Remarkable Reactivity Difference in Oxygen-Substituted versus Non-Oxygen-Substituted Bromoalkynes in Cu(I)-Catalyzed Cross-Coupling Reactions: Total Synthesis of (−)-S-18-Hydroxyminquartynoic Acid

Benjamin W. Gung* and Godwin Kumi

Department of Chemistry and Biochemistry, Miami University, Oxford, Ohio 45056

gungbw@muohio.edu

Received April 16, 2003

The conjugated tetraacetylenic natural product (S)-18-hydroxyminquartynoic acid (2) is synthesized in five linear steps and 17.7% overall yield from commercially available 1,2,5,6-O-disopropylidene mannitol. The key step is a one-pot three-component Cadiot–Chodkiewicz reaction affording the tetryne unit. The oxygen-substituted bromoalkyne 10 was found to react at a much faster rate than the non-oxygen-substituted bromoalkyne 6 in the key step. The undesired symmetric cross-coupling by 10 generates a symmetric tetryne intermediate, which undergoes a nucleophilic addition by 1 equiv of ethylamine. This side reaction is suppressed by controlling the order and rate of addition of each component and by reducing the amount of ethylamine.

Introduction

Naturally occurring polyacetylenes are an intriguing class of natural products.1–7 Along with (−)-minquartynoic acid (1) and (E)-15,16-dihydrominquartynoic acid (3), 18-hydroxyminquartynoic acid (2) was isolated from a chloroform extract of the twigs of Ochanostachys amantacea from southeast Asia.8 In recent in vitro tests, all three polyacetylenes show potent cytotoxicity against 10 different tumor cell lines.5 The structures of these polyacetylenes are fascinating. They are optically active, with each compound containing a conjugated polyyne, one or two hydroxy group(s), and a carboxylic acid function, Figure 1. Widespread interest has recently appeared in the synthetic studies of the natural acetylenic compounds.9–15

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

The main challenge in the total synthesis of these polyyne natural products is the highly reactive nature of the intermediate terminal diynes and triynes.16–18 Recently, we reported the first total synthesis of (−)-minquartynoic acid (1) using a three-component Cadiot–Chodkiewicz reaction,19 Scheme 1.18 The idea was to avoid the isolation of the reactive terminal diyne and triyne intermediates.


10.1021/jo0334990 CCC: $25.00 © 2003 American Chemical Society
Published on Web 06/28/2003
and to obtain the relatively stable internal tetrayne in an one-pot reaction. Such a three-component cross-coupling reaction involves two individual cross-coupling steps. Statistically only one-third of the desired asymmetric cross-coupling product (9) is expected and the other two-thirds of the reaction products (7 and 8) are the results of two symmetric cross-couplings. This statistical ratio is based on the assumption that the two bromoalkynes (4 and 6) involved have identical reactivities. Indeed all three expected products were isolated in our recent synthesis of (−)-minquartynoic acid, Scheme 1. However, when the same conditions were applied in the present study, none of the desired product was isolated. In this manuscript, we wish to report the observation of a remarkable difference in reactivities among the bromoalkynes (6, 10, and 14) in the Cu(I)-catalyzed cross-coupling reactions, which is at variance with the expectations based on statistics. We also report the conditions for a concise synthesis of (S)-18-hydroxyminquartynoic acid.

Results and Discussion

By adopting the same strategy as for the synthesis of (−)-minquartynoic acid (1), we had hoped that (−)-18-hydroxyminquartynoic acid (2) would be available from a three-component cross-coupling of butadiyne 5 and bromoalkynes 6 and 10, Scheme 2. The bromoalkyne 10 should be available from β-glyceraldehyde,20 and butadiyne 5 can be prepared in one step from commercially available 1,4-dichloro-2-butyne.21 Bromoalkyne 6 is obtained from commercially available azelaic acid monomethyl ester in four steps.18

Thus, starting from aldehyde 11,20 dibromodefin 12 was obtained quantitatively using a combination of Ph₃P and CBr₄ as shown in Scheme 3.22 The desired bromoalkyne 10 was obtained by the elimination of one molar HBr from 12 under previously reported conditions.23

With bromoalkyne 10 in hand, a Cadiot–Chodkiewicz coupling was attempted with butadiyne 5 and bromoalkyne 6. Disappointing results were obtained using the conditions for the synthesis of (−)-minquartynoic acid (1 mmol of each of the three reactants were dissolved in a 2 mL 1:1 mixture of methanol and 70% ethylamine aqueous solution with 5 mol % of NH₂OH·HCl and 5 mol % of CuCl, and the mixture was stirred at 0−25 °C for 3 h). Although TLC seemed to show three spots as expected from a statistical cross-coupling of the three components, the most consistent product after workup and chromatographic purification did not contain the fragment from carboxylic acid 6. Instead, the 1H NMR spectrum of the product shows four different methyl groups. Bromoalkyne 10 undergoes rapid cross-coupling with butadiyne followed by the addition of 1 equiv of ethylamine. The enamine product 13 was consistently obtained in good yield, and its structure was identified by a full battery of spectroscopic methods. There is apparently a large difference in the reactivity between bromoalkyne 10 and bromoalkyne 6.

[Reference citations omitted for brevity]
ethers are weaker Lewis bases than alkyl ethers. A because (1) it is a sterically bulky group and (2) silyl complex/alkyne cycloaddition reactions. For the change of reaction course in carbene-chromium chromium intermediate was proposed to be responsible similar effect of propargylic oxygen coordination to a group is a. However, very little symmetric cross-coupling of the increased reactivity of group is a. The proposed mechanism for the Cu(I)-catalyzed cross-coupling of a bromoalkyne with a terminal alkylene involves an acetylenic copper intermediate. We expect that the oxygen substitutions next to the triple bond facilitate the coordination of the intermediate alkynyl-copper (RP-Cu) species to the triple bond of the bromoalkyne and subsequent coupling to the other terminal acetylenic carbon, Figure 2.

It seems reasonable to suggest that the remarkable difference in reactivity between bromoalkynes 6 and 10 or 14 is due to the oxygen substitution in the latter. However, very little symmetric cross-coupling of the bromoalkyne 4 was observed in the synthesis of (−)-minquartynoic acid (1). Bromoalkyne 4 has one oxygen substituent at the propargylic position and the protecting group is a tert-butylidemethylsilyle (TBS) ether. The increased reactivity of 10 or 14 can be attributed to the second oxygen substitution at the homopropargylic carbon as shown in Figure 2. Furthermore, the TBS protecting group in 4 could attenuate the coordination effect because (1) it is a sterically bulky group and (2) silyl ethers are weaker Lewis bases than alkyl ethers. A similar effect of propargylic oxygen coordination to a chromium intermediate was proposed to be responsible for the change of reaction course in carbene-chromium complex/alkyne cycloaddition reactions.

Summary

The condition for a highly efficient synthesis of (S)-18-hydroxyminquartynoic acid (2) has been found. The total synthesis is completed in a mere five linear steps and 17.7% overall yield from the commercially available 1,2,5,6-O-disopropylidene mannitol. This synthesis confirms the efficiency of the three-component Cadiot–Chodkiewicz coupling reaction in the preparation of conjugated tetraynes. This study also reveals a remarkable difference in the reactivity of oxygen-substituted versus non-oxygen-substituted bromoalkynes. Finally, a solution to circumvent the addition of amines to the tetrayne intermediates is also documented in this report.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reagents were purchased from commercial sources and used directly without further purification. Compounds 5, 6, 11, and 12 were prepared according to reported procedures. Purification of reaction products was carried out by flash chromatography using silica gel 40–63 μm (230–400 mesh), unless otherwise stated. Reactions were monitored by 1H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% KMnO4 solution followed by heating. Chemical shifts are recorded in ppm (δ) using tetramethylsilane (H, C) as the internal reference. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz.

Preparation of 3,4-O-Isopropylidene-1,1-dibromobut-1-en-3,4-diol (12).

A 500-mL round-bottom flask was charged with a stirring bar and a solution of PPh3 (48.6 g, 185 mmol) in 200 mL of CH2Cl2. The mixture was stirred and cooled to 0 °C, after which CBr4 (30.9 g, 92.3 mmol) was added over a period of 15 min. The reaction was allowed to warm to room temperature with stirring for 30 min. It was recrystallized of 11 (6 g, 46.1 mmol) in 10 mL of CH2Cl2 was added. The reaction mixture was allowed to warm to room temper-
Synthesis of (−)-S-18-Hydroxyminquartynoic Acid

A 300-mL round-bottom flask was charged with a stirring bar and a solution of dibromoalkene 12 (3.0 g, 10.5 mmol) in 110 mL of THF and cooled to −100 °C with stirring. At this temperature, 12.6 mL (12.6 mmol) of NaN(SiMe$_3$)$_2$ (1 M solution in THF) was added. After 3 h, the reaction mixture was diluted with 200 mL of ether and quenched with 200 mL of saturated NH$_4$Cl solution. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layer was washed with brine and dried over MgSO$_4$. The solvents were removed with a rotary evaporator, and the crude mixture was purified using flash column chromatography. A colorless oil (1.78 g, 81%) was obtained:

**Preparation of 3,4-Diol (10).**

A 50-mL round-bottom flask was charged with a stirring bar, 600 mg (2.94 mmol) of the bromoalkyne 10, 55 mg (0.29 mmol) of p-TsOH, and 25 mL of MeOH. The mixture was stirred at 40 °C for 36 h. The solvent was removed using a rotary evaporator, and the crude mixture was purified using flash column chromatography. A white solid (425 mg, 88%) was isolated: mp 88–91 °C; [α]$_D$ = −14.2 (c 0.1, MeOH); $^1$H NMR (200 MHz, CD$_2$OD) δ 4.7 (1H, dd, J = 1.6, 4.5 Hz), 4.1 (1H, dd, J = 6.4, 1.7 Hz), 3.9 (1H, dd, J = 4.3, 6.1 Hz), 3.0 (2H, q, J = 5.4 Hz), 1.5 (3H, s, H-6), 1.4 (3H, s), $^{13}$C NMR (50 MHz, acetone-d$_6$) δ 110.4 (C-5), 79.0 (C-2), 69.9 (C-3) 66.4 (C-4), 46.1 (C-1), 26.1 (C-6), 25.6 (C-7); IR (film) 2900, 2253, 1253, 1096.

**Preparation of Enamine (13).**

A 10-mL round-bottom flask was charged with a stirring bar, 3.4 mg (0.10 mmol) of NH$_2$OH.HCl, 1 mL of MeOH, and 0.3 mL of Et$_3$NH$_2$. A solution of the two bromaalkynes 10, 165 mg, 0.81 mmol and 6, 200 mg, 0.81 mmol in 0.5 mL of H$_2$O. A solution of the two butadiynes 5 (0.81 mmol, 0.32 mL of 2.5 M solution) in MeOH was added. The flask was cooled to 0 °C, and a solution of the butadiyne 5 (0.81 mmol, 0.32 mL of 2.5 M solution) in MeOH was added. CuCl (4 mg, 0.04 mmol) was added shortly afterward. The reaction was stirred at 0 °C for 1 h. When the starting materials were consumed, the reaction mixture was diluted with 20 mL of ether and quenched with 20 mL of KCN/ NH$_4$Cl solution. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic extract was washed with brine and dried over MgSO$_4$. Solvents were removed with a rotary evaporator, and the crude mixture was purified with flash column chromatography. A colorless oil was isolated (81 mg, 58% yield): $^1$H NMR (200 MHz, CDCl$_3$) δ 5.14 (1H, t, J = 7.0 Hz), 5.1 (1H, s), 4.9 (1H, t, J = 5.9 Hz), 4.20 (1H, t, J = 5.9 Hz), 4.16 (1H, s), 4.0 (1H, t, J = 6.0 Hz), 3.8 (1H, dd, J = 1.5, 6.0 Hz), 3.0 (2H, q, J = 5.4 Hz), 1.5 (6H, two -CH$_3$, s, overlap), 1.46 (3H, s), 1.41 (3H, s), 1.2 (3H, t, J = 7.3); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 161.3, 111.2, 110.6, 79.8, 78.1, 78.0, 74.3, 71.9, 70.1, 67.3, 67.0, 66.5, 66.1, 37.9, 32.0, 26.5, 26.4, 26.3, 25.6, 14.0; [α]$_D$ = −58.1 (c 0.1, CHCl$_3$); IR (film) 3154, 2986, 2986, 2936, 2859, 2253, 2160, 1709, 1589, 1264; UV (MeOH) $\lambda_{max}$ 373, 350, 330, 278, 264; LCMS calcd for C$_{20}$H$_{25}$NO$_4$ + H $\lambda_{max}$, observed 344.2.

A 10-mL round-bottom flask was charged with a stirring bar, 0.8 mL of MeOH, 0.8 mL of Et$_3$NH$_2$ (70% aqueous solution), and an aqueous solution of NH$_2$OH-HCl (2.5 mg, 0.04 mmol) in 0.5 mL of H$_2$O. A solution of the two bromaalkynes 10, 165 mg, 0.81 mmol and 6, 200 mg, 0.81 mmol in 2 mL of MeOH was added. The flask was cooled to 0 °C, and a solution of the butadiyne 5 (0.81 mmol, 0.32 mL of 2.5 M solution) in MeOH was added. CuCl (4 mg, 0.04 mmol) was added shortly afterward. The reaction was stirred at 0 °C for 1 h. When the starting materials were consumed, the reaction mixture was diluted with 20 mL of ether and quenched with 20 mL of KCN/ NH$_4$Cl solution. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic extract was washed with brine and dried over MgSO$_4$. Solvents were removed with a rotary evaporator, and the crude mixture was purified with flash column chromatography. A colorless oil was isolated (81 mg, 58% yield): $^1$H NMR (200 MHz, CDCl$_3$) δ 5.14 (1H, t, J = 7.0 Hz), 5.1 (1H, s), 4.9 (1H, t, J = 5.9 Hz), 4.20 (1H, t, J = 5.9 Hz), 4.16 (1H, s), 4.0 (1H, t, J = 6.0 Hz), 3.8 (1H, dd, J = 1.5, 6.0 Hz), 3.0 (2H, q, J = 5.4 Hz), 1.5 (6H, two -CH$_3$, s, overlap), 1.46 (3H, s), 1.41 (3H, s), 1.2 (3H, t, J = 7.3); $^{13}$C NMR (50 MHz, CDCl$_3$) δ 161.3, 111.2, 110.6, 79.8, 78.1, 78.0, 74.3, 71.9, 70.1, 67.3, 67.0, 66.5, 66.1, 37.9, 32.0, 26.5, 26.4, 26.3, 25.6, 14.0; [α]$_D$ = −58.1 (c 0.1, CHCl$_3$); IR (film) 3154, 2986, 2986, 2936, 2859, 2253, 2160, 1709, 1589, 1264; UV (MeOH) $\lambda_{max}$ 373, 350, 330, 278, 264; LCMS calcd for C$_{20}$H$_{25}$NO$_4$ + H $\lambda_{max}$, observed 344.2.
MHz, CD$_3$OD) δ 4.4 (1H, dd, J = 6.1, 5.7 Hz), 3.6 (2H, d, J = 6.2 Hz) 2.4 (2H, t, J = 2.6 Hz), 2.3 (2H, t, J = 7.5 Hz), 1.6–1.2 (10H, m, overlap); $^{13}$C NMR (50 MHz, CD$_3$OD) δ 176.7, 82.0, 78.2, 68.9, 65.7, 64.8, 63.6, 62.9, 62.7, 59.9, 59.2, 33.9, 29.0 28.8, 28.8, 28.0, 25.0, 18.9; IR (film) 3365, 2934, 2490, 2362, 2225, 2073, 1716, 1100; UV (MeOH) $\lambda_{max}$ 214, 216, 221, 241; HRMS calcd for C$_{18}$H$_{20}$O$_4$ Na 323.1259, found 323.1241

Acknowledgment. This research is supported in part by a grant from the National Institutes of Health (GM60263). Acknowledgment is also made to the donors of the Petroleum Research Fund (PRF 36841-AC4) administered by the American Chemical Society.

Supporting Information Available: $^{13}$C NMR spectra for compounds 2, 11, and 13–15. This material is available free of charge via the Internet at http://pubs.acs.org.

J O0344900