Synthesis of Natural Polyacetylenes Bearing Furan Rings

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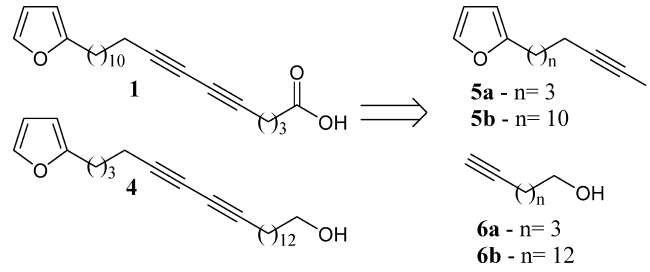
The first total syntheses of four new polyacetylene compounds have been achieved using convergent routes, which involved Cadiot−-Chodkiewicz copper-catalyzed cross-coupling reactions to sp−sp centers as the key steps. 19-Furan-2-ylnonadeca-5,7-diynoic acid (**1**), 19-furan-2-ylnonadeca-5,7-diynoic acid methyl ester (**2**), 2-pentacosa-7,9-diynylfuran (**3**), and 21-furan-2-ylhenicosa-14,16-diyn-1-ol (**4**) were stable and could be readily identified, isolated, and purified in high overall yields.

Conjugated triple bonds 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.[1] These polyacetylenes have proven to be important biologically active compounds that can be used as antibacterial,[2] antimicrobial,[3] antifungal, and antiviral agents.[4] They also exhibit larvicidal activity[5] and cytotoxicity toward a range of cell lines.[6] In addition, they are key structural moieties in synthetic compounds with unusual electrical, optical, or structural properties, which have found applications in material science.[7]

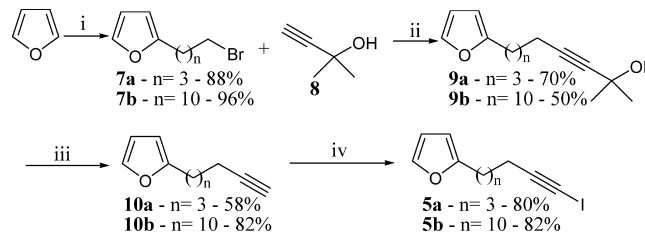
Recently, four new polyacetylenes, 19-furan-2-yl-nonadeca-5,7-diynoic acid (**1**), 19-furan-2-ylnonadeca-5,7-diynoic acid methyl ester (**2**), 2-pentacosa-7,9-diynylfuran (**3**), and 21-furan-2-ylhenicosa-14,16-diyn-1-ol (**4**) (Figure 1) were isolated from the roots of *Polyalthia evecta*, a small tree found in the northeastern part of Thailand.[8] These compounds were found to have potent antiplasmodial and antiviral activities against Herpes simplex type 1.

As part of our efforts toward the synthesis and biological activity of heterocyclic and polyacetylenic compounds,[9] we became interested in the development of a synthesis route and the relationship between the structure and biological properties of these four bioactive polyenes. The present paper deals with a convergent route for the first synthesis of polyacetylenes **1**−**4** (Figure 1), using copper-catalyzed cross-coupling reactions to sp−sp centers, as the key steps. Metal-catalyzed acetylenic cross-coupling has been extensively employed for the synthesis of a wide variety of organic compounds ranging from small organic molecules to macromolecules, including polyacetylenes.[10]

Scheme 1. Retrosynthetic Analysis of Polyacetylenes **1** and **4**



Scheme 2. Synthesis of Fragment **5a** and **5b**[a]



[a] Reagents and conditions: (i) THF, 1 equiv of *n*-BuLi at −20 °C, 4 h, 1,4-dibromobutane or 1,11-dibromoundecane at −20 °C to rt, overnight; (ii) HMPA/THF (3 mL/mmol; 1:2), 2 equiv of *n*-BuLi (−78 °C), 18 h, rt; (iii) NaOH, toluene, reflux; 12 h; (iv) THF, 1 equiv of *n*-BuLi at −20 °C, 1 h, THF/I_2 at −40 °C to rt, overnight.

Results and Discussion

The retrosynthetic analysis of polyacetylenes **1** and **4**, based on metal-catalyzed acetylenic cross-coupling, afforded two basic fragments, furyl iodide systems **5a** and **5b** and acetylenic alcohols **6a** and **6b**, which differ only in the number of carbons in the chain (Scheme 1).

The furyl iodides **5a** and **5b** were synthesized according to Scheme 2. Our synthesis started with the alkylation of 2-furyllithium (prepared from the metalation of furan using 1 equiv of *n*-BuLi in THF at −20 °C for 4 h)[11] with 1,4-dibromobutane or 1,11-dibromoundecane,[12] yielding the corresponding bromides **7a** ($n = 3$) in 88% and **7b** ($n = 10$) 96% yield, respectively. The reaction of commercially available alcohol **8** with 2 equiv of *n*-BuLi, at −78 °C, gave the dilithiated intermediate that reacted with **7a** or **7b** in the presence of HMPA/THF (3 mL/mmol; 1:2) as solvent, at room temperature,[13] yielding the corresponding alcohols **9a** and **9b** in 70% and 50% yield, respectively. The removal of the protecting group on the triple bond of **9** was carried out with NaOH in toluene under reflux,[14] affording the terminal alkynes **10a** in 58% and **10b** in 82% yield. Compounds **10a** and **10b** were transformed into the corresponding fragments **5a** and **5b** by reaction with 1 equiv of *n*-BuLi followed by the reaction of lithium acetylide intermediate with 1 equiv of iodine[15] in 80% and 82% yield, respectively (Scheme 2).

The synthesis of polyacetylenes **1** and **2** were carried out following the sequence showed in Scheme 3. The copper-catalyzed Cadiot−Chodkiewicz[16] coupling of fragment **5b** ($n = 10$) with the commercial alcohol **6a** using CuI and pyrrolidine[17] yielded **11** (75%). Oxidation with PDC in DMF[18] provided acid **1** in 49% yield. Esterification of **1** using MeOH in the presence of $SOCl_2$[19] afforded the corresponding polyacetylenic ester **2** in 65% yield.

The synthesis of fragment **6b** (Scheme 4) began by the treatment of 2-propyn-1-ol with **2** equiv of *n*-BuLi in HMPA/THF[13] (3 mL/mmol; 1:2) to generate the corresponding lithium dianion, which was subsequently quenched with 1-bromododecane to afford alcohol **12** in 85% yield. This compound was subjected to prototropic migration of the triple bond with potassium 3-aminopropanamide (KAPA)[20] to afford the terminal alkyne **6b** in 70%

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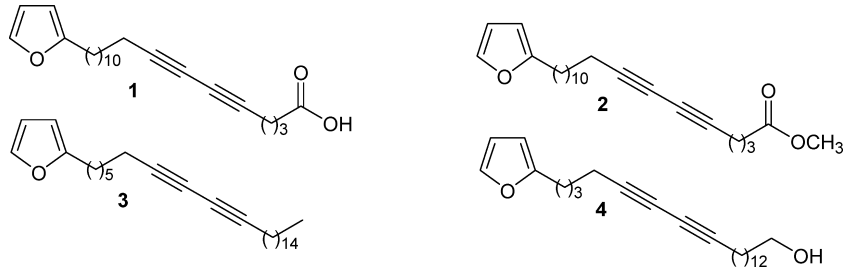
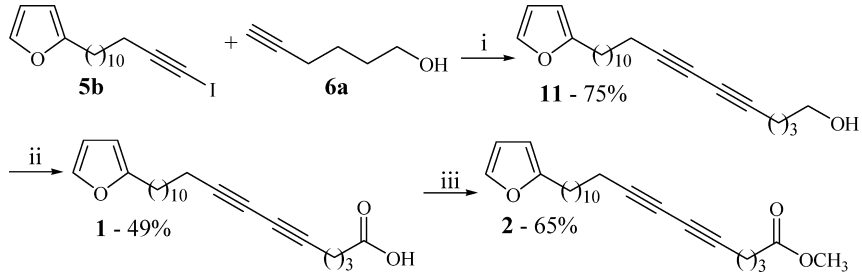


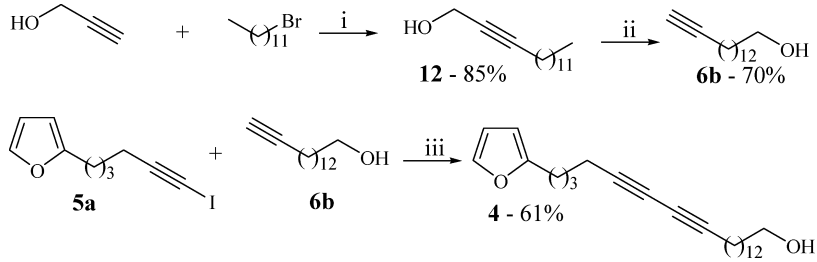
Figure 1. Polyacetylenes 19-furan-2-ylnonadeca-5,7-diynoic acid (**1**), 19-furan-2-ylnonadeca-5,7-diynoic acid methyl ester (**2**), 2-pentacosa-7,9-diynylfuran (**3**), and 21-furan-2-ylhenicosa-14,16-diyn-1-ol (**4**) isolated from the roots of *Polyalthia evecta.*

Scheme 3. Synthesis of Polyacetylenes **1** and **2**[a]



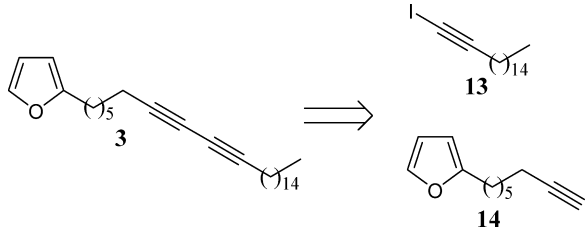
[a] Reagents and conditions: (i) pyrrolidine, CuI, overnight, rt; (ii) PDC, DMF, 4 h, rt; (iii) MeOH, $SOCl_2$, 15 h, rt.

Scheme 4. Synthesis of Polyacetylene **4**[a]



[a] Reagents and conditions: (i) HMPA/THF (3 mL/mmol; 1:2), 2 equiv of *n*-BuLi (−78 °C), 18 h, rt; (ii) $KHN(CH_2)_3NH_2$, 12 h, r.t.; (iii) pyrrolidine, CuI, overnight, rt.

Scheme 5. Retrosynthetic Analysis of Polyacetylene **3**



yield. Subsequent coupling of fragment **5a** and **6b** using CuI and pyrrolidine[17] gave the polyacetylene **4** in 61% yield.

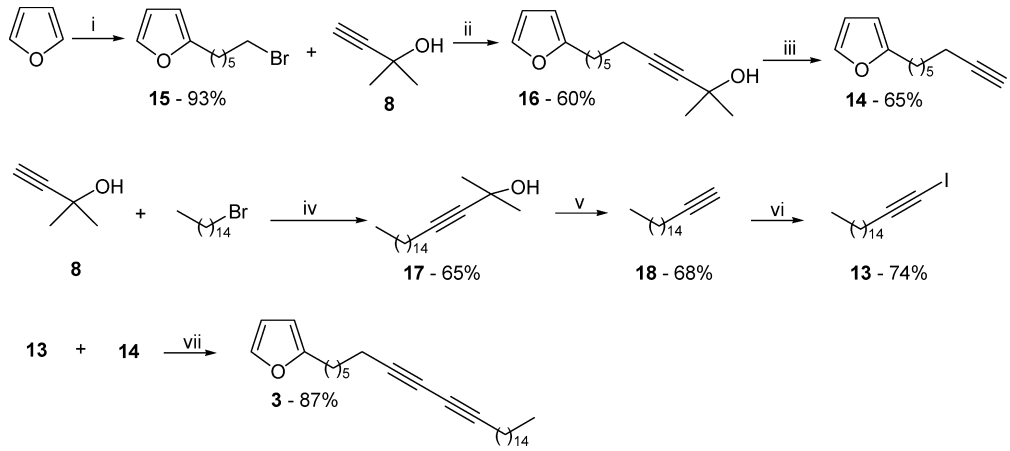
Following the successful sp−sp connection for the retrosynthesis described in Scheme 1, the preparation of polyacetylenic **3** was performed following a parallel route (Scheme 5).

The nucleophilic fragment **14** was the first targeted precursor, and its synthesis was achieved starting with deprotonation of the commercial furan with *n*-BuLi in THF, generating the 2-lithium furan intermediate. The alkylation of this anion using 1,6-dibromohexane gave the bromide[12] **15** in 93% yield. Deprotonation of both terminal alkyne and hydroxy groups of **8**, using 2 equiv of *n*-BuLi, at −78 °C, followed by treatment of the dianion with bromide **15** using HMPA/THF[13] (3 mL/mmol; 1:2) as solvent, led to the expected condensation product **16** in acceptable yield (50%). Deprotection of the triple bond by base treatment (NaOH/toluene, reflux)[14] gave fragment **14** in a yield of 65% (Scheme 6).

Further, we synthesized fragment **13** (Scheme 6) by alkylation of the dilithium derivative prepared from the alcohol **8** with commercial 1-bromopentadecane,[13] yielding protected acetylene **17** (65%). Deprotection removed the acetylene protected group[14] selectively to generate the free acetylene **18** in 68% yield. The terminal alkyne produced was converted to the corresponding alkynyl iodide **13** by treatment with *n*-BuLi/iodine[15] in 74% yield. Finally, with subunits 1**3** and **14** in hand, Cadiot−Chodkiewicz cross-coupling was carried out using CuI and pyrrolidine[17] at room temperature, providing the target diyne **3** in 87% yield (Scheme 6).

In summary, the efficient total synthesis of the four natural polyacetylenes **1**−**4** has been achieved using highly convergent routes. These involved copper-catalyzed cross-coupling reactions to afford sp−sp centers as the key step. It is noteworthy that the polyacetylene counterparts were, in all cases, highly unsaturated 1,3-diyne moieties that were stable and could be isolated, purified, and identified. In addition, the spectroscopic data of compounds **1**−**4** are in agreement with the data reported by Phonkerd and coworkers.[8] Specifically, in order to study the structure−activity relationships of these natural polyacetylenes and to evaluate changes to the length of the carbon chains of these compounds, the syntheses of analogues of these diynes are currently underway in our laboratories.

Scheme 6. Synthesis of Polyacetylene **3**[a]



[a] Reagents and conditions: (i) THF, 1 equiv of *n*-BuLi at −20 °C, 4 h, 1,6-dibromohexane at −20 °C to rt, overnight; (ii) HMPA/THF (3 mL/mmol; 1:2), 2 equiv of *n*-BuLi (−78 °C), 18 h, rt; (iii) NaOH, toluene, reflux, 12 h; (iv) HMPA/THF (3 mL/mmol; 1:2), 2 equiv of *n*-BuLi (−78 °C), 18 h, rt; (v) NaOH, toluene, reflux, 12 h; (vi) THF, 1 equiv of *n*-BuLi at −20 °C, 1 h, THF/I_2 at −40 °C to rt, overnight; (vii) pyrrolidine, CuI, overnight, rt.

Experimental Section

General Experimental Procedures. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz. Spectra were recorded in $CDCl_3$ solutions. The chemical shifts are reported (ppm) using the δ 7.26 signal of $CDCl_3$ (^{1}H NMR) and the δ 77.23 signal of $CDCl_3$ (^{13}C NMR) as internal standards. EIMS were obtained on a Shimadzu GCMS-QP2010Plus spectrometer. High-resolution mass spectra were recorded on a double-focusing magnetic sector mass spectrometer using EI at 70 eV. IR spectra were obtained from a Shimadzu IR-Prestige-21 spectrometer. Column chromatography was performed using silica gel (230−400 mesh). Thin-layer chromatography (TLC) was performed using silica gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor or acidic vanillin. The following solvents were dried and purified by distillation from the reagents indicated: tetrahydrofuran from sodium with a benzophenone ketyl indicator. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen or argon. Unless otherwise mentioned, all chemicals and materials were used as received from commercial suppliers without further purification.

General Procedure for the Preparation of the 2-(*n*-Bromo-*n*-alkyl)furan Derivatives.[12] Dry THF (40 mL) was cooled to −20 °C in a 100 mL two-neck flask, and *n*-butyllithium (10 mL of 2.4 M solution in hexane, 24 mmol) was added with stirring under Ar. Freshly distilled furan (1.7 mL, 24 mmol) was added, dropwise, into the *n*-butyllithium solution. The mixture was stirred for 4 h at −20 °C, then the appropriate alkyl bromide (20 mmol) was added dropwise with vigorous stirring, and the mixture was left overnight at room temperature. The reaction was quenched by the addition of saturated NH_4Cl aqueous solution (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was separated and dried over $MgSO_4$, and the solvent removed under reduced pressure using a rotary evaporator. The residue was purified by column chromatography on silica gel using *n*-hexane as eluent to give 2-(*n*-bromo-*n*-alkyl)furan. Selected spectra and analytical data for 2-(4-bromobutyl)furan (**7a**): This compound (3.555 g) was prepared in 88% yield as yellow oil, from 1,4-dibromobutane: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33−7.27 (m, 1H), 6.32−6.24 (m, 1H), 6.03−5.95 (m, 1H), 3.42 (t, J = 6.5 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 2.07−1.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 140.91, 110.0, 105.0, 33.4, 32.0, 27.0, 26.5; MS (EI, 70 eV) *m*/*z* (relative intensity) 201 (23), 122 (17), 94 (26), 80 (100), 53 (34); HRMS *m*/*z* calcd for $C_8H_{11}BrO$ 201.9993, found 201.9998.

2-(6-Bromohexyl)furan (15). This compound (4.278 g) was prepared in 93% yield from 1,6-dibromohexane: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34−7.25 (m, 1H), 6.33−6.20 (m, 1H), 6.02−5.92 (m, 1H), 3.43−3.33 (m, 2H), 2.68−2.54 (m, 2H), 1.96−1.76 (m, 2H), 1.74−1.53 (m, 2H), 1.52−1.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 140.5, 109.9, 104.6, 33.8, 32.5, 28.1, 27.8, 27.7, 27.2; MS (EI, 70 eV) *m*/*z* (relative intensity) 229 (14), 150 (14), 122 (8), 94 (14), 80 (100), 52 (10); HRMS *m*/*z* calcd for $C_{10}H_{15}BrO$ 230.0306, found 230.0309.

2-(11-Bromoundecyl)furan (7b). In a reaction similar to that of **7a**, 1,11-dibromoundecane yielded 5.760 g (96%) of **7b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.27 (m, 1H), 6.29−6.25 (m, 1H), 5.98−5.94 (m, 1H), 3.40 (t, J = 6.8 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 1.85 (quint, J = 7.1 Hz, 2H), 1.62 (quint, J = 7.1 Hz, 2H), 1.37−1.15 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 140.4, 109.9, 104.4, 33.8, 32.7, 29.4, 29.3, 29.3, 29.2, 29.0, 28.6, 28.1, 27.9, 27.9; MS (EI, 70 eV) *m*/*z* (relative intensity) 299 (26), 218 (17), 136 (14), 122 (32), 94 (87), 80 (100), 52 (22); HRMS *m*/*z* calcd for $C_{15}H_{25}BrO$ 300.1088, found 300.1091.

General Procedure for the Copper-Catalyzed Coupling Reaction of Alkynes with Iodide Derivative.[17] To a two-neck round-bottom flask, under Ar, were added the appropriate iodide (1 mmol), the pyrrolidine (3 mL), and the alkyne (1.2 mmol) at room temperature. The temperature was decreased to 0 °C, and CuI (0.038 g, 0.2 mmol) was added. The reaction mixture was allowed to stir at room temperature overnight. After this time, the solution was diluted by satured NH_4OH/NH_4Cl aqueous solution (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was separated and dried over $MgSO_4$, and the solvent was removed under reduced pressure using a rotary evaporator. The residue was purified by column chromatography on silica gel using EtOAc/*n*-hexane (40:60) as eluent. Selected spectra and analytical data for **21-furan-2-ylhenicosa-14,16-diyn-1-ol (4)**: yield 0.240 g (65%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30−7.27 (m, 1H), 6.30−6.25 (m, 1H), 6.01−5.96 (m, 1H), 3.66−3.58 (m, 2H), 2.63 (t, J = 7.3 Hz, 2H), 2.30−2.20 (m, 4H), 1.77−1.70 (m, 2H), 1.61−1.46 (m, 10H), 1.41−1.22 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 140.7, 110.0, 104.8, 77.7, 68.0, 65.5, 65.1, 63.0, 32.8, 29.5, 29.5, 29.5, 29.4, 29.4, 29.4, 29.0, 28.8, 28.3, 27.7, 27.3, 27.1, 25.7, 19.1, 18.9; MS (EI, 70 eV) *m*/*z* (relative intensity) 366 (27), 350 (4), 224 (14), 182 (67), 157 (100), 128 (94), 80 (80), 54 (46); IR (KBr) (ν_{max}, cm^{-1}) 3420, 3124, 2922, 2846, 2183, 2140, 1597, 1506, 1467, 1415, 1176, 1141, 1058, 1035, 1003, 883; HRMS *m*/*z* calcd for $C_{25}H_{38}O_2$ 370.2872, found 370.2877.

2-Pentacosa-7,9-diynylfuran (3): yield 0.356 g (89%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.27 (m, 1H), 6.29−6.25 (m, 1H), 5.99−5.95 (m, 1H), 2.61 (t, J = 7.4 Hz, 2H), 2.24 (t, J = 6.7 Hz, 4H), 1.68−1.59 (m, 2H), 1.58−1.47 (m, 4H), 1.46−1.31 (m, 6H), 1.30−1.21 (m, 22H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 140.6, 109.9, 104.5, 77.5, 77.2, 65.3, 65.2, 31.9, 29.6, 29.6, 29.6, 29.6, 29.6, 29.4, 29.3, 29.0, 28.8, 28.5, 28.4, 28.3, 28.1, 27.8, 27.8, 22.6, 19.1, 19.1, 14.0; MS (EI, 70 eV) *m*/*z* (relative intensity) 406 (21), 210 (30), 130 (40), 104 (36), 90 (53), 80 (100), 54 (25); IR (KBr) (ν_{max}, cm^{-1}) 3128, 2911, 2843, 2180, 2141, 1599, 1506, 1469, 1418, 1175, 1138, 1069, 1005, 883; *anal.* (%) calc for $C_{29}H_{46}O$, C 84.81, H 11.21, found C 84.61, H 10.87.

19-Furan-2-ylnonadeca-5,7-diyn-ol (11): yield 0.256 g (75%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33−7.27 (m, 1H), 6.20−6.24 (m, 1H),

5.99−5.92 (m, 1H), 3.67 (t, $J = 6.2$ Hz, 2H), 2.61 (t, $J = 7.4$ Hz, 2H), 2.39−2.16 (m, 5H), 1.75−1.54 (m, 6H), 1.39−1.19 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 140.5, 109.9, 104.4, 77.6, 76.8, 65.6, 65.1, 62.1, 31.6, 29.4, 29.4, 29.3, 29.2, 29.0, 28.9, 28.7, 28.2, 27.9, 27.8, 24.5, 19.0, 18.9; MS (EI, 70 eV) *m/z* (relative intensity) 342 (1), 310 (5), 156 (22), 130 (29), 94 (53), 80 (100), 66 (19); *anal*. (%) calc for $C_{23}H_{34}O_2$, C 80.65, H 10.01, found C 80.44, H 9.78.

Synthesis of 19-Furan-2-ylnonadeca-5,7-diynoic Acid (1).[18] Pyridinium dichromate (PDC) (0.66 g, 1.75 mmol) was added to the solution of alcohol **11** (0.17 g, 0.5 mmol) in DMF (1 mL). The mixture was stirred for 4 h and poured into H_2O. The product was extracted with Et_2O (3×). The organic extract was washed successively with H_2O and dilute HCl solution and dried over $MgSO_4$, and the solvent removed under reduced pressure using a rotary evaporator. The residue was purified by column chromatography on silica gel using EtOAc/*n*-hexane (40:60) as eluent: yield 0.872 g (49%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.27 (m, 1H), 6.30−6.23 (m, 1H), 5.99−5.93 (m, 1H), 2.60 (t, $J = 7.5$ Hz, 2H), 2.49 (t, $J = 7.4$ Hz, 2H), 2.35 (t, $J = 6.9$ Hz, 2H), 2.24 (t, $J = 7.0$ Hz, 2H), 1.84 (quint, $J = 7.1$ Hz, 2H), 1.62 (quint, $J = 7.1$ Hz, 2H), 1.51 (quint, $J = 7.3$ Hz, 2H), 1.35−1.23 (m, 14H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 179.1, 156.5, 140.5, 109.9, 104.4, 78.0, 75.6, 66.3, 64.9, 32.5, 29.5, 29.4, 29.4, 29.3, 29.1, 29.0, 28.7, 28.2, 27.9, 27.9, 23.1, 19.1, 18.5; IR (KBr) (ν_{max}, cm^{-1}) 3446−2370, 2918, 2846, 2150, 1690, 1598, 1508, 1463, 1443, 1412, 1205, 1180, 1009, 885; *anal*. (%) calc for $C_{23}H_{32}O_3$, C 77.49, H 9.05, found C 77.82, H 8.83.

Synthesis of 19-Furan-2-ylnonadeca-5,7-diynoic Acid Methyl Ester (2).[19] To a solution of **1** (0,178 g, 0.5 mmol) in absolute MeOH (1 mL) was added 0.03 mL of $SOCl_2$. The mixture was stirred at room temperature for 15 h, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using EtOAc/*n*-hexane (20:80) as eluent: yield 0.121 g (65%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30−7.27 (m, 1H), 6.29−6.25 (m, 1H), 5.98−5.94 (m, 1H), 3.67 (s, 3H), 2.60 (t, $J = 7.5$ Hz, 2H), 2.44 (t, $J = 7.3$ Hz, 2H), 2.33 (t, $J = 6.8$ Hz, 2H), 2.23 (t, $J = 7.0$ Hz, 2H), 1.84 (quint, $J = 7.0$ Hz, 2H), 1.62 (quint, $J = 7.3$ Hz, 2H), 1.50 (quint, $J = 7.3$ Hz, 2H), 1.34−1.22 (m, 14H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.3, 156.5, 140.5, 109.9, 104.4, 77.9, 75.8, 66.2, 65.0, 51.5, 32.6, 29.4, 29.4, 29.3, 29.2, 29.1, 29.0, 28.7, 28.2, 27.9, 27.9, 23.4, 19.1, 18.6; IR (neat) (ν_{max}, cm^{-1}) 3462, 3115, 2924, 2852, 2256, 2164, 1597, 1506, 1462, 1435, 1159, 1148, 1074, 1074, 1107, 885; *anal*. (%) calc for $C_{24}H_{34}O_3$, C 77.80, H 9.25, found C 77.52, H 8.79.

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Supporting Information Available: Experimental procedures, additional experimental details for the preparation of all compounds, and ^{1}H and ^{13}C NMR spectra for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Senn, M.; Gunzenhauser, S.; Brun, R.; Séquin, U. *J. Nat. Prod.* **2007**, *70*, 1565. (b) Tian, Y.; Wei, X.; Xu, H. *J. Nat. Prod.* **2006**, *69*, 1241. (c) Parish, C. A.; Huber, J.; Baxter, J.; Gonzalez, A.; Collado, J.; Platas, G.; Diez, M. T.; Vicente, F.; Dorso, K.; Abruzzo, G.; Wilson, K. *J. Nat. Prod.* **2004**, *67*, 1900. (d) Lerch, M. L.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **2003**, *66*, 667. (e) Faulkner, D. *J. Nat. Prod. Rep.* **1995**, *12*, 223.

(2) Young, K.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K.; Zhang, C.; Kodali, S.; Galgoci, A.; Painter, R.; Brown-Driver, V.; Yamamoto, R.; Silver, L. L.; Zheng, Y.; Ventura, J. I.; Sigmund, J.; Ha, S.; Basilio, A.; Vicente, F.; Tormo, J. R.; Pelaez, F.; Youngman, P.; Cully, D.; Barrett, J. F.; Schmatz, D.; Singh, S. B.; Wang, *J. Antimicrob. Agents* **2006**, *50*, 519.

(3) (a) Kobaisy, M.; Abramowski, Z.; Lermer, L.; Saxena, G.; Hancock, R. E. W.; Towers, G. H. N.; Doxsee, D.; Stokes, R. W. *J. Nat. Prod.* **1997**, *60*, 1210. (b) Fusetani, N.; Toyoda, T.; Asai, N.; Matsunaga, S.; Maruyama, T. *J. Nat. Prod.* **1996**, *59*, 796.

(4) Rashid, M. A.; Gustafson, K. R.; Cardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **2001**, *15*, 21.

(5) Arnason, J. T.; Philogene, B. J. R.; Berg, C.; MacEachern, A.; Kaminski, J.; Leitch, L. C.; Morand, P.; Lam, J. *Phytochemistry* **1986**, *25*, 1609.

(6) Ito, A.; Cui, B.; Chavez, D.; Chai, H.-B.; Shin, Y. G.; Kawanishi, K.; Kardono, L. B. S.; Riswan, S.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 246.

(7) (a) Luu, T.; Elliott, E.; Slepkov, A. D.; Eisler, S.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *Org. Lett.* **2005**, *7*, 51. (b) Eisler, S.; Slepkov, A. D.; Elliot, E.; Luu, T.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2005**, *127*, 2666. (c) Umeda, R.; Morinaka, T.; Sonoda, M.; Tobe, Y. *J. Org. Chem.* **2005**, *70*, 6133. (d) Marsden, J. A.; Haley, M. M. *J. Org. Chem.* **2005**, *70*, 10213.

(8) Kanokmedhakul, S.; Kanokmedhakul, K.; Kanikeaw, I.; Phonkerd, N. *J. Nat. Prod.* **2006**, *69*, 68.

(9) (a) Stein, A. L.; Alves, D.; da Rocha, J. T.; Nogueira, C. W.; Zeni, G. *Org. Lett.* **2008**, *10*, 4983. (b) Alves, D.; Luchese, C.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2007**, *18*, 6726. (c) Prediger, P.; Moro, A. V.; Nogueira, C. W.; Savegnago, L.; Menezes, P. H.; Rocha, J. B. T.; Zeni, G. *J. Org. Chem.* **2006**, *71*, 3786. (d) Barros, O. S. D.; Nogueira, C. W.; Stangherlin, E. C.; Menezes, P. H.; Zeni, G. *J. Org. Chem.* **2006**, *71*, 1552. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (f) Oliveira, J. M.; Zeni, G.; Malvestiti, I.; Menezes, P. H. *Tetrahedron Lett.* **2006**, *47*, 8183. (g) Alves, D.; Nogueira, C. W.; Zeni, G. *Tetrahedron Lett.* **2005**, *46*, 8761. (h) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (i) Zeni, G.; Panatieri, R. B.; Lissner, E.; Menezes, P. H.; Braga, A. L.; Stefani, H. A. *Org. Lett.* **2001**, *6*, 819.

(10) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874.

(11) Zeni, G.; Lüdtke, D. S.; Nogueira, C. W.; Panatieri, R. B.; Braga, A. L.; Silveira, C. C.; Stefani, H. A.; Rocha, J. B. T. *Tetrahedron Lett.* **2001**, *42*, 8927.

(12) Lissi, A. E.; Encinas, V. M.; Castañeda, F.; Olea, A. F. *J. Phys. Chem.* **1980**, *84*, 251.

(13) Cossy, J.; Pete, J. P. *Tetrahedron Lett.* **1986**, *27*, 573.

(14) Neenan, T. X.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 2489.

(15) Coleman, B. E.; Cwynar, V.; Hart, D. J.; Havas, F.; Mohan, J. M.; Patterson, S.; Ridenour, S.; Schmidt, M.; Smith, E.; Wells, A. J. *Synlett* **2004**, 1339.

(16) Since the use of Cadiot−Chodkiewicz classical conditions led to a lower yield of cross-coupling product, we carried out the reaction under Alami's improved conditions.[17]

(17) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.

(18) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399.

(19) Kazemi, F.; Kiasat, A. R.; Mombaini, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2004**, *179*, 1187.

(20) Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333.

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