Pergamon

Tetrahedron Letters 41 (2000) 7367–7371

TETRAHEDRON LETTERS

Total synthesis of (–)-pateamine, a novel polyene bis-macrolide with immunosuppressive activity from the sponge *Mycale* sp.

Modesto J. Remuiñán and Gerald Pattenden*

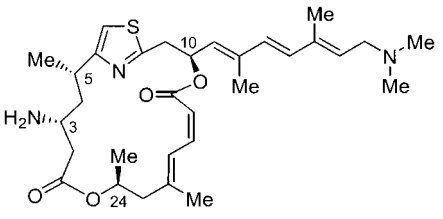
School of Chemistry, The University of Nottingham, Nottingham NG7 2RD, UK

Received 5 June 2000; accepted 20 July 2000

Abstract

A concise and convergent synthesis of the polyene thiazole-containing 19-membered bis-lactone (−)-pateamine **1** is described. The synthesis features both the intra- and intermolecular Stille sp^2–sp^2 coupling reactions to elaborate the *E,Z*-diene macrolide core and the side-chain all-*E* polyene portion of the natural product, and highlights the scope for enantiopure sulfinimine intermediates in the synthesis of chiral β-amino ester moieties in complex structures.

Pateamine **1** is a unique thiazole-containing 19-membered-bis-lactone isolated from the marine sponge *Mycale* sp.[1] The compound exhibits potent immunosuppressant properties with low cytotoxicity.[1,2] The bis-lactone core in pateamine accommodates four asymmetric centres together with an *E,Z*-1,3-diene unit, and is substituted by an unusual all-*E* trienamine residue. Degradative studies, in tandem with synthetic work and NMR measurements, have led to the stereochemical assignment shown in structure **1**, to naturally occurring (–)-pateamine,[3] and this assignment has been vindicated by total synthesis.[4] In an earlier communication we described a



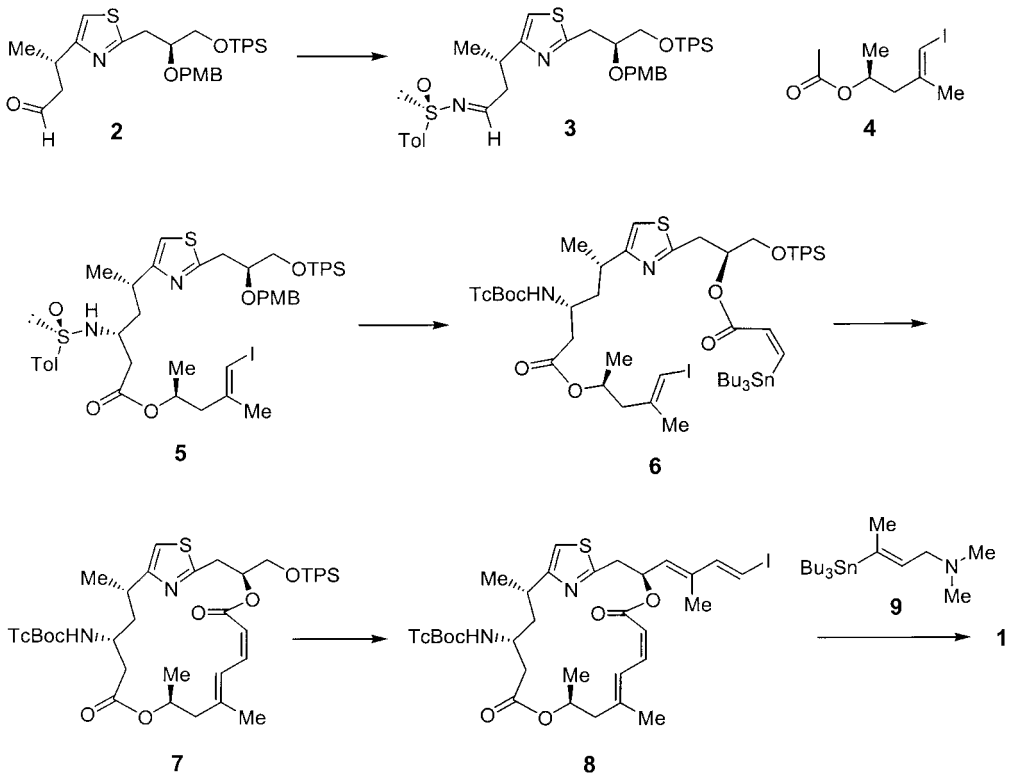
1

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01241-7

concise approach to the 19-membered bis-lactone core in pateamine.[5] In this Letter we summarise the extension to this study, culminating in a total synthesis of this intriguing secondary metabolite.

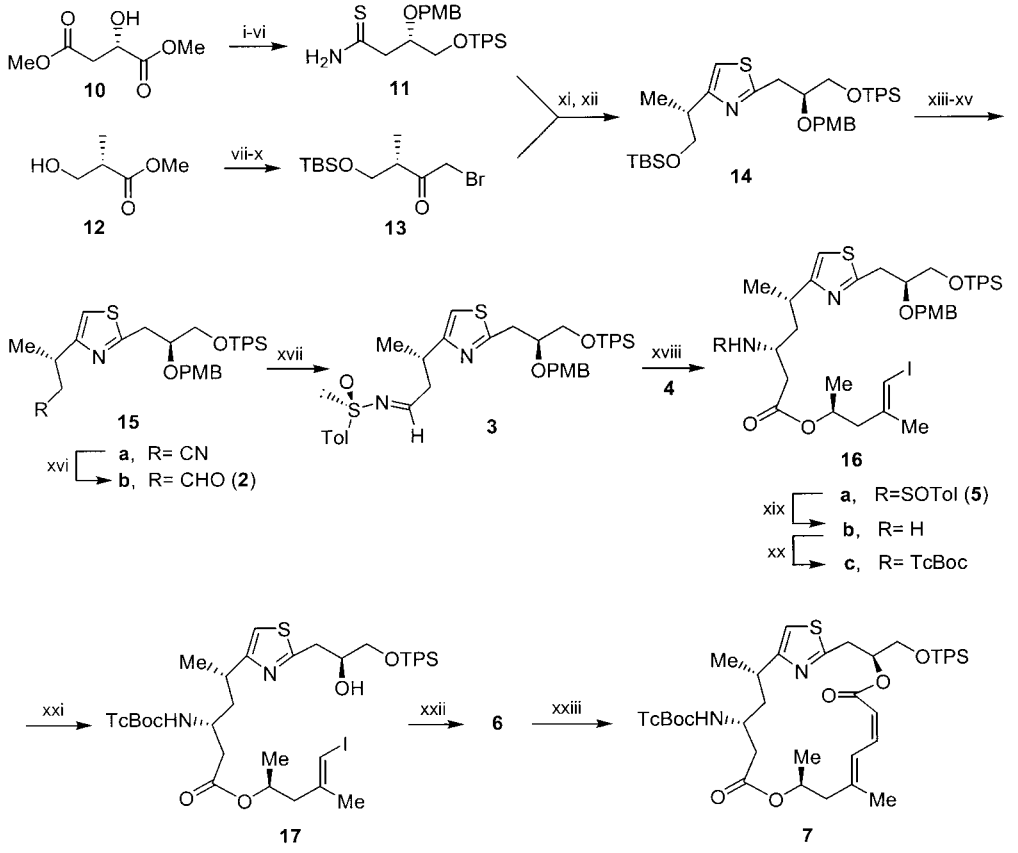
The synthetic approach we adopted to pateamine **1** was based on: (i) elaboration of the thiazole propanal **2** from chiral pool starting materials; (ii) conversion of the propanal **2** to the β-amino ester **5** via the corresponding enantiopure sulfinimine **3** and reaction with the enolate derived from the acetate **4**; (iii) elaboration of **5** to **6** followed by an intramolecular Stille coupling reaction leading to the bis-lactone core **7**; and finally (iv) homologation of the side chain in **7** to the vinyl iodide **8** and an intermolecular Stille reaction with the aminostannane **9** (Scheme 1).



Scheme 1.

Thus, starting with commercially available dimethyl L-malate **10** and (*S*)-methyl 3-hydroxy-2-methylpropionate **12**, the thioamide **11** and the α-bromoketone **13,** respectively were first elaborated using well established methods. A modified Hantzsch thiazole synthesis,[6] between **11** and **13**, next produced the substituted thiazole **14**. Cleavage of the TBS protecting group in **14** followed by a one carbon homologation from the resulting alcohol, via the nitrile **15a**, then led to the thiazole propanal intermediate **15b** (≡**2**) (Scheme 2). Using the procedure described by Davis et al.[7a] treatment of the aldehyde **2** with (*R*)-*p*-toluenesulfinamide in the presence of titanium ethoxide at 50°C next led to the sulfinimine **3** (64%) which, on reaction with the enolate derived from the chiral acetate **4**[8] at –78°C, gave the substituted β-amino ester **16a** with 85% diastereoselectivity in 63% yield.[7b] Cleavage of the *p*-toluenesulfinyl group in **16a**, by treatment with TFA-methanol, then provided the free β-amino ester **16b** whose configuration was established unambiguously using the NMR spectroscopic procedure reported by Riguera et al.[9] The amine **16b** was

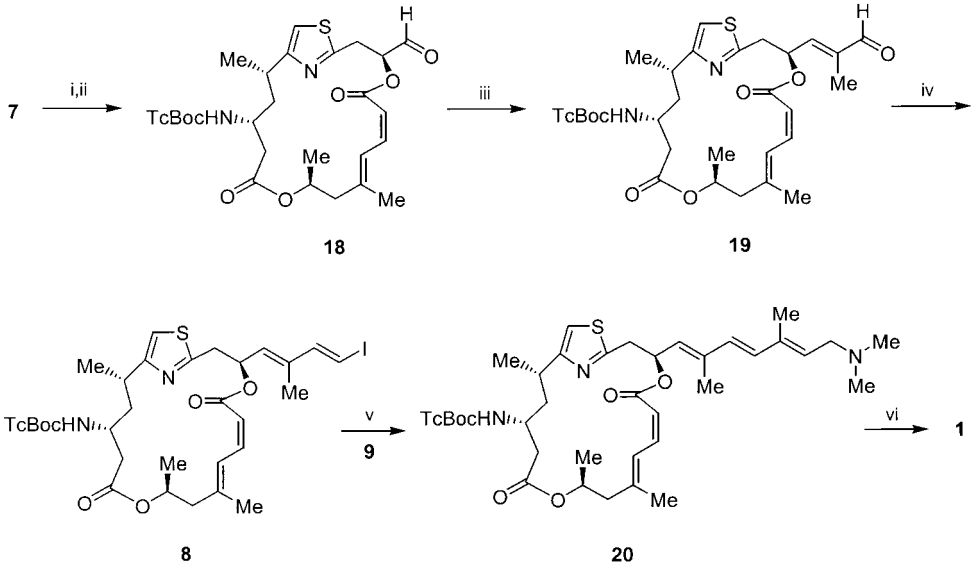
next protected as the corresponding TcBoc carbamate **16c** prior to cleavage of the PMB ether, leading to the carbinol **17**. Esterification of *Z*-3-tri-*n*-butylstannylpropenoic acid[10] with the resulting secondary alcohol **17** under Yamaguchi conditions[11] then led to the key intermediate **6**. When the stannane-iodide **6** was treated with Ph_3As–Pd(0) dibenzylideneacetone in DMF at 55°C[12] for 1 h, it underwent smooth sp^2–sp^2 coupling with complete preservation of the *E*/*Z* stereochemistry in the starting material leading to the 19-membered bis-lactone diene core **7** in pateamine in 65% yield (Scheme 2).



Scheme 2. **Reagents and conditions:** (i) $BH_3{\cdot}SMe_2$, $NaBH_4$, THF, 92%; (ii) TPSCl, Et_3N, DMAP, DCM, rt, 12 h, 93%; (iii) PMBoc(=NH)CCl_3, CSA, DCM, rt, 3 days, 76%; (iv) LiOH, H_2O/THF, rt, 12 h, 90%; (v) $ClCO_2Et$, Et_3N, NH_4OH, rt, 30 min, 93%; (vi) Lawesson's reagent, THF, rt, 30 min, 99%; (vii) TBSCl, Et_3N, DMAP, DCM, rt, 24 h, 95%; (viii) HNMeOMe·HCl, $AlMe_3$, DCM, Δ, 5 h, 61%; (ix) 1.5 equiv. MeMgBr, THF, 0°C, 1 h, 94%; (x) LiHMDS, –78°C, TMSCl, Br_2, 86%; (xi) 2,6-lutidene, DCM, rt, 12 h; (xii) $(CF_3CO)_2O$, Py, DCM, –30°C, 30 min, 64% (two steps); (xiii) AcOH/THF/H_2O, rt, 12 h, 92%; (xiv) MsCl, Et_3N, DCM, 0°C, 1 h; (xv) NaCN, DMSO, 60°C, 6 h, 77% (two steps); (xvi) DIBAL, toluene, 0°C, 2 h, 85%; (xvii) (*R*)-tolylsulfinamide, $Ti(OEt)_4$, DCM, 50°C, 4 h, 64%; (xviii) LiHMDS, THF, –78°C, 10 min, 63%; (xix) TFA, MeOH, rt, 4 h, 95%; (xx) TcBocCl, Py, DCM, 0°C, 2 h, 89%; (xxi) DDQ, DCM, H_2O, rt, 2 h, 87%; (xxii) (*Z*)-3-tributylstannylpropenoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, –30°C, 1 h, 67%; (xxiii) $Pd(dba)_2$, Ph_3As, DMF, 55°C, 1 h, 65%

A number of procedures to install the all-*E*-trienamine side chain in pateamine, starting from the substituted bis-lactone **7**, were examined. Ultimately, we used a route which proceeded via the vinyl iodide **8** and featured an intermolecular Stille coupling with the vinylstannane **9**.

Thus, deprotection of **7** followed by oxidation of the resulting alcohol using the pyridine-buffered Dess–Martin procedure first led to the aldehyde **18** (Scheme 3). Homologation of **18** using 2-(triphenylphosphoranylidene)propionaldehyde next gave the *E*-α,β-unsaturated aldehyde **19** exclusively, which was then converted into the all-*E*-iodotriene **8** using the procedure of Takai.[13] Treatment of a mixture of **8** and **9** with $Pd(CH_3CN)_2Cl_2$[14] in DMF at room temperature for 6 h resulted in their smooth coupling[15] and the formation of TcBoc pateamine **20**, $[\alpha]^{24}{}_D$ –235.0 (c 0.1, $CHCl_3$), which had identical spectroscopic properties to those of the same compound prepared by a different route by Romo et al. [Lit.[4] $[\alpha]^{26}{}_D$ –243.5 (c 0.46, $CHCl_3$)]. Finally, deprotection of **20**, following the procedure of Ciufolini et al.[16] using a Cd/Pb couple with NH_4OAc, gave (–)-pateamine **1** showing NMR spectroscopic and chiroptical data which were identical to those described for the natural product.



Scheme 3. **Reagents and conditions:** (i) TBAF, AcOH, THF, rt, 24 h, 78%; (ii) Dess–Martin, Py, DCM, 2 h, rt, 70%; (iii) 2-(triphenylphosphoralidene)propionaldehyde, 3 h, Δ, 73%; (iv) $CrCl_2$, CHI_3, THF, 1.5 h, rt, 68%; (v) $Pd(CH_3CN)_2Cl_2$, DMF, rt, 6 h, 36%; (vi) 10% Cd–Pb, 1 M NH_4OAc, THF, rt, 5 h, 73%

Acknowledgements

We thank the EU for a Marie Curie Fellowship (to M.J.R.) and Pfizer Ltd (purchase of consumables) for their support of this work.

References

1. Northcote, P. T.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett*. **1991**, *32*, 6411.
2. See also references cited in Ref. 4 below.
3. Rzasa, R. M.; Romo, D.; Stirling, D. J.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett*. **1995**, *36*, 5307.
4. Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc*. **1998**, *120*, 12237.
5. Critcher, D. J.; Pattenden, G. *Tetrahedron Lett*. **1996**, *37*, 9107.

6. (a) Brendenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1992**, *22*, 3029. (b) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473.
7. (a) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403. (b) For a review of the chemistry of sulfinimines, see: Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13.
8. The acetate **4** was prepared from the corresponding alcohol which has been described previously (see Ref. 5).
9. López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724.
10. Ethyl *Z*-3-(tributylstannyl)propenoate was prepared from ethyl propiolate, see: Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. Saponification of the ethyl ester with lithium hydroxide then gave *Z*-3-(tributylstannyl)propenoic acid.
11. Inanaga, J.; Hirata, K.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
12. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
13. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
14. (a) Rudisill, D. E.; Castonguay, L. A.; Stille, J. K. *Tetrahedron Lett.* **1988**, *29*, 1509. (b) Smith III, A. B.; Maleczka, R. E.; Leazer Jr., J. L.; Leahy, J. W.; McCauley, J. A.; Condon, S. M. *Tetrahedron Lett.* **1994**, *35*, 4911.
15. A similar Stille coupling reaction was used by Romo et al. in their synthesis of pateamine (see Ref. 4).
16. Dong, Q.; Anderson, C. E.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 5681. This method was also used by Romo et al. in their synthesis of pateamine (see Ref. 4).