ORGANIC LETTERS

2001
Vol. 3, No. 11
1713−1715

First Total Synthesis of (±)-Taxifolial A and (±)-*iso*-Caulerpenyne

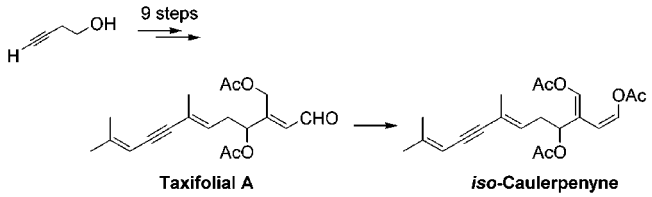
Laurent Commeiras, Maurice Santelli, and Jean-Luc Parrain*

Laboratoire de Synthèse Organique associé au CNRS (UMR 6009), Faculté des Sciences de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

jl.parrain@lso.u-3mrs.fr

Received March 28, 2001

ABSTRACT



The first synthesis of (±)-taxifolial A and *iso*-caulerpenyne was accomplished. The key steps in the sequence are (1) the stereoselective assembly of a vinyltin derived from butynediol and a functionalized aldehyde and (2) the construction of the dienyne moiety via a Stille cross-coupling.

The proliferation of the tropical green seaweed *Caulerpa taxifolia* which has massively invaded the Mediterranean from Italy to Spain is one of the major marine ecological concerns for the last two decades. This toxic seaweed, as other caulerpales, develops an efficient strategy against the endemic flora by emitting secondary metabolites.[1] Compared to other Caulerpa species in the tropics, *Caulerpa taxifolia* contains large amount of caulerpenyne **1**, a sesquiterpene isolated and first identifed from *Caulerpa prolifera*.[2,3] Its biological activity has been well described.[4] For example, caulerpenyne inhibits the proliferation of the fibroblastic cell line BHK 21/C13 from baby hamster kidney and the division of sea urchin eggs.[5] The cytoxicity was also demonstrated in various tumor cell lines,[6] and **1** was evaluated as a toxicological risk to humans.[7] Several secondary metabolites were also identified and could be involved in the toxicity of *C. taxifolia* from the Mediterranean (Figure 1).[8]

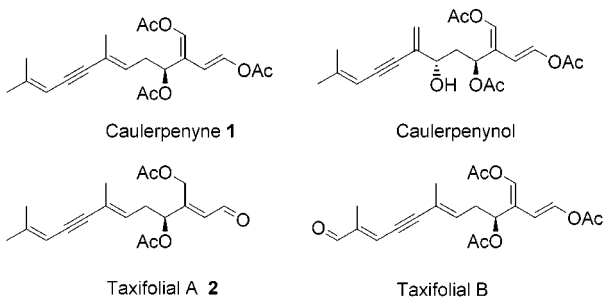


Figure 1.

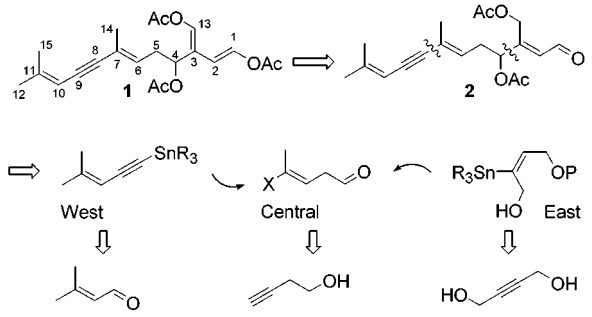
A few synthetic transformations from caulerpenyne, isolated from *C. taxifolia*, have been reported.[9] However, no synthetic route toward caulerpenyne **1** has been reported to date.

(1) Faulkner, D. J. *Nat. Prod. Rep.* **1987**, *4*, 540−542.
(2) Amico, V.; Oriente, G.; Piatelli, M.; Tringali, C. *Tetrahedron Lett.* **1978**, 3593−3596.
(3) Valls, R.; Artaud, J.; Amade, P.; Vicente, N.; Piovetti, L. *J. Chromatogr. A* **1994**, *663*, 114−118.
(4) Paul, V. J.; Fenical, W. *Phytochemistry* **1985**, *24*, 2239−2243.
(5) Lemée, R.; Pesando, D.; Durand-Clement, M.; Dubreuil, A.; Meinesz, A.; Guerriero, A.; Pietra, F. *J. Appl. Phycol.* **1993**, *5*, 485−493.
(6) Fischer, J. L.; Lemee, R.; Formento, P.; Caldani, C.; Moll, J. L.; Pesando, D.; Meinesz, A.; Grelier, P.; Pietra, F.; Guerriero, A.; Milano, G. *Anticancer Res.* **1995**, *15*, 2155−2160.
(7) Parent-Massin, D.; Fournier, V.; Amade, P.; Lemée, R.; Durand-Clement, M.; Delescluse, C.; Pesando, D. *J. Toxicol. Environ. Health* **1996**, *47*, 47−59.
(8) Guerriero, A.; Meinesz, A.; d'Ambrosio, M.; Pietra, F. *Helv. Chim. Acta* **1992**, *75*, 689−695.
(9) (a) Guerriero, A.; Dependori, D.; D'Ambrosio, M.; Pietra, F. *Helv. Chim. Acta* **1995**, *78*, 1755−1762. (b) Guerriero, A.; D'Ambrosio, M.; Durante, M.; Dini, F.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1994**, 2083−2084. (c) Guerriero, A.; D'Ambrosio, M. *Eur. J. Org. Chem.* **1999**, 1985−1990.

10.1021/ol015903r CCC: $20.00
Published on Web 05/09/2001

The main structural features of **1** are a diacetoxybutadiene moiety, a secondary acetate stereocenter, and a dienyne function in which the trisubstituted double bond C6−C7 presents an *E* configuration. Scheme 1 outlines our strategy

Scheme 1. Retrosynthesis of Caulerpenyne

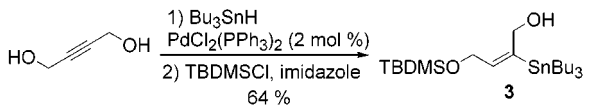


for synthesizing caulerpenyne and one of its metabolites taxifolial A **2** which could be considered as a good precursor of **1**.

Our planned synthesis of **1** called for the initial preparation of taxifolial **2**. Aldehyde **2** was constructed by a coupling reaction between the vinylstannanes (east segment) (tin−lithium exchange) derived from butynediol and the aldehyde of the central part. The carbon skeleton was achieved through a Stille reaction between the residual vinyl iodide function of the central part and an alkynyl stannane (west fragment). The control of the configuration of the trisubstituted double bond was accomplished via stannylcupration and iododestannylation reactions.

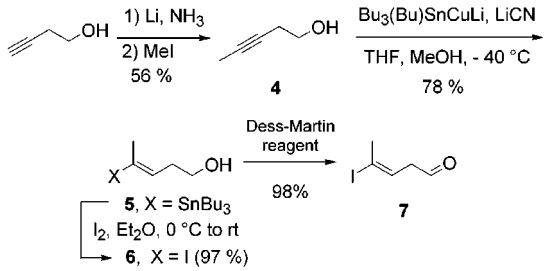
Synthesis of the vinyl segment **3** began with palladium complex catalyzed hydrostannation[10] of but-2-ynediol to give (*E*)-vinyltin reagent in which the more accessible alcohol function was selectively protected as *tert*-butyldimethylsilyl ether in 64% yield over two steps (Scheme 2).[11] It should be noted that approximately 5% of the other monoprotected regioisomer was also obtained but was eliminated during the purification step.

Scheme 2



The preparation of iodoaldehyde **7** is summarized in Scheme 3. Lithium acetylide derived from butynol was alkylated with methyl iodide to give **4** in 56% yield.[12] The stereo- and regioselective stannylcupration using the Lipshutz

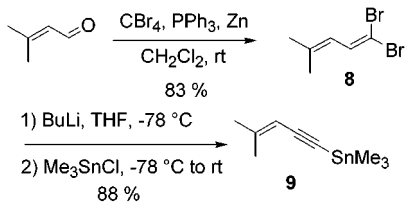
Scheme 3



reagent in the presence of methanol cleanly furnished vinyltin **5** in 78% yield.[13] The stannylcupration reaction gave two regioisomers observed by TLC and confirmed by ^{1}H NMR and ^{119}Sn NMR on the crude mixture (ratio 93/7 in favor of **5**). After purification by column chromatography, the up to 98% selectivity was established by GC/MS (see Supporting Information). The configuration of the double bond was established on the basis of the H−Sn coupling constant ($^{3}J_{Sn-H}$ = 70 Hz) which is consistent with an (*E*)-vinylstannane. Iododestannylation[14] with iodine in ether afforded quantitatively and stereoselectively the corresponding iodopentenol **6** in which the (*E*)-configuration of the trisubstituted double bond was established by NOESY experiment. The alcohol **6** was then oxidized with Dess−Martin periodinane,[15] providing the central segment **7**. The sensitive iodo aldehyde was found to be sufficiently pure to be used without purification (41% over four steps).

The west fragment was prepared via the Corey alkynylation reaction.[16] Commercially available 3,3-dimethylacrolein was reacted with the reagent prepared from carbon tetrabromide, zinc, and triphenylphosphine to give *gem*-dibromo diene **8**. Treatment of **8** with butyllithium (2 equiv) followed by addition of trimethyltin chloride afforded the stannylenyne **9** in 88% yield (73% from dimethylacrolein; Scheme 4).

Scheme 4



The assembly of the fragments **3**, **7**, and **9** and the construction of the carbon skeleton of caulerpenyne is

(10) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

(11) (a) Barrett, A. G. M.; Barta, T. E.; Flygare, J. A. *J. Org. Chem.* **1989**, *54*, 4246−4249. (b) Steinig, A. G.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 1333−1344.

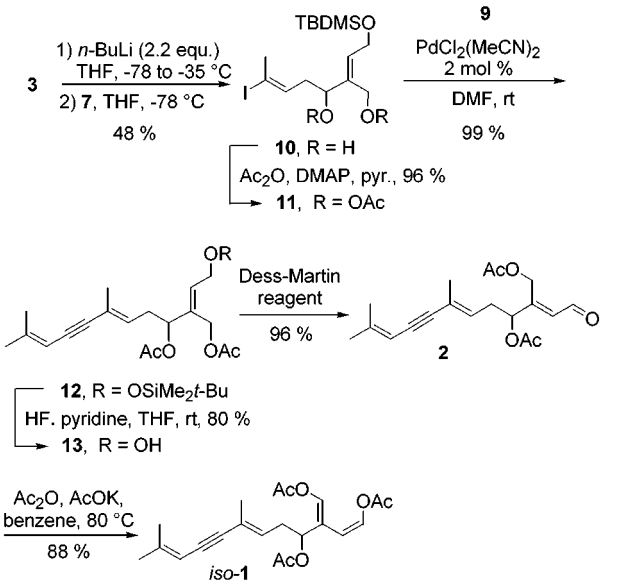
(12) Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275−2285.

(13) (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065−2068. (b) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1991**, *32*, 6333−6336. (c) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768−7780.

(14) (a) Baekelmans, P.; Gielen, M.; Malfroid, P.; Nasielski, J. *Bull. Soc. Chim. Belg.* **1968**, *77*, 85−88. (b) Fargeas, V.; Le Ménez, P.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron* **1996**, *52*, 6613−6634.

(15) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

Scheme 5



described in the Scheme 5. The coupling reaction between central segment **7** and the carbanion generated by tin−lithium exchange reaction[11] on the east segment **3** gave diol **10** in fair yield (48%).[17] At this stage, the two hydroxyl groups of **10** were protected as acetates using acetic anhydride and a catalytic amount of DMAP in pyridine to give bis-acetate **11** (96%). The carbon skeleton of caulerpenyne was achieved in a high yield through a Stille cross-coupling between the vinyl iodide **11** and the west segment **9** using 2 mol % of bis-acetonitrile palladium chloride in DMF.[14b,18] Using the tributylstannyl analogue of **9**, only 30% yield of **12** was obtained in mixture with the starting materials after 48 h.

Desilylation[19] of **12** by the complex HF/pyridine provided **13**,[20] whose primary hydroxyl group was oxidized by Dess−Martin periodinane,[15] affording (±)-taxifolial A **2** in 96% yield (Scheme 4). The data of this synthetic taxifolial A (500 MHz ^{1}H NMR $CDCl_3$, 75 MHz ^{13}C NMR $CDCl_3$, IR spectra, and TLC mobility) are in agreement with those reported in the literature.[8] The quenching the dienol of **2** with acetic anhydride in the presence of potassium acetate (3 equiv) led to *iso*-caulerpenyne in 88% yield.[21] Indeed, the ^{1}H NMR spectra established that the configuration of the C1−C2 double bond was *Z* instead of *E* as in the natural product.[22] The trisubstituted C3−C15 double bond exhibits the *E* configuration similarly to the natural caulerpenyne (NOESY experiment). Attempts to isomerize the terminal double bond using acetic acid failed to afford the *E* configuration of the C1−C2 double bond. To explain the configuration of the *Z* C1−C2 double bond, a more stable *S-cis* conformation of the enal function could be involved in the formation of the (*E*,*Z*)-dienol.

In conclusion, the first total synthesis of taxifolial A and *iso*-caulerpenyne was carried out in good yield. The overall yields of **2** and *iso*-**1** were 14% and 20%, respectively, in 9 and 10 steps from 3-butyn-1-ol. Further modifications to prepare enantiopure caulerpenyne are currently in progress.

Acknowledgment. Prof. R. Walls is gratefully acknowledged for valuable discussions and for providing NMR data of caulerpenyne. We also thank CNRS and MESR for providing financial support to L.C.

Supporting Information Available: Typical experimental procedure for the preparation of **1**−**13**. ^{1}H and ^{13}C spectra for **7**, **10**, **12**, **13**, **2**, and *iso*-**1**. NOESY spectrum for *iso*-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015903R

(16) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *14*, 3769−3770. (b) Hollingworth, G. J.; Richecoeur, A. M. E.; Sweeney, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2833−2836.

(17) The transmetalation step of the coupling reaction was found to be incomplete, and the vinyl tin **3** was recovered in 40% yield. Attempts using 3 equiv of BuLi failed to give better results. The selectivity of the cross-coupling was determined by ^{1}H NMR on the crude mixture, but was difficult.. After purification by column chromatography, the GC analysis established that the product contains a minor impurity (<2%) that we were unable to firmly characterize on the basis of mass spectra (see GC chromatogram in the Supporting Information). Finally, ^{1}H and ^{13}C NMR confirmed the high regio- and stereoselectivity.

(18) (a) Negishi, E. *Acc. Chem. Res*. **1982**, *15*, 340−348. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508−524. (c) Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.−L. *Synlett* **1999**, 141−143.

(19) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011−4013.

(20) **13** was obtained in a separable mixture with the isomer resulting from an acylotropy of the primary acetate function. Using tetrabutylammonium fluoride as a deprotecting agent, acylotropy reaction largely occurred, providing a mixture of mono-, di-, and triacetate isomers of **13**.

(21) Keana, J. F. W.; Eckler, P. E. *J. Org. Chem.* **1976**, *41*, 2625−2628.

(22) The level of selectivity of this step is estimated to be up to 95% (established by ^{1}H NMR and ^{13}C NMR analysis).