Synthesis of Polyacetylenic Acids Isolated from *Heisteria acuminata*

Gilson Zeni,* Rodrigo B. Panatieri, Eliseo Lissner, Paulo H. Menezes,[‡] Antonio L. Braga, and Hélio A. Stefani[§]

Departamento de Química, Laboratório de Bioquímica Toxicológica, UFSM, 97105-900 Santa Maria, RS, Brazil

gzeni@.quimica.ufsm.br

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Four linear polyacetylenic compounds were synthesized. Pentadeca-6,8,10-triynoic acid 1 and octadeca-8,10,12-triynoic acid 2 were synthesized by using acetylene coupling reactions. The syntheses of (*Z*)-hexadec-11-en-7,9-diynoic acid 3 and (*Z*)-octadec-12-en-7,9-diynoic acid 4 by using vinylic telluride coupling reactions were accomplished.

Several examples of polyacetylenic compounds have been isolated in recent years.¹ New linear polyacetilenic compounds 1, 2, 3, and 4 (Scheme 1) were isolated from the



bark of *Heisteria acuminata* by bioassay-guided fractionation.² These compounds were found to have potent antiinflammatory activity by inhibition of cyclooxygenase (COX) and 5-lipoxygenase (5-LO).³ Polyacetylenes have also been reported previously in the literature as potent inhibitors of the arachidonic acid metabolism.⁴ Therefore, it may be inferred that compounds 1-4 are, at least in part, responsible for the antiinflammatory activity of preparations of *Heisteria acuminata* bark used in folk medicine.⁵

The unusual structure, the interesting biological activities, and the low availability of these compounds from natural sources encouraged us to synthesize them. In a previous work we have already reported the synthesis of polyacetylenic montiporic acids A and B⁶ (Scheme 2). In this Letter we wish to describe an easy route to compounds 1-4.

The retrosynthetic analysis of polyacetylenic acids 1 and 2 afforded two basic fragments: alkyldiyne system B and



[‡] Present address: Departamento de Química Fundamental, UFPE, Recife, PE, Brazil.

[§] Present address: Faculdade de Ciências Farmacêuticas, USP, São Paulo, SP, Brazil.

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acetylenic alcohol **A**, which differ only in the number of carbons in the chain (Scheme 3).



The alkyldiynes **B** were synthesized according to Scheme 4. The appropriate terminal acetylene (n = 3 or 4) was



^{*a*} (i) *n*-BuLi, THF/I₂; (ii) pyrrolidine, CuI; (iii) NaOH, xylene, reflux; (iv) *n*-BuLi, THF/I₂; (v)2 equiv of *n*-BuLi, THF/HMPA; (vi) KNH(CH₂)₃NH₂; (vii) pyrrolidine, CuI; (viii) CrO₃/H₂SO₄, -10 °C.

converted into the 1-iodoacetylene **5** by treatment with *n*-BuLi/iodine⁷ in 78% (n = 3) and 82% (n = 4) yields. Coupling reaction of **5** with **6** in the presence of pyrrolidine/ CuI⁸ yielded **7** in 95% and 93% yields, respectively, which by treatment with NaOH in xylene under reflux⁹ afforded the diynes **8** in 70% and 73% yields. Compounds **8** were then transformed into the corresponding fragment **B** by using again *n*-BuLi/I₂ in 85% and 87% yields, respectively.

The synthesis of fragment **A** (Scheme 4) started with alkylation of the lithium derivative of propargylic alcohol with 1-bromobutane or 1-bromohexane,¹⁰ yielding the corresponding alcohols **9** in 83% and 89% yields. These compounds were then subjected to prototropic migration of triple bond with KAPA¹¹ to afford the desired terminal acetylenic alcohols (fragment **A**) in 87 and 85% yields. Subsequent coupling reaction of fragments **A** and **B** using CuI and pyrrolidine⁸ yielded **10** in 90% and 93%. Oxidation with chromium oxide/H₂SO₄¹² afforded the desired acids **1** and **2** in 58% and 60% yields, respectively. The overall yield of the sequence was 30% (**1**) and 34% (**2**).

The retrosynthetic analysis of polyacetylenic acids **3** and **4** afforded two fragments: vinylic telluride **C** and 1,3-alkylidyine system **D** (Scheme 5).



The fragment **D** was synthesized following the sequence shown in Scheme 6, by the same procedure used for the synthesis of compound **8** (Scheme 4). The overall yields of fragment **D** were 40% and 43%.

Further, we synthesized fragment C (Scheme 6) by hydrotelluration¹³ of the appropriate alkyne. The desired

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(15) Compound **1**. ¹H NMR (400 MHz, CD₃OD) δ 0.95 (3 H, t, J = 7.1Hz); 1.43 (2 H, sex, J = 7.5 Hz); 1.54 (2 H, quint, J = 7.5 Hz); 1.58 (2 H, quint, J = 7.6 Hz); 1.70 (2 H, quint, J = 7.5 Hz); 2.30 (2 H, t, J = 7.5 Hz); 2.33 (2 H, quint, J = 6.9 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 13.30; 18.92; 19.25; 22.00; 24.10; 27.80; 30.20; 60.50; 60.90; 65.83; 66.42; 78.50; 79.83. MS m/z (%): 230 (55), 128 (100), 91 (50), 41 (32). Compound 2. ¹H NMR (400 MHz, CD₃OD) δ 0.90 (3 H, t, J = 7.3 Hz); 1.40 (2 H, quint, J = 7.5Hz); 1.41 (2 H, quint, J = 7.5 Hz); 1.43 (2 H, sex, J = 7.3 Hz); 1.47 (2 H, quint, J = 7.5 Hz); 1.52 (2 H, quint, J = 7.3 Hz); 1.66 (2 H, quint, J = 7.3Hz); 2.23 (2 H, t, J = 7.3 Hz); 2.28 (2 H, t, J = 7.3 Hz); 2.30 (2 H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.60; 19.25; 19.40; 22.10; 28.15; 28.75; 28.83; 29.80; 30.23; 60.40; 60.50; 65.83; 65.95; 79.20; 79.40; MS m/z (%): 272 (20), 230 (8), 129 (100), 41 (70). Compound 3. ¹H NMR (400 MHz, CD₃OD) δ 0.93 (3 H, t, J = 7.2 Hz); 1.36 (2 H, sex, J = 7.3Hz); 1.39 (2 H, quint, J = 7.5 Hz); 1.55 (2 H, quint, J = 7.3 Hz); 1.63 (2 H, quint, J = 7.6 Hz); 2.29 (2 H, t, J = 7.3 Hz); 2.35 (2 H, td, J = 7.0; 0.7 Hz); 5.48(1 H, dt, J = 10.7; 1.1 Hz); 6.07 (1 H, dt, J = 10.7; 7.5 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 13.90; 19.55; 22.30; 24.35; 28.00; 28.43; 30.45; 31.30; 34.05; 65.54; 72.30; 78.24; 84.38; 108.14; 147.81. MS m/z (%): 246 (8), 146 (30), 129 (50), 117 (100), 91 (68). Compound 4. ¹H NMR (400 MHz, CD₃OD) δ 0.93 (3 H, t, J = 7.2 Hz); 1.31 (2 H, quint, J = 7.3 Hz); 1.35 (2 H, quint, J = 7.3 Hz); 1.37 (2 H, sex, J = 7.5 Hz); 1.39 (2 H, quint, J = 7.5 Hz); 1.42 (2 H, quint, J = 7.4 Hz); 1.42 (2 H, quint, J = 7.5 Hz); 1.61 (2 H, quint, J = 7.3 Hz); 2.28 (2 H, t, J = 7.4 Hz); 2.31 (2 H, td, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.34 (2 H, qd, J = 6.9; 1.2 Hz); 5.42 (1 H, dt, J = 7.4; 0.6 Hz); 2.8 Hz = 7.4; 0.6 Hz); 2.8 Hz = 7.4; 0.6 Hz = 7.4; 10.9; 1.2 Hz); 6.07 (1 H, dt, J = 10.9; 7.6 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 14.02; 19.75; 22.36; 24.87; 28.39; 28.71; 28.88; 29.06; 30.05; 31.00; 65.34; 72.22; 78.29; 84.71; 108.26; 147.95. MS m/z (%): 271 (10), 245 (6), 187 (30), 164 (27), 117 (100), 91 (65).

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Scheme 6^a



^{*a*} (i) 2 equiv of *n*-BuLi, THF/HMPA; (ii) KNH(CH₂)₃NH₂; (iii) 2 equiv of *n*-BuLi, THF/I₂; (iv) pyrrolidine, CuI; (v) NaOH, xylene, reflux; (vi) THF, rt; (vii) EtOH, reflux; (viii) PdCl₂/CuI, MeOH/Et₃N; (ix) CrO₃/H₂SO₄, -10 °C.

vinylic tellurides were obtained in a 6:1 mixture of regioisomers, which were separated by column chromatography in 48% yield. These compounds were then coupled to the appropriate alkyldiynes **D** using PdCl₂/CuI in methanol¹⁴ to afford **11** with the desired *Z* geometry of the double bond. Chromium oxide/H₂SO₄¹² (Scheme 4) gave the polyacetylenic acid **3** and **4**. The overall yields of the sequence were 24% (**3**) and 22% (**4**). The spectroscopy data¹⁵ (¹H and ¹³C NMR) of compounds **1**–**4** are in agreement with the data reported by Wagner² and co-workers. In summary, we have achieved the total synthesis of four natural products with biological activity and very limited access, using coupling-based methodologies.

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