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Total Synthesis of (*S*)-(−)-(*E*)-15,16-Dihydrominquartynoic Acid: A Highly Potent Anticancer Agent

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The conjugated entriyne natural product, (*S*)-(*E*)-15,16-dihydrominquartynoic acid (**1**), is synthesized in five linear steps and 30% overall yield from the known aldehyde **11**. The key step is a one-pot in situ desilylation/Cadiot−Chodkiewicz coupling reaction affording the entriyne unit. The bromoalkyne **6** with an *ω*-carboxylic acid group was found to undergo a copper-catalyzed cross-coupling reaction producing the desired diyne intermediate **10**, while the corresponding *ω*-ester bromoalkyne **14** failed to couple with triethylsilylacetylene under a variety of conditions.

Introduction

Three polyacetylenic natural products (**1**−**3**) were recently isolated from a chloroform extract of *Ochanostachys amentacea*, a tree with edible fruits indigenous to Western Malaysia and parts of Indonesia, in amounts of 1, 20, and 8 mg, respectively, from 750 g of dry twigs.[1] While all three compounds showed anticancer activities, (*E*)-15,16-dihydrominquartynoic acid (**1**) showed the most potent activity against the human hormone-dependent prostate and ovarian cancer cell lines.[1] (*E*)-15,16-dihydrominquartynoic acid (**1**) is similar to (−)-minquartynoic acid (**2**)[2,3] and 18-hydroxyminquartynoic acid (**3**), in that it contains a chiral secondary alcohol and a carboxylic acid functionality, Figure 1, but differs in that it contains a conjugated entriyne unit, rather than a tetracetylene unit.

In response to recent interest in synthetic efforts embarked on natural acetylenic compounds,[4−10] we recently reported the total synthesis of (*S*)-minquartynoic acid **2** and (*S*)-18-hydroxyminquartynoic acid **3**, Scheme 1.[11,12] The main challenge in the total synthesis of these polyyne natural products is the highly reactive nature of the intermediate terminal diynes and triynes.[11,13,14]

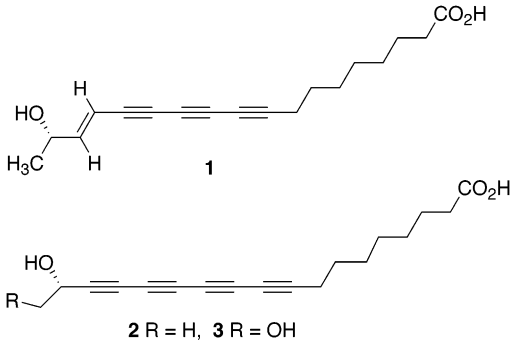
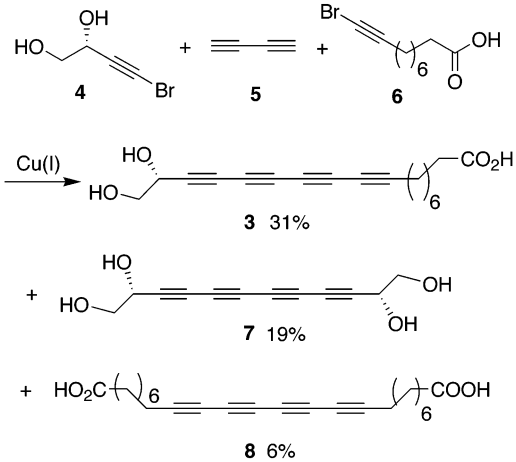


FIGURE 1. Cytotoxic polyacetylenes from *O. amentacea*: (*E*)-15,16-dihydrominquartynoic acid (**1**), (*S*)-minquartynoic acid (**2**), and (*S*)-18-hydroxyminquartynoic acid (**3**).

SCHEME 1



Our approach was to avoid the highly reactive terminal diyne or triyne intermediates by using a three-component one-pot Cadiot−Chodkiewicz cross-coupling reaction,[15] Scheme 1.[11] By varying the order and time of reagent

(1) Ito, A.; Cui, B. L.; 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*, 246−248.
(2) Marles, R. J.; Farnsworth, N. R.; Neill, D. A. *J. Nat. Prod.* **1989**, *52*, 261−266.
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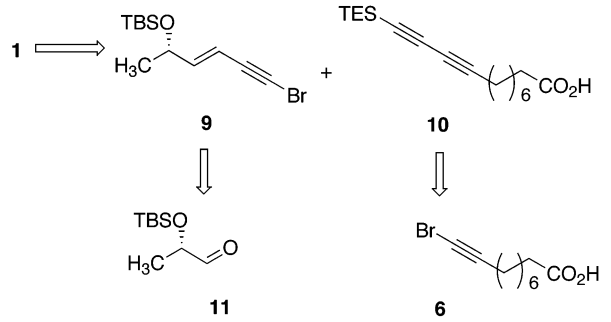
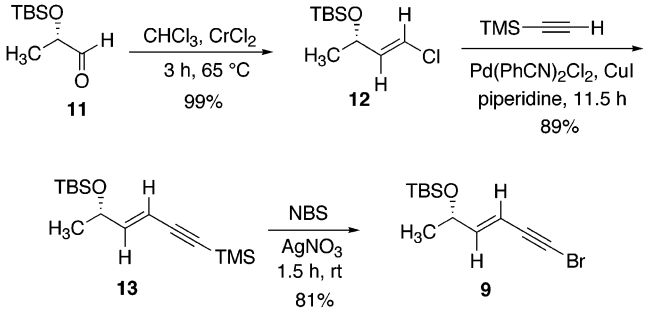
SCHEME 2



SCHEME 3



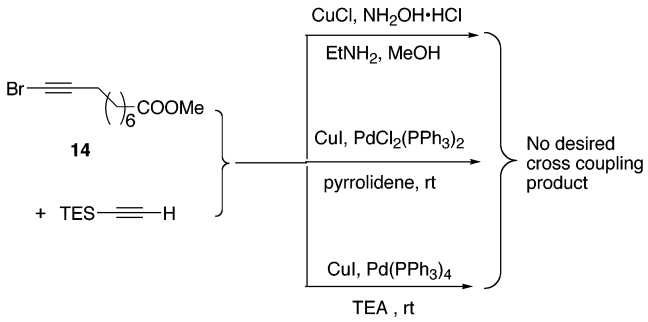
addition, we were able to obtain a reasonable yield for otherwise a statistical coupling reaction. Although we have successfully synthesized both compounds **2** and **3**, the statistical nature of the final coupling step was unsatisfactory. Here we report the total synthesis of the third member in this group of natural products, (*E*)-15,16-dihydrominquartynoic acid (**1**), using a convergent and nonstatistical approach. We also detail the conditions to synthesize the required reactive diyne intermediate involved in the total synthesis.

Results and Discussion

A convergent plan for the synthesis of (*E*)-15,16-dihydrominquartynoic acid (**1**) calls for the retrosynthetic disconnection depicted in Scheme 2. To obtain target compound **1** most efficiently one should consider a cross-coupling between enyne bromide **9** and diyne **10** to divide the conjugated four multiple bonds into two halves. Enyne bromide **9** and the diyne **10** in turn should be available from the known aldehyde **11**[16] and our recently prepared bromoalkyne **6**,[11] respectively.

The preparation of enyne bromide **9** is depicted in Scheme 3. The known aldehyde **11** was prepared from (*S*)-methyl lactate in two steps,[16] which was then treated with a suspension of $CrCl_2$ in $CHCl_3$ according to the procedure of Takai to give a high yield and high diastereoselectivity (*E*/*Z* ratio = 95:5) of vinyl chloride **12**.[17] The cross-coupling of **12** with trimethylsilylacetylene proceeded smoothly under the conditions ($Pd(PhCN)_2Cl_2$, CuI, piperidine) reported by Alami and Linstrumelle.[18,19] In situ desilylation−bromination of enyne **13** to bromo alkyne **9** was accomplished under mild conditions.[20]

SCHEME 4



With bromoalkyne **9** in hand, our attention turned to the right-hand half of the target, which contains an unsymmetrically substituted 1,3-diyne. Symmetrically substituted 1,3-diynes can be prepared by oxidative coupling of terminal alkynes.[21] Unsymmetrically substituted 1,3-diynes should be obtained by cross-coupling reactions using either Cadiot−Chodkiewicz conditions or modified Sonogashira conditions.[22] A recent report uses an alkylidene rearrangement reaction to prepare aryl- and alkyldiynes.[23] The key step involves the treatment of the precursor, vinyl dibromide, with butyllithium, a strong base that does not tolerate carbonyl functional groups. In our case, the desired 1,3-diyne is unsymmetrical and carries a carboxylate group at one end. Therefore, the metal-catalyzed cross-coupling reaction should be the most direct and efficient methodology in the preparation of the diyne **10**.

Our first attempt for the preparation of the desired 1,3-diyne was a standard Cadiot−Chodkiewicz coupling reaction (CuCl, $HONH_2$·HCl, $EtNH_2$, MeOH)[24] using the bromoalkyne **14**[11] and triethylsilylacetylene, Scheme 4. No desired coupling product was obtained. We then tried the modified procedure reported by Alami using a palladium cocatalyst (CuI and $PdCl_2(Ph_3P)_2$) and pyrrolidine as the solvent[25] and also Sonogashira coupling conditions (CuI and $Pd(Ph_3P)_4$) with Et_3N as the solvent.[18] The latter procedure has been used to prepare 1-phenyl-6-trimethylsilyl-1,3,5-hexatriyne in 29% yield.[26]

Unfortunately, none of these methods afforded any desired coupling product. The major mass recovery was the corresponding debrominated ester. We suspected that triethylsilylacetylene was unreactive compared to normal terminal acetylenes since Alami has reported successful cross-coupling of several terminal alkynes to 1-bromo-1-hexyne.[25]

(13) Haley, M. M.; Bell, M. L.; English, J. J.; Johnson, C. A.; Weakley, T. J. R. *J. Am. Chem. Soc.* **1997**, *119*, 2956−2957.
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(15) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597−647.
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(23) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339−1347.
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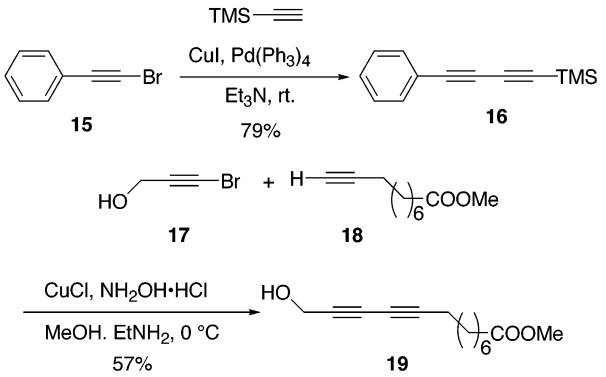
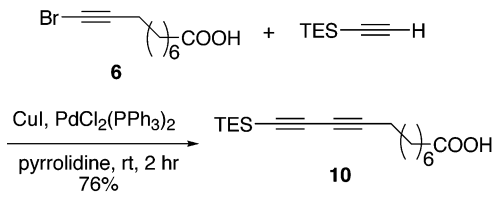
(25) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763−2766.
(26) Bruce, M. I.; Hall, B. C.; Kelly, B. D.; Low, P. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1999**, 3719−3728.

SCHEME 5



SCHEME 6



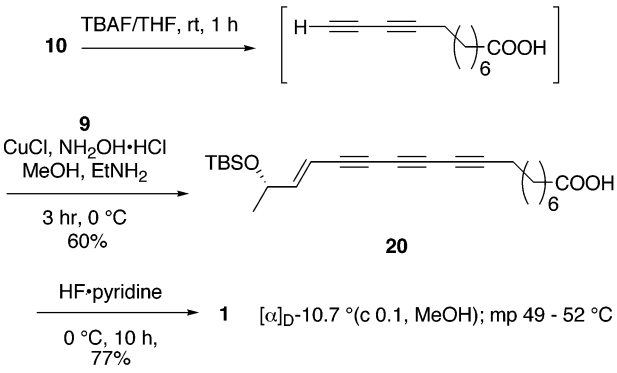
However, when 1-bromo-2-phenylacetylene **15** was treated with trimethylsilylacetylene under Sonogashira coupling conditions, a 79% yield of 1-trimethylsilyl-4-phenyl-1,3-butadiyne **16** was isolated. Furthermore, when 3-bromopropargyl alcohol **17** was allowed to react with terminal acetylene **18** under the standard Cadiot−Chodkiewicz coupling conditions (CuCl, $HONH_2$·HCl, $EtNH_2$, MeOH),[24] a 57% yield of diyne **19** was obtained, Scheme 5.

These results indicate that the cross-coupling reaction is very sensitive to substrate structures. Both the phenyl group in **15** and the hydroxymethyl group in **17** enhance the reactivity of the corresponding bromoalkyne toward the coupling reaction. Recently, we have observed a rate increase in the Cadiot−Chodkiewicz coupling reaction when the substrate bromoalkyne was oxygen-substituted at the propargylic position.[12] The rate increase was attributed to a better coordination facilitated by the propargylic oxygen substituent. Our current observation is similar to the reported effects. It is reasonable to suggest that the improved reactivity observed with bromoalkynes **15** and **17** is also due to facilitated coordination to the palladium or copper catalyst, respectively.

On the basis of the results shown in Schemes 4 and 5, modification of the reaction conditions did not lead to successful cross-coupling reactions. Changes in the bromoalkyne structure did, however, give positive results. A temporarily installed propargylic substituent in **14** may enhance its reactivity toward the cross-coupling reaction. However, it would be troublesome to remove the substituent at a latter stage. A seemingly unrelated simple modification of **14** was carried out, and the methyl ester was hydrolyzed to the corresponding acid **6**. Under the conditions of Alami (CuI and $PdCl_2(Ph_3P)_2$ with pyrrolidine as the solvent),[25] the desired coupling product **10** was obtained in 76% yield.

The exact mechanism for the beneficial effect of the carboxylate group in the cross-coupling reaction is not clear at the present time. It is possible that the carboxylate group facilitates the coordination of the palladium catalyst by the triple bond through intramolecular bidentate coordination, which in turn allows the triethylsilylacetylene to coordinate on the palladium catalyst and the coupling to occur. Regardless of the mechanism, we were pleased to obtain the protected terminal diyne **10**. With diyne **10** in hand, the next target reaction was the cross-coupling between bromoalkyne **9** and diyne **10**. To avoid the isolation of the terminal diyne, we decided to follow a one-pot desilylation−coupling procedure.

SCHEME 7



One-pot desilylation−oxidative coupling of trialkylsilyl-protected terminal alkynes have been reported. Haley et al. reported a one-pot desilylation−dimerization reaction of alkynyltrimethylsilane in the presence of K_2CO_3 and $Cu(OAc)_2$.[27] Fallis and co-workers reported an in situ desilylation−oxidative dimerization of (trialkylsilyl)-acetylenes using *n*-BuN_4F and $Cu(OAc)_2$.[14] The corresponding protocol to prepare unsymmetrically substituted 1,3,5-polyynes appears to be unknown. However, organometallic compounds with polyacetylenic bridges have been prepared using similar procedures.[26,28] In the preparation of organorhenium compounds with a $(\equiv)_n$-*p*-C_6H_4Me ($n = 3, 4$) ligand, Gladysz and co-workers have reported a sequence involving desilylation with *n*-BuN_4F followed by a Cadiot−Chodkiewicz coupling reaction. After a few trials with different proportions of reagents and different solvents, we were able to obtain the desired cross-coupling product **20** in 60% yield by treatment of **10** with 1 equiv of *n*-BuN_4F in THF for 1 h followed by the addition of **9**, CuCl, $HONH_2$·HCl, $EtNH_2$, and MeOH and stirring at 0 °C for 3 h. The final step is the removal of the *tert*-butyldimethylsilyl ether protecting group using HF−pyridine complex to yield (*E*)-15,16-dihydrominquartynoic acid (**1**) in 77% yield. The spectroscopic data recorded for the synthetic sample are consistent with that reported for the natural product.

Summary

A potent anticancer polyacetylenic natural product, 15,16-dihydrominquartynoic acid **1**, has been synthesized in five linear steps and 30% overall yield from the known aldehyde **11**. Various reaction conditions of cross-coupling were studied in the preparation of the terminal trialkylsilyl-protected 1,3-diyne **10**, and a seemingly unrelated

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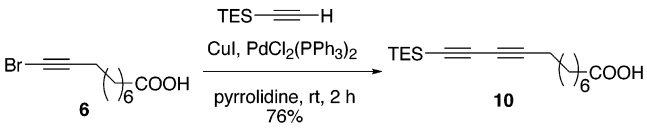
change from an ω-ester function to an ω-carboxylic acid group led to the successful coupling. Although the exact mechanism is unclear at the present time, it is possible that the ω-carboxylate group facilitates the coordination of the triple bond to the palladium catalyst by forming an intramolecular bidentate ligand. Since compound **1** was isolated in only 1 mg from 750 g of dry plants, the total synthesis of **1** provides easy access for further biological testing. Studies along these lines are currently underway in our laboratories.

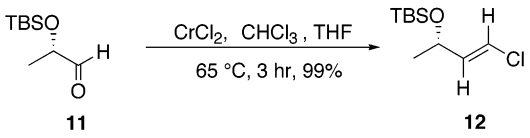
Experimental Section

Preparation of 12-(Triethylsilyl)-dodeca-9,11-diynoic Acid (10).



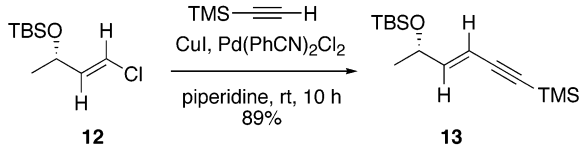
To a solution of triethylsilylacetylene (0.15 mL, 0.86 mmol) in 5 mL of pyrrolidine were added $PdCl_2(PPh_3)_2$ (0.02 mmol, 15 mg), CuI (0.04 mmol, 7.5 mg), and bromoalkyne **6** (0.86 mmol, 100 mg). The reaction was stirred at room temperature, and the progress was monitored by TLC. When the starting material was consumed, the reaction mixture was cooled to 0 °C and diluted with 5 mL of saturated NH_4Cl. It was extracted with 10 mL of ether, and the organic layer was separated. The aqueous layer was acidified with HCl and extracted twice with ether. The combined organic layers were washed with dilute HCl and brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the crude mixture was purified using silica gel chromatography. An oil (171 mg, 76%) was obtained: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.5 (4H, overlap), 1.8−1.1 (10H, m), 1.0 (9H, t, J = 7 Hz), 0.7 (16H, q, J = 7 Hz); ^{13}C (NMR 50 MHz, $CDCl_3$) 180.5, 89.8, 81.4, 79.7, 66.1, 66.1, 34.4, 29.3, 29.1, 29.0, 28.4, 25.0, 7.8, 4.7; IR (BEAT) 3300, 2932, 2223, 2104, 1706, 1458, 1236, 907; MS calcd for $C_{18}H_{30}O_2Si$ 306.2, found m/z 305.2 (M − 1, 100%).

Preparation of Vinyl Chloride 12.



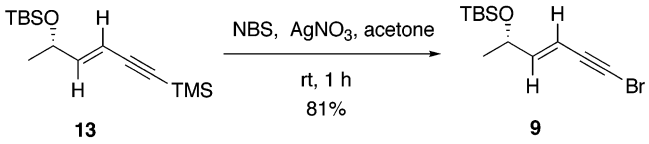
To a suspension of 1.2 g (9.6 mmol) of anhydrous $CrCl_2$ in 16 mL of THF was added a solution of 0.3 mL (3.2 mmol) of chloroform and aldehyde **11** (292 mg, 1.6 mmol) in 8 mL of THF over a period 15 min. The reaction mixture was heated to 65 °C with stirring. The reaction progress was monitored with TLC analysis. When the starting material was consumed (∼3 h), the reaction mixture was poured into 40 mL of water, and the resulting mixture was extracted three times with 16 mL portions of ether. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvents were removed by rotary evaporation. The crude mixture was purified by silica gel chromatography. An oil (337 mg, 99%) was obtained: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.17 (1H, d, J = 17.1 Hz), 5.97 (1H, dd, J = 5.2 Hz, 13.2 Hz), 4.36 (1H, m), 1.26 (3H, d, J = 6 Hz), 0.92 (12H, s), 0.09 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 118.1, 68.1, 26.2, 24.7, 18.6, −4.37, −4.42; $[\alpha]_D$ −9.2° (c 0.1, CH_3COCH_3); IR (CH_2Cl_2) 2999, 2932, 1633, 1462, 1094, 910, 833.

Preparation of (5*S*)-(3*E*)-1-Trimethylsilyl-5-(*tert*-butyldimethylsilyloxy)-3-hexen-1-yne 13.



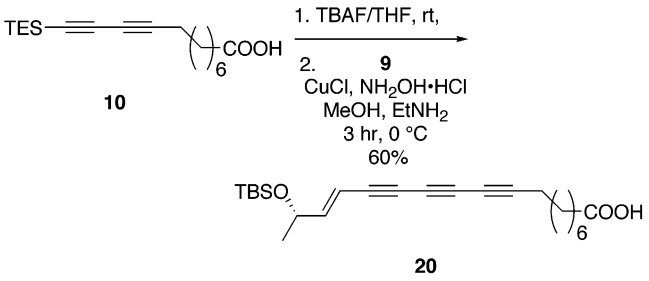
To a round-bottom flask charged with a stirring bar was added $Pb(PhCN)_2Cl_2$ (88 mg, 0.23 mmol), followed by the addition of 25 mL of piperidine. Vinyl chloride **12** (900 mg, 4.5 mmol), TMS−acetylene (880 mg, 9.0 mmol, 1.27 mL), and CuI (85 mg, 0.45 mmol) were then added in that order. The progress of the reaction was monitored by TLC. When all the starting material was consumed, the reaction was quenched with 50 mL of saturated NH_4Cl and stirred for 20 min. The aqueous layer was extracted three times with a 50 mL portion of ether. The combined organic layers were washed with 30 mL of 2 M HCl and also 30 mL of $NaHCO_3$ and then twice with water. The organic layer was dried over $MgSO_4$, and the solvents were removed by rotary evaporation. The crude mixture was purified by silica gel chromatography. An oil (1.02 g, 89%) was obtained: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.25 (1H, dd, J = 4.5, 15.9 Hz), 5.71 (1H, d, J = 15.9 Hz), 4.35 (1H, m), 1.20 (3H, d, J = 6.4 Hz), 0.93 (9H, s), 0.23 (9H, s), 0.09 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 149.2, 108.0, 104.1, 94.8, 68.7, 32.0, 26.2, 18.9, 0.4, −4.4; IR (neat) 3010, 2929, 2144, 1590, 1463, 1249, 909; MS calcd for $C_{15}H_{30}OSi_2$ 282.2, found m/z 282.2 (M, 100%).

Preparation of (5*S*)-(3*E*)-1-Bromo-5-(*tert*-butyldimethylsilyloxy)-3-hexen-1-yne 9.



A suspension was prepared with $AgNO_3$ (6 mg, 0.035 mmol), enyne **13** (100 mg, 0.35 mmol), and NBS (80 mg, 0.42 mmol) in 5 mL of acetone. The reaction was stirred at room temperature, and the progress of the reaction was monitored by TLC. When the starting material was consumed (∼1 h), the reaction was cooled to 0 °C, diluted with 20 mL of water, and stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted twice with 20 mL portions of ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude mixture was purified using silica gel chromatography after the solvent was removed. An oil (81.6 mg, 80%) was obtained: $[\alpha]_D$ −14.5° (c 0.1, CH_3COCH_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.37 (1H, dd, J = 4.5 Hz, 16 Hz), 5.68 (1H, d, J = 15.8 Hz), 4.40 (1H, m), 1.24 (3H, d, J = 4.7), 0.94 (9H, s) 0.10 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 149.7, 107.6, 78.9, 68.6, 49.5, 26.2 24.3, 18.2, −4.4; IR (neat) 3050, 2929, 2157, 1610, 1472, 1149, 909; MS calcd for $C_{12}H_{21}BrSi$ 288.1, found m/z 288.1 and 290.1

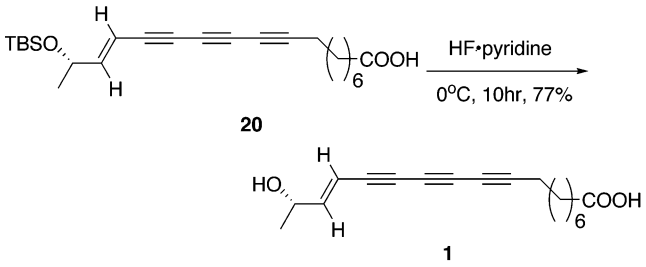
Preparation of the TBS Ether of 15,16-Dihydrominquartynoic Acid 20.



To a solution of diyne **10** (900 mg, 3 mmol) in 4 mL of THF was added 3.6 mL (3.6 mmol) of 1 M TBAF in THF, and the resulting solution was stirred for 1 h at room temperature.

After the disappearance of the starting material, 10 mL of MeOH and 10 mL of $EtNH_2$ were added to the reaction flask at 0 °C, followed by 10 mg (0.15 mmol) of CuCl and 11 mg (0.15 mmol) of $NH_2OH{\cdot}HCl$. Enyne **9** in 1 mL of THF was slowly added over a period of 30 min. The progress of the reaction was monitored by TLC. When the starting material was consumed, the reaction mixture was diluted with 25 mL of ether and quenched with 10 mL of saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was acidified with HCl and extracted twice with ether. The combined organic layers were washed with brine, and the solvents were removed by rotary evaporation. The crude mixture was purified with silica gel chromatography. An oil (721 mg, 60.1%) was obtained: $[\alpha]_D$ −13.9° (*c* 0.1, CH_3COCH_3); ^1H NMR (200 MHz, $CDCl_3$) δ 6.41 (1H, dd, J = 4.2 Hz, 15.7 Hz), 5.76 (1H, d, J = 15.9 Hz), 4.40 (1H, m), 2.4 (4H, m), 1.70−1.23 (15H, m), 0.93 (9H, s), 0.09 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 179.9, 153.0, 106.5, 82.6, 75.2, 74.8, 68.7, 67.1, 66.2, 60.1, 34.3, 29.3, 29.1, 29.0, 28.4, 26.2, 25.0, 24.2, 19.9, 18.6, −4.4; IR (BEAT) 3300, 3154 2929, 2215, 1707, 1463, 1148; MS calcd for $C_{24}H_{36}O_3Si$ 400.3, found *m*/*z* 399.3 (M − 1, 100%).

Preparation of (*E*)-15,16-Dihydrominquartynoic Acid 1.



To a solution of entriyne **20** (40 mg, 0.104 mmol) in 3 mL of THF was added 0.2 mL of HF·pyridine at 0 °C. The resulting mixture was allowed to warm to room temperature with stirring. The progress of the reaction was monitored by TLC. When the starting material was consumed, the reaction mixture was diluted with 15 mL of ether and slowly neutralized with saturated $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the crude mixture was purified by silica gel chromatography. An amorphous solid (23 mg, 77%) was obtained: $[\alpha]_D$ −10.7° (*c* 0.1, MeOH); mp 49−52 °C; UV (MeOH) λ_{max} 205, 212, 231, 243, 258, 273, 290, 309, 331 nm; ^1H NMR (200 MHz, $CDCl_3$) δ 6.45 (1H, dd, J = 6.3 Hz, 15.8 Hz), 5.80 (1H, d, J = 16.1 Hz), 4.43 (1H, m), 2.39 (4H, m), 1.80−1.00 (15H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 179.9, 151.8, 107.9, 82.9, 75.6, 74.1, 68.4, 67.4, 66.1, 59.1, 34.3, 29.2, 29.1, 29.0, 28.3, 25.0, 23.3, 19.9; IR (neat) 3599, 3300, 3055, 2985, 2411, 2307, 2214, 1709, 1550, 1423, 1265, 896; HRMS calcd for $C_{18}H_{22}O_3$ + Na 309.1467, found 309.1479.

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Supporting Information Available: General experimental procedures and ^{13}C NMR spectra for compounds **9**, **10**, **20**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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