

STERESELECTIVE SYNTHESSES OF THREE DIFFERENT CLASSES OF NEOLIGNANS FROM THE SAME STARTING MATERIALS

Thomas A. Engler,* Dong (Donna) Wei and Michael A. Letavic
Department of Chemistry, University of Kansas, Lawrence, Kansas 66045-0046

ABSTRACT: Lewis Acid catalyzed reactions of 2-alkoxy-5-allyl-1,4-benzoquinones with styrenes can be manipulated to form either the burchellin or guianin neolignans, or 4-allyl-2-aryl-3-methyl-2,3-dihydrobenzofurans.

Neolignans are naturally occurring dimers of propenylphenols.¹ More than fifteen different types of neolignan frameworks have been isolated, including those found in burchellin, 1, guianin, 2, and kadsurenone, 4; a related framework is 3 which has not been observed in a natural product to our knowledge. Interest in the neolignans arises from their widespread occurrence and diverse biological activity.^{1b-d} We have reported syntheses of the carbon frameworks 4 and 5 starting with reactions of styrenes with 2-alkoxy-, and 2-alkoxy-6-alkyl-1,4-benzoquinones.² We now report a new method to selectively form compounds with frameworks 1, 2 or 3 via reactions of 2-alkoxy-5-allyl-1,4-benzoquinones.³

Reactions of styrenes 6 with quinones 7⁴ promoted by excess Ti(IV), either as TiCl₄ or a reagent prepared from mixtures of TiCl₄:Ti(OiPr)₄^{2d}, produced cyclobutanes 8 and 9 with the former as the major, if not exclusive, product (Scheme I and Table, entries 1-8). The formation of 8 was unexpected based on previous mechanistic hypothesis.² However, the SnCl₄-promoted reactions of 6 with 7 at -78 °C gave either the cyclobutane 9 (entries 9-11, 13, 14) or, in the case of 6a with 7b, the bicyclic adduct 13a (Ar=C₆H₅, entry 12). Products 8, 9 and 13a were all isolated as single diastereomers.^{5,6} Upon warming the SnCl₄-promoted reactions of 6b/c with 7b to -30 °C (entries 15-16), mixtures of the keto-enol tautomers 15 and 16 were found which may result from rearrangement of 9 via 14. Methylation of the mixtures gave 17 [Ar=3,4-(OCH₃)₂C₆H₃, 64%]⁷ and burchellin, 1 (80%), respectively.⁶

Treatment of cyclobutanes 8 and 9 with CF₃CO₂H in CF₃CH₂OH or THF at room temperature or above effected their rearrangement to 12⁵ (in 45-68% yields) and 13a (in 39-74% yields), respectively, presumably via intermediates 10 and 11. Small amounts of quinones 7a/b (9-32%) were also found resulting from fragmentation of 10/11. The dihydrobenzofurans 12 were formed as a mixture of trans and cis isomers with the former predominating (8-12:1). The bicyclic products 13a were again formed as single diastereomers⁶ and were evidently

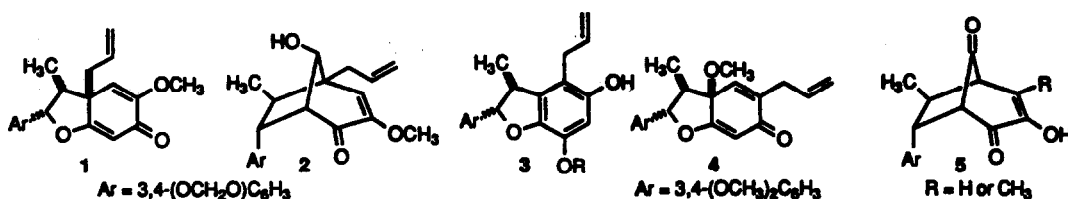


Table. Lewis Acid Promoted Reactions of Styrenes **6** with 2-Allyl-5-alkoxy-1,4-benzoquinones **7**.

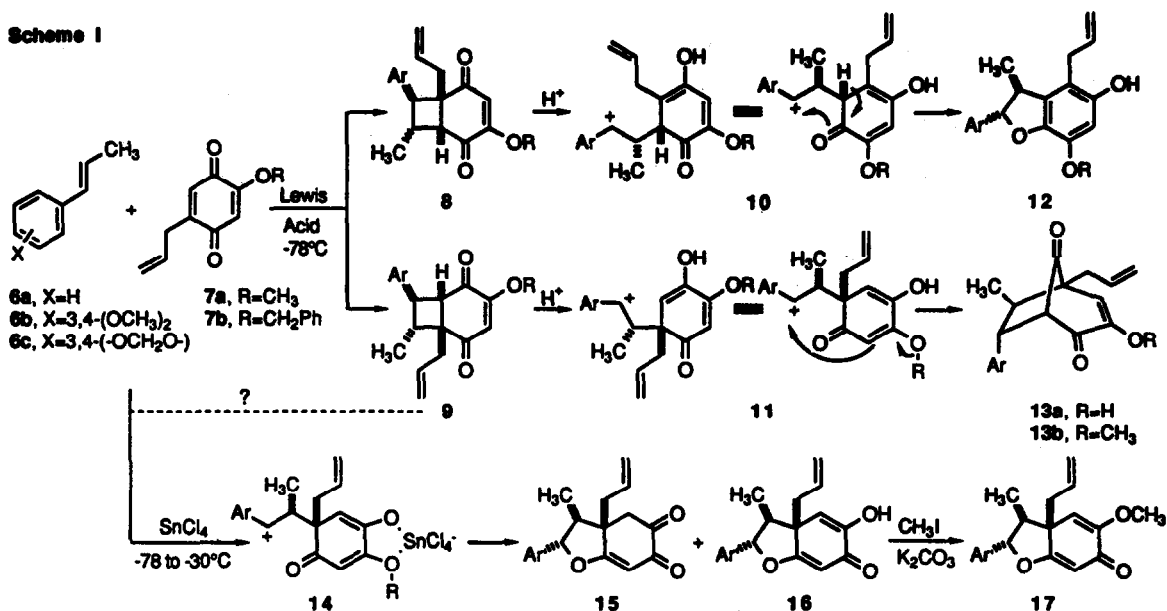
Entry	Styrene	Quinone	Lewis Acid (equiv) ^a	Temp(°C)	%Yields ^b (ratio)		
					8/9	13	15/16
1	6a	7a	TiCl ₄ (2)	-78	97 (1:0)	- ^c	- ^c
2	6a	7a	TiCl ₄ (4)	-78	70 (1:0)	-	-
3	6b	7a	Ti(IV)-solid nd (4.5) ^e	-78	83 (1:0)	-	-
4	6b	7a	5:1 TiCl ₄ :Ti(OiPr) ₄ (2)	-78	72 (4:1)	-	-
5	6b	7a	2:1 TiCl ₄ :Ti(OiPr) ₄ (3)	-78	76 (3:1)	-	-
6	6c	7a	3:1 TiCl ₄ :Ti(OiPr) ₄ (2)	-78	83 (1:0)	-	-
7	6c	7a	Ti(IV)-solid nd (2.3) ^e	-78	92 (5.7:1)	-	-
8	6c	7b	Ti(IV)-solid nd (1.5) ^e	-78	91 (2.5:1)	-	-
9	6a	7a	SnCl ₄ (2)	-78	34 (0:1)	-	-
10	6b	7a	SnCl ₄ (1)	-78	75 (0:1)	-	-
11	6c	7a	SnCl ₄ (1)	-78	87 (0:1)	-	-
12	6a	7b	SnCl ₄ (1.5)	-78→-60	-	71	-
13	6b	7b	SnCl ₄ (2)	-78	80 (0:1)	-	16
14	6c	7b	SnCl ₄ (2)	-78	86 (0:1)	-	-
15	6b	7b	SnCl ₄ (1)	-78→-30	-	-	78
16	6c	7b	SnCl ₄ (1)	-78→-30	-	-	69

a) With respect to quinone. b) Isolated yields. c) Indicates that none of this product was isolated. d) An off-white precipitate prepared by mixing TiCl₄ and Ti(OiPr)₄ is a 5:1 proportion in CH₂Cl₂ at r.t.; the solid is separated and dried under vacuum.^{2d} e) By weight with respect to quinone.

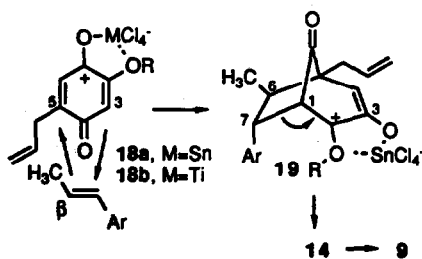
produced from **11** by intramolecular attack of the carbocation center on the enol ether moiety followed by dealkylation. In contrast, at -30 °C the related intermediates **14** underwent C-O bond formation and dealkylation to give **15/16**. In **14**, coordination of the Sn(IV) to the enol ether oxygen apparently lowers the nucleophilicity of the carbon-carbon double bond. Methylation of **13a** with CH₃I/K₂CO₃ in acetone gave **13b** (in 75-89% yield), one of which [Ar=3,4-(OCH₂O)C₆H₃] has been previously converted to the natural product guianin, **2**.^{3a,6}

One rationale for the selective formation of **8**, **9** and **13** involves an equilibrium between coordination of the Lewis acid to **7** at either the C-1 or C-4 carbonyl to give **18** and **20**, respectively (Schemes II and III). The former may be favored due to chelation effects, however, the C-4 oxygen is more basic. Then, with SnCl₄ as catalyst, cycloaddition of **18a** with the styrene stereoselectively gives the O-stabilized carbocation **19** (thermodynamic control, Scheme II); the aryl group of the styrene would be expected to occupy an endo position with respect to the pentadienyl carbocation moiety in the cycloaddition.^{2,3} Cleavage of the C-1/C-7 bond then gives the benzylic carbocation **14** and, at -78 °C, intramolecular addition of the cationic carbon to the "tin-enolate" moiety occurs to yield **9**. The trans relationship between the aryl and methyl groups on the cyclobutane ring in **9** would be expected for steric reasons and since the bond between C-5 and C-6 is established in the initial cycloaddition and remains intact during the rearrangement of **19** to **9**, the relative stereochemistry of the remaining stereogenic centers follows from the cycloaddition. The formation of **13** in reaction of **6a** with **7b** results from debenylation of **19**.^{2c} In reactions of **6b/c**, debenylation of **19** does not compete with the cleavage of the C-1/C-7 bond to give **14** (and then **9**) due to stabilization of the carbocation center in **14** by the aromatic

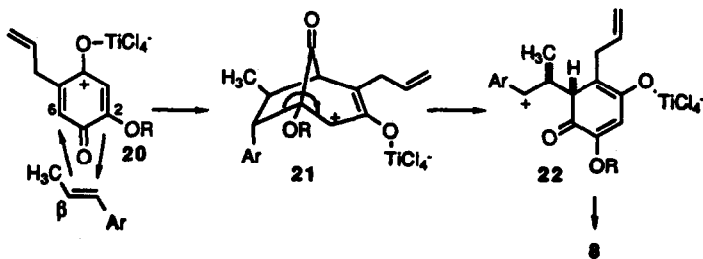
Scheme I



Scheme II



Scheme III



ring substituents. With excess Ti(IV) as catalyst, the product expected from cycloaddition of Ti(IV)-quinone complex 20 to give 21 and then 22 and 8 is found (Scheme III). This may be due to several factors. In an equilibrium mixture of 18b and 20, the cycloaddition across C-3/C-5 of the former with the styrene may be slower than cycloaddition across C-2/C-6 of the latter due to steric factors imposed by the C-5 allyl group. Thus, formation of 21 may be kinetically determined. Alternatively, the Ti(IV) may bind to the π -face of the quinone activating both C-2/C-6 and C-3/C-5 of the complex to cycloaddition,⁷ and the latter is again slower due to steric hindrance to bond formation between C- β of the styrene and C-5 of the complex. A third possibility is that a quinone-[Ti(IV)]₂ complex⁸ may be involved and cycloaddition across C-2/C-6 is again favored for steric reasons.⁹

In any event, the noteworthy point of this report is that although reactions of 2-alkoxy- and 2-alkoxy-6-alkyl-1,4-benzoquinones produce only one regioisomeric cyclobutane or bicyclic-adduct 5, reactions of quinones 7 can be manipulated to obtain selectively either the burchellin neolignans 15/16, the cyclobutane 8, or the regioisomeric cyclobutane 9. The latter two products can then be rearranged specifically to 12 and 13, respectively, which represent two additional types of neolignan frameworks.¹⁰

ACKNOWLEDGMENTS. This work was supported financially by the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation and Eli Lilly and Company. We thank Professor Steve Angle for helpful discussions, spectral data and sharing the results of his experiments prior to publication.

REFERENCES AND NOTES.

1. a) Gottlieb, O. R.; Yoshida, M. In "Natural Products of Woody Plants I" Rowe, J. W., Ed.; Springer-Verlag: Berlin, 1989; p. 439. b) Gottlieb, O. R. *Prog. Chem. Org. Nat. Prod.* 1978, 35, 1. c) Pongpipom, M. M.; Bugianesi, R. L.; Brooker, D. R.; Yue, B. -Z.; Hwang, S.-B.; Shen, T.-Y. *J. Med. Chem.* 1987, 30, 136. d) Hirano, T.; Wakasugi, A.; Oohara, M.; Oka, K.; Sashida, Y. *Planta Med.* 1991, 57, 331. e) Hattori, M.; Hada, S.; Watahiki, A.; Ihara, W.; Shu, Y.-Z.; Kakiuchi, N.; Mizuno, T.; Namba, T. *Chem. Pharm. Bull.* 1986, 34, 3885. f) See also, Agrawal, P. K.; Thakur, R. S. *Org. Mag. Res.* 1985, 23, 389.

2. a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* 1988, 110, 7931. b) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *ibid.* 1991, 113, 5068. c) Engler, T. A.; Letavic, M. A.; Combrink, K. D.; Takusagawa, F. *J. Org. Chem.* 1990, 55, 5810. d) Engler, T. A.; Letavic, M. A.; Takusagawa, F. *Tetrahedron Lett.* 1992, in press.

3. For leading references to previous synthetic efforts, see reference 2 and a) Büchi, G.; Mak, C. -P. *J. Am. Chem. Soc.* 1977, 99, 8073. b) Angle, S. R.; Turnbull, K. D. *ibid.* 1990, 112, 3698. c) Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc. Perkin Trans I* 1988, 2305. d) Shizuri, Y.; Shigemori, H.; Suyama, K.; Nakamura, K.; Okuno, Y.; Ohkubo, M.; Yamamura, S. In "Studies in Natural Products Chemistry, Vol. 8" Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; p. 159. e) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* 1992, 57, 2135.

4. Prepared in >64% yield by TiCl_4 catalyzed reaction of 2-methoxy- and 2-benzyloxy-1,4-benzoquinone^{2c} with allyltrimethylsilane; see, Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* 1977, 4041.

5. All compounds were characterized by high field ^1H (500 MHz) and ^{13}C (125 MHz) NMR, IR and/or exact mass. All ^1H and ^{13}C resonances were assigned by ^1H - ^1H decoupling and heteronuclear multiple bond correlation (HMBC) experiments and the stereochemistry in cyclobutanes 8/9 was unambiguously determined by ^1H - ^1H NOE experiments.^{2a}

6. The high field ^{13}C and ^1H spectra of 13 and 1/17 were consistent with data reported previously. For 13; see references 3b/c. For 1/17; see references 1b/f and, a) Wenkert, E.; Gottlieb, H. E.; Gottlieb, O. R.; Pereira, M. O. da S.; Formiga, M. D. *Phytochemistry* 1976, 15, 1547. b) Filho, R. B.; Figliuolo, R.; Gottlieb, O. R. *ibid.* 1980, 19, 659. c) Gottlieb, O. R.; DaSilva, M. L.; Ferreira, Z. S. *ibid.* 1975, 14, 1825. d) Aiba, C. J.; Fernandes, J. B.; Gottlieb, O. R.; Maia, J. G. S. *ibid.* 1975, 14, 1597. We also thank Professor Angle for copies of additional spectra of compounds related to 13, and 1/17.

7. a) Hendrickson, J. B.; Singh, V. *J. Chem. Soc.; Chem. Commun.* 1983, 837. b) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* 1991, 113, 8973.

8. a) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* 1985, 24, 112. b) Schultz, A. G.; Lee, H. *Tetrahedron Lett.* 1992, 33, 4397.

9. Of course, other mechanistic possibilities exist. For example, direct alkylation of the the Lewis acid-quinone complex may give 14 or 22 without proceeding through 19/21. As suggested by Swenton,^{3e} the same π stacking interactions that favor the endo aryl orientation in the cycloaddition may also favor this orientation in a direct alkylation reaction. Although the results do not discount alternate mechanisms, the cycloaddition mechanism nicely explains the facts and is useful as a working model for predictive purposes.

10. During the preparation of this manuscript, Professor Steve Angle informed us that bicyclo [3.2.1] octenediones related to 13b rearrange to benzofuranoids related to 17 upon treatment with TiCl_4 at -78°C and warming to room temperature. See also, reference 3a.