yield: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6 Hz, CH_3CH), 2.23 (s, 3 H, $O(CH_3)C{=}C$), 4.74 (q, 1 H, H10), 5.85 (d, J = 3 Hz, H3, 6.14 (d, J = 3 Hz, H4); $[\alpha]^{25}_D$ -4.90° ($CHCl_3$).

A small amount of the unsaturated ketone **9** was also isolated in about 15% yield: mp 110-112 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J = 6 Hz, 3 H, CH_3CH), 2.23 (s, 3 H, $CH_3C{=}O$), 4.70 (q, 1 H, H10), 5.04 (dd, J = 2, 16 Hz, H3), 6.60 (dd, J = 4.5, 6 Hz, H4); $[\alpha]^{25}_D$ +2.99° ($CHCl_3$); mass spectrum, m/e (CI isobutane) 229 (loss of H_2O). Both **8** and **9** could be isolated by chromatography on reverse-phase silica by elution with 10% acetonitrile-water.

Acetylation of 2,5-Disubstituted Furan. The hydroxy 2,5-disubstituted furan **8a** (0.310 g, 1.36 mmol) was acetylated with a mixture of acetic anhydride (0.60 mL) and pyridine (0.72 mL). The resulting acetate was purified by preparative thin-layer chromatography, using EtOAc/PE (20:80) to give the acetoxy 2,5-disubstituted furan **8b**: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6 Hz, 3 H, CH_3CH) 2.00 (s), 2.14 (s, CH_3CO), 2.29 (s, 3 H, $O(CH_3)C{-}C$), 4.04 (dd, J = 2, 10 Hz, H9), 4.39 (dd, J = 2, 5 Hz, H7, 4.77 (q, H10), 4.90 (m, H8), 5.91 (d, J = 10 Hz, H6), 5.91 (d, J = 3 Hz, H3), 6.32 (d, J = 3 Hz, H4); mass spectrum, m/e (CI, methane) 312, 253, 209, 149.

Preparation of Ketone 9 4,6-*O*-Ethylidene-D-galactose (7) (1.03 g, 5 mmol), Wittig reagent (6.93 g, 21 mmol), and acetonitrile (50 mL) were refluxed with stirring for 60 h. The reaction mixture was cooled to room temperature and poured into ice-cold water, and excess Wittig reagent and triphenylphosphine oxide were filtered off. The aqueous portion was saturated with sodium chloride and thoroughly extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, and the solvent filtered off the sodium sulfate and concentrated in vacuo to a pale-yellow oil. The mixture was purified by preparative thin-layer chromatography, using ethyl acetate as the eluent to give the ketone **9** (0.566 g) in 55% yield.

A small amount of the 2,5-disubstituted furan **8a** derivative was also isolated in about 10% yield.

Acknowledgment. We thank Professor W. Bailey of the University of Connecticut for obtaining the ^{13}C NMR. We are grateful for financial support of the research by Grants CA 27115 and AM 21888 from the National Institutes of Health.

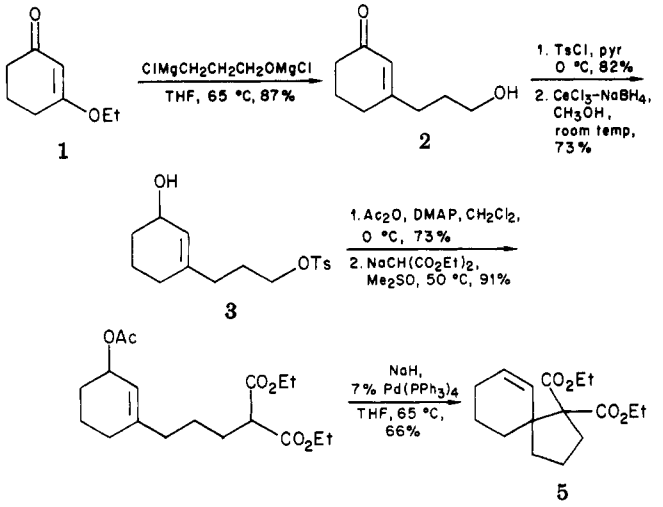
Communications

Palladium-Catalyzed Preparation of Carbon and Oxygen Spirocycles

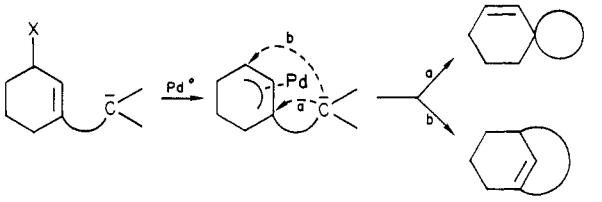
Summary: A variety of substituted spiro[5.5]undecene and spiro[5.4]decene systems have been prepared by utilizing π-allylpalladium chemistry in the key ring-forming step.

Sir: Numerous carbon-carbon bond-forming reactions[1,2] have been applied to the often considerable challenge of the preparation of spirocycles. In order to possess optimal utility, any general methodology dedicated to this purpose should provide the following features in the crucial formation of the quaternary center: (1) complete stereospecificity; (2) ease of preparation of the required precursors; (3) considerable tolerance of additional functionality; (4) potential asymmetric induction. π-Allylpalladium chemistry can fully meet all the stated criteria,[3-5] as well as allow relatively mild reaction conditions for spirocyclization and catalytic use of the metal. Its application to the preparation of spirocycles is detailed in this paper.

Scheme I



The key intermediate required for the palladium-catalyzed spirocyclization is shown below. Reaction of an



allylic ester (e.g., X = OAc) with tetrakis(triphenylphosphine)palladium(0) yields the bisphosphine allyl cation. Cyclization of this compound could, in principle, take place on either terminus of the allyl unit. Cyclization path a leads to the desired spirocycle, while b yields a *trans*-cycloalkenyl system, which for the ring sizes of most interest for spirocyclic natural products ([5.5], [5.4], [4.4]) would be an anti-Bredt olefin. Although there is the intriguing possibility of stabilization of such species[6,7] by the

(1) Recent metal-based routes to spirocycles: Semmelhack, M. F.; Yamashita, A. *J. Am. Chem. Soc.* **1980**, *102*, 5924. Pearson, A. J. *Acc. Chem. Res.* **1980**, *13*, 463. Macdonald, T. L.; Mahalingam, S. *J. Am. Chem. Soc.* **1980**, *102*, 2113. Godleski, S. A.; Meinhart, J. D.; Miller, D. J.; Van Wallendael, S. *Tetrahedron Lett.* **1981**, 2247.

(2) Review articles on preparation of spirocylces: Martin, S. F. *Tetrahedron* **1980**, *36*, 419. Krapcho, A. P. *Synthesis* **1978**, 77; **1976**, 425; **1974**; 383. Recently reported routes to spirocycles: Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Strickland, S. M.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400. Altenbach, H. J. *Angew. Chem., Init. Ed. Engl.* **1979**, *18*, 940.

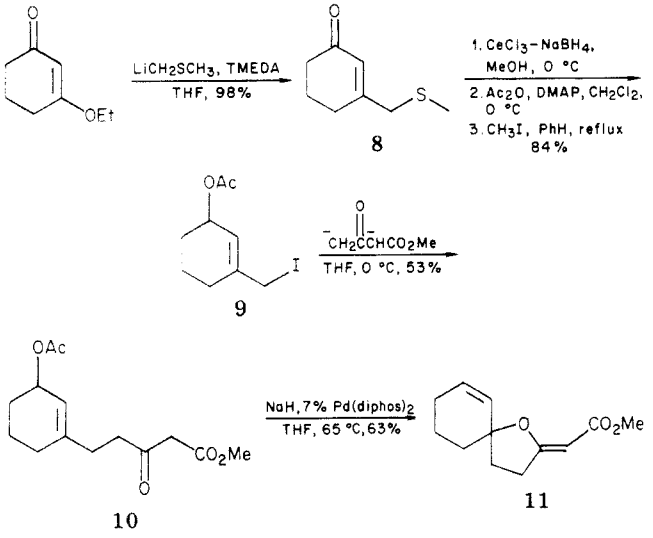
(3) Stereospecificity in π-allyl alkylation, i.e., complete retention of configuration with respect to the allylic C-X bond in nucleophilic addition and inversion in attack on π-allyl: Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611. Inversion in initial oxidative addition: Wong, P. K.; Van, K. S. Y.; Stille, J. K. *Ibid.* **1974**, *96*, 5956.

(4) Chemospecificity in π-allyl alkylation: Trost, B. M.; Dietsche, T. J.; Fullerton, T. J. *J. Org. Chem.* **1974**, *39*, 737.

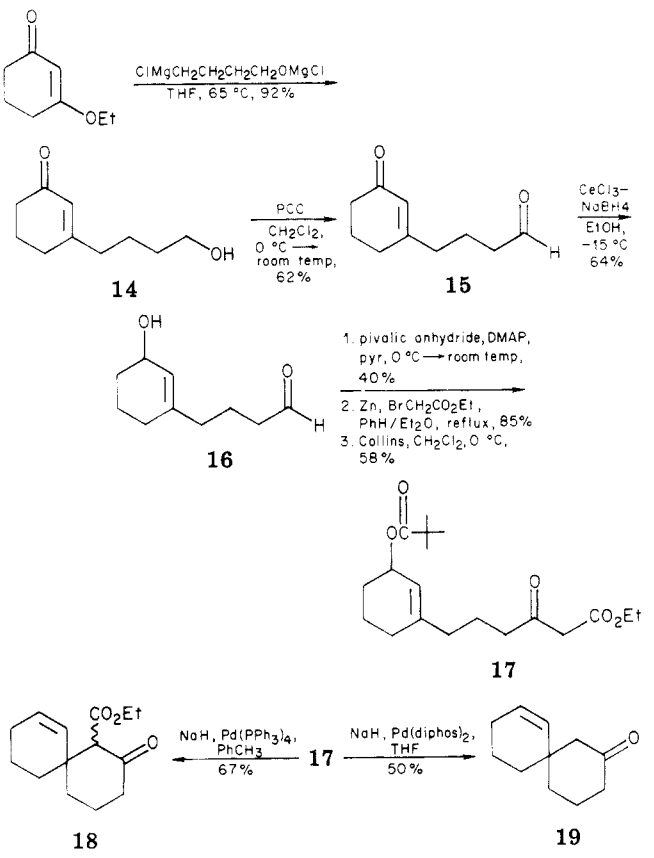
(5) Asymmetric induction via the use of chiral phosphines on Pd: Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200.

0022-3263/82/1947-0381$01.25/0

Scheme II

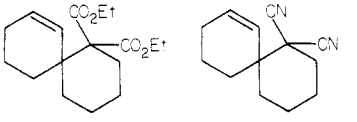


Scheme III



metal, in the event no evidence for their formation was detected.

Scheme I details the preparation and utilization of a malonate derivative in the palladium-catalyzed cyclization. Assembly of the π-allyl precursor was initiated by reaction of the Normant Grignard reagent[8] derived from 3-chlorobutanol with the vinylogous ester **1** (87%). Tosylation of the incipient primary alcohol[8] **2** under standard conditions (82%), followed by $CeCl_3$–$NaBH_4$[9] reduction (73%) of the enone, provided the allylic alcohol **3**.[10] Acetylation (73%) and alkylation with diethyl sodiomalonate (91%) afforded the required π-allyl precursor (**4**).[10] Treatment of a THF solution of **4** with 1 equiv of NaH, followed by 7 mol % of $Pd(PPh_3)_4$ and heating at reflux for 6 h gave the spirocyclic compound **5**[10] in 66% yield. In strict analogy, spirocycles **6** and **7**[10] were also constructed.[11,12]



6 7

Investigation of the spirocyclization of a synthetically more useful β-keto ester anion is shown in Scheme II. The sequence is initiated by reaction of the vinylogous ester **1** with the anion of dimethyl sulfide[13] to give **8** in 97% yield. Reduction ($CeCl_3$–$NaBH_4$), acetylation (Ac_2O, DMAP),[14] and iodination (MeI)[15] provided the iodoallylic acetate **9**[10] (84% yield for three steps). Treatment of **9** with the dianion of methyl acetoacetate[16] supplies the π-allyl precursor **10**[10] (53%). Reaction of the sodium anion of **10** with 7 mol % of $Pd(diphos)_2$[17,18] in refluxing THF for 4 h produced the spirofuran **11**[10] in 63% yield as the only cyclized material isolated.[11] Attempted isomerization of this O-alkylated species to the thermodynamically more stable C-alkylated material by using the conditions found by Trost[19] and Tsuji[20] to effect this reaction in monocyclic

(6) For examples of metal-stabilized strained olefins see: Bennett, M. A.; Yoshida, T. *J. Am. Chem. Soc.* **1978**, *100*, 1750. Jason, M. E.; McGinnety, J. A.; Wiberg, K. B. *Ibid.* **1974**, *96*, 6531.

(7) We are currently actively investigating the preparation of such species.

(8) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, *3013*.

(9) Luche, J. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(10) Partial spectral characterization for these compounds is as follows. **3**: ^{1}H NMR δ 7.8 (d, 2 H, J = 10 Hz), 7.4 (d, 2 H, J = 10 Hz), 5.6 (s, 1 H), 4.1 (t + br s, 3 H), 2.5 (s, 3 H), 1.4–2.5 (m, 11 H); IR 3250–3500 cm^{-1}; mass spectrum (20 eV), m/e 310. **4**: ^{1}H NMR δ 5.4 (s, 1 H), 5.2 (s, 1 H), 4.2 (q, 4 H, J = 8 Hz), 3.3 (t, 1 H, J = 7.5 Hz), 2.0 (s, 3 H), 1.4–2.0 (m, 12 H) 1.2 (t, 6 H, J = 8 Hz); IR 1730 cm^{-1}; mass spectrum, m/e 284. **5**: ^{1}H NMR δ 5.7 (d, 1 H, J = 11 Hz), 5.5 (d, 1 H, J = 11 Hz), 4.1 (q, 4 H, J = 7.5 Hz), 1.4–2.3 (m, 12 H), 1.24 (t, 6 H, J = 7.5 Hz); IR 1735 cm^{-1}; mass spectrum, m/e 280; ^{13}C NMR δ 131.2 (d), 126.8 (d), 77.9 (s), 60.7 (t), 50.9 (t), 39.0 (s), 32.4 (t), 30.7 (t), 24.7 (q), 22.4 (t), 21.4 (t), 21.2 (t), 21.1 (t), 14.0 (t). **6**: ^{1}H NMR δ 6.0 (d, 1 H, J = 11 Hz), 5.6 (d, 1 H, J = 11 Hz), 4.1 (q, 4 H, J = 7 Hz), 1.4–2.3 (m, 14 H), 1.2 (t, 6 H, J = 7 Hz); IR 1725 cm^{-1}; mass spectrum, m/e 294; ^{13}C NMR δ 176.1 (s), 170.8 (s), 132.9 (d), 126.7 (d), 61.3 (s), 60.5 (t), 39.5 (s), 33.6 (t), 29.2 (t), 28.9 (t), 24.9 (q), 21.8 (t), 21.0 (t), 18.8 (t), 14.0 (t). **7**: H NMR δ 6.0 (d, 1 H, J = 11 Hz), 5.7 (d, 1 H, J = 11 Hz), 1.3–2.2 (m, 14 H). **9**: ^{1}H NMR δ 5.6 (s, 1 H), 5.3 (s, 1 H), 3.0 (s, 2 H), 2.0 (s, 3 H), 1.9 (s, 3 H), 1.0–1.9 (m, 6 H); IR 1745 cm^{-1}; mass spectrum, m/e 280. **10**: ^{1}H NMR δ 5.5 (s, 1 H), 5.3 (s, 1 H), 3.7 (s, 3 H), 3.5 (s, 2 H), 2.7 (t, 2 H, J = 7 Hz), 2.3 (m, 2 H), 2.0 (s, 3 H), 1.2–1.9 (m, 6 H); IR 1730 cm^{-1}; mass spectrum, m/e 225. **11**: ^{1}H NMR δ 5.9 (d, 1 H, J = 10 Hz), 5.6 (d, 1 H, J = 10 Hz), 5.2 (s, 1 H), 3.6 (s, 3 H), 3.2 (t, 2 H), 1.0–2.4 (m, 8 H); IR 1710, 1640 cm^{-1}; mass spectrum, m/e 208; ^{13}C NMR δ 176, 169, 132, 129, 89, 87, 51, 35, 34, 30, 25, 20. **12**: ^{1}H NMR δ 6.0 (d, 1 H, J = 10 Hz), 5.7 (d, 1 H, J = 10 Hz), 3.7 (s, 3 H), 1.5–2.6 (m, 10 H); IR 1710, 1650 cm^{-1}; mass spectrum, m/e 208; ^{13}C NMR δ 167 (d), 131 (d), 130 (d), 101 (s), 85 (s), 51 (q), 42 (t), 34 (t), 25 (t), 20 (t), 15 (q). **15**: ^{1}H NMR δ 9.6 (s, 1 H), 5.8 (s, 1 H), 1.8–2.4 (m, 12 H); IR 1735 cm^{-1}; mass spectrum, m/e 166. **16**: ^{1}H NMR δ 9.6 (s, 1 H), 5.5 (s, 1 H), 4.1 (s, 1 H), 1.6–2.4 (m, 1 H); IR 3618, 353+5 (br), 1730 cm^{-1}; mass spectrum, m/e 150. **17**: ^{1}H NMR δ 12.0 (s, 0.2 H), 5.4 (s, 1 H), 5.1 (s, 1 H), 4.1 (q, 2 H, J = 7.5 Hz), 3.4 (s, 1.8 H), 2.5 (t, 2 H), 1.4–2.1 (m, 10 H), 1.3 (t, 3 H, J = 7.5 Hz), 1.2 (s, 9 H); IR 1710–1735 (br) cm^{-1}; mass spectrum, m/e 338. **18** the spectra showed a mixture of epimers. The material was decarboxylated to **19** and then hydrogenated to the known[25] saturated ketone; observed spectra agreed with literature reported values.

(11) Performance of the necessary control reactions demonstrated the intimate involvement of the metal catalyst in these reactions.

(12) The reaction times for formation of the six-membered ring analogues are generally 2–3 times longer.

(13) Peterson, D. J. *J. Org. Chem.* **1967**, *32*, 1717.

(14) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

(15) Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144.

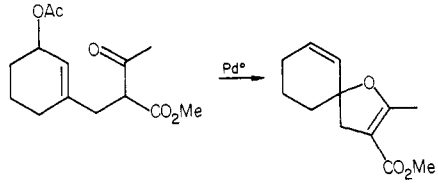
(16) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(17) $(diphos)_2Pd$ realized the cyclization at lower temperature and better yields than $Pd(PPh_3)_4$.

(18) Direct treatment of the product of the dianion alkylation (no workup) of **9** with $Pd(diphos)_2$ gave the spirocycle but in lower yield.

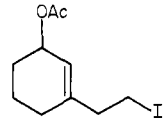
systems was unsuccessful. Utilization of a variety of Lewis acid and protic acid catalysts in conjunction with a number of palladium complexes also met with failure.

The spirofuran 12[10] was prepared in quantitative yield by treatment of the methyl acetoacetate monoanion alkylation product of 9 under the usual cyclization conditions.[11]



12

Attempted use of the homoallylic iodoacetate 13 in the



13

methyl acetoacetate dianion reaction resulted largely in the formation of the conjugated diene. As a result, a new route to the β-keto ester precursor of a spiro[5.5]undecene system was developed as shown in Scheme III. Pyridinium chlorochromate oxidation[21] of the previously prepared enone alcohol 14[8] yielded the aldehyde 15[10] (63%). Specific reduction of 15 to the allylic alcohol–aldehyde 16[10] was accomplished by the use of the $CeCl_3$–$NaBH_4$ reagent.[22] Preparation of the π-allyl precursor 17[10] was completed by pivalation (40%), Reformatsky reaction on the aldehyde with ethyl bromoacetate (85%), and Collins oxidation[23] (58%). Treatment of the sodium hydride generated anion of 17 with 10 mol % of $Pd(PPh_3)_4$ in toluene at 120 °C in a sealed tube (14 h) yielded only the C-alkylated β-keto ester 18[10] (67%). Use of the $Pd(diphos)_2$ catalyst in THF under similar conditions gave directly the decarboxylated spirocyclic ketone 19.[10] The more forcing conditions required for cyclization (relative to 10 → 11) are presumably due to the lower propensity of the pivalate (vs. acetate) to undergo oxidative addition and/or the inherent slower rate of six- relative to five-membered ring formation. Subjection of 10 to comparable reaction conditions did not provide C-alkylated material.

Pearson[1] has noted similar behavior in the iron diene catalyzed spirocyclization of β-keto esters, which he rationalized on the basis of Baldwin's rules (i.e., five O-alkylates, six C-alkylates). We believe that the inherent degree of reversibility in the cyclization (six membered ≫ five membered) is a more likely explanation.[24]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the NIH (Grant No. GM-27328) for support of this work.

Registry No. 1, 5323-87-5; 2, 61589-86-4; 3, 80206-58-2; 4, 80206-59-3; 5, 80206-60-6; 6, 80206-61-7; 7, 80206-62-8; 8, 58775-64-7; 9, 80206-63-9; 10, 80206-64-0; 11, 80206-65-1; 12, 80206-66-2; 14, 78877-14-2; 15, 74457-25-3; 16, 80206-67-3; 17, 80206-68-4; 18, 80206-69-5; 19, 79539-12-1.

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Received August 20, 1981

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(20) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, 1475.
(21) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(22) Luche, J.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
(23) Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M.; *J. Am. Chem. Soc.* **1981**, *103*, 1501.
(24) We have noted in several other spirocycles the greater tendency of the six-membered ring analogues to open at the spiro center.
(25) White, J. D.; Ruppert, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 1808.

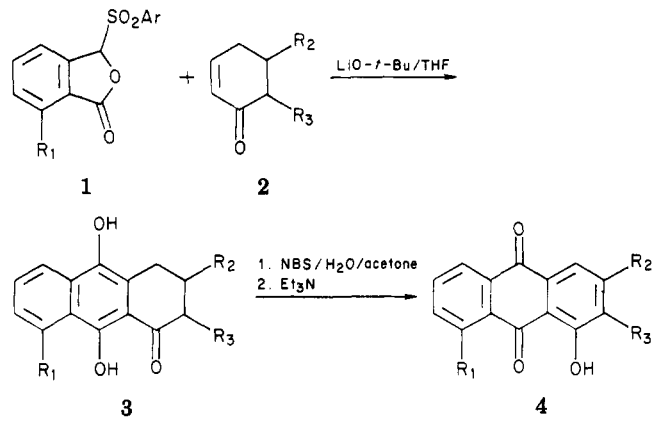
Novel Oxidative Transformation: Regiospecific Preparation of Naturally Occurring 1-Hydroxyanthraquinones

Summary: A brief reaction sequence for synthesis of the naturally occurring anthraquinones 1-hydroxyanthraquinone (**4a**), 1-hydroxy-2-methylanthraquinone (**4b**), pachybasin (**4c**), chrysophanol (**5a**), and rhein (**5c**) has been developed.

Sir: We have found that treatment of 9,10-dihydroxy-1,2,3,4-tetrahydroanthracen-1-ones (**3**) with *N*-bromosuccinimide (NBS) in acetone–water followed by quenching with triethylamine results in oxidative transformation to 1-hydroxyanthraquinones (**4**) in good yield. This finding has been employed to develop a general reaction sequence for preparation of the naturally occurring 1-hydroxyanthraquinones **4a–c**, chrysophanol (**5a**), and rhein (**5c**).

The intermediate tetrahydroanthracenones **3** were prepared by using the annelation methodology we developed earlier for regiospecific synthesis of polycyclic aromatic systems possessing a 1,4-dihydroxy aromatic fragment and an electron-withdrawing group at the 2-position.[1-3] Analogous condensations of the anion[4] of sulfones 1[1,5] with

Scheme I[a]



[a] a, $R_1 = R_2 = R_3 = H$; b, $R_1 = R_2 = H$, $R_3 = CH_3$; c, $R_1 = R_3 = H$, $R_2 = CH_3$; d, $R_1 = OCH_3$, $R_2 = CH_3$, $R_3 = H$; e, $R_1 = OCH_3$, $R_2 = CO_2CH_3$, $R_3 = H$.

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(4) Lithium *tert*-butoxide, used as a base in the reaction, was obtained by adding *n*-butyllithium (3.02 equiv) to a solution of *tert*-butanol (3.2 equiv) in dry THF at 0 °C.
(5) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H. *Synthesis* **1980**, 72.

0022-3263/82/1947-0383$01.25/0