2.80 (ddd, 1 H, J = 19.7, 4.6, 4.6 Hz, CH), 3.40 (s and m, 4 H, CH_3O and HCO), 3.58 (t, 2 H, J = 4.3 Hz, CH_2CH_2), 3.75 (m, 2 H, CH_2CH_2), 3.79 (s, 3 H, CO_2CH_3), 3.99 (m, 1 H, HCOMEM), 4.74 (d, 1 H, J = 4.1 Hz, HCO allylic), 4.84 (AB, 2 H, J = 7.2 HZ, OCH_2O), 6.98 (dd, 1 H, J = 4.6, 2.3 Hz, C=CH); IR ($CDCl_3$) 3400 (OH), 1710 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{12}H_{20}O_7 \cdot H_2O$ 258.1103, found 258.1105.

Dehydrogenation of (−)-(*S*)-20. To 20.2 mg (0.086 mmol) of dihydropyrone sulfoxide (−)-**20** in 10 mL of benzene was added 200 mg of active manganese dioxide.[19] The reaction mixture was heated at reflux in a 90 °C oil bath. Heating was continued until the reaction was complete (TLC 1:1 CH_2Cl_2–Et_2O). When the mixture had cooled to room temperature, the brownish-black suspension was filtered through a pad of Celite and washed exhaustively with 100 mL of each of the following solvents: benzene, dichloromethane, chloroform, ethyl acetate, and acetone. Concentration afforded 5 mg of crude product, which was purified by preparative TLC with dichloromethane–ethyl ether (1:1) as the eluent yielding 4.5 mg (0.019 mmol, 22%): $[\alpha]^{25}_D$ −136.9° (c 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H, CH_3), 6.49 (dd, 1 H, J = 6.7, 5.1 Hz, H-5), 7.26 (d, 2 H, J = 8.0 Hz, Ar), 7.54 (dd, 1 H, J = 5.1, 2.1 Hz, H-6), 7.70 (d, 2 H, J = 8.0 Hz, Ar), 8.08 (dd, 1 H, J = 6.7, 2.1 Hz, H-4).

The enantiomeric purity of (−)-(*S*)-**1** was determined by using the chiral shift reagent Eu(hfc)$_3$. Complexation of racemic pyrone sulfoxide **1** with 0.58 equiv of Eu(hfc)$_3$ produced two diastereotopic signals of equal intensity for H-4 at δ 15.34 and δ 15.01. Complexation of pyrone sulfoxide (−)-(*S*)-**1** with 0.58 equiv of Eu(hfc)$_3$ produced a similar downfield shift with only one diastereotopic resonance present.

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Acknowledgment. We thank the NIH (Grant GM 30052) for financial support. Purchase of a 400-MHz NMR spectrometer was made possible by the NIH (Grant 1510 RR01934) and by the NSF (Grant PCM-83-03776). We also thank Professor Bruce Ganem (Cornell University) for kindly providing an NMR spectrum of cyclohexadiene **17**.

Total Synthesis of 11-Deoxydaunomycinone and Analogues by a Tandem Claisen–Diels–Alder Strategy

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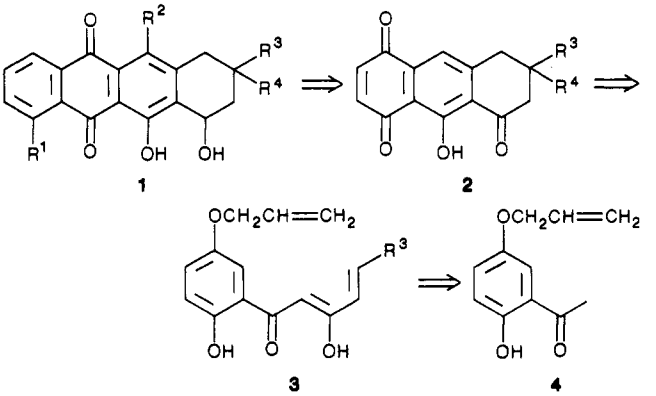
11-Deoxydaunomycinone (**6**), its 4-deoxy analogue **5**, and 1-methoxy-4,11-dideoxyduanomycinone were prepared by a sequence involving an intramolecular acyl transfer reaction followed by a tandem Claisen–Diels–Alder reaction. The resulting diketone could be oxidized to naphthoquinone **11** with DDQ. This quinone was then treated with either 1-[(trimethylsilyl)oxy]butadiene or 1-methoxy-1,3-cyclohexadiene to provide adducts that could be transformed into **5** and **6**. Unfortunately, the presence of the C-7 carbonyl group *decreased* the regioselectivity of **11** in Diels–Alder reactions.

After more than a decade of intense activity, the synthesis of anthracycline antibiotics remains an active area of research.[1] In large part, this is due to the isolation and characterization of new and highly active anthracyclines. Compounds such as 11-deoxyduanomycin, aclacinomycin, and nogalomycin are perhaps the most active of the newer anthracyclines.[2] One structural feature that these compounds have in common is that the hydroxyl group that is present at C-11 in most anthracyclines has been replaced by a hydrogen atom. These compounds exhibit dramatically lower cardiac toxicities than their 11-hydroxy counterparts. As a consequence, aclacinomycin has become a clinically useful drug.[3]

While many elegant solutions to the synthesis of anthracyclines have been advanced, some problems still remain. For example, the C-7 hydroxyl group (anthracycline numbering) is almost always introduced by way of the solvolysis of a benzylic halide. This method is often inefficient, especially on a large scale. A better strategy would be to incorporate a hydroxyl group or its precursor into a synthetic intermediate at a much earlier stage. Additionally, the recent interest[4] in anthracyclines that are halogenated in the D ring has increased the need for a direct synthetic route that allows rapid entry to a variety of D ring modified compounds.

Scheme I



(1) *Tetrahedron Symposium in Print No. 17*, **1984**, 40. Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.

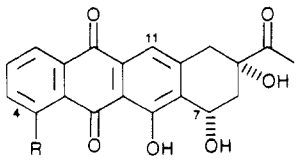
(2) Arcamone, F. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic: New York, 1980; Chapter 1.

(3) Tone, H.; Nishida, H.; Takeuchi, T.; Umezawa, H. *Drugs Exp. Clin. Res.* **1985**, *11*, 9. Tone, H.; Takeuchi, T.; Umezawa, H. *Curr. Chemother. Immunother. Proc. Int. Congr. Chemother., 13th, 1983* **1983**, *12*, 211/1.

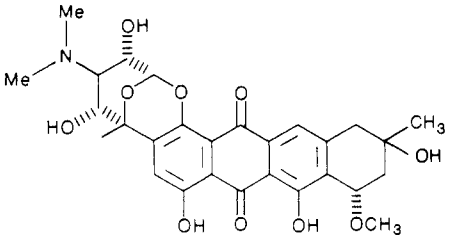
(4) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *52*, 713.

0022-3263/87/1952-4841$01.50/0

We recently reported that a tandem Claisen–Diels–Alder sequence followed by oxidation with DDQ provided naphthoquinones such as **2** in good to excellent overall yields.[5] Quinone **2** represents an attractive intermediate for the synthesis of 11-deoxyanthracyclines,[6] especially ones with a modified D ring. The overall pathway to anthraquinone **1** is illustrated in Scheme I. A prerequisite for the successful elaboration of quinone **2** into **1** is the identification of a suitable group for R^3. This group must be compatible with the reaction conditions for both the acyl-transfer reaction and the tandem Claisen–Diels–Alder reaction.

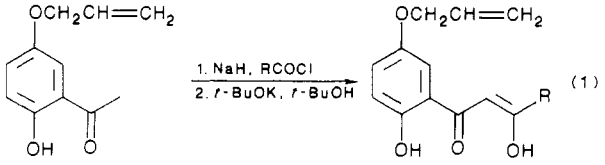


5: R = H
6: R = OCH_3



7

Originally, we examined the 1-propenyl group as a suitable R^3 group. An advantage of this choice was that the acid chloride of commercially available sorbic acid could be used in the acyl-transfer reaction. Although the acyl-transfer reaction with sorboyl chloride worked well, the resulting propenyl group could not be reproducibly oxidized to an aldehyde. The acyl-transfer step was then conducted with a variety of acid chlorides to define a range of usable groups for R^3. The results are shown in Table I.

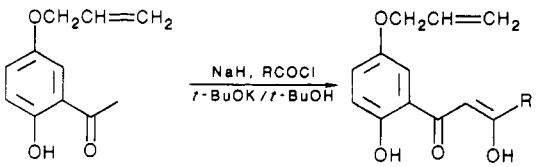


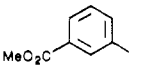
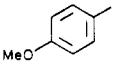
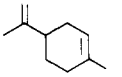
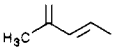
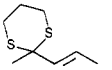
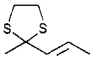
(1)

8

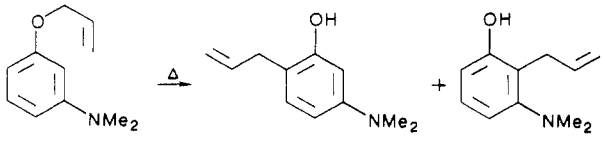
Unsaturated acid chlorides with electron-withdrawing groups or electron-donating groups in the beta position (see Table I, entries 7–10) do not afford the desired acyl-transfer product. In these cases, hydroxy ketone **4** was recovered. The problem here is the actual acyl-transfer reaction, since the phenol esters from the sodium hydride step could be isolated in high yield. The electron-withdrawing groups in the β position make the carbonyl of the phenol esters more electrophilic. Intramolecular O-acylation of the ketone enolate may then occur. The resulting enol ester would likely be cleaved by the aqueous workup. A rationale for the recovery of starting material when R^3 was an electron-donating group is not obvious. Fortunately, the ethylene dithioketal moiety was stable to the acyl-transfer conditions. The requisite acid chloride could be prepared in four steps from aqueous pyruvaldehyde.[7]

Table I. Synthesis of β-Diketones



entry	R	% yield
1		50
2		68
3		69
4		64
5		62
6		70
7	$CH_3COCH{=}CH$	
8	$CH_3O_2CCH{=}CH$	
9	$CH_3O(CH_3)C{=}CH$	
10	$ClCH{=}CH$	
11	$PhSCH{=}CH$	64
12		69
13		71

The tandem Claisen–Diels–Alder reaction involves a regioselective Claisen rearrangement followed by an intramolecular Diels–Alder reaction. The origin of the excellent regioselectivity of the Claisen rearrangement when an acyl group is present in the meta position has not yet been defined. Extended Hückel calculations show no evidence of bond fixation. Analysis of the regioisomeric Claisen transition states by FMO theory does not predict any selectivity. A paper by Kruse and Cha suggests that comparing the relative stability of the valence bond resonance forms before aromatization can explain the selectivity.[8] However, we have not been able to identify other regioselective Claisen reactions by applying this rationale. For example, a dimethylamino group would be predicted to show a preference; in fact, it gives almost equal amounts of the two Claisen rearrangement products (eq 2).



(2)

55% 45%

The tandem Claisen–Diels–Alder reaction of **9** afforded an 85% isolated yield of diketone **10**, as shown in Scheme II. Diketone **10** was a 3:1 mixture of diastereomers. On the basis of our earlier work, a trans relationship between

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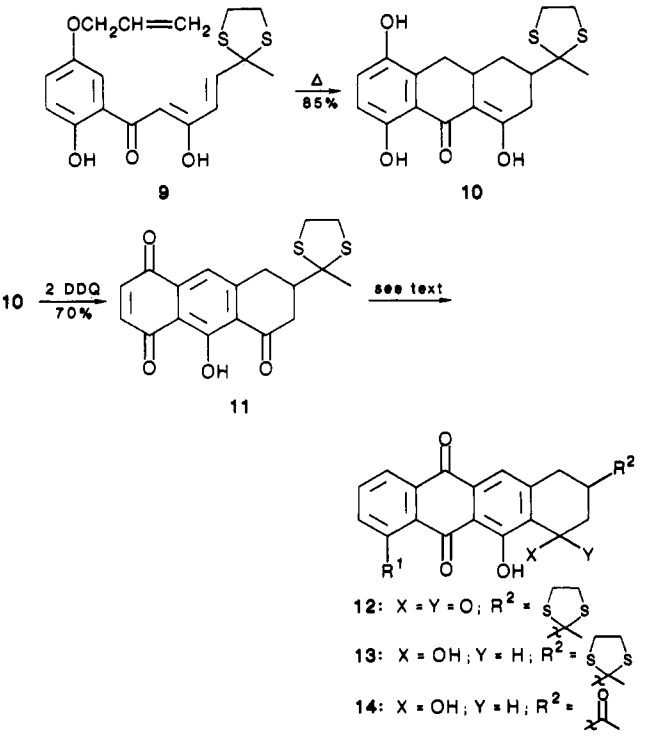
(6) Syntheses: (a) Bauman, J. G.; Barber, R. B.; Gless, R. D.; Rapoport, H. *Tetrahedron Lett.* **1980**, *21*, 4777. (b) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Nouv. J. Chim.* **1983**, *7*, 205. (c) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, *22* 3711. (d) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688. (e) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7372. (f) Abdallah, A. A.; Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Bull. Soc. Chim. Fr.* **1986**, 93.

(7) Fridinger, T. L.; Henery-Logan, K. R. *J. Heterocycl. Chem.* **1971**, *8*, 469.
(8) Kruse, L. I.; Cha, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1333.

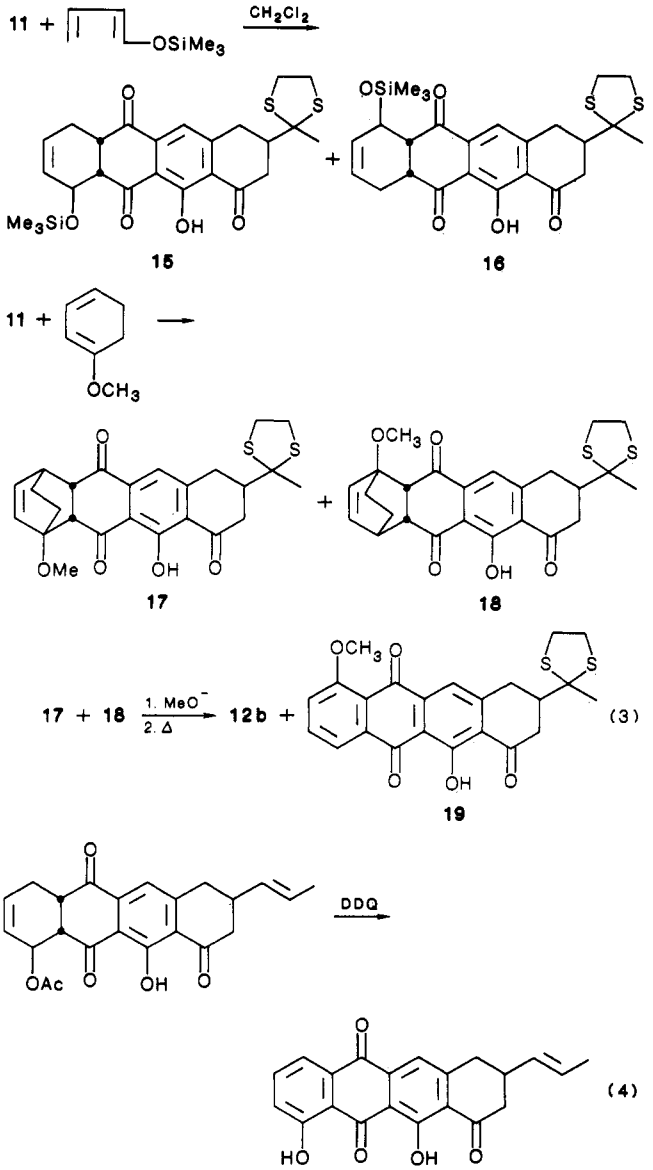
Scheme II[a]



[a] For 12–14: a, R^1 = H; b, R^1 = OCH_3.

the methine proton and R^3 was expected. This was not verified in this case, since only one of the stereogenic centers would remain after the next step. Because of solubility problems, dioxane was used for the DDQ oxidation. Naphthoquinone **11** was produced in 70% yield.

Since Rodrigo and others have shown that the hydroxyl group at C-9 could be introduced by hydroxylation of a ketone enolate anion, naphthoquinone **11** is a viable precursor to anthracyclinones **5** and **6**.[9] A regioselective Diels–Alder reaction should ensue because the hydroxyl group at C-6 is expected to direct the cycloaddition. This expectation is based on a classic paper by Boeckmann and co-workers wherein Diels–Alder reactions of 5-hydroxy-1,4-naphthoquinone were shown to be highly regioselective.[10] This directing effect has often been used in anthracycline synthesis. Initially, we reacted 1-[(trimethylsilyl)oxy]butadiene with quinone **11**. The reaction of **11** with 1-[(trimethylsilyl)oxy]butadiene produced a 4:3 ratio of two regioisomeric products (eq 3). Both adducts could be readily transformed into anthraquinone **12** by treatment with 2 equiv of triethylamine in methylene chloride. Catalysis with boron trifluoride etherate had little effect on the regioselectivity. However, when the Diels–Alder reaction was conducted with 1 equiv of freshly fused zinc chloride at −20 °C, a 50:1 ratio of isomers was obtained. Oxidation of this product, tentatively identified as **15**, with either Jones reagent,[11] DDQ in benzene, trityl tetrafluoroborate,[12] MnO_2, or PCC afforded a complex mixture of products containing the desired hydroxyanthraquinone, a deoxyanthraquinone derived from loss of TMSOH, and other unidentified byproducts. This result was in contrast to the analogous oxidation of the Diels–Alder adduct shown in eq 4.[3] Presumably, the

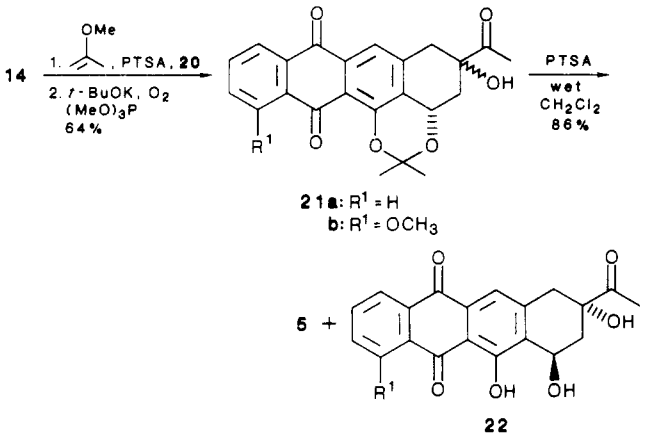


ethylene dithioketal moiety was responsible for the complexity. Adduct **15** could be hydrolyzed to the alcohol with 0.1 N HCl in THF. Unfortunately, neither a Swern oxidation (oxalyl chloride, Et_3N, Me_2SO), a Collins oxidation, nor an oxidation with buffered PCC provided a good yield of the desired hydroxyanthraquinone.[13]

Introduction of the methoxyl group was achieved by reaction of **11** with 1-methoxy-1,3-cyclohexadiene in CH_2Cl_2. This reaction generated a 1.8:1 ratio of adducts **17** and **18**. The selectivity of this reaction could be improved with zinc chloride (0.3 equiv), but the yield was low. Interestingly, with 1 equiv of zinc chloride, the Diels–Alder adduct was not obtained. The major product in this case was a cyclohexenone. Catalysis with $AlCl_3$ led to a complex mixture of products. The ratio of adducts **17** and **18** was also affected by solvent polarity. With DMSO as solvent, an 8:1 ratio of **18** to **17** could be achieved. This solvent effect is surprising and may arise from the disruption of internal hydrogen bonding by the polar solvent. Aromatization with NaOMe in MeOH followed by Ag_2O in hot xylene[14] produced anthraquinones **12b** and **19**, which could be readily separated by chromatography. As the results

(9) Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597.
(10) Boeckmann, R. K., Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.
(11) Yamamoto, K.; Suzuki, K.; Tsuji, J. *Chem. Lett.* **1978**, 649.
(12) Jung, M. E. *J. Org. Chem.* **1976**, *41*, 1479.
(13) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567.
(14) Pyrek, J. S.; Achmatowicz, O.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673.

Scheme III



described above indicate, the directing effect of the hydroxyl group in **11** is diminished in comparison to 5-hydroxy-1,4-naphthoquinone. It is likely that preferential hydrogen bonding with the ketone at C-7 is attenuating the directing effect. All attempts either to selectively protect or to reduce ($NaBH_4$; $NaBH_3CN$, MeOH; Et_3SiH, CF_3CO_2H) the C-7 ketone in either **11** or the corresponding hydroquinone failed.

The reaction of quinone **11** with very electron rich dienes was also examined. The reaction with 1,4-bis[(trimethylsilyl)oxy]-1,3-cyclohexadiene and **11** produced a naphthohydroquinone, the reduction product of **11**. The reaction with 1-ethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene led to the decomposition of **11**.

Both **12a** and **12b** could be reduced with sodium cyanoborohydride in CH_2Cl_2/MeOH containing acetic acid to maintain a pH of 5.[15] The ethylene dithioketal moiety was then cleaved with $HgCl_2$ and HgO in aqueous acetonitrile. The resulting hydroxy ketones were in a ratio of 10:1, with the major component being the cis isomer. The synthesis of **5** and **6** is shown in Scheme III. The preparation of **5** from **14a** involved the protection of the benzylic alcohol as an acetonide followed by hydroxylation of the ketone enolate by the method of Rodrigo. Deprotection with PTSA in wet CH_2Cl_2 afforded a 2:1 mixture of **5** and diastereomer **22a**. The conversion of **22a** into **5** was possible by using literature procedures. Quinone **14b** was then reacted by the same sequence to produce the C-7 epimer of **6**, **22b**, in 38% overall yield from **14b**. This has been converted to **6** by Gesson with TFA.[16]

The strategy described above offers a direct route to 11-deoxyanthracyclines.[17] In addition to avoiding the benzylic oxidation/solvolysis tact for the introduction of the 7-hydroxyl group, this route permits some flexibility with regard to D-ring substitution. From naphthoquinone **11**, anthracyclines can be prepared in only seven steps.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Perkin-Elmer Model 1320 spectrometer. Nuclear magnetic resonance spectra were determined on a Nicolet 300-MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform instrument and on the Nicolet 300-MHz instrument. High-resolution mass spectra were determined on a Kratos mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

4-Oxo-2-pentenoyl Chloride, Ethylene Dithioketal. A solution of the ethane dithioketal of pyruvaldehyde (3.00 g, 20 mmol) and (carbethoxymethylene)triphenylphosphorane (7.05 g, 20 mmol) was heated at reflux in methylene chloride for 8 h. The solvent was removed in vacuo. After ether was added, the suspension was filtered. The filtrate was concentrated and purified by chromatography on silica gel with 8:1 hexanes/ether. The yield was 91%. This product was hydrolyzed with 1.3 equiv of KOH in 95% ethanol at room temperature for 6 h to afford a crude acid, which was taken directly on to the acid chloride. To a suspension of hexane-washed NaH (0.66 g, 13.7 mmol) in dry benzene (20 mL) at 0 °C was added the crude acid in 15 mL of benzene. Oxalyl chloride (1.30 mL, 15 mmol) was then added, and the solution was allowed to warm to room temperature over 3 h. The mixture was filtered, concentrated, and distilled at 110–115 °C (10 mmHg). The yield for this step was 81%: NMR ($CDCl_3$) δ 1.93 (s, 3 H), 3.38 (br s, 4 H), 6.12 (d, J = 16 Hz, 1 H), 7.22 (d, J = 16 Hz, 1 H); IR (film) 1750, 1602, 1268, 1115, 1015, 770, 670 cm^{-1}.

General Procedure for the Acyl-Transfer Step. To a suspension of hexane-washed NaH (1.1 equiv) in THF (1 mL/mmol) was added a solution of the hydroxy ketone (1 equiv) in THF. The resulting solution was stirred for 10 min at 0 °C. The acid chloride (1.05 equiv) was then added dropwise, and the solution was stirred at 0 °C for 20 min. A complex of t-BuOK/t-BuOH (2.1 equiv) was then added in one portion. The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with water and ether and acidified with 6 N HCl to pH 6. The aqueous layer was extracted twice with ether. The organic layer was extracted with brine, dried, and concentrated. The crude product was chromatographed on silica gel. **9**: 300-MHz NMR ($CDCl_3$) δ 1.98 (s, 3 H), 3.30–3.52 (m, 4 H), 4.48–4.53 (m, 2 H), 5.27–5.48 (m, 2 H), 6.00–6.17 (m, 2 H), 6.15 (s, 1 H), 6.90–7.15 (m, 4 H), 11.75 (s, 1 H), 14.60 (s, 1 H); IR (film) 1640, 1570, 1487, 1284 cm^{-1}; HRMS, m/e calcd for $C_{18}H_{20}O_4S_2$ 364.08033, found 364.0801.

Thermolysis of Diketone 9. A solution of diketone **9** (0.210 g, 0.58 mmol) in 6 mL of benzene containing a crystal of hydroquinone was deoxygenated and sealed in a glass tube. It was heated at 240 °C for 18 h. The reaction mixture was cooled, concentrated, and purified by column chromatography to afford an 86% yield of **10**. On larger scales, the yields ranged from 75–85%.

10: mixture of diastereomers in a 3:1 ratio. Major diastereomer: 300-MHz NMR ($CDCl_3$) δ 1.82 (s, 3 H), 1.92–2.00 (m, 2 H), 2.30–3.10 (m, 6 H), 3.35–3.42 (m, 4 H), 4.59 (s, 1 H), 6.71 (d, J = 8.7 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 11.57 (s, 1 H), 13.97 (s, 1 H); HRMS, m/e calcd 364.08031, found 364.08009; IR (film) 1620, 1587, 1470 cm^{-1}.

DDQ Oxidation to Naphthoquinone 11. To a solution of **10** (0.430 g, 1.18 mmol) in 20 mL of dry dioxane was added DDQ (0.590 g, 2.60 mmol). The solution was stirred for 8 h from 0 °C to room temperature. The resulting suspension was filtered, concentrated, and chromatographed on silica gel with methylene chloride to give a 70% yield of quinone **11**. **11**: 300-MHz NMR ($CDCl_3$) δ 1.86 (s, 3 H), 2.52–3.52 (m, 9 H), 6.94 (d, J = 1 Hz, 2 H), 7.26 (d, J = 1 H, 1 H), 13.63 (s, 1 H); IR (film) 1670, 1638, 1597, 1376, 1200 cm^{-1}; HRMS, m/e calcd 362.0646, found 362.0647.

Diels–Alder Reactions of Naphthoquinone 11. A solution of the quinone **11** (1 equiv) and the diene (3 equiv) in the requisite solvent (10 mL/mmol of **11**) was stirred from 0 °C to room temperature until TLC showed that no **11** was present. The solvent and excess diene were removed under reduced pressure.

15, 16: 300-MHz NMR ($CDCl_3$) δ −0.275 and −0.278 (s, 9 H), 1.84 and 1.88 (s, 3 H), 2.04–2.21 (m, 2 H), 2.48–3.52 (m, 11 H), 4.38–4.46 (m, 1 H), 5.74–5.96 (m, 2 H), 6.92 (s, 1 H), 13.28 (s, 1 H), 13.61 and 13.67 (s, 1 H); IR (film) 1693, 1638, 1372, 1252, 1216 cm^{-1}. HRMS, m/e calcd for $M^+ - Me_3SiOH$ 412.0803, found 412.0807.

Adducts **17** and **18** (1.8:1 ratio): 300-NMR ($CDCl_3$) δ 1.45–2.05 (m, 6 H), 1.87 (s, 3 H), 2.40–3.52 (m, 10 H), 3.45 and 3.47 (s, 3 H), 5.85–6.10 (m, 2 H), 7.16 (s, 1 H), 13.35 and 13.55 (s, 1 H); IR

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($CDCl_3$) 1680, 1632, 1600, 1370, 1120 cm^{-1}.

Anthraquinone 12a. To the crude Diels–Alder adduct in methylene chloride (15 mL/mmol) at 0 °C was added triethylamine (2 equiv). The solution was allowed to warm to room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and acidified with 1 N HCl to pH 5. The organic layers were washed with brine, dried, and concentrated. The crude product was chromatographed on silica gel with 3% ethyl acetate in methylene chloride. The overall yield from naphthoquinone **11** was 69%. **12a**: 300-MHz NMR ($CDCl_3$) δ 1.90 (s, 3 H), 2.55–2.82 (m, 2 H), 3.02–3.57 (m, 7 H), 7.70 (s, 1 H), 7.77–7.88 (m, 2 H), 8.20–8.47 (m, 2 H), 13.95 (s, 1 H); IR (film) 1674, 1633, 1592, 1258, 843 cm^{-1}. HRMS, m/e calcd 410.0641, found 410.0640.

Anthraquinone 12b. To a 1 M solution of sodium methoxide in methanol (7 mL, 7 mmol) at 0 °C were added the crude Diels–Alder reaction products (0.550 g, ca. 1.2 mmol) in a mixture of THF and MeOH. The solution was stirred at room temperature for 30 min. Glacial acetic acid was added to neutralize the sodium methoxide. The solution was diluted with ethyl acetate and extracted with brine. The organic layer was dried, filtered, and concentrated. The crude product was then purified by flash chromatography with 10:1 methylene chloride/ethyl acetate to give 0.321 g of the 4-methoxy quinone and its hydroquinone and 0.174 g of the 1-methoxy hydroquinone. The mixture of the desired quinone and hydroquinone and silver oxide was heated in 10 mL of xylene at reflux for 30 min. The hot solution was filtered, and the product was precipitated by adding pentane. Filtration chromatography with 5:1 methylene chloride/ethyl acetate afforded the desired quinone as a yellow-orange solid in 84% yield. **12b**: 300-MHz NMR ($CDCl_3$) δ 1.88 (s, 3 H), 2.52–2.80 (m, 2 H), 3.00–3.22 (m, 2 H), 3.28–3.50 (m, 5 H), 4.06 (s, 3 H), 7.37 (d, J = 8 Hz, 1 H), 7.60 (s, 1 H), 7.72 (t, J = 8 Hz, 1 H), 7.70 (d, J = 7.5 Hz, 1 H), 14.14 (s, 1 H); Mass spectrum, m/e 442, 379, 322, 119; HRMS, m/e calcd 442.0908, found 442.0901. **19**: 300-MHz NMR ($CDCl_3$) δ 1.88 (s, 3 H), 2.55–3.47 (m, 9 H), 4.06 (s, 3 H), 7.37 (d, J = 7 Hz, 1 H), 7.59 (s, 1 H), 7.72 (t, J = 7 Hz, 1 H), 7.88 (d, J = 7 Hz, 1 H), 13.86 (s, 1 H).

Sodium Cyanoborohydride Reduction of Keto Quinones. To a solution of the keto quinone (1 equiv) in methylene chloride (8 mL/mmol) and MeOH (8 mL/mmol) was added glacial acetic acid (10 mL/mmol), followed by sodium cyanoborohydride (7 equiv). The reaction mixture was stirred for 3 h and then diluted with methylene chloride and washed with water. The crude product was usually subjected to the deprotection step. The yields of **13a** and **13b** were 87% and 60%, respectively. **13a**: 300-MHz NMR ($CDCl_3$) δ 1.88 (s, 3 H), 1.70–1.92 (m, 2 H), 2.10–2.22 (m, 1 H), 2.47–3.46 (m, 6 H), 5.14–5.26 (m, 1 H), 7.60 (s, 1 H), 7.75–7.90 (m, 2 H), 8.20–8.40 (m, 2 H), 13.50 (s, 1 H); IR (film) 3535, 1670, 1630, 1592, 1384, 1368 cm^{-1}; HRMS, m/e calcd 412.0803, found 412.0807. **13b**: 300-MHz NMR ($CDCl_3$) δ 1.84 (s, 3 H), 2.16 (br t, J = 10 Hz, 1 H), 2.66–2.95 (m, 2 H), 3.15–3.50 (m, 5 H), 4.06 (s, 3 H), 4.38 (s, 1 H), 5.21 (br t, J = 9 Hz, 1 H), 7.34 (d, J = 8 Hz, 1 H), 7.55 (s, 1 H), 7.73 (t, J = 8 Hz, 1 H), 7.93 (d, J = 7.5 Hz, 1 H), 13.92 (s, 1 H).

Removal of the Ethylene Dithioketal Group. To a stirred solution of the thioketal (1 equiv) in 4:1 acetonitrile/water was added $HgCl_2$ (2 equiv) and HgO (2 equiv). The reaction was vigorously stirred for 12 h at room temperature. It was then filtered, and the filtrate was washed with water and dried over sodium sulfate. The crude product was chromatographed on silica gel with hexanes/ethyl acetate. The yields of **14a** and **14b** were 90% and 88%, respectively. **14a**: 300-MHz NMR ($CDCl_3$) δ 2.12–2.57 (m, 2 H), 2.31 (s, 3 H), 2.83–2.9 (m, 2 H), 3.17–3.28 (m, 1 H), 5.20–5.28 (m, 1 H), 7.64 (s, 1 H), 7.81–7.83 (m, 2 H), 8.25–8.30 (m, 2 H), 13.39 (s, 1 H); IR (film) 3535, 1711, 1670, 1630, 1593, 1384, 1352, 1268 cm^{-1}; HRMS, m/e calcd 336.0998, found 336.1001. **14b**: 300-MHz NMR ($CDCl_3$) δ 2.10–2.55 (m, 2 H), 2.30 (s, 3 H), 2.45–2.55 (m, 1 H), 2.82–2.96 (m, 2 H), 3.13–3.25 (m, 1 H), 4.08 (s, 3 H), 5.24 (t, J = 6 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.61 (s, 1 H), 7.76 (t, J = 7 Hz), 7.97 (d, J = 7.5 Hz, 1 H), 13.84 (s, 1 H); HRMS, m/e calcd 366.11034, found 366.11034.

Formation of Acetonide 20. To hydroxy ketone **14a** (30 mg, 0.089 mmol) in 7 mL of methylene chloride was added 2-methoxypropene (0.14 mL, 1.43 mmol) followed by a small crystal of PTSA in methylene chloride. The reaction was stirred at room temperature for 3 h. It was diluted and washed with saturated bicarbonate solution and then brine. The organic layer was dried, concentrated, and subjected to flash chromatography with 3:2 hexanes/ethyl acetate. The yield of acetonide **20** was 77%. **20a** (higher R_f diastereomer): 300-MHz NMR ($CDCl_3$) δ 1.59 (s, 3 H), 1.63 (s, 3 H), 2.21 (s, 3 H), 2.38–2.47 (m, 2 H), 2.92–3.14 (m, 3 H), 4.86–4.92 (m, 1 H), 7.36–7.57 (m, 3 H), 7.70 (s, 1 H), 8.26–8.29 (m, 1 H); IR (film) 1714, 1657, 1604, 1589, 1330 cm^{-1}; HRMS, m/e calcd 376.1311, found 376.1307. **20a** (lower R_f diastereomer): 300-MHz NMR ($CDCl_3$) δ 1.70 (s, 3 H), 1.74 (s, 3 H), 2.31 (s, 3 H), 2.48–2.57 (m, 2 H), 2.94–3.20 (m, 3 H), 4.93–5.10 (m, 1 H), 7.68–7.80 (m, 3 H), 8.18–8.29 (m, 2 H); IR (film) 1713, 1670, 1589, 1343, 1273, 1142 cm^{-1}.

Formation of Hydroxy Ketone 21a. The acetonide **20** (40 mg, 0.107 mmol) and trimethyl phosphite (70 mg, 0.37 mmol) were dissolved in 10 mL of dry *tert*-butyl alcohol and 6 mL of THF and cooled to −23 °C. Oxygen was then bubbled through the solution and the *t*-BuOK/*t*-BuOH complex in 3 mL of *tert*-butyl alcohol and 2 mL of THF was quickly added. The reaction was quenched by adding 1 mL of water and then carbon dioxide gas was bubbled through the solution until it was neutral. The solvent was removed in vacuo, and ethyl acetate was added. The organic layer was washed with brine, dried, and concentrated. After flash chromatography on silica gel, a 77% yield of **21a** was obtained. **21a**: 300-MHz NMR ($CDCl_3$) δ 1.62 and 1.64 (s, 3 H), 1.74 and 1.76 (s, 3 H), 2.27 and 2.45 (s, 3 H), 2.78–3.34 (m, 4 H), 3.60 (s, equatorial OH, 1 H), 4.31 (s, axial OH, 1 H), 4.87–4.93 and 5.23–5.28 (m, 1 H), 7.66–7.82 (m, 3 H), 8.16–8.28 (m, 2 H); IR (film) 3480, 1712, 1670, 1590, 1343, 1275 cm^{-1}; HRMS, m/e for $M^+ - H_2O$ calcd 374.1154, found 374.1156.

Formation of 5 and 22. To the acetonide (29 mg, 0.073 mmol) in 3 mL of wet methylene chloride was added a small crystal of PTSA. After 3 h, the solution was diluted, washed with 10% sodium bicarbonate solution, and dried. The crude product was subjected to flash chromatography on silica gel with 2:3 hexanes/ethyl acetate to afford **5** (14.5 mg) and **22** (7.5 mg). **5**: 300-MHz NMR ($CDCl_3$) δ 2.08–2.42 (m, 2 H), 2.42 (s, 3 H), 3.03 (dd, J = 2.4 Hz, 17.7 Hz, 1 H), 3.28 (d, J = 17.7 Hz, 1 H), 3.62 (d, J = 4.8 Hz, 1 H), 4.58 (s, 1 H), 5.36 (br s, 1 H), 7.64 (s, 1 H), 7.81–7.84 (m, 2 H), 8.28–8.33 (m, 2 H), 13.26 (s, 1 H); IR (film) 3480, 1710, 1670, 1630, 1592, 1380, 1350 cm^{-1}; HRMS, m/e calcd 352.0947, found 352.0944. **22a**: 300-MHz NMR ($CDCl_3$) δ 2.19–2.42 (m, 2 H), 2.40 (s, 3 H), 2.78 (dd, J = 8.1 Hz, 16.8 Hz, 1 H), 3.40 (br d, J = 16.8 Hz, 1 H), 3.83 (s, 1 H), 4.17 (d, J = 1.8 Hz, 1 H), 5.38–5.46 (m, 1 H), 7.63 (s, 1 H), 7.81–7.85 (m, 2 H), 8.28–8.34 (m, 2 H), 13.5 (s, 1 H). **22b**: 300-MHz NMR ($CDCl_3$) δ 2.17–2.50 (m, 2 H), 2.39 (s, 3 H), 2.76 (d, J = 18 Hz, 1 H), 3.39 (d, J = 18 Hz, 1 H), 3.82 (s, 1 H), 4.08 (s, 3 H), 4.25 (s, 1 H), 5.42 (t, J = 8 Hz), 7.38 (d, J = 8 Hz, 1 H), 7.56 (s, 1 H), 7.77 (t, J = 8 Hz, 1 H), 7.96 (d, J = 7.5 Hz, 1 H), 13.94 (s, 1 H); HRMS, m/e calcd 382.1053, found 382.1051.

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Registry No. **3** (R^3 = CH_3CH=CH), 110295-45-9; (±)-**5**, 77312-61-9; **8** (R = 5-bromo-2-furanyl), 110295-15-3; **8** (R = *m*-$MeOC(O)C_6H_4$), 110295-16-4; **8** (R = *p*-$MeOC_6H_4$), 110295-17-5; **8** (R = 4-(1-methylethenyl)-1-cyclohexen-1-yl), 110295-18-6; **8** (R = (*E*)-$CH_3C(=CH_2)CH$=CH), 110295-19-7; **8** (R = (*E*)-CH_2=CHCH=CH), 110295-20-0; **8** (R = PhSCH=CH), 110295-21-1; **8** (R = (*E*)-2-(2-methyl-1,3-dithian-2-yl)ethenyl), 110295-22-2; **8** (R = (*E*)-2-(2-methyl-1,3-dithiolan-2-yl)ethenyl), 110295-23-3; (±)-**10** (isomer 1), 110295-24-4; (±)-**10** (isomer 2), 110295-25-5; (±)-**11**, 110295-26-6; (±)-**12a**, 110295-30-2; (±)-**12b**, 110295-31-3; (±)-*cis*-**13a**, 110295-33-5; (±)-*trans*-**13a**, 110295-34-6; (±)-*cis*-**13b**, 110295-35-7; (±)-*trans*-**13b**, 110295-36-8; (±)-*cis*-**14a**, 110295-37-9; (±)-*trans*-**14a**, 110295-38-0; (±)-*cis*-**14b**, 110295-39-1; (±)-*trans*-**14b**, 110295-40-4; **15**, 110295-27-7; **15** C-4 alcohol, 110313-47-8; **16**, 110313-45-6; **17**, 110295-28-8; **18**, 110295-29-9; **19**, 110295-32-4; (±)-**20a** (isomer 1), 110295-41-5; (±)-**20a** (isomer 2), 110295-42-6; (±)-**21a** (isomer 1), 110295-43-7; (±)-**21a** (isomer 2), 110295-44-8; (±)-**22a**, 77312-62-0; (±)-**22b**, 82863-14-7; **45**, 82217-72-9; **55**, 110295-47-1; $EtOC(O)CH$=PPh_3, 1099-45-2; $MeOC(O)$-*m*-$C_6H_4C(O)Cl$, 3441-03-0; *p*-$MeOC_6H_4C(O)Cl$, 100-07-2; (*E*)-$CH_3C(=CH_2)CH$=$CHC(O)Cl$, 66343-30-4; CH_2=$CHCH$=CH-

C(O)Cl, 20448-91-3; $CH_3C(O)CH{=}CHC(O)Cl$, 110295-11-9; $MeOC(O)CH{=}CHC(O)Cl$, 78140-66-6; $MeOC(CH_3){=}CHC(O)Cl$, 110295-12-0; $ClCH{=}CHC(O)Cl$, 54358-89-3; $PhSCH{=}CHC(O)Cl$, 1077-15-2; (*E*)-$CH_2{=}CHCH{=}CHOSiMe_3$, 63383-46-0; *m*-$Me_2NC_6H_4OCH_2CH{=}CH_2$, 110295-46-0; pyruvaldehyde ethylene dithioketal, 26419-66-9; 2-[2-(ethoxycarbonyl)ethenyl]-2-methyl-1,3-dithiolane, 110295-09-5; 2-(2-carboxyethenyl)-2-methyl-1,3-dithiolane, 110295-10-8; 5-bromo-2-furancarbonyl chloride, 26726-16-9; 4-(1-methylethenyl)-1-cyclohexene-1-carbonyl chloride, 90554-83-9; 2-(3-chloro-3-oxo-1-propen-1-yl)-2-methyl-1,3-dithiane, 110295-13-1; 2-(3-chloro-3-oxo-1-propen-1-yl)-2-methyl-1,3-dithiolane, 110295-14-2; 2-acetyl-4-[(2-propen-1-yl)-oxy]phenol, 40815-75-6; 1-methoxy-1,3-cyclohexadiene, 2161-90-2; 1,4-bis[(trimethylsilyl)oxy]-1,3-cyclohexadiene, 59733-55-0; 3-(2-methyl-1,3-dithiolan-2-yl)-5,8,9-trihydroxy-3,4,5,8-tetrahydroanthracen-1(2*H*)-one, 110313-46-7; sorboyl chloride, 2614-88-2.

Diiodosilane. 1. A Novel Reagent for Deoxygenation of Alcohols and Ethers

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Diiodosilane (DIS), which has never been used previously in organic synthesis, has been shown to exhibit properties and reactivities that are complementary to those of iodotrimethylsilane. This new reagent was used to cleave and deoxygenate ethers and alcohols with high selectivity for secondary oxygen functions. Synthesis of DIS is easily and rapidly carried out by reacting phenylsilane with iodine.

Introduction

Use of organosilicon reagents in organic synthesis has expanded bewilderingly over the past decade. Iodotrimethylsilane (TMSI) is one of the most important such reagents, offering a broad variety of useful functional group transformations under mild conditions.[1] Its unique properties and high reactivity arise from a combination of the relatively high Lewis acidity of silicon (with a specific affinity to oxygen functionalities) and the strong nucleophilicity of iodide ion. These properties of TMSI make it a versatile and selective reagent for cleavage of carbon–oxygen bonds.

Therefore, it is quite surprising that despite the many reports on synthetic applications of TMSI, very little effort was devoted to attempts to modify the reactivity of the Si–I bond and thereby to obtain new reagents with novel chemical properties. There were, however, some investigations devoted to altering the steric demands of the reagent, designing iodotrialkylsilanes with bulkier alkyl groups, such as *t*-$BuMe_2SiI$ or *t*-$BuPh_2SiI$.[2] These modifications, however, did not affect the basic properties and selectivities of the reagent, e.g., its preference for cleaving methyl ethers rather than primary and secondary alkyl ethers. Moreover, the reactivity pattern of Cl_3SiI (prepared in situ from tetrachlorosilane and sodium iodide)[3] was also similar to that of TMSI, as was a combination of trichloromethylsilane and sodium iodide, despite its reduced reactivity.[4] Nevertheless, modifications of either the Lewis acidity or nucleophilicity of this family of reagents could lead to modified reactivity profiles and, in particular, alternative chemoselectivities. In fact, during attempts to generate TMSI in situ from various organosilicon precursors,[1] including TMSCl and NaI,[5] hexamethyldisilane and iodine,[6] allyltrimethylsilane and iodine,[7] $PhSiMe_3$ and iodine,[8] etc., it was noticed that the combination of reagents exhibited properties that differed from those of preformed TMSI. The latter combination, for example, exhibited enhanced efficiency in cleaving alkyl aryl ethers.[8,9] The altered behavior of these systems seems to be associated with the precursors whose characteristics differ from those of TMSI (e.g., acidity and nucleophilicity).

In our search for new modes of reactivity of yet unrecognized iodosilane reagents, we discovered that diiodosilane (DIS) is an extremely useful reagent, exhibiting properties and reactivities that are complementary to those of TMSI. In this paper, we present an easy and rapid synthesis of DIS and demonstrate this reagent's application to cleavage and deoxygenation of alcohols and ethers with chemoselectivities that are complementary to those of the iodotrialkylsilanes.

Results and Discussion

Preparation of DIS. DIS[10] was first prepared almost 50 years ago by reaction of silane, HI, and aluminum iodide.[11] However, apart from occasional studies on the properties of this rather exotic compound, it has never

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