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Total Synthesis of Ulapualide A, a Novel *tris*-Oxazole Containing Macrolide from the Marine Nudibranch *Hexabranchus sanguineus.*

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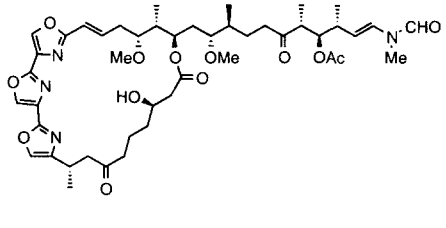
Abstract: A total synthesis of ulapualide A **1**, whose relative stereochemistry was assigned on the basis of an earlier molecular mechanics study of its hypothetical metal chelated complex **2**, is described.

Amongst the most fascinating family of metabolites to be isolated from marine organisms in recent years is ulapualide A **1** and its relatives found in nudibranchs and sponges.[1] These intriguing 'ulapualide' molecules, which include the halichondramides,[2] kabiramides,[3] and mycalolides,[4] display novel and unusual structures based on three contiguous oxazole rings forming part of a macrolide ring to which is attached a lipid-like side chain that terminates in an *N*-methyl-*N*-alkenylformamide group. Members of the ulapualides show a wide range of interesting and unusual biological activities, including antileukaemic, antifungal and ichthyotoxic properties. Although the gross structure of members of the ulapualides are secure, their relative stereochemistries have not been established in spite of considerable effort. Several years ago we entertained the notion that the ulapualides with their macrocyclic cavities incorporating nitrogen and oxygen ligands and their side chains containing several oxy-donor atoms in chelating arrangements could behave as ligands for metal chelation. Subsequently, we carried out a molecular mechanics study on 'dummy' metal chelated ulapualide A, *e.g.* **2**, using varying combinations of its oxygen and nitrogen atom ligating sites which permitted us to predict the relative stereochemistry shown in formula **1** for ulapualide A.[5] This somewhat unconventional approach to structure analysis was more significant than we had anticipated in that it showed that the stereochemistry of a major part of the polyol side chain in ulapualide A **1** correlated with corresponding chiral centres in scytophycin B,[6,7] a related metabolite whose structure has been established by X-ray crystallographic measurements.



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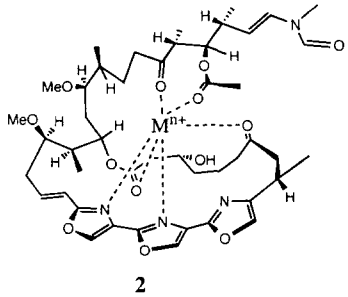

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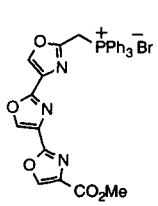
Since carrying out these molecular mechanics studies, we have been anxious to answer any critics of the procedure by attempting to effect a total synthesis of ulapualide A having the predicted relative stereochemistry shown in formula **1**. We now describe the realisation of this objective, and the synthesis of a member of this intriguing family of ulapualide marine metabolites, for the first time.

In earlier publications [8] we have discussed fully our synthetic strategy to ulapualide A **1** which was based on elaboration of the *tris*-oxazole unit **3** and the protected polyol aldehyde **4**, followed by their coupling to **5**, attachment of a keto-phosphonate residue producing **6**, and macrocyclisation *via* an intramolecular Wadsworth-Emmons olefination leading to **7**; the synthesis was then to be completed by manipulation of the functionality in **7** and simultaneous introduction of the terminal *N*-methyl-*N*-alkenylformamide residue. Hitherto, this strategy had produced the macrocyclic core **7a** of ulapualide A, incorporating all the correct stereocentres at C3 and along the C25 – C40 portion of the natural product.[9] For convenience of selective deprotection of hydroxy group functionality in completing the synthesis of ulapualide A from the advanced precursor **7** we repeated a synthesis leading to **7b** with the C3-OH group protected at its *t*-butyldiphenylsilyl ether.



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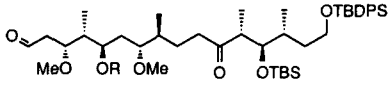

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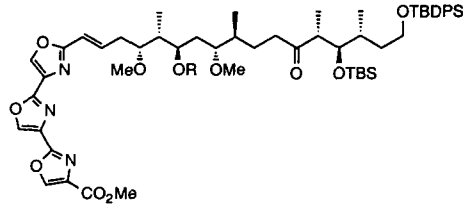

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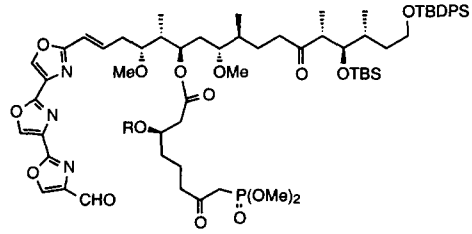

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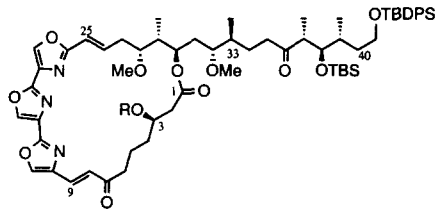
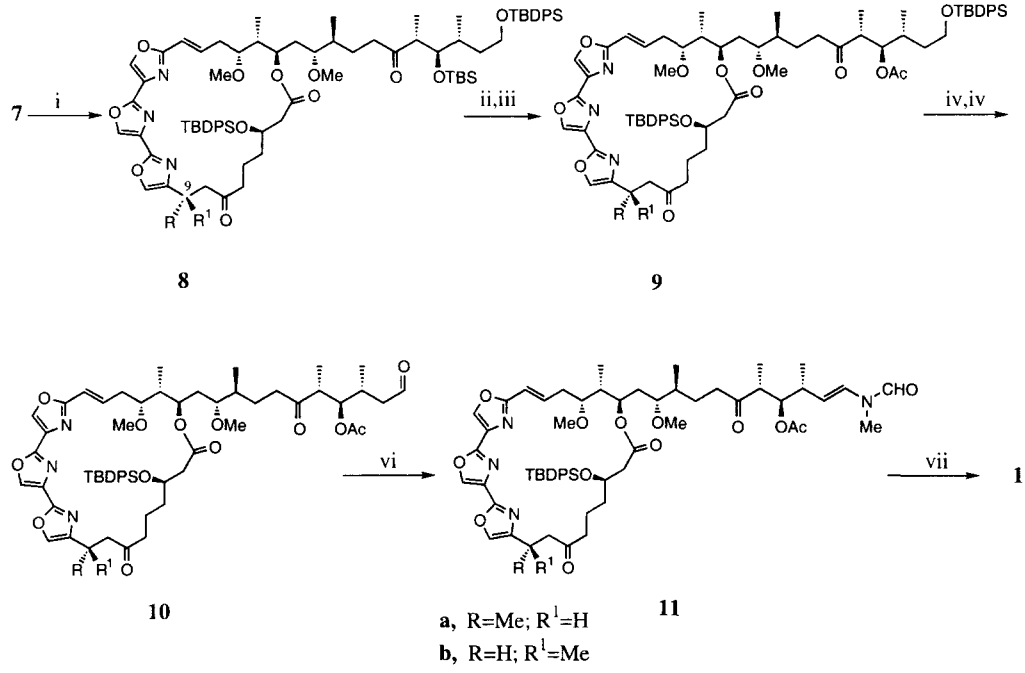


7 **a**, R=MOM
b, R=OTBDPS

Treatment of the enone **7b** with lithium dimethylcuprate in ether at 0°C next led to a 3:2 mixture of C9 methyl epimers of **8** which could be separated cleanly and preparatively by column chromatography. Comparison of n.m.r. spectroscopic data between the epimers of **8** and natural ulapualide A,[10] together with consideration of our molecular mechanics modelling data, led us to conclude that the major product from the methyl cuprate addition to **7b** had the α-methyl (natural?) orientation, *ie.* **8a.** Deprotection of the *t*-butyldimethylsilyl ether in either epimer of **8** was smoothly accomplished using trimethylsilyl triflate at –78°C, and acetylation of the resulting secondary alcohol then produced the corresponding acetates **9a** and **9b.** Treatment of the acetate **9a** with HF-pyridine in THF at 25°C for 1.5h led to selective deprotection of the primary alcohol *t*-butydiphenylsilyl protection group, and oxidation of the resulting alcohol using Dess Martin periodinane then

gave the corresponding aldehyde **10a**; the same synthetic methods were also used to convert **9b** into **10b.** When a solution of either **10a** or **10b** in benzene was heated with *N*-methylformamide in the presence of pyridine *p*-toluenesulphonic acid for 10-12h,[11] chromatography gave the *E*-isomers of the corresponding *N*-methyl-*N*-alkenylformamides **11a** and **11b** respectively in 40% yield. The synthesis of ulapualide A **1** and its C9-methyl epimer were then completed following deprotection of the t-butyldiphenlysilyl ether group in **11a** and **11b** using HF-pyridine (26h; 25°C).



Reagents : i, Me_2CuLi,Et_2O,0°C,55%; ii, TMSOTf,-78°C,85%; iii, Ac_2O,DMAP,pyridine,90%; iv, HF.pyridine,85%; v, Dess-Martin periodinane,90%; vi, NHMeCHO,PPTS,benzene,40%; vii, HF.Py,pyridine,THF,80%.

Scheme 1

The proton n.m.r. spectra recorded for the C9 α- and β- methyl epimers of **1** were almost identical and for all intents and purposes, superimposable on the n.m.r. spectroscopic data recorded for natural ulapualide A. Furthermore the diastereoisomer we had assigned the C9 α - methyl configuration, *i.e.* **1,** did not separate from natural ulapualide A in mixed h.p.l.c. analysis and it showed an optical rotation $[\alpha]_D^{25}$ – 43.3 (c 0.3, MeOH); *cf* natural ulapualide $[\alpha]_D^{25}$ – 42.9 (c 0.163, MeOH). The c.m.r. spectroscopic data recorded for synthetic **1** and natural ulapualide A were identical (*i.e.* within *ca* 0.5 p.p.m.) except for the C33 – methyl absorption which occurs at δ 15.5 p.p.m. in natural ulapualide in comparison with δ 14.2 (Δδ = 1.3 p.p.m.) in the synthetic material **1**. We are unable to account for this small difference in chemical shift at this time.

In summary, we have achieved a total synthesis of a member of the intriguing *tris*–oxazole macrolide based marine metabolites, *i.e.* ulapualide A **1**, for the first time. The relative stereochemistry of natural **1** had been assigned earlier on the basis of a molecular mechanics study of its hypothetical metal chelated complex **2**. Our

total synthesis of **1** vindicates this approach to structure analysis in the case of the ulapualides, *ie.* our synthetic ulapualide A displayed n.m.r spectroscopic and optical rotation data together with chromatographic behaviour closely similar to those recorded for the natural product isolated from the nudibranch *Hexabranchus sanguineus*.[1]

Acknowledgements

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7. For a synthesis of the related metabolite aplyronine see Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.*, **1993**, *115*, 11020 and Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutuo, T.; *ibid*, **1994**, *116*, 7443.
8. See Chattopadhyay, S. K.; Pattenden, G. *Synlett*, **1997**, 1345 and extensive references and bibliography contained therein.
9. The carbon skeleton of ulapualide A is numbered as shown in reference 1, reporting its isolation.
10. All new compounds showed satisfactory n.m.r spectroscopic and mass spectrometry data. The C9-methyl carbon absorbed at δ 19.3 p.p.m. in the c.m.r. spectrum of the major (α-methyl ?) diastereoisomer of **8**, compared to δ 19.1 p.p.m in natural (C9 α-methyl ?) ulapualide A, and δ 20.0 p.p.m in the minor (β-methyl ?) diastereoisomer of **8**. The relevant c.m.r data for synthetic **1** (with corresponding data reported for naturally derived ulapualide in parentheses) were: δ 9.1, C52-Me (9.1); 13.4, C49-Me (13.4); 14.2, C50-Me (15.5); 18.9, C54-Me (18.9); 19.2, C46-Me (19.5); 20.9, OCOMe (20.9); 28.1, C-9 (27.7); 34.0, C29 (34.5); 37.3, C40 (37.2); 39.9, C34 (39.8); 40.4, C38 (40.3); 57.6, C28-OMe (57.6); 57.8, C33-OMe (58.1); 68.7, C3 (68.4); 72.9, C30 (73.0); 80.0, C28 (80); 81.1, C33 (81.8)p.p.m.
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