ORGANIC LETTERS

2003
Vol. 5, No. 20
3725−3728

Synthesis of Callyberynes A and B, Polyacetylenic Hydrocarbons from Marine Sponges

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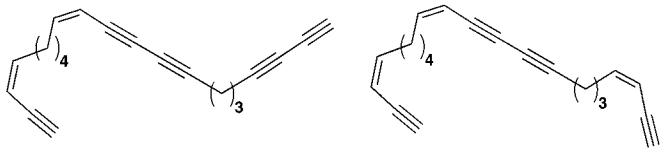
Received July 29, 2003

ABSTRACT



Callyberyne A Callyberyne B

Callyberynes A and B, polyacetylenic hydrocarbons from *Callyspongia* sp., have been synthesized for the first time using highly convergent approaches based on optimized Cadiot–Chodkiewicz (Alami, Vasella) and sequential Sonogashira cross-coupling reactions.

Linear polyacetylenes are a rapidly growing class of sponge metabolites,[1] some of which show remarkable biological activities (antifungal, antimicrobial, cytotoxic, antiviral, antitumoral, and enzyme-inhibitory)[2] and play important ecological roles (inducing metamorphosis of sessile marine animals, preventing fouling by barnacle larvae, and inhibiting fertilization of starfish gametes).[3,4] Although these compounds can exhibit a wide structural variety on both chain lengths and functionalities, examples of polyacetylenic hydrocarbons from marine organisms are relatively rare and characteristic of the family Callyspongiidae (genera *Siphonochalina* and *Callyspongia*).

Fusetani[4] and Umeyama[5] have independently reported the isolation, from Japanese marine *Callyspongia* sp., of several new polyacetylenes structurally related to the known (−)-siphonodiol (**1**),[6] including C-21 hydrocarbonated callyberynes A (**2**) (also referred to as callypentayne) and B (**3**) (Scheme 1), the latter showing a potent metamorphosis-inducing activity in the ascidian *Halocynthia roretzi* (ED_{100} = 0.25 μg/mL).[4]

Surprinsingly, no publication dealing with the synthesis of members of this family has been reported to date despite their increasing number[7] and the almost 20 years that have elapsed since the parent siphonodiol's first isolation.[6a]

As part of our ongoing projects on the chemistry of natural and synthetic polyenes and polyenynes,[8] we became interested in the development of successful approaches to this family of bioactive polyacetylenes. We herein describe a highly efficient, convergent route for the first synthesis of

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(7) Twelve metabolites related to siphonodiol (three hydrocarbons, five triols, two sulfates, and one dihydro- and one tetrahydro derivative) have been described to date. See refs 2−4 and also: Uno, M.; Ohta, S.; Ohta, E.; Ikegami, S. *J. Nat. Prod.* **1996**, *59*, 1146.

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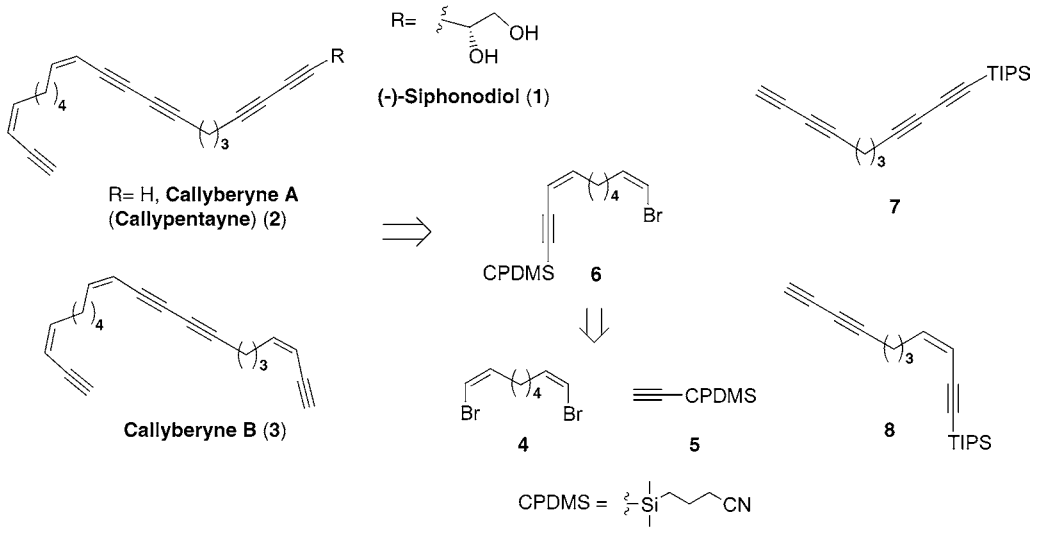
10.1021/ol0354270 CCC: $25.00
Published on Web 08/29/2003

Scheme 1. Retrosynthetic Analysis

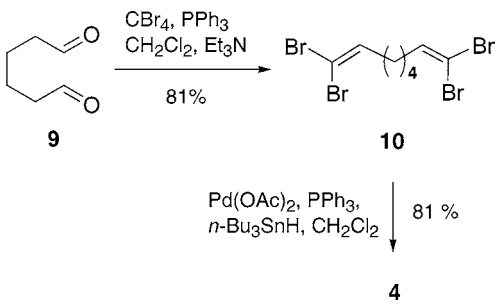


callyberynes A (**2**) and B (**3**) using sequential Sonogashira[9] and modified Cadiot−Chodkiewicz[10] cross-coupling reactions as key steps.

The retrosynthetic analysis (Scheme 1) led to (1*Z*,7*Z*)-1,8-dibromoocta-1,7-diene (**4**) as a valuable intermediate. A strategy involving orthogonally protected α,ω-dialkynes[11] would allow the preparation of the suitable polyyne counterparts **7** and **8**. Stereoselective sequential assembly of di-*cis*-dibromodiene **4** with the novel polar [(3-cyanopropyl)-dimethylsilyl]acetylene (CPDMSA)[12] (**5**), to give the common west fragment **6**, and with the 1,3-diyne moieties **7** or **8** would furnish the respective skeleton frameworks.

Synthesis of intermediate **4** is outlined in Scheme 2. Smooth heterogeneous oxidative cleavage of *trans*-cyclohexane-1,2-diol with $NaIO_4$ supported on silica gel afforded hexane-1,6-dial (**9**), quantitatively.[13] Treatment of **9** with CBr_4 and PPh_3 under Corey−Fuchs conditions allowed the bis-elongation of the chain to give 1,1,8,8-tetrabromoocta-1,7-diene (**10**), in good yield. Pd-catalyzed hydrogenolysis of **10** with Bu_3SnH[14] occurred stereoselectively, at both endings, to deliver **4** in 66% overall yield.

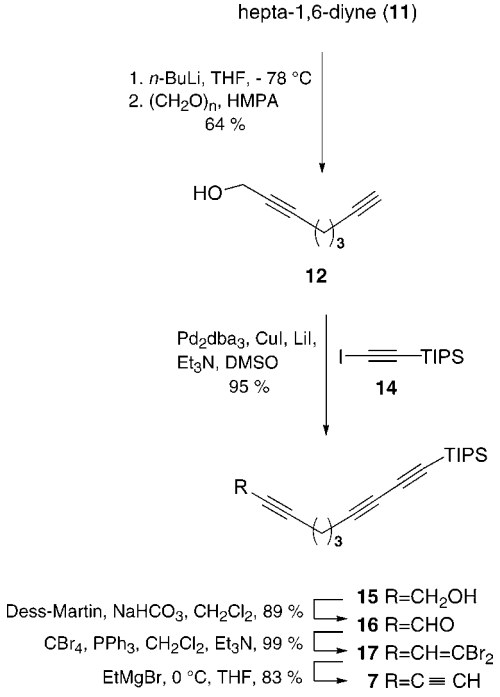
Scheme 2. Synthesis of Di-*cis*-dibromodiene **4**



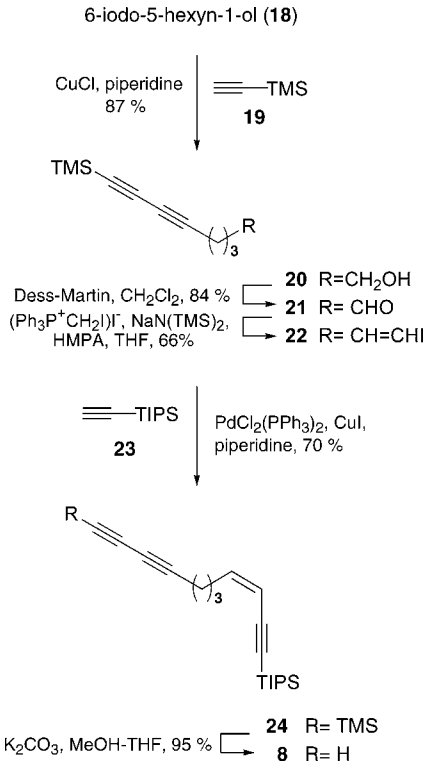
Next, our efforts were directed toward the preparation of east building blocks **7** and **8**.

Synthesis of tetrayne **7** (Scheme 3) involved selective monohydroxymethylation [^{n}BuLi, $(CH_2O)_n$, THF−HMPA] of commercially available hepta-1,6-diyne to give octa-2,7-diynol (**12**) in 64% yield.[15] Gratifyingly, Cadiot−Chodkiewicz cross-coupling of **12** with iodotriisopropylsilylacetylene (**14**), under Vasella's modified conditions [Pd_2dba_3, CuI, LiI, Et_3N, DMSO],[10c] afforded TIPS-protected propargylic triynol **15** in 95% yield. Dess−Martin periodinane oxidation and subsequent Corey−Fuchs homologation of the aldehyde **16** to a terminal acetylene, via dibromoolefin **17**, provided 1-triisopropylsilylundeca-1,3,8,10-tetrayne (**7**) in 73% combined yield for the last three steps.

Scheme 3. Synthesis of Tetrayne **7**



Scheme 4. Synthesis of Enetriyne **8**



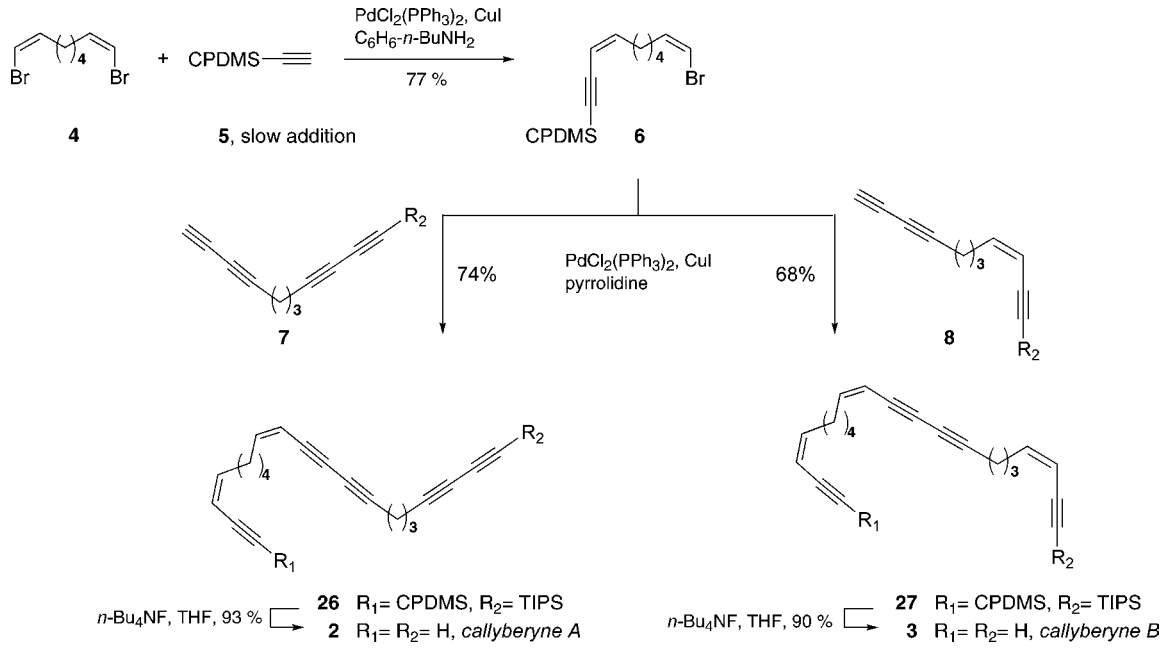
Similar methodologies were employed to synthesize enetriyne **8** (Scheme 4). Cadiot−Chodkiewicz cross-coupling of 6-iodo-5-hexynol (**18**)[16] with trimethylsilylacetylene, under Alami's modified conditions [CuI, piperidine],[10d] gave the TMS-protected diynol **20** in 87% yield. Dess−Martin oxidation and cis-stereoselective Stork's iodoolefination[17] of aldehyde **21** led to (*Z*)-iodoenediyne **22** in 55% combined yield. Sonogashira cross-coupling [$PdCl_2(PPh_3)_2$, CuI, piperidine] of **22** with triisopropylsilylacetylene afforded the differentially bis-protected enetriyne **24** in 70% yield. Basic methanolysis allowed selective removal of TMS group to obtain (3*Z*)-1-triisopropylsilylundec-3-ene-1,8,10-triyne (**8**) in 95% yield.

With all intermediates in hand, we faced the key final sequential Sonogashira cross-couplings (Scheme 5). Reaction of dibromide **4** and CPDMSA (**5**), to obtain the desired monocoupled product **6**, worked satisfactorily [$PdCl_2(PPh_3)_2$, CuI, C_6H_6][18] only after considerable fine-tuning of the reaction parameters, which included slow addition of alkyne to an excess of dibromide (1:2.5 relative molar ratio) and use of *n*-$BuNH_2$ as a base, giving rise to (1*Z*,7*Z*)-1-bromo-10-[(3′-cyanopropyl)dimethylsilyl]deca-1,7-dien-9-yne (**6**) in 77% yield. CPDMS-acetylene's high-polarity allows for simple and high-yield chromatographic separation of the coupling products.[19]

Although few examples of Sonogashira couplings with 1,3-diynes are known, mostly due to the difficulties associated with the synthesis and the stability of such intermediates,[20] the reactions of (*Z*)-vinylbromide **6** with either of the two 1,3-diyne moieties **7** or **8** occurred smoothly [$PdCl_2(PPh_3)_2$, CuI, pyrrolidine, rt] to give stable skeleton frameworks **26** and **27** in 74 and 68% yields, respectively. Finally, fluoride-induced cleavage of both terminal silyl-protecting groups led to the target callyberynes A (**2**) and B (**3**) in 93 and 90% yields, respectively. Their physical and spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, IR) were found to be identical in all respects with those reported for the natural products.[4,5]

In summary, we have described for the first time an expeditious synthesis of callyberynes A (**2**) and B (**3**), starting from easily available materials and using highly convergent

Scheme 5. Completion of the Synthesis of Callyberynes A and B



approaches, which involved modified Cadiot−Chodkiewicz and sequential Sonogashira cross-coupling reaction as key steps.[21] The synthesis of other members of this family of bioactive marine polyacetylenes, including parent (−)-siphonodiol (**1**), are now in progress in our laboratory and will be reported elsewhere.[22]

Acknowledgment. We thank the Ministerio de Ciencia y Tecnologia (Spain) and the European Regional Development Fund (Project BQU2002-02135) and Xunta de Galicia (Project PGIDT00PXI20901PR) for financial support.

Supporting Information Available: Experimental procedures, spectroscopic data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Minor bisprotected product nona-2,7-diyne-1,9-diol (**13**) was also obtained, in 3% yield, and easily separated by flash chromatography (silica gel, hexane/ethyl acetate 70:30). For similar reaction conditions, see: (a) Hillard, R.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1977**, *99*, 4058. (b) Rank, E.; Brückner, R. L. *Eur. J. Org. Chem.* **1998**, *1045*, 5.

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(19) The product resulting from the dicoupling reaction (3*Z*,9*Z*)-1,12-bis-[(3′-cyanopropyl)dimethylsilyl]dodeca-3,9-diene-1,11-diyne (**25**) was also obtained, in 8−10% yield, and easily separated by flash chromatography (silica gel, hexane/ethyl acetate 90:10).

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(21) Full spectroscopic and analytical data have been obtained for all compounds reported herein. Spectral data for selected intermediates: **(1*Z*,7*Z*)-1-Bromo-10-[(3′-cyanopropyl)dimethylsilyl]deca-1,7-dien-9-yne (6).** Yellow oil. IR (CsI): 2246 cm^{-1}. ^1H NMR (250.13 MHz, C_6D_6) δ: 0.06 (6H, s, $SiMe_2$), 0.3−0.4 (2H, m, $2H_{1'}$), 1.2−1.3 (6H, m, $2H_4 + 2H_5 + 2H_{2'}$), 1.50 (2H, t, $J = 6.9$ Hz, $2H_{3'}$), 2.0−2.1 (2H, m, $2H_3$), 2.2−2.3 (2H, m, $2H_6$), 5.44 (1H, d, $J = 10.9$ Hz, H_8), 5.6−5.7 (2H, m, $H_2 + H_7$), 5.84 (1H, d, $J = 6.9$ Hz, H_1). ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: −2.0, 15.5, 20.2, 20.4, 27.3, 27.8, 29.1, 29.8, 96.2, 103.0, 107.6, 109.0, 119.4, 134.4, 145.2. MS (EI) *m*/*z* (%): 340 (1), 338 (MH^+, 1), 324 (4), 322 (4), 258 (1), 126 (100). HRMS: calcd for $C_{16}H_{24}NSiBr$, 337.0861; found, 337.0859. **1-Triisopropylsilylundeca-1,3,8,10-tetrayne (7).** Yellow oil. IR (CsI): 3310 cm^{-1}. ^1H NMR (250.13 MHz, $CDCl_3$) δ: 1.08 (21H, m, TIPS), 1.78 (2H, q, $J = 6.8$ Hz, $2H_6$), 1.98 (1H, s, H_{11}), 2.42 (4H, t, $J = 6.8$ Hz, $2H_5 + 2H_7$). ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 11.3, 18.2, 18.4, 18.5, 26.6, 64.9, 65.6, 66.8, 68.2, 76.8, 76.9, 80.7, 89.7. MS (EI) *m*/*z* (%) 296 (M^+, 6), 253 (37), 211 (69), 183 (100), 164 (40). HRMS: calcd for $C_{20}H_{28}Si$, 296.1960; found, 296.1960. **(3*Z*)-1-Triisopropylsilylundec-3-ene-1,8,10-triyne (8).** Yellow oil. IR (CsI): 3311 cm^{-1}; ^1H NMR (250.13 MHz, $CDCl_3$) δ: 1.08 (21H, m, TIPS), 1.68 (2H, q, $J = 7.3$ Hz, $2H_6$), 1.96 (1H, s, H_{11}), 2.28 (2H, t, $J = 7.3$ Hz, $2H_7$), 2.44 (2H, dt, $J = 7.7, 7.3$ Hz, $2H_5$), 5.56 (1H, d, $J = 11.1$ Hz, H_3), 5.92 (1H, dt, $J = 11.1, 7.7$ Hz, H_4). ^{13}C NMR (62.90 MHz, $CDCl_3$) δ: 11.2, 18.6, 18.7, 27.3, 29.5, 64.6, 65.0, 68.4, 77.8, 95.6, 103.3, 110.9, 143.0. MS (CI) *m*/*z* (%) 299 (MH^+, 4), 298 (M^+, 2), 255 (68), 213 (91), 157 (100). HRMS: calcd for $C_{20}H_{31}Si$, 299.2195; found, 299.2198.

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