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Synthesis of Marine Polyacetylenes Callyberynes A−C by Transition-Metal-Catalyzed Cross-Coupling Reactions to sp Centers

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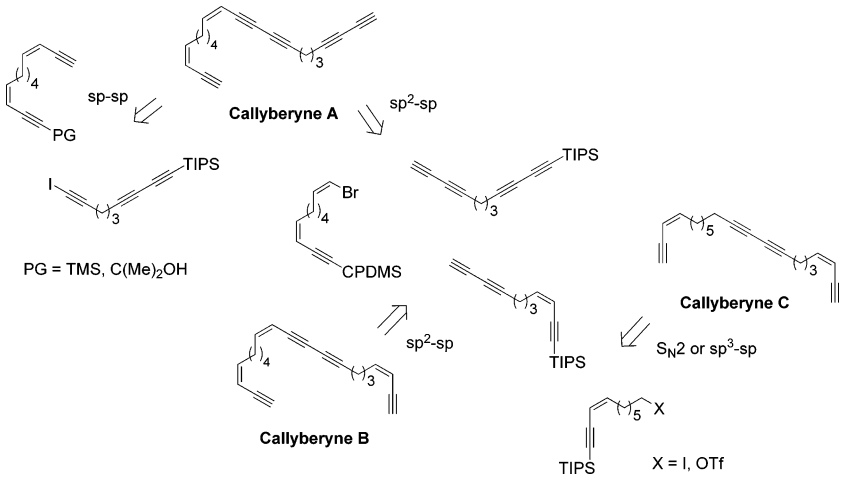

Efficient total syntheses of the sponge-derived hydrocarbon polyacetylenes callyberynes A−C have been achieved using metal-catalyzed cross-coupling reactions of highly unsaturated 1,3-diyne fragments as the key steps, namely: Cadiot-Chodkiewicz reaction under Alami's optimized conditions (sp−sp), sequential Sonogashira reaction of a *cis*,*cis*-divinyl dihalide (sp^2−sp), and Kumada−Corriu reaction of an unactivated alkyl iodide (sp^3−sp). This last approach constitutes the first application of a metal-catalyzed sp^3−sp Kumada−Corriu cross-coupling reaction to the synthesis of a natural product.

Introduction

The carbon−carbon triple bond is a ubiquitous structural feature of organic molecules.[1] Conjugated polyacetylenes are common structural units in a large number of natural products, many of which exhibit potent and varied biological activities and play important ecological roles.[2] In addition, they are also key structural moieties in synthetic compounds with unusual electrical, optical, or structural properties, which have found applications in materials science.[3] Consequently, renewed interest has recently appeared in the synthetic studies of both natural and unnatural acetylenic compounds.[4]

Transition-metal-catalyzed cross-coupling reactions are widely recognized as selective, high-yielding methods for the synthesis of organic compounds and have proven to be one of the most powerful arsenals for the formation of carbon−carbon bonds to sp centers.[5] However, the highly reactive nature of the intermediates involved in the total synthesis of conjugated polyacetylenes often presents a major challenge.

The vast majority of the metal-catalyzed acetylenic cross-coupling processes requires substrates having an sp or sp^2 carbon

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at or immediately adjacent to an electrophilic center. Polyacetylenic compounds are usually obtained through coupling of two acetylenic fragments.[6] Symmetrical 1,3-diynes can be prepared by oxidative coupling of terminal alkynes. Unsymmetrically disubstituted 1,3-diynes are more often obtained by the Cadiot−Chodkiewicz cross-coupling of a bromoacetylene with a terminal alkyne in the presence of a copper(I) salt and an aliphatic amine.[7] Some catalytical versions have been described together with examples of Pd−Cu cocatalysis.[8] Alami[9] has reported improved conditions for the coupling of terminal alkynes with 1-iodoalkynes in pyrrolidine that employ a copper catalyst and do not require a palladium cocatalyst. This optimized version can be advantageously used in the case of aliphatic 1-alkynes, which are known to give low yields of cross-coupling products under classical Cadiot−Chodkiewicz conditions.

The transition-metal-catalyzed cross-coupling reaction of metal acetylides with vinyl/aryl halides is an important reaction in organic synthesis since it provides a straight method for sp^2−sp carbon−carbon coupling.[10] The palladium-catalyzed cross-coupling reactions of terminal alkynes with sp^2 halides/triflates, in the presence (Sonogashira−Hagihara alkynylation)[11] or in the absence (Heck alkynylation)[12] of a copper cocatalyst, are even more useful synthetically and have been extensively used in the stereospecific synthesis of conjugated enynes.[13]

Palladium-catalyzed couplings in which the electrophile is sp^3-hybridized have been, however, rather uncommon.[14] Slow oxidative addition of the alkyl halide/triflate to palladium and facile intramolecular β-hydride elimination of the alkylmetal intermediate are two likely causes for this comparative lack of attention. However, a number of conditions have been developed recently to enhance the reactivity of the aliphatic C−X bonds and/or to stabilize the resulting organometallic intermediate so that the desired coupling can be achieved.[15] Regarding alkynylation, to the best of our knowledge, only two examples are described in the literature employing terminal alkynes and electrophilic sp^3 centers.[16] Luh[17] has reported that $Pd_2(dba)_3$−Ph_3P-catalyzed Kumada−Corriu coupling reactions of unactivated alkyl bromides or iodides with an alkynyl nucleophile (Mg or Li) led to Csp^3−Csp bond formation in good yields; the source of palladium appears to be decisive (palladium acetate is not an effective catalyst), and Ph_3P performs as the best ligand in what seems to be a reductive elimination-controlled process. On the other hand, Fu[18] has developed a Pd/N-heterocyclic carbene-based catalyst that achieves Sonogashira coupling of terminal alkynes with an array of fuctionalized, unactivated, β-hydrogen-containing alkyl bromides and iodides, under mild conditions.

As part of our ongoing projects on developing efficient and selective routes to natural and synthetic polyenes and polyenynes,[19] we became interested in a synthetically unexplored, rapidly growing group of linear, bioactive marine polyacetylenes isolated from the family Callyspongiidae. Fusetani[20] and Umeyama[21] have independently reported the isolation, from Japanese *Callyspongia* sp., of three C21 hydrocarbon polyacetylenes: callyberyne A (also referred to as callypentayne) (**1**), callyberyne B (**2**), and callyberyne C (also referred to as callytetrayne) (**3**) (Scheme 1). The three metabolites were structurally related to the known (−)-siphonodiol (**4**),[22] and biogenetically, they were considered most likely to be produced by decarboxylation of a C22 fatty acid precursor in the sponge. As some other members of this family,[23] callyberynes A (**1**) and C (**3**) exhibited potent metamorphosis-inducing activity in the ascidian *Halocynthia roretzi*, with ED_{100} values of 0.25 μg/mL.[20]

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(16) Examples of metal-catalyzed cross-coupling reactions of alkynyl stannanes with alkyl halides have been already described; see, for instance, ref 14d.

(17) Yang, L.-M.; Huang, L.-F−; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461−1463.

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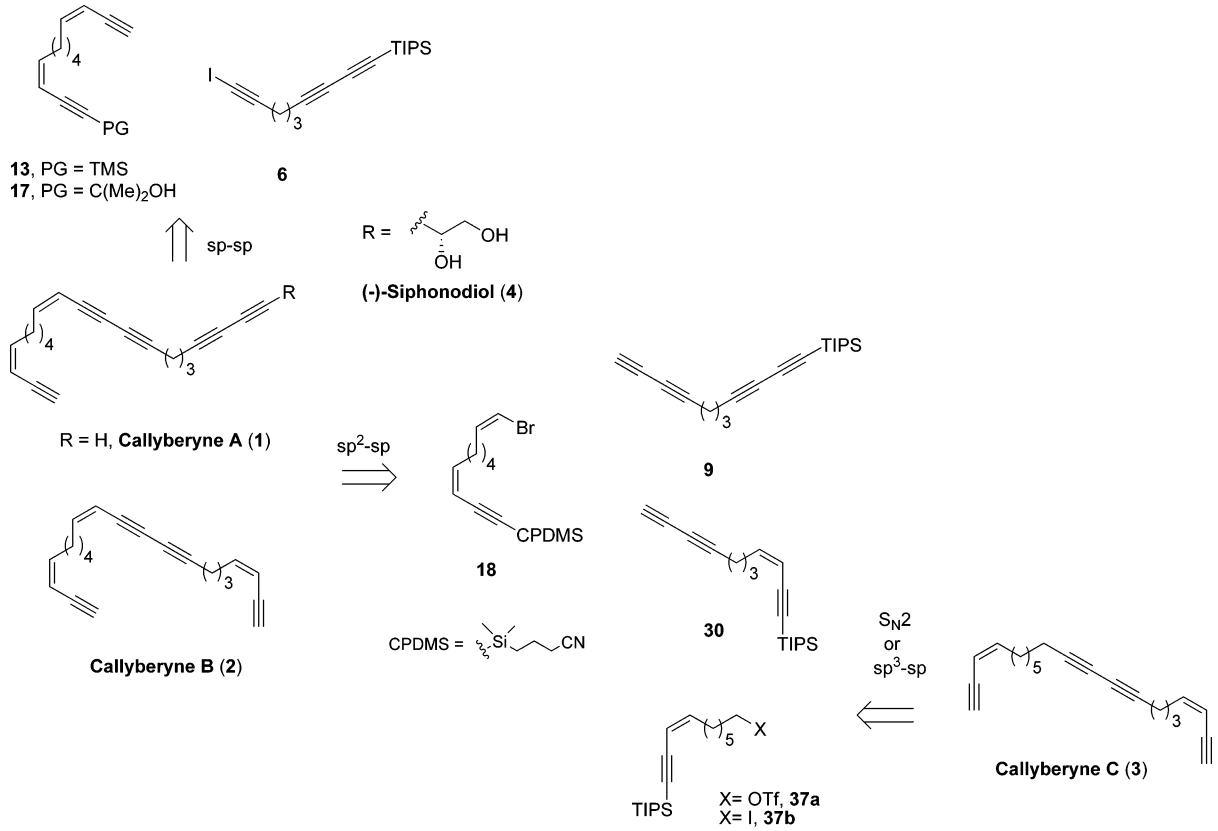
(23) The family includes around 20 structurally related compounds, among them four C_{21} hydrocarbons, four C_{22} alcohols, five triols, two sulfates, one dihydro derivative, and one tetrahydro derivative. See refs 2b, 25, 26, and references cited therein.

SCHEME 1. Retrosynthetic Analysis



The highly unsaturated nature of these new marine polyacetylenes prompted us to investigate their synthesis by routes that would allow us to apply new cross-coupling reactions and/or to test standard cross-coupling reactions by employing structurally complex building blocks.[24] As a result, we have already reported a communication on the synthesis of hydrocarbon callyberynes A (**1**) and B (**2**),[25] and we have recently described the first, stereoselective total synthesis of the parent compound (−)-siphonodiol (**4**)[26] using highly convergent approaches that involved optimized Cadiot−Chodkiewicz and sequential Sonogashira cross-coupling reactions as the key steps. We want to disclose herein the full account of our efforts toward the total synthesis of callyberynes A−B together with the first total synthesis of the related callyberyne C (**3**).

The overall retrosynthetic analysis is summarized in Scheme 1. The convergent approaches to the three polyacetylenes rely on bond disconnections at the central sp centers and employ transition-metal-catalyzed alkynylation reactions (sp−sp, sp^2−sp, or sp^3−sp) as the pivotal steps. The high structural resemblance of the three natural products will allow the use of common synthetic building blocks. The strategy requires the preparation of several highly unsaturated, monoprotected intermediates so the choice of suitable acetylenic protecting groups will be critical to successfully achieve monodeprotection of both symmetrically and orthogonally diprotected polyynes.

Results and Discussion

Synthesis of Callyberyne A (1). We envisioned that the skeletal framework of callyberyne A (**1**) could be constructed through two alternative routes involving either Cadiot−Chodkiewicz (sp−sp) or Sonogashira (sp^2−sp) cross-coupling reactions as key steps (Scheme 1).

Initial efforts led us to consider the Cadiot−Chodkiewicz reaction between the iodotriyne **6** and the monoprotected dienediynes **13** or **17** as the most straightforward disconnection. Thus, 9-iodo-1-triisopropylsilylnona-1,3,8-triyne (**6**) was easily available from 1-triisopropylsilylnona-1,3,8-triyne (**5**)[25] by treatment with *n*-BuLi/iodine (89%) (Scheme 2).

The monoprotected (3*Z*,9*Z*)-1-trimethylsilyldodeca-3,9-diene-1,11-diyne (**13**) and (5*Z*,11*Z*)-2-methyltetradeca-5,11-diene-3,13-diyn-2-ol (**17**) were chosen as suitable building blocks since they could a priori be synthesized by monodeprotection of readily available symmetrically disubstituted precursors (**12** and **16**, respectively) (Scheme 3). It is well established that bis(trimethylsilyl)acetylenes can be monodesilylated by treatment with MeLi·LiBr complex in THF followed by hydrolysis.[27] Selective unmasking of silyl groups has also been described by employing $NaBH(OMe)_3$.[28] As an alternative, partial deprotec-

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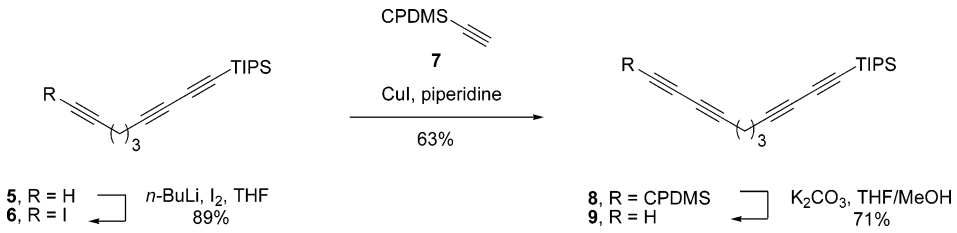
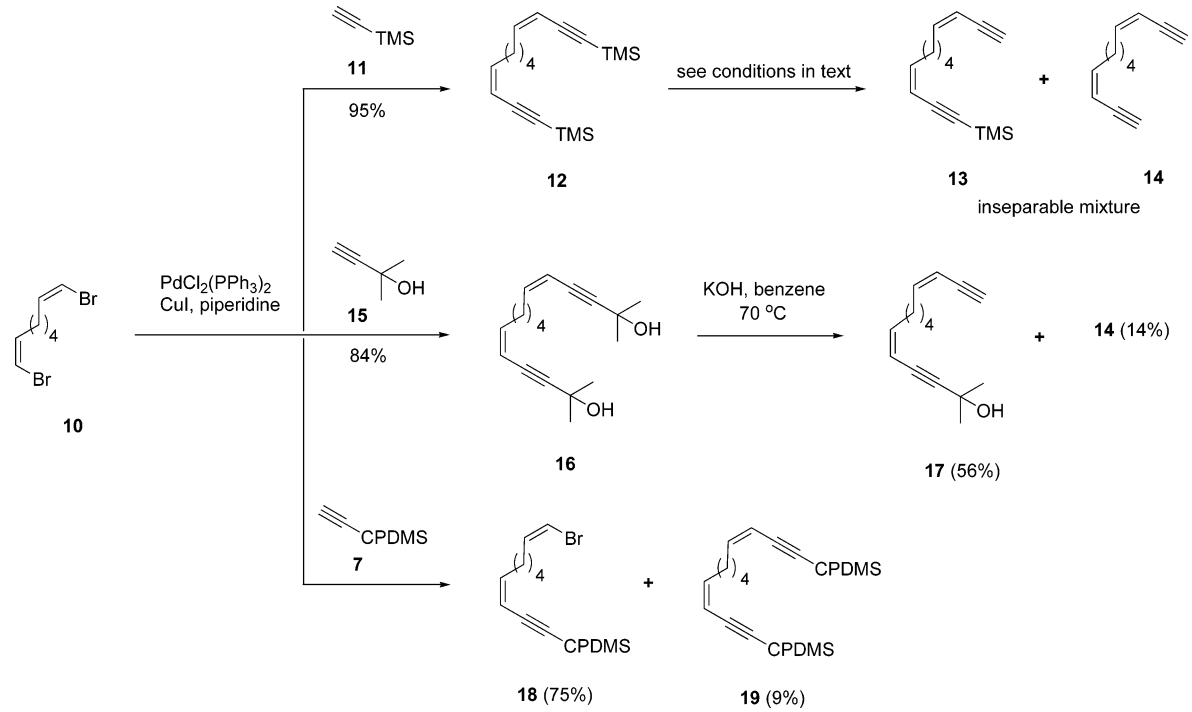
SCHEME 2



SCHEME 3



tion of bis-*tert*-propargyl alcohols can be successfully achieved by heating in benzene or toluene solution under basic conditions for short reaction times, a base-catalyzed "retro-Favorsky" elimination of acetone being the driving-force of the reaction.[29] Accordingly, the synthesis of the target monoprotected diene-diyne **13** started with the preparation of the putative precursor (3*Z*,9*Z*)-1,12-bis(trimethylsilyl)dodeca-3,9-diene-1,11-diyne (**12**), which was obtained in excellent yield by double Sonogashira cross-coupling reaction of dibromide **10**[25,26] with an excess of trimethylsilylacetylene (**11**) [$PdCl_2(Ph_3P)_2$, CuI, piperidine, 95%]. Selective monoprotodesilylation of **12** proved, however, to be discouraging. In fact, the first attempt using 1 equiv of MeLi·LiBr complex (1.5 M in ether, rt) gave rise to a complex mixture of mono and bis-desilylated products (**13** and **14**) together with some recovered starting material; the three compounds showed a very similar chromatographic mobilities and product purification was therefore extremely difficult. Disappointingly, the same problem was found when $NaBH(OMe)_3$ or 1 equiv of CsF was used, and therefore, compound **13** could not be prepared efficiently.

Due to the difficulties found in the preparation of pure examples of fragment **13**, we next focused on the synthesis of (5*Z*,11*Z*)-2-methyltetradeca-5,11-diene-3,13-diyn-2-ol (**17**) (Scheme 3). Palladium-catalyzed double alkynylation of (1*Z*,7*Z*)-1,8-dibromoocta-1,7-diene (**10**) with an excess of 2-methyl-3-butyn-2-ol (**15**), under the same above conditions, afforded (5*Z*,11*Z*)-2,15-dimethylhexadeca-5,11-diene-3,13-diyne-2,15-diol (**16**) in 84% yield. Rewardingly, partial deprotection of **16** could be achieved by heating its benzene solution at 70 °C for 2 h in the presence of potassium hydroxide, leading to the desired **17** in a moderate 56% yield. Monodeprotected **17** appeared also accompanied by small amounts of fully deprotected (3*Z*,9*Z*)-dodeca-3,9-diene-1,11-diyne (**14**) (14%) and some recovered starting material, but in this case, the polarity of the protecting hydroxyl group allowed an easy chromatographic separation. Attempts to improve the yield by employing longer reaction times, higher temperatures or by changing the solvent (toluene, methanol, *i*-PrOH) were fruitless, the harshness of the conditions leading to an increase of deprotection or decomposition.

With subunits **6** and **17** in hand, Cadiot−Chodkiewicz cross-coupling was carried out under Alami's improved conditions [CuI, piperidine] to afford (5*Z*,11*Z*)-2-methyl-23-triisopropylsilyltricosa-5,11-diene-3,13,15,20,22-pentayn-2-ol (**20**) in a 60% yield (Scheme 4).[30] Unfortunately, the subsequent deprotection step proved again to be troublesome. Attempts to carry out

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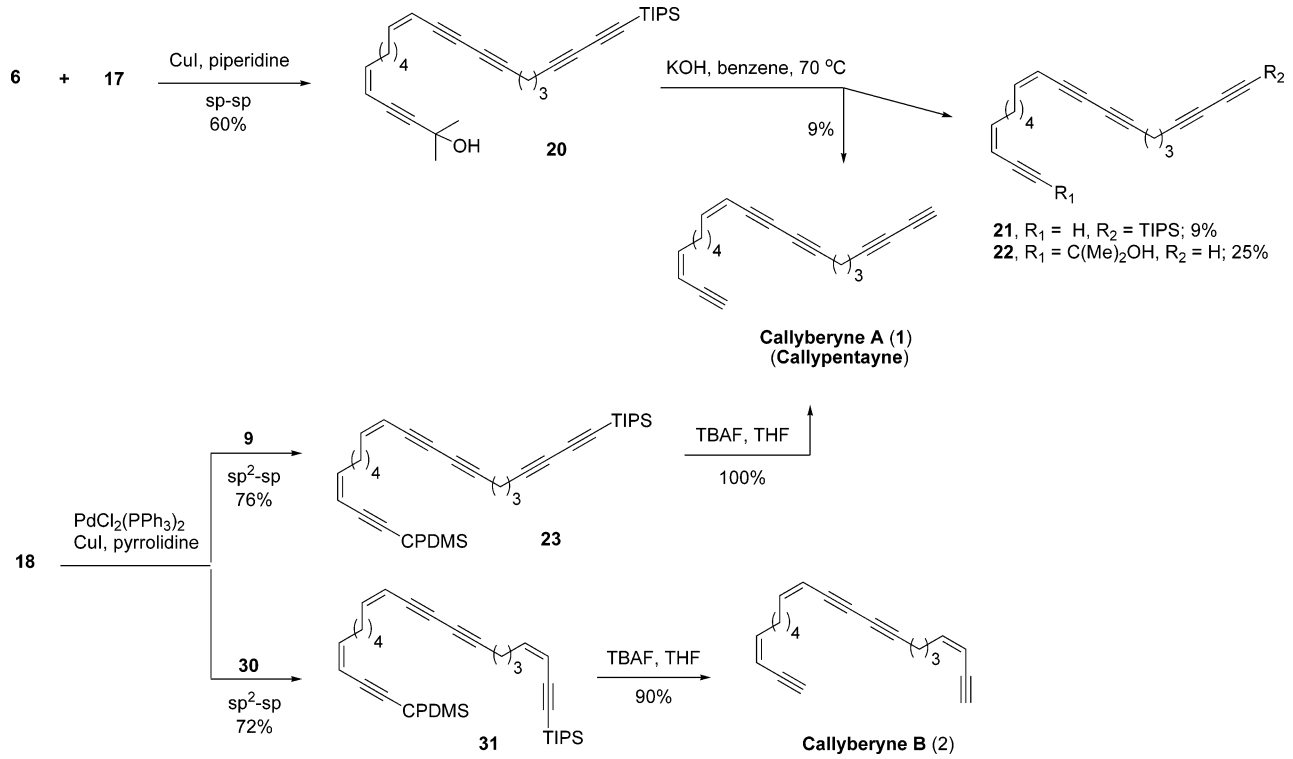
(30) The use of Cadiot−Chodkiewicz classical conditions (5% CuCl, 30% NH_2OH, $EtNH_2$, MeOH−H_2O) led to a lower yield of cross-coupling product **33** (<25%).

SCHEME 4



simultaneous deprotection of both silyl and hydroxyl protecting groups by base-treatment (KOH/benzene/MeOH, 70 °C, 31 h) gave rise to only a very low yield of callyberyne A (**1**) (9%); instead, the partially deprotected (3*Z*,9*Z*)-1-triisopropylsilylhenicosa-3,9-diene-1,11,13,18,20-pentayne (**21**) (9%) and (5*Z*,11*Z*)-2-methyltricosa-5,12-diene-3,13,15,20,22-pentayn-2-ol (**22**) (25%) were also obtained, the latter being the major product of this reaction.

Consequently, in light of the numerous difficulties found in the designed Cadiot−Chodkiewicz (sp−sp) route to callyberyne A, we turned our attention to the alternative sp^2−sp disconnection which would disassemble the target molecule into two fragments of similar size, employing a Sonogashira cross-coupling reaction to join the subunits C1−C10 (**18**) and C11−C21 (**9**) (Scheme 1).

The skeleton would be constructed by succesive replacement of the bromine atoms of (1*Z*,7*Z*)-1,8-dibromoocta-1,7-diene (**10**) by alkynes. The *cis*-bromovinyl moiety **18** could be available through reaction of **10** with the novel [(3-cyanopropyl)-dimethylsilyl]acetylene (CPDMSA) (**7**) (Scheme 3).[31] After optimization of the reaction conditions, we found that the use of substoichiometric amounts of the alkyne reactant (3:1 molar ratio) and the employment of dilute solutions (0.05 M for the alkyne) were clearly in favor of the monocoupled product (3*Z*,9*Z*)-10-bromo-1-[(3′-cyanopropyl)dimethylsilyl]deca-3,9-dien-1-yne (**18**) (75% isolated yield). The polarity of the CPDMS protecting group allowed the easy separation of the dicoupled side product (3*Z*,9*Z*)-1,12-bis-[(3′-cyanopropyl)dimethylsilyl]dodeca-3,9-diene-1,11-diyne (**19**), which was obtained in less than 10% yield.[32]

On the other side, the right-hand segment tetrayne **9** was easily prepared from iodotriyne **6** through a two-step sequence involving coupling with CPDMSA (**7**) under Alami's conditions (CuI, piperidine) to produce the differentially protected tetrayne **8** in 63% yield and basic methanolysis (K_2CO_3 in wet THF/MeOH) to remove selectively the cyanopropyldimethylsilyl moiety in 71% yield (Scheme 2).

The assembly of the skeleton of callyberyne A (**1**) requires the Sonogashira cross-coupling reaction between fragments **9** and **18** (Scheme 4). In comparison with 1-alkynes, the use of 1,3-diynes as the acetylenic component in such coupling is scarce, mainly due to difficulties associated with the synthesis and especially the stability of these intermediates.[33,34] However, despite its highly unsaturated structure, 1-triisopropylsilylundeca-1,3,8,10-tetrayne (**9**) was shown to be remarkably stable, and reaction with (3*Z*,9*Z*)-10-bromo-1-[(3′-cyanopropyl)dimethylsilyl]deca-3,9-dien-1-yne (**18**) proceeded smoothly [$PdCl_2(PPh_3)_2$, CuI, pyrrolidine, rt, 2 h] to furnish the skeletal framework (3*Z*,9*Z*)-1-[3′-cyanopropyl) dimethylsilyl]-21-triisopropylsilylhenicosa-3,9-diene-1,11,13,18,20-pentayne (**23**) in a

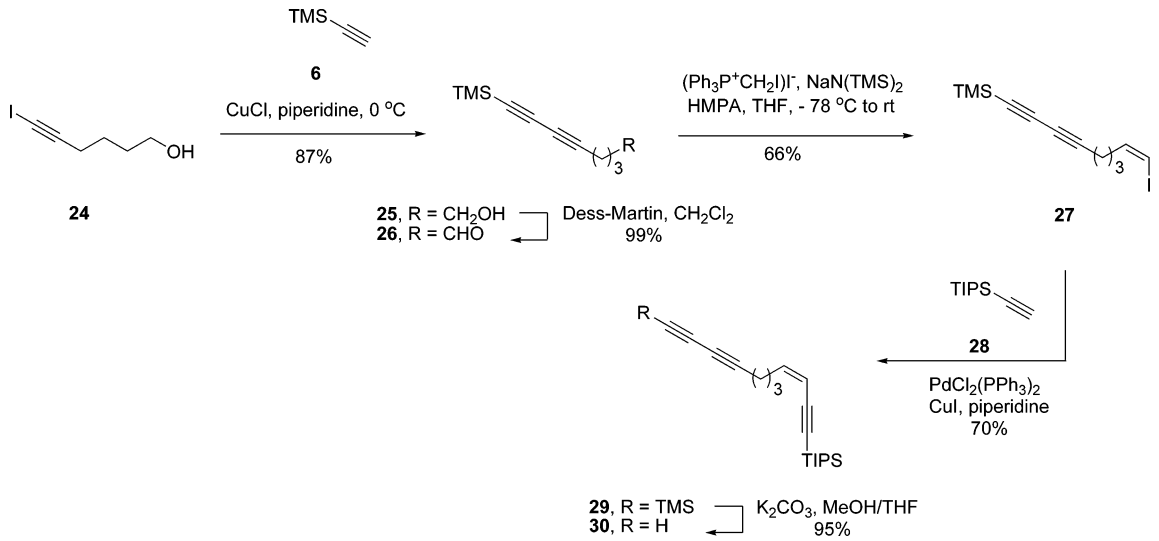
(31) CPDMS-acetylene combines the mild conditions necessary to remove the TMS protecting group with the high polarity of the hydroxyl-containing protecting groups, allowing for the simple and high yield chromatographic separation of its palladium-catalyzed coupling products. See: Höger, S.; Bonrad, K. *J. Org. Chem.* **2000**, *65*, 2243−2245.

(32) For other mono-cross-coupling reaction conditions, see: (a) Khatyr, A.; Ziessel, R. *J. Org. Chem.* **2000**, *65*, 7814−7824. (b) Kosinki, C.; Hirsch, A.; Heinemann, F. W.; Hampel, F. *Eur. J. Org. Chem.* **2001**, 3879−3890. (c) Hu, Q.-S.; Sun, C.; Monoghan, C. E. *Tetrahedron Lett.* **2002**, *43*, 927−930. (d) Kitamura, C.; Saito, K.; Nakagawa, M.; Ouchi, M.; Yoneda, A.; Yamashita, Y. *Tetrahedron Lett.* **2002**, *43*, 3373−3376.

(33) (a) Balova, I. A.; Morozkina, S. N.; Knight, D. W.; Vasilevsky, S. F. *Tetrahedron Lett.* **2003**, *44*, 107−109. (b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **2003**, *44*, 9087−9090. (c) Sabitha, G.; Reddy, Ch. S.; Srihari, P.; Yadav, J. S. *Synthesis* **2003**, 2699−2704. (d) Balova, I. A.; Sorokoumov, V. N.; Morozkina, S. N.; Vinogradova, O. V.; Knight, D. W.; Vasilevsky, S. F. *Eur. J. Org. Chem.* **2005**, 882−888.

(34) To avoid the use of highly reactive terminal diyne or triyne intermediates in the synthesis of polyyne natural products, Gung has recently developed a new approach based on a three-component one-pot Cadiot−Chodkiewicz cross-coupling reaction; see: Gung, B. W.; Kumi, G. *J. Org. Chem.* **2004**, *69*, 3488−3492.

SCHEME 5



remarkable 76% yield. It must be noted that the choice of the amine had a significant impact on the efficiency of this cross-coupling and the use of pyrrolidine, instead of piperidine (the standard amine used for coupling of 1-alkynes), appeared to be crucial for the success of the reaction with 1,3-diynes.[35]

Finally, fluoride-induced cleavage of both terminal silyl-protecting groups led to the target callyberyne A (**1**) in quantitative yield. Following this highly convergent sp^2-sp route, the total synthesis of callyberyne A (**1**) was completed in three steps with a 57% overall yield from [(3′-cyanopropyl) dimethylsilyl]acetylene (**7**).

Synthesis of Callyberyne B (2). Since the successful sp^2-sp disconnection for the synthesis of callyberyne A (**1**), the preparation of callyberyne B (**2**) was performed following a parallel route (Scheme 1). The required left-hand fragment, (1*Z*,7*Z*)-1-bromo-10-[(3′-cyanopropyl)dimethylsilyl]deca-1,7-dien-9-yne (**18**), was common to both metabolites. The synthesis of the right-hand fragment, protected enetriyne **30**, is outlined in Scheme 5. Cadiot−Chodkiewicz cross-coupling of 6-iodo-5-hexyn-1-ol (**24**) with trimethylsilylacetylene (**6**), under modified Alami's conditions [CuCl, piperidine, 0 °C], gave the TMS-protected diynol **25** (87% yield) which was quantitatively oxidized using Dess−Martin periodinane.[36] Aldehyde **26** was subjected to a Stork/Zhao[37] modified Wittig reaction [$(Ph_3P^+-CH_2I)I^-$, $NaN(TMS)_2$, HMPA, THF, −78 °C] to give, stereoselectively, the homologated (*Z*)-1-iodo-9-trimethylsilylnon-1-ene-6,8-diyne (**27**) in 66% yield (12:1 *Z*/*E* ratio). Sonogashira cross-coupling [$PdCl_2(PPh_3)_2$, CuI, piperidine] of the *Z*-vinyliodide **27** with triisopropylsilylacetylene (**28**) afforded, after purification, the orthogonally protected *Z*-enetriyne **29** in 70% yield as a single isomer. Finally, basic methanolysis allowed selective removal of TMS group to obtain (*Z*)-1-triisopropylsilylundec-3-ene-1,8,10-triyne (**30**) in 95% yield.

Cross-coupling reaction of the *cis*-vinyl bromide **18** with the 1,3-diyne unit **30**, under the same Sonogashira conditions described above [$PdCl_2(PPh_3)_2$, CuI, pyrrolidine] (Scheme 4), proceeded again uneventfully to give rise to (3*Z*,12*Z*,18*Z*)-21-[(3′-cyanopropyl)dimethylsilyl]-1-triisopropylsilylhenicosa-3,-12,18-triene-1,8,10,20-tetrayne (**31**) in a good yield (72%). Deprotection of both silyl groups with TBAF in THF led to callyberyne B (**2**) in 90% yield.

Following this highly convergent sp^2-sp route, the total synthesis of callyberyne B (**2**) was completed in three steps with a 49% overall yield, again from [(3′-cyanopropyl)dimethylsilyl]-acetylene (**7**).

Synthesis of Callyberyne C (3). At the time that we initiated our approaches to this family of marine polyacetylenes, there were no reports in the literature regarding metal-catalyzed cross-coupling reactions of alkynes with alkyl electrophiles. The obvious strategy for the synthesis of callyberyne C, at that moment, implied the dissection of the skeleton into two major fragments C1−C11 (**30**) and C12−C21 (**37**) to be joined by an S_N2 displacement (Scheme 1).

The nucleophilic fragment, (*Z*)-1-triisopropylsilylundec-3-ene-1,8,10-triyne (**30**), had been previously employed in the synthesis of callyberyne B (**2**). The electrophilic subunit **37**, either as a triflate or halide, could be easily prepared from *Z*-10-triisopropylsilyldec-7-en-9-yn-1-ol (**36**), which could in turn be synthesized from the known 7-*tert*-butyldiphenylsilyloxyheptanal (**32**),[38] as depicted in Scheme 6. Following this sequence, the vinyl *gem*-dibromoolefin **33** was obtained, in excellent yield (96%), by Wittig homologation of **32** in the presence of PPh_3 and CBr_4. Palladium-catalyzed stereoselective hydrogenolysis of **33** with *n*-Bu_3SnH was then performed,[39] yielding the desired *Z*-vinyl bromide **34** (93% yield) which, on treatment with TBAF at 0 °C, furnished the alcohol **35** in 83% yield. Sonogashira cross-coupling reaction of **35** with triisopropylsilylacetylene (**28**) [$PdCl_2(PPh_3)_2$, CuI, piperidine] delivered enynol **36** in 79% yield.

Initially, we chose a triflate as the alkylating agent since alkynylation of alkyl triflates with alkynyllithiums is known to

(35) The influence of the amine in the success of copper-catalyzed cross-coupling reactions is well-known: Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403−6406 and ref 9.

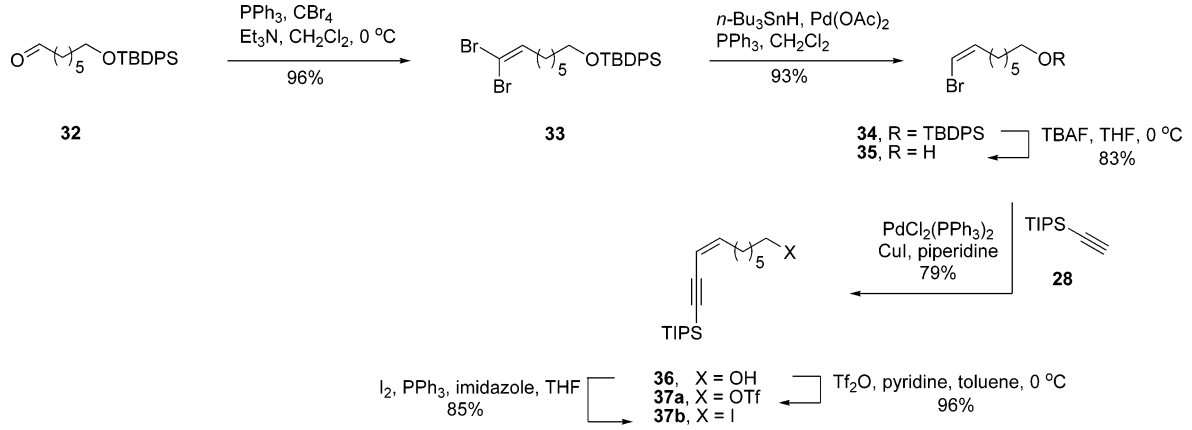
(36) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(37) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174.

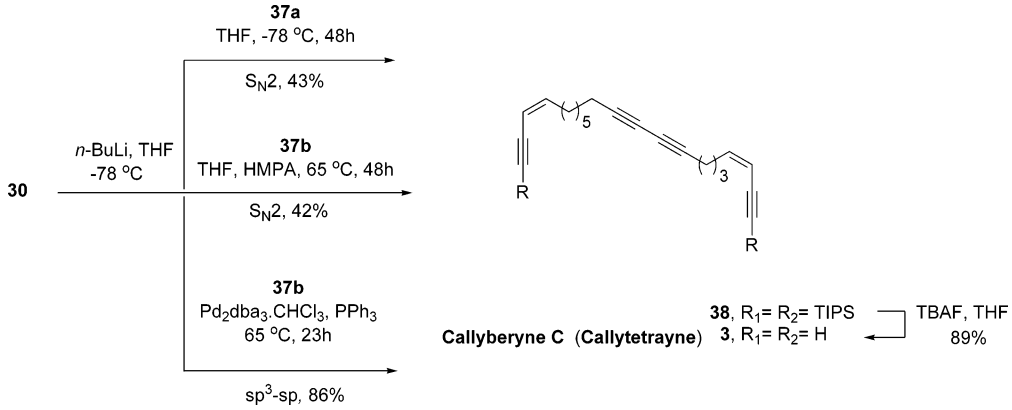
(38) Jones, G. B.; Huber, R. S.; Chapman, B. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1797−1809.

(39) (a) Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* **1996**, *37*, 6759−6762. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716−5717. (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965−8975.

SCHEME 6



SCHEME 7



occur under relatively mild conditions.[40] Therefore, *Z*-10-trifluoromethanesulfonyloxy-1-triisopropylsilyldec-3-en-1-yne (**37a**) was prepared from alcohol **36** by treatment with Tf_2O and pyridine in toluene at 0 °C (Scheme 6). The isolated yield of crude triflate was nearly quantitative (96%) but the product proved to be unstable and showed decomposition upon column chromatography; so, it had to be prepared inmediately before alkynylation and used without purification.

Deprotonation of the terminal 1,3-diyne **30** with *n*-butyllithium at −78 °C, followed by addition of the lithiated acetylene to an excess of triflate **37a** in THF led to the expected condensation product (3*Z*,18*Z*)-1,21-bis(triisopropylsilyl)henicosa-3,18-diene-1,8,10,20-tetrayne (**38**), although in a modest yield (43%) (Scheme 7). Since the unstable nature of the triflate appeared as the most likely cause of this diminished yield, we decide to use an iodide as the leaving group. Consequently, enynol **36** was converted to (*Z*)-10-iodo-1-triisopropylsilyldec-3-en-1-yne (**37b**) [I_2/Ph_3P/imidazole, 85% yield] (Scheme 6), which was reacted with the lithium acetylide generated from **30**. However, the halide displacement did not improve the previous yield, even when an excess of HMPA was used as cosolvent and the reaction mixture was heated at 65 °C for 48 h, affording **38** in practically the same yield (42%) (Scheme 7).[41]

As we have anticipated, Luh[17] and Fu[18] have recently expanded the scope of the metal-catalyzed alkynylation cross-coupling reactions, reporting the first successful examples of palladium-catalyzed sp^3-sp cross-coupling of alkynes with unactivated, β-hydrogen-containing alkyl halides. In view of the unsatisfactory results obtained in the S_N2 displacement, we decided to apply these new conditions (which would imply the same subunits **30** and **37b**) to the synthesis of callyberyne C (**3**).

We first faced the modified Sonogashira reaction, which use N-heterocyclic carbene ligands, developed by Fu. Following this, to a solution of 1,3-bis(1-adamantyl)imidazolium chloride, CuI, [(π-allyl)PdCl]$_2$, and Na_2CO_3 in a mixture of Et_2O−DMF (2:1) were added sequentially, under argon atmosphere, solutions of the diyne **30** and the iodide **37b** in the same solvent. The heterogeneous mixture was vigorously stirred at 40 °C, but after 16 h of reaction, only traces of **38** were detected, recovering most of the starting materials.

We then tried the Kumada−Corriu reaction of alkyl halides with alkynyl nucleophiles recently described by Luh. In this case, we were pleased to find that, by adding dropwise the lithium acetylide (prepared from **30** by treatment with *n*-BuLi at −78 °C in THF), under argon, to a heated (65 °C) solution of $Pd_2(dba)_3$, Ph_3P, and iodide **37b** in THF, compound **38** could be obtained, after 23 h of reaction, in an excellent 86% yield (Scheme 7). Finally, subsequent TBAF desilylation cleanly provided the target natural product, as a yellow oil, in 89% yield.

(40) For a recent application of triflates in S_N2 displacements, see: Armstrong-Chong, R. J.; Matthews, K.; Chong, J. M. *Tetrahedron* **2004**, *60*, 10239−10244.

(41) Yields of S_N2 reactions using terminal 1,3-diynes and alkyl halides as partners are often modest even when simpler fragments than used in this manuscript are employed, see, for example: Fiandanese, V.; Bottalico, D.; Cardellicchio, C.; Marchese, G.; Punzi, A. *Tetrahedron* **2005**, *61*, 4551−4556.

Following this highly convergent sp^3-sp route, the total synthesis of callyberyne C (**3**) was completed in seven steps with a 38% overall yield from 7-*tert*-butyldiphenylsilyloxyheptanal (**32**).

Conclusions

In summary, efficient total syntheses of the marine hydrocarbon polyacetylenes callyberynes A−C (**1**−**3**) have been achieved using highly convergent routes,[42] which involved metal-catalyzed cross-coupling reactions to sp centers as the key steps, namely: Alami's optimized conditions of the classical Cadiot−Chodkiewicz reaction (sp−sp), sequential Sonogashira reactions of a *cis*,*cis*-divinyl dihalide (sp^2-sp), and Kumada−Corriu reaction of an unactivated alkyl iodide under the conditions recently reported by Luh (sp^3-sp).

It is noteworthy that the acetylenic counterparts were, in all the cases, highly unsaturated 1,3-diyne moieties which were shown to be remarkably stable and could be isolated, purified, and coupled effectively.

In particular, we want to emphasize that the Kumada−Corriu alkynylation cross-coupling reaction between an sp^3-hybridized iodide and the lithium acetylide of a terminal 1,3-diyne turned out in high yields as compared with the equivalent S_N2 displacement reaction. To our knowledge, this approach to callyberyne C constitutes the first application of a metal-catalyzed sp^3-sp Kumada−Corriu reaction to the synthesis of a natural product.

Experimental Section

(3*Z*,9*Z*)-1-[(3′-Cyanopropyl)dimethylsilyl]-21-triisopropylsilylhenicosa-3,9,diene-1,11,13,18,20-pentayne (23). A solution of 1-triisopropylsilylundeca-1,3,8,10-tetrayne (**9**) (0.250 g, 0.84 mmol) in degassed pyrrolidine (1 mL) was added to a solution of (1*Z*,7*Z*)-1-bromo-10-[(3′-cyanopropyl)dimethylsilyl]deca-1,7-dien-9-yne (**18**) (0.140 g, 0.42 mmol), $PdCl_2(PPh_3)_2$ (0.030 g, 0.04 mmol), and CuI (0.008 g, 0.04 mmol) in the same solvent (4 mL), and the reaction mixture was stirred for 2 h. Saturated aqueous solution of NH_4Cl (20 mL) was then added, and the organic phase was extracted with ether (3 × 20 mL). The ethereal fractions were washed with brine (3 × 60 mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography (hexane/ethyl acetate 90:10) afforded the title compound (0.175 g, 76% yield) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (6H, s), 0.8−0.9 (2H, m), 1.0−1.1 (21H, m), 1.4−1.5 (4H, m), 1.7−1.8 (4H, m), 2.3−2.5 (10H, m), 5.49 (2H, d, J = 10.8 Hz), 5.98 (1H, dt, J = 10.8, 7.5 Hz), 6.05 (1H, dt, J = 10.8, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.6 (2 × CH_3), 11.4 (3 × CH), 15.9 (CH_2), 18.5 (CH_2), 18.7 (6 × CH_3), 18.9 (CH_2), 20.6 (CH_2), 20.7 (CH_2), 26.9 (CH_2), 28.2 (CH_2), 28.4 (CH_2), 30.3 (CH_2), 30.6 (CH_2), 66.1 (C), 66.7 (C), 72.4 (C), 77.1 (C), 77.9 (C), 80.6 (C), 83.1 (C), 89.7 (C), 96.4 (C), 103.3 (C), 108.1 (CH), 109.1 (CH), 119.6 (C), 145.5 (CH), 147.5 (CH); IR (CsI) ν 2244 (C≡N), 2224, 2147, 2104 (C≡C) cm^{-1}; MS (CI) *m*/*z* 554 (MH^+, 3), 510 (3), 279 (6), 167 (22), 149 (70), 126 (100); HRMS (CI) calcd for $C_{36}H_{52}NSi_2$ 554.3638, found 554.3641.

(3*Z*,9*Z*)-Henicosa-3,9-diene-1,11,13,18,20-pentayne [Callyberyne A, Callypentayne] (1). To a solution of **23** (0.061 g, 0.11 mmol) in anhydrous THF (2 mL) was added *n*-Bu_4NF (1.0 M solution in THF, 0.36 mL, 0.36 mmol), and the mixture was allowed to react for 5 h at room temperature. The mixture was diluted with ether (3 mL), washed with brine (3 × 3 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (hexane/ethyl acetate 95:5) afforded the title compound (0.030 g, quantitative yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4−1.5 (4H, m), 1.78 (2H, q, J = 6.9 Hz), 1.98 (1H, s), 2.3−2.5 (8H, m), 3.08 (1H, d, J = 1.7 Hz), 5.4−5.5 (2H, m), 5.99 (1H, dt, J = 10.8, 7.5 Hz), 6.04 (1H, dt, J = 10.8, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (CH_2), 18.7 (CH_2), 26.7 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 30.0 (CH_2), 30.5 (CH_2), 64.9 (CH), 65.5 (C), 66.2 (C), 68.2 (C), 72.5 (C), 76.8 (C), 77.9 (C), 80.4 (C), 81.3 (CH), 82.9 (C), 108.2 (CH), 108.3 (CH), 145.7 (CH), 147.7 (CH); IR (CsI) ν 3296 (≡C−H), 2226 (C≡C) cm^{-1}; MS (CI) *m*/*z* 273 (MH^+, 4), 272 (M^+, 5), 229 (67), 215 (75), 203 (71), 165 (66), 28 (100); HRMS (CI) calcd for $C_{21}H_{21}$ 273.1643, found 273.1634.

(3*Z*,12*Z*,18*Z*)-21-[(3′-Cyanopropyl)dimethylsilyl]-1-triisopropylsilylhenicosa-3,12,18-triene-1,8,10,20-tetrayne (31). Following the same procedure described for **23**, treatment of (1*Z*,7*Z*)-1-bromo-10-[(3′-cyanopropyl)dimethylsilyl]deca-1,7-dien-9-yne (**18**) (0.060 g, 0.18 mmol) and (*Z*)-1-triisopropylsilylundec-3-ene-1,8,-10-triyne (**30**) (0.110 g, 0.37 mmol) with $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) and CuI (0.004 g, 0.02 mmol) in degassed pyrrolidine (4 mL) for 1 h afforded, after purification by flash chromatography (hexane/ethyl acetate 98:2), the title compound (0.072 g, 72% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (6H, s), 0.7−0.8 (2H, m), 1.0−1.1 (21H, m), 1.4−1.5 (4H, m), 1.70 (2H, q, J = 7.3 Hz), 1.8−1.9 (2H, m), 2.3−2.5 (10H, m), 5.48 (2H, d, J = 10.3 Hz), 5.55 (1H, d, J = 11.0 Hz), 5.9−6.1 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.2 (2 × CH_3), 11.8 (3 × CH), 16.3 (CH_2), 19.1 (6 × CH_3), 19.8 (CH_2), 20.9 (CH_2), 21.2 (CH_2), 28.1 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 31.0 (CH_2), 65.9 (C), 72.5 (C), 78.7 (C), 84.6 (C), 95.8 (C), 96.8 (C), 103.7 (2xC), 108.7 (CH), 109.5 (CH), 111.0 (CH), 120.0 (C), 143.4 (CH), 145.9 (CH), 147.5 (CH); IR (CsI) ν 2245 (C≡N), 2146 (C≡C) cm^{-1}; MS (CI) *m*/*z* 557 (MH^+, 1), 556 (M^+, 3), 512 (4), 279 (7), 167 (19), 149 (57), 126 (96), 29 (100); HRMS (EI) calcd for $C_{36}H_{54}NSi_2$ 556.3795, found 556.3803.

(3*Z*,12*Z*,18*Z*)-Henicosa-3,12,18-triene-1,8,10,20-tetrayne [Callyberyne B] (2). Following the same procedure described for **1**, treatment of a solution of **31** (0.050 g, 0.09 mmol) in THF (1 mL) with *n*-Bu_4NF (1.0 M in THF, 0.36 mL, 0.36 mmol) for 25 min afforded, after purification by flash chromatography (hexane/ethyl acetate 95:5), the title compound (0.022 g, 90%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.4−1.5 (4H, m), 1.68 (2H, q, J = 7.3 Hz), 2.3−2.5 (8H, m), 3.09 (2H, t, J = 2.8 Hz), 5.4−5.5 (3H, m), 5.9−6.1 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (CH_2), 27.4 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 29.4 (CH_2), 30.0 (CH_2), 30.4 (CH_2), 65.6 (C), 72.2 (C), 78.2 (C), 80.1 (C), 80.4 (C), 81.3 (CH), 81.8 (CH), 84.2 (C), 108.2 (CH), 108.3 (CH), 109.3 (CH), 144.2 (CH), 145.7 (CH), 147.4 (CH); IR (CsI) ν 3294 (≡C−H), 2233, 2146 (C≡C) cm^{-1}; MS (CI) *m*/*z* 275 (MH^+, 3), 181 (50), 179 (77), 156 (21), 155 (72), 92 (16), 91 (100), 79 (88); HRMS (CI) calcd for $C_{21}H_{23}$ 275.1800, found 275.1794.

(3*Z*,18*Z*)-1,21-Bis(triisopropylsilyl)henicosa-3,18-diene-1,8,10,-20-tetrayne (38). To a well-stirred solution of (*Z*)-1-triisopropylsilylundec-3-ene-1,8,10-triyne (**30**) (0.050 g, 0.17 mmol) in THF (0.30 mL), cooled at −78 °C, was added *n*-BuLi (1.6 M in hexanes, 0.10 mL, 0.16 mmol), and the mixture was allowed to react for 5 min at that temperature. It was then added, dropwise, to a solution of (*Z*)-10-iodo-1-triisopropylsilyldec-3-en-1-ynol (**37b**) (0.030 g, 0.07 mmol), Pd_2dba_3·$CHCl_3$ (0.010 g, 0.01 mmol), and PPh_3 (0.010 g, 0.04 mmol) in THF (0.20 mL), and the mixture was allowed to react for 23 h at 65 °C. It was diluted with saturated aqueous solution of NH_4Cl (2 mL), and the organic phase was extracted with Et_2O (3 × 2 mL). The combined ethereal fractions were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane) afforded the title compound (0.036 g, 86%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0−1.1 (42H, m), 1.3−1.6 (8H, m), 1.6−1.7 (2H, m), 2.2−2.3 (4H, m), 2.36 (2H, dc, J = 1.2, 7.2 Hz), 2.45 (2H, dc, J = 1.1, 7.4 Hz), 5.51 (1H, dt, J = 10.9, 1.2 Hz), 5.55 (1H, dt, J = 10.9, 1.1 Hz), 5.93 (1H, dt, J =

(42) The spectroscopic and physical data (^{1}H NMR, ^{13}C NMR) of the synthetic compounds were found to be identical to those published for the natural products (see refs 20 and 21).

10.9, 7.4 Hz), 5.95 (1H, dt, J = 10.9, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4 (6 × CH), 18.8 (12 × CH_3), 19.0 (CH_2), 19.3 (CH_2), 27.8 (CH_2), 28.3 (CH_2), 28.7 (2 × CH_2), 28.8 (CH_2), 29.7 (CH_2), 30.2 (CH_2), 65.3 (C), 65.6 (C), 76.8 (C), 77.6 (C), 94.7 (C), 95.4 (C), 103.4 (C), 103.8 (C), 109.6 (CH), 110.6 (CH), 143.1 (CH), 144.8 (CH); IR (CsI) ν 2146 (C≡C) cm^{-1}; MS (CI) m/z 589 (MH^+, 28), 588 (M^+, 18), 545 (50), 461 (12), 431 (11), 270 (22), 157 (100), 129 (50), 115 (89); HRMS (CI) calcd for $C_{39}H_{65}Si_2$ 589.4625, found 589.4622.

(3*Z*,18*Z*)-Henicosa-3,18-diene-1,8,10,20-tetrayne (Callyberyne C, Callytetrayne) (3). Following the same procedure as described for **1**, treatment of a solution of **38** (0.016 g, 0.028 mmol) in THF (0.28 mL) with *n*-Bu_4NF (1.0 M solution in THF, 0.12 mL, 0.12 mmol) for 1 h afforded, after purification by flash chromatography (hexane), the title compound as a colorless oil (0.007 g, 89% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3−1.6 (8H, m), 1.6−1.7 (2H, m), 2.2−2.4 (6H, m), 2.44 (2H, c, J = 7.3 Hz), 3.08 (1H, d, J = 2.0 Hz), 3.10 (1H, d, J = 2.1 Hz), 5.45 (1H, dd, J = 11.0, 2.0 Hz), 5.49 (1H, dd, J = 11.3, 2.1 Hz), 5.9−6.0 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9 (CH_2), 19.3 (CH_2), 27.6 (CH_2), 28.3 (CH_2), 28.6 (2 × CH_2), 28.7 (CH_2), 29.5 (CH_2), 30.2 (CH_2), 65.3 (C), 65.7 (C), 76.8 (C), 77.6 (C), 80.2 (C), 80.5 (C), 81.2 (CH), 81.7 (CH), 108.1 (CH), 109.1 (CH), 144.2 (CH), 145.8 (CH); IR (CsI) ν 3293 (≡C−H), 2097 (C≡C) cm^{-1}; MS (CI) m/z 277 (MH^+, 7), 276 (M^+, 14), 251 (19), 233 (37), 219 (66), 205 (98), 193 (83), 179 (98), 155 (100), 129 (77), 91 (66); HRMS (EI) calcd for $C_{21}H_{24}$ 276.1878, found 276.1884.

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Supporting Information Available: General methods, experimental procedures for selected intermediates, and ^{1}H−^{13}C NMR for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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