Tetrahedron Letters,Vol.29,No.38,pp 4827-4830,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

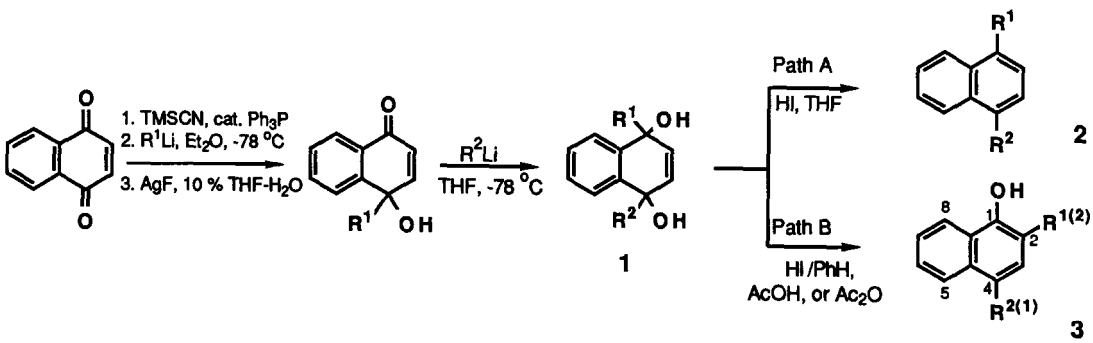
Competitive Dienone-Phenol Type Rearrangements for the Regioselective Preparation of 2,4-Disubstituted-Naphth-1-ols

Jeffrey A. Dodge and A. Richard Chamberlin*

Department of Chemistry
University of California
Irvine, California 92717

Summary: *The regioselective preparation of 2,4-substituted-naphth-1-ols via a variant of the dienone-phenol rearrangement is described.*

The regiocontrolled preparation of polysubstituted aromatic rings has long been of interest. Notable recent advances in this area include the selective elaboration of existing rings[1] and the ingenious use of aliphatic or alicyclic precursors.[2] In preparing substituted polycyclic aromatic compounds[3] by standard HI reduction[4] (*e.g.* **1** to **2**), we noted the persistent formation of small amounts of phenolic by-products (**3**). With only minor changes in reaction conditions, however, it was found that the naphthol **3** is the *sole* product. These conditions, described below, provide a simple and regioselective approach to such 2, 4-alkyl- or aryl-naphthols that is complementary to existing methods.

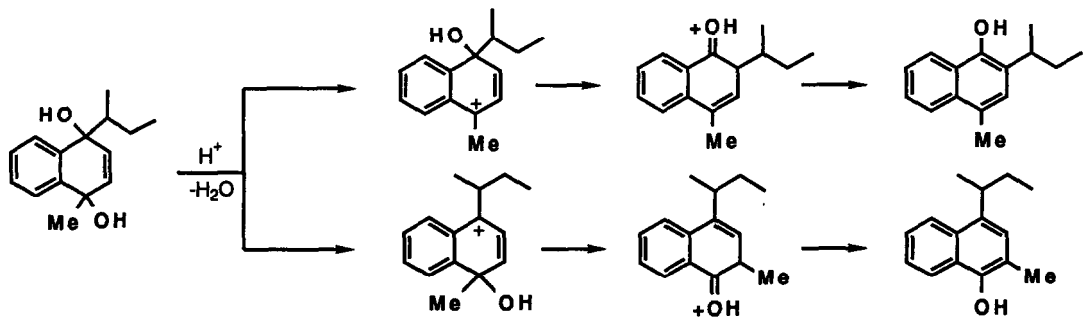


1 **2** **3**

Preparation of the precursor **1** consists of initial mono-protection of 1,4-naphthoquinone as the α–siloxy nitrile (1.3 eq. TMSCN, cat. Ph_3P, CH_2Cl_2, 0 ° C, 2 h) followed by addition of the appropriate alkyl- or aryllithium (1.3 eq., THF, –78 ° C, 1 h), and finally deprotection (1 eq. AgF, 10% aqueous THF, room temperature, 0.5 h) to give the mono-addition product in good yields.[5,6] Addition of a second organolithium (3 eq., THF, –78 ° C, 1 h, aqueous NH_4Cl quench) yields the corresponding diol **1**.[7] In most cases, including

those in which the R groups of the diol are identical (Table), addition of the nucleophiles to the unprotected quinone results in lower yields (15-30 %) than when the TMSCN/Ph_3P protection sequence is employed. Reduction of the diol **1** with aqueous HI in THF[4] (path a) gives the expected 1,4-disubstituted naphthalene skeleton **2**. However, employing benzene or acetic acid as solvent under similar acidic conditions[8] gives the corresponding 2,4-disubstituted-naphth-1-ol **3**, presumably *via* a dienone-phenol type mechanism,[9,10] *i.e.*, protonation followed by loss of water, R group migration, and enolization to the naphthol. The reason for the dramatic solvent dependency of this reaction is still unclear, but it allows essentially complete control of the product distribution.

For symmetrical diols (Table, entries 1-4), the rearrangement can proceed to give only a single phenolic product, in which the 2- and 4-positions are substituted equivalently. A more interesting situation arises when the starting material is an *unsymmetrically* substituted diol (Table, entries 5-8). In these cases, there are two possible dienone-phenol type rearrangements, each giving a different regioisomer. For example, rearrangement and aromatization of the *s*-butyl/methyl-substituted diol (Table, entry 6) gives an approximately 6:1 mixture in which the predominant product arises from selective migration of the *s*-butyl group in the rearrangement.



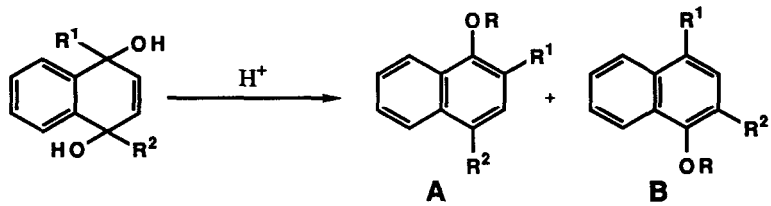
Either of two factors could, in principle, control the regioselectivity of this process: (1) the relative rate of formation of the initial carbocations (i.e. preferential formation of the more stable cation followed by migration of the allylic R group), or (2) the relative migratory aptitudes of R^1 and R^2 (after rapid reversible carbocation formation). In the cases examined, phenyl, *s*-butyl, and *n*-butyl substituents migrated preferentially compared to methyl. Likewise, phenyl migration was preferred to *n*-butyl (Table, entry 7). These migratory aptitudes are the same as those for the simple dienone-phenol rearrangement, in which alkyl group migration (rather than carbocation formation) has been shown to be rate determining,[11] and further are consistent with case (2) above but not case (1). Although the ratios (Table, entries 5-8) are modest, the isolated yields of the major products are good in most cases and the isomers are easily separable by flash or radial chromatography.[12]

The structural assignments of all regioisomeric pairs were made by difference NOE measurements (500 MHz). For example, the major naphthol obtained from the rearrangement of the *s*-butyl/methyl-substituted diol (Table, entry 6), gives unambiguous NOE effects (benzene-d_6) in the following experiments: (a) irradiation of the C(1) OH proton (δ 4.61) results in the enhancement of the C(8) *peri* proton (δ 8.15), (b) irradiation of the benzylic methine proton (δ 2.66) gives enhancement at both the C(1) OH proton and the C(3) proton (δ 7.07) and (c) irradiation of the benzylic methyl group (δ 2.43) exhibits an effect at the C(3) proton as well as the C(5)

peri proton (δ 7.79). Such enhancements are clearly consistent with *s*-butyl migration. Conversely, for the minor regioisomer, irradiation of the benzylic methine group (δ 3.32) gives an NOE enhancement (benzene-d_6) at the adjacent C(5) *peri* proton(δ 7.99).

This methodology provides an operationally simple method for the preparation of 2,4-substituted-1-naphthols from commercially available starting materials, affording a regioselective route to potential 5-lipoxygenase inhibitors[13] as well aromatic sesquiterpenes isolated from the Heterotheca species.[14]

TABLE. NAPHTHOL FORMATION FROM SYMMETRICALLY AND UNSYMMETRICALLY SUBSTITUTED NAPHTHOQUINONE DIOLS.



entry	diol R^1	diol R^2	reaction conditions	R	naphthol ratio A	naphthol ratio B	isolated yield (%) A	isolated yield (%) B
1	Me		Ac_2O, reflux	Ac	---		89	---
2	*n*-butyl		AcOH, reflux	H	---		78	---
3	Ph		AcOH, reflux	H	---		94	---
4	*m*-$CH_3OC_6H_4$		AcOH, reflux	H	---		73	---
5	*n*-butyl	Me	HI, PhH	H	5	1[a]	43	7
6	*s*-butyl	Me	HI, PhH	H	6	1[a]	82	13
7	Ph	*n*-butyl	HI, PhH	H	5	1[a]	54	9
8	Ph	Me	HI, PhH	H	>30	1[b]	77	0

[a] based on isolated yields [b] determined by ^{1}H NMR

Acknowledgement: Support of this work by the National Institutes of Health (NS-25401 and a Career Development Award to ARC) is gratefully acknowledged.

References and Notes:

1. For recent representative examples see (a) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137. (b) Semmelhack, M. F.; Ho, S.; Steigerwald, M.; Lee, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 4397. (c) Katsuura, K.; Snieckus, V. *Can. J. Chem.* **1987**, *65*, 124. (d) Sibi, M. P.; Dankwardt, J. W.; Snieckus, V. *J. Org. Chem.* **1986**, *51*, 271. (e) Hrytsak, M.; Etkin, N.; Durst, T. *Tetrahedron Lett.* **1986**, 5679.

2. For a general review see Bamfield, P.; Gordon, P. F. *Chem Soc. Rev.* **1984**, *13*, 441. Other specific examples include (a) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (b) Vollhardt, K. P. C.; Lecker, S. H.; Nguyen, N. H. *J. Am. Chem. Soc.* **1986**, *108*, 856. (c) Tius, M. A.; Thurkauf, A. *Tetrahedron Lett.* **1986**, 4541. (d) Tius, M. A.; Gomez-Galeno, J. *Tetrahedron Lett.* **1986**, 2571. (e) Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1983**, 4939.

3. Dodge, J. A.; Chamberlin, A. R. *Tetrahedron Lett.* **1988**, 1359.

4. Rio, G. *Ann. Chem.* **1954**, *9*, 182.

5.(a) Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350. (b) Evans, D. A.; Hoffman, J. M.; Truesdale, L.K. *J. Am. Chem. Soc.* **1973**, *95*, 5822.

6. Commercially available alkyllithiums (methyl-, *n*-butyl-, and *s*-butyllithium) were used. Aryllithiums were prepared from the corresponding arylbromide by halogen-metal exchange with *n*-BuLi (THF, – 78 ° C) immediately prior to use.

7. A single diol product was isolated in each case, for which the relative stereochemistry was not determined.

8. Typical procedures: (a) The phenyl substituted diol (Table, entry 3) (55 mg, 0.17 mmol was heated in neat AcOH (3 mL) for 2 h. Removal of the solvent *in vacuo* gave a crude oil which was purified chromatographically (radial, SiO_2, 1 mm, 9:1 hexanes-ether) to give 48 mg (94 %) of the naphthol. (b) To the *s*-butyl/methyl diol (Table, entry 6) (52 mg, 0.22 mol) in benzene (5 mL) was added 4 drops of 57 % aq. HI and the reaction was allowed to stir for 10 min before the addition of water (3 mL) and sodium metabisulfite. Ether extraction, drying ($MgSO_4$), removal of the solvent *in vacuo*, and *immediate* chromatography (radial, SiO_2, 1 mm, 9:1 hexanes-ether) gave 38 mg (82 %) of the regioisomer A and 6 mg (13 %) of B. In general, the naphthols produced were relatively unstable and decomposed upon standing at room temperature. However, acetylation enhances their stability considerably.

9.For reviews of the dienone-phenol rearrangement see (a) Waring, A. J. *Adv. Alicyclic Chem.* **1966**, *1*, 129. (b) Miller, B. *Mech. Mol. Mgr.* **1968**, *1*, 247. (c) Perkins, M. J.; Ward, P. *Mech. Mol. Mgr.* **1971**, *4*, 55.

10. There are several examples of a similar dienone-phenol type (alternatively a vinylogous pinacol) rearrangement in a related 1,4-benzoquinone system. See (a) Wessely, F.; Holzer, L.; Vilcsek, H. *Monatsh. Chem.* **1952**, *83*, 1253. (b) Wessely, F.; Holzer, L.; Langer, F.; Schinzel, E.; Vilcsek, H. *Monatsch. Chem.* **1955**, *86*, 831.

11 (a) Pilkington, J. W. ; Waring, A. J. *J. Chem. Soc., Perkins Trans. 2* **1976**, 1349 and references cited therein. (b) Vitullo, V. P. ; Grossman, N. *J. Am. Chem. Soc.* **1972**, *94*, 3844. For other examples of preferential migration of alkyl and/or aryl groups see (c) Palmer, J. D.; Waring, A. J. *J. Chem. Soc., Perkins Trans. 2* **1979**, 1089. (d) Vitullo, V. P.; Logue, E. A. *J. Org. Chem.* **1972**, *37*, 3339. (e) Carlin, R. B.; Sivaramakrishnan, K. P. *J. Org. Chem.* **1970**, *35*, 3368. (f) Marx, J. N.; Argyle, J. C.; Norman, L. R. *J. Am. Chem. Soc.* **1974**, *96*, 2121.

12. All precursors and major regioisomeric naphthol products gave satisfactory proton and carbon NMR, high resolution mass spectra, and infrared spectra. Minor regioisomers were characterized by their proton NMR and mass spectra. In each case, both major and minor regioisomeric naphthols gave satisfactory NOE enhancements with regard to the assigned structures, as described in the text.

13. Batt, D.G. Eur. Pat. Appl. EP 201,1071 (*Chem. Abstr.* **1987**, *107*, 52007e).

14. (a) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1976**, *109*, 2021. (b) Bohlmann, F.; Mailahn, W. *Chem. Ber.* **1981**, *114*, 1091. (c) Adachi, K.; Taniguchi, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1655. (d) Adachi, K.; Masahito, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 651.

(Received in USA 31 May 1988)