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Synthetic Studies towards Novel *tris*-Oxazole based Macrolides of Marine Origin. Stereocontrolled Synthesis of the C20-C35 Fragment in Ulapualide A

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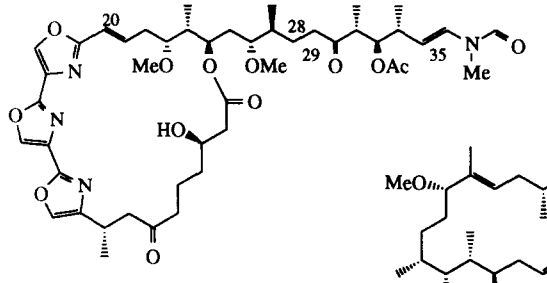
Abstract: The C20-C35 subunit **3** in ulapualide A **1** has been synthesised in enantiomerically pure form using a combination of the Evans aldol reaction, controlled ring opening reactions of chiral epoxides, and Brown's asymmetric allylboration reaction, to set up the eight chiral centres in the key intermediates **4** and **5**. An olefination reaction between **4** and **5**, followed by hydrogenation of **23**, and protection of the resulting alcohol **24** then led to **3**.

Ulapualide A **1** is a member of a novel family of *tris*-oxazole containing macrolides which were first isolated from the egg masses of the nudibranch *Hexabranchus*.[1] Similar, structurally related, macrolides which differ only according to alternations in oxidation pattern and methyl group substitutions along the aliphatic backbone have been isolated from other nudibranchs and from sponges, and these have been variously called halichrondramides, kabiramides and mycalamides.[2] The family of 'ulapualides' show a range of interesting and unusual biological activities, including anti-leukaemic, anti-fungal and ichthyotoxic properties. They have structures based on a macrocyclic cavity incorporating nitrogen and oxygen ligands, and a side chain containing several oxy-donor atoms in chelating arrangements. Although the gross structures of the



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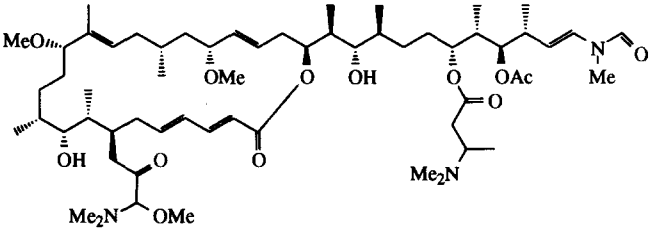
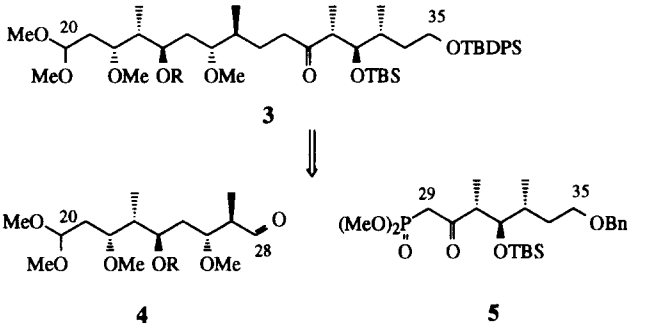


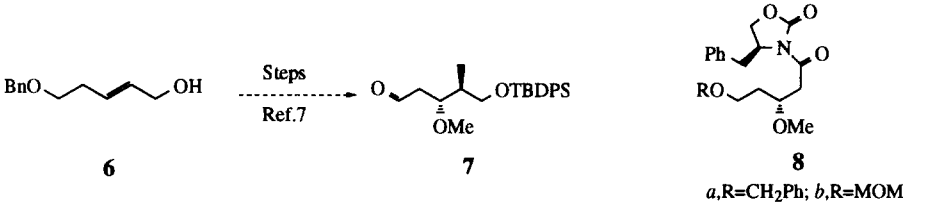
2

ulapualides are secure, their stereochemistries are less well-defined. In other studies we have carried out a molecular mechanics study of ulapualide A **1**, and of its various metal chelated complexes, in order to predict the stereochemistry shown in structure **1** for the natural product.[3] Indeed, this study demonstrated that the relative stereochemistries of the methyl and oxy groups along the (C20-C35) side chain in ulapualide A correlate precisely with the same stereocentres in the related scytophycins, from blue green alga *Scytonema pseudotiofmanni*,[4] and with the more recently isolated aplyronine A **2**, a constituent of the sea hare *Aplysia kurodai*.[5] As part of our studies towards a total synthesis of the ulapualide A structure **1**, we now describe a stereocontrolled synthesis of the C20-C35 fragment **3**.[6,7] The strategy we followed is highlighted in Scheme 1, requiring access to the chiral aldehyde **4** and the chiral phosphonate **5** as the two key intermediates.



Scheme 1

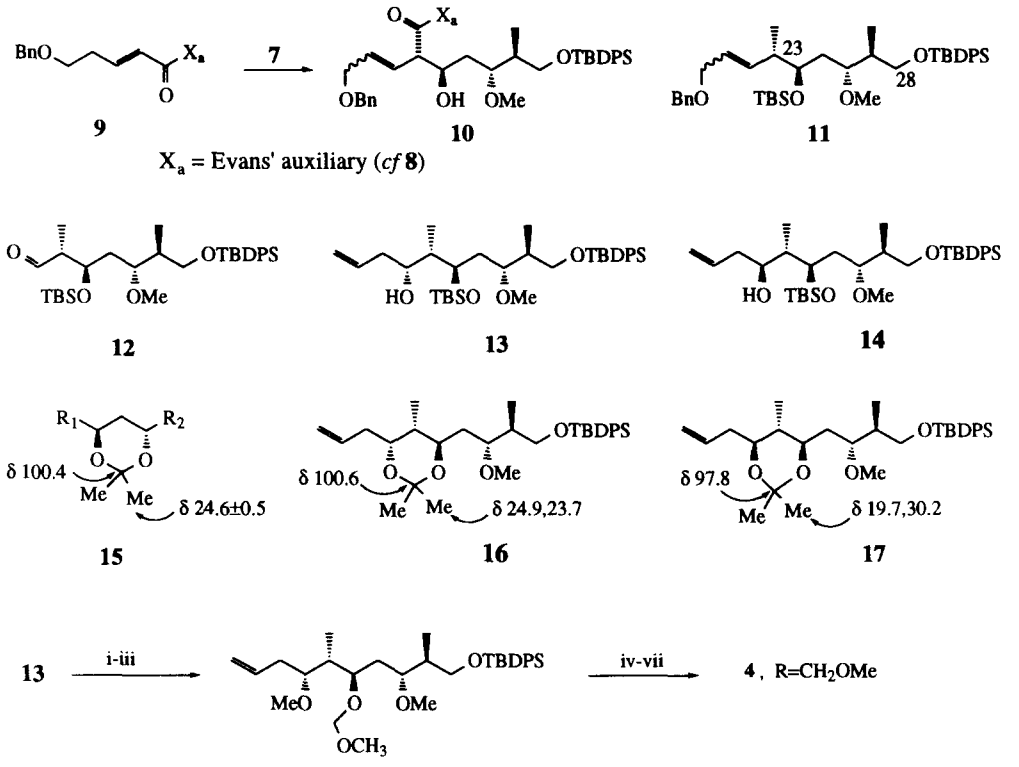
Our initial plan was to elaborate the C20-C28 segment **4** by starting with an Evans aldol reaction between the imide **8** and the chiral aldehyde **7** we had synthesised earlier from 5-benzyloxy-*E*,2-pentenol **6**.[7] In spite of much experimentation however, attempted aldol reactions between **7** and either **8a** or **8b**, produced only the products of elimination of methanol from the starting materials, or led to recovered starting materials. We next examined the aldol reaction between **7** and the boron enolate derived from the unsaturated imide **9**.[8]



6 **7** **8**

a,R=CH_2Ph; *b*,R=MOM

This reaction proceeded smoothly, and led to the *anti*-aldol product **10** as a 1:1 mixture of *Z*-and *E*-alkenes in 70% yield(de>95%). In readiness for oxidative cleavage of the double bond in **10**, the imide residue in **10** was next reduced to the corresponding C23 α-methyl (*cf* ref 7), and the C24 β–hydroxy group was protected as its silyl ether, producing **11**. Ozonolysis of **11** at -78°C, followed by a reductive work-up procedure using PPh_3, then led to the aldehyde **12** in 80% yield, $[\alpha]_D$= -3.7 (c 5.7, $CHCl_3$). The addition of Brown's (+)-allyldiisopinocamphenylborane[9] to the aldehyde **12** proceeded in a highly diastereoselective manner (de 89%), and after chromatography, gave rise to the required C22 α-hydroxy triol **13**, $[\alpha]_D$ =10.9(c4.23,$CHCl_3$) in 65-70% yield. The stereochemistry of the newly formed C22-OH centre in **13** followed from extensive n.m.r. experiments [including 1H COSY, C-H correlation, homonuclear decoupling and nOe data, matching of computer predicted coupling constants[10]], together with correlation of ^{13}C chemical shift data for the acetonide **16** derived from **13** (and its diastereoisomer **17**) with those data reported in the literature for authentic *syn* - and *anti*-1,3-diol acetonides;[11] these data are collected on formulae (**15**; predicted shift data), (**16**; data from **13**), and (**17**; data from the diastereoisomer of **14** produced after reaction between the aldehyde **12** and (-)-allyldiisopinocamphenylborane). Having established the stereochemical integrity of the secondary alcohol **13**, it was then elaborated to the key aldehyde precursor **4** (C20-C28 segment), $[\alpha]_D$=13.1(c1.27, $CHCl_3$), accommodating five of the eight chiral centres in the ulapualide side chain **3**, by the straightforward seven step sequence shown in Scheme 2.

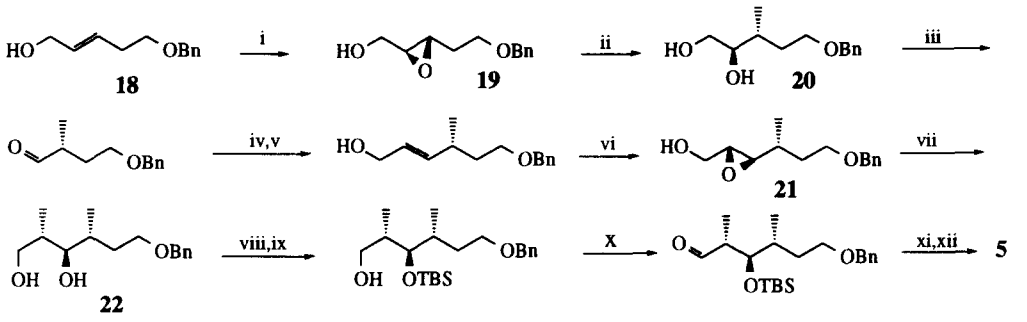


Reagents : i, MeOTf, 2,6-di-tert-butylpyridine, 95%; ii, PPTS, ethanol, 90%; iii, MOM-Cl, ^{i}-Pr_2NEt, 95%; iv, O_3, PPh_3, 89%; v, TMOF, MeOH, pTSA, 98%; vi, TBAF, 100%; vii, TPAP, NMMO, 89%.

Scheme 2

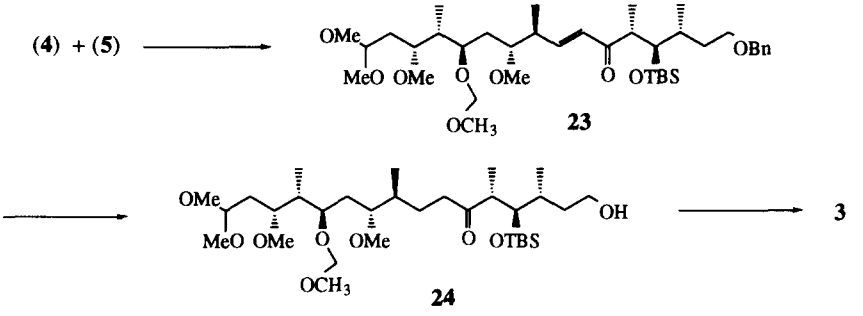
The synthesis of the phosphonate **5**, $[\alpha]_D$= -79.9 (c 2.54, $CHCl_3$), was achieved in twelve steps starting from the *E*-allylic alcohol **18** and featured the regiospecific chiral epoxide ring opening reactions (**19**→**20**) and (**21**→**22**) as key reactions (Scheme 3).[12,15] The Wadsworth-Emmons coupling reaction between the phosphonate **5** and the aldehyde **4** was next smoothly accomplished in 95% yield using barium hydroxide in wet THF as a medium.[13] Hydrogenation of the resulting *E*-alkene **23**, in the presence of Pearlman's catalyst,[14] then resulted in simultaneous reduction of the alkene double bond and hydrogenation of the benzyl protecting group producing the alcohol **24**, $[\alpha]_D$=-5.7(c0.8,$CHCl_3$), in quantitative yield. The target C20-C35 segment **3** of ulapualide A was then elaborated from **24** by straightforward silylation using t-butyldiphenylsilyl chloride in the presence of imidazole.

In summary, the C20-C35 subunit **3** in ulapualide A has been synthesised in enantiomerically pure form using a combination of the Evans aldol reaction, controlled ring opening reactions of chiral α-epoxy alcohols,[12] and Brown's asymmetric allylboration reaction[9] to set up the eight chiral centres in **3**.[15] Further studies directed towards a total synthesis of the stereostructure **1** for ulapualide A, *via* a coupling reaction between **3** and the *tris*-oxazole unit[6] in the natural product, are underway.



Reagents:i, (+)-DET, $Ti(O^iPr)_4$,t-BuOOH,76%; ii, Me_3Al; iii, $NaIO_4$, 84%; iv, Ph_3PCHCO_2Et, 94%; v, DIBAL, 96%; vi,(-)- DET, $Ti(O^iPr)_4$, t-BuOOH, 85%; vii, MeMgBr, CuI, THF; $NaIO_4$, MeOH - H_2O, 89%; viii, TBDMS -OTf, 2,6-Lutidine, 100%; ix, PPTS, MeOH, DCM, 96%; x, TPAP, NMMO, 94%; xi, $MePO(OMe)_2$, n-BuLi, 90%; xii, PDC, DMF, 92%.

Scheme 3



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15 Satisfactory spectroscopic data, together with microanalysis or mass spectrometry data were obtained for all new compounds.The enantiomeric purity of the epoxy-alcohols **19** and **21** were determined by Mosher's ester analysis.

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