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Total Synthesis of (±)-Magnofargesin

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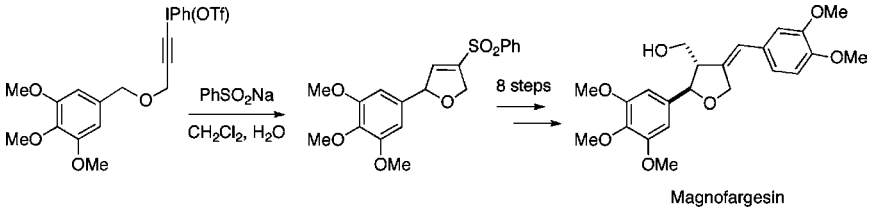
ABSTRACT



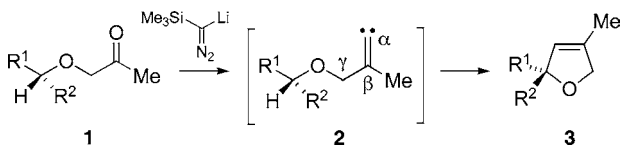
A convenient method for the preparation of 2,5-dihydrofurans by using the chemistry of alkynyl(phenyl)iodonium salts is reported. Treatment of 3-alkoxy-1-alkynyl(phenyl)iodonium triflates with sodium benzenesulfinate generates an alkylidenecarbene, which undergoes [1,5]-C-H insertion to form 2-substituted 4-benzenesulfonyl-2,5-dihydrofurans in reasonable yield. These cyclic vinyl sulfones are functionalized in such a way as to make them useful starting materials for the preparation of lignans. The application of this methodology to the first total synthesis of (±)-magnofargesin is disclosed.

Substituted 2,5-dihydrofurans have proven to be valuable building blocks for the preparation of tetrahydrofuran-based natural products and consequently there is considerable interest in the development of synthetic routes to this ring system.[1] The activation of carbon−hydrogen bonds, via the [1,5]-insertion of alkylidenecarbenes **2**,[2] is notable in this regard since it offers rapid access to five-membered heterocycles, including 2,5-dihydrofurans **3**, and proceeds with retention of configuration at the site of insertion (Scheme 1).[3]

As part of an ongoing study of the synthesis of five-membered heterocycles through carbene C−H insertion,[4] we have previously reported the application of the transformation shown in Scheme 1 to the synthesis of [4.5]spiroketal glycosides.[4b,c] In this case, intermediate **2** was generated by addition of trimethylsilyldiazomethyllithium to oxopropyl ketones **1**.[5] While this method of vinylidene formation is convenient, the requirement that the carbene β substituent be alkyl-based, to suppress Fritsch−Buttenberg−Wiechell (FBW) rearrangement of **2**,[2a] places some limitations on the utility of the insertion products **3**.[6]

In this context, we became interested in the generation and cyclization of γ-alkoxy alkylidenecarbenes **6** that bear an arylsulfonyl group at the β position (Scheme 2). Pioneering work by Stang[7a] and Ochiai[7b] and subsequent studies by Feldman[8] have demonstrated that these intermediates are readily accessible through Michael-type addition of sodium arylsulfinates to alkynyliodonium salts, are resistant to FBW rearrangement, and undergo [1,5]-insertion to form synthetically useful cyclic vinyl sulfones. Herein, we report the development of the idea outlined in Scheme 2 and its

Scheme 1



(1) For approaches to 2,5-dihydrofurans, see: (a) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challeppan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038. (b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502. (c) Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem. Eur. J.* **2003**, *9*, 4442. (d) Bravo, F.; Viso, A.; Castillon, S. *J. Org. Chem.* **2003**, *68*, 1172. (e) Donohoe, T. J.; Raoof, A.; Freestone, G. C.; Linney, I. D.; Cowley, A.; Helliwell, M. *Org. Lett.* **2002**, *4*, 3059. (f) Duffy, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1555. (g) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.

(2) For reviews of the chemistry of alkylidenecarbenes, see: (a) Knorr, R. *Chem Rev.* **2004**, *104*, 3795. (b) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 6, 1164. (c) Taber, D. F. In *Methods of Organic Chemistry*, 4th ed.; Helmchen, G., Ed.; Georg Thieme Verlag: New York, 1995; Vol. E21, p 1127. (d) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274.

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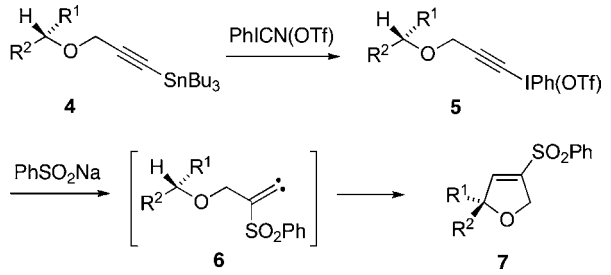
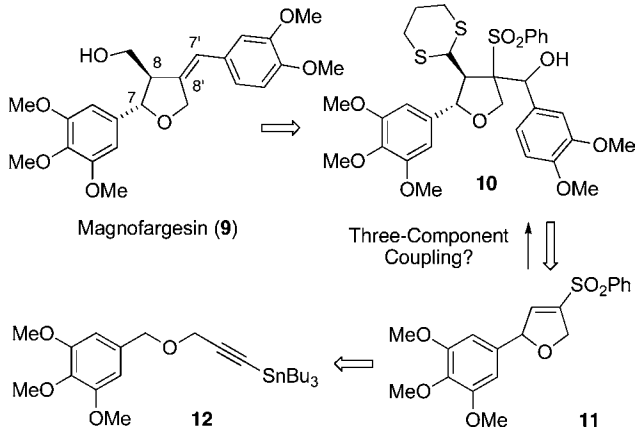
Scheme 2



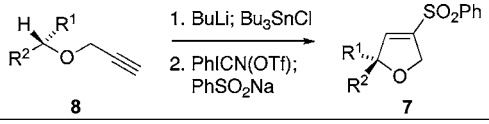
application to the first total synthesis of the lignan natural product, magnofargesin (**9**, Scheme 3).

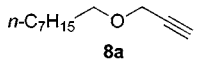
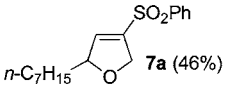
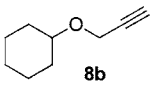
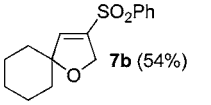
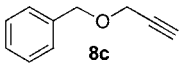
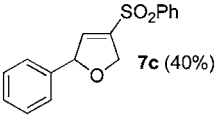
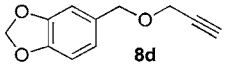
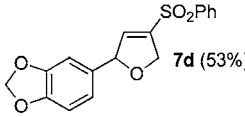
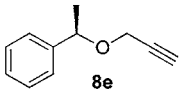
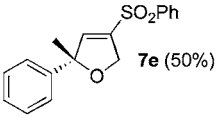
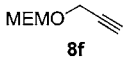
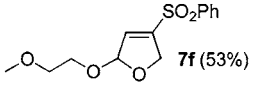
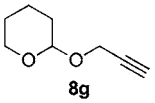
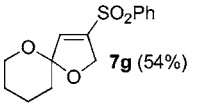
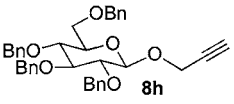
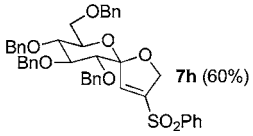
Scheme 3



Our study commenced with the preparation of alkynylstannanes **4a**−**h** from the corresponding propargyl ethers **8a**−**h**, through sequential treatment with *n*-BuLi and *n*-Bu_3SnCl in THF. After isolation,[9] exposure of these products to Stang's reagent (PhI(CN)OTf)[10] in CH_2Cl_2 rapidly generated the corresponding alkynyliodonium salts **5**. Finding the isolation of these unstable compounds to be troublesome, we opted to forego purification and instead carry out the insertion reaction directly. Thus upon addition of a 0.1 M aqueous solution of sodium benzenesulfinate to **5**, insertion occurred in situ to provide dihydrofurans **7** in moderate overall yield from **8**. As indicated in Table 1, this sequence

Table 1. Preparation of 3-Phenylsulfonyl-2,5-dihydrofurans **7**[a]



entry	substrate	product (yield, %)[b]
1	 **8a**	 **7a** (46%)
2	 **8b**	 **7b** (54%)
3	 **8c**	 **7c** (40%)
4	 **8d**	 **7d** (53%)
5	 **8e**	 **7e** (50%)
6	 **8f**	 **7f** (53%)
7	 **8g**	 **7g** (54%)
8	 **8h**	 **7h** (60%)

[a] Reagents and conditions: (1) **8**, *n*-BuLi (1.1 equiv), THF, −78 °C, *n*-Bu_3SnCl (1.0 equiv), −78 °C, 6 h. (2) PhICN(OTf) (1.1 equiv), CH_2Cl_2, −42 °C, 45 min, then $PhSO_2Na$ (1.1 equiv), H_2O, 45 min. [b] Isolated yield of **7** over two steps, after purification by flash chromatography.

of reactions is applicable to a range of substrates, most notably acetals **8g** and **8h** which were converted to the corresponding spiroketals. That there appears to be little

(3) For preparation of 2,5-dihydrofurans via alkylidenecarbene insertion, see: (a) Akiyama, M.; Isoda, Y.; Nishimoto, M.; Kobayashi, A.; Togawa, D.; Hirao, N.; Kuboki, A.; Ohira, S. *Tetrahedron Lett.* **2005**, *46*, 7483. (b) Hobley, G.; Stuttle, K.; Wills, M. *Tetrahedron* **2003**, *59*, 4739 and other papers in this series. (c) Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927. (d) Ohira, S.; Noda, I.; Mizobata, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 3375. (e) Kunishima, M.; Hioki, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, *35*, 7253. (f) Ohira, S.; Okai, K.; Moritani, T. *Chem. Commun.* **1992**, 721. (g) Baird, M. S.; Baxter, A. G. W.; Hoorfar, A.; Jefferies, I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2575. (h) Buxton, S. R.; Holm, K. H.; Skattebøl, L. *Tetrahedron Lett.* **1987**, *27*, 2167. (i) Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086.

(4) (a) Wardrop, D. J.; Bowen, E. G. *Chem. Commun.* **2005**, 5106. (b) Wardrop, D. J.; Zhang, W.; Fritz, J. *Org. Lett.* **2002**, *4*, 489. (c) Wardrop, D. J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389. (d) Wardrop, D. J.; Velter, A. I.; Forslund, R. E. *Org. Lett.* **2001**, *3*, 2261.

(5) (a) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869. (b) Colvin, E. W.; Hamill, B. J. *Chem. Commun.* **1973**, 151.

(6) Similar restrictions are associated with the use of 1,1-dihalogenoalkenes and 1-halogenoalkenes and as alkylidenecarbene precursors: see, refs 3e and 3i, respectively.

(7) (a) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (b) Ochiai, M. In *Hypervalent Iodine Chemistry*: *Modern Developments In Organic Synthesis*; Wirth T., Ed.; Springer-Verlag: Berlin, Germany, 2003; Vol. 224, p 5.

(8) For an account of this work, see: Feldman, K. S. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier Academic Press: London, UK, 2004; Vol. 4, p 133.

(9) Since alkynylstannanes **8** displayed variable stability toward silica gel, they were used in the iodonium transfer reaction without further purification.

(10) Stang, P. J.; Williamson, B. L.; Zhdankin, V. V. *J. Am. Chem. Soc.* **1991**, *113*, 5870.

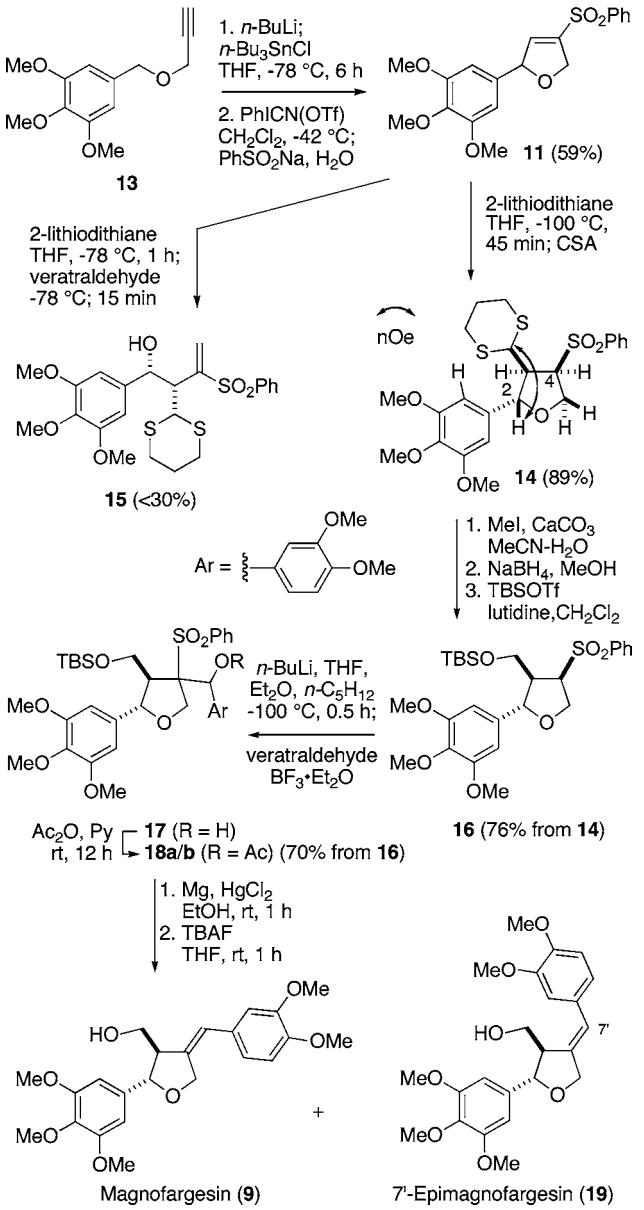
correlation between the efficiency of C−H insertion and the nature of the C−H bond undergoing reaction is likely a reflection of the highly reactive, undiscriminating nature of the alkylidenecarbene intermediates generated during this reaction. Having established the viability of this methodology, we turned our attention to its application to natural product synthesis.

The dried and pulverized flower buds of *Magnolia fargessi*, also known as "*shin-i*", have been used for centuries in China and Japan as *materia medica*. While traditionally this material has been indicated for the relief of nasal congestion and headaches, more recently it has proven to be a rich source of natural products, including several biologically active lignans.[11] Isolated by Miyazawa and coworkers in 1995 from "*shin-i*", (−)-magnofargesin (**9**) is an antagonist of platelet-activating factor (PAF), which reverses leukotriene D4-induced bronchoconstriction in guinea pigs with an LD_{50} of 19 μM (Scheme 3).[12] PAF is a potent phospholipid activator and mediator of many leukocyte functions, including platelet aggregation, inflammation, and anaphylaxis. Antagonists of PAF are of potential therapeutic value for the treatment of asthma and as protective agents against ischemic injury.[13]

Retrosynthetically, we envisioned that, after construction of the target's furanoid skeleton from **12**, via C−H insertion, both the C-8 hydroxymethyl group and the right-hand C-8′ "arm" of the lignan system could be installed in a one-pot, three-component coupling operation (Scheme 3). Specifically, we anticipated that addition of 2-lithio-1,3-dithiane to **12** would proceed from the less hindered face to generate an α-sulfonyl anion at C-8′.[14] Alkylation of this intermediate with veratraldehyde would then provide β-hydroxysulfone **11** from which the C7′−C8′ alkene could be installed through reductive elimination.[15]

Our route to (±)-magnofargesin (**9**) commenced from 3,4,5-trimethoxybenzyl progargyl ether (**13**), which was converted to stannane **12**, as previously described (Scheme 4). Sequential exposure of **12** to cyanophenyliodonium triflate and aqueous sodium benzenesulfinate then provided dihydrofuran **11** in 59% yield.[16] Although treatment of **11** with 2-lithiodithiane in THF, at −78 °C, now resulted in vinyl sulfone addition, unexpectedly, attempts to trap the resulting α-sulfonyl anion with a range of aldehydes, including veratraldehyde, failed. In all cases, a complex, intractable mixture of products, which included vinyl sulfone **15**, the

Scheme 4



product resulting from β-elimination of the conjugate base of **14**, was obtained. The instability of the anionic intermediate was not entirely unanticipated since Knochel has previously noted that related 3-phenylsulfonyl tetrahydrofurans also undergo ring opening upon exposure to *n*-BuLi.[17] Guided by Craig's observations of these systems,[18] we carried out the metalation−addition process at −100 °C in anticipation that the α-sulfonyl anion would be stable at this temperature. While we believe that deprotonation of **16** occurred under these conditions, the subsequent reaction with veratraldehyde proved to be impractically slow. As a result, we opted to intercept the α-sulfonyl anion by protonation and install the C8′ side chain in a stepwise fashion. Thus, sequential

(11) Jung, K. Y. N.; Kim, D. S.; Oh, S. R.; Park, S. H.; Lee, I. S.; Lee, J. J.; Shin, D. H.; Lee, H. K. *J. Nat. Prod.* **1998**, *61*, 80 and references therein.

(12) (a) Miyazawa, M.; Hiroyuki, K.; Kameoka, H. *Phytochemistry* **1996**, *42*, 531. (b) Miyazawa, M.; Kasahara, H.; Kameoka, H. *Nat. Prod. Lett.* **1995**, *7*, 205. (c) Myazawa, M. Lignan derivative and its use as a bronchodilator; Japanese Kokai Tokkyo Koho JP 06065224, 1994; *Chem. Abstr.* **1994**, *121*, 91784.

(13) Singh, M.; Saraf, M. K. *Drug Future* **2001**, *26*, 883.

(14) (a) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903. (b) Fuchs, P. L.; Braish, T. L.; Saddler, J. C. *J. Org. Chem.* **1988**, *53*, 3647.

(15) Kocienski, P. J. Reductive Elimination, Vicinal Deoxygenation and Vicinal Desilylation. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 6, Chapter 5.2, p 975.

(16) This reaction was carried out on scales of up to 8 mmol without incident.

(17) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455.

(18) Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron* **1999**, *55*, 13471 and other papers in this series.

treatment of **11** with 2-lithiodithiane and camphorsulfonic acid (CSA) at −100 °C provided **14** as a single diastereomer in excellent yield. The relative stereochemistry of the C-2 and C-3 stereogenic centers in **14** was confirmed by a NOESY experiment, which revealed the correlation shown in Scheme 4.[19] Alkylative hydrolysis of the dithiane group was accomplished under mild conditions (MeI, $CaCO_3$)[20] and the resulting aldehyde immediately reduced with sodium borohydride to provide the corresponding primary alcohol. Protection of this functionality as a *tert*-butyldimethylsiyl ether then gave compound **16** in excellent overall yield from **14**.

With a route to **16** established, we now readdressed the issue of sulfone alkylation. Although attempts to condense veratraldehyde with lithiated **16** in THF at −100 °C failed to provide **17**, use of Wicha's protocol[21] proved to be more fruitful. Thus, metallaton of **16** with *n*-BuLi as before, followed by sequential addition of $BF_3{\cdot}Et_2O$ and veratraldehyde provided a mixture of unstable β-hydroxysulfones **17** in low yield (<40%).[22] In this case, a significant quantity of starting material **16** was also recovered. While extension of the deprotonation time failed to increase the degree of conversion, the use of the Trapp mixture (THF/Et_2O/pentane, 4:4:1),[23] which unlike THF does not become viscous at low temperatures, led to a significant improvement in efficiency. That mixture **17** readily underwent retroaddition upon exposure to silica gel is most likely a consequence of the sterically congested nature of these β-hydroxysulfones.[24] To circumvent this problem, **17** was immediately acetylated after workup to provide **18** as a mixture of diastereomers in good overall yield. Introduction of the exocyclic olefin was now accomplished by exposure of mixture **18** to magnesium amalgam in ethanol.[25] Under these conditions, reductive elimination proceeded efficiently to provide a 10:9 ratio of *E* and *Z* isomers. Unable to separate this mixture by flash chromatography, the *tert*-butyldimethylsilyl protecting group was removed with TBAF to yield a mixture of magnofargesin (**9**) and 7′-*epi*-magnofargesin (**19**) with high efficiency (83%). Separation of these products by semipreparative HPLC then gave a sample of synthetic (±)-magnofargesin (**9**), whose spectral data (^1H and ^{13}C NMR) were in complete agreement with those reported by Miyazawa for the natural material.[12]

In summary, we report a new strategy for the preparation of 3-phenylsulfonyl-2,5-dihydrofurans **7** involving the [1,5]-C-H insertion of alkylidenecarbenes generated from readily accessible alkynyl(phenyl)iodonium triflates **5**. This methodology was successfully employed in the first total synthesis of the natural product magnofargesin (**9**), which was accomplished in 10 steps and in an overall yield of 12%.

Acknowledgment. We gratefully thank the National Institutes of Health (GM-59157) for financial support of this work.

Supporting Information Available: Full experimental procedures and spectral data for compounds **7a**−**h**, **8a**−**h**, **11**, and **13**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0609053

(19) The relative stereochemistry at C-4 could not be unambiguously assigned, but is presumed to be that shown in Scheme 4.

(20) Fetizon, M.; Jurion, M. *Chem. Commun.* **1972**, 382.

(21) Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J. *Tetrahedron* **1988**, *44*, 4989.

(22) Attempts to purify β-hydroxysulfone **17** by flash chromatography resulted in its reversion to **16**.

(23) (a) Köebrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41. (b) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, UK, 1994; p 8.

(24) The reaction of sterically hindered sulfonyl anions with aldehydes is known to be reversible: (a) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089. (b) Keck, G. E.; Savin, K. A.; Welgarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194.

(25) Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett.* **1995**, *36*, 5607.