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Synthetic studies towards oxylipins: total synthesis of Constanolactones A and B

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Abstract

The sequential addition of functionalised chains onto a 1,2-diformylcyclopropane synthon provides rapid access to cyclopropyl oxylipins, as demonstrated here by the total synthesis of Constanolactones A–B. These eicosanoids of marine origin have been prepared in five steps, first by the regioselective ɣ-addition of 1-trialkylsilyloxy-1-ethoxybutadiene to (1*S*,2*S*)-1-formyl-2-(thexyldimethylsilyloxymethyl)cyclopropane, then, after functional group modifications, addition of a (1*E*,3*S*,5*Z*)-3-hydroxyundeca-1,5-dienyl organometallic.

Keywords: eicosanoids; cyclopropanes; alkylation; dienes.

Marine organisms are a rich source of new natural products from which numerous oxidised fatty acid metabolites, the so-called oxylipins, have recently been isolated.[1] Among these, compounds exhibiting a lactone and a cyclopropane ring emerge as a rich and growing family (Scheme 1, top).[1–3]

The observation that the cyclopropyl lactone oxylipins always exhibit a central cyclopropane fragment bearing two adjacent substituents in a *cis*- or *trans*-relationship, usually both being a hydroxymethylene group, led us to design a very general strategy for their synthesis. Indeed, successive nucleophilic additions of appropriate side-chain precursors to reagents corresponding to *cis*- or *trans*-1,2-diformyl cyclopropane synthons should, a priori, lead to any of them (Scheme 1, bottom). In order to validate this strategy, we embarked on the synthesis of Constanolactones A and B (CL A–B), isomeric at the C9 position, and isolated from a red alga *Constantinea simplex* growing on the North-Pacific American rim.[4] CL A–B, as with other related oxylipins, are eicosanoid natural products and probably arise from arachidonic acid,[5] as well as prostaglandins, leucotrienes and lipoxins. Although still unknown, the biological activities of these cyclopropyl eicosanoids might be important and useful in medicine owing

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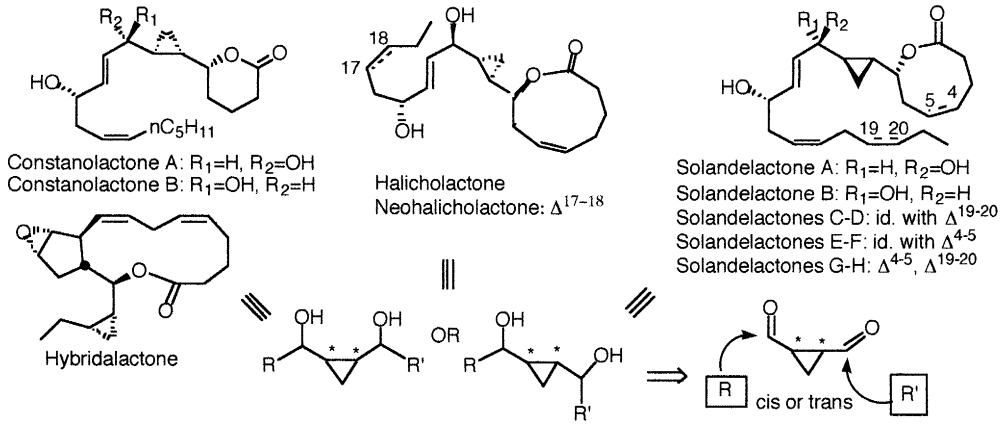
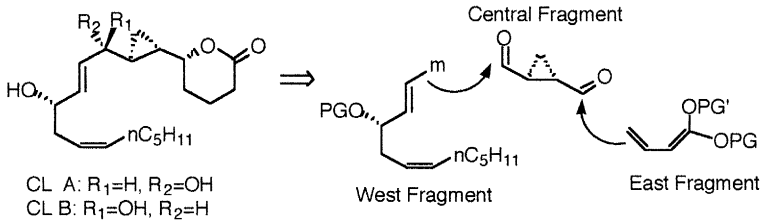


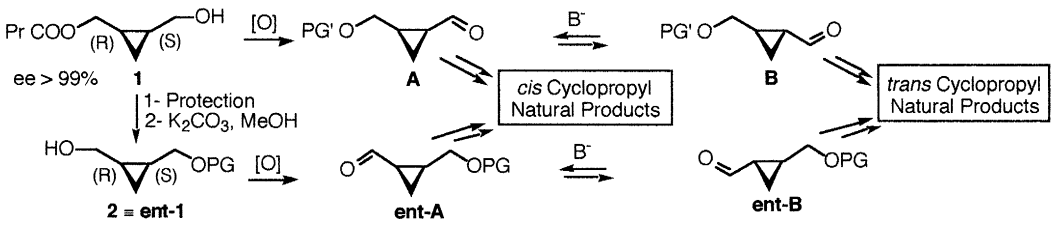
Scheme 1.

to their similarity with the known eicosanoids mentioned above. These facts, and the scarcity of these compounds, are now leading to increasing interest in their synthesis,[6] and during the course of our studies an interesting total synthesis of CL A–B based on a biomimetic route has been reported;[6b] such a route cannot, however, be extended to other oxylipins.[7] A more recent report dealing with the synthesis of the C_1–C_{10} fragment[6a] prompted us to disclose here our own more general approach.



Scheme 2.

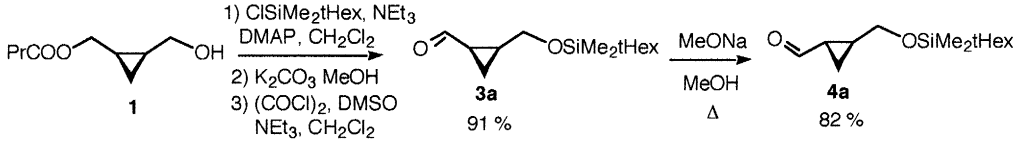
Applied to CL A–B, our sequential addition strategy would lead to three fragments (Scheme 2): (i) a *trans*-1,2-diformyl cyclopropane synthon (Central Fragment); (ii) a four-carbon synthon having a carbonyl group and nucleophilic at the γ-position relative to that carbonyl (East Fragment); and (iii) a nucleophilic (*E*)-vinyl organometallic bearing a hydroxyl group and a *Z* double bond on an 11-carbons chain (West Fragment). The latter could be obtained[8] either by hydrometallation of the corresponding acetylene[9,10a] or by metal–halogen exchange of the corresponding *trans* vinyl halide.[10b,11] For the East Fragment, we envisaged using the addition of 1,1-dialkoxy-1,3-butadienes onto the aldehyde group of the Central Fragment. Such dienes are known to react with aldehydes and related species in Mukaiyama-type reactions,[12,13] and if a γ-addition can be achieved, the resulting δ-hydroxy-α,β-unsaturated ester should be easily converted to the required lactone. The equivalent of the Central Fragment could be



Scheme 3.

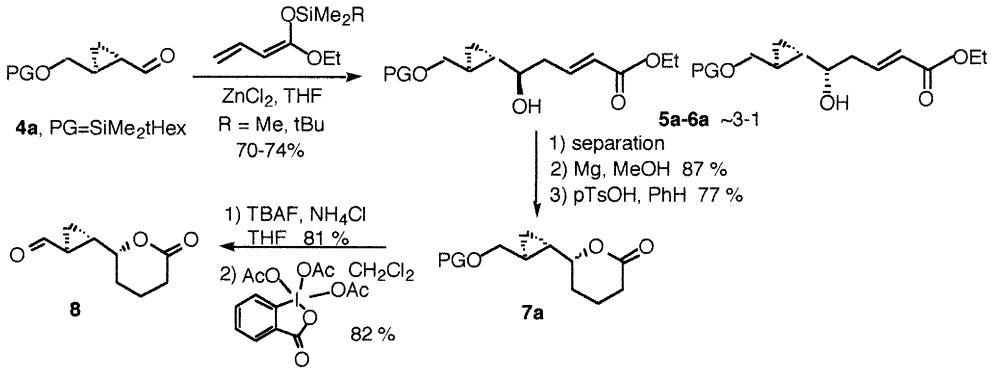
obtained from (1*S*,2*R*)-2-butyryloxymethyl-1-hydroxymethyl cyclopropane **1**, readily available in high enantiomeric purity by an enzymatic process.[14] The advantage of **1** over asymmetric cyclopropanations[15] is due to its pseudosymmetric nature which offers a convenient access to *cis*- as well as *trans*-cyclopropyl natural compounds of various absolute configurations at the cyclopropane carbons (Scheme 3).

In order to match the (6*S*,8*R*-CL numbering) absolute configuration of the selected targets, **1**[14,16] was transformed into its formal enantiomer **2a** by silylation with chlorodimethylthexylsilane[17] using the Chaudhary–Hernandez conditions[18] and then transesterification (Scheme 4). Swern oxidation,[19] followed by isomerisation with sodium methoxide in refluxing methanol, provided the silylated *trans*-2-hydroxymethyl-1-formyl cyclopropane **4a** in good overall yields.



Scheme 4.

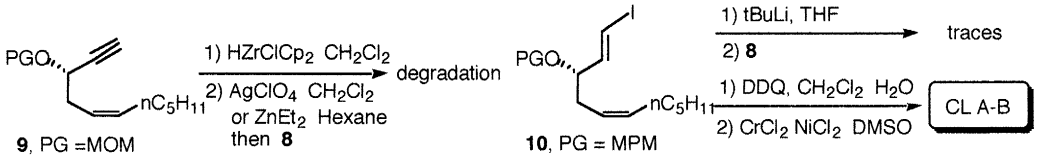
The introduction of the East Chain was achieved, as expected, by a Mukaiyama-type addition of 1,1-dialkoxy dienes to the cyclopropyl aldehyde **4a** (Scheme 5). As demonstrated by Fleming's pioneering work,[20] control of site selectivity in such dienes (α- versus γ-addition) can be achieved by either electronic or steric adjustment of the diene structure, 1-silyloxy-1-alkoxy butadiene being one of the best compromises.



Scheme 5.

Indeed, 1-silyloxy-1-ethoxy butadienes[12,21] selectively reacted at their γ-position with the aldehyde **4a** in the presence of zinc chloride as Lewis acid (Scheme 5). Due to precedents in Mukaiyama's aldolisations,[22] some stereoselectivity was expected during this addition. However, two diastereoisomeric δ-hydroxy α,β-unsaturated esters **5a**–**6a** were obtained with a modest selectivity (dr 3–1) whatever the experimental conditions used.[23] Nevertheless, both diastereoisomers can easily be separated by chromatography. Isolated with a 50–55% yield, the major isomer, which later proved to be the right one, was then reduced by treatment with magnesium powder in methanol[24] and lactonised with a catalytic amount of *para*-toluenesulfonic acid in refluxing benzene. The cyclopropyl lactone **7a** so obtained proved to be quite sensitive and its desilylation could only be performed in the presence of a proton source to avoid degradation. The resulting alcohol was best oxidised into the required *trans* aldehyde **8** using the mild Dess–Martin method.[25] This compound proved to be identical in all aspects, including its optical rotation to the intermediate obtained in optically pure form by White and Jensen[6b] after separation of the isomers formed by a biomimetic cyclisation of a chiral epoxide.

For the completion of the synthesis, an organometallic corresponding to the West Fragment must be introduced (Scheme 2). Hydrozirconation of terminal alkyne would provide the required (*E*)-vinyl organometallic; however, such vinyl chlorozirconium species are not nucleophilic enough for direct addition onto aldehydes to proceed.[26] Their nucleophilicity can, nevertheless, be enhanced by abstraction of the chloride leaving a cationic zirconium species able to react with aldehydes.[27] Transmetallation to a zinc organometallic would also solve this problem.[28] However, applied to the acetylene **9**, obtained from 1,3-propanediol,[9] and the aldehyde **8**, these methods proved to be unsuccessful (Scheme 6). The alternative sequence based on halogene–metal exchange also proved to be unsuccessful. Only a few percent of the expected addition products were isolated from a complex reaction mixture when the vinyl iodide **10**, obtained from (*S*)-malic acid,[11] was treated with *t*-BuLi and the so-formed vinyl lithium added to **8** at low temperature (Scheme 6). The Kishi–Nozaki procedure[29] already used in the sole CL A–B synthesis so far reported[6b] was eventually used. Deprotection of the *para*-methoxybenzyl group in **10** was efficiently achieved by treatment with DDQ in a mixture of dichloromethane and water.[30] The hydroxylated vinyl iodide so formed proved to be identical in all aspects, especially its optical rotation,[31] with the compound already described and obtained through a lengthly sequence from D-arabinose.[6b] This compound was then submitted to the reported conditions[6b] in the presence of the aldehyde **8**, yielding an overall 51% of the expected CL A–B as a 1.2 to 1 mixture of diastereoisomers. Spectroscopic and optical rotation data of these synthetic materials were in excellent agreement with those reported either for the natural products[4] or the synthetic materials.[6b]



Scheme 6.

In summary, the total synthesis of Constanolactones A–B has been completed using the sequential additions of already-constructed chains to a chiral equivalent of 1,2-diformylcyclopropane. The present work has demonstrated the validity of this general approach for the synthesis of the cyclopropyl containing oxylipins. Further studies are now in progress in this area.

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