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# On the construction of 2-substituted 1,4-diacetoxybutadiene moiety: application to the synthesis of (±)-caulerpenyne

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**Abstract**—The synthesis of 2-substituted 1,4-diacetoxybutadiene derivatives with a partial control of stereochemistry is described from two potentially precursor enals by a judicious choice of experimental conditions ($Ac_2O$/DMAP in $Et_3N$). These conditions have been successfully applied in the first total synthesis of caulerpenyne. 

Marine algae of the order Caulerpales are known for their chemical defence against predators by producing secondary metabolites. The majority of these compounds are sesquiterpenoids and diterpenoids, often acyclic. The terminal 1,4-diacetoxybutadiene moiety is a functional group common to most of these metabolites and uniquely found in this group of marine algae. Nowadays, more than 30 toxins with this moiety have been isolated from the Udoteaceae and Caulerpaceae families such as caulerpenyne, flexiline, dihydrorhipocephaline and crispatenine (Fig. 1).[1]

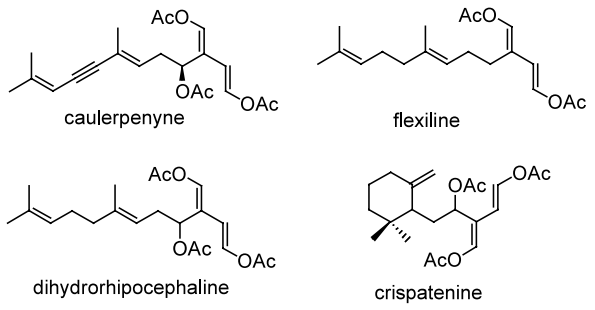
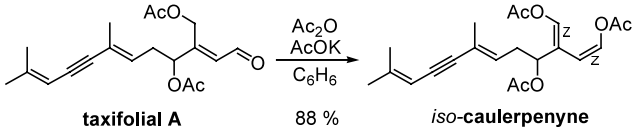



**Figure 1.**

The 1,4-diacetoxybutadiene moiety represents an acetylated bis-enol form of the 1,4-dialdehyde constellation, to which a high degree of biological activity is generally attributed. Indeed, some of metabolites containing this moiety have been implicated in chemical defence against grazing fishes and invertebrates in herbivore-rich tropical waters and this has, for example, been proposed to explain the proliferation from Italy to Spain of *Caulerpa taxifolia*, a tropical green seaweed accidentally introduced in the Mediterranean sea. From *Caulerpa taxifolia* were isolated nine mono- and sesquiterpenes such as caulerpenyne[2] (CYN) which represents the main toxin of this algae. CYN is well known for its important biological activity: it inhibits the proliferation of the fibroblastic cell line BHK 21/C13 from baby hamster kidney and the division of sea urchin eggs.[3] Its cytotoxicity was also demonstrated in various tumour cell lines[4] and recently it was demonstrated that CYN has an antiproliferative activity on tumour cell line SK-N-SH and modifies the microtubule network.[5] To provide material for a more extensive biological evaluation, we have previously described the total synthesis of taxifolial A, another secondary metabolite extracted from *Caulerpa taxifolia*.[6] Nevertheless, its transformation into caulerpenyne failed and only *iso*-caulerpenyne was obtained by trapping the dienyl enol of taxifolial A (Scheme 1).

Here we present studies towards the preparation and the control of stereochemistry of the (*E*,*Z*)-2-substituted diacetoxybutadienyl derivatives and its application in the synthesis of caulerpenyne.




**Scheme 1.** Synthesis of *iso*-caulerpenyne.

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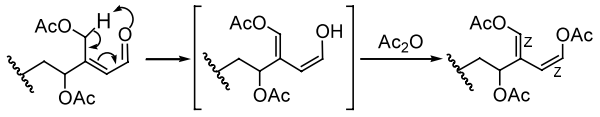
To explain the configuration of the diacetoxy butadiene moiety of *iso*-caulerpenyne obtained, we thought that the dienol having the (*Z*,*Z*)-configuration is kinetically formed from taxifolial A in its *s-cis* conformation (Scheme 2).



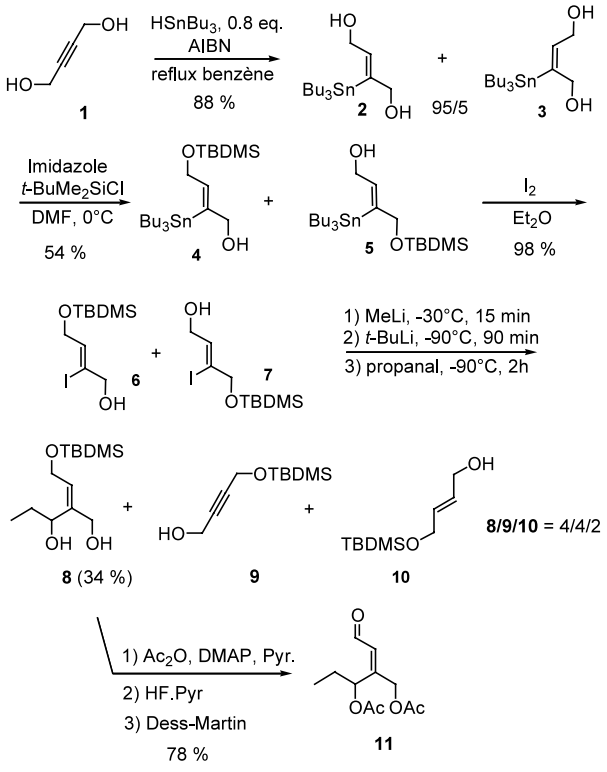

**Scheme 2.**

In order to find optimal conditions to generate *Z*,*E* diacetoxybutadiene, we decided to prepare two model compounds able to lead to the above mentioned moiety. So, we planned to prepare a simplified analogue of taxifolial A in which the double bond exhibits two different fixed configurations. Firstly, as the (*E*)-configuration of taxifolial A led to non-natural configurations of the diene, we prepared enal **11** following the route described in Scheme 3. Radical addition of tributylstannyl hydride on butynediol **1** led to an inseparable 95/5 mixture of vinyltin **2** and **3** in 88% yield that was separated by mono protection using *tert*-butyldimethylsilyl chloride in the presence of imidazole. This protection furnished, in 54% yield, regioisomers **4** and **5** that gave an equimolecular mixture of vinyliodides **6** and **7** after iododestannylation with iodine in ether. Iodine–lithium exchange at low temperature with *tert*-butyllithium (3 equiv.) led only to the allyl alcohol **10**.

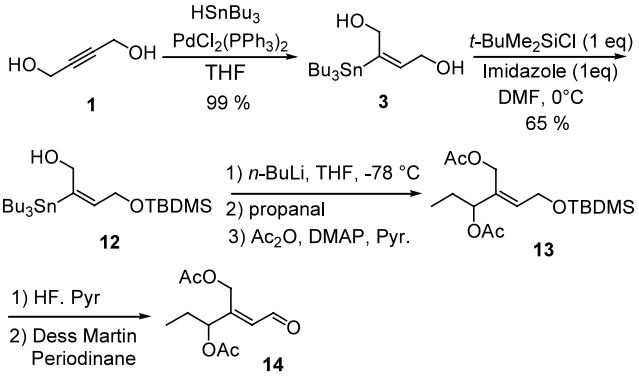
To explain the sole formation of **10**, we propose that the iodine–lithium exchange occurred before the metallation of the alcohol function. This problem was solved using 1 equiv. of methyllithium followed by treatment of the reaction mixture with *tert*-butyllithium.[7] Trapping the vinyllithium intermediate with propanal led to a 4/4/2 mixture of **8**, **9** and **10** in which the desired diol **8** was isolated in 34% yield (from the mixture of alcohols **6** and **7**). The overall low yield of this reaction could be explained by the presence of a large amount of monoprotected butynediol **9** which was exclusively formed from vinyliodide **7** by β-elimination. Finally, diol **8** was acetylated using acetic anhydride, deprotected with HF/pyridine and oxidised with Dess–Martin periodinane to give **11** in 78% yield (over three steps).

The second model was prepared using a similar procedure used in our previous synthesis of taxifolial A (Scheme 4). Enal **14** was obtained in 56% yield over four steps from **12**.

The formation of the butadiene moiety was first investigated using enal **11**. Conditions used in the synthesis of *iso*-caulerpenyne, i.e. $Ac_2O$ and potassium acetate in refluxing benzene, yielded mainly disubstituted 1,4-diacetoxybutadiene **15** (60%). The configuration of the tetrasubstituted double bond of **15** was assigned on the basis of NOESY NMR experiments (Scheme 5).

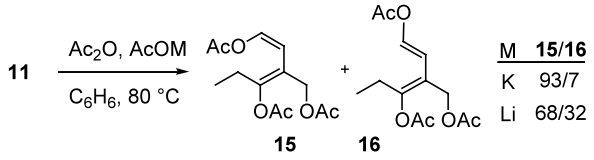



**Scheme 3.**




**Scheme 4.**

A similar experiment conducted with lithium acetate in place of potassium acetate led to a 68/32 mixture of **15** and **16** in good yield. Once more, the enal in its *s-cis* conformation drives the dienol formation leading to **15** and **16**.[8] The unique configuration of the tetrasubstituted double bond could certainly be explained by the minimisation of 1,3-allylic strains. As the model **11** did not furnish the natural diacetoxybutadiene moiety, we turned our attention to the study of model **14**.

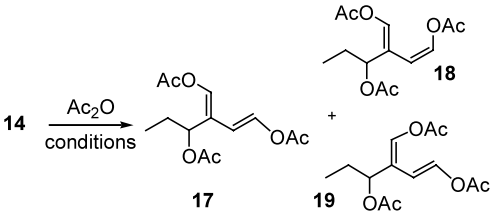



**Scheme 5.**

Firstly, we tested acetate salts other than potassium acetate. The reactions were performed with 1.5 equiv. of M(OAc)n, 3 equiv. of acetic anhydride at 80°C and followed by $^1$H NMR. CuOAc, $Cu(OAc)_2$, $Mg(OAc)_2$, and $Pb(OAc)_2$ did not give the expected diacetoxybutadienyl derivatives and led to a complex mixture of several unidentified products, among them numerous aldehydes. LiOAc, CsOAc and $Zn(OAc)_2$ afforded cleanly a mixture of isomers **17**, **18** and **19**. As a slight trend, if the cation exhibits some Lewis acidity, the *E*/*Z* isomer was obtained in each case. Nevertheless, the desired isomer **17** was always obtained as minor isomer (Scheme 6, Table 1).

Tertiary amines were also used. $NEt_3$ as base/solvent, 3 equiv. of $Ac_2O$ with 5% of DMAP at 80°C gave better results than those observed in the use of $M(OAc)_n$. Reactions, checked by GC, were rapid and afforded cleanly a 24/75/<1 mixture of (*E*,*Z*)/(*Z*,*Z*)/(*E*/*E*) isomers. The same reaction performed with 1 or 3 equiv. of DMAP gave the best results with a ratio of 45/55 of (*E*,*Z*)/(*Z*,*Z*) isomers with no evidence of **19** being formed. Other amines such as pyridine or Hunig's base led to larger amount of isomer **19**. It should be noted that treatment of enal **14** with LiHMDS, NaHMDS or KHMDS at −78°C in THF followed by quenching with $Ac_2O$ did not furnish the desired dienes.

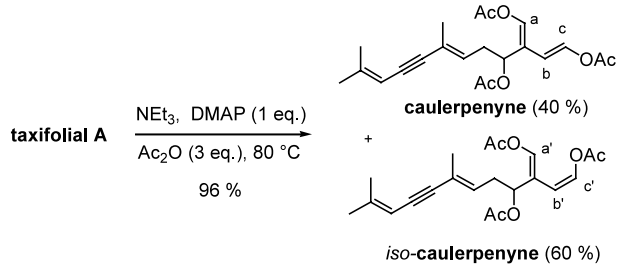
Finally, we applied the following conditions (3 equiv. of $Ac_2O$, 1 equiv. of DMAP, $NEt_3$ at 80°C)[9] to taxifolial A that yielded a 96% mixture of 40/60 of (±)-caulerpenyne with the (*E*,*Z*) configuration of the diacetoxybutadiene moiety and (±)-*iso*-caulerpenyne with the (*Z*,*Z*) configuration (Scheme 7). Their stereochemistry was established by the $^1$H NMR spectrum ($J_{b\text{-}c}$ = 12.7 Hz characteristic of H-H *E*-coupling constant and $J_{b'\text{-}c'}$ = 7.3 Hz characteristic of H–H *Z*-coupling constant) and a $^1$H NMR NOESY experiment (presence of cross peak between $H_a$ and $H_b$ and presence of low relationship between $H_{a'}$ and $H_{b'}$). Moreover, the data of the synthetic (±)-caulerpenyne are in agreement with those reported in the literature (500 MHz $^1$H NMR $CDCl_3$ and $C_6D_6$, 125 MHz $^{13}$C NMR $CDCl_3$ and TLC mobility).




**Scheme 6.**

**Table 1.** Preparation of diacetoxybutadiene from **14**

| Conditions | **17** | **18** | **19** |
|---|---|---|---|
| LiOAc, $C_6H_6$, 80°C | 27 | 73 | – |
| CuOAc, $C_6H_6$, 80°C | – | – | – |
| $Cu(OAc)_2$, $C_6H_6$, 80°C | – | – | – |
| $Mg(OAc)_2$, $C_6H_6$, 80°C | – | – | – |
| $Pb(OAc)_2$, $C_6H_6$, 80°C | – | – | – |
| CsOAc, $C_6H_6$, 80°C | 10 | 90 | – |
| $Zn(OAc)_2$, $C_6H_6$, 80°C | 45 | 41 | 14 |
| $Et_3N$, 80°C | 11 | 88 | – |
| $Et_3N$, DMAP (5 mol%), 80°C | 24 | 75 | <1 |
| $Et_3N$, DMAP (1 equiv.), 80°C | 45 | 54 | <2 |
| $Et_3N$, DMAP (3 equiv.), 80°C | 45 | 55 | Trace |
| $Et_3N$, DMAP (5 mol%), rt | 29 | 69 | <2 |
| $Et_3N$, DMAP (1 equiv.), 80°C | 20 | 78 | <2 |
| Pyr., DMAP (5 mol%), rt | 38 | 47 | 15 |
| Pyr., DMAP (5 mol%), 80°C | 20 | 72 | 8 |
| *i*-$Pr_2NEt$, DMAP (1 equiv.), rt to 80°C | 51 | 32 | 17 |
| *i*-$Pr_2NEt$, DMAP (1 equiv.), 80°C | 37 | 56 | 7 |




**Scheme 7.**

In conclusion, the first total synthesis of (±)-caulerpenyne was carried out in good yield 6% over 10 steps from but-3-yn-1-ol.

In summary, we have designed and synthesised two enals, potential precursors of 2-substituted 1,4-diacetoxy-butadiene derivatives. We found that the partial control of stereochemistry could be obtained by a judicious choice of experimental conditions. Finally, the conditions found have been successfully applied in the first total synthesis of (±)-caulerpenyne.

## Acknowledgements

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9. In a Schlenk tube, under a nitrogen atmosphere, was placed 50 mg (0.15 mmol) of taxifolial A, 18.4 mg (0.15 mmol) of DMAP, 42 μL (0.45 mmol) of $Ac_2O$ and 4 mL of $NEt_3$. The mixture was warmed to 80°C and the reaction was monitored by GC. After disappearance of the started material, the mixture was concentrated under vacuum and purified by chromatography on silica gel (pentane/ethyl acetate: 8/2) to give a 40/60 mixture of caulerpenyne and *iso*-caulerpenyne in 96% yield.
(±)-Caulerpenyne: $^1$H NMR (500 MHz, $CDCl_3$) 1.79 (s, 3H), 1.81 (s, 3H), 1.86 (s, 3H), 2.05 (s, 3H), 2.13 (s, 3H), 2.17 (s, 3H), 2.45 (dt, $J$=14.7/7.5 Hz, 1H), 2.63 (dt, $J$=14.7/7.5 Hz, 1H), 5.33 (s, 1H), 5.67 (bt, $J$=7.5 Hz, 1H), 5.80 (d, $J$=12.6 Hz, 1H), 5.85 (t, $J$=7.5 Hz, 1H), 7.23 (s, 1H), 7.62 (d, $J$=12.6, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) 17.8, 20.7 (2C), 21.0, 21.2, 24.9, 32.1, 68.9, 85.3, 94.1, 105.3, 109.3, 118.7, 121.6, 129.9, 134.3, 137.0, 148.2, 167.1, 167.9 and 170.0.
(±)-*iso*-Caulerpenyne: $^1$H NMR (500 MHz, $CDCl_3$) 1.79 (s, 3H), 1.80 (s, 3H), 1.86 (s, 3H), 2.02 (s, 3H), 2.19 (s, 6H), 2.36 (dt, $J$=14.5/7.3, 1H), 2.54 (dt, $J$=14.5/7.3, 1H), 5.18 (d, $J$=7.3 Hz, 1H), 5.32 (s, 1H), 5.66 (bt, $J$=7.3 Hz, 1H), 5.86 (t, $J$=7.3 Hz, 1H), 7.22 (d, $J$=7.3 Hz, 1H), 7.81 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) 17.8, 20.85, 20.89, 21.0, 21.2, 24.9, 32.4, 68.7, 85.2, 94.2, 103.6, 105.3, 116.9, 121.5, 129.9, 135.2, 137.6, 148.2, 167.2, 167.4, 170.0.