iodide bis-ester **15**: δH (CDCl_3 , 400MHz) 7.21 (1H, d, $J=12.8$ Hz), 6.86 (1H, m), 6.76 (1H, s), 6.74 (1H, d, $J=12.8$ Hz), 5.96 (1H, s), 5.76 (1H, d, $J=15.6$ Hz), 5.28 (1H, m), 5.08 (1H, m), 3.78 (2H, m), 3.41 (1H, dd, $J=14.9$, 5.3 Hz), 3.32 (1H, dd, $J=14.9$, 7.0 Hz), 3.10 (1H, m), 2.70 (1H, m), 2.53 (1H, dd, $J=13.9$, 7.9 Hz), 2.40 (1H, m), 2.37 (1H, dd, $J=13.9$, 5.6 Hz), 1.86 (3H, s), 1.50 (6H, m), 1.30 (6H, m), 1.28 (3H, d, $J=6.7$ Hz), 1.22 (3H, d, $J=6.5$ Hz), 1.05-0.85 (15H, m), 0.90 (9H, s), 0.05 (3H, s), 0.04 (3H, s).
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- (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585; (b) Farina, V. *Pure & Appl. Chem.* **1996**, 68, 73.
- Data for the triene bis-lactone pateamine precursor **2b**: δH (500MHz; CDCl_3) 7.08 (1H, dm, $J=11.5$ Hz), 6.71 (1H, dd, $J=11.5$, 11.5 Hz), 6.69 (1H, s), 6.64 (1H, m), 5.65 (1H, dm, $J=16.5$ Hz), 5.49 (1H, d, $J=11.5$ Hz), 5.38 (1H, m), 5.05 (1H, m), 3.81 (1H, dd, $J=10.9$, 4.9 Hz), 3.75 (1H, dd, $J=10.9$, 4.8), 3.31 (1H, dd, $J=14.3$, 2.3), 3.14 (1H, dd, $J=14.3$, 11.4), 3.01 (1H, m), 2.67 (1H, ddd, $J=14.7$, 10.0, 10.0), 2.46 (1H, dm, $J=14.7$), 2.41 (1H, dd, $J=13.0$, 11.3), 2.13 (1H, dm, $J=13.0$), 1.80 (3H, d, $J=0.8$ Hz), 1.32 (3H, d, $J=7.0$ Hz), 1.26 (3H, d, $J=6.1$), 0.91 (9H, s), 0.09 (3H, s), 0.08 (3H, s). δC (125MHz; CDCl_3) 166.4 (s), 166.2 (s), 164.8 (s), 159.6 (s), 146.3 (d), 144.5 (s), 140.8 (d), 124.7 (d), 122.9 (d), 114.9 (d), 113.3 (d), 72.4 (d), 67.5 (d), 64.9 (t), 47.3 (t), 39.2 (t), 35.9 (d), 35.3 (t), 25.9 (3xq), 21.6 (q), 21.0 (q), 18.3 (s), 16.8 (q), -5.3 (2xq). HRMS (FAB): Calc. for $\text{C}_{27}\text{H}_{42}\text{NO}_5\text{SiS}$ ($\text{M}+\text{H}^+$): 520.2553, found m/z 520.2583.
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