COMMUNICATION

Total synthesis of the polyenoyltetramic acid mycotoxin erythroskyrine †

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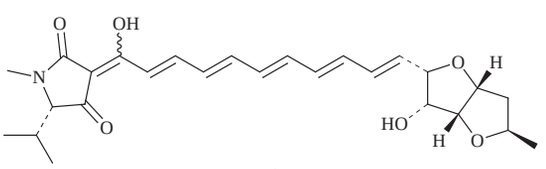
Received (in Cambridge) 16th December 1998, Accepted 22nd December 1998

The first total synthesis of erythroskyrine, a polyenoyltetramic acid mycotoxin and principal pigment of *Penicillium Islandicum* Sopp., is described using a palladium(II) catalysed oxycarbonylation to create the furan-derived bicyclic portion 3 and the phosphonate ester 5 to furnish both the polyenoyl chain and the *N*-methyl (*S*)-valine derived tetramic acid terminus.

The family of naturally occurring compounds containing the acyltetramic acid moiety enjoys a wealth of additional structural features together with a diversity of biological activity which includes antibiotic, antiviral, antitumour and antiulcerative properties. This together with the growing number of tetramic acids has attracted a great deal of interest from chemists over the years.[1]

A notable member of this class of natural products is erythroskyrine **1**, a polyenoyltetramic acid and the principal pigment



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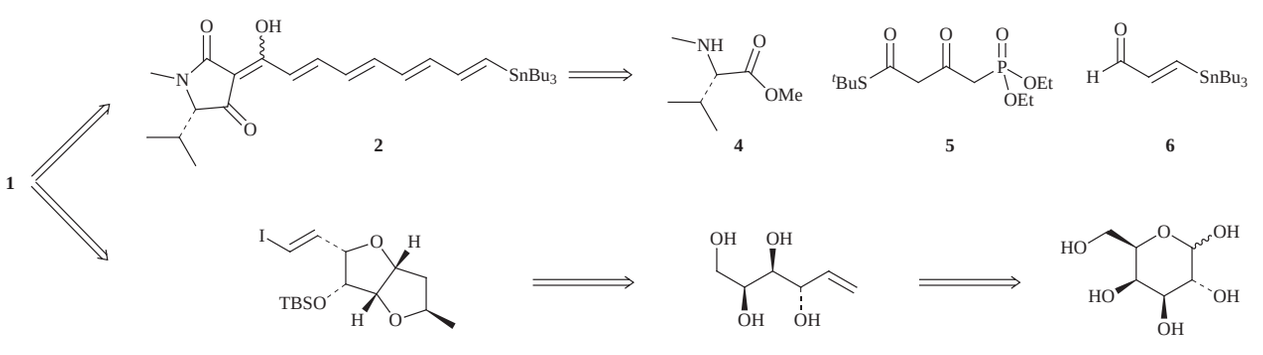
of *Penicillium Islandicum* Sopp., first isolated by Howard and Raistrick in 1949[2] and again in 1954.[3] Erythroskyrine is a mycotoxin which exhibits antibiotic action against several *Staphylococcus* species.[3] Reisolation of erythroskyrine in 1964 by Shoji *et al.*[4] allowed partial structure elucidation, but it was not until 1988 that an unambiguous absolute and relative stereochemical assignment of **1** was obtained by Beutler and co-workers.[5] As well as containing an *N*-methyl (*S*)-valine derived acyltetramic acid terminus, erythroskyrine was found to contain a central fully conjugated all (*E*)-pentaene chain attached to a furan derivative. Its unique and challenging structure has eluded a total synthesis to date, although two reports on the synthesis of the furan derivative have recently appeared in the literature.[6,7]

Owing to these interesting structural motifs and the potential to exploit methods developed in our individual groups we embarked on a collaborative synthetic project towards this natural product. Here we wish to report the first total synthesis of erythroskyrine **1**.

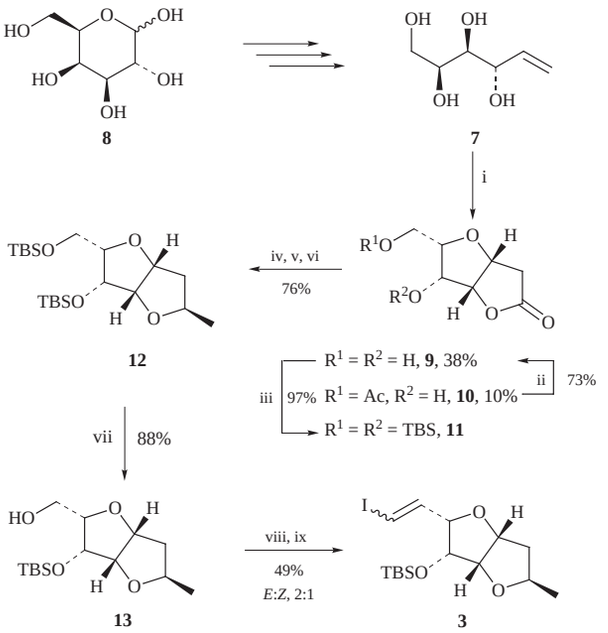
Our analysis of the synthetic problem suggested a convergent coupling of two key components; namely a suitably protected furan derivative **3** bearing an (*E*)-vinyl iodide side chain with an acyltetramic acid polyene fragment **2** bearing a tributyltin group at its terminus. Fragment **2** in turn was clearly available from *N*-methyl (*S*)-valine methyl ester **4**,[8] phosphonate ester **5**[9] and a β-tributylstannyl acrolein unit **6**[10] while fragment **3** could be prepared using a palladium(II) catalysed oxycarbonylation of D-galactose **8** derived tetraol **7**.

The preparation of the furan derivative **3** began with tetraol **7** which was readily prepared from commercially available D-galactose in five steps using the literature procedures.[11] This material was subjected to our recently reported palladium(II) catalysed oxycarbonylation reaction affording the desired bicyclic lactone **9**[12] in 38% yield and the acetylated derivative **10** in 10% yield. Treatment of **10** with sodium carbonate in absolute methanol at room temperature resulted in a smooth deacetylation (73%) affording a further quantity of **9**. Lactone **9** possessed the correct relative and absolute stereochemistry for the natural product and in addition contained suitable functionality necessary for further transformation to the vinyl iodide **3**.

Protection of the free hydroxy groups in **9** with *tert*-butyldimethylchlorosilane and imidazole in dimethylformamide at 40 °C overnight gave **11** in 97% yield. A highly stereoselective incorporation of the *exo*-methyl group at C2 was then possible using a three step sequence. Partial reduction of the lactone using diisobutylaluminium hydride (2 equiv.) in toluene at −78 °C afforded a crude mixture of lactols which in turn was treated with acetic anhydride (2 equiv.) and 4-dimethylaminopyridine (3 equiv.) in dichloromethane at 0 °C to give the



1 **2** **3** **4** **5** **6** **7** **8**



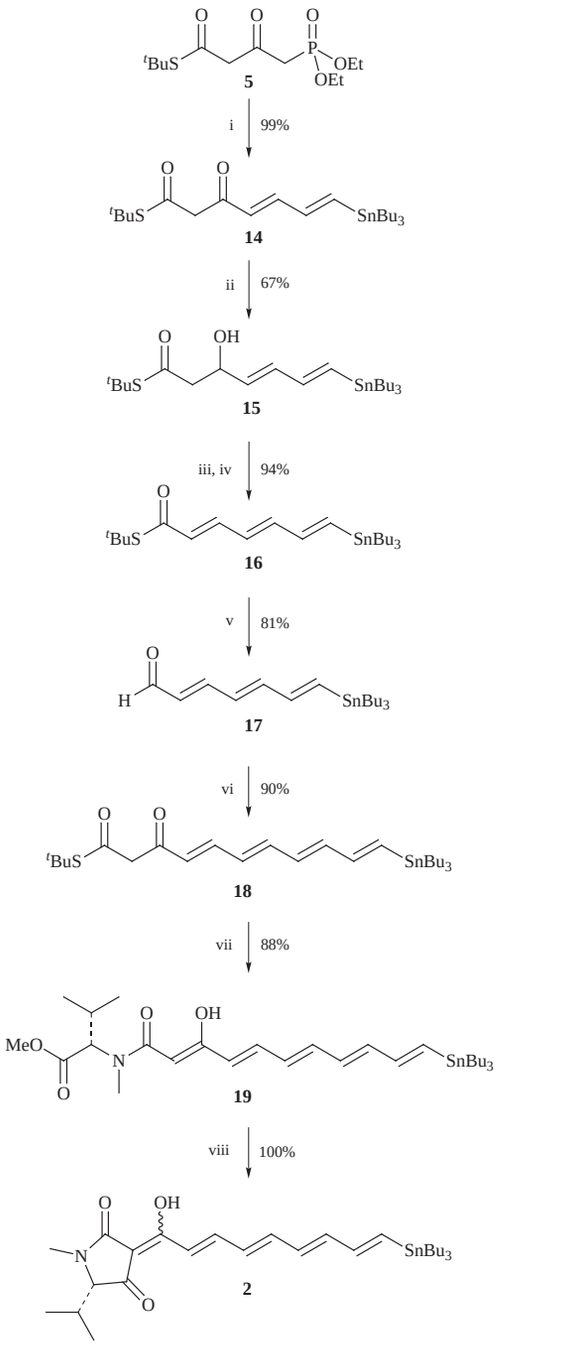
Scheme 1 *Reagents and conditions*: i, $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3 equiv.), AcONa (3 equiv.), CO (1 atm), AcOH, RT, 33 h; ii, Na_2CO_3 (0.5 equiv.), MeOH, RT, 2 h; iii, Imidazole (5 equiv.), TBDMSCl (2.4 equiv), DMF, 40 °C, 15 h; iv, DIBAL (2 equiv.), toluene, −78 °C, 10 min; v, Ac_2O (2 equiv.), DMAP (3 equiv.), CH_2Cl_2, 0 °C, 30 min; vi, Me_3Al (3 equiv.), CH_2Cl_2, −30 to −15 °C over 15 min; vii, TFA–H_2O (9:1), CH_2Cl_2, −7 to −6 °C, 11 min; viii, $(COCl)_2$ (2 equiv.), DMSO (4 equiv.), CH_2Cl_2, −78 °C then **13**, Et_3N, −78 °C–RT over 30 min; ix, $CrCl_2$ (8 equiv.), CHI_3 (2 equiv.), THF, 0 °C for 30 min then RT, 4.5 h.

corresponding anomeric acetate derivative. Stereoselective carbon–carbon bond formation was then possible using trimethylaluminium (3 equiv.) in dichloromethane at −30 to −15 °C. This approach afforded the desired *exo*-methylated material **12** in 76% yield over three steps.

Selective mono deprotection of the primary hydroxy group of **12** was achieved by rapid reaction of a chilled (−7 to −6 °C) dichloromethane solution with aqueous trifluoroacetic acid (90%) affording alcohol **13** in 88% yield. Homologation of **13** to the desired coupling component **3** was then possible using a two step Swern[13]–Takai[14] procedure. Thus oxidation of **13** by the standard Swern oxidation protocol afforded the crude aldehyde intermediate. A solution of this material and iodoform in tetrahydrofuran at room temperature was then added to a slurry of chromium(II) chloride in tetrahydrofuran at 0 °C. After warming to room temperature and stirring for an additional 4.5 hours an aqueous work-up afforded a separable mixture of regioisomeric iodoalkenes (*E*)-**3** and (*Z*)-**3** in the ratio of 2:1, and 49% combined yield over two steps (Scheme 1).

Unambiguous stereochemical assignment of **3** was achieved, after removal of the *tert*-butyldimethylsilyl group, using single crystal X-ray structure analysis.[15]

The synthesis of acyltetramic acid portion **2** utilised a modification of methodology previously developed within our laboratory. The known compound **6** was chosen as a suitable starting material in this sequence. Treatment of phosphonate ester **5** with potassium *tert*-butoxide (2.1 equiv.) at room temperature followed by aldehyde **6** at −78 to 0 °C afforded diene **14** in quantitative yield and with >30:1, *E*:*Z* selectivity. Reduction of the keto group with sodium borohydride in chilled methanol–isopropanol gave **15** in 67% yield. Acetylation of this material under standard conditions and subsequent treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at −30 °C to room temperature afforded the trienyl stannane **16** in 94% yield over two steps and with >30:1, *E*:*Z* selectivity. Diisobutylaluminium hydride reduction proceeded smoothly affording aldehyde **17** directly in 81% yield. Trienal **17** was subsequently subjected to the identical and optimised Horner–Wadsworth–Emmons type reaction described above affording **18** in high yield, high selectivity (*E*:*Z*, >30:1) and



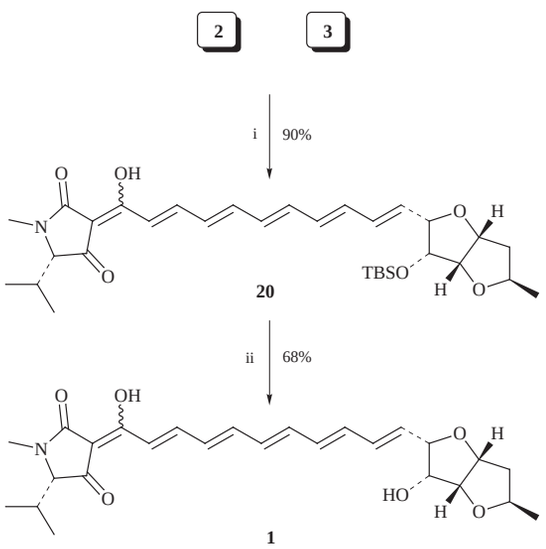
Scheme 2 *Reagents and conditions*: i, ^{t}BuOK (2.1 equiv.), THF, RT then **6** (0.71 equiv.), −78 to 0 °C, 30 min; ii, $NaBH_4$ (2.5 equiv.), MeOH–^{i}PrOH (2:1), −10 to −5 °C over 15 min; iii, Ac_2O (2 equiv.), DMAP (2.5 equiv.), CH_2Cl_2, RT, 10 min; iv, DBU (3 equiv.), THF, −30 °C to RT over 2 h; v, DIBAL (1.05 equiv.), toluene, −78 °C, 10 min; vi, **5**, ^{t}BuOK (2.1 equiv.), THF, RT then **17** (0.71 equiv.),−78 to 0 °C, 30 min; vii, **4**·HCl (3 equiv.), Et_3N (4 equiv.), CF_3COOAg (2 equiv.), THF, 0 °C, 40 min; viii, MeONa (5 equiv.), MeOH, 25 °C, 90 s.

with minimal purification. Aminolysis of the *tert*-butyl thioester with *N*-methyl (*S*)-valine methyl ester occurred readily, mediated by silver trifluoroacetate in tetrahydrofuran at 0 °C following a modification of our previously reported procedure. The Lacey–Dieckmann cyclisation[16] of ester **19** to acyltetramic acid **2** required some optimisation owing to the sensitivity of the tributylstannane product towards attempted chromatographic purification. Under the optimal conditions a 25 °C solution of **19** in freshly distilled methanol was treated with a freshly prepared solution of sodium methoxide (5 equiv.) in methanol for 90 seconds before saturated ammonium chloride solution was added to quench the reaction mixture. Aqueous work-up afforded essentially pure acyltetramic acid **2** as an equilibrating mixture of enol forms in the ratio 4:1. No further purification was attempted on this material (Scheme 2).

With both partners in hand we then looked at the key Stille[17] coupling reaction of vinyl iodide (*E*)-**3** with the tributylstannane **2**. This reaction proceeded well using an excess of the stannane **2** (1.2 equiv.) and bis-trifurylphosphinepalladium(II) chloride (0.1 equiv.) in *N*,*N*-dimethylformamide at room temperature for 100 minutes and afforded, after work-up and purification by size exclusion chromatography on Sephadex LH-20 eluting with methanol–dichloromethane (1 : 1), erythroskyrine *tert*-butyldimethylsilyl ether **20** in 90% yield and as an equilibrating mixture of enol forms in the ratio 4 : 1.

The final deprotection to erythroskyrine **1** was achieved using neat formic acid as solvent at room temperature for only 5 minutes followed by rapid removal of volatiles *in vacuo*. This method proved particularly convenient as no aqueous work-up procedure was necessary and all side products and excess reagents were volatile. Purification by HPLC on reversed-phase silica afforded erythroskyrine **1** in 68% yield. The ^{1}H and ^{13}C NMR, IR, UV, LRMS, and HRMS spectra and the specific rotation $[\alpha]_D^{32}$ +42.5 (*c* 0.12, EtOH) {lit.,[4b] $[\alpha]_D$ +46.9 (*c* 0.2, EtOH)} of synthetic erythroskyrine were in good agreement with the reported data for the natural product (Scheme 3).

In summary, we have reported an expeditious route to the polyenoyltetramic acid erythroskyrine **1** using some of the chemistry developed in our respective laboratories.



Scheme 3 *Reagents and conditions*: i, **2** (1.2 equiv.), (*E*)-**3** (1 equiv.), $[P(Fur)_3]_2PdCl_2$ (0.1 equiv.), DMF, RT, 100 min; ii, HCOOH (98%), RT, 5 min.

Acknowledgements

We thank the EPSRC (to DJD), the Novartis Research Fellowship (to SVL), the Slovak Grant Agency (project No. 1/4210/97) and Pfizer Inc., Groton, USA for financial support.

Notes and references

† Dedicated to the memory of our dear friend Professor Ralph Raphael.

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Communication 8/09823I