Total Synthesis of Terpenoids Isolated from Caulerpale Algae and Their Inhibition of Tubulin Assembly

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Abstract: Total synthesis of four analogue terpenoids isolated from *Caulerpa taxifolia* was achieved in good yield with a total control of each double bond. Biological tests to compare the activities of in vitro tubulin polymerisation between the natural caulerpenyne and the synthetic caulerpenyne and its derivatives were also performed.

Key words: total synthesis, caulerpenyne, dihydrorhipocephalin, furocaulerpin, terpenoids, microtubule polymerisation

Introduction

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. To date, more than thirty toxins with this moiety have been isolated from the Udoteaceae and Caulerpaceae families such as caulerpenyne, flexiline, dihydrorhipocephalin and crispatenine (Figure 1).[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 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, **1**) which represents the main secondary metabolite of this algae.

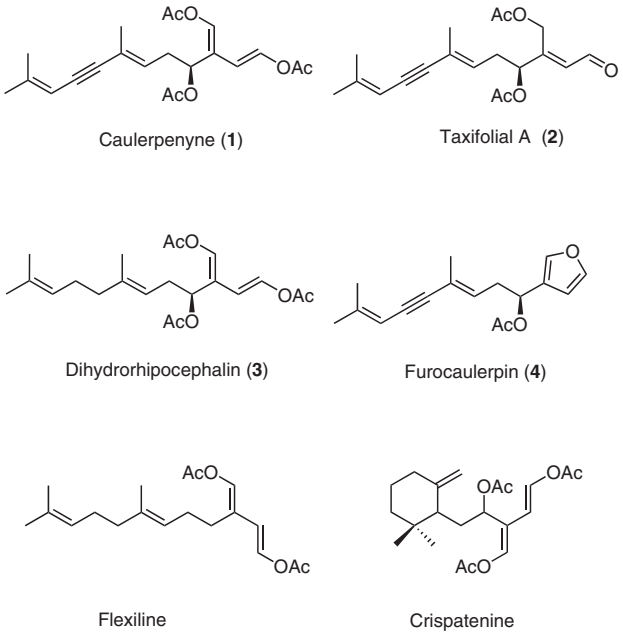

Figure 1 Some of the toxins isolated from Udoteaceae and Caulerpaceae algae

CYN is well known for its important biological activity: it displays antineoplastic and antibacterial properties.[3] It inhibits the first division of sea urchin eggs without affecting fertilization[4] and induces a transient cytoplasmic acidification followed by an efflux of protons.[5] In addition, CYN alters ATP-dependent Ca^{2+} storage in intracellular organelles, protein phosphorylation, and DNA synthesis.[4] Moreover, Fischel et al. showed that CYN inhibited growth in eight human cancer cell lines.[6] Their study showed that in the presence of CYN, cells exhibited an early and marked shift into S phase followed by a blockage in the G_2/M phase. Recently, we have demonstrated that natural CYN induced an inhibition of neuroblastoma SK-N-SH cell line with an inhibitory concentration of 8±1 μM after 24 hours of incubation. No blockage in G_2/M phase but an increase in cell death was observed. By immunofluorescence of the tubulin cytoskeleton, we observed a modification of the microtubule network in presence of natural CYN. Moreover, natural CYN inhibits the tubulin polymerisation *in vitro* with an

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Biographical Sketches

Laurent Commeiras, born in 1975 in Marseille (France), received his Ph.D. in 2002 from the Université Paul Cézanne of Marseille working on the total synthesis of terpenoids isolated from Caulerpale algae under the supervision of Dr. Jean-Luc Parrain. After postdoctoral research in the laboratory of Professor Sir Jack E. Baldwin at the University of Oxford (UK), he became Lecturer at the University of Marseille. His research interests include the total synthesis of natural and biological compounds.

Julien Bourdron was born in Saint-Gaudens (France) in 1981. He has studied chemistry at the chemical engineering school of Marseille (ENSSPICAM) and at the Université Paul Cézanne of Marseille. He is now in the third year of his Ph.D. under the supervision of Drs. Jean-Luc Parrain and Vincent Peyrot, working on the synthesis and biological evaluation of Caulerpenyne and derivatives.

Soazig Douillard was born in 1973. She is postgraduated in Biotechnology from the University of Compiègne (France). She spent two years studying actin dynamics and cell migration at the University of Bristol (England). She is now involved in biophysics research working on the microtubule cytoskeleton at the Faculty of Pharmacy of Marseille.

Pascale Barbier was born in Toulon (France) in 1968. She received her Ph.D. in biochemistry in 1996 from University of Paris XI working on the interaction of new analogues of colchicine with tubulin. She is now lecturer at the Faculty of Pharmacy of Marseille. Her research interests are the interaction mechanism of synthetic or natural drugs with tubulin, an essential constituent of the cytoskeleton.

Nicolas Vanthuyne was born in Lille (France) in 1977. He studied chemistry at the chemical engineering school of Marseille and at the Université Paul Cézanne of Marseille, where he received his Ph.D. under the supervision of Professor Christian Roussel in 2004, working on synthesis and evaluation of chiral selectors. He is currently working on separation of enantiomers by chiral HPLC. His research interests include chiral recognition mechanisms, dynamic stereochemistry and synthesis of heterocyclic atropisomers.

Vincent Peyrot was born in Gap (France) in 1957. Doctor in pharmacy since 1980, he received his Ph.D. in Pharmacology in 1986 from University of Marseille. He was promoted to Professor in biophysics at the Faculty of Pharmacy of Marseille in 1998 and his research interests are in biophysical ligand-receptor interactions.

Jean-Luc Parrain obtained, in 1990, his Ph.D. in Chemistry at the University of Nantes (France) under the supervision of Professor Jean-Paul Quintard. After post-doctoral studies in the laboratory of Professor Steve Davies at University of Oxford, he joined the CNRS as chargé de recherche at the laboratory of Organic Synthesis of the University of Nantes. In 1995, he moved to the University of Marseille and then was appointed a CNRS director of research in 2001. His research interests include new catalytic reactions toward new synthetic methods, development of new organotin and silicon reagents and total synthesis of natural compounds.

inhibitory concentration of 21±2 μM. By electronic microscopy, we concluded that CYN induced aggregation of tubulin which may be responsible for the microtubule inhibition.[7]

In order to study the structure-activity relationship concerning the pharmacophore requirements, to prove the significant role of the diacetoxybutadiene moiety in biological effects of such terpenoids and to evaluate the role of the chiral centre, the terminal alkyl chain and stereochemistry of diacetoxybutadiene moiety, we have undertaken the first total racemic synthesis of CYN (**1**) and the first total synthesis of three other natural analogues of CYN: taxifolial A (**2**), dihydrorhipocephalin (**3**) and furocaulerpin (**4**).

This article is a full account of the synthesis of CYN (**1**) and three other, naturally occurring analogous terpenoids **2**, **3** and **4**[8] completed by the biological evaluations/comparisons on the in vitro inhibition of the polymerisation of microtubules for each of enantiomeric and diastereomeric forms of all synthetic metabolites.

Results and Discussion

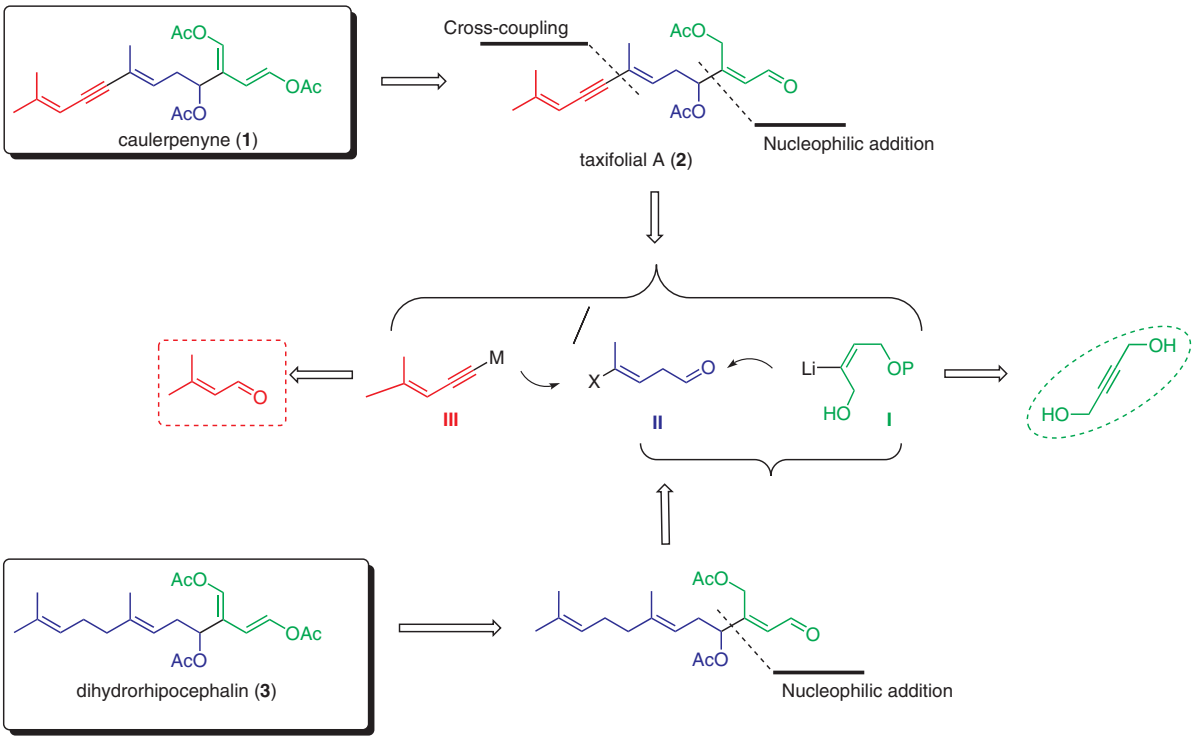
In this part, we describe the synthesis of CYN (**1**) and the other natural secondary metabolites [taxifolial A (**2**), dihydrorhipocephalin (**3**) and furocaulerpin (**4**)] in racemic and enantio-enriched forms.

Synthesis of Caulerpenyne (1) and Dihydrorhipocephalin (3)

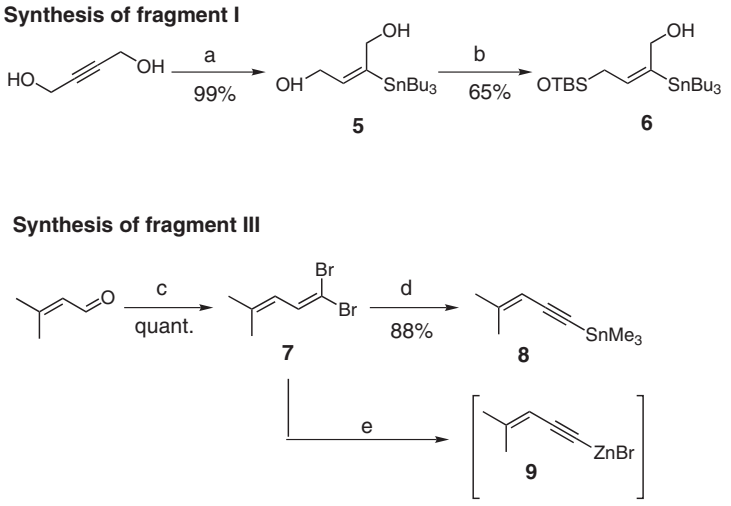
Our planned synthesis of **1** and **3** (Scheme 1) called for the initial preparation of common functionalized fragments **I** and **II** (X = halogen for CYN and X = alkyl for **3**). The main structural features of CYN (**1**) are a diacetoxybutadiene moiety, a secondary acetate stereocentre, and a dienyne function in which the trisubstituted central double bond presents an *E* configuration. Our strategy for synthesizing caulerpenyne (**1**) is based on the synthesis of one of its metabolites taxifolial A (**2**). Aldehyde **2** was constructed by coupling of three fragments **I**, **II** and **III.**

Synthesis of fragment **I** (Scheme 2) began with a palladium complex catalyzed hydrostannation reaction[9] of but-2-yndiol to give *E*-alkenyltin reagent **5** in which the more accessible alcohol function was selectively protected as *tert*-butyldimethylsilyl ether in 64% yield over two steps.[10] Synthesis of the fragment **III** (Scheme 2) was performed via the Corey alkynylation reaction.[11] Commercially available 3,3-dimethylacrolein was reacted with the reagent prepared from carbon tetrabromide, zinc and triphenylphosphine to give *gem*-dibromodiene **7**. Treatment of **7** with butyllithium (2 equiv) followed by addition of trimethyltin chloride afforded the corresponding alkynyl stannane **8** in 88% yield over two steps. If we want to realize a Negishi coupling the alkynyllithium can be trapped by zinc dibromide to afford the nonisolable alkynylzinc **9**.

With fragments **I** and **III** in hand, we next focussed our attention towards the synthesis of fragment **II** which was found more difficult than the two others. The main prob-



Scheme 1 Retrosynthetic analysis of the synthesis of caulerpenyne and others

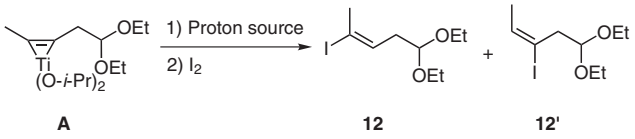


Scheme 2 Synthesis of fragments **I** and **III**. *Reagents and conditions*: a) Bu_3SnH, $PdCl_2(PPh_3)_2$; b) TBDMSCl, imidazole; c) CBr_4, PPh_3, Zn, r.t.; d) (i) BuLi, –78 °C, (ii) Me_3SnCl, –78 °C to r.t.; e) (i) BuLi, –78 °C, (ii) $ZnBr_2$

lem is to prepare a functionalised homoallylic aldehyde controlling the regio- and stereoselectivity of the double bond. The synthesis began with the formation of the allenylaluminum reagent, from propargyl bromide promoted by a catalytic amount of mercuric chloride, which reacts at low temperature with triethyl orthoformate to give the corresponding 1,1-diethoxybut-3-yne (**10**).[12] Then, the methylation reaction of **10** was performed with 1) lithium amide in ammonia and 2) methyl iodide to afford **11** in 65% yield.[13] The next step is the construction of the vinyl iodide with an *E* configuration. First of all, we turned our attention to the hydrozirconation-iododemetallation reactions using the Schwartz's reagent.[14] Unfortunately, after several experiments, these conditions did not furnish the expected alkenyl iodide. Similar results were observed with the carboalumination-iododemetallation reaction described by Miller using a chloroalkyne instead of methylalkyne **11** as starting material.[15] Another method to create functionalised double bond is to use Kulinkovich's reagent[16] well studied by Sato.[17] Our first intention was to generate the alkyne-titanium complex, then add, at first, iodine then NH_4Cl as electrophiles sources to obtain the desired alkenyl iodide **12**. In this case, we observed 1) a low rate of conversion with 70% recovery of starting material, 2) the formation of two alkenyl iodide regioisomers **12** and **12′** (20%) in 1:1 ratio, and 3) 10% of alkene **13** produced from the hydrolysis of complex **A** (Scheme 3).

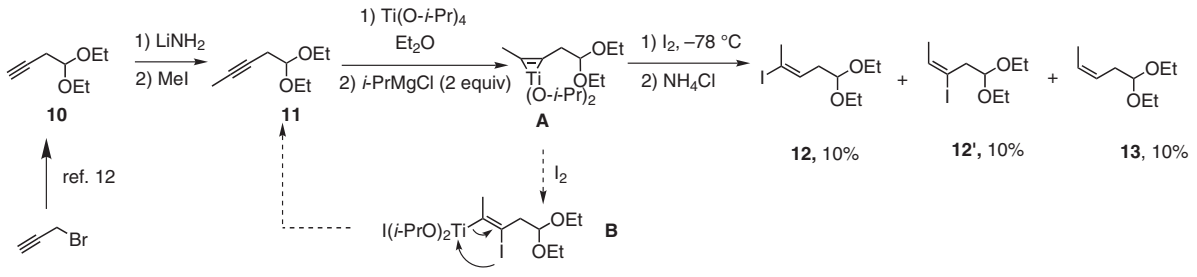
To explain the large amount of unreacted starting material **11**, we propose that the intermediate iodo–titanium complex **B** can undergo a β-elimination process to form **11** (Scheme **3**).

To avoid this problem, we chose to invert the order of the addition of electrophiles (Scheme 4): the proton source was added first followed by the iodine. Using acetic acid as first electrophile, the reaction furnished a 73:27 regioisomeric mixture of **12** and **12′**. With this encouraging result, we tried several proton sources at different temperatures. The best result was obtained when the reaction was conducted at –70 °C with isopropanol affording a 90:10 mixture of **12** and **12′** (Table 1).



Scheme 4 Decomposition of alkyne–titanium complex with proton sources (Table 1)

Unfortunately, even though this reaction gave interesting results, these two regioisomers could not be separated by chromatography on silica gel, which is not acceptable for the final stages of the synthesis. So, we turned our atten-



Scheme 3 Synthesis of **12** via alkyne–titanium complex

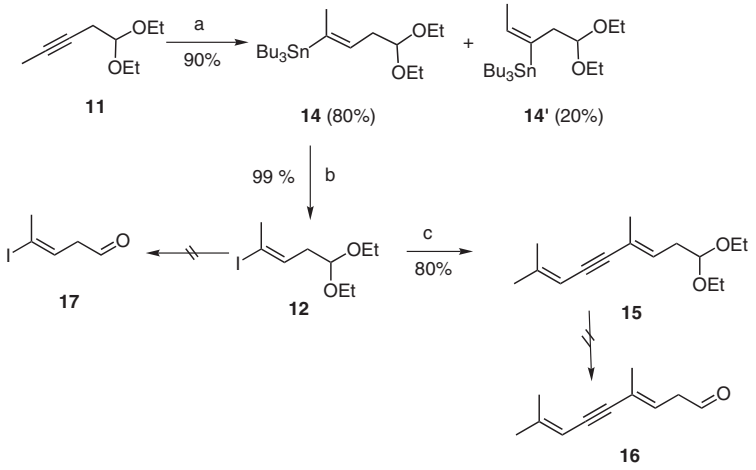
Table 1 Effect of Different Electrophiles on the Yield of Vinyl Iodide **12**

H^+	T (°C)	Time (h)	**12** (%)	**12′** (%)
CH_3CO_2H	–50/–60	1	73	27
	–100	1	70	30
CF_3CO_2H	–50/–60	1	77	23
i-PrOH	–50/–60	1	89	11
	–70	2	90	10
t-BuOH	–50/–60	1	77	23

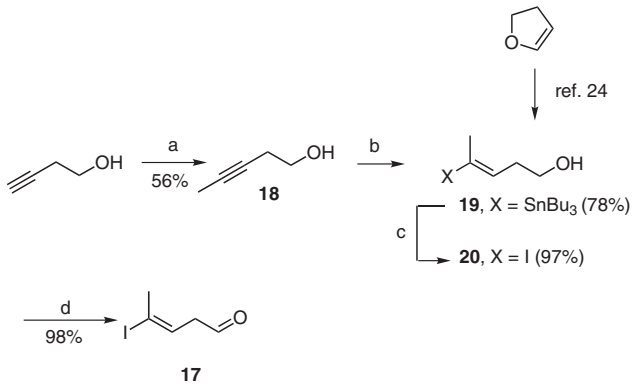
tion towards the preparation of alkenyltin reagents, easily made by hydrostannation or stannylcupration reactions, and easier to separate than iodide analogues. The palladium-catalysed hydrostannation reaction furnished in 68% yield the corresponding alkenyltin reagent **14** and **14′** as a 1:1 mixture of two regioisomers. To increase the regioselectivity of the reaction, we realized a stannylcupration reaction.[18] Using three equivalents of Lipshutz's reagent, at –78 °C, a 8:2 mixture of **14/14′** was obtained in 90% yield. A similar reaction conducted in methanol and at –10 °C furnished, in 78% yield, a separated 88:12 mixture in favour of **14**. The attribution of the configuration of the double bond was based on the H–Sn coupling constant ($^3J_{Sn,H}$ = 65 Hz) which is consistent with an *E*-vinylstannane. Iododestannylation reaction[19] with iodine in diethyl ether afforded in 99% the corresponding alkenyl iodide **12** with retention of configuration (Scheme 5).

The assembly of the three fragments began with the Negishi cross-coupling between the alkynylzinc reagent **9** and the vinyl iodide **12** (Scheme 5).[20] This reaction, catalysed by 5% of $PdCl_2(MeCN)_2$, furnished in 80% yield the desired compound **15**. To realise the second assembly, the acetal function must be deprotected to an aldehyde. We used several conditions (formic acid,[21] acetic acid, $FeCl_3$/H_2O,[22] $LiBF_4/H_2O$[23]), but none gave satisfactory results. In all the case, the desired aldehyde **16** was obtained as a mixture with the aldehyde that results from the isomerisation of the central double bond (more than 30%) and other undetermined aldehydic products. Such a compound being very sensitive in the following reaction condition prompted us to invert the coupling steps by first coupling the central fragment **II** with the fragment **I**. But once again, the obtaining of the corresponding aldehyde (**17**) was a problem. Even using neutral conditions, such as 5 to 10% of $FeCl_3$ or 5 equivalents of water in refluxing acetone, the reaction well furnished the corresponding aldehyde **17**. However, the aldehyde was unstable on silica gel, and the presence of other impurities made the purification of the crude aldehyde difficult, and it was not pure enough to be used at the end of the synthesis.

The hydrolysis of the ketal function revealing as a real problem, we chose to introduce the aldehyde via an alcohol. So we revised the synthesis of the central fragment and started from 2,3-dihydrofuran (Scheme 6). The Wadman–Kocienski rearrangement, as already described by Pancrazi et al., afforded **19** with complete regio- and stereoselectivity.[24] The configuration of the double bond was established on the basis of the H–Sn coupling constant ($^3J_{Sn,H}$ = 70 Hz) which is consistent with an *E*-alkenylstannane. The alkenylstannane **19** was also prepared from but-3-yn-1-ol using the following sequence. The lithium acetylide derived from but-1-ynol was alkylated with methyl iodide to give pentynol **18** in 56% yield.[13] The stereo- and regioselective stannylcupration using Lipshutz reagent in the presence of methanol cleanly furnished vinyltin reagent **19** in 78% yield. Iododestannylation reaction with iodine in diethyl ether afforded quantitatively the corresponding iodopentenol **20** which was then oxidized with Dess–Martin periodinane[25] providing the central segment **17**. The sensitive iodo aldehyde was found to be sufficiently pure to be used without purification (41% over four steps).



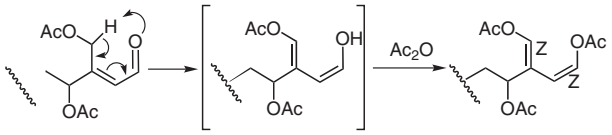
Scheme 5 Synthesis of **12** via iododestannylation reaction. *Reagents and conditions*: a) $Bu_3(Bu)SnCuLi{\cdot}LiCN$ (3 equiv), –78 °C; b) I_2, Et_2O; c) **9**, $PdCl_2(PPh_3)_3$, THF, r.t.



Scheme 6 New synthesis of fragment **II**. *Reagents and conditions*: a) (i) $LiNH_2/NH_3$, (ii) MeI; b) $Bu_3(Bu)SnCuLi{\cdot}LiCN$, MeOH, –40 °C; c) I_2, 0 °C to r.t.; d) Dess–Martin reagent

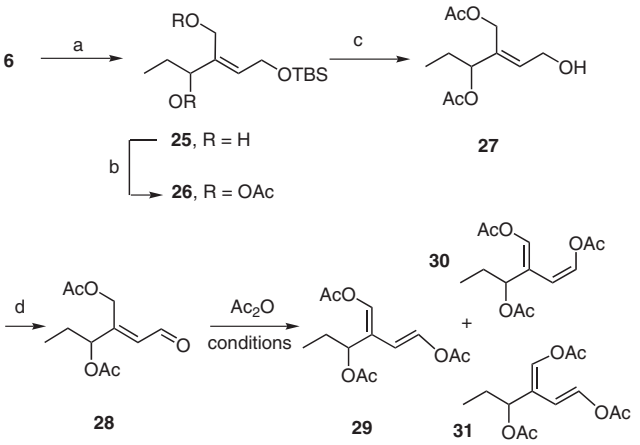
The coupling of the different fragments **6**, **8** and **17** and the construction of carbon skeleton of the caulerpenyne is described in Scheme 7. The coupling reaction between the second segment **17** and the carbanion generated by tin–lithium exchange reaction[9] on the first segment **6** gave diol **21** in fair yield (56%). At this stage, the two hydroxyl groups of **21** were protected as acetate using acetic anhydride and a catalytic amount of DMAP in pyridine to give bis-acetate **22** (96%). The carbon skeleton **23** of caulerpenyne was achieved in a high yield through a Stille cross-coupling between the vinyl iodide **22** and the fragment **III** (**8**) using 5 mol% of bis-acetonitrile palladium chloride in DMF.[20b,26] At this stage, it should be noted that no isomerisation product resulting from a palladium insertion reaction into the allylic acetate moiety was observed proving that the carbon–iodine insertion of palladium is largely favoured over the allylic acetate insertion. Desilylation[27] of **23** by the HF/pyridine complex provided primary alcohol **24**,[28] which was oxidized by Dess–Martin periodinane, affording (±)-taxifolial A [(±)-**2**] in 96% yield. Subsequent transformation of **2** into caulerpenyne (**1**) failed: upon attempted trapping the dienyl enol of taxifolial A using acetic anhydride in the presence of potassium acetate (3 equiv) only *iso*-caulerpenyne was obtained in 88% yield.[29]

To explain the configuration of the diacetoxybutadiene moiety of *iso*-caulerpenyne obtained, we propose that the dienol having the *Z,Z* configuration is kinetically formed from taxifolial A in its *s-cis* conformation (Scheme 8).

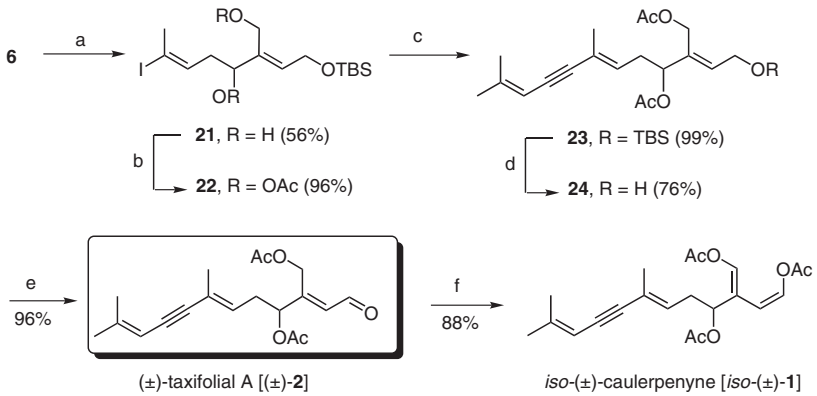


Scheme 8 Formation of kinetically favoured *Z,Z* configuration in **1**

In order to find optimal conditions to generate (*Z,E*)-diacetoxybutadiene, we decided to prepare a model compound that would be able to lead to the above mentioned moiety. Hence, we planned to prepare a simplified analogue of taxifolial A using a similar procedure (Scheme 9). Enal **28** was obtained in 56% yield over 4 steps from **6**.[30]



Scheme 9 Synthesis of a model compound. *Reagents and conditions*: a) (i) BuLi (2.2 equiv), –78 to –35 °C, (ii) propanal, –78 °C; b) Ac_2O, DMAP, pyridine, r.t.; c) HF/pyridine, r.t.; d) Dess–Martin reagent

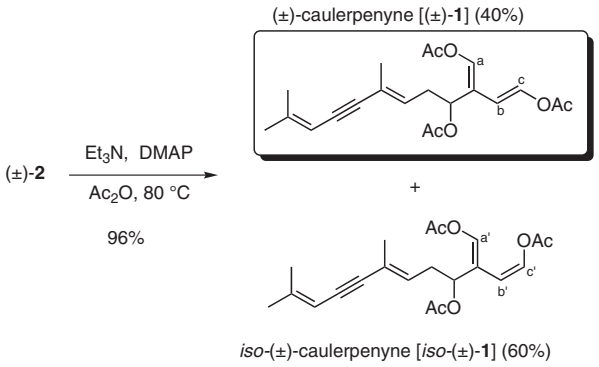


Scheme 7 Synthesis of (±)-taxifolial A (**2**) and *iso*-(±)-caulerpenyne (*iso*-**1**). *Reagents and conditions*: a) (i) BuLi (2.2 equiv), –78 to –35 °C, (ii) **17**, –78 °C; b) Ac_2O, DMAP, pyridine; c) **8**, $PdCl_2(MeCN)_2$, DMF; d) HF/pyridine, r.t.; e) Dess–Martin reagent; f) KOAc, Ac_2O, benzene, 80 °C

Firstly, we tested acetate salts other than potassium acetate (Table 2). The reactions were performed with 1.5 equivalents of $M(OAc)_n$, 3 equivalents of acetic anhydride at 80 °C and followed by ^1H NMR spectroscopy. 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 **29**, **30** and **31**. As a slight trend, if the cation exhibits some Lewis acidity, the *E*/*Z*-isomer was obtained in each case. Nevertheless, the desired isomer **29** was always obtained as the minor isomer.

Tertiary amines were also used. Et_3N as base/solvent, 3 equivalents 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 equivalents of DMAP gave the best results with a ratio of 45:55 of *E*,*Z*/*Z*,*Z* isomers with no evidence of **31** being formed. Other amines such as pyridine or Hunig's base led to a larger amount of isomer **31**. It should be noted that treatment of enal **28** 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 equivalents of Ac_2O, 1 equivalent of DMAP, Et_3N at 80 °C – to taxifolial A (**2**) that yielded a 96% mixture of 40:60 of (±)-caulerpenyne [(±)-1] with the *E*,*Z* configuration of the diacetoxybutadiene moiety and *iso*-(±)-caulerpenyne [*iso*-(±)-**1**] with the *Z*,*Z* configuration (Scheme 10). Their stereochemistry was established by the ^1H NMR spectrum ($J_{b,c}$ = 12.7 Hz characteristic of H-H *E*-coupling constant and $J_{b',c'}$ = 7.3 Hz characteristic of H-H *Z*-coupling constant) and a ^1H 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 [(±)-**1**] are in agreement with those reported in the literature (500 MHz ^1H NMR $CDCl_3$ and C_6D_6 and 125 MHz ^{13}C NMR $CDCl_3$). Moreover, the mixture (±)-**1** and *iso*-(±)-**1** was purified by semi-preparative chiral HPLC to give (+)-**1**, (–)-**1**, *iso*-(+)-**1** and *iso*-(–)-**1** in enantiomerically pure forms.



Scheme 10 Synthesis of (±)-caulerpenyne (**1**)

On top of the biological activity of the diacetoxybutadiene moiety, we wanted to know if the terminal unsaturated alkyl chain of CYN has a role. So, we investigated the synthesis of dihydrorhipocephalin (**3**), a sesquiterpene isolated from *Penicillus capitatus* and *Udotea cyathiformis* and which represents 10% of the chloroform extracts in both species.[31] Dihydrorhipocephalin (**3**) exhibits the same structure as CYN (**1**) except the internal triple bond which is replaced by a single bond. Our synthesis plan for dihydrorhipocephalin (**3**) was based on that used for **1** and called for the initial preparation of two fragments **I** and **II** in which fragment **I** was the same as that used in the synthesis of CYN (**1**). Homogeranial (fragment **II**) can be obtained from the corresponding homogeraniol **32**.

Compound **32** was synthesized in two steps using Kocienski's procedure[32] where the key step is the stereo- and regioselective construction of the central trisubstituted double bond through a Wenkert reaction. Homogeranial **33** was then obtained by Dess–Martin periodinane oxida-

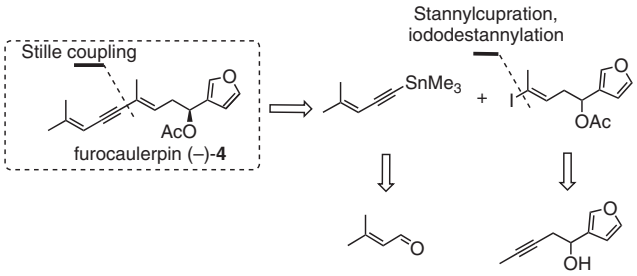
Table 2 Tested Reaction Conditions for the Preparation of Diacetoxybutadiene **29**

Conditions	**29** (%)	**30** (%)	**31** (%)	Conditions	**29** (%)	**30** (%)	**31** (%)
LiOAc, C_6H_6, 80 °C	27	73	–	Et_3N, DMAP (5 mol%), 80 °C	24	75	<1
CuOAc, C_6H_6, 80 °C	–	–	–	Et_3N, DMAP (1 equiv), 80 °C	45	54	<2
$Cu(OAc)_2$, C_6H_6, 80 °C	–	–	–	Et_3N, DMAP (3 equiv), 80 °C	45	55	trace
$Mg(OAc)_2$, C_6H_6, 80 °C	–	–	–	Et_3N, DMAP (5 mol%), r.t.	29	69	<2
$Pb(OAc)_2$, C_6H_6, 80 °C	–	–	–	Et_3N, DMAP (1 equiv), 80 °C	20	78	<2
CsOAc, C_6H_6, 80 °C	10	90	–	Pyridine, DMAP (5 mol%), r.t.	38	47	15
$Zn(OAc)_2$, C_6H_6, 80 °C	45	41	14	Pyridine, DMAP (5 mol%), 80 °C	20	72	8
Et_3N, 80 °C	11	88	–	*i*-Pr_2NEt, DMAP (1 equiv), r.t. to 80 °C	51	32	17
				i-Pr_2NEt, DMAP (1 equiv), 80 °C	37	56	7

tion of the primary hydroxyl group of homogeraniol **32** in quantitative yield. The coupling of the two fragments **6** and **26** was achieved via the cross-coupling reaction between **33** and the carbanion generated by tin–lithium exchange reaction on **6** which gave diol **34** in fair yield (47%). At this stage, the two hydroxyl groups were protected as acetates and desilylation of **35** by the HF/pyridine complex provided **36**. The primary hydroxyl group was oxidized by Dess–Martin periodinane furnishing in quantitative yield the aldehyde **37**. A mixture of 3 equivalents of Ac_2O, 1 equivalent of DMAP, Et_3N at 80 °C afforded, in 80% yield, a mixture of 45:55 of (±)-dihydrorhipocephalin [(±)-**3**] with *E*,*Z* configuration of diacetoxybutadiene moiety and (±)-*iso*-dihydrorhipocephalin [*iso*-(±)-**3**] with *Z*,*Z* configuration (Scheme 11). The configuration of the diacetoxybutadiene moiety was confirmed by ^{1}H NMR and ^{1}H NMR NOESY experiments. The mixture (±)-**3** and *iso*-(±)-**3** was purified by semi-preparative chiral HPLC to give *iso*-(+)-**3**, *iso*-(–)-**3**, (+)-**3** and (–)-**3** in enantiomeric pure form.

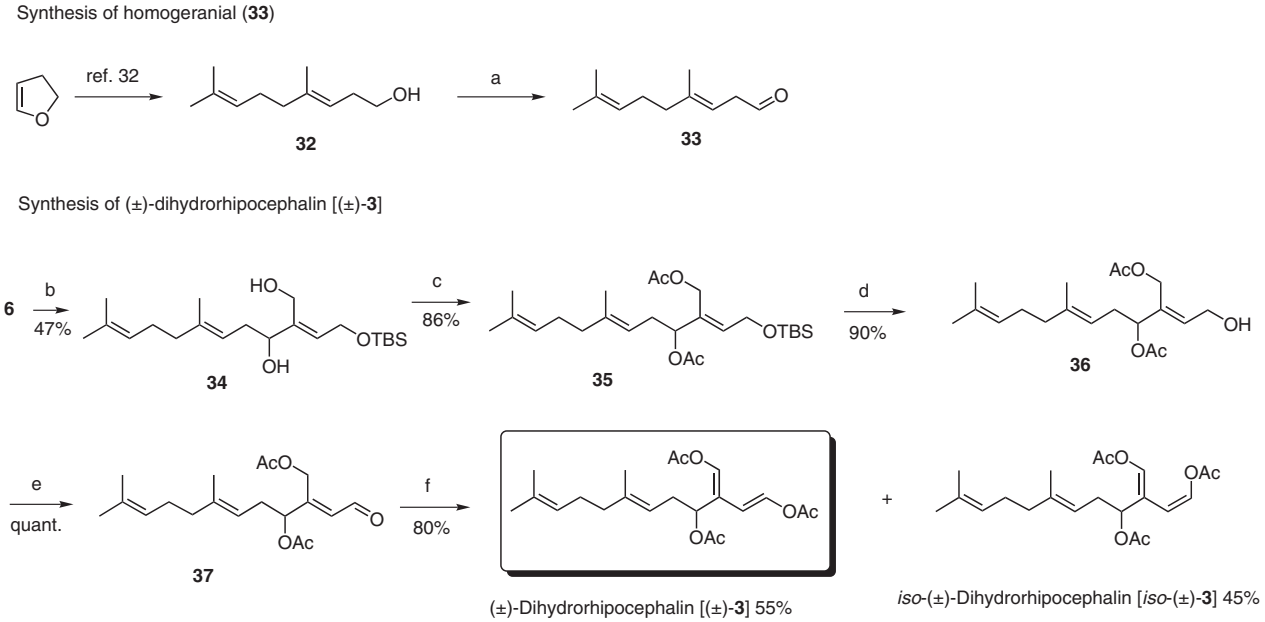
Enantioselective Synthesis of Furocaulerpin

Finally, the last natural compound, analogue of **1**, was furocaulerpin (**4**), extracted and identified from *Caulerpa prolifera* by De Napoli et al. in 1981.[33] Compared to **1**, this secondary metabolite presents a furan ring instead of a diacetoxybutadiene moiety. Our synthesis plan of furocaulerpin (**4**) was also based on that used for CYN and called for the initial preparation of two fragments. Thus, construction of **4** involved a Stille reaction between the residual vinyl iodide function of a first fragment and an alkynylstannane **8** (second fragment) already prepared for the synthesis of CYN (**1**). For this analogue, we opted for an enantioselective synthesis where the control of the chiral centre would be achieved through an enzymatic resolution (Scheme 12).



Scheme 12 Retrosynthetic scheme

The synthesis of the first fragment (Scheme 13) began with condensation of allenylmagnesium bromide to 3-furaldehyde furnishing the crude alcohol **38** in 99% yield.[34] The next step was methylation of **38**. First the hydroxyl function was protected as tetrahydropyranyl ether using dihydropyran in the presence of small amount of PPTS. Then the methylation of protected **38** was performed with 1) $LiNH_2/NH_3$ and 2) MeI to afford **40** in 99% yield over three steps. After acetic acid hydrolysis of **40** (84%), we turned our attention to the enzymatic resolution of alcohol **41**. To this end, we examined the transesterification of **41** with vinyl acetate and various lipases under standard conditions. Best results in conversion rate and in enantiomeric excess were obtained with *Pseudomonas fluorescens* (see Table 3). In a study of enzymatic resolution of secondary alcohols by the lipases from *Pseudomonas* sp. Burgess has proposed a simple ac-



Scheme 11 Synthesis of (±)-dihydrorhipocephalin [(±)-**3**]. *Reagents and conditions*: a) Dess–Martin reagent, 0 °C to r.t.; b) (i) BuLi (2.2 equiv), –78 to –35 °C, (ii) **33**, –78 °C; c) Ac_2O, DMAP, pyridine; d) HF/pyridine, r.t.; e) Dess–Martin reagent; f) Et_3N, Ac_2O, DMAP, 80 °C

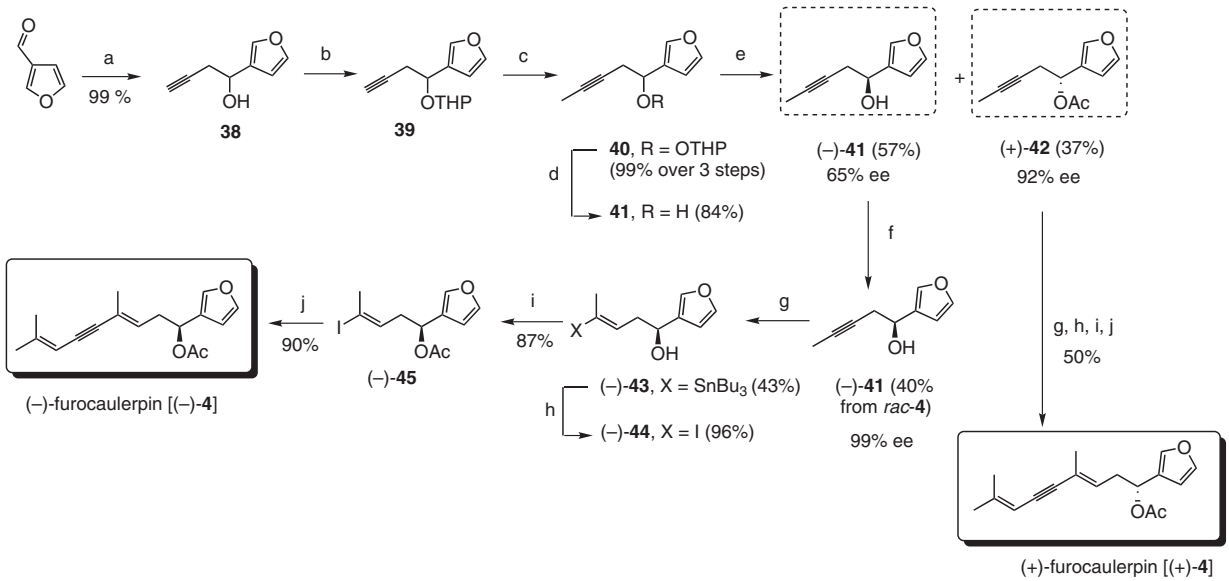
tive site model for predicting the enantioselectivity.[35,36] This model predicts that alcohols resolved most efficiently have one small and one relatively large group attached to the hydroxymethine functionality. According to this model, we assume that only *R*-isomer of **41** was transformed into acetate **42**. After 26 hours at room temperature, the active enzyme was recovered for re-use after filtration. Separation by chromatography on silica gel afforded a 57% yield of the alcohol (–)-**41** (65% ee) and a 37% yield of the acetate (+)-**42** {$[\alpha]_D^{24}$ +41.4 (*c* = 1, $CHCl_3$), 92% ee}. The remaining alcohol (–)-**41** was resubjected to the same conditions of enzymatic transesterification using the recovered enzyme. The progress of the reaction was monitored by chiral phase analytical GC until one enantiomer of the starting material was completely consumed. After 100 h, (–)-**41** {$[\alpha]_D^{24}$ –32.8, (*c* = 1, $CHCl_3$)} was obtained in 40% overall yield and 99% ee.

Starting from (–)-**41** and (+)-**42**, the first fragment was prepared via the stannylcupration of the triple bond followed by iododestannylation. The stannylcupration reaction of (+)-**42** using the stannyl cuprate $Bu_3Sn(Bu)CuLi{\cdot}LiCN$ (Lipshutz reagent) at –78 °C gave unexpected products. A 4:6 mixture of alcohol (+)-**41** and vinylstannane (+)-**43** was obtained using three equivalents of Lipshutz reagent whereas six equivalents furnished a 2:8 mixture of the same products. After purification, pure vinylstannane (+)-**43** {$[\alpha]_D^{24}$ +10 (*c* = 1, $CHCl_3$)} was obtained in 58% yield with a surprising total regio- and stereoselectivity (*E* configuration). It should be noted that in each attempt we conducted, the acetate function was removed. The formation of alcohol (+)-**41** could be explained by the addition of a butyl moiety of the alkenylcuprate intermediate to the ester carbonyl group followed by a retrostannylcupration giving the corresponding alcohol.

Table 3 Results in Conversion Rate and in Enantiomeric Excess

Lipase	Time (h)	Conv (%)	ee (%)
Candida antartica	120	42	88
Candida cylindracea	72	12	–
Mucor miehei	96	<5	–
Aspergillus niger	72	6	–
Ps. cepacia	12	46	91
Ps. fluorescens	8	45	94
Rhizopus arrhizus	72	<5	–
Rhizopus niveus	72	<5	–
Hog pancreas	96	<5	–

In contrast, clean access of (–)-**43** from (–)-**41** was found to depend on temperature and the presence of methanol. In each case and independently of the number of equivalent of the Lipshutz reagent, the stannylcupration in presence or not of methanol was incomplete (10% of conversion without MeOH at –78 °C, 70% with MeOH at –40 °C and 76% at –10 °C). After purification, pure vinylstannane (–)-**43** {($[\alpha]_D^{24}$ –11.7 (*c* = 1, $CHCl_3$)} was obtained in 43% yield. Iododestannylation of (+)-**43** and (–)-**43** with iodine in diethyl ether yielded respectively 99% and 96% of the corresponding vinyl iodides (+)-**44** {$[\alpha]_D^{24}$ +12.3 (*c* = 1, $CHCl_3$)} and (–)-**44** {$[\alpha]_D^{24}$ –13.0 (*c* = 1, $CHCl_3$)}. The hydroxyl group of (+)-**44** and (–)-**44** was protected as acetate using acetic anhydride and a catalytic amount of DMAP in pyridine providing respectively (+)-**45** in 93% yield {$[\alpha]_D^{24}$ +25 (*c* = 1, $CHCl_3$), 92% ee} and (–)-**45** in



Scheme 13 Synthesis of furocaulerpin. *Reagents and conditions*: a) allenylmagnesium bromide, –78 to 0 °C; b) DHP, PPTS, CH_2Cl_2; c) (i) $LiNH_2/NH_3$, (ii) MeI; d) AcOH–H_2O–THF, 45 °C; e) vinyl acetate, hexane, *Ps. fluorescens*, 26 h; f) vinyl acetate, hexane, *Ps. fluorescens*, 100 h; g) $Bu_3Sn(Bu)CuLi{\cdot}LiCN$ (4 equiv), MeOH, –10 °C; h) I_2, Et_2O, 0 °C to r.t.; i) Ac_2O, DMAP, pyridine; j) **8**, $PdCl_2(MeCN)_2$, DMF

87% yield {$[\alpha]_D^{24}$ –26.6 (c = 1 $CHCl_3$), ee >99%}. The last step of the synthesis is the coupling reaction between alkenyl iodide (+)-**4** and (–)-**45** with stannylenyne **8** using 5 mol% of bis-acetonitrile palladium chloride, giving non-natural (+)-furocaulerpin [(+)-**4**] {$[\alpha]_D^{24}$ +13.8 (c = 1, $CHCl_3$)} in 94% yield and (–)-furocaulerpin [(–)-**4**] ($[\alpha]_D^{24}$ –14.6, c = 1, $CHCl_3$)} in 90% yield. The data of this synthetic (–)-furocaulerpin [(–)-**4**] (500 MHz ^{1}H NMR $CDCl_3$, 50 MHz ^{13}C NMR $CDCl_3$ and GC/MS) are in agreement with those reported in the literature.

Biological Testing

The effect of each enantiomer of caulerpenyne (**1**), *iso*-caulerpenyne (*iso*-**1**) and analogues (±)-**2**, *iso*-(+)-**3**, *iso*-(–)-**3**, (+)-**3**, (–)-**3**, (+)-**4**, (–)-**4**, on the in vitro polymerisation of pure tubulin was investigated by turbidimetry. As for the natural product,[7] tubulin (15 μM) was incubated for 35 min at 37 °C without (control) or with various concentrations of CYN or analogues in Mg^{2+}-free polymerisation buffer. After 35 min, 10 mM $MgCl_2$ was added to the samples (Figure 2) to induce the formation of microtubules. In the control experiment, turbidity increased with time resulting in a typical sigmoid curve with a lag time, a drastic increase in the turbidity and a plateau value corresponding to the amount of microtubules formed (Figure 2, upper trace). With increasing concentrations of (+)-caulerpenyne [(+)-**1**], the rate of assembly as well as the final amount of microtubules were decreased and the turbidity generated by the self-assembly of 15 μM tubulin was reduced to half the control value at a concentration of 14 ± 2 μM (inset Figure 2). After 35 min of polymerisation process, the samples were cooled to 10 °C and all the samples totally depolymerised. Similar experiments were investigated for (–)-caulerpenyne and its analogues *iso*-(+)-**1**, *iso*-(–)-**1**, (±)-**2**, *iso*-(+)-**3**, *iso*-(–)-**3**, (+)-**3**, (–)-**3**, (+)-**4** and (–)-**4** and are summarized in Table 4.

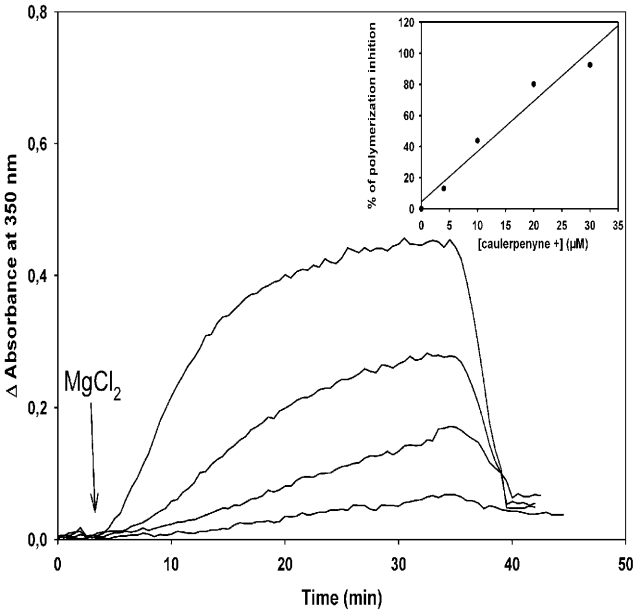


Figure 2 Inhibition of tubulin polymerisation by (+)-caulerpenyne

Both (+)- and (–)-dihydrorhipocephalin (**3**), as well as *iso*-(+)-dihydrorhipocephalin [*iso*-(+)-**3**], have a half inhibitory concentration IC_{50} around 50 μM. So, replacement of the internal triple bond by a CH_2–CH_2 linkage leads to a non significant decrease of the activity on tubulin polymerisation. Curiously, in the case of *iso*-(–)-dihydrorhipocephalin [*iso*-(–)-**3**], the activities of the two enantiomers were largely different as *iso*-(+)-dihydrorhipocephalin [*iso*-(+)-**3**] is three times more powerful than *iso*-(–)-dihydrorhipocephaline [*iso*-(–)-**3**]).

Hence, the presence of the internal triple bond, the configuration of the chiral centre and the configuration of the diacetoxybutadiene moiety do not appreciably influence the activity on tubulin polymerisation compared to CYN.

However, racemic taxifolial A (±)-**2** is inactive at a concentration below 200 μM and (+)- and (–)-furocaulerpin (**4**) have a half inhibitory concentration IC_{50} of about 100–200 μM. These results confirm that biological activities of CYN could be attributed to the diacetoxybutadiene moiety as has been predicted biologists.

Conclusion

We have accomplished the first total synthesis of several metabolites isolated from algae order caulerpales. The activity on tubulin polymerisation of such terpenoids is mainly due to the presence of the diacetoxybutadiene moiety. The configuration of the chiral centre, the configuration of the diacetoxybutadiene moiety and the unsaturated terminal chain were not significant. Investigations to

Table 4 Half-Inhibitory Concentrations of CYN and Analogues on Pure Tubulin Polymerisation

Metabolites	IC_{50} (μM)
natural (+)-caulerpenyne	21 ± 2
(–)-caulerpenyne	14 ± 2
(+)-caulerpenyne	34 ± 3
(+)-furocaulerpin	101 ± 16
(–)-furocaulerpin	171 ± 27
(±)-taxifolial A	>200
iso-(+)-caulerpenyne[37]	31 ± 3
iso-(–)-caulerpenyne[37]	54 ± 9
(+)-dihydrorhipocephalin[37]	52 ± 8
(–)-dihydrorhipocephalin[37]	57 ± 15
iso-(+)-dihydrorhipocephalin[37]	40 ± 9
iso-(–)-dihydrorhipocephalin[37]	123 ± 14

specify the interaction with the tubulin system are ongoing and should help to provide new details concerning the mechanism of action of this interesting class of terpenes.

All reactions sensitive to oxygen and moisture were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker AC200, AC300, AM400 or AC500 spectrometers. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). Chemical shifts for ^{13}C NMR were reported in ppm relative to the central line of a triplet at 77.1 ppm for $CDCl_3$. IR spectra were recorded on a Perkin-Elmer 1600 Fourier Transform Infrared spectrophotometer and are reported in wave numbers (cm^{-1}). Mass spectra (MS) were obtained on a Hewlett Packard apparatus (engine 5989A) at 70 eV in the GC/MS mode. Enantiomeric excess (ee) was determined by the ratio of the peak areas obtained by GC separation using a chiral phase (WCOT Fused Silica 25 m × 0.25 mm Coating CP CHIRASIL-DEX CB DF = 0.25). High resolution mass spectra were measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer. Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Reagents and solvents were commercial grades and were used as supplied. CH_2Cl_2, benzene, and toluene were distilled from CaH_2 and stored over molecular sieves 4 Å. THF and Et_2O were distilled from sodium benzophenone prior to use. DMF and hexanes were purchased anhydrous and stored over molecular sieves 4Å under argon. PE refers to the fraction boiling in the range 30–40 °C.

The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, and on-line Jasco CD-1595 circular dichroism. Hexane and propan-2-ol, HPLC grade, were degassed and filtered on a 0.45 μm membrane before use. The column used is Whelk-O1 (*S*,*S*) (250 × 4.6 mm) from Regis (Morton Grove, USA). The sign given by the on-line circular dichroism is the sign of the product in the solvent used for the chromatographic separation. The four analyses were performed at 25 °C, with hexane–propan-2-ol (95:5) as mobile phase and 1 mL/min as flow-rate, with UV and CD at 220 nm. Semi-preparative separations were performed on an unit composed of Merck D-7000 system manager, Merck-Hitachi L-6000 pump, Rheodyne valve with a 500 μL loop and a Merck-Hitachi L-4000 UV-detector. For dihydrorhipocephalin and *iso*-dihydrorhipocephalin, Whelk-O1 (*S*,*S*) (250 × 4.6 mm) was used with hexane–propan-2-ol (95:5) as mobile phase, 1 mL/min as flow-rate and UV at 220 nm. For caulerpenyne, Chiralpak AD (250 × 10 mm), an amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase available from Chiral Technology Europa (Illkirch, France) was used with hexane–propan-2-ol (98:2) as mobile phase, 4.5 mL/min as flow-rate and UV at 220 nm. For *iso*-caulerpenyne, Chiralcel OD (250 × 10 mm), a cellulose tris(3,5-dimethylphenylcarbamate) chiral stationary phase available from Chiral Technology Europa (Illkirch, France) was used with hexane–propan-2-ol (95:5) as mobile phase, 4.5 mL/min as flow-rate and UV at 220 nm.

Compounds **4**, **38**–**45** were prepared according reference 8e.

(*E*)-2-Tributylstannylbut-2-ene-1,4-diol (5)[9]

To a THF solution (15 mL) of but-2-yn-1,4-diol (2.58 g, 30 mmol) and $PdCl_2(PPh_3)_2$ (420 mg, 2 mol%) was added dropwise a THF solution (20 mL) of Bu_3SnH (9.68 mL, 36 mmol) over a period of 1 h. The originally light yellow solution abruptly turned orange-brown. After stirring for 15 min, THF was evaporated under vacuum. The crude product was then purified by flash chromatography (PE–Et_2O, 6:4 to 2:8) to give **5**; yield: 11.3 g (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.93 (m, 15 H, 3 × CH_3, 3 × CH_2), 1.23–1.35 (m, 6 H, 3 × CH_2), 1.43–1.53 (m, 6 H, 3 × CH_2), 1.64 (br t, $^3J_{H,H}$ = 5.6 Hz, 1 H, OH), 1.73 (br t, $^3J_{H,H}$ = 5.2 Hz, 1 H, OH), 4.18 (br t, $^3J_{H,H}$ = 5.4 Hz, 2 H, CH_2), 4.36 (br d, $^3J_{H,H}$ = 3.7 Hz, $^3J_{Sn,H}$ = 37 Hz, 2 H, CH_2), 5.77 (br t, $^3J_{H,H}$ = 5.4 Hz, $^3J_{Sn,H}$ = 67 Hz, 1 H, CH).

(*E*)-4-*tert*-Butyldimethylsilyloxy-2-tributylstannylbut-2-en-1-ol (6)[10]

To a solution of **5** (3.8 g, 10 mmol) in DMF (100 mL) at 0 °C was added imidazole (0.68 g, 10 mmol) and *tert*-butyldimethylsilyl chloride (1.5 g, 10 mmol). The solution was stirred at 0 °C for 6 h, then crushed ice (2.5 g) was added. The solution was diluted with Et_2O (200 mL), washed with sat. aq NH_4Cl solution, dried ($MgSO_4$) and evaporated. The crude product was then purified by flash chromatography (PE–Et_2O, 10:0 to 9:1) to give **6**; yield: 3.19 g (65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, 2 × CH_3), 0.84–0.92 (m, 15 H, 3 × CH_3, 3 × CH_2), 0.88 (s, 9 H, 3 × CH_3), 1.23–1.53 (m, 12 H, 6 × CH_2), 1.80 (br t, $^3J_{H,H}$ = 5.5 Hz, 1 H, OH), 4.20 (br d, $^3J_{H,H}$ = 5.4 Hz, $^4J_{Sn,H}$ = 15 Hz, 2 H, CH_2), 4.32 (br d, $^2J_{H,H}$ = 5.5 Hz, $^3J_{Sn,H}$ = 37 Hz, 2 H, CH_2), 5.68 (br t, $^3J_{H,H}$ = 5.4 Hz, $^3J_{Sn,H}$ = 69 Hz, 1 H, CH).

1,1-Dibromo-4-methylpent-1,3-diene (7)[11b]

CBr_4 (24.87 g, 75 mmol), Ph_3P (19.67 g, 75 mmol) and Zn dust (4.9 g, 75 mmol) were placed in a dry 500-mL round-bottomed flask under N_2. The flask was cooled to 0 °C and CH_2Cl_2 (300 mL) was added to the mixture of the solids, giving a green suspension. The reaction mixture was allowed to warm to r.t. and was then stirred for 24 h, after which time it was pink in colour. 3-Methylbut-2-enal (2.89 mL, 30 mmol) was then added via syringe and the mixture stirred for a further 2 h. The now purple suspension was transferred to a large conical flask, pentane (400 mL) was added and the resultant solution was filtered. The residue was dissolved in CH_2Cl_2 (200 mL) and then more pentane (500 mL) was added. This was also filtered and the combined filtrates were concentrated to a colourless oil. This was triturated with pentane (20 mL) and filtered through a short pad of silica to remove Ph_3PO. After removal of solvents in vacuum, gem-dibromodiene **7** was obtained as colourless oil; yield: 7.20 g (quant).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (s, 3 H, CH_3), 1.78 (s, 3 H, CH_3), 5.83 (m, $^3J_{H,H}$ = 10.6 Hz, 1 H, CH), 7.07 (d, $^3J_{H,H}$ = 10.6 Hz, 1 H, CH).

1-Trimethylstannyl-4-methylpent-3-en-1-yne (8)

To a solution of **7** (1 g, 4.2 mmol) in THF (15 mL) under N_2 at –78 °C, was added dropwise BuLi (2.5 M, 3.5 mL, 8.8 mmol). The clear yellow solution was stirred at –78 °C for 1.5 h and then Me_3SnCl (710 mg, 3.57 mmol) was added. After warming to r.t., the mixture was quenched with H_2O and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered and concentrated under vacuum to give **8**; yield: 763 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.25 (s, $^2J_{Sn,H}$ = 59 Hz, 9 H, 3 × CH_3), 1.74 (s, 3 H, CH_3), 1.87 (s, 3 H, CH_3), 5.25 (s, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –7.7 ($^1J_{Sn,C}$ = 404 Hz, CH_3), 21.1 (CH_3), 24.7 (CH_3), 94.8 (C), 105.7 (CH), 107.3 (C), 149.1 (C).

^{119}Sn NMR (149.21 MHz, $CDCl_3$): δ = –67.73.

MS (EI, 70 eV): *m*/*z* (%), organotin fragments = 244 ($M^{+\cdot}$, 18), 229 (100), 199 (32), 120 (10).

4-Methylpent-3-en-1-yn-1-zinc Bromide (9)

To a solution of **7** (0.72 g, 3 mmol) in THF (10 mL) under N_2 at –78 °C, was added dropwise BuLi (2.5 M, 2.5 mL, 6.3 mmol). The clear yellow solution was stirred at –78 °C for 1.5 h and then $ZnBr_2$ (740 mg, 3.3 mmol) was added. The resulting solution was warmed to r.t. and the corresponding alkynylzinc was used as such for the next step.

1,1 Diethoxypent-3-yne (11)[38]

To a solution of Li (7.6 g, 0.11 mol), $Fe(NO_3)_3$ (15 mg) and NH_3 (150 mL), was added 1,1-diethoxybut-3-yne (**10**; 14.2 g, 0.1 mol) at –40 °C. The mixture was stirred at –40 °C for 2 h then MeI (6.3 mL, 0.1 mol) was added. After 48 h, the reaction was quenched with sat. aq NH_4Cl solution and the aqueous layer was extracted with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by distillation (bp 113 °C/50 Torr) to give 1,1-diethoxypent-3-yne **11**; yield: 10.2 g (65%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.2 (t, $^3J_{H,H}$ = 7 Hz, 6 H, 2 × CH_3), 1.76 (t, $^5J_{H,H}$ = 2.6 Hz, 3 H, CH_3), 2.45 (dq, $J_{H,H}$ = 5.5, 2.6 Hz, 2 H, CH_2), 3.44–3.73 (m, 4 H, 2 × CH_2), 4.58 (t, $^3J_{H,H}$ = 5.5 Hz, 1 H, CH).

(*E*)-2-Tributylstannyl-5,5-diethoxypent-2-ene (14)

CuCN (0.86 g, 9.6 mmol) was suspended in freshly distilled THF (24 mL), cooled at –78 °C and treated with BuLi in hexane (2.5 M, 7.7 mL, 19.2 mmol). The mixture was allowed to react until a homogenous solution was obtained. Then, at –78 °C, Bu_3SnH (5.16 mL, 19.2 mmol) was added dropwise via a syringe. Stirring was continued and, over ca. 15 min, the solution turned yellow and H_2 gas was liberated. 1,1-Diethoxypent-3-yne (**11**; 0.5 g, 3.2 mmol) was added. The reaction was followed by TLC (3 h) and quenched with sat. aq NH_4Cl solution. The mixture was filtered and the aqueous layer was extracted with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (PE–Et_2O, 98:2) to afford a separable mixture (8.2) of two regioisomers **14** and **14′**; yield: 1.30 g (90%).

14

IR (film): 1613, 1120, 1061, 861 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.65–1.00 (m, 15 H, 3 × CH_3, 3 × CH_2), 1.18 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, 2 × CH_3), 1.18–1.60 (m, 12 H, 6 × CH_2), 1.82 (br s, 3 H, CH_3), 2.45 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, CH_2), 3.41–3.72 (m, 2 H, CH_2), 4.50 (t, $^3J_{H,H}$ = 6 Hz, 1 H, CH), 5.52 (br t, $^3J_{H,H}$ = 6.7 Hz, $^3J_{Sn,H}$ = 65 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.2 ($^1J_{Sn,C}$ = 322 Hz, 3 × CH_2), 13.8 (3 × CH_3), 15.4 (2 × CH_3), 19.4 (CH_3), 27.5 ($^3J_{Sn,C}$ = 55 Hz, 3 × CH_2), 29.2 ($^2J_{Sn,C}$ = 19 Hz, 3 × CH_2), 32.9 ($^3J_{Sn,C}$ = 54 Hz, CH_2), 61.2 (2 × CH_2), 102.7 (CH), 134.8 ($^2J_{Sn,C}$ = 32 Hz, CH), 140.6 (C).

HRMS: *m/z* calcd for $C_{21}H_{45}O_2Sn$ [M + H]$^+$: 449.2442; found: 449.2446.

(*E*)-2-Iodo-5,5-diethoxypent-2-ene (12)

To a solution of **14** (0.2 g, 0.54 mmol) in anhyd Et_2O (2 mL), was added dropwise I_2 (0.136 g, 0.45 mmol) in anhyd Et_2O (2 mL) at 0 °C. The mixture was stirred 2 h at r.t. and quenched with 1 M aq KF solution (1 mL) and acetone (1 mL). After stirring for 2 h, the solution was filtered through a pad of Celite and the aqueous layer was extracted with Et_2O. The organic layers were washed with sat. aq $Na_2S_2O_3$ solution, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography (PE–Et_2O, 10:0 to 98:2) to give **12**; yield: 127 mg (quant).

IR (film): 1645, 1130, 1070, 930 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, $^3J_{H,H}$ = 7 Hz, 6 H, 2 × CH_3), 2.30–2.37 (m, 2 H, CH_2), 2.37 (br s, 3 H, CH_3), 3.40–3.71 (m, 4 H, 2 × CH_2), 4.46 (t, $^3J_{H,H}$ = 5.7 Hz, 1 H, CH), 6.15 (br t, $^3J_{H,H}$ = 7.4 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3 (2 × CH_3), 27.9 (CH_3), 35.3 (CH_2), 61.7 (2 × CH_2), 95.7 (C), 101.5 (CH), 135.6 (CH).

HRMS: *m/z* calcd for $C_9H_{18}IO_2$ [M + H]$^+$: 285.0352; found: 285.0352.

(6*E*)-9,9-Diethoxy-2,6-dimethylnona-2,6-dien-4-yne (15)

To a solution of **9** (2.11 mmol) prepared as described above, was added dropwise (*E*)-2-iodo-5,5-diethoxypent-2-ene (**12**; 0.2 g, 0.7 mmol) in THF (1.6 mL). Then, $PdCl_2(MeCN)_2$ (15 mg, 0.058 mmol) was added and the resulting mixture was stirred for 16 h at r.t. The reaction was quenched with sat. aq NH_4Cl solution and the aqueous layer was extracted with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (PE–Et_2O, 10:0 to 95:5) to give **15**; yield: 132 mg (80%).

IR (film): 2177, 1667, 1120, 1060, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, $J_{H,H}$ = 7 Hz, 6 H, 2 × CH_3), 1.79 (br s, 3 H, CH_3), 1.81 (br s, 3 H, CH_3), 1.87 (br s, 3 H, CH_3), 2.42 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2), 3.44–3.66 (m, 4 H, 2 × CH_2), 4.48 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, CH), 5.34 (br s, 1 H, CH), 5.78 (br t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3 (2 × CH_3), 17.8 (CH_3), 20.9 (CH_3), 24.8 (CH_3), 33.6 (CH_2), 61.4 (2 × CH_2), 84.7 (C), 94.5 (C), 102.1 (CH), 105.4 (CH), 120.4 (C), 130.8 (CH), 147.7 (C).

HRMS: *m/z* calcd for $C_{15}H_{25}O_2$ [M + H]$^+$: 237.1855; found: 237.1851.

Pent-3-yn-1-ol (18)[13]

To a solution of Li (0.367 g, 0.0528 mol), $Fe(NO_3)_3$ (15 mg) and NH_3 (200 mL) was added but-3-yn-1-ol (0.926 g, 13.2 mmol) at –40 °C. The mixture was stirred at –40 °C for 2 h, then MeI (4.11 mL, 66 mmol) was added. After 12 h, the reaction was quenched with sat. aq NH_4Cl solution and the aqueous layer was extracted with EtOAc. The organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (PE–Et_2O, 6:4 to 4:6) to give pent-3-yn-1-ol (**18**); yield: 610 mg (56%).

IR (film): 3340, 1046 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (t, $^5J_{H,H}$ = 2.6 Hz, 3 H, CH_3), 1.90 (br t, $^3J_{H,H}$ = 6.1 Hz, 1 H, OH), 2.42 (tq, $J_{H,H}$ = 6.1, 2.6 Hz, 2 H, CH_2), 3.69 (q, $^3J_{H,H}$ = 6.1 Hz, 2 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 3.1 (CH_3), 22.7 (CH_2), 61.0 (CH_2), 75.6 (C), 77.1 (C).

MS (EI, 70 eV): *m/z* (%) = 84 ($M^{+\cdot}$, 16), 55 (13), 54 (100), 53 (40), 52 (10), 51 (18), 50 (15), 43 (10), 41 (11), 39 (59).

(*E*)-4-Tributylstannylpent-3-en-1-ol (19)[24a]

CuCN (0.639 g, 7.13 mmol) was suspended in freshly distilled THF (20 mL), cooled at –78 °C and treated with BuLi in hexane (2.5 M, 5.7 mL, 14.3 mmol). The mixture was allowed to react until a homogenous solution was obtained. Then, at –78 °C, Bu_3SnH (3.84 mL, 14.3 mmol) was added dropwise via a syringe. Stirring was continued and, over ca. 10 min, the solution turned yellow and H_2 gas was liberated. MeOH (10.59 mL, 0.26 mol) was then added, and the mixture was allowed to warm to –40 °C and pent-3-yn-1-ol (**18**; 0.2 g, 2.38 mmol) was added. The reaction was followed by TLC and quenched with sat. aq NH_4Cl solution. The mixture was filtered and aqueous layer was extracted with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude product (93:7 ratio of regioisomers) was purified by column chromatography on silica gel (PE–Et_2O, 8:2) to give **19**; yield: 700 mg (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.89 (m, 15 H, 3 × CH_3, 3 × CH_2), 1.24–1.49 (m, 13 H, 6 × CH_2, OH), 1.85 (br s, $^3J_{Sn,H}$ = 44 Hz, 3 H, CH_3), 2.41 (br q, $^3J_{H,H}$ = 6.1 Hz, 2 H, CH_2), 3.64 (br q, $^3J_{H,H}$ = 6.2 Hz, 2 H, CH_2), 5.50 (br t, $^3J_{H,H}$ = 7 Hz, $^3J_{Sn,H}$ = 70 Hz, 1 H, CH).

(*E*)-4-Iodopent-3-en-1-ol (20)[24a]

To a solution of **19** (0.355 g, 0.95 mmol) in anhyd Et_2O (4 mL), was added dropwise I_2 (0.29 g, 1.14 mmol) in anhyd Et_2O (4 mL) at 0 °C. The mixture was stirred for 2 h at r.t. and quenched with 1 M aq KF solution (2 mL) and acetone (2 mL). After stirring for 2 h, the solution was filtered through a pad of Celite and the aqueous layer was extracted with EtOAc. The organic layers were washed with sat. aq $Na_2S_2O_3$ solution, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography (PE–Et_2O, 9:1 to 0:10) to give **20**; yield: 193 mg (97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (br t, $^3J_{H,H}$ = 5.7 Hz, 1 H), 2.29 (m, 2 H, CH_2), 2.39 (br s, 3 H, CH_3), 3.64 (br q, $^3J_{H,H}$ = 6.2 Hz, 2 H, CH_2), 6.17 (br t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH).

(*E*)-4-Iodopent-3-en-1-al (17)

To a stirred solution of **20** (0.1 g, 0.47 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added Dess–Martin periodinane (0.26 g, 0.61 mmol). The reaction mixture was stirred under N_2 at r.t. and followed by TLC. After disappearance of the starting material, the mixture was poured into a separating funnel containing sat aq $Na_2S_2O_3$/$NaHCO_3$ solution (26 mL, 1:1) and shaken vigorously for 5 min. The aqueous layer was extracted with Et_2O and the organic layers were washed with sat. aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under vacuum to give crude **17**; yield: 97 mg (98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 3.15 (d, $^3J_{H,H}$ = 7 Hz, 2 H, CH_2), 6.33 (t, $^3J_{H,H}$ = 7 Hz, 1 H, CH), 9.60 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (CH_3), 44.9 (CH_2), 98.2 (C), 129.6 (CH), 197.2 (CH).

2-[2-(*tert*-Butyldimethylsilyloxy)ethylidene]-6-iodohept-5-ene-1,3-diol (21)

To a solution of **6** (1.66 g, 3.37 mmol) in THF (55 mL) at –78 °C was added dropwise BuLi (2.5 M, 3 mL, 7.41 mmol). The reaction mixture was warmed to –35 °C for 2 h and then cooled to –78 °C, then (*E*)-4-iodopent-3-en-1-al (**17**; 0.85 g, 4.04 mmol) was added dropwise. The solution was kept at –78 °C for 1 h and quenched with sat. aq NH_4Cl solution. The aqueous layer was extracted with EtOAc. The organic layers were washed with sat. aq NH_4Cl solution, dried ($MgSO_4$) and concentrated under vacuum. The crude product was then purified by flash chromatography (PE–Et_2O, 3:7) to afford **21**; yield: 778 mg (56%).

IR (film): 3400, 1606, 1033, 837 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6 H, 2 × CH_3), 0.89 (s, 9 H, 3 × CH_3), 2.14 (br d, $^3J_{H,H}$ = 4.1 Hz, 1 H, OH), 2.30–2.46 (m, 2 H, CH_2), 2.38 (s, 3 H, CH_3), 2.60 (br t, $^3J_{H,H}$ = 6 Hz, 1 H, OH), 4.15–4.22 (m, 3 H, CH_2, CH), 4.27 (d, $^3J_{H,H}$ = 6 Hz, 2 H, CH_2), 5.71 (t, $^3J_{H,H}$ = 6 Hz, 1 H, CH), 6.16 (br t, $^3J_{H,H}$ = 6.8 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 27.9 (CH_3), 36.9 (CH_2), 58.1 (CH_2), 59.5 (CH_2), 74.6 (CH), 95.8 (C), 129.1 (CH), 136.8 (CH), 141.4 (C).

MS (EI, 70 eV): *m*/*z* (%) = 379 ($M^{+\cdot}$ – H_2O – Me, 20), 378 (14), 377 (63), 337 (27), 267 (18), 263 (47), 251 (13), 249 (12), 245 (23), 211 (11), 181 (14), 161 (13), 153 (48), 137 (17), 136 (64), 135 (100), 134 (12), 133 (61), 123 (34), 115 (35), 109 (13), 108 (16), 107 (51), 105 (23), 99 (33), 95 (19), 93 (52), 91 (14), 89 (35), 83 (21), 75 (42), 73 (30), 71 (43).

HRMS: *m*/*z* calcd for $C_{15}H_{30}IO_3Si$ [M + H]$^+$: 413.1009; found: 413.1007.

2-[2-(*tert*-Butyldimethylsilyloxy)ethylidene]-1,3-diacetoxy-6-iodohept-5-ene (22)

A solution of diol **21** (0.190 g, 0.46 mmol), Ac_2O (0.173 mL, 1.84 mmol) and DMAP (4.6 mg) in pyridine (5 mL) was stirred overnight. The mixture was quenched with sat. aq $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the organic layers were washed with sat. aq $CuSO_4$ solution and H_2O, dried ($MgSO_4$) and concentrated under vacuum to give **22**; yield: 217 mg (96%).

IR (film): 1742, 1638, 1430, 1027, 837, 778 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, 2 × CH_3), 0.88 (s, 9 H, 3 × CH_3), 2.03 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.35–2.48 (m, 2 H, CH_2), 2.36 (s, 3 H, CH_3), 4.29 (d, $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2), 4.60 (s, 2 H, CH_2), 5.22 (t, $^3J_{H,H}$ = 6.4 Hz, 1 H, CH), 5.82 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, CH), 6.06 (br t, ^3J(H,H) = 6.8 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2 (2 × CH_3), 18.3 (C), 20.9 (CH_3), 21.1 (CH_3), 25.9 (3 × CH_3), 27.8 (CH_3), 34.5 (CH_2), 59.46 (CH_2), 59.50 (CH_2), 73.9 (CH), 96.4 (C), 132.1 (C), 134.7 (CH), 135.3 (CH), 169.8 (C), 170.5 (C).

MS (PCI, CH_4, 70 eV): *m*/*z* (%) = 437 ($M^{+\cdot}$ – CH_3COO, 15), 379 (16), 378 (21), 377 (100), 249 (17), 245 (47), 159 (21), 135 (25), 89 (24), 61 (26).

HRMS: *m*/*z* calcd for $C_{19}H_{34}IO_5Si$ [M + H]$^+$: 497.1220; found: 497.1215.

2-[2-(*tert*-Butyldimethylsilyloxy)ethylidene]-1,3-diacetoxy-6,10-dimethylundecadi-5,9-en-7-yne (23)

In a dry 10-mL Schlenk tube, a solution of **22** (0.1 g, 0.2 mmol) in DMF (2 mL) was added to $PdCl_2(MeCN)_2$ (2.6 mg, 0.01 mmol). The solution was degassed and 1-trimethylstannyl-4-methylpent-3-en-1-yne (**8**; 0.073 g, 0.3 mmol) was added and the reaction mixture immediately became black. The solution was stirred at r.t. and after disappearance of diacetate **22**, H_2O was added and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O, dried ($MgSO_4$) and concentrated under vacuum. Chromatography (PE–Et_2O, 8:2) furnished **23**; yield: 90 mg (99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, 2 × CH_3), 0.86 (s, 9 H, 3 × CH_3), 1.78 (s, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.38–2.53 (m, 2 H, CH_2), 4.28 (d, $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2), 4.60 (s, 2 H, CH_2), 5.22 (t, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH), 5.31 (br s, 1 H, CH), 5.66 (br t, $^3J_{H,H}$ = 7.4 Hz, 1 H, CH), 5.82 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 (2 × CH_3), 17.8 (CH_3), 18.3 (C), 20.9 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 24.9 (CH_3), 25.9 (3 × CH_3), 32.8 (CH_2), 59.58 (CH_2), 59.64 (CH_2), 74.7 (CH), 85.2 (C), 94.2 (C), 105.3 (CH), 121.2 (C), 130.7 (CH), 132.4 (C), 134.6 (CH), 148.1 (C), 170.0 (C), 170.7 (C).

MS (EI, 70 eV): *m*/*z* (%) = 448 ($M^{+\cdot}$, 1), 197 (23), 155 (10), 133 (32), 105 (21), 61 (24), 83 (10), 77 (16), 75 (84), 73 (76), 57 (11), 55 (11), 43 (100), 41 (27).

HRMS: *m*/*z* calcd for $C_{25}H_{41}O_5Si$ [M + H]$^+$: 449.2723; found: 449.2724.

4-Acetoxy-3-acetoxymethyl-7,11-dimethyldodecatri-2,6,10-en-8-yn-1-ol (24)

To a solution of **23** (150 mg, 0.334 mmol) in THF (5 mL) was quickly added an excess of HF/pyridine (0.153 mL). The reaction was monitored by TLC. After disappearance of the starting material, the mixture was concentrated under vacuum. The crude product (95:5 ratio of isomers) was then purified by flash chromatography (PE–EtOAc, 6:4) to give **24**; yield: 85 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (br s, 3 H, CH_3), 1.80 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, CH_3), 1.87 (br s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.40–2.55 (m, 2 H, CH_2), 4.26 (d, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2), 4.64 (d, $^2J_{H,H}$ = 12.4 Hz, 1 H, CH_2), 4.72 (d, $^2J_{H,H}$ = 12.4

Hz, 1 H, CH_2), 5.22 (t, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH), 5.33 (br s, 1 H, CH), 5.66 (tq, $J_{H,H}$ = 7.4, 1.2 Hz, 1 H, CH), 5.94 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 24.8 (CH_3), 32.8 (CH_2), 58.3 (CH_2), 59.5 (CH_2), 74.5 (CH), 85.2 (C), 94.0 (C), 105.2 (CH), 121.2 (C), 130.1 (CH), 133.0 (C), 134.3 (CH), 148.2 (C), 170.1 (C), 171.0 (C).

HRMS: *m*/*z* calcd for $C_{19}H_{27}O_5$ [M + H]$^+$: 335.1859; found: 335.1862.

Taxifolial A [(±)-2][39]

To a stirred solution of alcohol **24** (46 mg, 0.14 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C was added Dess–Martin periodinane (88 mg, 0.2 mmol). The reaction mixture was stirred under argon at r.t. and monitored by TLC. After disappearance of the starting material, the mixture was poured into a separating funnel containing sat. aq $Na_2S_2O_3$/$NaHCO_3$ solution (9 mL, 1:1) and shaken vigorously for 5 min. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with sat. aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under vacuum to give crude taxifolial A [(±)-**2**]; yield: 52 mg (96%).

^{1}H NMR (500 MHz, C_6D_6): δ = 1.47 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 1.82 (s, 3 H, CH_3), 2.21 (m, 2 H, CH_2), 4.59 (d, $^2J_{H,H}$ = 13.8 Hz, 1 H, CH_2), 4.76 (d, $^2J_{H,H}$ = 13.8 Hz, 1 H, CH_2), 5.28 (t, $^3J_{H,H}$ = 6.3 Hz, 1 H, CH), 5.43 (s, 1 H, CH_3), 5.83 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H, CH), 6.03 (d, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH), 9.86 (d, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 3 H, CH_3), 1.81 (s, 3 H, CH_3), 1.87 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.53 (m, 2 H, CH_2), 5.00 (d, $^2J_{H,H}$ = 13.8 Hz, 1 H, CH_2), 5.10 (d, $^2J_{H,H}$ = 13.8 Hz, 1 H, CH_2), 5.32 (m, 1 H, CH), 5.33 (s, 1 H, CH), 5.67 (br t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH), 6.12 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 10.09 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH).

^{13}C NMR (75 MHz, C_6D_6): δ = 17.9 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 21.0 (CH_3), 24.6 (CH_3), 32.8 (CH_2), 59.1 (CH_2), 73.0 (CH), 86.4 (C), 94.6 (C), 106.2 (CH), 122.5 (C), 129.0 (CH), 129.7 (CH), 147.9 (C), 154.0 (C), 169.2 (C), 169.6 (C), 189.5 (CH).

(1*Z*,3*E*) and (1*Z*,3*Z*)-1,4-Diacetoxy-2-(1-acetoxyprop-1-yl)but-1,3-diene (29 and 30)

In a Schlenk tube, under N_2, was placed **28** (15 mg, 0.065 mmol), DMAP (8 mg, 0.065 mmol), Ac_2O (18.5 μL, 0.2 mmol) and Et_3N (0.5 mL). The mixture was warmed to 80 °C and the reaction was monitored by GC. After disappearance of the starting material, the mixture was concentrated under vacuum and purified by chromatography on silica gel (pentane–EtOAc, 8:2) to give a 45:65 mixture **29** and **30**; yield: 14.3 mg (85%).

^{1}H NMR (300 MHz, C_6D_6): δ = 0.79 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3), 0.83 (t, $^3J_{H,H}$ = 7 Hz, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.58 (s, 9 H, 3 × CH_3), 1.67 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.45–1.92 (m, 4 H, 2 × CH_2); characteristic signals of **29**: 5.76 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, CH), 6.07 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH), 7.36 (s, 1 H, CH), 7.92 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, CH); characteristic signals of **30**: 5.11 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH), 6.14 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.35 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH), 8.22 (s, 1 H).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, $^3J_{H,H}$ = 7.5 Hz, 6 H, 2 × CH_3), 1.48–1.89 (m, 4 H, 2 × CH_2), 2.01 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.18 (s, 6 H, 2 × CH_3), 5.73–5.80 (m, 3 H, 3 × CH); characteristic signals of **29**: 7.22 (s, 1 H, CH), 7.57 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, CH); characteristic signals of **30**: 5.15 (d, ^3J(H,H) = 7.2 Hz, 1 H, CH), 7.20 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH), 7.82 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.5 (CH_3), 9.8 (CH_3), 20.71 (CH_3), 20.74 (CH_3), 21.1 (CH_3), 20.8 (2 × CH_3), 21.2 (CH_3), 25.9 (CH_2), 26.1 (CH_2), 70.8 (CH), 71.0 (CH), 103.8 (CH), 109.4 (CH), 117.1 (C), 119.0 (C), 134.3 (CH), 135.0 (CH), 137.0 (CH), 137.7 (CH), 167.2 (C), 167.3 (C), 167.4 (C), 167.9 (C), 170.2 (2 × C).

***Iso*-caulerpenyne [*iso*-(±)-1]**

A solution of taxifolial A [(±)-**2**; 44 mg, 0.132 mmol], KOAc (19.5 mg, 0.198 mmol), Ac_2O (0.037 mL, 0.396 mmol) in benzene (3 mL) was heated at reflux. After disappearance of the starting material, the mixture was concentrated under vacuum. The crude product was then purified by flash chromatography (hexane–Et_2O, 8:2) to give *iso*-caulerpenyne [*iso*-(±)-**1**]; yield: 43 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 2.19 (s, 6 H, 2 × CH_3), 2.36 (dt, $^2J_{H,H}$ = 14.5, 7.3 Hz, 1 H, CH_2), 2.54 (dt, $^2J_{H,H}$ = 14.5, 7.3 Hz, 1 H, CH_2), 5.18 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 5.32 (s, 1 H, CH), 5.66 (br t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 5.86 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.22 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.81 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8 (CH_3), 20.85 (CH_3), 20.89 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 24.9 (CH_3), 32.4 (CH_2), 68.7 (CH), 85.2 (C), 94.2 (C), 103.6 (CH), 105.3 (CH), 116.9 (C), 121.5 (C), 129.9 (CH), 135.2 (CH), 137.6 (CH), 148.2 (C), 167.2 (C), 167.4 (C), 170.0 (C).

Caulerpenyne [(±)-1][2]

In a Schlenk tube, under N_2, was placed taxifolial A [(±)-**2**; 50 mg, 0.15 mmol], DMAP (18.4 mg, 0.15 mmol), Ac_2O (42 μL, 0.45 mmol) and Et_3N (4 mL). The mixture was warmed to 80 °C and the reaction was monitored by GC. After disappearance of the starting material, the mixture was concentrated under vacuum and purified by chromatography on silica gel (pentane–EtOAc, 8:2) to give a 40:60 mixture of caulerpenyne [(±)-**1**] and *iso*-caulerpenyne [*iso*-(±)-**1**]; yield: 54 mg (96%).

Caulerpenyne [(±)-**1**]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, CH_3), 1.81 (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.45 (dt, $^2J_{H,H}$ = 14.7, 7.5 Hz, 1 H, CH_2), 2.63 (dt, $^2J_{H,H}$ = 14.7, 7.5 Hz, 1 H, CH_2), 5.33 (s, 1 H, CH), 5.67 (br t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH), 5.80 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, CH), 5.85 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH), 7.23 (s, 1 H), 7.62 (d, $^3J_{H,H}$ = 12.6, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (CH_3), 20.7 (2 × CH_3), 21.0 (CH_3), 21.2 (CH_3), 24.9 (CH_3), 32.1 (CH_2), 68.9 (CH), 85.3 (C), 94.1 (C), 105.3 (CH), 109.3 (CH), 118.7 (C), 121.6 (C), 129.9 (CH), 134.3 (CH), 137.0 (CH), 148.2 (C), 167.1 (C), 167.9 (C) et 170.0 (C).

Homogeranial (33)

To a stirred solution of homogeraniol (**32**; 0.4 g, 2.38 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added Dess–Martin periodinane (2.00 g, 4.75 mmol). The reaction mixture was stirred under argon at r.t. and monitored by TLC. After disappearance of the starting material, the mixture was poured into a separating funnel containing sat. aq $Na_2S_2O_3$/$NaHCO_3$ solution (200 mL, 1:1) and shaken vigorously for 5 min. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with sat. aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under vacuum to give crude homogeranial **33**; yield: 396 mg (quant).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.58 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 2.06 (m, 4 H, 2 × CH_2), 3.11 (br d, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2), 5.00–5.13 (m, 1 H, CH), 5.29 (br t, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH), 9.60 (t, $^3J_{H,H}$ = 2.1 Hz, 1 H, CH).

^{13}C NMR (50 MHz, C_6D_6): δ = 16.4 (CH_3), 17.7 (CH_3), 25.8 (CH_3), 26.9 (CH_2), 39.9 (CH_2), 43.4 (CH_2), 113.9 (CH), 124.5 (CH), 131.5 (C), 140.5 (C), 198.0 (CH).

HRMS: *m*/*z* calcd for $C_{11}H_{19}O$ [M + H]$^+$: 167.1436; found: 167.1432.

(2*E*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-3-hydroxymethyl-7,11-dimethyldodeca-2,6,10-triene (34)

To a solution of **6** (0.935 g, 1.91 mmol) in THF (30 mL) at –78 °C was added dropwise BuLi (2.5 M, 1.68 mL, 4.19 mmol). The reaction mixture was warmed to –35 °C for 2 h and then cooled to –78 °C, then homogeranial **33** (0.380 g, 2.28 mmol) was added dropwise. The solution was kept at –78 °C for 1 h and quenched with sat. aq NH_4Cl solution. The aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude product was then purified by flash chromatography (PE–Et_2O, 4:6) to afford **34**; yield: 320 mg (47%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, 2 × CH_3), 0.86 (s, 9 H, 3 × CH_3), 1.55 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.92–2.10 (m, 4 H, 2 × CH_2), 2.17–2.43 (m, 2 H, CH_2), 2.75 (br s, 1 H, OH), 3.15 (br s, 1 H, OH), 4.11 (br t, $^3J_{H,H}$ = 7 Hz, 1 H, CH), 4.16 (br s, 2 H, CH_2), 4.25 (br d, $^3J_{H,H}$ = 6.1 Hz, 2 H, CH_2), 4.99–5.11 (m, 2 H, 2 × CH), 5.63 (t, $^3J_{H,H}$ = 6.1 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.2 (2 × CH_3), 16.3 (CH_3), 17.7 (CH_3), 18.3 (C), 25.7 (CH_3), 25.9 (3 × CH_3), 26.6 (CH_2), 34.7 (CH_2), 39.8 (CH_2), 58.4 (CH_2), 59.5 (CH_2), 75.7 (CH), 119.7 (CH), 124.1 (CH), 128.8 (CH), 131.6 (C), 138.8 (C), 141.8 (C).

HRMS: *m*/*z* calcd for $C_{21}H_{41}O_3Si$ [M + H]$^+$: 369.2825; found: 369.2824.

(2*E*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-acetoxy-3-acetoxymethyl-7,11-dimethyldodeca-2,6,10-trienes (35)

A solution of **34** (0.217 g, 0.59 mmol), Ac_2O (0.221 mL, 2.35 mmol) and DMAP (3.6 mg, 0.03 mmol) in pyridine (4.5 mL) was stirred until the disappearance of the starting material. Then the mixture was quenched with sat. aq $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with sat. aq $CuSO_4$ solution and H_2O, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography (PE–Et_2O, 8:2) to give **35**; yield: 230 mg (86%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, 2 × CH_3), 0.86 (s, 9 H, 3 × CH_3), 1.56 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 1.89–2.10 (m, 4 H, 2 × CH_2), 2.22–2.47 (m, 2 H, CH_2), 4.28 (d, $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2), 4.59 (s, 2 H, CH_2), 4.96–5.06 (m, 2 H, 2 × CH), 5.21 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H, CH), 5.80 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1 (2 × CH_3), 16.3 (CH_3), 17.7 (CH_3), 18.3 (C), 20.9 (CH_3), 21.2 (CH_3), 25.7 (CH_3), 25.9 (3 × CH_3), 26.7 (CH_2), 32.3 (CH_2), 39.8 (CH_2), 59.6 (CH_2), 59.7 (CH_2), 75.5 (CH), 118.8 (CH), 124.1 (CH), 131.5 (C), 132.7 (C), 134.3 (CH), 138.4 (C), 170.1 (C), 170.7 (C).

MS (EI, 70 eV): *m*/*z* (%) = 332 ($M^{+\cdot}$ – 2 × CH_3COOH, 11), 263(14), 213 (11), 201 (34), 159 (20), 157 (11), 145 (21), 131 (15), 119 (13), 117 (84), 105 (12), 93 (12), 91 (13), 81 (11), 77 (12), 75 (100), 69 (28), 45 (16), 41 (26).

HRMS: *m*/*z* calcd for $C_{25}H_{45}O_5Si$ [M + H]$^+$: 453.3036; found: 453.3039.

(2*E*,6*E*)-4-Acetoxy-3-acetoxymethyl-7,11-dimethyldodeca-2,6,10-trien-1-ol (36)

To a solution of **35** (224 mg, 0.5 mmol) in THF (7 mL) was quickly added an excess of HF/pyridine (0.455 mL). The reaction was monitored by TLC. After the disappearance of the starting material, the mixture was concentrated under vacuum. The crude product (95:5 ratio of isomers) was purified by flash chromatography (PE–Et_2O, 5:5 to 0:10) to give **36**; yield: 130 mg (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.93–2.04 (m, 5 H, 2 × CH_2, OH), 2.02 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.29–2.45 (m, 2 H, CH_2), 4.25 (br t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2), 4.62 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, CH_2), 4.72 (d, $^3J_{H,H}$ = 12.5 Hz, 1 H, CH_2), 5.01–5.06 (m, 2 H, 2 × CH), 5.21 (t, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH), 5.93 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.2 (CH_3), 17.6 (CH_3), 20.9 (CH_3), 21.1 (CH_3), 25.6 (CH_3), 26.5 (CH_2), 32.3 (CH_2), 39.7 (CH_2), 58.3 (CH_2), 59.6 (CH_2), 75.3 (CH), 118.6 (CH), 124.0 (CH), 131.5 (C), 132.6 (CH), 134.6 (C), 138.4 (C), 170.2 (C), 171.0 (C).

HRMS: *m*/*z* calcd for $C_{19}H_{31}O_5$ [M + H]$^+$: 339.2172; found: 339.2172.

(2*E*,6*E*)-4-Acetoxy-3-acetoxymethyl-7,11-dimethyldodeca-2,6,10-trienal (37)

To a stirred solution of **36** (60 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Dess–Martin periodinane (150 mg, 0.35 mmol). The reaction mixture was stirred under argon at r.t. and monitored by TLC. After disappearance of the starting material, the mixture was poured into a separating funnel containing sat. aq $Na_2S_2O_3$/$NaHCO_3$ solution (15 mL, 1:1) and shaken vigorously for 5 min. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with sat. aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under vacuum to give crude aldehyde **37**; yield: 59 mg (quant).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.93–2.07 (m, 4 H, 2 × CH_2), 2.03 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.38–2.43 (m, 2 H, CH_2), 4.94 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H, CH_2), 4.96–5.07 (m, 2 H, 2 × CH), 5.10 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H, CH_2), 5.29 (t, $^3J_{H,H}$ = 6.1 Hz, 1 H, CH), 6.07 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH), 10.06 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (CH_3), 17.7 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 25.7 (CH_3), 26.5 (CH_2), 32.2 (CH_2), 39.7 (CH_2), 59.3 (CH_2), 73.8 (CH), 117.5 (CH), 123.9 (CH), 128.9 (CH), 131.7 (C), 139.6 (C), 154.7 (C), 169.9 (C), 170.2 (C), 190.4 (CH).

HRMS: *m*/*z* calcd for $C_{19}H_{29}O_5$ [M + H]$^+$: 337.2015; found: 337.2019.

(±)-Dihydrorhipocephalin [(±)-3] and *iso*-(±)-Dihydrorhipocephalin [*iso*-(±)-3)][31]

In a Schlenk tube, under N_2, were placed **37** (23 mg, 0.068 mmol), DMAP (8.3 mg, 0.068 mmol), Ac_2O (19 μL, 0.2 mmol) and Et_3N (1.5 mL). The mixture was warmed to 80 °C and the reaction was followed by GC. After disappearance of the starting material, the mixture was concentrated under vacuum and purified by flash chromatography (pentane–EtOAc, 8:2) to give a 45:55 mixture of (±)-dihydrorhipocephalin [(±)-**3**] and *iso*-(±)-dihydrorhipocephalin [*iso*-(±)-**3**]; yield: 20 mg (80%).

^{1}H NMR (500 MHz, $CDCl_3$), (±)-dihydrorhipocephalin [(±)-**3**]: δ = 1.57 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.93–2.05 (m, 4 H, 2 × CH_2), 2.03 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.37 (dt, $J_{H,H}$ = 14.3, 7.3 Hz, 1 H, CH_2), 2.52 (dt, $J_{H,H}$ = 14.3, 7.3 Hz, 1 H, CH_2), 5.02–5.05 (m, 2 H, 2 × CH), 5.80 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, CH), 5.83 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.20 (s, 1 H, CH), 7.61 (d, $^3J_{H,H}$ = 12.7 Hz, 1 H, CH).

^{1}H NMR (500 MHz, $CDCl_3$), *iso*-(±)-dihydrorhipocephalin [*iso*-(±)-**3**]: δ = 1.57 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.93–2.05 (m, 4 H, 2 × CH_2), 2.01 (s, 3 H, CH_3) 2.18 (s, 6 H, 2 × CH_3), 2.26 (dt, $J_{H,H}$ = 14.3, 7.3 Hz, 1 H, CH_2), 2.44 (dt, $J_{H,H}$ = 14.3, 7.3 Hz, CH_2), 5.02–5.05 (m, 2 H, 2 × CH), 5.20 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 5.85 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.21 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.80 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$), (±)-dihydrorhipocephalin [(±)-**3**] and *iso*-(±)-dihydrorhipocephalin [*iso*-(±)-**3**]: δ = 16.3 (CH_3), 16.4 (CH_3), 17.7 (2 × CH_3), 20.8 (2 × CH_3), 20.85 (CH_3), 20.88 (CH_3), 21.1 (CH_3), et 21.2 (CH_3), 25.7 (2 × CH_3), 26.7 (2 × CH_2), 31.6 (CH_2), 31.9 (CH_2), 39.79 (CH_2), 39.82 (CH_2), 69.4 (CH), 69.5 (CH), 104.0 (CH), 109.5 (CH), 117.3 (C), 118.06 (CH), 118.11 (CH),

119.2 (C), 124.0 (2C, CH), 131.60 (C), 131.61 (C), 134.0 (CH), 134.9 (CH), 137.0 (CH), 137.5 (CH), 138.8 (C), 138.9 (C), 167.2 (C), 167.3 (C), 167.5 (C), 167.9 (C), 170.1 (2 × C).

Biology

Lamb brain pure tubulin was purified from brain soluble extract by $(NH_4)_2SO_4$ fractionation and ion exchange chromatography. Then, pure tubulin was stored in liquid N_2 and prepared for use.[40] Tubulin concentration was determined spectrometrically at 275 nm in 6 M guanidine hydrochloride (E_{275} nm = 1.09 $L{\cdot}g^{-1}{\cdot}cm^{-1}$) or in 0.5% sodium dodecyl sulfate in neutral aqueous buffer (E_{275} nm = 1.07 $L{\cdot}g^{-1}{\cdot}cm^{-1}$). The buffer solution used to polymerize pure tubulin consisted of 20 mM sodium phosphate buffer, 1 mM EGTA, 3.4 M glycerol, and 0.1 mM GTP, pH 6.95. After 35 min of incubation at 37 °C with CYN analogues or DMSO (control), the polymerisation reaction was started by addition of 10 mM $MgCl_2$. To determine the inhibitory effect, we calculated the difference between the polymerisation plateau value and the depolymerisation plateau value and expressed it in percent of inhibition relative to the control.

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