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TETRAHEDRON: *ASYMMETRY*

A chiron approach to the cyclopropyl lactone oxylipins

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Abstract

Enantiomerically pure key intermediates for the synthesis of constanolactones A and B and solandelactones A, B, E and F, the hydroxy-protected (3*S*,5*Z*)-undec-1-yn-5-en-3-ol and (3*S*,1*E*,5*Z*)-1-iodoundec-1,5-dien-3-ol, have been obtained in nine steps starting from (*S*)-malic acid.

The metabolism of fatty acids by marine organisms provides a unique source of novel and diverse compounds, the so-called oxylipins.[1–3] Cyclopropyl lactone seems to be an often encountered motif among them, as judged from the isolation of hydridalactone,[4] constanolactones,[5] halicho- and neohalicholactone,[6] and more recently solandelactones.[7] Although still unknown, the biological activities of these cyclopropyl compounds might be important and useful in physiology and medicine owing to their structural and biogenetic similarities with the bioactive mammalian eicosanoids.[1,8] With the goal of providing enough materials and analogs, we have developed a general approach towards these cyclopropyl oxylipins.[9,10] In this communication, we present two routes starting from (*S*)-malic acid toward two key intermediates for the synthesis of constanolactones A–B (CL A–B) and solandelactones A–B and E–F (SL A–B and E–F).

CL A–B and SL A–B and E–F are diastereoisomeric at the carbinol position adjacent to the cyclopropyl lactone motif, and they both exhibit a common end chain with a *Z* and an *E* double bond and an allylic alcohol having the *S* absolute configuration. Therefore, they should both be obtainable in a convergent way by addition of a (3*S*,1*E*,5*Z*)-3-hydroxyundeca-1,5-dienyl organometallic to a formyl cyclopropyl lactone (west and east fragments respectively in Scheme 1).[11] Such an organometallic would be conveniently obtained by hydrometallation of the corresponding acetylenic derivative, (3*S*,5*Z*)-undec-5-en-1-yn-3-ol **6**, or by halogen–metal exchange of the corresponding (3*S*,1*E*,5*Z*)-1-haloundec-1,5-dien-3-ol **5**[12] (Scheme 2). Both compounds could be obtained from the same aldehyde **4** by homologation to either an acetylenic group or a 1-haloalkene. This aldehyde (2*S*,4*Z*)-2-hydroxydec-4-enal **4**[13] could in turn be obtained from the natural (*S*)-malic acid through a reduction–oxidation sequence and a stereoselective Wittig reaction (Scheme 2).

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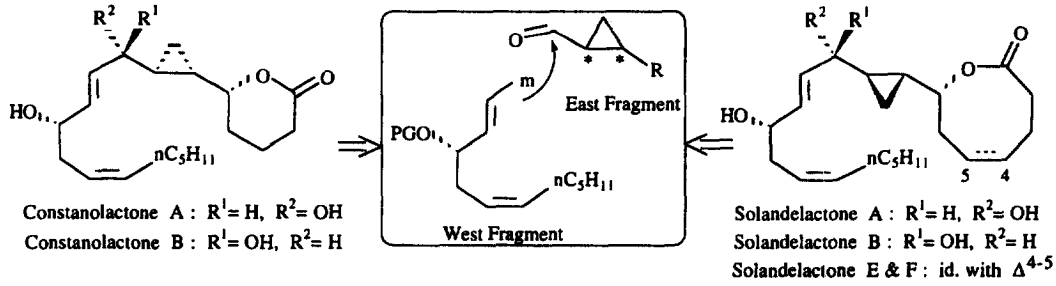
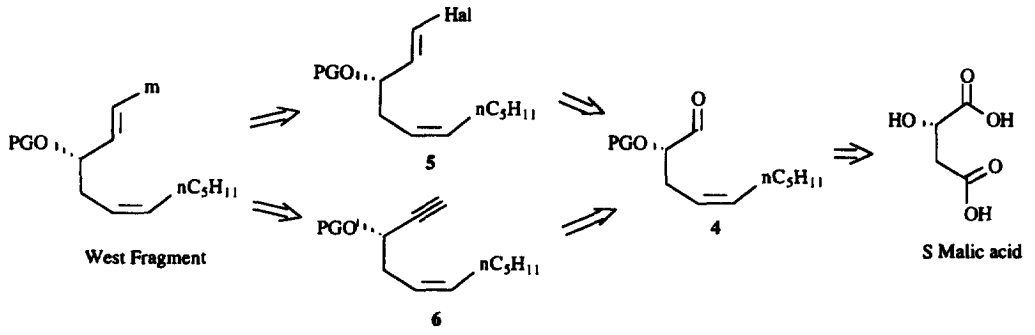


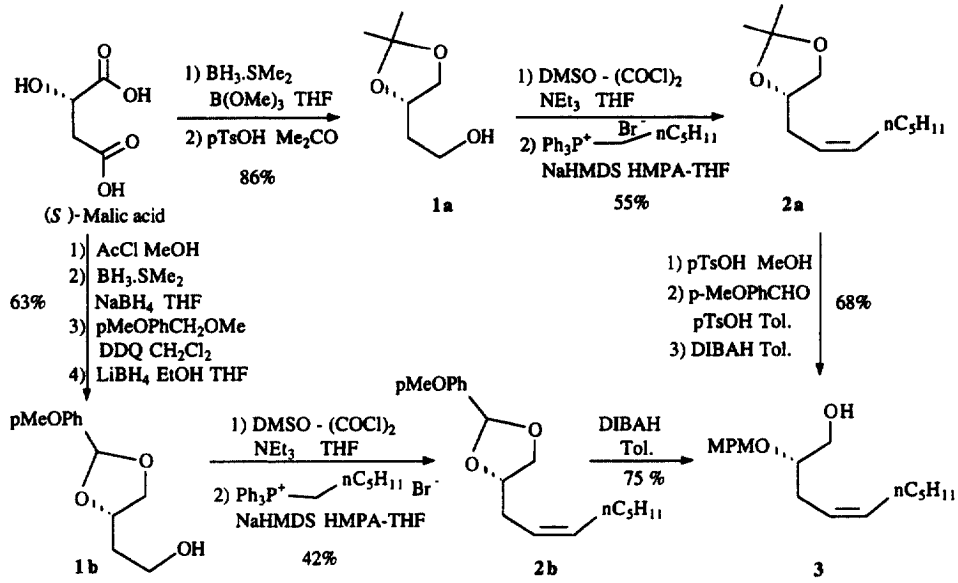
Scheme 1.



Scheme 2.

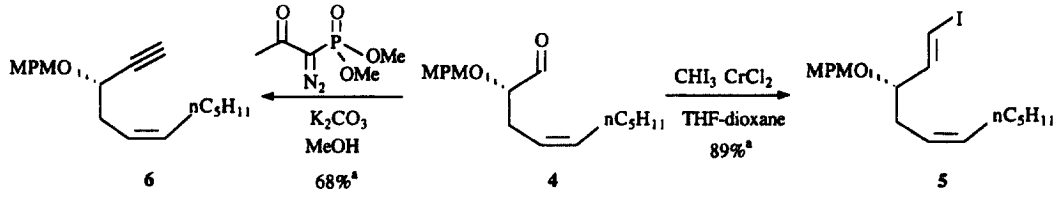
The sequences toward the aldehyde **4** are described in Scheme 3. (*S*)-Malic acid was first totally reduced to the corresponding triol **1**.[14] The 1,2-diol unit in this compound was then protected as an acetonide and the third alcohol oxidized through a Swern reaction.[15] Due to the instability of the so-obtained aldehyde, the oxidation and the subsequent stereoselective Wittig reaction were performed in a one-pot procedure which led to the alkene **2a** with a good overall yield.[16] The conditions of the Wittig step ensured the exclusive formation of the required *Z* double bond.[17] We then planned to use the Rychnovsky procedure[18] which should have achieved a selective deprotection of the enediol acetonide **2a**, liberating the free primary alcohol while maintaining the secondary protected. This methodology, however, proved to be inefficient in our hands. Therefore, we turned to more conventional methods. Complete deprotection, reprotection of the diol as a *para*-methoxyphenyl methylene ketal[19] and subsequent ketal reduction[20] provided the required enediol **3** monoprotected at the secondary alcohol. To avoid such protection–deprotection steps, we experimented an alternative route to the corresponding alcohol **3**. Starting from the dimethylester of (*S*)-malic acid, the Moriwake's procedure[21] provided the monoreduced ester. Protection of the so-obtained 1,2-diol as a *para*-methoxyphenyl methylene ketal was achieved.[19a] The remaining ester was then reduced and the corresponding alcohol **1b** oxidized. A Wittig reaction in the conditions mentioned above afforded the *Z* alkene **2b**. Regioselective opening[20] of the *para*-methoxybenzylidene ketal provided the alcohol **3**. Oxidation of the free primary alcohol in **3** then led to the required aldehyde intermediate **4** which was directly used without purification in the next step.

This key aldehyde **4** must then be homologated either to a terminal acetylene or a 1-haloalkene (Scheme 4). Different procedures have been described to achieve such transformations.[22] Since a (*E*)-1-haloalkene was required, the Takai reaction[23] known to be highly *E* stereoselective was used. Condensation of the aldehyde **4** with iodoform in the presence of chromium dichloride yielded the expected (3*S*,1*E*,5*Z*)-3-*para*-methoxyphenylmethoxy-1-iodoundec-1,5-diene **5** as the major isomer in good yield when the Evans modification was used.[24] The terminal acetylene can be obtained either



Scheme 3.

directly from the aldehyde[25] or in a two-step procedure.[26] Although the two-step procedure also provides an alternative to the Takai reaction for the formation of a 1-haloalkene,[27] we chose the direct homologation of the aldehyde to the terminal acetylene. Addition of dimethyl diazophosphonate, generated in situ using the Hohira conditions,[25] to the aldehyde **4** gave the expected acetylene **6** in good yields.



Scheme 4. (a) Yields over two steps starting from **3**

The enantiomeric excess of both **5** and **6** was secured after deprotection of the *para*-methoxybenzyl group[28] and comparison of their specific rotations with literature values.[29] Two key enantiomerically pure intermediates for the synthesis of constanolactones A–B and solandelactones A–B and E–F as well as other eicosanoids[12] have thus been obtained in nine steps from (*S*)-malic acid with good overall yield (22 or 28%, **6** or **5** respectively).

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