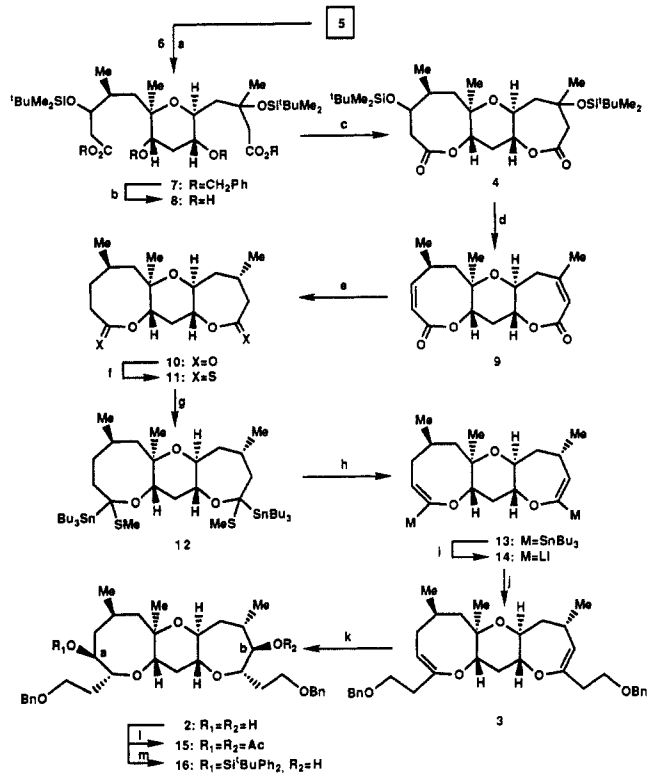
Scheme II. Synthesis of the BCD Ring Fragment of Brevetoxin A[a]



[a] Reagents and conditions: (a) 1.0 equiv of $ZnBr_2$, ether, −78 °C, then 3.0 equiv of **6**, 30 min, 81%; (b) H_2, $Pd(OH)_2$, THF, 25 °C, 3 h, 100%; (c) 2.5 equiv of $(pyrS)_2$, 2.5 equiv of PPh_3, CH_2Cl_2, 25 °C, 1 h, then 2.2 equiv of $AgClO_4$, toluene, 115 °C, 4 h, 76%; (d) (i) 1.0 equiv of HF·pyr, THF, 0 °C, 3 h, 85%, then 1.2 equiv of Martin's sulfurane, CH_2Cl_2, 0 °C, 30 min, 87%, (ii) 1.0 equiv of HF·pyr, THF, 0 °C, 4 h, 92%, then 1.2 equiv of Martin's sulfurane, CH_2Cl_2, 0 °C, 30 min, 92%; (e) H_2, 10% Pd on C, THF, 25 °C, 4 h, 100%; (f) 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylenes, 115 °C, 3 h, 63%; (g) 3.0 equiv of nBu_3SnLi, THF, −78 °C, 10 min, then 6.0 equiv of CH_3I, −78 °C, 15 min, 86%; (h) 4.0 equiv of $(CuOTf)_2$, benzene, 4.05 equiv of pentamethylpiperidine, 25 °C, 45%; (i) 3.0 equiv of nBuLi, THF, −78 °C, 5 min; (j) 5.0 equiv of (benzyloxy)ethyl triflate, 25 equiv of HMPA, 10 equiv of Et_3N, THF, −78 to 25 °C, 45 min, 65%; (k) 4.0 equiv of thexylborane, THF, 0 °C, 5 h, then 20 equiv of NaOH, 20 equiv of H_2O_2, 0 °C, 2 h, 73%; (l) 4.0 equiv of DMAP, 3.0 equiv of Ac_2O, CH_2Cl_2, 0 °C, 2 h, 90%; (m) 1.5 equiv of $^tBuPh_2SiCl$, 3.0 equiv of imidazole, DMF, 25 °C, 24 h, 82%.

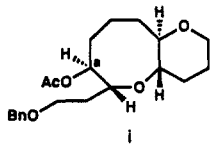
tallographic analysis[11] of diol **2** confirmed the structures of these compounds (see ORTEP drawing, Figure 1). Capitalizing on the difference in the steric environment of the two hydroxyl groups in **3**, the mono(silyl ether) **16** was easily formed under standard conditions (82% yield).

The described chemistry offers a stereoselective route to the BCD ring system of brevetoxin A (**1**) which is appropriately functionalized for further elaboration. The synthesis demonstrates new synthetic technology for the construction of medium-size cyclic ethers from thionolactones via organostannanes and follows a highly economical strategy designed by recognizing the subtle symmetry present in the targeted intermediate **2**.

Acknowledgment. We express our many thanks to Drs. G. Furst and J. Dykins of the University of Pennsylvania for NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, the National Science Foundation, Merck Sharp and Dohme USA, Glaxo Research Laboratories USA, and Hoffman LaRoche USA.

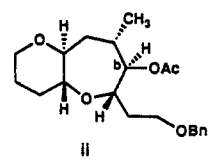
Supplementary Material Available: A scheme with reagents and conditions for the synthesis of intermediate **5** and listing of selected R_f, $[\alpha]$, ^1H NMR, and mass spectroscopic data for compounds **5**, **9**, **11**, **13**, **3**, **2**, and **16** as well as crystallographic data for compound **2** (18 pages). Ordering information is given on any current masthead page.

(10) These models include compounds i and ii, which were structurally defined by X-ray crystallographic analysis.[11]



i

[H_6: δ 4.9, ddd, J=10.0, 10.0, 2.5 Hz]



ii

[H_5: δ 4.8, dd, J=5.2, 5.2 Hz]

(11) We thank Dr. P. Carroll of the University of Pennsylvania for the X-ray crystallographic analyses described in this paper. Details will be published in a full account of this work.

Trifluoromethanesulfonic Acid Catalyzed Electrophilic Sulfuration of Alkanes (Cycloalkanes) with Elemental Sulfur to Dialkyl (Dicycloalkyl) Sulfides[1a,b]

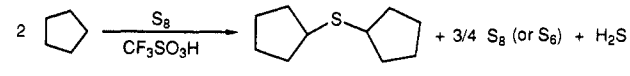
George A. Olah,* Qi Wang, and G. K. Surya Prakash*

Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry University of Southern California Los Angeles, California 90089-1661

Received January 11, 1990

Selective functionalization of saturated hydrocarbons to the corresponding monosubstituted derivatives is a most desirable goal in hydrocarbon chemistry. We have found several superacid catalyzed electrophilic substitution reactions of alkanes such as alkylation,[2] oxyfunctionalization,[3] halogenation,[4] nitration[5] and formylation.[6] The key to these reactions lies in the σ-donor ability of C–H and C–C bonds under superacidic conditions.[7]

In continuation of these studies, we now report the facile electrophilic sulfuration of saturated hydrocarbons with elemental sulfur in trifluoromethanesulfonic acid medium. Heating of elemental sulfur with excess cyclopentane in trifluoromethanesulfonic acid (serving also as the reaction medium) in a stainless steel autoclave at 150 °C for 12 h gave, after cooling of the reaction mixture to room temperature followed by aqueous workup, dicyclopentyl sulfide in 46% isolated yield (based on the amount of sulfur consumed).



(1) (a) Dedicated to Professor Paul v. R. Schleyer for his 60th birthday. (b) Electrophilic Reactions at Single Bonds. 24. Part 23: Olah, G. A.; Heiliger, L.; Aniszfeld, R.; Prakash, G. K. S. *New. J. Chem.* In press.

(2) (a) Olah, G. A.; Farooq, O.; Krishnamurthy, V. V.; Prakash, G. K. S.; Laali, K. *J. Am. Chem. Soc.* **1985**, *107*, 7541 and references cited therein. (b) Olah, G. A.; Farooq, O.; Prakash, G. K. S. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley Interscience: New York, 1989; Chapter 2.

(3) (a) Olah, G. A.; Parker, D. A.; Yoneda, N. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 909. (b) Olah, G. A.; Ernst, T. D.; Rao, C. B.; Prakash, G. K. S. *New J. Chem.* **1989**, *13*, 791.

(4) Olah, G. A.; Gupta, B. G. B.; Farnia, M.; Felberg, J. D.; Ip, W. M.; Husain, A.; Karpeles, R.; Lammertsma, K.; Mehrotra, A. K.; Trivedi, N. *J. Am. Chem. Soc.* **1985**, *107*, 7097 and references cited therein.

(5) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*, VCH Publishers: New York, 1989; Chapter 2.

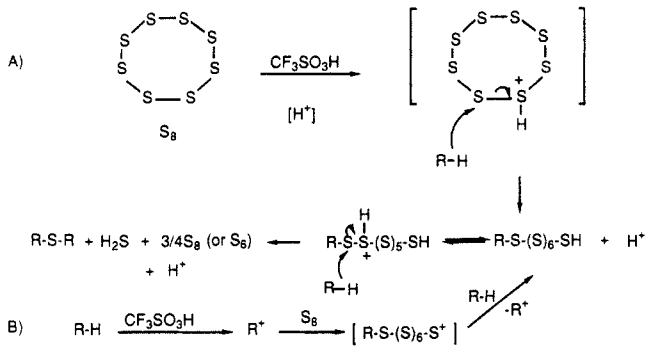
(6) Olah, G. A.; Farooq, O.; Marcelli, M.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1988**, *110*, 864.

(7) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley Interscience: New York, 1985.

(8) 2-Propanethiol on treatment with trifluoromethanesulfonic acid exclusively gave diisopropyl sulfide.

0002-7863/90/1512-3697$02.50/0

Scheme I



Isobutane under similar reaction conditions at 125 °C and a 10-h reaction time gave 33% diisobutyl sulfide. Even though the

$$2\ (CH_3)_3CH \xrightarrow[CF_3SO_3H]{S_8} [(CH_3)_2CHCH_2]_2S + H_2S$$

tertiary C–H σ-bond in isobutane is more electron rich than the primary methyl C–H σ-bonds, only the latter undergo reaction due to their steric accessibility. Alternatively, if the reaction proceeded by protolytic ionization of the alkane (vide infra), the secondary butyl cation formed would react with S_8. Any tertiary butyl cation formed would be too hindered to react with S_8.

Propane when reacted at 125 °C under similar conditions gave diisopropyl sulfide in 29% yield after a 10-h reaction time with a trace of *n*-propyl isopropyl sulfide. However, on prolonged

$$2\ CH_3CH_2CH_3 \xrightarrow[CF_3SO_3H]{S_8} [(CH_3)_2CH]_2S + H_2S$$

reaction at 150 °C for 62 h, a 1.1:1 mixture of diisopropyl sulfide and *n*-propyl isopropyl sulfide is obtained in 47% isolated yield.[9]

Other alkanes such as cyclohexane, cyclooctane, *n*-butane, and norbornane (bicyclo[2.2.1]heptane) are also reactive under the reaction conditions. However, they gave more complex mixtures of sulfides along with other byproducts. In the case of cyclooctane, the major products are aromatics. The norbornane skeleton underwent cleavage under the reaction conditions. In the case of methane and ethane, no reaction was observed under the present reaction conditions.

The suggested mechanism of the new sulfuration reaction of alkanes involves electrophilic sulfuration as depicted in Scheme I. The reaction could involve intermediate formation of thiols followed by bimolecular condensation to the sulfides.[8] Either protolytic activation of sulfur (path A) or protolytic ionization of the alkane (cycloalkane) resulting in a carbocation which alkylates sulfur (path B) can account for the observed results. Observation of isomerized products indicates intermediate formation of carbocations either by protolysis of alkanes by the superacid or reversible ionization of the thiols or sulfide products.

The observed results are in accordance with the proposed mechanism. Hydrogen sulfide is a byproduct of the reaction. Some elemental sulfur is leftover after the reaction, and trifluoromethanesulfonic acid acts as a protic catalyst. In its absence, no reaction takes place under the reaction conditions. As the acid is also used as the reaction medium, turnover numbers cannot be determined, but no loss of acid was observed in the reactions. Moreover, trifluoromethanesulfonic acid is only a mildly oxidizing superacid system, and no byproducts such as sulfoxides or sulfones were observed. Neither was any dehydrogenation of alkanes (cycloalkanes) observed under the reaction conditions with elemental sulfur alone. In the reactions no di- or polysulfuration products were obtained.

Lewis acid catalyzed sulfur insertion into aromatic compounds was well-known previously.[10] Even $AlCl_3$-catalyzed reaction of alkanes with sulfur was reported[11] but gave only complex mixtures of products. The presently described superacid–catalyzed sulfuration is the first selective, preparatively useful sulfuration reaction of saturated hydrocarbons. Further studies are underway to exploit the utility of this potentially significant new reaction.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

(9) Trifluoromethanesulfonic acid was found not to isomerize diisopropyl sulfide.

(10) Voronkov, M. G.; Vyazankin, N. S.; Deryagina, E. N.; Nakhmanovich, A. S.; Usov, V. A. *Reactions of Sulfur with organic Compounds*; Pizey, J. S., Ed.; Consultants Bureau: New York, 1987; Chapter 3.

(11) (a) Hopff, H.; Roggero, R.; Valkanas, G. Rev. *Chim. (Bucharest)* **1962**, *7*, 921; *Chem. Abstr.* **1964**, *61*, 4201. (b) Geigi, J. R. Br. Patent 783,037, 1957; *Chem. Abstr.* **1958**, *52*, 3860.

The Chemistry of a Quinone Methide Proposed To Be an Intermediate in Neolignan Biosynthesis

Steven R. Angle* and Kenneth D. Turnbull

Department of Chemistry
University of California, Riverside
Riverside, California 92521-0403

Received November 24, 1989

Neolignans comprise a class of pharmacologically active secondary plant metabolites that are formally derived from the oxidative coupling of two propenylphenols.[1,2] Gottlieb and coworkers have studied many of these compounds in detail and propose that quinone methide **1** is a common branch point in the biosynthesis of three structurally different types of neolignans (Scheme I).[3] This suggestion is quite intriguing, since it requires the quinone methide to react selectively with one of three different internal nucleophiles: (a) C-alkylation of the β-diketone to afford the bicyclo[3.2.1]octene skeleton found in *epi*-guianin **2**, (b) O-alkylation of the β-diketone to afford the hydrobenzofuran skeleton found in *epi*-burchellin **3**, or (c) attack of the alkene followed by capture of the resulting cation by the β-diketone oxygen to afford the spiro[5.5]undecane skeleton found in futoenone **4**.[3,4] The proposed bifurcation of quinone methide **1** might be directed enzymatically or chemically. Pathways a and b both involve the β-diketone and can be expected to be facile reactions; however, pathway c requires a relatively poor nucleophile, the alkene, to participate in a cyclization in the presence of the more nucleophilic β-diketone. In spite of the extensive isolation and chemical investigations by Gottlieb[3,5] and synthesis work by Büchi[6] and others,[2,4,7] the chemistry of the proposed quinone methide intermediate has not been explored. Our previous work on the

(1) For leading references on the pharmacological activity of neolignans see: (a) Gottlieb, O. R. In *New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutic Activity*, Proceedings of the First International Congress, 1976; Wagner, H., Wolff, P. M., Eds.; Springer Verlag: Berlin, 1977; p 227. (b) Gottlieb, O. R. *Quim. Nova* **1984**, *7*, 250.

(2) For current reviews on the isolation, chemistry, and synthesis of lignans and neolignans see: (a) Gottlieb, O. R. *Fortsch. Chem. Org. Naturst.* **1978**, *35*, 1. (b) Gottlieb, O. R. *Rev. Latinoamer. Quim.* **1974**, *5*, 1. (c) Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537. (d) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75. (e) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. (f) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499.

(3) (a) Gottlieb, O. R.; De Alvarenga, M. A.; Castro, O. C.; Giesbrecht, A. M. *Phytochemistry* **1977**, *16*, 1801. (b) Barbosa-Filho, J. M.; Yoshida, M.; Gottlieb, O. R. *An. Acad. Bras. Ci.* **1987**, *59*, 335. See also ref 2a and references cited therein.

(4) Isolation and synthesis of futoenone: Ogiso, A.; Kurabayashi, M.; Takahashi, S.; Mishima, H.; Woods, M. C. *Chem. Pharm. Bull.* **1970**, *18*, 105.

(5) For leading references see: (a) Gottlieb, O. R.; Da Silva, M. L.; Ferreira, Z. S. *Phytochemistry* **1975**, *14*, 1825. (b) Gottlieb, O. R.; De Alvarenga, M. A.; Brocksom, U.; Yoshida, M. *J. Chem. Soc., Chem. Commun.* **1978**, 831. See also ref 2a.

(6) (a) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (b) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717. (c) Büchi, G.; Mak, C.-P. *J. Org. Chem.* **1981**, *46*, 1. (d) Büchi, G.; Chu, P.-S. *J. Am. Chem. Soc.* **1981**, *103*, 2718.

(7) For recent examples and leading references see: (a) Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 5011. (b) Thomas, E. J.; Mortlock, S. V.; Seckington, J. K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2305. (c) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931.

0002-7863/90/1512-3698$02.50/0