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

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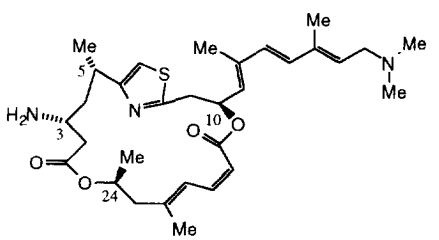
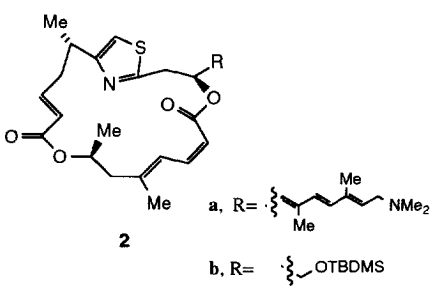
Abstract: A concise synthesis of the 19-membered *bis*-lactone core **2b** present in pateamine **1** using chiral pool starting materials and featuring an intramolecular Stille coupling reaction as a key stratagem, is described. Copyright © 1996 Elsevier Science Ltd

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 experiments[3] 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.

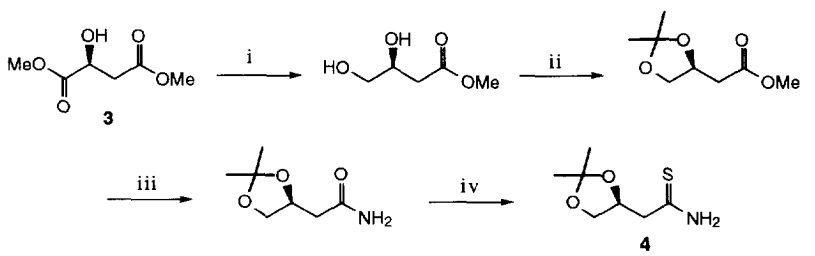


1



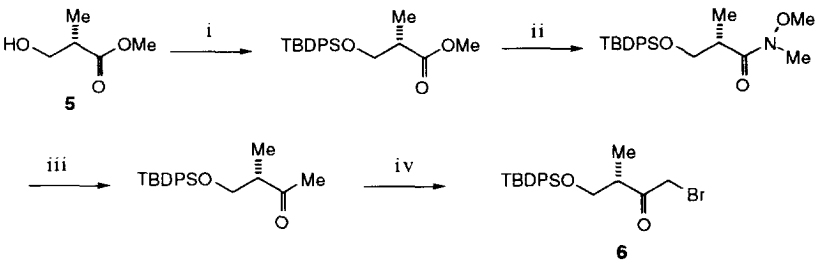
2

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. BH_3-SMe_2 complex, THF, r.t, 30 min, 5mol % $NaBH_4$, 0°C→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 %.

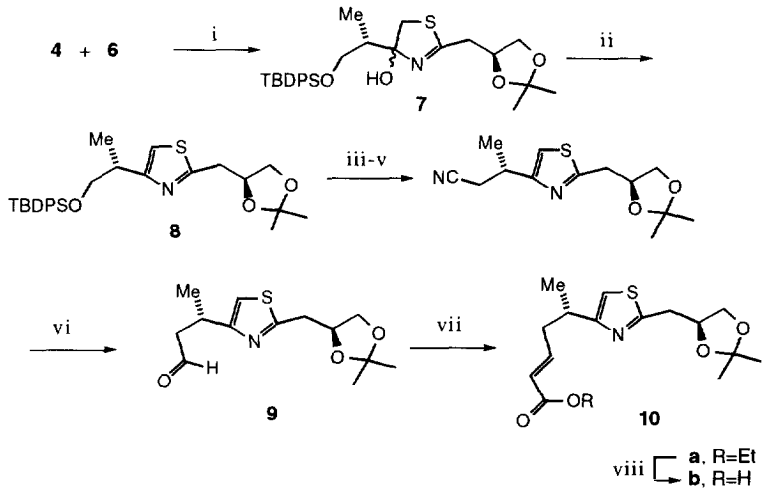
Scheme 1



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. $LiN(SiMe_3)_2$, THF, -78°C, 1 hr, 3.0 eq. TMS-Cl, -78°C→0°C→-78°C, 2.0 eq. Br_2, 30 min, 95% yield.

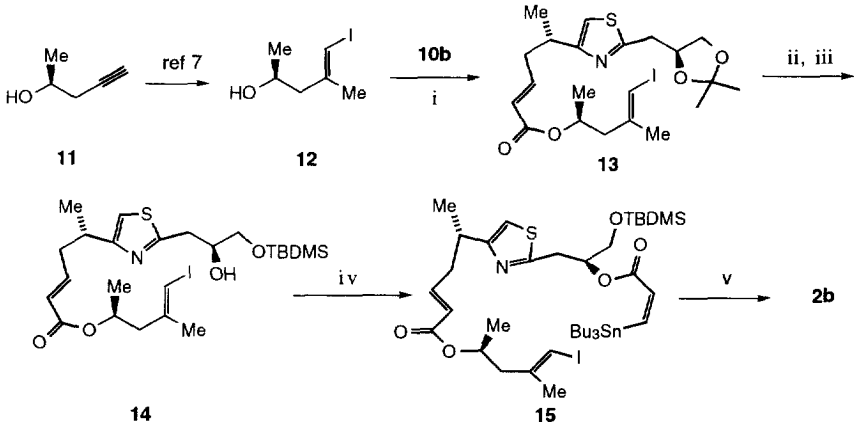
Scheme 2

The Hantzsch reaction[5] 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 iodination[7] of the known alkyne **11**, using literature conditions.[8] Esterification of the carboxylic acid **10b** with **12** under Steglich's conditions[9] then led to **13** which, after manipulation of the protecting groups, was next converted into the secondary alcohol **14**. Esterification of *Z*-3-tributylstannylpropenoic acid[10] 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 conditions[12]) it underwent rapid sp^2-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. $(CF_3CO)_2O$, 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. $LiOH.H_2O$, 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 1.0eq. DMAP, toluene, 0°C to r.t, 3 hr, 63%; v, Pd(0), Ph_3As, DMF, 50°C, 2 hr, 72%.

Scheme 4

Acknowledgements: We thank the EPSRC and Zeneca Strategic Funding for support of this research. We also thank Dr J M Clough (Zeneca Agrochemicals) for his interest in this study.

References and Notes

1. Northcote, P. T.; Blunt, J. W.; Munroe, M. H. G. *Tetrahedon Lett.* **1991**, 32, 6411.
2. Rzasa, R. M.; Romo, D.; Stirling, D. J.; Blunt, J. W.; Munroe, M. H. G. *Tetrahedron Lett.* **1995**, 36, 5307.
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5. For the Holzapfel modification of the Hantzsch thiazole synthesis see: (a) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Syn. Commun.* **1990**, 20, 2235; (b) Bredenkamp, M. W.; Holzapfel, C. W.; Synman, R. M; van Zyl, W. J. *Synth. Commun.* **1992**, 22, 3029. This procedure has previously been used in our laboratories, see: (c) Pattenden, G.; Thom, S. M. *Synlett*, **1993**, 215; (d) Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett*, **1995**, 417.
6. All new compounds showed satisfactory spectroscopic data together with mass spectrometric data:

   Selected ^{1}H-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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9. Neises, B.; Steglich, W. *Angew. Chem Int. Ed. Engl.* **1978**, 17, 522.
10. Ethyl Z-3-(tributylstannyl)propenoate was prepared from ethyl propiolate, see: Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B.; *J. Chem. Soc. Perkin Trans. 1*, **1994**, 1689. Saponification of the ethyl ester with lithium hydroxide then gave *Z*-3-tributylstannylpropenoic acid.
11. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989.
12. (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585; (b) Farina, V. *Pure & Appl. Chem.* **1996**, 68, 73.
13. 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 $C_{27}H_{42}NO_5SiS$ ($M+H^+$): 520.2553, found *m/z* 520.2583.
14. For intramolecular Stille reactions applied to natural product synthesis from our laboratories, see for example: (a) ref. 5(c) above; (b) Boyce, R. J.; Pattenden, G. *Tetrahedron Lett.*, **1996**, 37, 3501; (c) Entwistle, D. A.; Jordon, S. I.; Montgomery, J.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1*, **1996**, 1315. Reference 14(c) also provides a bibliography of other examples of the use of the intramolecular Stille reaction in synthesis.

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