with 5-chloro-1-phenyl-1*H*-tetrazole (6.33 g, 35.1 mmol) and K_2CO_3 (10.53 g, 76.3 mmol) for 24 h. The reaction mixture was cooled, diluted with H_2O (500 mL), and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and filtered. The filtrate, on evaporation to dryness and trituration with ether, gave a white solid: 14.0 g (92.6%); mp 108 °C (lit.[15] mp 121–123 °C); mass spectrum, *m/e* 431 (M^+). Similarly prepared from **4b** was **3-*O*-(1-phenyltetrazol-5-yl)-*N*-*n*-propylnormorphine hydrochloride (4e)**: 79.4% yield; mp 144–146 °C. Anal. Calcd for $C_{26}H_{27}N_5O_3$·HCl·0.5H_2O: C, 62.09; H, 5.77; N, 13.97. Found: C, 62.13; H, 5.83; N, 13.88.

3,6-Bis-*O*-(1-phenyltetrazol-5-yl)morphine Hydrochloride (4f). To a suspension of sodium hydride (0.68 g, 28.3 mmol) in THF (5 mL) was added a solution of **3** (1.0 g, 3.5 mmol) in 50 mL of acetone, and the mixture was stirred for 1 h. A solution of 5-chloro-1-phenyl-1*H*-tetrazole (1.5 g, 8.3 mmol) in 45 mL of THF was gradually added to the above suspension, and stirring was continued for 0.5 h. The reaction was terminated by carefully adding a few drops of H_2O, and then the mixture was diluted further with 50 mL of H_2O. The aqueous phase was extracted from $CHCl_3$, washed with H_2O, dried over $MgSO_4$, and filtered. The filtrate was evaporated, and the crude material was purified on a column by using silica gel and $CHCl_3$/MeOH (20:1) as the eluant to yield 1.4 g (70%) of **4f**. The base was converted into the hydrochloride salt by using Et_2O–HCl: mp 180–181 °C; $[\alpha]^{22.5}_{578}$ −54.1° (*c* 0.1452, MeOH); mass spectrum, *m/e* 573 (M^+), 530 ($M^+ - CH_2N-CH_3$). Anal. Calcd for $C_{31}H_{27}N_9O_3$: C, 64.92; H, 4.71; N, 21.99. Found: C, 65.03; H, 4.81; N, 21.98.

(*R*)-(+)-10-*O*-(1-Phenyltetrazol-5-yl)apomorphine Hydrochloride (5a). A solution of **4d** (1.4 g, 3.25 mmol) in CH_3SO_3H (5 mL) was heated at 90–95 °C for 1 h. The solution was cooled and added dropwise to a saturated solution of $NaHCO_3$. After neutralization, the suspension was extracted from $CHCl_3$, dried over $MgSO_4$, treated with charcoal, filtered, and evaporated to dryness to yield 0.9 g (67.4%) of **5a**. The free base was converted into the HCl salt by adding Et_2O–HCl: mp 182–188 °C; $[\alpha]^{23.5}_{578}$ +43.2° (*c* 0.132, MeOH); mass spectrum, *m/e* 411 (M^+), 368 ($M^+ - CH_2N-CH_3$), 325 (368 − HN_3), 266 (M^+ − phenyltetrazoly), 206 (325 − C_6H_5NCO). Anal. Calcd for $C_{24}H_{21}N_5O_2$·HCl·H_2O: C, 61.87; H, 5.16; N, 15.05. Found: C, 62.30; H, 5.31; N, 15.05.

The similar rearrangement of **4f** in CH_3SO_3H led to **5a** in comparable yields. Similarly prepared from **4e** (2.0 g, 4.05 mmol) was (*R*)-(+)-10-*O*-(1-phenyltetrazol-5-yl)-*N*-*n*-propylnorapomorphine hydrochloride (**5b**): yield 1.6 g (89.9%); mp 175–178 °C; $[\alpha]^{23.5}_{578}$ +30.8° (c 0.175, MeOH). Anal. Calcd for $C_{36}H_{25}N_5O_2$·HCl·H_2O: C, 63.22; H, 5.67; N, 14.18. Found: C, 62.73; H, 5.76; N, 14.01.

(*R*)-(−)10-*O*-(1-Phenyltetrazol-5-yl)-11-methoxyaporphine Hydrochloride (6a). To an etheral solution of CH_2N_2 (3.0 g in 300 mL of ether) was added **5a** (1.1 g, 268 mmol), and the resulting suspension was stirred overnight and filtered. Evaporation of the filtrate gave chromatographically pure product, 1.1 g (96.7%). The free base was converted into the hydrochloride by adding Et_2O–HCl: mp 146–155 °C; $[\alpha]^{23.5}_{578}$ −62.4 (*c* 0.0834, MeOH); mass spectrum, *m/e* 425 (M^+), 280 (M^+ − phenyltetrazolyl), 249 (280 − OCH_3), 237 (280 $-CH_2N-CH_3$). Anal. Calcd for $C_{25}H_{23}N_5O_2$·HCl·H_2O: C, 62.56; H, 5.42; N, 14.60. Found: C, 62.87; H, 5.53; N, 14.73.

Similarly prepared from **5b** (1.4 g, 3.2 mmol) and CH_2N_2 was **(*R*)-(−)-10-*O*-(1-phenyltetrazol-5-yl)-11-methoxy-*N*-*n*-propylnoraporphine hydrochloride (6b)**: 1.1 g (76.4%); mp 152–155 °C; $[\alpha]^{23.5}_{578}$ −68.1 (*c* 0.163, MeOH); mass spectrum, *m/e* 453 (M^+). Anal. Calcd for $C_{27}H_{27}N_5O_2$·HCl·H_2O: C, 63.84; H, 5.91; N, 13.79. Found: C, 63.94; H, 5.97; N, 14.35.

(*R*)-(−)-11-Methoxyaporphine Hydrochloride (7a). A solution of **6a** (1.0 g, 2.35 mmol) in 90 mL of acetic acid with 5% Pd/C (1.1 g) was hydrogenolyzed in a Parr apparatus at room temperature and 45 psi of H_2 for 11 days. The catalyst was removed by filtration, and the solvent was evaporated to dryness. The semisolid product was dissolved in $CHCl_3$ and treated with 10% of KOH. The organic layer was separated, washed with brine and H_2O, dried over $CaSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography with silica gel and Et_2O–hexane (1:1) as the eluant to yield 0.35 g (56.2%) of product. The free base was converted to the hydrochloride salt with Et_2O–HCl and gave a white precipitate of **7a**: mp 235–242 °C; $[\alpha]^{22}_{578}$ −74.9°, $[\alpha]^{22}_{548}$ −101.2° (*c* 0.0494, MeOH); mass spectrum, *m/e* 265 (M^+), 264 (M^+ − 1), 222 ($M^+ - CH_2N - CH_3$), 206 (222 − CH_3). The compound showed identical R_f values on TLC when compared with (±)-**7a** prepared previously.[3] Anal. Calcd for $C_{18}H_{19}NO$·HCl: C, 71.64; H, 6.30; N, 4.64. Found: C, 71.63; H, 6.46; N, 4.66.

(*R*)-(−)-11-Methoxy-*n*-propylnoraporphine Hydrochloride (7b). This compound was similarly prepared from **6b** (0.9 g, 1.99 mmol) to give **7b**: 0.32 g (50%); mp 227–229 °C; $[\alpha]^{26}_{578}$ −69.9°, $[\alpha]^{26}_{546}$ −89.32° (*c* 0.0515, MeOH); mass spectrum, *m/e* 293 (M^+), 292 (M^+ − 1), 264 (M^+ − Et), 262 ($M^+ - OCH_3$), 251 ($M^+ - C_3H_6$), 235 ($M^+ - NHC_3H_7$). Anal. Calcd for $C_{20}H_{23}NO$·HCl·0.25H_2O: C, 71.86; H, 7.34; N, 4.19. Found: C, 71.47; H, 7.54; N, 4.36.

(*R*)-(−)-11-Hydroxyaporphine Hydrobromide (2a). A suspension of **7a** (0.2 g, 0.66 mmol) in 4 mL 48% HBr was heated at 115–120 °C for 4 h. In 1 h a clear solution was obtained which on further heating gave a brown precipitate. The mixture was allowed to cool, filtered, washed with ether, and dried. The powder was dissolved in a minimum quantity of MeOH, treated with charcoal, and filtered. The filtrate was added dropwise to Et_2O with stirring. The resulting white precipitate was filtered and dried to yield **2a**: 0.16 g (73%); mp 280–281 °C; $[\alpha]^{22}_{578}$ −51.76°, $[\alpha]^{22}_{546}$ −75.29° (*c* 0.0425, MeOH). Anal. Calcd for $C_{17}H_{17}NO$·HBr: C, 61.45; H, 5.4; N, 4.22. Found: C, 61.24; H, 5.58, N, 4.05.

Similarly prepared from **7b** was **(*R*)-(−)-11-hydroxy-*N*-*n*-propylnoraporphine hydrobromide (2b)**: mp 270 °C $[\alpha]^{26}_{546}$ −52.63° (*c* 0.0228, MeOH). Anal. Calcd for $C_{19}H_{21}NO$·HBr: C, 63.33; H, 6.11; N, 3.89. Found: C, 63.03; H, 6.22; N, 3.73.

Enantiomeric Purity Determinations. A 10-mg sample of each of (±)-2b and (−)-2b was treated with 4 μL of triethylamine and extracted from 3 mL of petroleum ether. The 500 μL of each extract were evaporated to dryness with N_2 and allowed to react with triethylamine (1 μL) and (−)-α-methylbenzyl isocyanate (5 μL, Aldrich) for 3 h at room temperature. A 10-μL sample of the reaction mixture was evaporated under a stream of N_2 and redissolved in 100 μL of mobile phase [45% CH_3CN/phosphate buffer (pH 2.1), 10 mM]. Chromatographic separations were carried out by using 54% CH_3CN/phosphate buffer (pH 2.1, 10 mM), and 0.2 μg of each carbamate derivative was injected.

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High-Yield Benzyne Synthesis of Diaryl Ethers

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For a synthesis of the antitumor agent deoxybouvardin,[1] we needed to prepare a diaryl ether linkage from protected tyrosine derivatives without racemization. The cuprous oxide catalyzed reaction of iodobenzenes with phenoxides

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Table I. Diaryl Ethers and Sulfides from Aryl Iodides and Phenols or Thiophenols

expt	reactants	products (% yield)
1	PhOH, PhI	PhOPh (80)
2	PhOH, *o*-MePhI	*o*-MePhOPh (25), *m*-MePhOPh (35)
3	PhOH, *p*-MePhI	*p*-MePhOPh (40), *m*-MePhOPh (20)
4	*m*-MePhOH, PhI	*m*-MePhOPh (80)
5	*p*-MePhOH, PhI	*p*-MePhOPh (80)
6	PhSH, PhI	PhSPh (100)
7	PhSH, *o*-MePhI	*o*-MePhSPh (50), *m*-MePhSPh (50)

gives a 40–77% yield of diphenyl ethers[2] but requires refluxing dimethylacetamide (~170 °C) for 24 h and would almost certainly racemize amino acids. In an effort to find milder conditions for these reactants, we tried as a catalyst tetrakis(triphenylphosphine)palladium(0), which is known to break the C-I bond in iodobenzene at 25 °C.[3] However, no diphenyl ether was observed until the temperature was raised to about 90 °C, and then only with Me_2SO as solvent and excess KO-*t*-Bu present (Table I, experiment 1). This procedure is essentially that used by Migita et al.[4] to make diaryl sulfides; they did not mention any attempts to prepare diaryl ethers by their procedure but did mention that they were unable to use it to make aryl alkyl ethers.

When we found that *o*-iodotoluene with phenoxide gives a mixture of *o*- and *m*-MePhOPh (experiment 2) and *p*-iodotoluene with phenoxide gives a mixture of *m*- and *p*-MePhOPh (experiment 3), we suspected a benzyne mechanism, and, indeed, when the catalyst was omitted, the yields remained the same. Previous efforts to make diaryl ethers via benzyne intermediates either failed or gave much lower yields (4–11%).[5] Though this procedure is unsuited for making deoxybouvardin due to orientation and racemization[6] problems, it provides a good route to diaryl ethers that come from symmetrical benzyne intermediates, as illustrated by 80% yield preparations of *m*-MePhOPh from iodobenzene and *m*-cresol (experiment 4) and *p*-MePhOPh from iodobenzene and *p*-cresol (experiment 5).

Diaryl sulfides have been prepared (a) from benzynes and thioaryloxides in liquid ammonia in 42–62% yield,[5a,7] (b) in up to 96% yield from aryl iodides and thioaryl oxides by an $S_{RN}1$ mechanism,[8] and (c) in up to 100% yield from aryl halides and thioaryl oxides with tetrakis(triphenylphosphine)palladium(0).[4] The latter experiments included reactions of thiophenoxide with iodobenzene and *p*-iodotoluene in Me_2SO at 100 °C, which gave a 75–83% yield of PhSPh and a 78% yield of *p*-MePhSPh, respectively. When the catalyst was omitted, the yields dropped to 22% (PhSPh) and 0% (*p*-MePhSPh).

As can be seen in experiments 6 and 7, our results with sulfur show that under our conditions the reactions go quantitatively without a catalyst by a benzyne mechanism. Possibly Migita and co-workers missed *m*-MePhSPh as a product from *o*-iodotoluene due to the similarity in GC retention times and ^1H NMR methyl absorptions of these two substances. In any case, our procedure gives excellent yields of diaryl sulfides without problems associated with an air-sensitive catalyst.

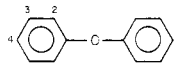
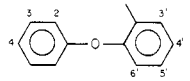
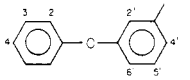
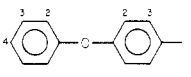
Experimental Section

^1H NMR spectra were run at 250 MHz on a Bruker WM250 spectrometer and at 60 MHz on a Varian EM-360 instrument. Mass spectra were run on a Varian MAT 311A spectrometer.

Diaryl Ethers and Sulfides. Me_2SO (16 mL) was dried over 4A molecular sieves and degassed with argon. The phenol or thiophenol (3 mmol) was added and stirred until totally dissolved. Potassium *tert*-butoxide (6 mmol) was added, and the mixture was stirred under argon for 20 min. The iodobenzene (2 mmol) was added, and the solution was heated at 90 °C overnight. The solution was added to 50 mL of water and extracted three times with 50 mL of ether. The organic phase was washed five times with 100 mL of 5% NaOH and five times with 100 mL of water. The ether solution was dried over $MgSO_4$ and filtered, and the ether was evaporated under reduced pressure. The residual diaryl ether or sulfide was evaporatively distilled (Kugelrohr) at 100–180 °C (0.1 mm), giving yields listed in Table I as indicated by ^1H NMR; Table II lists NMR parameters obtained on the pure ethers.

PhOPh was identified by ^1H NMR, GC, and MS comparisons with an authentic sample; when prepared in the presence of $(Ph_3P)_4Pd$, it was contaminated with 4% of biphenyl (GC–MS and ^1H NMR). Experiments 4 and 5 gave *m*-MePhOPh and *p*-MePhOPh respectively, containing no visible impurities (^1H NMR). Preparative GC on SE-30 silicone oil of the products from experiment 3 gave base line separation of *o*-MePhOPh and *m*-MePhOPh and a pure sample of the former for ^1H NMR. *m*-MePhOPh and *p*-MePhOPh had the same retention time on this GC column. PhSPh was identified by comparing its ^1H NMR

Table II. ^1H NMR Shifts and ^1H–^1H Coupling Constants for Diphenyl Ethers

	chemical shift, δ (multiplicity followed by coupling constants, Hz)			
position				
2	7.00 (dd, 8.7, 1.1)	6.90 (dd, 8.7, 1.1)	7.00 (dd, 8.6, 1.1)	6.98 (dd, 8.6, 1.1)
3	7.33 (~t, 8.0)	7.3 (~t, 8.2)	7.33 (~t, 8.0)	7.31 (dd, 8.6, 7.4)
4	7.09 (tt, 7.4, 1.1)	7.06 (~t, 7.4)	7.09 (tt, 7.4, 1.1)	7.06 (tt, 7.4, 1.1)
2′			6.83 (~s)	6.91 (d, 8.6)
3′		7.25 (d, 7.4)		7.13 (d, 8.6)
4′		7.16 (td, 7.4, 1.5)	6.91 (~d, 7.4)	
5′		7.30 (~t, 7.4)	7.21 (~t, 7.7)	
6′		7.08 (dd, 7.2, 1.5)	6.81 (dd, 8.5, 1.9)	
Me		2.24 (s)	2.33 (s)	2.33 (s)

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spectrum with that in the Sadtler index. *o*-MePhSPh and *m*-MePhSPh were identified by the analogy of their GC retention times and methyl group ^{1}H NMR chemical shifts (δ 2.29 and 2.37, respectively) with those for the corresponding ethers (Table II). The sulfide aromatic proton absorptions in the NMR, unlike those of the ethers, are not essentially first order at 250 MHz and consist of many lines in the δ 7.1–7.4 range.

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Registry No. PhOH, 108-95-2; PhI, 591-50-4; *o*-MePhI, 615-37-2; *p*-MePhI, 624-31-7; *m*-MePhOH, 108-39-4; *p*-MePhOH, 106-44-5; PhSH, 108-98-5; PhOPh, 101-84-8; *o*-MePhOPh, 3991-61-5; *m*-MePhOPh, 3586-14-9; *p*-MePhOPh, 1706-12-3; PhSPh, 139-66-2; *o*-MePhSPh, 13963-35-4; *m*-MePhSPh, 13865-48-0; potassium *tert*-butoxide, 865-47-4; benzyne, 462-80-6.

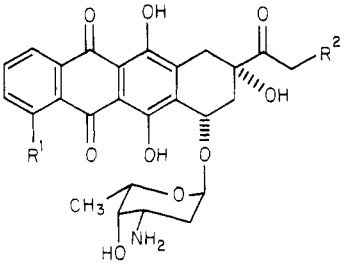
Communications

A New General Regiocontrolled Synthesis of Anthracyclinones Using Cycloaddition of Homophthalic Anhydrides to 2-Chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-Ethanediyl Acetal

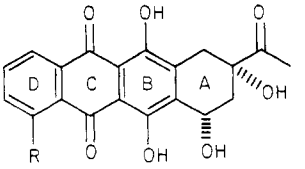
Summary: The cycloaddition of 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone 1,2-ethanediyl acetal (**10**) with homophthalic anhydrides **6** and **9** furnished the adducts **19** and **25**, which were readily converted into 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (**23**) and 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (**27**), late stage precursors to 4-demethoxydaunomycinone (**4**) and daunomycinone (**5**).

Sir: The anthracycline antibiotics daunomycin (**1**), adriamycin (**2**), and carminomycin (**3**) are effective antineoplastic agents against a variety of experimental tumors and some types of human cancer.[1] Over the past several years several elegant regiospecific syntheses of their aglycones have been reported.[2] We now communicate our recent work in this area, which provides a novel and potentially useful route to 4-demethoxydaunomycinone (**4**) and daunomycinone (**5**).

Recently we reported that condensation of homophthalic anhydride **6** with juglone (**7**) produced the tetracyclic compound **8** as the sole product (Scheme I).[3] We have now used this regiospecific cycloaddition for the synthesis of anthracyclinones **4** and **5**. Thus, our synthetic strategy to **4** and **5**, which is outlined in Scheme II, centers on the one-step construction of a linear tetracycle bearing oxygen functionalities (hydroxy or oxo group) in both B and C rings through cycloaddition of homophthalic anhydrides



1, $R^1 = OCH_3$; $R^2 = H$
2, $R^1 = OCH_3$; $R^2 = OH$
3, $R^1 = OH$; $R^2 = H$



4, R = H
5, R = OCH_3

6 and **9** to the appropriately functionalized quinone **10**.

The preparation of the chloroquinone acetal **10** was achieved in 65% overall yield from commercially available[4] 2,6-dichlorobenzoquinone (**11**) by the three-step sequence shown in Scheme III. Diels–Alder reaction of 2-[(trimethylsilyl)oxy]butadiene (**12**)[5] with **11** (ether or benzene, 35–60 °C, 3–6 h, under argon) led to the adduct **13**.[6] Mild acetalization[7] of **13** by the method of Larson[8] (ethylene

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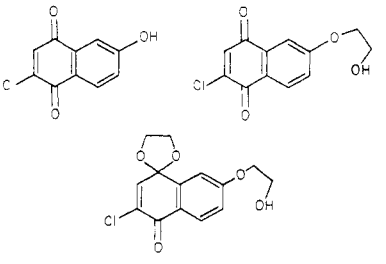
(6) Although the stereochemistry of **13** could not be determined with certainly, the endo adduct is expected as the major product from consideration of similar cycloadditions.[9]

(7) Normal acetalization condition (ethylene glycol–*p*-TsOH in refluxing benzene) of **13** or acetalization after dehydrochlorination of **13** readily caused aromatization and preferentially gave the naphthoquinones shown below.



(8) (a) Larson, G. L.; Hernandez, A. *J. Org. Chem.* **1973**, *38*, 3935. (b) *Synth. Commun.* **1974**, *4*, 61.

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