ORGANIC LETTERS

2001
Vol. 3, No. 6
819−821

Synthesis of Polyacetylenic Acids Isolated from *Heisteria acuminata*

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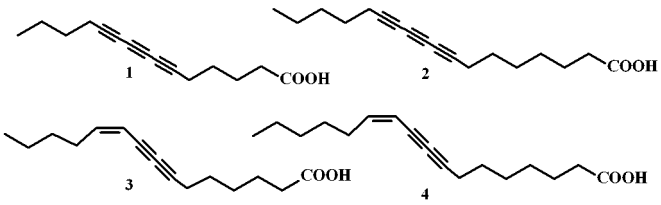
Received December 1, 2000

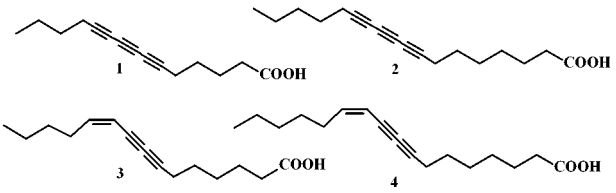
ABSTRACT



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

Scheme 1

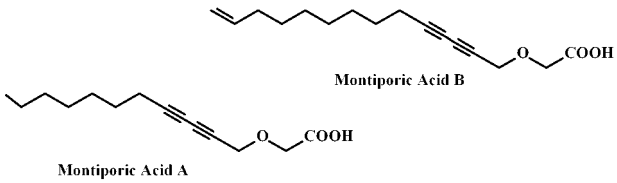


bark of *Heisteria acuminata* by bioassay-guided fractionation.[2] These compounds were found to have potent antiinflammatory activity by inhibition of cyclooxygenase (COX) and 5-lipoxygenase (5-LO).[3] Polyacetylenes have also been reported previously in the literature as potent inhibitors of the arachidonic 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 B[6] (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

Scheme 2



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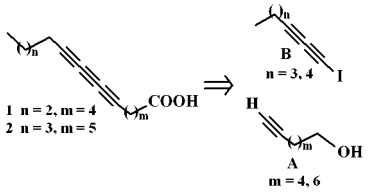
(2) Kraus, M. C.; Neszmélyi, A.; Holly, S.; Wiedemann, B.; Nenniiger, A.; Torssell, G. B. K.; Bohlin, L.; Wagner, H. *J. Nat. Prod.* **1998**, *61*, 422.

10.1021/ol006946v CCC: $20.00
Published on Web 02/21/2001

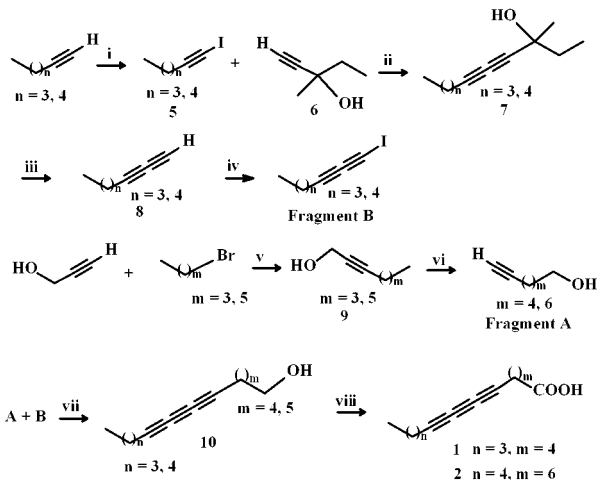
acetylenic alcohol **A**, which differ only in the number of carbons in the chain (Scheme 3).

Scheme 3



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

Scheme 4[a]



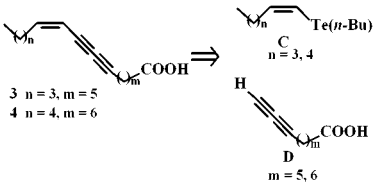
[a] (i) *n*-BuLi, THF/I_2; (ii) pyrrolidine, CuI; (iii) NaOH, xylene, reflux; (iv) *n*-BuLi, THF/I_2; (v)2 equiv of *n*-BuLi, THF/HMPA; (vi) $KNH(CH_2)_3NH_2$; (vii) pyrrolidine, CuI; (viii) CrO_3/H_2SO_4, −10 °C.

converted into the 1-iodoacetylene **5** by treatment with *n*-BuLi/iodine[7] in 78% (n = 3) and 82% (n = 4) yields. Coupling reaction of **5** with **6** in the presence of pyrrolidine/CuI[8] yielded **7** in 95% and 93% yields, respectively, which by treatment with NaOH in xylene under reflux[9] afforded the diynes **8** in 70% and 73% yields. Compounds **8** were then transformed into the corresponding fragment **B** by using again *n*-BuLi/I_2 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 KAPA[11] 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 pyrrolidine[8] yielded **10** in 90% and 93%. Oxidation with chromium oxide/H_2SO_4[12] 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).

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 hydrotelluration[13] of the appropriate alkyne. The desired

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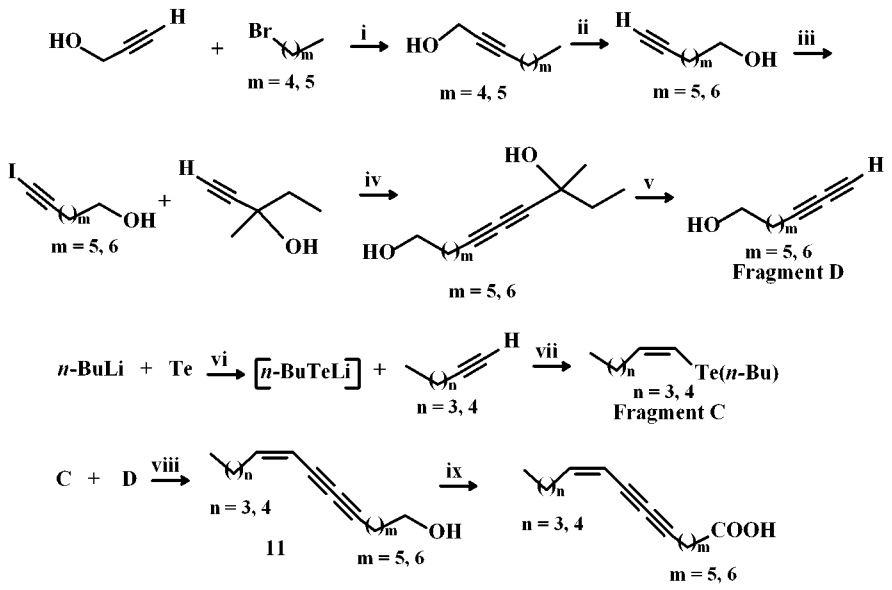
(15) Compound **1**. ^{1}H NMR (400 MHz, CD_3OD) δ 0.95 (3 H, t, J = 7.1 Hz); 1.43 (2 H, sex, J = 7.5 Hz); 1.54 (2 H, quint, J = 7.5 Hz); 1.58 (2 H, quint, J = 7.6 Hz); 1.70 (2 H, quint, J = 7.5 Hz); 2.30 (2 H, t, J = 7.5 Hz); 2.33 (2 H, quint, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.30; 18.92; 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**. ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (3 H, t, J = 7.3 Hz); 1.40 (2 H, quint, J = 7.5 Hz); 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 = 7.3 Hz); 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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**. ^{1}H NMR (400 MHz, CD_3OD) δ 0.93 (3 H, t, J = 7.2 Hz); 1.36 (2 H, sex, J = 7.3 Hz); 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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**. ^{1}H NMR (400 MHz, CD_3OD) 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 = 10.9; 1.2 Hz); 6.07 (1 H, dt, J = 10.9; 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 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).

Scheme 6[a]



[a] (i) 2 equiv of *n*-BuLi, THF/HMPA; (ii) $KNH(CH_2)_3NH_2$; (iii) 2 equiv of *n*-BuLi, THF/I_2; (iv) pyrrolidine, CuI; (v) NaOH, xylene, reflux; (vi) THF, rt; (vii) EtOH, reflux; (viii) $PdCl_2$/CuI, MeOH/Et_3N; (ix) CrO_3/H_2SO_4, −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 $PdCl_2$/CuI in methanol[14] to afford **11** with the desired *Z* geometry of the double bond. Chromium oxide/H_2SO_4[12] (Scheme 4) gave the polyacetylenic acid **3** and **4**. The overall yields of the sequence were 24% (**3**) and 22% (**4**). The spectroscopy data[15] (^1H and ^{13}C NMR) of compounds **1**−**4** are in agreement with the data reported by Wagner[2] 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.

Acknowledgment. We are grateful to the FAPERGS, CNPq, FIPE (UFSM) for financial support. The autors are also grateful to Professor Joachim Demnitz (UFPE) for the revision of this manuscript.

OL006946V