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Synthesis of polyacetylenic acids isolated from *Nanodea muscosa*

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Abstract—The first total synthesis of two linear polyacetylenic compounds is described. The synthesis of (*E*)-octadec-13-en-11-ynoic acid **1** and (*E*)-octadec-13-en-9,11-diynoic acid **2** by using the vinylic telluride coupling reaction was accomplished.

Several examples of acetylenic and polyacetylenic compounds have been isolated in recent years.[1] Many of these natural products have shown biological activities ranging from antibacterial, fungicidal and in vitro antitumor properties to cell division inhibition.[2] In addition, these compounds could also be potent inhibitors of the arachidonic acid metabolism.[3] Recently, two new linear polyacetylenic acids [(13*E*)-octadec-13-en-11-ynoic acid] **1** and [(13*E*)-octadec-13-en-9,11-diynoic acid] **2** (Fig. 1) were isolated from the aerial parts of *Nanodea muscosa*, a small herb found in extreme southern regions of South America.[4] These authors also elucidated the structure of compounds **1** and **2** by spectroscopic methods and assigned their absolute stereochemistry.

In a previous work, we have already reported the synthesis of polyacetylenic acids isolated from *Heisteria acuminata*, utilizing, as a tool, the tellurium chemistry.[5]

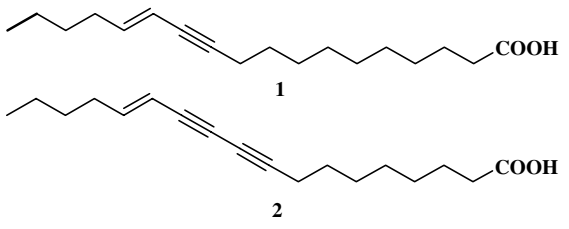

Figure 1.

Many different classes of organotellurium compounds have been prepared and studied to date, vinylic tellurides are certainly the most useful and promising compounds in view of their usefulness in the organic synthesis.[6] In addition to their utility in the field of organic chemistry, toxicological and pharmacological aspects of organotellurium compounds have also been recently reviewed.[7]

However, the use of tellurium chemistry for the synthetic organic chemists or as a tool in organic synthesis has been hampered due to a bad reputation related to the bad smell, toxicity or instability of these compounds. In fact, these comments are correct to a particular group of the tellurium compounds, but they are not a rule for all tellurium compounds. In our lab, we have used a lot of different classes of tellurium compounds and observed that tellurides or ditellurides, bearing an alkyl group with a low molecular weight, present a bad smell. Conversely, when these alkyl groups present any additional substituent, the corresponding tellurides or ditellurides are practically odorless.

Other tellurium compounds, such as trihalides, diaryl tellurides and ditellurides are solid, very stable (can be stored in the lab in a simple flask for a long time) and completely odorless. In addition, the vinylic tellurides, one of the most used classes of tellurium compounds, containing an aromatic, aliphatic saturated or unsaturated chains, which are odorless compounds, can be easily prepared, purified and stored as a common chemical used in the lab. Another reason that has hindered the development of the organotellurium chemistry is that the toxicological studies are still scarce in the literature, however, they are meant. Some authors have

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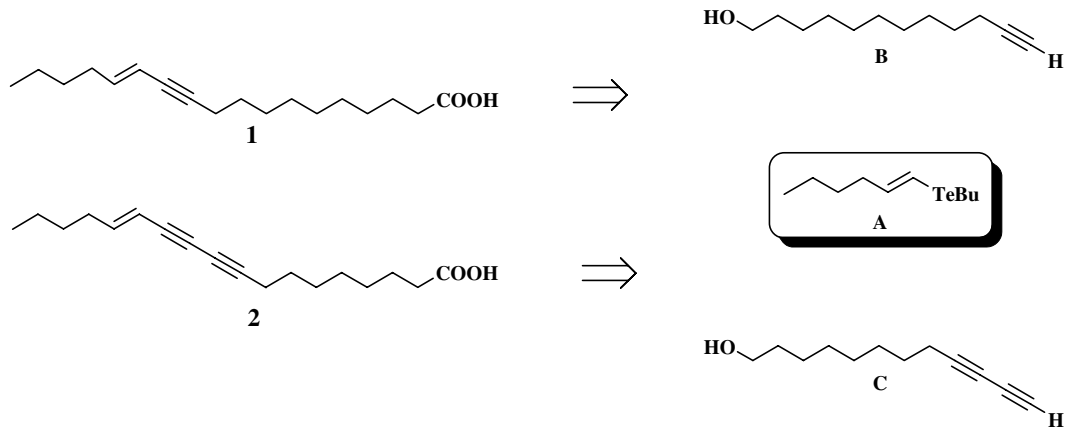


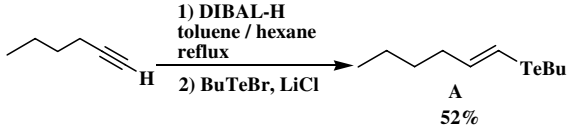
Scheme 1.

described that organotellurium compounds are less toxic than their selenium derivatives[8] and others have indicated that organotellurium compounds are more toxic than organoselenium compounds.[7] We are sure that no highly specialized techniques are required in the handling of organotellurium compounds and work with these compounds is very similar to work with any other classes of chemical compounds such as organoselenium, organosulfur, organotin and organophosphorus.

As a part of our efforts toward the total synthesis of polyacetylenic natural products,[5,9] we became interested in the synthesis of these two polyacetylenic acids **1** and **2**. The challenge of this synthesis is to build the requisite *E*-stereochemistry of the double bond. It could be easily achieved using one of the most important behaviors of the vinylic tellurides; their high stereospecific synthesis and reactivity.

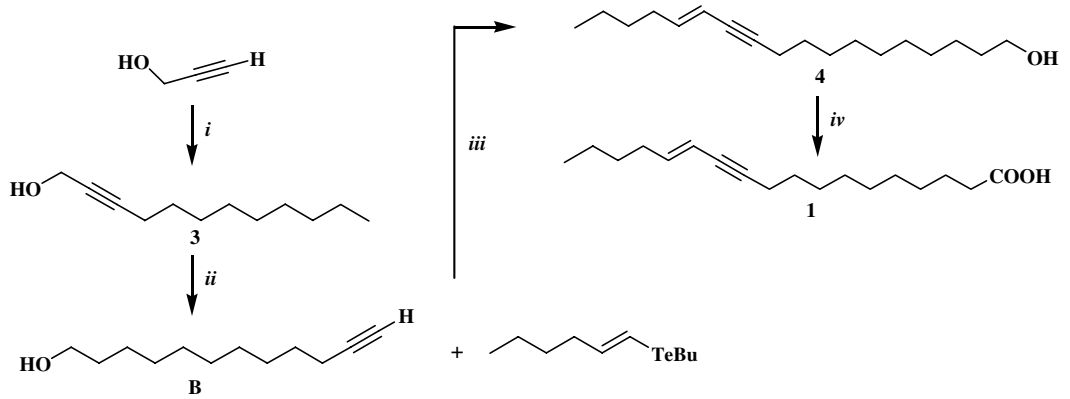
The retrosynthetic analysis of compounds **1** and **2** afforded three basic fragments: (*E*)-vinylic telluride **A**, alkyne **B** and 1,3-alkadiyne system **C**. Both polyacetylenic acids **1** and **2** could be derived from the (*E*)-vinylic telluride **A**, a key intermediate to this synthesis (Scheme 1).

Firstly, we synthesized the (*E*)-vinylic telluride **A** by the hydroalumination of the 1-hexyne followed by the reaction with BuTeBr/LiCl in 52% yield (Scheme 2).[10]

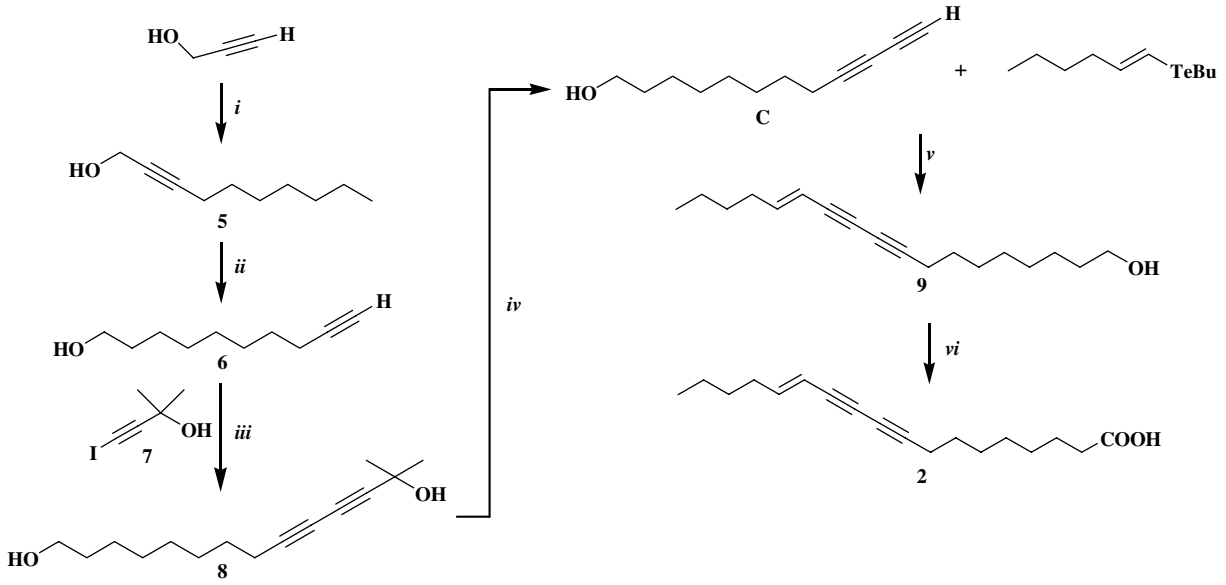


Scheme 2.

Polyacetylenic acid **1** was synthesized following the sequence shown in Scheme 3. The synthesis of alkynyl system **B** began by the treatment of propargylic alcohol with 2 equiv of *n*-BuLi in HMPA/THF[11] to generate the corresponding dianion, which was subsequently quenched with 1-bromononane to afford alcohol **3** in 83% yield. This compound was subjected to prototropic migration of triple bond with potassium 3-aminopropanamide (KAPA)[12] to afford the desired terminal acetylenic alcohol **B** in 78% yield. The cross-coupling reaction of **B** with the (*E*)-vinylic telluride **A** using $PdCl_2$/CuI in methanol[13] afforded **4** in 75% yield, with the desired *E* geometry of the double bond. The coupling reaction occurs with the retention of the double bond geometry since starting from pure *E* adduct of the vinylic tellurides only *E* enynes **4** were obtained. The stereochemistry of the obtained enynes was easily established, since the ^{1}H NMR spectrum of compound **4** showed a doublet of triplets at 6.03 ppm with coupling constant of 15.7 and 7.1 Hz and a doublet of triplets at



Scheme 3. Reagents and conditions: (i) 2 equiv of *n*-BuLi, THF, HMPA, 1-bromononane, 83%. (ii) $KHN(CH_2)_3NH_2$, 78%. (iii) $PdCl_2$, CuI, MeOH, Et_3N, 75%. (iv) PDC, DMF, 80%.



Scheme 4. Reagents and conditions: (i) 2 equiv of *n*-BuLi, THF, HMPA, 1-bromoheptane, 80%. (ii) $KHN(CH_2)_3NH_2$, 76%. (iii) Pyrrolidine, CuI, 4-iodo-2-methylbut-3-yn-2-ol, 85%. (iv) NaOH, toluene, reflux, 71%. (v) $PdCl_2$, CuI, MeOH, Et_3N, reflux, 74%. (vi) PDC, DMF, 78%.

5.44 ppm with coupling constant of 15.7 and 1.4 Hz. These coupling constants confirm the trans relationship of the hydrogens attached to the double bond.

Next, the oxidation of **4** using PDC in DMF[14] gave polyacetylenic acid **1** in 80% yield. The overall yield of total synthesis was 38%.

Polyacetylenic acid **2** was synthesized according to Scheme 4. The synthesis of fragment **C** started with the alkylation of the dilithium derivative of propargylic alcohol with 1-bromoheptane,[11] yielding alcohol **5** in 80%. This compound was subjected to prototropic migration of triple bond with KAPA[12] to afford terminal acetylenic alcohol **6** in 76% yield. Subsequent coupling reaction of acetylenic alcohol **6** with alkynyl iodide **7** using CuI and pyrrolidine[15] yielded diyne **8** in 85%. Treatment of compound **8** with NaOH in toluene under reflux[16] afforded 1,3-alkadiyne system **C** in 71% yield. This terminal diyne was coupled to the (*E*)-vinylic telluride **A** using $PdCl_2$/CuI in methanol,[13] under reflux, giving the enediyne system **9** in 74% yield. The oxidation with PDC in DMF[14] provided the corresponding polyacetylenic acid **2** (78%). The overall yield of this total synthesis was 21%.

The spectroscopy data[17] (^1H and ^{13}C NMR) of compounds **1** and **2** are in agreement with the data reported by Ravelo and co-workers.[4]

In summary, we have completed, for the first time, the total synthesis of two natural products in mild reaction conditions and in satisfactory yields, using palladium cross-coupling-based methodologies and vinylic tellurides as a key intermediate. We have shown in this study that the use of vinylic tellurides is an efficient strategy to achieve stereospecifically double bonds in polyunsaturated natural products. The investigation on the pharmacology and toxicology, as well as, the structure–activity relationship of these compounds will be reported elsewhere in the near future.

Acknowledgements

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17. (13*E*)-Octadec-13-en-11-ynoic acid (**1**): yellow oil; ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 6.04 (dt, $J = 15.7$; 6.9 Hz, 1H), 5.44 (dt, $J = 15.7$; 1.8 Hz, 1H), 2.24–2.39 (m, 4H), 2.07 (q, $J = 7.4$ Hz, 2H), 1.15–1.50 (m, 18H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 13.8, 19.3, 22.1, 24.7, 28.7, 28.8, 29.0, 29.1, 29.2, 29.3, 31.0, 32.6, 33.9, 79.2, 88.6, 109.8, 143.3, 179.6. (13*E*)-Octadec-13-en-9,11-diynoic acid (**2**): yellow oil; ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 6.27 (dt, $J = 15.9$, 7.3 Hz, 1H), 5.48 (d, $J = 15.9$ Hz, 1H), 2.37–2.28 (m, 4H), 2.11 (q, $J = 7.1$ Hz, 2H), 1.63 (quint., $J = 7.4$ Hz, 2H), 1.53 (quint., $J = 7.4$ Hz, 2H), 1.34 (m, 10H), 0.89 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 13.8, 19.5, 22.1, 24.6, 28.2, 28.6, 28.7, 28.9, 30.7, 32.9, 33.9, 65.3, 72.8, 74.1, 83.4, 108.6, 148.2, 179.3.