First total synthesis of (–)-caulerpenynol†

Laurent Commeiras,* Jérôme Thibonnet and Jean-Luc Parrain*

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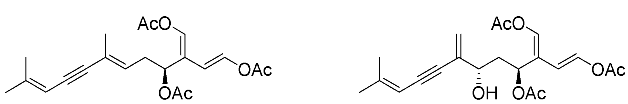
The first diastereoselective synthesis of the antimicrobial and cytotoxic agent (–)-caulerpenynol 2 has been achieved in relatively few steps from the commercially available (*S*)-malic acid.

Introduction

Some metabolites from tropical algae have been described as implicated in chemical defence against grazing fishes and invertebrates in herbivore-rich tropical waters[1] and has been proposed as an explanation for the unhindered proliferation of *Caulerpa taxifolia*, a tropical green seaweed, accidentally introduced in the Mediterranean. Compared to other *Caulerpa* species in the tropics, *Caulerpa taxifolia* contains large amount of caulerpenyne **1**, a sesquiterpene isolated from 10 different species of *Caulerpa* and was first identified from *Caulerpa prolifera.*[2] Among its biological activities, which are attributed to the diacetoxybutadiene moiety, caulerpenyne **1** inhibits the proliferation of the fibroblastic cell line BHK 21/C13 from baby hamster kidneys and the division of sea urchin eggs.[3] The cytotoxicity was also demonstrated in various tumor cell lines[4] and recently it was shown that caulerpenyne **1** has antiproliferative activity against the tumor cell line SK-N-SH and modifies the microtubule network.[5] In addition, several secondary metabolites were identified and could contribute to the toxicity of *C. taxifolia* from the Mediterranean (Fig. 1). Among these metabolites, caulerpenynol **2** was isolated and identified in 1993 by Guerriero *et al.*[6] The antibacterial and cytotoxic activities of **2** were evaluated against prokaryotic marine bacteria, and unicellular eukaryotes ciliate protists, and **2** proved to be the most active of the terpenes of *C. taxifolia* with the exception of two bacteria.[6]



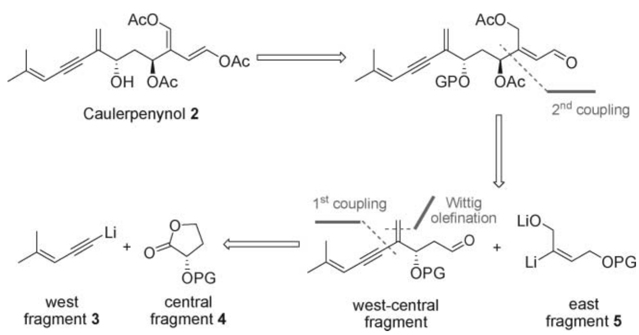
Caulerpenyne **1** Caulerpenynol **2**

Fig. 1

Inspired by the pronounced biological activities of **2** and to provide material for a more extensive biological evaluation, we have undertaken the total synthesis of caulerpenynol **2**. To the best of our knowledge, only few synthetic transformations (epoxidation) from **1** to caulerpenynol **2** have been reported in the literature[6,7] but no total synthesis of **2** has been realized.

Results and discussion

The main structural features of **2** are a terminal 1,4-diacetoxybutadiene moiety, an en-yn-ene moiety, two chiral centers and a 1,3-*anti*-diol moiety in which one alcohol function is protected as acetate. As outlined in Scheme 1, our strategy for synthesizing **2** called for the initial preparation of three fragments referred to as west, central and east. We considered that the assembly of three fragments could be obtained through two C–C coupling reactions. The first coupling was realized between alkynyl lithium **3** (west fragment obtained from Fritsh-Buttenberg-Wiechell rearrangement) and lactone **4** (central fragment). The carbon skeleton was achieved through a second coupling between vinyllithium **5** (east fragment obtained from a tin-lithium exchange) and the corresponding west-central fragment.



Scheme 1 Retrosynthetic scheme of caulerpenynol **2**.

Synthesis of the key central fragment (Scheme 2) started from the commercially available (*S*)-malic acid, which was transformed in three steps, in high yield and multigram scale, into the known lactone **6**.[8] First, (*S*)-malic acid was protected as an acetonide (2,2-dimethoxypropane, *p*-TsOH), the carboxylic acid was then reduced to the alcohol using BH_3-THF. This unstable product immediately rearranged to (*S*)-3-hydroxybutyrolactone **6** in the presence of *p*-TsOH. Lastly, the alcohol function of **6** was protected as the triethylsilyl ether to give the central fragment **7** (71% yield over four steps).

Synthesis of the western fragment was performed *via* the Corey-Fuchs alkynylation reaction.[9] Commercially available 3,3-dimethylacrolein was first converted quantitatively into the known corresponding *gem*-dibromide, which by treatment with 2 eq. of *n*-BuLi generated alkynyl lithium **3** by a Fritsch-Buttenberg-Wiechell rearrangement.

The remaining east fragment **10** was prepared in two steps from the commercially available but-2-yn-1,4-diol *via* a

Aix-Marseille Université, Institut des Sciences Moléculaires de Marseille iSm2, UMR 6263, équipe STeRéO, Campus Scientifique de Saint Jérôme, service 532, 13397, Marseille cedex 20, France. E-mail: laurent.commeiras@univ-cezanne.fr, jl.parrain@univ-cezanne.fr; Fax: +33 4 91 28 91 87; Tel: +33 4 91 28 91 26

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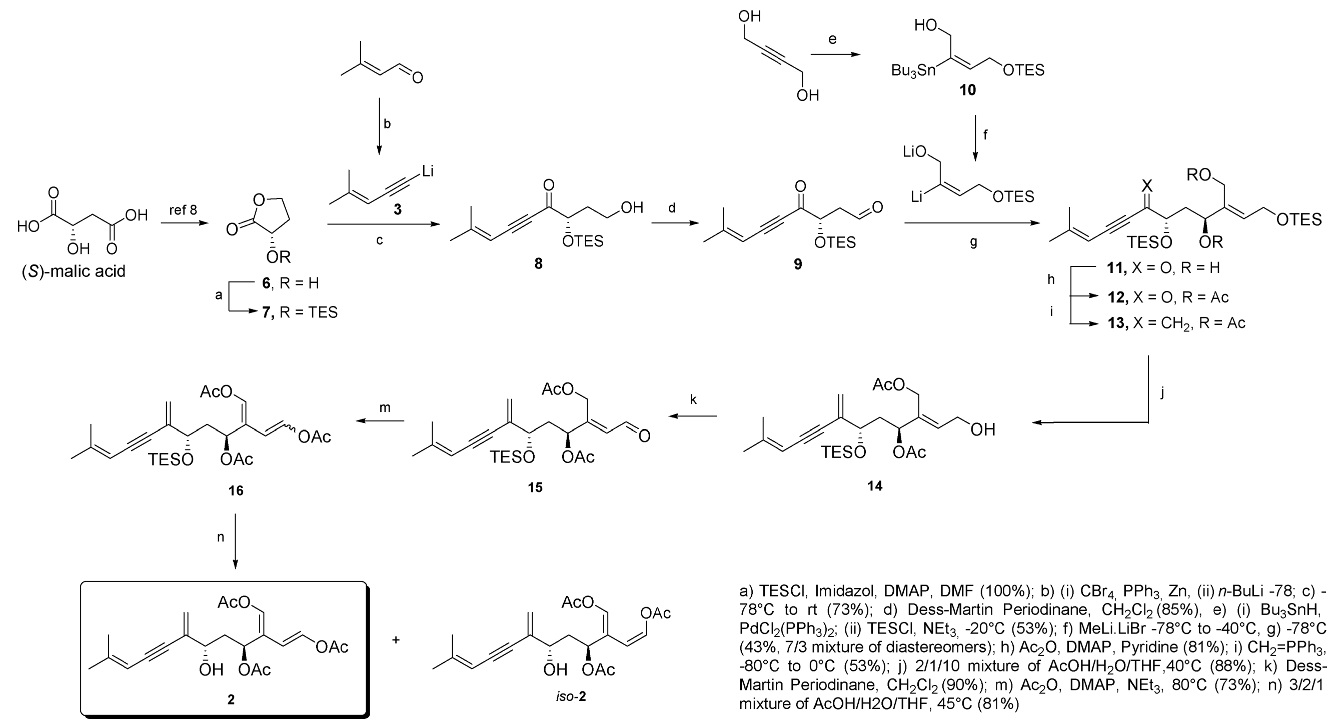

Scheme 2 Synthesis of caulerpenynol **2**.

palladium-catalyzed hydrostannation reaction, giving quantitatively the known (*E*)-vinyltin reagent.[10] Subsequent selective protection of the less hindered primary alcohol as a triethylsilyl ether furnished **10** in 53% overall yield for the two-step transformation.

Construction of the carbon skeleton of (–)-caulerpenynol **2** started by a coupling reaction between the central fragment **7** and the alkynyllithium **3** to furnish the corresponding alcohol **8**, which was then oxidized using Dess-Martin periodinane to afford aldehyde **9**. The carbon skeleton of caulerpenynol was achieved through a second coupling reaction between **9** and a vinyl lithium reagent generated by tin-lithium exchange reaction on **10**, giving diol **11** in 43% yield as a 7/3 mixture (based on ^{13}C NMR) of separable diastereomers in favour of *anti* diastereomer.[11] The mixture of isomers were separated and purified by flash chromatography.[12]

At this stage, both hydroxy groups of the major *anti* isomer **11** were protected as the acetates to give bis-acetate **12** which was subjected to olefination reaction using standard conditions to afford **13**. Selective cleavage of the primary allylic triethylsilyl ether in the presence of the secondary allylic triethylsilyl ether was performed with a 2/1/10 mixture of AcOH/H_2O/THF at 40 °C, furnishing the desired primary alcohol **14**,[13] which was further oxidized with Dess-Martin periodinane into aldehyde **15**. To generate the diacetoxybutadiene moiety, we employed conditions developed in our group (NEt_3, DMAP, Ac_2O at 80 °C) and applied for the synthesis of other natural products.[14] The TES-protected caulerpenynol **16** was obtained in a 53/47 *E*/*Z* diastereomeric mixture. Finally, a 3/2/1 mixture of AcOH/H_2O/THF at 45 °C was used to remove the triethylsilyl protecting group, cleanly affording a 52/48 diastereomeric mixture of caulerpenynol **2** and *iso*-caulerpenynol *iso*-**2** separable by HPLC. The physical and spectroscopic data (mass, ^{1}H NMR, ^{13}C NMR, optical rotation) of our synthetic material are in complete agreement with those reported for the naturally derived caulerpenynol,[6,15] confirming our prediction of the relative and absolute configuration of *anti*-diastereomer **11**.

Conclusion

In summary, the first diastereoselective total synthesis of the metabolite (–)-caulerpenynol **2** has been reported in relatively few steps.

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Notes and references

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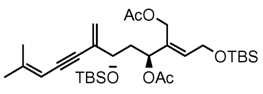

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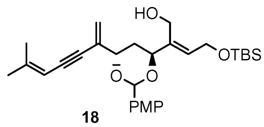

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