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First Stereoselective Syntheses of (−)-Siphonodiol and (−)-Tetrahydrosiphonodiol, Bioactive Polyacetylenes from Marine Sponges

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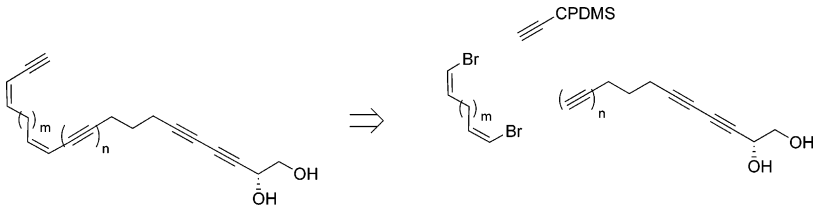

The first stereoselective total syntheses of the bioactive marine polyacetylenes (−)-siphonodiol and (−)-tetrahydrosiphonodiol were achieved using highly convergent approaches based on optimized Cadiot−Chodkiewicz and sequential Sonogashira cross-coupling reactions.

Introduction

Straight-chain polyacetylenes represent a rapidly growing class of sponge metabolites that can display great structural variations on both chain lengths and functionalities. Several sponge-derived polyacetylenes have been found to exhibit interesting biological activities including antimicrobial, cytotoxic, antitumor, antiviral, immunosuppressant, and enzyme inhibitory. In addition, some of these compounds play important ecological roles such as inducing metamorphosis of ascidian larvae, preventing fouling by barnacle larvae, or inhibiting fertilization of starfish gametes.[1]

(−)-Siphonodiol (**1**) (Scheme 1) is a C_{23} polyacetylene diol, isolated from the family *Callyspongiidae* (genera Siphonochalina[2,3] and Callyspongia[4,5]), head of an increasing group of around 20 structurally related compounds that includes four C_{21} hydrocarbons (callyberynes A−C[4,5] and aikupikamine B[6]), four C_{22} alcohols (callyspongenols A−C and dehydrosiphonochalynol),[7] five triols,[4] two sulfates (callyspongines A and B),[8] one dihydro- and one tetrahydroderivatives.[3] The highly unsaturated structures of these metabolites were determined by spectroscopic methods, and the absolute configuration of the chiral center, in the optically active members, was shown to be *R* according to the CD exciton chirality method applied to the corresponding di-*p*-dimethylaminobenzoates.[3]

(−)-Siphonodiol (**1**) exhibits antifungal (weak activity against *Trichophyton asteroides*, MIC 25.0 μg/mL) and antibacterial (medium activity against *Staphylococcus aureus*, MIC 12.5 μg/mL, and *Streptococcus pyogenes* C-203, MIC 6.2 μg/mL) properties as well as strong inhibitory activity against gastric H,K-ATPase (IC_{50} 1.0 $\times$ 10^{-5} M).[2,3]

As part of an extensive biofouling project, searching for secondary metabolites that might act as enviromentally safe antifoulants, Fusetani has reported that several polyacetylenes from this family, including the parent siphonodiol, constitute the first examples of acetylenic derivatives that influence both larval settlement and metamorphosis of sessile marine animals.[4,9] They exhibit potent metamorphosis-inducing activity in the ascidian

(1) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *23*, 15−61 and previous reports in this series.
(2) Tada, H.; Yasuda, F. *Chem. Lett.* **1984**, 779−780.
(3) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1987**, *28*, 4311−4312.
(4) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Nat. Prod.* **1997**, *60*, 126−130.
(5) Umeyama, A.; Nagano, C.; Arihara, S. *J. Nat. Prod.* **1997**, *60*, 131−133.
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(8) Uno, M.; Ohta, S.; Ohta, E.; Ikegami, S. *J. Nat. Prod.* **1996**, *59*, 1146−1148.
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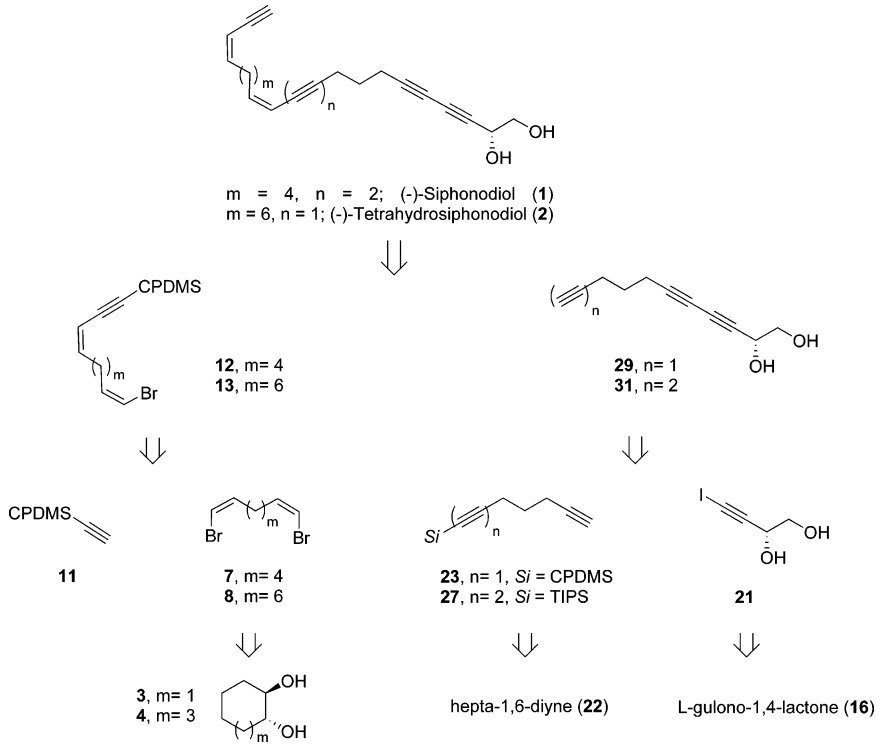
SCHEME 1. Retrosynthetic Analysis



Halocynthia roretzi (ED_{100} values ranging from 0.13 to 0.25 μg/mL) and antifouling activity against the barnacle *Balanus amphitrite* (ED_{50} values ranging from 0.24 to 4.5 μg/mL).

Surprisingly, to our knowledge, no synthesis of members of this group of polyacetylenes has been described despite their remarkable biological activities and the fact that more than 20 years have elapsed since the siphonodiol's first isolation in 1984.[2] As part of our studies on the chemistry of natural and synthetic polyenes and polyenynes,[10] we became interested in the total synthesis of these metabolites, and we have recently published an efficient route to two hydrocarbon polyacetylenes from this family, callyberynes A and B.[11]

In this paper we report the first stereoselective total synthesis of the parent (−)-siphonodiol (**1**) and the related bioactive metabolite (−)-tetrahydrosiphonodiol (**2**),[12] starting from easily available materials and using highly convergent approaches that involve modified Cadiot−Chodkiewicz[13] and sequential Sonogashira[14] cross-coupling reactions as the key steps.

Results and Discussion

Our retrosynthetic analysis is outlined in Scheme 1. We envisioned that both metabolites could be constructed from the di-*cis*-dibromodienes **9** or **10** following a common strategy that would imply stereoselective sequential sp^2−sp cross-coupling reactions. Thus, the assembly of **9** or **10** with the novel polar [(3′-cyanopropyl)dimethylsilyl]-acetylene (CPDMSA)[15] (**11**) would led to the west fragments **12** or **13**, which would react with the polyacetylene diol moieties **31** and **29**, respectively, to furnish the corresponding skeleton frameworks **1** and **2**. Chiral synthons **29** and **31** might be derived from the sp−sp cross-coupling reaction of monoprotected alkynes **23** and **27** with the common intermediate (*R*)-4-iodobut-3-yne-1,2-diol (**21**) which, in turn, could be conveniently synthesized from L-gulono-1,4-lactone (**16**), taking advantage of the chiral pool of natural products.

The preparation of (3*Z*,9*Z*)-10-bromo-1-[(3'-cyanopropyl)dimethylsilyl]deca-3,9-dien-1-yne (**12**), west building block in the route to (−)-siphonodiol (**1**), has been already described by our group during the synthesis of callyberynes A and B.[11] The reaction sequence (Scheme 2) involved oxidative cleavage of *trans*-cyclohexane-1,2-diol (**3**) to give hexane-1,6-dial (**5**) quantitatively, bis-elongation of the chain under Corey−Fuchs conditions

(10) For some significant publications of our group in the chemistry of polyenes and polyenynes, see: (a) Iglesias, B.; Torrado, A.; de Lera, A. R.; López, S. *J. Org. Chem.* **2000**, *65*, 2696−2705. (b) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2003**, *68*, 1938−1946. (c) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 377−379. (d) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783−786. (e) Rodríguez, D.; Martínez-Esperón, M. F.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2004**, *69*, 3842−3848.

(11) López, S.; Fernández-Trillo, F.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 3725−3728.

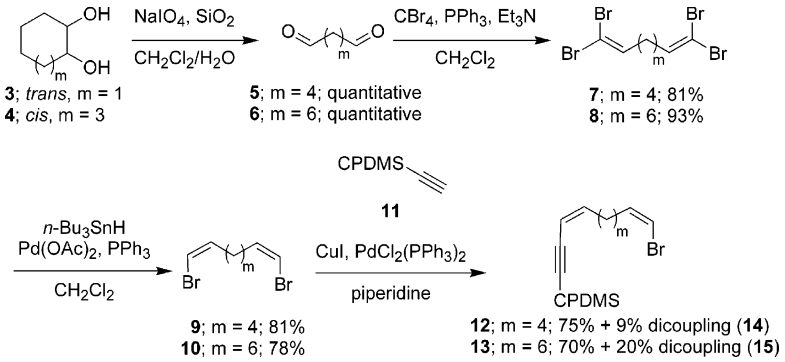
(12) (−)-Tetrahydrosiphonodiol also shows strongly inhibitory activity against gastric H, K-ATPase with IC_{50} of 1.0×10^{-5} M; see ref 3.

(13) (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 551−562. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2633−2657.

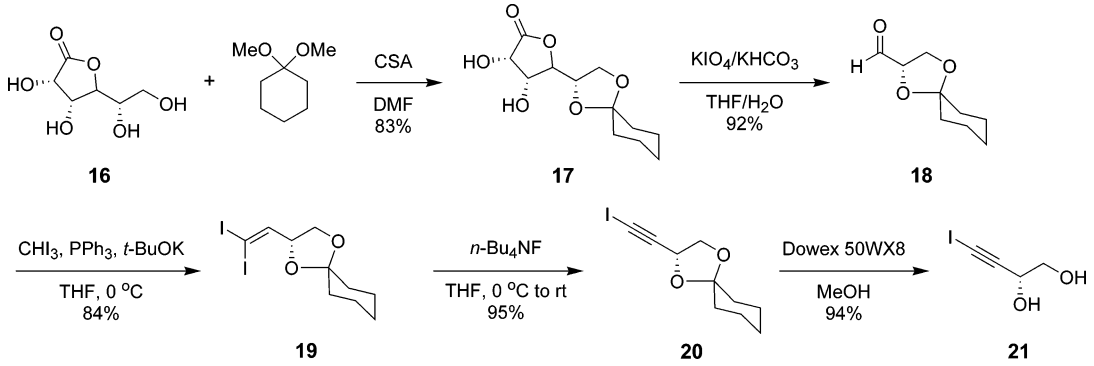
(14) (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 521−549. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 230. (c) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566−1568. (d) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017.

(15) 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.

SCHEME 2



SCHEME 3



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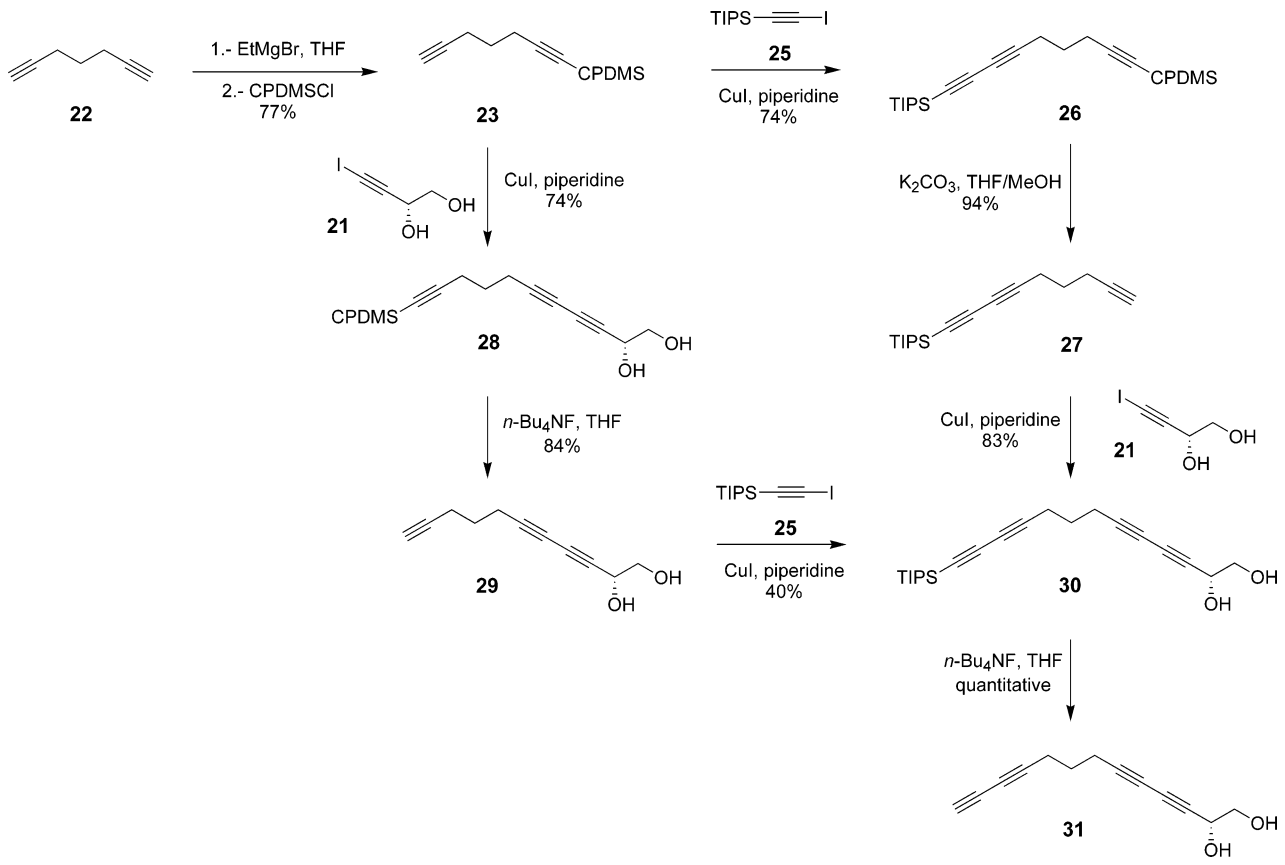
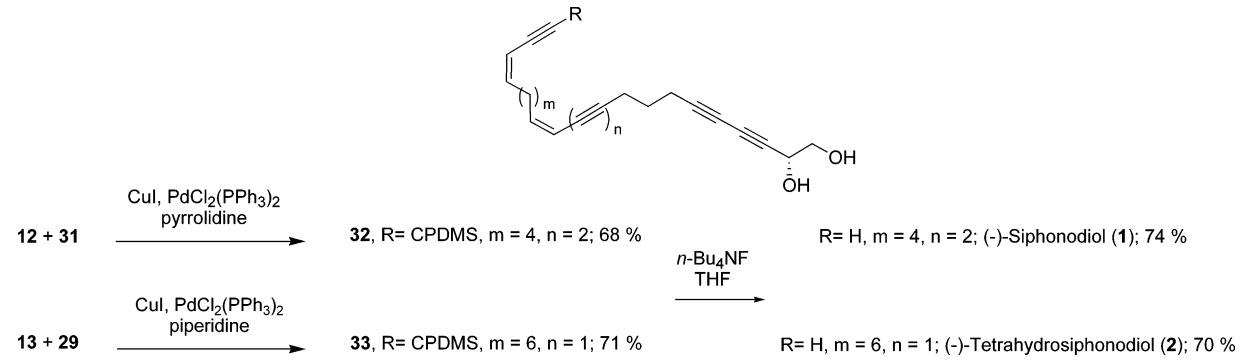


(CBr$_4$ and PPh$_3$ in Et$_3$N)[16] to afford the bis-*gem*-tetrabromide **7**, and stereoselective Pd-catalyzed hydrogenolysis with *n*-Bu$_3$SnH[17] at both endings of the chain to deliver (1*Z*,7*Z*)-1,8-dibromoocta-1,7-diene (**9**) in 66% overall yield from **3**. The Sonogashira reaction of **9** with CPDMSA (**11**) was successfully carried out with PdCl$_2$-

SCHEME 5



$(PPh_3)_2$ and CuI in piperidine, using an excess of bromide (ca. 3:1 molar ratio), to furnish the monocoupled product **12** in good yield (75%) together with a small proportion (9%) of the dicoupled product (3*Z*,9*Z*)-1,12-bis[(3′-cyanopropyl)dimethylsilyl]dodeca-3,9-diene-1,11-diyne (**14**). The CPDMS-acetylene's high polarity allowed for the simple and high-yield chromatographic separation of the coupling products.[15]

The same methodology was employed to synthesize the analogous fragment (3*Z*,11*Z*)-12-bromo-1-[(3'-cyanopropyl)dimethylsilyl]dodeca-3,11-dien-1-yne (**13**), "left-half" in the synthesis of (−)-tetrahydrosiphonodiol (**2**) (Scheme 2). The key intermediate (1*Z*,9*Z*)-1,10-dibromodeca-1,9-diene (**10**) was readily obtained in a three-step sequence from *cis*-cyclooctane-1,2-diol (**4**) (72% overall yield). Sonogashira mono cross-coupling of **10** with CPDMSA (**11**) led to the desired **13** in 70% yield together with a minor ammount of the dicoupled product (3*Z*,11*Z*)-1,14-bis[(3′-cyanopropyl)dimethylsilyl]tetradeca-3,11-diene-1,13-diyne (**15**) (20%), which again could be easily separated by chromatography.

The synthetic pathway to (*R*)-4-iodobut-3-yne-1,2-diol (**21**), a fragment required for the construction of east building blocks **29** and **31**, is illustrated in Scheme 3. Protection of the C_5,C_6-hydroxyl groups in L-gulono-1,4-lactone (**16**) with cyclohexanone dimethyl ketal followed by smooth heterogeneous periodate oxidation provided 2,3-*O*-cyclohexylidene-L-glyceraldehyde (**18**) in 76% overall yield from **16**.[18] We decided to protect the diol as a cyclohexylidene ketal because of the improved characteristics of this group, with regard to other conventionally employed ketals (isopropylidene),[19] which enable straightforward synthesis and storage of its derivatives. Attempts to use a one-pot procedure[20] for the direct conversion of aldehyde **18** into the acetylenic iodide **20** by using triphenylphosphine, triiodomethane, and *t*-BuOK failed in our hands, leading to an inseparable mixture of alkyne and iodoalkyne. Consequently, we carried out the transformation in a two-step sequence through the 1,1-diiodoalkene intermediate **19** (CHI_3, PPh_3, *t*-BuOK, THF, 0 °C, 84%), which was treated with *n*-Bu_4NF to conveniently induce monodehydroiodination[21] providing the (*R*)-1,2-*O*-cyclohexylidenedioxy-4-iodobut-3-yne (**20**)[22] in 95% yield. Finally, removal of the cyclohexylidene group (Dowex 50WX8, methanol)[23] afforded the novel (*R*)-iodoalkynediol **21**,[24] as a white amorphous solid, in excellent yield (94%) and enantiomeric excess (≥98%) as determined by ^{1}H NMR analysis on its (*R*)-α-methoxyphenylacetic (MPA) diester.[25]

The synthesis of (*R*)-trideca-3,5,10,12-tetrayne-1,2-diol (**31**) started with the monoprotection of commercially available 1,6-heptadiyne (**22**) (CPDMSCl, EtMgBr, THF) to give 1-[(3′-cyanopropyl)dimethylsilyl]hepta-1,6-diyne (**23**) in 77% yield (Scheme 4).[26] Cadiot−Chodkiewicz cross-coupling of **23** with iodotriisopropylsilylacetylene (**25**), under Alami's optimized conditions (CuI, piperidine),[27] led to the orthogonally bis-protected 1,3,8-nonatriyne **26** in 74% yield. Basic methanolysis allowed the selective removal of the CPDMS group to obtain 1-triisopropylsilylnona-1,3,8-nonatriyne (**27**) in 94% yield. The subsequent sp−sp coupling of **27** with iodoalkynediol **21**, under the same Alami conditions, provided the TIPS-protected tetraynediol **30** (83%), which was desilylated with *n*-Bu_4NF in THF to afford **31** as yellow crystals in quantitative yield. Similarly, (*R*)-undeca-3,5,10-triyne-1,2-diol (**29**), required for the synthesis of (−)-tetrahydrosiphonodiol (**2**), was readily obtained from intermediates **21** and **23** through a two-step sequence involving sp−sp coupling (CuI, piperidine, 74%) and deprotection of the silyl group (*n*-Bu_4NF, THF, 84%) (Scheme 4). An alternative preparation of (*R*)-13-triisopropylsilyltrideca-3,5,10,12-tetrayne-1,2-diol (**30**) by sp−sp coupling of fragments **25** and **29** did not improve the above route, yielding **30** in a poor (40%) yield.

With all intermediates in hand, we faced the final sp^2−sp cross-couplings (Scheme 5). The Sonogashira reaction between the (3*Z*,11*Z*)-12-bromo-1-[(3′-cyanopropyl)dimethylsilyl]dodeca-3,11-dien-1-yne (**13**) and the (*R*)-undeca-3,5,10-triyne-1,2-diol (**29**) was carried out under standard conditions [$PdCl_2(PPh_3)_2$, CuI, piperidine] to afford stable (2*R*,12*Z*,20*Z*)-23-[(3′-cyanopropyl)dimethylsilyl]tricosa-12,20-diene-3,5,10,22-tetrayne-1,2-diol (**33**) in 71% yield. Subsequent TBAF desilylation cleanly provided the target (−)-tetrahydrosiphonodiol (**2**) as a yellow oil in 70% yield. The spectroscopic and physical data [^{1}H and ^{13}C NMR, IR] of the synthetic compound were found to be identical to those published for the natural product.[3,28]

The assembly of the skeleton framework of (−)-siphonodiol (**1**) would require the Sonogashira reaction between the *cis*-vinylbromide **12** and the 1,3-diyne moiety **31**. Although few examples of Sonogashira couplings with 1,3-diynes are known, most likely because of the instability of such intermediates,[29,30] in our case, the reaction of (3*Z*,9*Z*)-10-bromo-1-[(3′-cyanopropyl)dimethylsilyl]deca-3,9-dien-1-yne (**12**) with (*R*)-trideca-3,5,10,12-tetrayne-1,2-diol (**31**) proceeded smoothly to give rise to the coupling product (2*R*,14*Z*,20*Z*)-23-[(3′-cyanopropyl)di-

methylsilyl]tricosa-14,20-diene-3,5,10,12,22-pentayne-1,2-diol (**32**) in 68% yield. The standard coupling conditions used until now for Sonogashira cross-couplings did not work in this case and the use of pyrrolidine instead of piperidine appeared to be a critical feature for the success of this coupling.[31] Unlike the analogous **33**, pentaynediol **32** turned out to be unstable and had to be immediately desilylated to provide, in good yield (74%), synthetic (−)-siphonodiol (**1**), which showed spectral properties identical to those reported for the natural compound.[2,3,32,33]

In summary, we have completed the first stereoselective total synthesis of the bioactive marine polyacetylenes (−)-siphonodiol (**1**) and (−)-tetrahydrosiphonodiol (**2**). Both products have been prepared from commercially available starting materials, via highly convergent routes, in 23% and 17% overall yield, respectively. Key features of the synthesis include stereoselective sequential Sonogashira cross-coupling reactions of the di-*cis*-dibromodienes **9** and **10** with the novel [(3′-cyanopropyl)-dimethylsilyl]acetylene (**11**) and with the highly unsaturated chiral diol moieties **29** and **31**. In the case of (−)-siphonodiol (**1**) this represents a rare example of successful Sonogashira assembly using an 1,3-diyne counterpart.

Experimental Section

(3*Z*,9*Z*)-10-Bromo-1-[(3′-cyanopropyl)dimethylsilyl]deca-3,9-dien-1-yne (12). To a solution of (1*Z*,7*Z*)-1,8-dibromoocta-1,7-diene (**9**) (1.70 g, 6.34 mmol), $PdCl_2(PPh_3)_2$ (0.20 g, 0.28 mmol), and CuI (0.06 g, 0.32 mmol) in degassed piperidine (42 mL) was added a solution of [(3′-cyanopropyl)dimethylsilyl]-acetylene (**11**) (0.34 g, 2.25 mmol) in degassed piperidine (2 mL), and the reaction mixture was stirred for 2 h. A saturated aqueous solution of NH_4Cl (50 mL) was then added, and the organic phase was extracted with ether (3 × 50 mL). The ethereal fractions were washed with brine (3 × 150 mL), dried, and concentrated. Flash chromatography (hexane/ethyl acetate 90:10) afforded the title compound (0.57 g, 75% yield) as a yellow oil, together with a small amount of the dicoupling product (3*Z*,9*Z*)-1,12-bis[(3′-cyanopropyl)dimethylsilyl]dodeca-3,9-diene-1,11-diyne (**14**) (0.04 g, 9% yield). Spectral data for **12**: ^{1}H NMR (250 MHz, C_6D_6) δ 0.06 (6H, s), 0.3−0.4 (2H, m), 1.2−1.3 (6H, m), 1.50 (2H, t, J = 6.9 Hz), 2.0−2.1 (2H, m), 2.2−2.3 (2H, m), 5.44 (1H, d, J = 10.9 Hz), 5.6−5.7 (2H, m), 5.84 (1H, d, J = 6.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0 (2 × CH_3), 15.5 (CH_2), 20.2 (CH_2), 20.4 (CH_2), 27.3 (CH_2), 27.8 (CH_2), 29.1 (CH_2), 29.8 (CH_2), 96.2 (C), 103.0 (C), 107.6 (CH), 109.0 (CH), 119.4 (C), 134.4 (CH), 145.2 (CH) ppm. IR (CsI) ν 2246 (C≡N), 2147 (C≡C) cm^{-1}. MS (CI) m/z (%) 340 (1), 338 (MH^+, 1), 337 (M^+, <1), 324 (4), 322 (4), 126 (100). HRMS (CI) calcd for $C_{16}H_{24}NSiBr$ 337.0861, found 337.0859. Spectral data for **14**: ^{1}H NMR (400 MHz, C_6D_6) δ 0.17 (12H, s), 0.7−0.8 (4H, m), 1.4−1.5 (4H, m), 1.7−1.8 (4H, m), 2.2−2.3 (4H, m), 2.37 (4H, t, J = 7.0 Hz), 5.45 (2H, dt, J = 10.9, 1.4 Hz), 5.95 (2H, dt, J = 10.9, 6.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.8 (4xCH_3), 15.7 (2 × CH_2), 20.4 (2 × CH_2), 20.6 (2 × CH_2), 28.2 (2 × CH_2), 30.2 (2 × CH_2), 96.4 (2 × C), 103.3 (2 × C), 109.1 (2 × CH), 119.6 (2 × C), 145.9 (2 × CH) ppm. IR (CsI) ν 2245 (C≡N), 2146 (C≡C) cm^{-1}. MS (CI) m/z (%) 409 (MH^+, 4), 408 (M^+, <1), 127 (57), 126 (100), 96 (27). HRMS (EI) calcd for $C_{24}H_{36}N_2Si_2$ 408.2417, found 408.2420.

(3*Z*,11*Z*)-12-Bromo-1-[(3′-cyanopropyl)dimethylsilyl]-dodeca-3,11-dien-1-yne (13). Following the procedure described above, treatment of (1*Z*,9*Z*)-1,10-dibromodeca-1,9-diene (**10**) (0.51 g, 1.72 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), and CuI (0.02 g, 0.11 mmol), in degassed piperidine (12 mL), with a solution of [(3′-cyanopropyl)dimethylsilyl]acetylene (**11**) (0.10 g, 0.66 mmol) in degassed piperidine (0.5 mL) for 3 h afforded, after purification by flash chromatography (hexane/ethyl acetate 80:20), the title compound as a yellow oil (0.17 g, 70% yield), together with 0.03 g (20%) of (3*Z*,11*Z*)-1,14-bis[(3′-cyanopropyl)dimethylsilyl]tetradeca-3,11-diene-1,13-diyne (**15**). Spectral data for **13**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.20 (6H, s), 0.7−0.8 (2H, m), 1.3−1.5 (8H, m), 1.7−1.8 (2H, m), 2.1−2.2 (2H, m), 2.3−2.4 (2H, m), 2.41 (2H, t, J = 7.0 Hz), 5.48 (1H, d, J = 10.9 Hz), 5.98 (1H, dt, J = 10.9, 7.5 Hz), 6.0−6.2 (2H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.7 (2 × CH_3), 15.8 (CH_2), 20.4 (CH_2), 20.7 (CH_2), 28.0 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.6 (CH_2), 30.3 (CH_2), 96.2 (C), 103.3 (C), 107.4 (CH), 108.9 (CH), 119.4 (C), 134.7 (CH), 146.7 (CH) ppm. IR (CsI) ν 2246 (C≡N), 2147 (C≡C) cm^{-1}. MS (CI) m/z (%) 368 (<1), 366 (MH^+, <1), 352 (4), 350 (4), 286 (3), 159 (3), 137 (9), 126 (100), 98 (17). HRMS (CI) calcd for $C_{18}H_{29}NSiBr$ 366.1253, found 366.1248. Spectral data for **15**: ^{1}H NMR (400 MHz, C_6D_6) δ 0.20 (12H, s), 0.7−0.8 (4H, m), 1.3−1.5 (8H, m), 1.7−1.9 (4H, m), 2.2−2.3 (4H, m), 2.43 (4H, t, J = 7.0 Hz), 5.50 (2H, d, J = 10.9 Hz), 5.90 (2H, dt, J = 10.9, 7.4 Hz) ppm. ^{13}C

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(17) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965−8975.

(18) The synthesis of 2,3-*O*-cyclohexylidene-L-glyceraldehyde (**18**) from 4,5-*O*-cyclohexylidene-L-arabinose dibenzyl dithioacetal has been described, but its optical rotation was not reported: Grauert, M.; Schöllkopf, U. *Liebigs Ann. Chem.* **1985**, 1817−1824. The enantiomer is, however, well documented: Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *48*, 1841−1844.

(19) Cyclohexylidene ketals address the problems associated with other conventionally employed protecting groups, as isopropylidene: its higher molecular weight renders derivatives less volatile and the higher lipophilicity of the resulting protecting glyceraldehyde makes easier its extraction from aqueous media. See: Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587−590.

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(32) As described for the natural product, synthetic (−)-siphonodiol was very labile at room temperature and even at 0 °C, but rather stable at −20 °C.

(33) The enantiomeric excesses of all the chiral diols on the series were assessed by integration of the respective signals due to the Hα to the phenyl group in the ^{1}H NMR spectrum of the (*R*)-α-methoxyphenyl acetic (MPA) diesters (see ref 25). In all cases the enantiomeric excesses were found to be higher than 98%.

NMR (100 MHz, $CDCl_3$) δ −1.6 (4 × CH_3), 15.8 (2 × CH_2), 20.5 (2 × CH_2), 20.7 (2 × CH_2), 28.7 (2 × CH_2), 29.0 (2 × CH_2), 30.5 (2 × CH_2), 96.3 (2 × C), 103.4 (2 × C), 108.8 (2 × CH), 119.6 (2 × C), 145.90 (2 × CH) ppm. IR (CsI) ν 2245 (C≡N), 2146 (C≡C) cm^{-1}. MS (CI) *m/z* (%) 437 (MH^+, 100), 421 (21), 394 (11), 297 (7), 269 (8), 126 (5). HRMS (EI) calcd for $C_{26}H_{40}N_2Si_2$ 436.2730, found 436.2728.

(*R*)-11-[(3′-Cyanopropyl)dimethylsilyl]undeca-3,5,10-triyne-1,2-diol (28). To a solution of (*R*)-4-iodobut-3-yne-1,2-diol (**21**) (0.23 g, 1.08 mmol) and 1-[(3′-cyanopropyl)dimethylsilyl]hepta-1,6-diyne (**23**) (0.58 g, 2.67 mmol)) in degassed piperidine (27 mL), cooled on an ice−water bath, was added CuI (0.05 g, 0.26 mmol), and the mixture was allowed to react for 1 h at room temperature. The mixture was poured in aqueous saturated solution of NH_4Cl (25 mL), and the organic layer was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (2 × 60 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (hexane/ethyl acetate 90:10) afforded the title compound as a yellow oil (0.24 g, 74% yield). $[\alpha]^{20}_D$ −32.1° (*c* 0.61, $CHCl_3$). ^1H NMR (250 MHz, $CHCl_3$) δ 0.15 (6H, s), 0.7−0.8 (2H, m), 1.7−1.8 (4H, m), 2.3−2.4 (6H, m), 3.7−3.8 (2H, m), 4.4−4.5 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8 (2 × CH_3), 15.8 (CH_2), 18.2 (CH_2), 18.8 (CH_2), 20.3 (CH_2), 20.5 (CH_2), 26.8 (CH_2), 63.4 (CH), 64.9 (C), 66.1 (CH_2), 70.7 (C), 73.6 (C), 80.5 (C), 83.6 (C), 107.1 (C), 119.7 (C) ppm. IR (CsI) ν 3406 (O−H), 2253 (C≡N), 2172 (C≡C) cm^{-1}. MS (CI) *m/z* (%) 302 (MH^+, 4), 281 (41), 256 (33), 159 (14), 126 (100). HRMS (EI) calcd for $C_{17}H_{23}NO_2Si$ 301.1491, found 301.1498.

(*R*)-Undeca-3,5,10-triyne-1,2-diol (29). To a solution of (*R*)-11-[(3′-cyanopropyl)dimethylsilyl]undeca-3,5,10-triyne-1,2-diol (**28**) (0.17 g, 0.56 mmol) in dry THF (11 mL) was added *n*-Bu_4NF (1.0 M solution in THF, 1.68 mL, 1.68 mmol), and the mixture was allowed to react at room temperature for 5 h. The mixture was diluted with ether (10 mL), washed with brine (3 × 12 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (CH_2Cl_2/ethyl acetate, 50:50) afforded the title compound as a light brown solid (0. 08 g, 84% yield). $[\alpha]^{20}_D$ −43.8° (*c* 1.16, $CHCl_3$). Mp 58−60 °C (dec). ^1H NMR (300 MHz, $CDCl_3$) δ 1.7−1.8 (2H, m), 1.96 (1H, s), 2.3−2.5 (4H, m), 3.6−3.7 (2H, m), 4.4−4.5 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5 (CH_2), 18.2 (CH_2), 26.9 (CH_2), 63.5 (CH), 64.9 (C), 66.2 (CH_2), 69.3 (CH), 70.8 (C), 73.4 (C), 80.7 (C), 82.9 (C) ppm. IR (CsI) ν 3385 (O−H), 3300 (≡C−H), 2256 (C≡C) cm^{-1}. MS (CI) *m/z* (%) 176 (M^+, 1), 159 (54), 129 (98), 116 (77), 91 (100). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.66; H, 6.96.

9-[(3′-Cyanopropyl)dimethylsilyl]-1-triisopropylsilylnona-1,3,8-triyne (26). Following the same procedure described for **28**, treatment of 2-iodo-1-triisopropylsilylacetylene (**25**) (0.25 g, 0.81 mmol) and 1-[(3′-cyanopropyl)dimethylsilyl]-hepta-1,6-diyne (**23**) (0.40 g, 1.84 mmol) in degassed piperidine (25 mL) with CuI (0.03 g, 0.20 mmol) for 1 h at room temperature afforded, after purification by flash chromatography (hexane/ethyl acetate 90:10), the title compound as a yellow oil (0.24 g, 74% yield). ^1H NMR (250 MHz, $CDCl_3$) δ 0.15 (6H, s), 0.7−0.8 (2H, m), 1.0−1.1 (21H, m), 1.7−1.8 (4H, m), 2.3−2.4 (6H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.6 (2 × CH_3), 11.3 (3 × CH), 15.9 (CH_2), 18.4 (CH_2), 18.6 (6 × CH_3), 19.1 (CH_2), 20.5 (CH_2), 20.7 (CH_2), 27.2 (CH_2), 66.5 (C), 77.4 (C), 80.5 (C), 83.5 (C), 89.8 (C), 107.2 (C), 119.6 (C) ppm. IR (CsI) ν 2246 (C≡N), 2224, 2174 (C≡C) cm^{-1}. MS (EI) *m/z* (%) 397 (M^+, <1), 354 (100), 242 (3), 183 (3), 157 (3), 105 (2). HRMS (EI) calcd for $C_{24}H_{39}NSi_2$ 397.2621, found 397.2617.

1-Triisopropylsilylnona-1,3,8-triyne (27). To a solution of 9-[(3′-cyanopropyl)dimethylsilyl]-1-triisopropylsilylnona-1,3,8-triyne (**26**) (0.45 g, 1.13 mmol) in a 1:1 THF/MeOH mixture (22 mL) was added anhydrous K_2CO_3 (0.64 g, 4.63 mmol), and the suspension was allowed to react for 1 h at room temperature. The mixture was diluted in a 1:2 ether/H_2O mixture (24 mL), and the organic phase was washed with H_2O (2 × 10 mL) and brine (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (hexane/ethyl acetate 98:2) afforded the title compound as a yellow oil (0.29 g, 94% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 1.0−1.1 (21H, m), 1.75 (2H, q, J = 7.0 Hz), 1.95 (1H, t, J = 2.5 Hz), 2.31 (2H, dt, J = 2.5, 7.0 Hz), 2.41 (2H, t, J = 7.0 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.2 (3 × CH), 17.6 (CH_2), 18.2 (CH_2), 18.5 (6 × CH_3), 27.0 (CH_2), 66.5 (C), 69.1 (CH), 77.3 (C), 80.3 (C), 82.9 (C), 89.9 (C) ppm. IR (CsI) ν 3309 (≡C−H), 2225, 2105 (C≡C) cm^{-1}. MS (EI) *m/z* (%) 272 (M^+, 8), 229 (95), 187 (21), 159 (100), 145 (67). HRMS (EI) calcd for $C_{18}H_{28}Si$ 272.1960, found 272.1961.

(*R*)-13-Triisopropylsilyltrideca-3,5,10,12-tetrayne-1,2-diol (30). Following the same procedure described for **28**, treatment of (*R*)-4-iodobut-3-yne-1,2-diol (**21**) (0.05 g, 0.24 mmol) and 1-triisopropylsilylnona-1,3,8-triyne (**27**) (0.17 g, 0.62 mmol) in degassed piperidine (5 mL) with CuI (0.01 g, 0.05 mmol) for 6 h at room temperature afforded, after purification by flash chromatography (CH_2Cl_2/ethyl acetate 95:5), the title compound as a light brown oil (0.07 g, 83% yield). $[\alpha]^{20}_D$ −14.8° (*c* 1.28, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.0−1.1 (21H, m), 1.79 (2H, q, J = 6.9 Hz), 2.4−2.5 (4H, m), 3.7−3.8 (2H, m), 4.50 (1H, t, J = 5.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (3 × CH), 18.4 (2 × CH_2), 18.6 (6 × CH_3), 26.7 (CH_2), 63.5 (CH), 65.1 (C), 66.2 (CH_2), 66.7 (C), 70.8 (C), 73.6 (C), 76.9 (C), 80.4 (C), 80.7 (C), 89.7 (C). IR (CsI) ν 3372 (O−H), 2224 (C≡C) cm^{-1}. MS (EI) *m/z* (%) 356 (M^+, 21), 325 (36), 295 (9), 225 (100), 197 (58), 179 (58), 165 (89). HRMS (EI) calcd for $C_{22}H_{32}SiO_2$ 356.2171, found 356.2180.

(*R*)-Trideca-3,5,10,12-tetrayne-1,2-diol (31). Following the same procedure described for **29**, treatment of a solution of (*R*)-13-triisopropylsilyltrideca-3,5,10,12-tetrayne-1,2-diol (**30**) (0.16 g, 0.45 mmol) in dry THF (5 mL) with *n*-Bu_4NF (1.0 M solution in THF, 1.35 mL, 1.35 mmol) for 6 h afforded, after purification by flash chromatography (hexane), the title compound as a light brown solid (0.09 g, quantitative yield). $[\alpha]^{20}_D$ −33.2° (*c* 0.45, $CHCl_3$). Mp: 83−85 °C (CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (2H, q, J = 7.0 Hz), 1.96 (1H, t, J = 1.0 Hz), 2.38 (2H, dt, J = 7.0, 1.0 Hz), 2.44 (2H, t, J = 7.0 Hz), 3.6−3.7 (2H, m), 4.4−4.5 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (CH_2), 18.5 (CH_2), 26.6 (CH_2), 63.6 (CH), 65.1 (CH), 65.2 (C), 65.7 (C), 66.3 (CH_2), 68.2 (C), 71.0 (C), 73.5 (C), 76.6 (C), 80.3 (C) ppm. IR (CsI) ν 3273 (≡C−H, O−H), 2224 (C≡C) cm^{-1}. MS (CI) *m/z* (%) 201 (MH^+, 3), 200 (M^+, 2), 153 (100). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.76; H, 6.35.

(2*R*,14*Z*,20*Z*)-23-[(3′-Cyanopropyl)dimethylsilyl]tricosa-14,20-diene-3,5,10,12,22-pentayne-1,2-diol (32). Following the same procedure described for **12**, treatment of (3*Z*,9*Z*)-10-bromo-1-[(3′-cyanopropyl)dimethylsilyl]deca-3,9-dien-1-yne (**12**) (0.025 g, 0.074 mmol), $PdCl_2(PPh_3)_2$ (0.006 g, 0.009 mmol), and CuI (0.002 g, 0.011 mmol), in degassed pyrrolidine (2 mL), with a solution of (*R*)-trideca-3,5,10,12-tetrayne-1,2-diol (**31**) (0.030 g, 0.150 mmol) in degassed pyrrolidine (1 mL) for 3 h afforded, after purification by flash chromatography (hexane/ethyl acetate 90:10), the title compound as a highly unstable yellow oil (0.023 g, 68% yield), which was used immediately in the next step. ^1H NMR (250 MHz, $CDCl_3$) δ 0.22 (6H, s), 0.7−0.8 (2H, m), 1.4−1.5 (4H, m), 1.7−1.9 (4H, m), 2.3−2.5 (10H, m), 3.7−3.8 (2H, m), 4.5−4.6 (1H, 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) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.6 (2 × CH_3), 15.9 (CH_2), 18.4 (CH_2), 18.7 (CH_2), 20.6 (CH_2), 20.8 (CH_2), 26.9 (CH_2), 28.2 (CH_2), 28.4 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 63.6 (CH), 66.3 (CH_2), 66.6 (C), 66.8 (C), 70.9 (C), 72.5 (C), 73.6 (C), 77.9 (C), 80.6 (C), 83.1 (C), 96.6 (C), 103.3 (C), 108.2 (CH), 109.1 (CH), 119.6 (C), 145.5 (CH), 147.6 (CH) ppm.

(2*R*,12*Z*,20*Z*)-23-[(3′-Cyanopropyl)dimethylsilyl]tricosa-12,20-diene-3,5,10,22-tetrayne-1,2-diol (33). Following the same procedure described for **12**, treatment of (3*Z*,11*Z*)-12-bromo-1-[(3′-cyanopropyl)dimethylsilyl]dodeca-3,11-dien-1-yne (**13**)(0.16 g, 0.44 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), and CuI (0.01 g, 0.05 mmol), in degassed piperidine (5 mL),

with a solution of (*R*)-undeca-3,5,10-triyne-1,2-diol (**29**) (0.13 g, 0.74 mmol) in degassed piperidine (3 mL) for 6 h afforded, after purification by flash chromatography (hexane/ethyl acetate 90:10), the title compound as a yellow oil (0.14 g, 71% yield). $[\alpha]^{20}_D$ −14.4° (*c* 0.06, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) 0.20 (6H, s), 0.7−0.8 (2H, m), 1.3−1.4 (8H, m), 1.7−1.8 (4H, m), 2.2−2.3 (4H, m), 2.4−2.5 (6H, m), 3.6−3.7 (2H, m), 4.4−4.5 (1H, m), 5.42 (1H, d, J = 10.6 Hz), 5.48 (1H, d, J = 10.9 Hz), 5.84 (1H, dt, J = 10.6, 7.3 Hz), 5.99 (1H, dt, J = 10.9, 7.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.6 (2 × CH_3), 15.9 (CH_2), 18.5 (CH_2), 18.8 (CH_2), 20.6 (CH_2), 20.7 (CH_2), 27.4 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 29.1 (2 × CH_2), 30.1 (CH_2), 30.5 (CH_2), 63.6 (CH), 64.8 (C), 66.3 (CH_2), 71.2 (C), 73.4 (C), 78.4 (C), 81.0 (C), 92.5 (C), 96.3 (C), 103.5 (C), 108.8 (CH), 109.0 (CH), 119.6 (C), 142.9 (CH), 146.0 (CH) ppm. IR (CsI) ν 3397 (O−H), 2254 (C≡N), 2147 (C≡C) cm^{-1}. MS (EI) *m/z* (%) 461 ($M^{+\cdot}$, <1),141 (28), 126 (55), 98 (100). HRMS (CI) calcd for $C_{29}H_{40}NO_2Si$ 462.2828, found 462.2826.

(−)-*R*-Siphonodiol (1). Following the same procedure described for **29**, treatment of a solution of (2*R*,14*Z*,20*Z*)-23-[(3′-cyanopropyl)dimethylsilyl]tricosa-14,20-diene-3,5,10,12,22-pentayne-1,2-diol (**32**) (0.015 g, 0.032 mmol) in dry THF (3 mL) with *n*-Bu_4NF (1.0 M solution in THF, 0.09 mL, 0.09 mmol) for 2 h afforded, after purification by flash chromatography (CH_2Cl_2/MeOH, 90:10), the title compound as an unstable yellow oil (0.008 g, 74%), which was kept under argon at −20 °C. $[\alpha]^{20}_D$ −6.4° (*c* 0.008, MeOH) [lit.[2] −6.7° (*c* 0.5, MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ 1.4−1.6 (4H, m), 1.80 (2H, q, J = 7.1 Hz), 2.3−2.5 (8H, m), 3.09 (1H, s), 3.7−3.8 (2H, m), 4.5−4.5 (1H, m), 5.4−5.5 (2H, m), 5.9−6.1 (2H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4 (CH_2), 18.8 (CH_2), 26.8 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 30.0 (CH_2), 30.5 (CH_2), 63.6 (CH), 64.9 (C), 66.1 (C), 66.2 (CH_2), 71.0 (C), 72.4 (C), 73.4 (C), 77.9 (C), 80.4 (C), 80.5 (C), 81.3 (CH), 82.9 (C), 108.1 (CH), 108.2 (CH), 145.8 (CH), 147.8 (CH) ppm. IR (CsI) ν 3373 (O−H), 3294 (≡C−H), 2224, 2258 (C≡C) cm^{-1}. MS (CI) *m/z* (%) 333 (MH^+, <1), 297 (20), 61 (100). HRMS (CI) calcd for $C_{23}H_{25}O_2$ 333.1854, found 333.1847. The spectroscopic data of the synthetic compound were identical to those described for the natural product.[2,3]

(−)-*R*-Tetrahydrosiphonodiol (2). Following the same procedure described for **29**, treatment of a solution of (2*R*,-12*Z*,20*Z*)-23-[(3′-cyanopropyl)dimethylsilyl]tricosa-12,20-diene-3,5,10,22-tetrayne-1,2-diol (**33**) (0.10 g, 0.21 mmol) in dry THF (2.5 mL) with *n*-Bu_4NF (1.0 M solution in THF, 0.64 mL, 0.64 mmol) for 6 h afforded, after purification by flash chromatography (CH_2Cl_2/MeOH, 90:10), the title compound as a yellow oil (0. 07 g, 70%). $[\alpha]^{20}_D$ −13.2° (*c* 0.004, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.3−1.4 (8H, m), 1.7−1.8 (2H, m), 2.2−2.3 (4H, m), 2.3−2.4 (4H, m), 3.07 (1H, s), 3.6−3.7 (2H, m), 4.4−4.5 (1H, m), 5.3−5.4 (2H, m), 5.84 (1H, dt, J = 10.6, 7.4 Hz), 6.01 (1H, dt, J = 10.8, 7.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4 (CH_2), 18.8 (CH_2), 27.4 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 29.0 (2 × CH_2), 30.1 (CH_2), 30.3 (CH_2), 63.6 (CH), 64.7 (C), 66.3 (CH_2), 71.2 (C), 73.3 (C), 78.4 (C), 80.6 (C), 81.1 (C), 81.2 (CH), 92.4 (C), 107.9 (CH), 109.0 (CH), 143.0 (CH), 146.1 (CH) ppm. IR (CsI) ν 3373 (O−H), 2255 (C≡C) cm^{-1}. MS (CI) *m/z* (%) 337 (M + 1, <1), 126 (100). HRMS (EI) calcd for $C_{23}H_{28}O_2$ 336.2089, found 336.2090. The spectroscopic data of the synthetic compound were identical to those described for the natural product.[3]

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Supporting Information Available: General methods, experimental procedures for selected intermediates. and ^1H−^{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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