LETTERS

A Convergent Synthesis of the *tris*-Oxazole Ring System in Ulapualide A and Related Marine Metabolites

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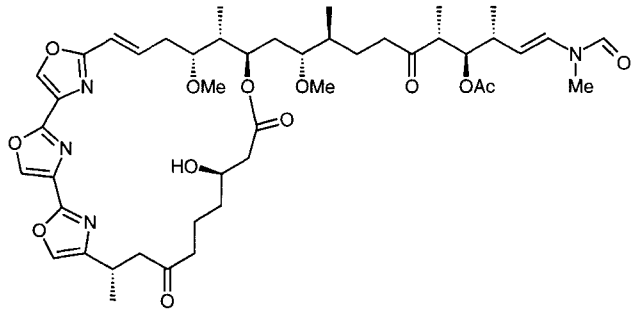
Abstract: A convergent synthesis of the fully functionalised *tris*-oxazole system **16**, found in the ulapualide family of marine macrolides, involving elaboration of the substituted oxazoles **13** and **8**, followed by their coupling to the amide **14** and manipulation of the third oxazole ring *via* the oxazoline intermediate **15**, is described.

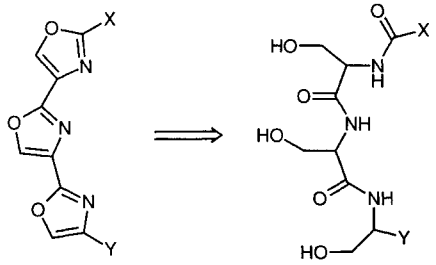
Natural product structures based on the presence of three contiguous 2,4-disubstituted oxazole rings are unique to the family of marine metabolites known as ulapualides, *eg* ulapualide A **1**.[1] The *tris*-oxazole unit **2** in these metabolites is most likely derived by cyclodehydration of an appropriately substituted *tris*-serine precursor, *eg* **3**, Y=CO_2R leading to the corresponding *tris*-oxazoline, followed by enzymic oxidation.[2] A related, *bis*-oxazole, unit is found in the natural product hennoxazole A [3] isolated from *Polyfibrospongia* sp, and muscoride A found in the freshwater cyanobacterium *Nostac muscorum*[4] shows a *bis*-oxazole core which is formally derived from two threonine residues.[5]

The first synthesis of the novel *tris*-oxazole unit in ulapualide A was described by ourselves,[6] and used a biomimetic type approach from three molecules of serine and three sequential oxazoline cyclisation-oxidation reactions. Other approaches to the same *tris*-oxazole unit have been described more recently, which highlight the scope for the Hantzsch oxazole synthesis[7] and for [3+2] cycloaddition reactions of acylcarbenes to nitriles in the elaboration of oxazoles.[8] Like our approach however, these alternative methods have been used in a linear, step-wise fashion. In relation to our studies of the total synthesis of ulapualide A[9] we required a convergent approach to the *tris*-oxazole unit in the natural product, which would permit the elaboration of the central oxazole ring as a final step, ultimately in an intramolecular fashion (see Scheme 1). In this *Letter* we demonstrate the scope for this approach with a concise synthesis of the *tris*-oxazole **16** involving elaboration of the substituted mono-oxazoles **13** and **8**, followed by their coupling to the amide **14** and manipulation of the third ring in **16** *via* **15**.

Thus, treatment of the serine-derived oxazolidine acid **4**[10] with serine methyl ester HCl first gave the corresponding amide **5** which on reaction with Burgess reagent[11] led to the oxazoline **6** as a mixture of



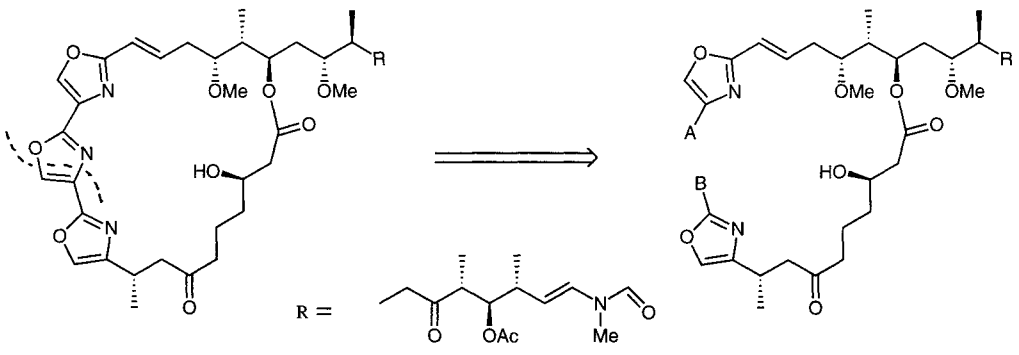
1



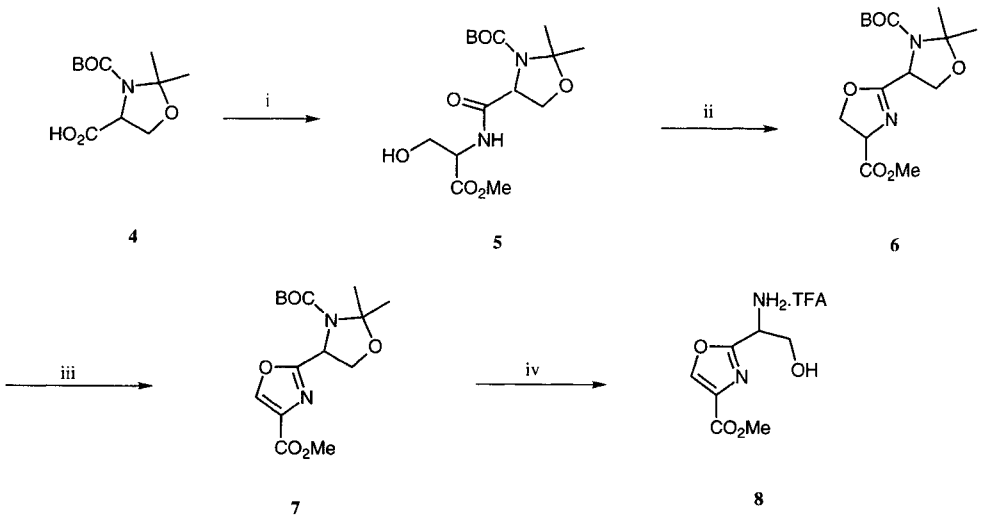
2 3

diastereoisomers. Oxidation of this mixture with CuBr/*t*-BuOOH[12] next led to the oxazole **7** which on deprotection with TFA produced the salt **8**. Using similar chemistry, the oxazole acid chloride **13** was derived from the benzyl ester **9** of serine[13] following conversion to the amide **10**, cyclisation to **11**, oxidation of the oxazoline **11** to the oxazole **12**, and finally manipulation of the acid ester to the corresponding acid chloride **13**.[14]

A coupling reaction between **13** and **8** in the presence of triethylamine then led to the intermediate *bis*-oxazole amide **14** which on cyclodehydration using Burgess reagent[11] followed by oxidation of the resulting *bis*-oxazole oxazoline **15** provided the doubly-differentiated



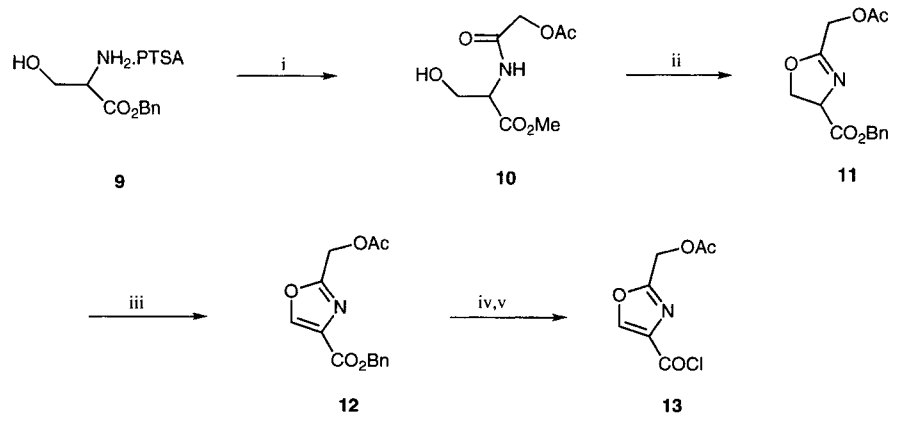
Scheme 1



4 5 6 7 8

Reagents and conditions : i, Serine OMe HCl,DCC / HOBt / Et_3N,0° ⟶r.t,18h,79%; ii,Burgess'reagent,THF,90°,1.5h,68%; iii,CuBr / $Cu(OAc)_2$/t-BuOOH,Benzene,reflux,5h, 78%;iv,dil.TFA,rt,1h,50%

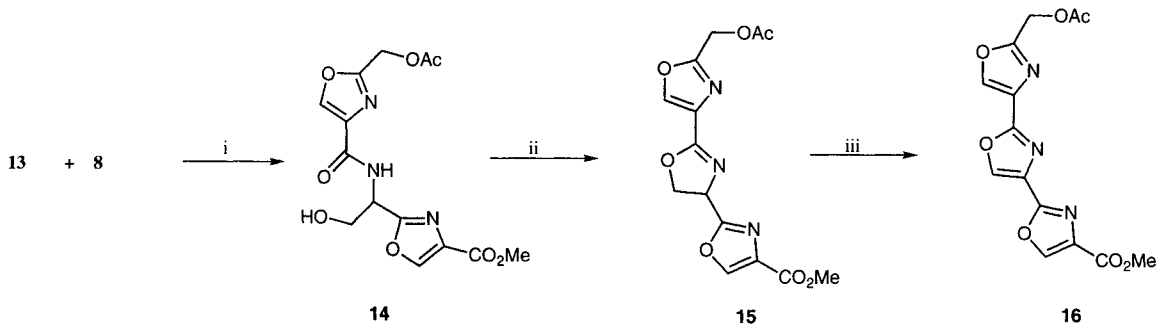
Scheme 2



9 10 11 12 13

Reagents and conditions : i,$AcOCH_2Cl$,Et_3N,0° ⟶ r.t.,18h,86%;ii,Burgess'reagent,THF,90°, 1h,66%;iii,$CuBr_2$,DBU,HMTA,CH_2Cl_2,r.t.,18h,58%;iv,H_2,Pd-C,EtOAc,16h,100%;v,$SOCl_2$, eflux,4h,quantitative

Scheme 3



14 15 16

Reagents and conditions : i,Et_3N,0° ⟶ rt,18h,69%; ii,Burgess' reagent,THF,90° ,2h,77%; iii,NiO_2,benzene,reflux,4h,40%

Scheme 4

tris-oxazole **16** (Scheme 4). This convergent synthesis of the *tris*-oxazole unit in ulapualide A, which proceeds in an overall yield of 7% from **9** has many attractions over the linear approaches described earlier, not least its possible application as the final macrocyclisation step to natural ulapualides. The development of this design, alongside others, towards a total synthesis of ulapualide A are in progress in our laboratories.

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(14) All new compounds showed satisfactory spectroscopic data together with microanalytical and/or accurate mass spectrometry data. Typical procedure:*conversion of* ***14*** *into* ***15*** *:* A solution of Burgess reagent (50 mg, 0.21 mmol) in THF (1.5 ml) was added to a solution of **14** (65 mg, 0.18 mmol) in THF (1.5 ml) and the mixture was heated in a sealed tube at 90°C for 1.5 hour. The mixture was cooled to room temperature,and then concentrated in vacuo to leave an oil. Purification by chromatography on silica gel using ethyl acetate as eluent gave **15** (50 mg, 77%) as a colourless oil. *conversion of* ***15*** *into* ***16*** **:** Freshly prepared NiO_2 (150 mg) was added in three portions to a refluxing solution of **15** (50 mg, 0.15 mmol) in dry benzene (3 ml) at one hour intervals. The mixture was heated under reflux for two more hours,and then filtered through celite. The filtrate was concentrated in vacuo to leave a viscous mass. Purification by chromatography on silica gel using ethyl acetate as eluent gave **16** (21 mg, 40%) as a colourless solid.