Total Synthesis

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The Changing Faces of Halogenated Marine Natural Products: Total Synthesis of the Reported Structures of Elatenyne and an Enyne from *Laurencia majuscula***

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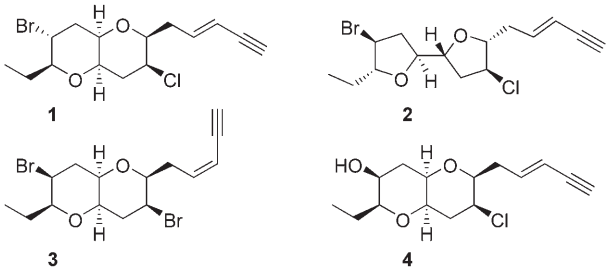
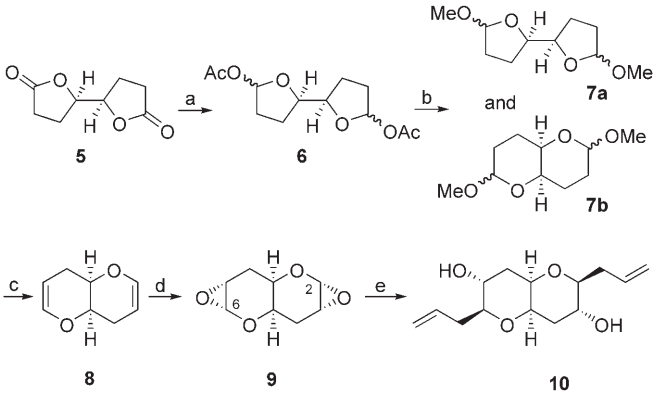
The structures of complex natural products are best confirmed by independent synthesis or X-ray crystallography. Advances in NMR spectroscopy over the last 20 years have greatly improved the ease with which the structures of complex molecules are solved; however, in cases where crystallography is not possible, regio- and stereocontrolled synthesis remains the best method for structure confirmation. In many cases, determining the connectivity through heteroatoms becomes a significant challenge in structure assignment by NMR spectroscopy, especially in otherwise closely related molecules. For example, consider the two natural products (*E*)-dactomelyne (**1**) and notoryne (**2**).[1,2] They both contain the same carbon and proton connectivity, and hence unambiguous structure assignment would be challenging on the basis of NMR experiments alone. The natural products **1** and **2** belong to a much wider group of C_{15} metabolites isolated from red algae and from marine organisms that feed on *Laurencia* species.[3] In 1986, the dibrominated natural product elatenyne was isolated by Hall and Reiss, and was assigned the pyrano[3,2-*b*]pyran structure **3** on the basis of extensive ^{1}H and ^{13}C NMR spectroscopic analyses.[4] More recently, the structure of a halogenated C_{15} natural product isolated from *L. majuscula* was disclosed as the pyrano[3,2-*b*]pyran **4**, again on the basis of extensive NMR spectroscopic analyses and by comparison with the structures **3** (reported for elatenyne) and (*E*)-dactomelyne (**1**).[5]



Elatenyne and the *L. majuscula* enyne were attractive targets for total synthesis because of their densely functionalized pyrano[3,2-*b*]pyran cores and embedded C_2 symmetry.[6,7] Herein, we report an efficient two-directional route to these halogenated secondary metabolites which rapidly established the central pyrano[3,2-*b*]pyran core and culminated in the total synthesis of structures **3** and **4**.[8,9] The spectroscopic data for the synthetic pyrano[3,2-*b*]pyrans **3** and **4** are inconsistent with those reported for the natural products, and we propose that both natural products are structurally related to notoryne **2** by having a core 2,2′-bifuranyl structure.

Our approach to the fused bicycles **3** and **4** is delineated in Scheme 1. The known bislactone **5**[10] was reduced with diisobutylaluminum hydride and the resulting intermediate aluminum alkoxides were trapped with acetic anhydride to give a mixture of the anomeric acetates **6**.[11] Exposure of the acetates **6** to acidic methanol gave a mixture of the methyl glycosides **7**, which on treatment with iodotrimethylsilane in acetonitrile gave solely the pyrano[3,2-*b*]pyran **8**.[12] ^{1}H NMR spectroscopic studies have demonstrated that this rearrangement proceeds by way of the corresponding anomeric iodides, with the pyrano[3,2-*b*]pyran bis(anomeric) iodide being greatly favored over the 2,2′-bifuranyl bis(anomeric) iodide at equilibrium.[13] Subsequent epoxidation under mild con-



Scheme 1. Synthesis of the pyrano[3,2-*b*]pyran core **10**. a) Diisobutylaluminum hydride, CH_2Cl_2, −78 °C, then Ac_2O, pyridine, DMAP, CH_2Cl_2, −78 °C, 14 h, then −78→−20 °C, 83%; b) MeOH, HCl, 90%; c) Me_3SiI, MeCN, RT, then $(Me_3Si)_2NH$; d) 3,3-dimethyldioxirane, $NaHCO_3$, CH_2Cl_2; e) $(CH_2{=}CHCH_2)_2Mg$, Et_2O, THF, −78 °C→RT, 57% overall from **7**. DMAP = 4-dimethylaminopyridine.

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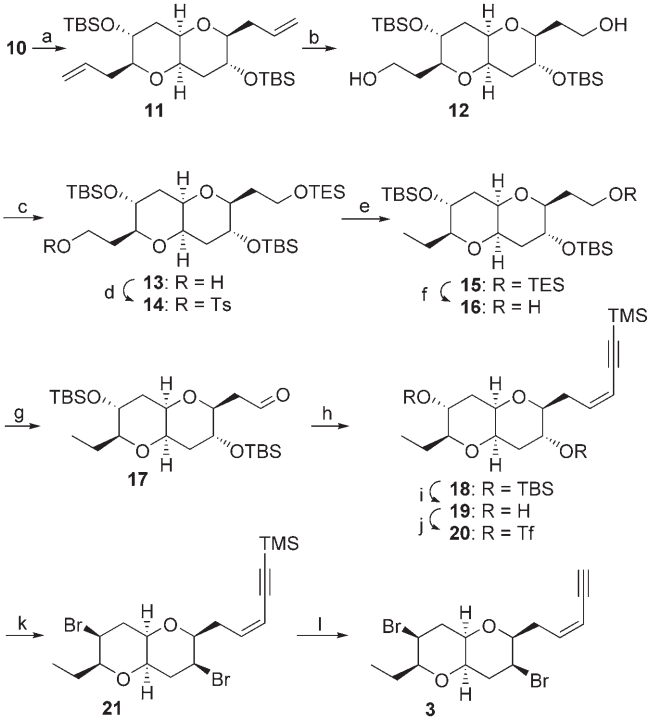
ditions provided the bis(epoxide) **9** as a relatively stable white crystalline solid. X-ray analysis of **9** confirmed that epoxidation had occurred on the more accessible convex face of the bis(enol ether) **8** as expected (see Supporting Information).

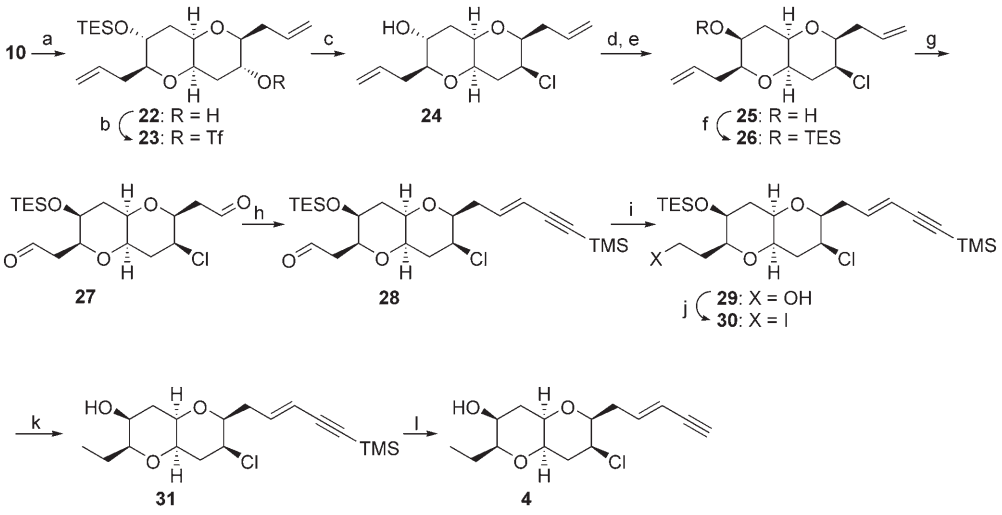
The bis(epoxide) **9** was opened with inversion of stereochemistry at C2 and C6 by treatment with diallylmagnesium to provide the corresponding C_2-symmetric diol **10**;[14] approximately 8% of an asymmetric diol is also formed under these conditions and corresponds to one epoxide of **9** being opened with inversion (an S_N2-like mechanism) and the other epoxide being opened with overall retention (an S_N1-like mechanism).[15] The sequence shown in Scheme 1 rapidly establishes the central pyrano[3,2-*b*]pyran system of **3** and **4** in five steps from the known lactone **5**.

The conversion of the diol **10** into the *cis*-enyne **3** is shown in Scheme 2. Protection of the diol **10** gave the bis(silyl ether) **11**, which on ozonolysis with a reductive workup yielded the diol **12**. Many attempts were made to desymmetrize **12** by formation of a monoiodide, -tosylate, or -aldehyde. Ultimately, the most efficient method for breaking the C_2 symmetry of **12** involved statistical protection using chlorotriethylsilane, which provided the unsymmetric alcohol **13** in good yield after one recycle.[16] The primary alcohol was readily reduced via the corresponding tosylate **14**[17] to provide the ethyl-substituted pyrano[3,2-*b*]pyran **15**, which was then transformed into the aldehyde **17** by using standard procedures.[18] The enyne side chain was installed with exclusive *Z* selectivity by using a Yamamoto–Peterson reaction to give **18**.[19] Removal of the two oxygen-protecting groups gave the bromination substrate **19**. The introduction of halogen atoms into tetrahydropyrans by substitution from the corresponding hydroxy groups has been reported to be very challenging.[20] After screening a wide variety of reagents, we discovered that exposure of the bis(triflate) **20**, derived from the diol **19**, to tetrabutylammonium bromide in toluene at reflux delivered the desired dibromide **21**, albeit in low yield.[21,22] Removal of the acetylene-protecting group gave the *cis*-enyne **3**.



Scheme 2. Synthesis of the reported structure of elatenyne (**3**). a) TBSOTf, Et_3N, CH_2Cl_2, 99%; b) O_3/O_2, CH_2Cl_2, MeOH, −78 °C, then Ph_3P, −78 °C, 2 h, then $NaBH_4$, −78 °C→RT, 2 h, 82%; c) Et_3SiCl, Et_3N, CH_2Cl_2, 70% after one recycle; d) TsCl, DMAP, Et_3N, CH_2Cl_2, 93%; e) $LiBHEt_3$, Et_2O, RT, 91%; f) K_2CO_3, MeOH, 98%; g) nPr_4NRuO_4, NMO, CH_2Cl_2, 4-Å MS, 95%; h) $Me_3SiC{\equiv}CCH_2SiMe_2tBu$, *t*BuLi, $Ti(OiPr)_4$, THF, −78 °C, add **17**, −78 °C→RT, 0.5 h, then $(Me_3Si)_2NK$, 75%; i) TsOH, MeOH, 22 h, 75%; j) Tf_2O, pyridine, CH_2Cl_2; k) nBu_4NBr, toluene, reflux, 2 h, 14% from **19**; l) nBu_4NF, THF, −5 °C, 98%. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Ts = toluene-4-sulfonyl, NMO = 4-methylmorpholine *N*-oxide, MS = molecular sieves, Tf = trifluoromethanesulfonyl.

The broader applicability of this synthetic strategy towards *cis*-fused pyrano[3,2-*b*]pyrans is illustrated by our synthesis of the enyne **4** (Scheme 3). Desymmetrization of the C_2-symmetric diol **10** was again achieved by silylation (with recycling) to provide the unsymmetric alcohol **22**.[23] The axial chlorine atom was introduced from the corresponding triflate **23** on exposure to tetrabutylammonium chloride in toluene at reflux to



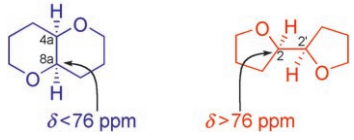
Scheme 3. Synthesis of the reported structure of the enyne from *L. majuscula* **4**. a) Et_3SiCl, imidazole, DMF, 64% after one recycle; b) Tf_2O, pyridine, CH_2Cl_2; c) nBu_4NCl, toluene, reflux, 2 h, then amberlite resin IR-120, MeOH, 45% from **22**; d) nPr_4NRuO_4, NMO, CH_2Cl_2, 4-Å MS, 65%; e) $NaBH_4$, MeOH, 87%; f) Et_3SiOTf, Et_3N, CH_2Cl_2, 99%, g) O_3/O_2, CH_2Cl_2, −78 °C, then Ph_3P, −78 °C, 0.5 h, then RT, 8 h, 95%; h) $Ph_3P^+CH_2C{\equiv}C\text{-}SiMe_3\text{-}Br^-$, *n*BuLi, THF, add **27**, −78→0 °C, 45%, (15% recovered **27**); i) $NaBH_4$, MeOH, 100%, j) I_2, PPh_3, imidazole, Et_2O, MeCN, RT, 72%; k) Zn, AcOH, MeOH, Et_2O, RT, then HCl, 96%; l) nBu_4NF, THF, RT, 92%.

yield the chloro alcohol **24** after acid treatment. This is a remarkable transformation given that a previous attempted synthesis of the dactomelynes had failed because the introducion of the axial chlorine atom through a substitution reaction from the corresponding hydroxy group proved impossible.[7]

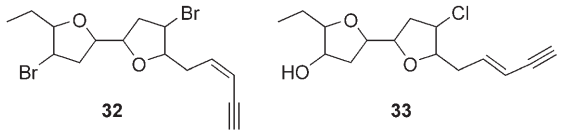
The remaining secondary hydroxy group in **24** was inverted by an oxidation[18]/reduction sequence to give **25**; thus all of the required stereochemistry for the synthesis of **4** was set. Crystals of alcohol **25** suitable for X-ray analysis were obtained and the crystal structure confirmed that all the substituents were on the concave face of the pyran[3,2-*b*]pyran system, with the chlorine atom and hydroxy groups being oriented axially (see Supporting Information). Protection of the hydroxy group of **25** to give the silyl ether **26** followed by ozonolysis (with triphenylphosphane workup) gave the bis(aldehyde) **27** in excellent yield.

Addition of one equivalent of a preformed solution of the ylide derived from (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide to a cold solution of the bis(aldehyde) **27** delivered the enyne **28** with high *E* selectivity (*E*/*Z* > 7:1).[24] The only other product isolated from this reaction was the corresponding bis(enyne) (17%). Reduction of the aldehyde **28**, conversion of the resulting alcohol **29** into the corresponding primary iodide **30**, and reductive removal of the iodine with zinc[25] provided the ethyl-substituted pyranopyran **31**. Removal of the acetylene-protecting group gave the *trans*-enyne **4**.[26]

Neither the spectroscopic data for synthetic **3** nor synthetic **4** corresponded with the literature data reported for their respective natural products.[4,5] The difficulty in unequivocally assigning the structures of complex natural products has recently been reviewed by Nicolaou and Snyder, and is further highlighted by the work described here.[27] During our synthetic studies towards the enynes **3** and **4**, we synthesized a large number of pyrano[3,2-*b*]pyran and 2,2′-bifuranyl compounds. Careful analysis of the ^{13}C NMR data of all of these compounds revealed that the ^{13}C NMR chemical shifts of the central oxygen-bearing carbon atoms fall into two distinct groups: for the pyrano[3,2-*b*]pyran, the ^{13}C NMR chemical shift of the C8a and C4a carbon atoms resonate at less than $\delta = 76$ ppm, whereas the corresponding carbon atoms (C2 and C2′) in the 2,2′-bifuranyls resonate at greater than $\delta = 76$ ppm (Scheme 4).[28] For elatenyne, the relevant carbon atoms resonate at $\delta = 79.5$ and 80 ppm, whereas for the pyrano[3,2-*b*]pyran **3** they resonate at $\delta = 71.3$ and 71.4 ppm. For the *L. majuscula* enyne the relevant carbon atoms resonate at $\delta = 77.9$ and 79.2 ppm, whereas for the synthetic pyrano[3,2-*b*]pyran **4** they resonate at $\delta = 73.9$ and 70.5 ppm. The difficulty in distinguishing between closely related structures (for example, **1** and **2**) by using NMR spectroscopic techniques alone, coupled with the general pattern of the ^{13}C NMR chemical shifts of the pyrano[3,2-*b*]pyran and 2,2′-bifuranyl units has led us to conclude that the overall structures of elatenyne and the enyne from *L. majuscula* are the 2,2′-bifuranyls **32** and **33**, respectively (Scheme 5). Further analysis of all the spectroscopic data for the natural products supports this proposal.[29–31]



Scheme 4. ^{13}C chemical shifts for pyrano[3,2-*b*]pyran and 2,2′-bifuranyl compounds.



Scheme 5. Proposed structures for elatenyne and the enyne from *L. majuscula*.

In summary, we have reported an efficient synthetic route to halogenated pyrano[3,2-*b*]pyrans which has culminated in the total synthesis of the putative structures of elatenyne **3** and an enyne isolated from *L. majuscula* **4**. Key features of our two-directional synthesis include: the rapid construction of the central pyrano[3,2-*b*]pyran core of **3** and **4** through a novel rearrangement of the anomeric acetates **6**, a regioselective Wittig reaction for the formation of the enyne **28**, and the introduction of the halogen atoms through substitution from the corresponding activated hydroxy groups. The spectroscopic data for **3** and **4** did not correspond with those reported for the natural products, which led us to propose revised structures for the natural products based upon a central 2,2′-bifuranyl core (Scheme 5). Reisolation of the natural products would allow further spectroscopic analysis to aid full structure determination. In the meantime, work is underway to predict the structures of elatenyne and the enyne from *L. majuscula* on the basis of a rational biosynthetic pathway and to confirm the stereochemistry of the natural products by stereoselective total synthesis.

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[1] For an isolation and structure determination of the dactomelynes, see: Y. Gopichand, F. J. Schmitz, J. Shelly, A. Rahman, D. van der Helm, *J. Org. Chem.* **1981**, *46*, 5192; reisolation: Z. Aydogmus, S. Imre, L. Ersoy, V. Wray, *Nat. Prod. Res.* **2004**, *18*, 43.
[2] For the isolation and structure determination of notoryne, see: H. Kikuchi, T. Suzuki, E. Kurosawa, M. Suzuki, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1763.
[3] K. L. Erickson in *Marine Natural Products*, *Vol. 5* (Ed.: P. J. Scheuer), Academic Press, New York, **1983**, p. 131.
[4] J. G. Hall, J. A. Reiss, *Aust. J. Chem.* **1986**, *39*, 1401.
[5] A. D. Wright, G. M. König, R. De Nys, O. Sticher, *J. Nat. Prod.* **1993**, *56*, 394.

[6] For a notable previous total synthesis of the dactomelynes, see: E. Lee, C. M. Park, J. S. Yun, *J. Am. Chem. Soc.* **1995**, *117*, 8017.
[7] For an attempted synthesis of the dactomelynes, see: A. P. Kozikowski, J. Lee, *J. Org. Chem.* **1990**, *55*, 863.
[8] For a summary of the advantages of two-directional synthesis, see: C. S. Poss, S. L. Schreiber, *Acc. Chem. Res.*, **1994**, *27*, 9.
[9] For an excellent review on desymmetrization and the two-directional synthesis of natural products, see: S. R. Magnuson, *Tetrahedron* **1995**, *51*, 2167.
[10] The bis(lactone) **5** has been synthesized in two steps from commercially available materials: M. E. Maier, S. Reuter, *Synlett* **1995**, 1029.
[11] D. J. Kopecky, S. D. Rychnovsky, *J. Org. Chem.* **2000**, *65*, 191.
[12] For the formation of *endo*-glycals using iodotrimethylsilane and hexamethyldisilazane, see: D. Craig, M. W. Pennington, P. Warner, *Tetrahedron Lett.* **1995**, *36*, 5815; L. A. Paquette, J. A. Oplinger, *J. Org. Chem.* **1988**, *53*, 2953.
[13] The anomeric acetates **6** gave the pyrano[3,2-*b*]pyran **8** in low yield on treatment with iodotrimethylsilane in acetonitrile.
[14] J. D. Rainier, S. P. Allwein, J. M. Cox, *J. Org. Chem.* **2001**, *66*, 1380.
[15] The asymmetric diol was inseparable at this stage and was removed after ozonolysis of **11**.
[16] The use of silyl protection to desymmetrize C_2-symmetric diols was reported by Poss and Schreiber[8].
[17] H. C. Brown, S. Krishnamurthy, *J. Am. Chem. Soc.* **1973**, *95*, 1669. Solvent effects in the reduction of halides and tosylates: S. Krishnamurthy, *J. Org. Chem.* **1980**, *45*, 2550.
[18] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.
[19] Y. Yamakado, M. Ishiguro, N. Ikeda, H. Yamamoto, *J. Am. Chem. Soc.* **1981**, *103*, 5568.
[20] L.-X. Gao, A. Murai, *Heterocycles* **1996**, *42*, 745.
[21] Bromination of the bis(triflate) **20** cannot occur from the ground state, O-inside conformation, and will be further slowed by the β-oxygen effect, see: S. S. Shaik, *J. Am. Chem. Soc.* **1983**, *105*, 4359. For discussion of the conformational preferences of pyrano[3,2-*b*]pyrans and related systems, see: R. W. Hoffmann, I. Münster, *Ann. Chem.* **1997**, 1143; A. G. Santos, R. W. Hoffmann, *Tetrahedron: Asymmetry* **1995**, *6*, 2767; M. Grabarnik, N. G. Lemcoff, R. Madar, S. Abramson, S. Weinman, B. Fuchs, *J. Org. Chem.* **2000**, *65*, 1636.
[22] The stereochemistry of the dibromide was established by analysis of the coupling constants (see the Supporting Information).
[23] The diol **10** contained an inseparable impurity which was removed after chlorination of **23**.
[24] The connectivity of the pyrano[3,2-*b*]pyran **28** (and hence the regiochemistry of the Wittig reaction) was firmly established by ^{1}H NMR COSY experiments. The origin of the regioselectivity of the Wittig reaction may be steric in nature because of the larger size of an OTES group with respect to a chlorine atom.
[25] The reported conditions were particularly effective: Z.-H. Peng, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 6018.
[26] The enyne **4** was isolated as an inseparable 8:1 mixture of *E* and *Z* isomers.
[27] For an excellent review regarding recent misassigned natural products, see: K. C. Nicolaou, S. A. Snyder, *Angew. Chem.* **2005**, *117*, 2086; *Angew. Chem. Int. Ed.* **2005**, *44*, 1012.
[28] In the vast majority of cases (> 98 %) C-4a and C-8a atoms in the pyrano[3,2-*b*]pyrans resonate below $\delta = 76$ ppm, and C-2 and C-2′ atoms in the 2,2′-bifuranyls resonate above $\delta = 76$ ppm. See the Supporting Information for key ^{13}C NMR chemical shifts for 74 synthetic pyrano[3,2-*b*]pyran and 27 synthetic 2,2′-bifuranyl compounds.
[29] In particular the mass spectra for both elatenyne and the enyne isolated from *L. majuscula* contain fragment ions which are readily explicable on the basis of a 2,2′-bifuranyl structure and are in close agreement with the fragmentation pattern reported and discussed for notoryne[2].
[30] It should be noted that at the time of the isolation of elatenyne no C_{15} halogenated 2,2′-bifuranyl natural products had been reported. A 2,2′-bifuranyl structure for elatenyne was considered less likely than the corresponding pyrano[3,2-*b*]pyran: J. G. Hall, PhD Thesis, La Trobe University (Australia), **1984**.
[31] Unlike a number of pyrano[3,2-*b*]pyrans we synthesized, neither elatenyne nor the enyne from *L. majuscula* are crystalline which may be partly because of the extra degree of freedom around the central C–C bond in 2,2′-bifuranyl units.

