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The Brosimum Allene: A Structural Revision

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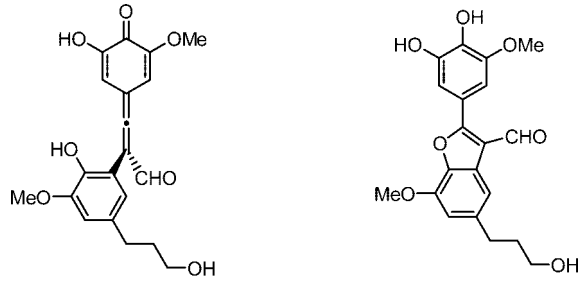
ABSTRACT



Insight derived from a synthetic model, calculated ^{13}C NMR data, and comparison to experimental data indicate that the proposed allenic structure A, originally assigned to an isolate from *Brosimum acutifolium* Huber, should be revised to B, a natural product and nonallenic substance, mururin C.

There are over 150 known allene-containing natural products.[1] Among these, the structure assigned to a component from the bark of *Brosimum acutifolium* Huber is arguably the most provocative (**A**, see above).[2] We believe this structure to be incorrectly assigned—indeed it seems doubtful that **A** represents a molecular arrangement isolable under standard conditions—and we provide evidence that this substance is identical to mururin C (**B**).[3] Accordingly, we begin with a discussion of the structural assigment of **A**, then turn to the interesting issue of the reactivity of this moiety, and end with a structural revision.

The original structure assigment of the *Brosimum* allene, reported in 2000 by Takashima et al., was based on HRMS and ^{1}H and ^{13}C NMR data, including two-dimensional NMR methods.[4] Interestingly, the ^{13}C NMR signal at 139 ppm was assigned to the central allenic carbon of **A**. The central carbon signal of allenes normally appears near 200 and often at about 210[5] (e.g., 200 for **1**,[6] 217 for **2**,[6] Figure 1). There are noteworthy exceptions. Whereas this signal appears at 189 ppm for difluoroallene **3**,[7] the corresponding signal for the tetramethoxy derivative **4**[8] appears at 114 and tetrafluoroallene **5**[6] appears at 118. Interestingly, related cumulenes,

[†] These authors contributed equally to this work.

(1) For an excellent overview, see: Krause, N.; Hoffmann-Roeder, A. *Modern Allene Chemistry*; Krause N., Hashmi A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; p 997.

(2) Takashima, J.; Asano, S.; Ohsaki, A. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2000**, *42*, 487.

(3) Takashima, J.; Asano, S.; Ohsaki, A. *Planta Med.* **2002**, *68*, 621.

(4) The two-dimensional NMR methods used in ref 2 were not disclosed.

(5) For representative examples, see: (a) Charrier, C.; Dorman, D. E.; Roberts, J. D. *J. Org. Chem.* **1973**, *38*, 2644. (b) van Dongen, J. P. C. M.; van Dijkman, H. W. D.; de Bie, M. J. A. *Rec. Trav. Chim.* **1974**, *93*, 29. (c) Stephany, R. W.; de Bie, M. J. A.; Drenth, W. *Org. Magn. Reson.* **1974**, *6*, 45. (d) Krudy, G. A.; Macomber, R. S. *J. Org. Chem.* **1978**, *43*, 4656. (e) Janssen, R. H. A. M.; Lousberg, R. J. J. C.; de Bie, M. J. A. *Rec. Trav. Chim.* **1981**, *100*, 85. (f) Dueker, A.; Szeimies, G. *Tetrahedron Lett.* **1985**, *26*, 3555. (g) Kanda, T.; Ando, Y.; Kato, S.; Kambe, N; Sonoda, N. *Synlett* **1995**, *n/a*, 745. (h) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392. (i) Bellavia-Lund, C.; Gonzalez, R.; Hummelen, J. C.; Hicks, R. G.; Sastre, A.; Wudl, F. *J. Am. Chem. Soc.* **1997**, *119*, 2946. (j) Liebeskind, L. S.; Pena-Cabrera, E. *Org. Synth.* **2000**, *77*, 135. (k) Miao, W.; Chung, L. W.; Wu, Y. D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 13326.

(6) Steur, R.; van Dongen, J. P. C. M.; de Bie, M. J. A.; Drenth, W.; de Haan, J. W.; van de Ven, L. J. M. *Tetrahedron Lett.* **1971**, *12*, 3307.

(7) Zens, A. P.; Ellis, P. D.; Ditchfield, R. *J. Am. Chem. Soc.* **1974**, *96*, 1309.

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e.g., quinoethylenes (Figure 1), are known and highly unstable in most cases.[9] ^{13}C NMR data for quinoethylenes have not been reported.

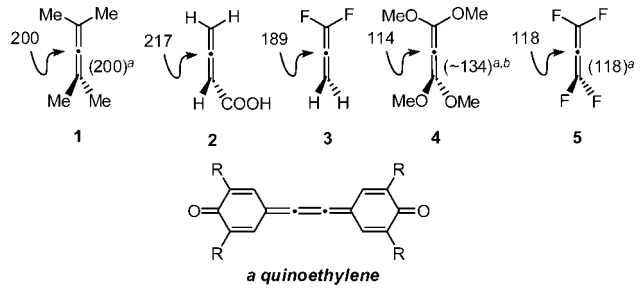


Figure 1. Allenic ^{13}C NMR signals: (a) calculated chemical shifts (see text); (b) the calculated shift varies with the C−OMe torsion angle.

Our studies began with computational modeling of the ^{13}C NMR expected for **A**. Geometry optimizations were performed with B3LYP [6-31G (2d, 2p)] and with HF [6-31G (2d, 2p)].[10] The spectral data were then calculated using several methods, including B3LYP, mPW1PW91, and HF.[11] Although the best fit was found for the B3LYP-optimized structure with B3LYP computed signals, no data set matched well. This set is shown along with the experimental data for **A** in Table 1 (**A**(expt) and **A**(calc)). Comparison of the observed signal assigned to C7 (139 ppm) to the computed chemical shift for this carbon (229 ppm) is most noteworthy. NMR signal prediction is as yet only approximate, but a differential of 90 ppm is extreme. Moreover, and without exception, all calculations predict the central allenic carbon signal of **A** to be ~230 ppm.[12]

The inability to computationally model this signal for **A** is in contrast to estimates of the central carbon signals of allenes **1** and **4** and, to a lesser degree, conformationally dynamic **5**. The calculated values of these allenes are given in parentheses in Figure 1. It thus appeared that there could well be a problem with the brosimum allene structural assigment.

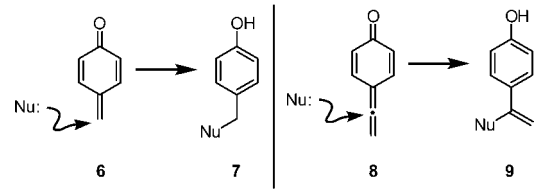
In a series of parallel investigations, we had set about meeting the synthetic challenge implicit to structure **A**. The allene of **A** is part of a functional array recognizable as an elaborated *p*-quinonemethide (**6**, Scheme 1). The high reactivity toward nucleophiles of molecules that house the quinonemethide substructure is recognized as largly a consequence of aromatization (**6** → **7**).[13] It is not unreasonable to anticipate this sort of transformation for cumulated quinonemethides (**8** → **9**). For **A**, the presence of the aldehyde should increase the reactivity of the system toward nucleophiles. In this regard, the proposed structure of this substance is most provocative.

Table 1. Computed and Experimental ^{13}C NMR Signals

position	*A*(expt)	*A*(calc)[a]	*B*(calc)[a]	*B*(expt)	*C*(calc)[a]
1	120.2	105.8	119.2	120.0	121.7
2	105.7	106.1	118.4	105.7	104.1
3	150.1	149.3	145.6	150.1	143.7
4	168.0	171.5	161.8	168.0	146.5
5	147.3	148.3	142.0	147.3	143.8
6	111.5	101.3	105.7	111.5	108.4
7	**139.1**	**229.3**	**140.5**	**139.1**	**132.4**
8	117.5	107.7	116.5	117.5	133.9
9	188.5	182.8	179.3	188.5	171.2
1′	141.6	131.7	138.8	141.6	137.4
2′	110.1	108.5	113.2	110.1	116.3
3′	150.1	144.1	141.9	150.1	144.0
4′	142.7	141.5	138.7	142.7	141.3
5′	128.5	117.3	128.6	128.5	129.0
6′	114.3	122.4	114.3	114.3	111.9
7′	33.6	36.2	35.9	33.6	36.1
8′	35.9	39.3	38.9	35.9	39.0
9′	62.3	66.7	67.0	62.3	66.7
3-OMe	56.9	55.0	57.8	56.9	55.3
3′-OMe	56.6	54.9	58.6	56.6	59.3

[a] GIAO/B3LYP/6-31G (2d, 2p)//B3LYP/6-31G (2d, 2p).

Scheme 1. Parent and Cumulated *p*-Quinonemethide



Scheme 2 and Table 2 present key data obtained from a synthetic model study. In principle, a phenol that contains a suitably positioned leaving group can be induced to eliminate it to give the brosimum allene arrangement (**10** → **11**, Scheme 2).[14] The silyl ether derived from aldehyde **12** was subjected to the action of isopropylmagnesium chloride and

(8) (a) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; Wiley-VCH: Weinheim, 2005; p 66. See also: (b) Saalfrank, R. W.; Maid, H. *Chem. Commun.* **2005**, *48*, 5953.

(9) (a) Zecher, D. C.; West, R. *J. Am. Chem. Soc.* **1967**, *89*, 153. (b) Koster, S. K.; West, R. *J. Org. Chem.* **1975**, *40*, 2300. (c) West, R.; Zecher, D. C.; Koster, S. K.; Eggerding, D. *J. Org. Chem.* **1975**, *40*, 2295.

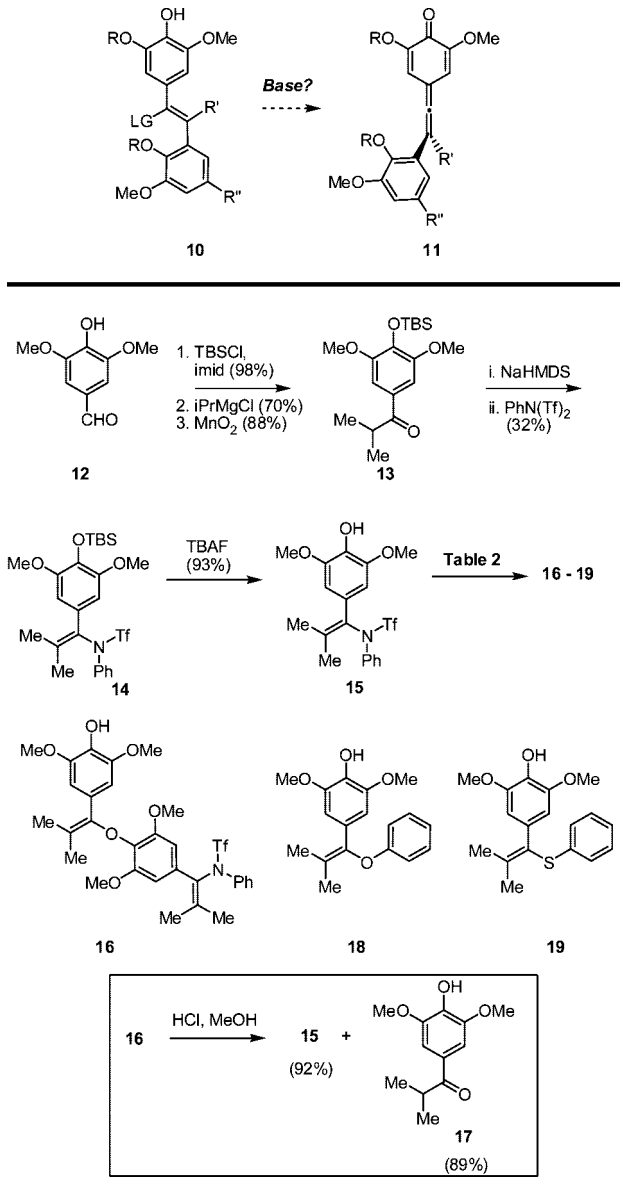
(10) All structures were fully optimized by analytical gradient methods using the Gaussian 03 suites: (a) Frisch, M. J.; Trucks, G. W.; Schlege, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; et al. Gaussian 03, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004 (see the Supporting Information for the full citation.)As indicated, density functional (DFT) calculations used the exchange potentials of: (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. They also used the correlation functional of: (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(11) See, for example: (a) Cimino, P.; Gomez-Paloma, L.; Duca, D.; Riccio, R.; Bifulco, G. *Magn. Reson. Chem.* **2004**, *42*, 26. (b) Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2895.

(12) See the Supporting Information for a complete list of computed ^{13}C NMR signals for **A**.

(13) For lead references on quinonemethide structure and reactivity, see: (a) Toteva, M. M.; Moran, M.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8814. (b) van de Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367. (c) Merijan, A.; Gardner, P. D. *J. Org. Chem.* **1965**, *30*, 3965.

Scheme 2



then oxidized to the corresponding ketone (**13**). Treatment with *N*-phenyltriflimide[15] gave **14**. Importantly, formation of vinyl sulfonamides related to **14** is known and thought to proceed by way of onium species related to **8**.[16] Treatment of **14** with TBAF gave **15** as an isolable and stable product.

The behavior of **15** under basic conditions is dependent on solvent, base, and where relevant, added nucleophile (**16**−**19**, Scheme 2). In neutral DMF/H_2O, **15** was stable at

(14) There is a strong analogy between this proposal and quinonemethide-forming eliminations, see for example ref 13. Moreover, oxidative conversion of **10** (LG = H) to **11** represents another potential route to this moiety.

(15) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

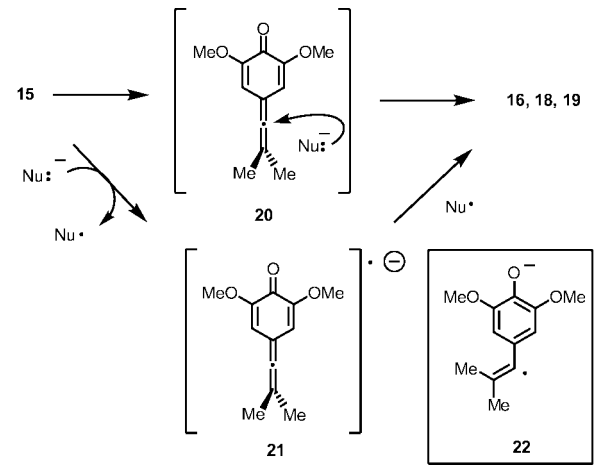
(16) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6184 The major byproduct of this reaction (50%) is the adduct derived from THF and then *N*-phenyltrifluoromethanesulfonamide addition to the TBS oxocarbenium analogue of **8** (see the Supporting Informationfor details and characterization of this substance). The use of ether as solvent for this reaction proved ineffective and gave **14** in 4% isolated yield.

Table 2. Reaction of **14** and **15** in DMF

entry	triflamide	base (equiv)	nucleophile (equiv)	product (yield, %)
1	**15**	none	H_2O (4)	no reaction
2	**14**	K_2CO_3 (4)	H_2O (4)	no reaction
3	**15**	K_2CO_3 (4)	H_2O (4)	**16** (60)
4	**15**	K_2CO_3 (4)	no added H_2O	**16** (59)
5	**15**	K_2CO_3 (4)	H_2O (12)	**16** (60)
6	**15**	K_2CO_3 (4)	H_2O (10% v/v)	**16** (55)
7	**15**	KOH (4)	H_2O (4)	**16** (45)
8	**15**	KOH (1)	H_2O (4)	**16** (49)
9	**15**	K_2CO_3 (4)	PhOH (1)	**18** (not formed)
10	**15**	K_2CO_3 (14)	PhOH (12)	**18** (47)
11	**15**	K_2CO_3 (4)	PhSH (4)	**19** (81)

room temperature, and no evidence of reaction was observed over the course of 48 h (entry 1, Table 2). Similarly, **14** was stable under basic conditions (entry 2). In contrast, over the course of 20 h, **15** slowly formed **16** (48%, entry 3) under conditions identical to those of entry 2. Mild acid hydrolysis of **16** gave ketone **17** (89%) and **15** (92%) (Scheme 2, see inset).[17] Although the apparent rate was slightly different, the exclusion of water from the reaction and the addition of excess water did not substantially influence the yield of **16** (entries 4−6, Table 2). The use of either a slight or large excess of potassium hydroxide also had only a marginal impact (entries 7 and 8). As shown in entry 9, the use of a near equivalent amount of phenol, instead of water, gave only **16**, with no evidence of **18**. A large excess of base and phenol, however, gave **18** in 47% yield. Moreover, use of thiophenol gave **19** in 81% yield.

Scheme 3. Mechanistic Rationale



A mechanistic rationale is depicted in Scheme 3. The phenoxide derived from deprotonation of **15** could promote

(17) The quality of the DMF was found to be important, as old DMF gave **17** directly (35−50%).

the loss of sulfonamide and give rise to allenic intermediate **20**. Addition of nucleophiles to **20** would lead to the observed products. The conversion of **15** to **20** is slow; thus, **15** is present in relative excess to **20** in all cases (entries 3−11). Depending on the nature of the other nucleophiles present, unreacted **15** adds to **20** to give **16**. According to this rationale, water and hydroxide must not competitively add to **20**. Phenoxide adds slowly and is competitive at high concentrations (compare entries 9 and 10), whereas benzenethiolate gives **19** in high yield by rapid and competitive addition to **20** (entry 11). A closely related pathway may also be relevant. Radical anion **21** (↔ **22**) may form from rapid electron transfer from a suitable nucleophile to **20** followed by radical coupling to give the observed products. This process should be fastest for benzenethiolate, slower for the phenoxide derived from **15**, and even slower for phenoxide. The other nucleophiles used in this study would not be good candidates for this pathway under these conditions. In light of these data, as well as available data on quinoethylenes and related compounds[9] and by analogy to quinonemethides,[13] species like **20** may not be sufficiently stable for observation and isolation under standard conditions.[18]

Based on the observations outlined above, we were led to consider an isomeric structure for the proposed brosimum allene and quickly arrived at benzofuran derivatives **B** and **C** as possible alternatives (Figure 2). The computed ^{13}C NMR signals for these compounds are given in Table 1 (**B**(calc) and **C**(calc)). Compound C is not a known substance. Compound **B** is mururin C, a natural product recently isolated from *B. acutifolium* by Takashima et al.[3,19] This structure assignment was based on HRMS, ^{1}H and ^{13}C NMR, including ^{1}H−^{1}H COSY, HMQC, and HMBC. The observed ^{13}C NMR signals for **B** are also shown in Table 1. The computed carbon signals for **B** match experiment and, most importantly, the experimental spectral data for **A** and **B** are identical (compare **A**(expt), **B**(calc), and **B**(expt)).[20]

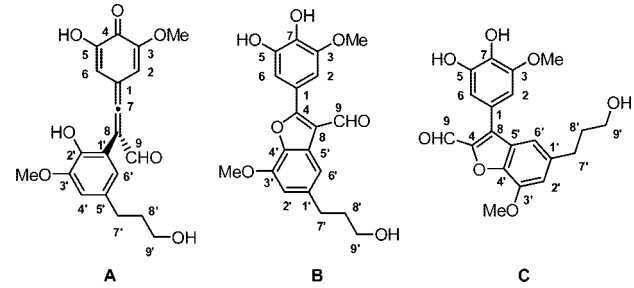


Figure 2. Isomers **A**, **B**, and **C** numbered for comparison

The data converge on the following conclusions: the brosimum allene isolate represented as **A** is incorrect. Although an allene in a context such as **A** or **20** may form as a transient species, it likely does not represent a molecular arrangement that can be isolated under standard conditions. The structure should be revised to **B** and does not include allene functionality.

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Supporting Information Available: Synthetic methods characterization data and computed ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) These observations do not speak to issues of biosynthesis and do not preclude analogous oxidative transformations (see ref 14).

(19) The relationship of **A** and **B**, although identical, is not obvious from the literature. See, for example, the literature related to **A**: (a) Dembitsky, V. M.; Maoka, T. *Prog. Lipid Res.* **2007**, *46*, 328. (b) Maurya, R.; Yadav, P. P. *Nat. Prod. Rep.* **2005**, *22*, 400. (c) Schumacher, D. D.; Mitchell, C. R.; Rozhkov, R. V.; Larock, R. C.; Armstrong, D. W. *J. Liq. Chromatogr. Relat. Technol.* **2005**, *28*, 169. (d) Rozhkov, R. V.; Larock, R. C. *Adv. Synth. Catal.* **2004**, *346*, 1854. (e) Hoffmann-Roeder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (f) Rozhkov, R. V.; Larock, R. C. *Tetrahedron Lett.* **2004**, *45*, 911. Conversly, no mention of **A** appears in the mururin C (**B**) literature; see: (g) Rodrigues, E.; Mendes, F. R.; Negri, G. *Central Nervous System Agents in Med. Chem.* **2006**, *6*, 211. (h) Takashima, J.; Komiyama, K.; Ishiyama, H.; Kobayashi, J.; Ohsaki, A. *Planta Med.* **2005**, *71*, 654. (i) Westcott, N. D.; Muir, A. D. *Phytochem. Rev.* **2004**, *2*, 401. (j) Lee, K.-H.; Xiao, Z. *Phytochem. Rev.* **2004**, *2*, 341. (k) Gao, S.; Feng, N.; Yu, S.; Yu, D.; Wang, X. *Planta Med.* **2004**, *70*, 1128. (l) Alcantara, A. F. de C.; Teixeira, A. F.; Felicio da S., I.; Batista de A., W.; Pilo-Veloso, D. *Quim. Nova.* **2004**, *27*, 371. (m) Takashima, J.; Ohsaki, A. *J. Nat. Prod.* **2002**, *65*, 1843.

(20) Understandably, structural misassignments, despite our many modern advantages, are not uncommon: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6012.