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Combining two-directional synthesis and tandem reactions. Part 4: A concise approach to the spirocyclic core of halichlorine and the pinnaic acids

Louise G. Arini,[a] Peter Szeto,[b] David L. Hughes[c] and Robert A. Stockman[a,*]

[a]*School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK*
[b]*GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*
[c]*X-Ray Crystallography Unit, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK*

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Abstract—A synthesis of the spirocyclic core structure of halichlorine, an inhibitor of the induced expression of VCAM-1 and the pinnaic acids, inhibitors of PLA_2, is presented. A two-directional strategy is employed, in conjunction with a tandem oxime formation/Michael addition/cycloaddition to form the key azaspirocyclic skeleton in a very direct manner.

Halichlorine (Fig. 1) was isolated from the marine sponge *Halichondria akadai* Kadota in 1996 and was found to inhibit the induced expression of VCAM-1 (vascular cell adhesion molecule 1), with an IC_{50} of 7 μg/mL.[1] VCAM-1 controls the recruitment of leukocytes into inflamed tissue during an immune response and has also been linked with the growth of tumour cells. Thus inhibitors of VCAM-1 are potentially useful in the treatment of atherosclerosis, coronary artery diseases, angina, noncardiovascular inflammatory diseases and cancer.[2] The structure of halichlorine was determined by extensive NMR studies, with its absolute stereochemistry being determined by enantiospecific synthesis of a degradation product.[1b] Pinnaic acid and tauropinnaic acid (Fig. 1) were isolated from the Okinawan bivalve *Pinna maricata* by Uemura and co-workers in 1996.[3] Their structures, which differ only in the substitution at C(1), were elucidated by extensive NMR and mass spectrometry. Both pinnaic acid and tauropinnaic acid were found to exhibit inhibitory activity towards phospholipase A_2 (PLA_2) in vitro, with IC_{50} values of 0.2 mM (pinnaic acid) and 0.09 mM (tauropinnaic acid). PLA_2 is implicated in the first step of the cascade of enzymatic reactions, which lead to the generation of inflammatory mediators,[4] and thus specific inhibitors of PLA_2 have been targeted as anti-inflammatory agents. The complex structure of the pinnaic acids and the structurally related halichlorine,[1] coupled with their interesting biological activity, has resulted in considerable interest from the synthetic community in recent years, including one total synthesis[5] and one formal synthesis[6] of halichlorine, two total syntheses[7] and a formal synthesis[6] of pinnaic acid and numerous studies towards these two targets.[8]

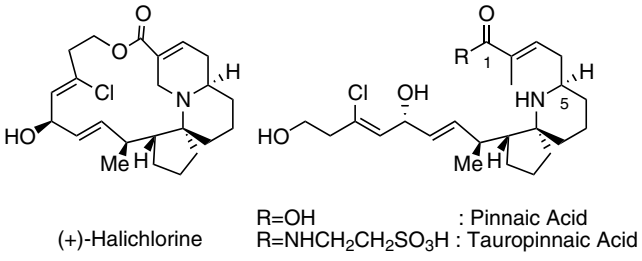

Figure 1. Structures of halichlorine and the pinnaic acids.

Two-directional synthesis and tandem reactions offer the possibility of substantially reducing the number of chemical operations required to synthesise complex target molecules of biological and material interest.[9] Recently we demonstrated the use of a two-directional

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* Corresponding author. Tel.: +44 01603 593890; fax: +44 01603 592003; e-mail: r.stockman@uea.ac.uk

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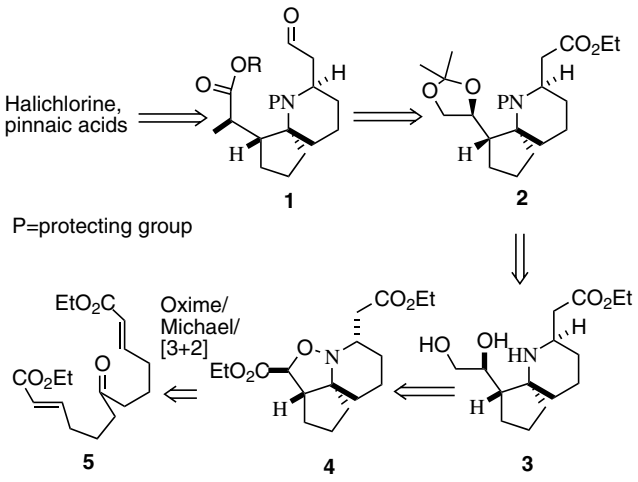


Scheme 1. Retrosynthetic analysis.

strategy directed towards the synthesis of the histrionicotoxin alkaloids.[10] Herein we report our findings in the employment of a two-directional synthesis/tandem cascade strategy for the synthesis of the spirocyclic core of halichlorine and the pinnaic acids.

Scheme 1 shows our retrosynthetic analysis. We reasoned that both halichlorine and pinnaic acid should be approachable through a common intermediate (**1**). Intermediate **1** should then be approachable through a series of functional group manipulations from **4**.

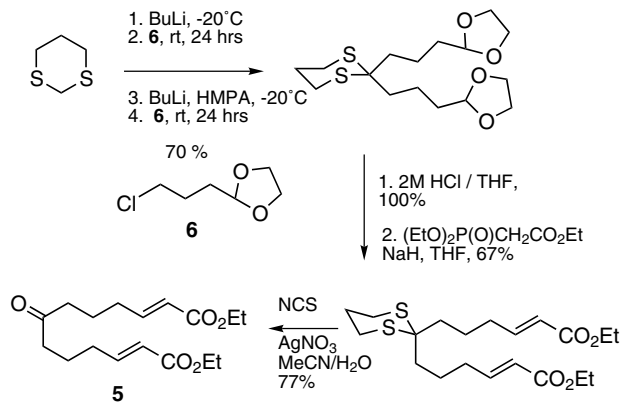
Tricycle **4** should be available by a tandem oxime formation/Michael addition/cycloaddition, which leads back to the symmetrical ketone **5**, which could be synthesised through a two-directional approach.

Initially we used a synthetic route to diester **5**, which was adapted from our studies on histrionicotoxin[10] (Scheme 2). Thus dithiane was doubly alkylated with the commercially available chloropropyldioxolane **6**. The resultant diacetal was hydrolysed, subjected to a double Wadsworth–Horner–Emmons reaction followed by hydrolysis of the dithioketal, which gave cyclisation precursor **5** in four steps and 36% overall yield from dithiane. However, the initial dialkylation was difficult to scale up due to a tricky purification by column chromatography and dithiane is a relatively expensive starting material, so a cheaper, more scaleable route was investigated.

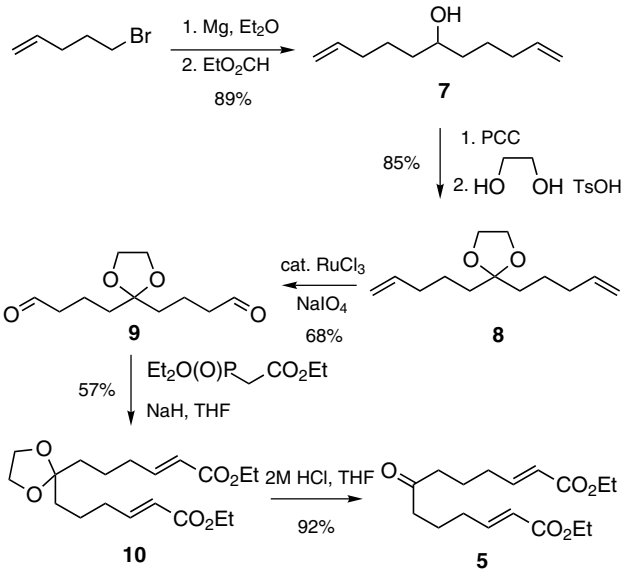
Using an electrophilic centrepiece for the two-directional approach, symmetrical alcohol **7** was formed by double addition of pent-5-enyl magnesium bromide on ethyl formate[11] (Scheme 3). Oxidation of the alcohol function of **7** and protection with ethylene glycol gave dialkene **8** in good overall yield.

Oxidative cleavage of both alkene functions of **8** was attempted initially using Lemieux and co-workers conditions[12] (catalytic osmium tetroxide with sodium periodate in THF/water), with good success. Yields of dialdehyde **9** in excess of 90% were achieved. However, this method was found to be limited due to the high dilution required for efficient stirring and thus not practical for large scales (>10 g). Catalytic ruthenium chloride/sodium periodate in acetonitrile/water[13] was found to give slightly poorer yields, but was practical on scales in excess of 10 g. Double Wadsworth–Horner–Emmons reaction of dialdehyde **9** with triethyl phosphonoacetate then gave the *E*,*E*′-dialkene **10** in 57% yield after purification. Removal of the ketal then gave our key cyclisation precursor **5** in 92% yield.

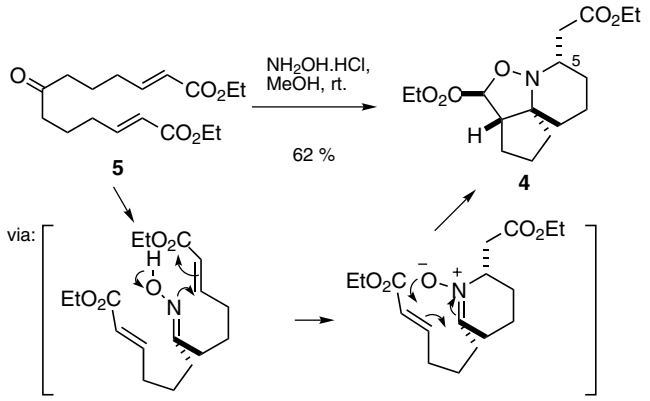
On treatment with hydroxylamine hydrochloride in the presence of sodium acetate, symmetrical ketone **5** was transformed into the [6,5,5]tricycle **4** in 62% yield, via a tandem oxime formation/Michael addition/1,4-prototopic shift/[3 + 2]-cycloaddition[14] (Scheme 4). This remarkable reaction significantly increases the complexity of the molecule, creating three ring systems and four stereogenic centres in one pot.[15] Our use of a two-direc-



Scheme 2. Initial synthesis of cyclisation precursor **5**.



Scheme 3. Scaleable synthesis of cyclisation precursor **5**.



Scheme 4. Tandem cyclisation to form tricycle **4**.

tional approach should allow for the easy installation of chiral auxiliaries for absolute stereochemical control in this cascade reaction.

The stereochemistry of C(5) in tricycle **4** is opposite to that required for pinnaic acid and halichlorine and thus we attempted a thermal retro-Michael addition/Michael addition reaction to epimerise this position, by heating **4** in refluxing chlorobenzene for 24 h (Scheme 4). However, we were only able to recover starting material (60%) and the [6,6,5]-tricyclic product **11** (39%), which we presume forms through a retro-[3 + 2]-cycloaddition/[3 + 2]-cycloaddition reaction. We reasoned that the constraints of the bicyclic isoxazoline ring of **4** may be preventing the required epimerisation (see X-ray structure of **4**, Fig. 2). Thus we concluded that the isoxazoline ring should be opened before epimerisation.

The ester function on the isoxazoline moiety of **4** was selectively reduced with sodium borohydride in ethanol in 66% yield (Scheme 5). Subsequent hydrogenation cleaved the *N–O* bond to give diol **12** in quantitative yield, which on heating in ethanol at reflux for several days, underwent clean epimerisation at C(5) to yield diol **13** with the correct relative stereochemistry for the core of halichlorine/pinnaic acid. We found that by carrying out the epimerisation in ethanol in a sealed tube at 120 °C, we could reduce the time required for complete conversion to 24 h. Protection of the diol with an aceto-

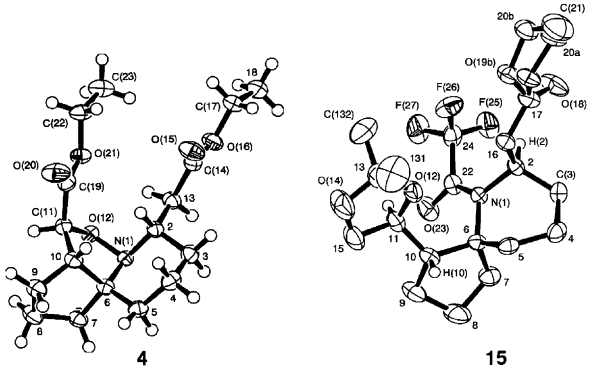
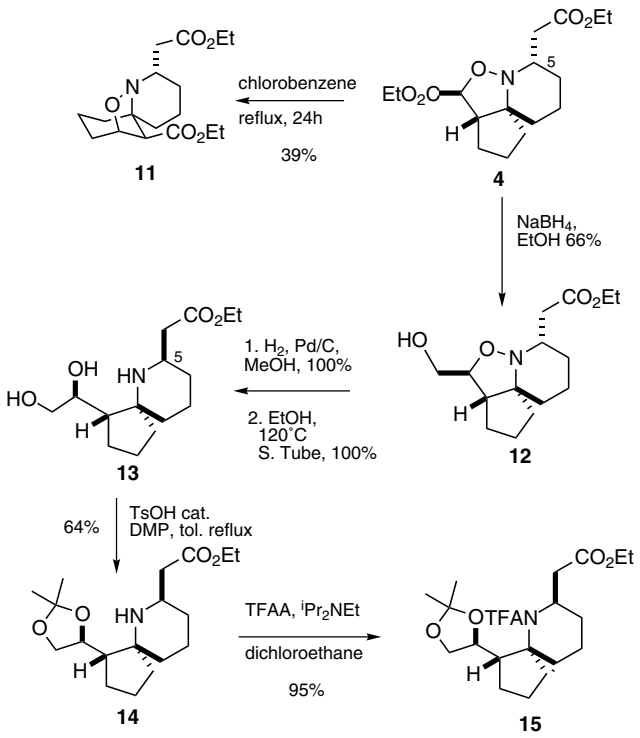


Figure 2. X-ray crystal structures of **4** and **15**.



Scheme 5. Conversion of diester **4** into protected azaspirocycle **15**.

nide function, followed by protection of the piperidine nitrogen with a trifluoroacetate group, gave fully protected spirocycle **15**.[16] X-ray crystallographic analysis of **15** confirmed epimerisation of C(5), although some disorder was noted in the orientation of the ester group (Fig. 2).

In conclusion, we have combined two-directional synthesis with a tandem cascade strategy to synthesise the spirocyclic core of halichlorine and pinnaic acid in a concise manner. Further studies to complete total syntheses of halichlorine and pinnaic acids, including the application of chiral auxiliaries and other desymmetrising catalytic systems in the key cyclisation, are on-going and our results will be reported in due course.

Acknowledgements

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15. Related cascade reactions have also been used by Lee and Zhao,[8n] Shishido and co-workers[8m] and White et al.[8k] in approaches towards halichlorine.
16. Data for **15**: mp 125–128 °C (from hexane); (Found: C, 57.17; H, 7.11; N, 3.26. $C_{20}H_{30}F_3NO_5$ requires C, 57.00; H, 7.17; N, 3.32); R_f 0.15 (1:1 hexane/ethyl acetate); ν_{max} (thin film)/cm^{-1} 1678, 1731; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.52 (1H, m), 4.16 (2H, m), 3.97 (2H, m), 3.40 (1H, m), 3.18 (1H, d, *J* 16.8), 2.78 (1H, dd, *J* 16.8 and 10.4), 2.35–1.47 (13H, m), 1.41 (3H, s), 1.27 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 171.7, 109.0 (C-2′), 76.2, 70.2, 68.8, 60.8, 58.4, 50.3, 39.6, 35.1, 34.6, 29.7, 27.3, 25.8, 25.9, 14.4, 13.9, signals too weak to observe for N*C*O*C*F$_3$; ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ 69.1 (3F, s); *m*/*z* (CI) 422 (M + 1, 100); HRMS: Found: 422.2154 $C_{20}H_{31}F_3NO_5$ (M + H) requires 422.2149.
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