Synthesis and X-Ray Crystallographic Structure of the Right-hand Hemisphere of Halicholactone and Neohalicholactone

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The synthesis and X-ray crystallographic structure of the right-hand hemisphere of the marine natural products halicholactone and neohalicholactone, which contains a nine-membered lactone and cyclopropane ring, is reported.

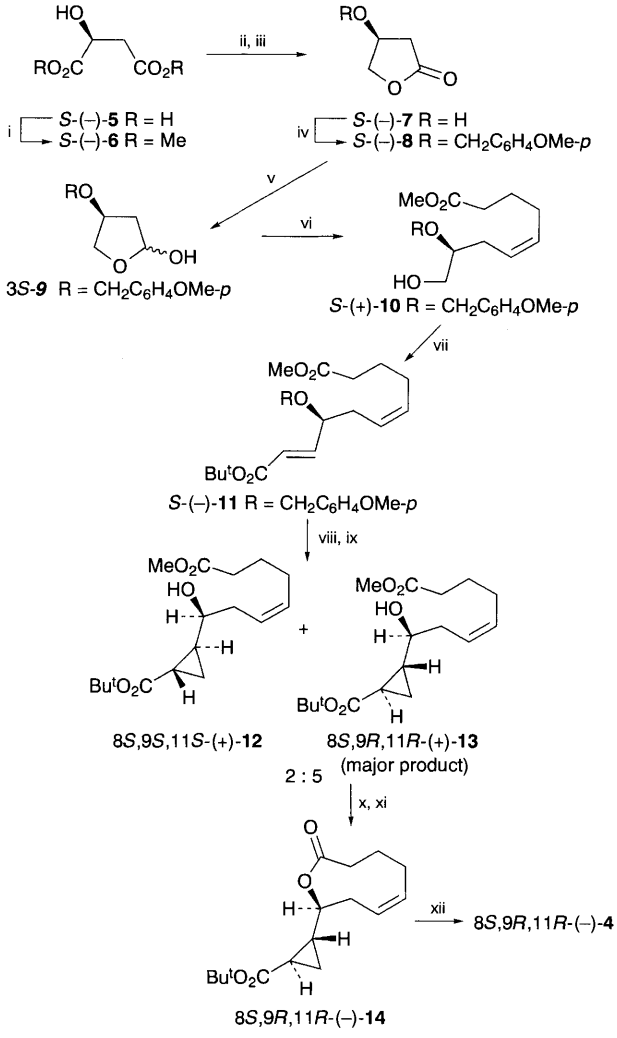
The marine metabolites halicholactone **1a** and neohalicholactone **1b**, both weak lipoxygenase inhibitors, were isolated from the sponge *Halichondria okadai* and first reported in 1989.[1] Both compounds contain 20 carbon atoms and have been proposed to be biosynthesised from arachidonic and eicosapetanenoic acid respectively. They therefore constitute a new series of eicosanoid metabolite. As well as important physiological properties, these compounds also contain a number of unusual structural features, including a nine-membered lactone and cyclopropane ring. The relative stereochemistry between all the chiral centres in **1b** was established by an X-ray crystallographic study,[1b] whilst the absolute configuration at the C-15 carbinol of **1a** was confirmed by degradation to a derivative of known absolute configuration.[1a] Taken together, and assuming a similar biosynthetic pathway, the absolute stereochemistry is predicted to be as shown. In this paper we describe a synthesis of the right-hand hemisphere of **1a** and **1b**, *i.e.* the fragment containing the nine-membered lactone and cyclopropane units, in enantiomerically pure form.

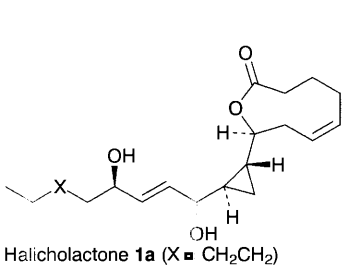
Our proposed synthesis of the target molecules involves a convergent route in which the reaction of a vinylic anion **2a** or **2b** with a common aldehyde **3** was a key step. In the case of M = ZnEt literature precedent suggests that an asymmetric ligand may be used to control the absolute stereochemistry in the coupling step.[2] Aldehyde **3** would in turn be available from the acid **4**. Our route to **4** is shown in Scheme 1.

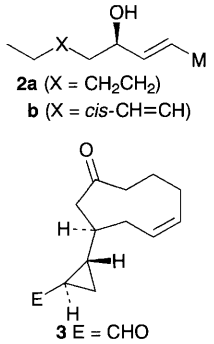
The conversion of *S*-malic acid **5** to the 3-hydroxy γ-lactone **7** was achieved following literature methods.[3] The choice of protecting group for the hydroxy function in **7** was critical to the success of the synthesis. Trialkylsilyl groups are known to be prone to migration to less hindered positions under certain circumstances,† whilst the conditions required for removal of a benzyl group would not be compatible with the unsaturated bonds in the molecule.[5] In practice, the *p*-methoxyphenylmethyl group (MPM) proved to be ideal, and was attached to give **8** in 73% yield using the trichloroacetimidate method.[6] Reduction of **8** to the lactol **9**, a mixture of diastereoisomers, was achieved using DIBAL-H at low temperature in toluene.

The reaction of **9** with the Wittig reagent derived from (4-carboxybutyl)triphenylphosphonium bromide, which would complete the synthesis of the nine-membered lactone precursor, proved to be troublesome.[4,7] Despite variation of the base, temperature and solvent, only low yields could be achieved. Holmes and coworkers recently published a synthesis of the 10-membered lactone ascidiatrienolide A using a similar Wittig reaction.[8] Application of a modified version of the Holmes conditions for this coupling gave, after methylation using methanolic HCl, the addition product **10** in 69% yield for the two steps.‡

Conversion of **10** to the unsaturated ester **11** was achieved in 66% yield using a Swern oxidation followed by reaction with







Scheme 1 *Reagents and conditions*: i, MeOH, AcOH, 74%; ii, $BH_3{\cdot}SMe_2$, $NaBH_4$, THF, 92%; iii, TFA, CH_2Cl_2, 80%; iv, $Cl_3CCNHOCH_2C_6H_4OMe$-*p*, cat. F_3CSO_3H, 73%; v, DIBAL-H, toluene, −20 °C, 84%; vi, $HO_2C(CH_2)_4PPh_3Br$, NaHMDS, then AcCl, MeOH, 69%; vii, Swern oxidation, then $Bu^tO_2CCH_2PO(OEt)_2$, DBU, LiCl, 66%; viii, $Me_3S(O)I$, NaH, DMSO, 74%; ix, DDQ, $CH_2Cl_2 : H_2O$, 18 : 1, 93%; x, LiOH, THF–MeOH–H_2O, 4 : 1 : 1, 100%; xi, Yamaguchi lactonisation,[12] 67%; xii, TFA, CH_2Cl_2, 100%

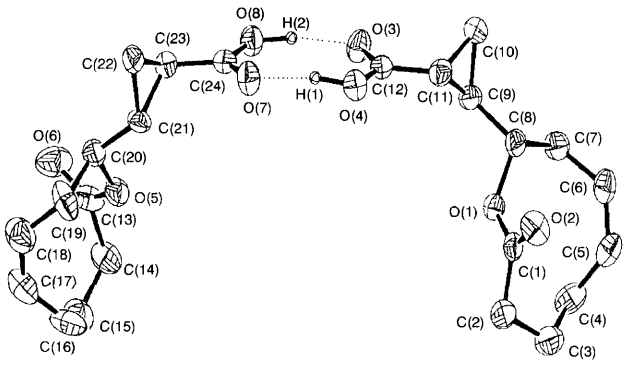


Fig. 1 X-ray crystallographic structure of 8*S*,9*R*,11*R*-(−)-**4**

the appropriate phosphonate ester under conditions described by Masamune and Roush.[9] The key cyclopropanation step was of some considerable concern, since a total of four diastereoisomers could be formed. However we assumed that if the stereochemistry of the centre adjacent to the hydroxy group could be controlled, then the appropriate *trans*-cyclopropane could be prepared by equilibration of the derived enolate in the reaction mixture. In the event we chose to use the trimethylsulfoxonium ylide method.[10] 2 equiv. of the ylide, generated by the reaction of the sulfoxonium salt with sodium hydride, followed by alcohol deprotection using DDQ[11] gave two diastereoisomers **12** and **13** in a 2 : 5 ratio, which were both assumed to contain *trans*-cyclopropane rings. The two diastereoisomeric alcohols **12** and **13** were easily separated by flash chromatography. The relative stereochemistry of the major isomer **13** was found to be appropriate for the total synthesis of **1a** and **1b**, as confirmed by an X-ray crystallographic analysis of the derived nine-membered lactone **4** (see below).

Completion of the synthesis of **4** was achieved by ester hydrolysis using lithium hydroxide followed by lactonisation using the Yamaguchi method[12] to give intermediate lactone **14** and finally acid-catalysed removal of the *tert*-butyl protecting group. The success of the lactonisation (67%) was gratifying since nine-membered lactones are known to be difficult to prepare.[8,13] However in our case the *cis*-double bond provides both an enthalpic and an entropic assistance to this process compared to the cyclisation of a saturated ring.[14] An X-ray crystallographic analysis of **4** showed the correct relative stereochemistry for the target molecule (Fig. 1).§ The structure, in which the unit cell contains two molecules hydrogen-bonded *via* the carboxylic acid groups, adopts a very similar conformation to the corresponding region of neohalicholactone itself.[1b]

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Footnotes

† This also proved to be the case during our synthetic investigations. Attempted conversion of **9** (R = SiBu^{t}Ph$_2$) to **10** (R = SiBu^{t}Ph$_2$) resulted in a considerable amount (80–90%) of migration of the silyl group to the primary alcohol. The migrated material could be converted to the nine-membered lactone using the Yamaguchi method, but subsequent attempts to remove the silyl group resulted in ring expansion to the more stable ten-membered lactone.[4]

‡ The conditions employed by Holmes[8] required the addition, by cannula tubing, of a cooled solution (−70 °C) of metallated lactol (NaHMDS base) to a cooled solution (−70 °C) of ylide (prepared using 2 equiv. of NaHMDS). Whilst this worked well for the preparation of **10** (R = CH_2Ph) extensive elimination of *p*-$MeOC_6H_4CH_2OH$ was observed in attempts to form **10** (R = $CH_2C_6H_4OMe$-*p*). We modified the procedure by adding the ylide to the metallated lactol at −70 °C, which prevents warming of the latter species during the transfer process. In addition we found that addition of a small quantity of THF to the solution of the metallated lactol was beneficial due to an improvement in solubility.

§ *Crystal data* for 8*S*,9*R*,11*R*-(−)-**4**. Crystal dimensons 0.3 × 0.3 × 0.5 mm. $C_{12}H_{16}O_4$, M = 224.2, monoclinic, a = 26.362(6), b = 6.890(3), c = 13.422(4) Å, β = 96.98(2)°, U = 2419.8 Å^3, space group $C2$, Z = 8, D_c = 1.23 g cm^{-3}, μ(Mo-Kα) = 0.90 cm^{-1}, F(000) = 960, Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leqslant \theta \leqslant 22°$. 1676 reflections were collected of which 1106 were unique with $I \geqslant 2\sigma(I)$. Data were corrected for Lorentz and polarization but not for absorption. The structure was solved by direct methods and refined using the SHELX[15] suite of programmes. The asymmetric unit consisted of 2 molecules (hydrogen bonded *via* the carboxylic groups) which were seen to be identical within the bounds of experimental error. Final residuals after 12 cycles of least squares were R = 0.0423, R_w = 0.0437, for a weighting scheme of $w = 1.2570/[\sigma^2(F) + 0.000618(F)^2]$. Max. final shift/esd was 0.000. The maximum and minimum residual densities were 0.07 and −0.06 e Å^{-3} respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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