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Synthetic Studies towards Halichondramides, and Related Novel *tris*-Oxazole Containing Macrolides from Marine Organisms. A Concise Route to the Keto-triol Formyl Enamine Moiety.

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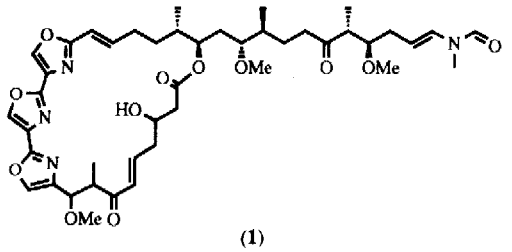
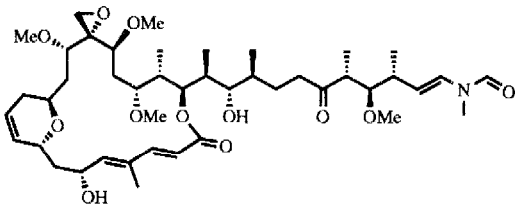
Key Words: Halichondramide; *tris*-oxazole; formyl enamines; macrolides.

Abstract: *A synthesis of the keto-triol formyl enamine moiety (3) in the marine metabolite halichondramide (1) is described. The synthesis features judicious application of the Evans chiral aldol protocol in combination with the controlled ring opening of chiral α-epoxy alcohol precursor molecules to elaborate the units (5) and (6). A Wadsworth-Emmons coupling between (5) and (6) next provided (18), which was then elaborated to (3) via the key intermediates (19) and (21).*

The halichondramides, *e.g.* (**1**), comprise a small group of novel 25-membered macrolides, which accommodate an unusual system of three contiguous oxazole rings as part of the macrocycle ring. They have been isolated from egg masses deposited by the marine nudibranch *Hexabranchus*,[1] and from sponges of the genus *Halichondria*.[2] Halichondramides are related structurally to the groups of *tris*-oxazole containing macrolides known as ulapualides,[3] kabiramides,[4] and mycalolides,[5] isolated from the same organisms. Members of this unique family of compound differ from each other only according to the oxidation patterns and alkyl group substitutions found in the aliphatic portions of their structures. The marine metabolites represented by (**1**) show a useful range of interesting biological activities, *e.g.* antifungal, anti-leukemic, ichthyotoxic, and we have pursued a fantasy built on the premise that this biological profile is in part associated with the capacity of the metabolites to sequester and transport metal ions *in vivo* using the several nitrogen and oxygen ligand binding sites in their structures.[6]



(**1**)

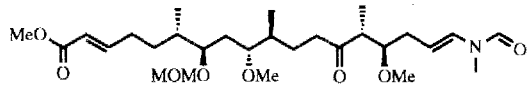


(**2**)

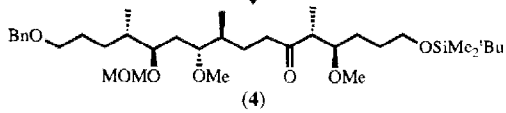
The relative stereochemistries of the halichondramides, ulapualides, kabiramides and mycalolides have not yet been fully established. Each of the compounds however, accommodates a keto-polyol side chain terminating in a novel formyl enamine residue, which is also found in scytophycin B (**2**), a related metabolite whose structure has been secured by X-ray measurements.[7] It seems likely therefore that these two classes of metabolites would posses identical stereochemistries at the several chiral centres along the side chain portions of their structures; *cf.* formulae (**1**) and (**2**).[8]

As part of a program towards the total synthesis of halichondramides and relatives, together with an evaluation of their metal chelating capabilities and correlation of these data with biological activity, we have earlier described a synthesis of the unique *tris*-oxazole ring system found in their structures.[9] In continuation of this program, we now describe a convergent synthesis of the keto-triol formyl enamine moiety (**3**) in halichondramide (**1**), which accommodates six of the asymmetric carbon centres in the natural product.

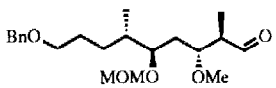
The design we followed for the synthesis of (**3**) relied on access to the differentially protected keto-pentol (**4**), which we planned to elaborate from the two sub-units (**5**) and (**6**) using a Wadsworth-Emmons coupling procedure. Both the units (**5**) and (**6**) show staggered (*anti*-)geometrical arrangements of their vicinal methyl and oxy functionality. We elected to elaborate these units, and the associated stereochemical detail, by applying the Evans chiral aldol protocol[10] in combination with the controlled ring opening of chiral α-epoxy alcohol precursor molecules by methyl nucleophiles.



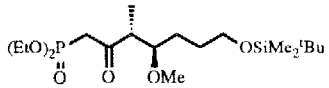
(**3**)



(**4**)

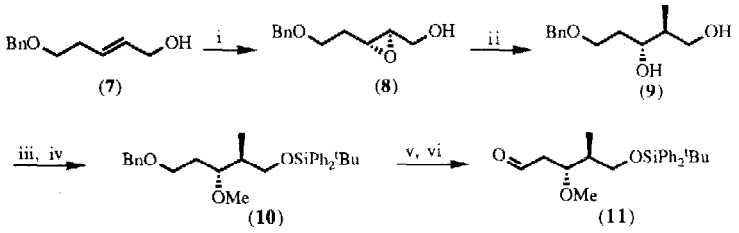


(**5**)



(**6**)

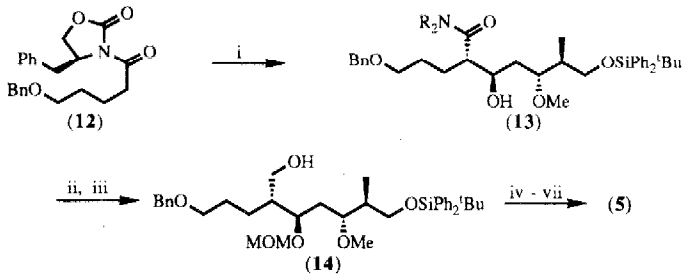
Thus, the aldehyde unit (**5**) was first prepared starting from the chiral epoxide (**8**)[11] derived from the *E*-allylic alcohol (**7**) using the Sharpless procedure[12] (Scheme 1). Addition of methylmagnesium bromide to the epoxy alcohol (**8**) in the presence of catalytic CuI was found to proceed in a regioselective manner and led largely (4:1) to the corresponding 1,3-diol (**9**) (60%). Following protection of the diol (**9**) as the mixed methyl ether-silyl ether (**10**), hydrogenolysis, and oxidation of the resulting primary alcohol next led to the protected aldehyde (**11**).



Reagents: i, (-)-DET, $Ti(O^iPr)_4$, ^tBuOOH (72%); ii, MeMgBr, CuI (60%); iii, $^tBu(Ph)_2SiCl$ (84%); iv, NaH, MeI (84%); v, H_2, $Pd(OH)_2$-C (100%); vi, $(COCl)_2$, DMSO, Et_3N (94%).

Scheme 1

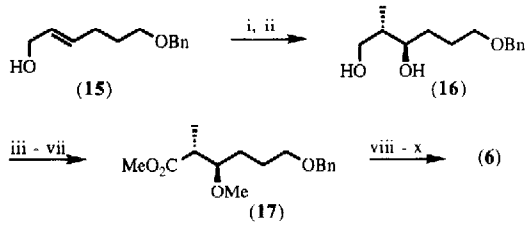
When the aldehyde (**11**) was added to a solution of the boron enolate produced from the Evans imide (**12**) (Scheme 2), a 58% yield of the anticipated *'anti-'* aldol product (**13**) was secured.[10] Protection of the *sec*-alcohol group in (**13**), followed by reduction with lithium methoxyborohydride,[13] then led to the corresponding carbinol (**14**) (83%). The alcohol (**14**) was then converted into the key aldehyde precursor molecule (**5**) in four high yielding steps, *i.e.* mesylation (98%), reduction (83%), silyl deprotection (100%), and Swern oxidation (89%).



Reagents: i, Bu_2BOTf, Et_3N, (**11**) (58%); ii, MOMCl, $^iPr_2NEt$ (75%); iii, $LiMeOBH_3$ (83%); iv, MsCl, $^iPr_2NEt$ (98%); v, $LiMeOBH_3$, Δ (83%); vi, Bu_4NF (100%); vii, $(COCl)_2$, DMSO, Et_3N (89%).

Scheme 2

The phosphonate intermediate (**6**), required for the projected coupling reaction with (**5**), was synthesised from the chiral 1,3-diol intermediate (**16**) which was itself produced from the *E*-allylic alcohol (**15**)[14] using an identical strategy to that used to synthesise (**9**) from (**7**) (see Scheme 3). After selective, alternate protection of (**16**), oxidation and esterification next produced the β-methoxy ester (**17**), which, following a further protection group interconversion, was used to acylate the anion derived from diethyl methylphosphonate, producing the phosphonate (**6**).

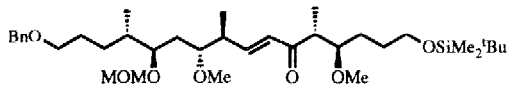


Reagents: i, (-)-DET, $Ti(O^iPr)_4$, ^tBuOOH (70%); ii, MeMgBr, CuI (50%); iii, $^tBu(Ph)_2SiCl$ (100%); iv, NaH, MeI (78%); v, Bu_4NF (80%); vi, PDC, DMF (72%); vii, AcCl, MeOH (91%); viii, H_2, $Pd(OH)_2$-C (98%); ix, $^tBuMe_2SiOTf$ (98%); x, $(EtO)_2P(O)Me$, BuLi (89%).

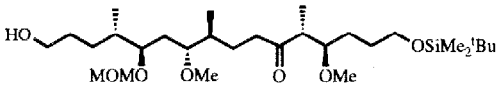
Scheme 3

The Wadsworth-Emmons coupling reaction between (**5**) and (**6**) proceeded smoothly in the presence of potassium hexamethyldisilylazide at -78°C, and led to the *E*-alkene (**18**) in 79% yield. Hydrogenation of (**18**) using Pearlman's catalyst[15] then resulted in simultaneous reduction [to (**4**)] and hydrogenolysis producing the carbinol (**19**). Swern oxidation of (**19**) next gave the corresponding aldehyde, which by Wittig reaction with methyl (triphenylphosphoranylidene)acetate led to the *E*-α,β-unsaturated ester (**20**). Elaboration of (**20**) to the

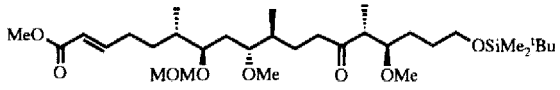
aldehyde (**21**), followed by reaction with *N*-methyl formamide under mild acid catalysis, finally gave the target keto-triol formyl enamine (**3**).



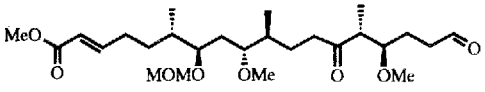
(**18**)



(**19**)



(**20**)



(**21**)

The ^{1}H n.m.r. spectroscopic data[16] recorded for (**3**) demonstrated that, like the natural halichondramides (**1**),[2] it was present as a 2:1 mixture of rotamers about the formate residue. Otherwise, the spectroscopic data indicated that the synthetic (**3**) was homogenous both constitutionally and isomerically, and furthermore showed several features in common with corresponding data for the side chain in natural halichondramide (**1**) and *seco*-halichondromamide.[2] Further research is now in progress to extend this work, alongside our earlier work, to the total synthesis of selected halichondramide and ulapualide metabolites.

Acknowledgements

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