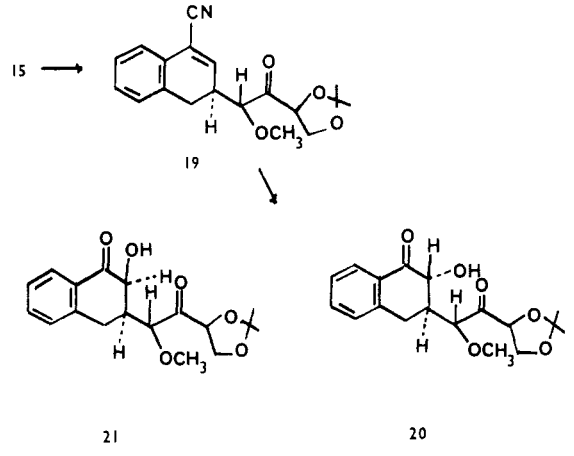
CuCl, it is cyclized to tetrahydrofuran **17** which has its pairs of cis substituents on opposite faces of the THF ring, a fairly uncrowded array. In contrast to the facile reaction of **15**, the cyclization of **16** to **18** did not take place even when subjected to identical experimental conditions for an extended time period. It is clear that **18** would have all four substituents on the same face of the THF ring and would thus be very congested. Hence we conclude that our major products from the Diels–Alder reaction do have the "natural" stereochemistry, and we can proceed with our synthetic scheme.

The Garegg modification of the Collins oxidation[10] of **15** afforded ketone **19** (25–89%, IR 1720 $cm^{-1}$) with the other product being a B-ring aromatized species due to uncontrollable overoxidation. A $Me_2SO$–TFAA method[11] produced ketone **19** in 90% yield reproducibly. Hydroxylation of the double bond of **19**, creating a hydroxy cyanohydrin which should become a hydroxy ketone,[12] was predicted to create the new hydroxyl at C2 with the correct stereochemistry since the sugar side chain at C3 should force attack from the opposite side. In the event, oxidation with triphenylmethylphosphonium permanganate at −78 °C yielded **20** (41%) and **21** (25%) easily separable by PLC.[13] The major product had an IR spectrum (1730, 1680 $cm^{-1}$) characteristic of the aglycone when its phenolic H bonding is blocked.[1] Its UV spectrum (247, 287 nm) is characteristic of an aromatic acyloin. The NMR of its acetate revealed, for the proton at C2, a $J_{2,3}$ of 12 Hz at $\delta$ 5.62 which is diagnostic for the trans diaxial stereochemistry of the protons in the natural product. Thus, we have in hand a compound that has the critical stereochemical features of the aureolic acids. There now remains the substantial task of constructing the correctly substituted precursors so as to complete the synthesis of the natural aglycone.[14,15]




(10) (a) Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267–70. (b) When PDC alone was used, the oxidation was much slower, and byproduct **17** was obtained. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

(11) Yoshimura, J.; Sato, K.; Hashimoto, H. *Chem. Lett.* **1977**, 1327–30.

(12) Freerksen, R. W.; Raggio, M. L.; Thoms, C. A.; Watt, D. S. *J. Org. Chem.* **1979**, *44*, 702–10. The cited report describes a thorough examination of reagents for the hydroxylation of unsaturated nitriles for the purpose of converting them to acyloins.

(13) Reischl, W.; Zbiral, E. *Tetrahedron* **1979**, *35*, 1109–10.

(14) We are grateful to Professor S. M. Weinreb for his many insights on the aureolic acid problem which he shared in numerous discussions, to Dr. L. Foley of Hoffmann-La Roche for her invaluable assistance in pinpointing the appropriate carbohydrate methodologies for our work, and finally for the Biomedical Sciences Research Support Grant RR 7150 to Fordham University which gave partial support to this project.

(15) The major elements of this report were the subject of a paper delivered at the American Chemical Society meeting in Washington, DC, Sept 1979, CARBO 44.

**Registry No.** **3**, 6809-91-2; **4**, 25512-65-6; **5**, 72727-00-5; **6**, 72777-12-9; **7**, 72727-01-6; **8**, 72727-02-7; **9**, 72727-03-8; **10**, 72777-13-0; **11**, 72727-04-9; **11a**, 72777-14-1; **12**, 72777-15-2; **13**, 72727-05-0; **14**, 72777-16-3; **15**, 72727-06-1; **16**, 72777-17-4; **17**, 72727-07-2; **19**, 72727-08-3; **20**, 72727-09-4; **21**, 72777-18-5.

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*Received November 30, 1979*

## Stereochemically Controlled Synthesis of Steroid Side Chains: Synthesis of Desmosterol

*Summary:* (20*R*)-Desmosterol, a versatile intermediate for the synthesis of vitamin D metabolites and numerous other steroids having a side chain modified at C-24 and/or C-25, can be synthesized stereospecifically and efficiently by starting from the readily available 16$\alpha$,17$\alpha$-epoxypregnenolone and employing the potassium-assisted oxy–Cope rearrangement as a key stereodirecting process at C-20.

*Sir:* The significant stereochemical dependence of the side chains on their activities of various physiologically active steroids, such as insect and crustacean molting hormones (ecdysones) and vitamin D metabolites, has been well documented.[1] Furthermore, recent isolations[2] of numerous sterols possessing unusual side-chain structures from marine sources have facilitated efforts toward the stereocontrolled synthesis of the steroid side chains, especially at C-20.[3,4] Unlike genuinely acyclic carbon chains,[5] steroid side chains have intrinsic advantages in their stereocontrolled synthesis, since the stereochemistry can be transmitted in their synthesis from the asymmetric and rigid steroid ring portions. Here we report a stereocontrolled, efficient steroid side-chain synthesis employing the concept of the stereochemical transmission via the oxy–Cope rearrangement (Scheme I).

The Wharton reaction,[6] with hydrazine hydrate in diethylene glycol and potassium hydroxide, of the tetrahydropyranyl (THP) ether derivative **2** (mp 123–124 °C) of the readily available 16$\alpha$,17$\alpha$-epoxypregnenolone[7] gave

(1) (a) Hikino, H.; Hikino, Y. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 256. (b) Nakanishi, K. *Pure Appl. Chem.* **1971**, *25*, 167. (c) DeLuca, H. F. *Handb. Physiol., Sect. 7: Endocrinol.* **1976**, *7*, 265.

(2) (a) Nes, W. R.; McKean, M. L. "Biochemistry of Steroids and Other Isoprenoids"; University Park Press: Baltimore, MD, 1977. (b) Minale, L.; Sodano, G. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977; p 87.

(3) (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Trost. B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. (c) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380.

(4) For a stereocontrolled synthesis of (20*S*)-20-isocholesterol, see: Koreeda, M.; Koizumi, N. *Tetrahedron Lett.* **1978**, 1641.

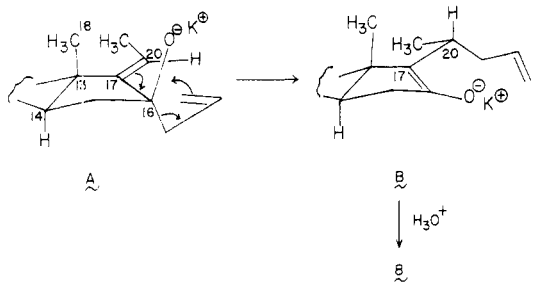
(5) See the following references and those cited therein for recent approaches to the synthesis of isoprenoid chains bearing chiral methyl centers which utilize chiral transmission via Claisen rearrangement: (a) Chan, K. K.; Cohen, N.; DeNoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (b) Cohen, N.; Eichel, W. F.; Lopretsi, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1976**, *41*, 3512. (c) Chan, K. K.; Saucy, G. *Ibid.* **1977**, *42*, 3828. (d) Chan, K. K.; Specian, A. C., Jr.; Saucy, G. *Ibid.* **1978**, *43*, 3435.

(6) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 2615.

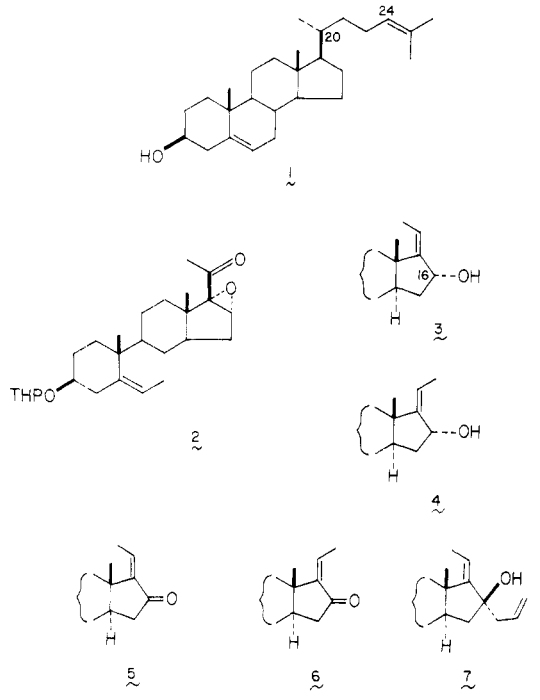
(7) Purchased from Sigma Chemical Co., St. Louis, MO.

0022-3263/80/1945-1172$01.00/0 

Scheme I

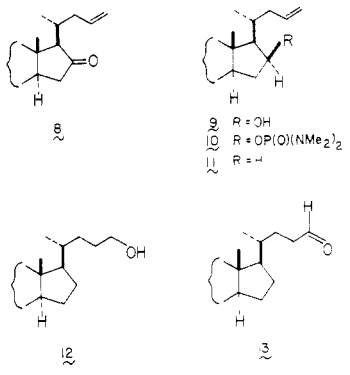


the two isomeric allylic alcohols **3** (mp 156–158 °C) and **4** (oil) in 64 and 19% yield, respectively.[8,9] The *E* isomer



**3** was oxidized with pyridinium dichromate–pyridinium trifluoroacetate complex[10] in $CH_2Cl_2$ at 0 °C for 3 h under argon to the *E* enone **5** (70%, mp 138–140 °C) as well as a small amount of the *Z* enone **6** (10%, mp 173–175 °C). The Grignard reaction of the *E* enone **5** with allylmagnesium bromide at 50 °C for 1 h in THF produced predominantly the 16β-hydroxy compound **7**,[11] as an amorphous powder, in 93% yield via the α side addition to the 16-ketone. The crucial step for the introduction of the *R* configuration at C-20 was effected by treating alcohol **7** with potassium hydride in refluxing dioxane for 1 h under argon, which produced the rearranged 20*R* keto olefin **8**[12] (mp 138–141 °C) as a single stereoisomer at C-17 and C-20 in 94% yield. The stereospecific generation of the 20*R* stereochemistry is ascribable to the chairlike transition state (A in Scheme I) involved in the potassium-assisted oxy-Cope rearrangement[13] of **7**.[14]

The removal of the 16-keto group in **8** by the Wolff–Kishner procedure proved to be sluggish. Therefore, the ketone **8** was first reduced to the 16β-alcohol **9**[15] ($LiAlH_4$,

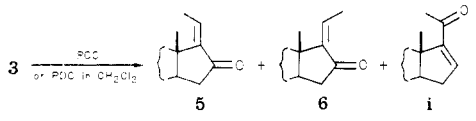


90%; mp 148–149 °C) and converted quantitatively to its phosphodiamidate derivative **10**[16] (mp 141–143 °C) with $(Me_2N)_2P(O)Cl$/TMEDA in THF. The phosphodiamidate **10** was then reduced to the 16-deoxy olefin **11**[17] (80%, mp 106–108°C) with lithium in liquid ammonia/THF.[18] The construction of the steroid side chain was completed as follows: (i) hydroboration of **11** with $BH_3{\cdot}SMe_2$ followed by alkaline-$H_2O_2$ treatment to give the alcohol **12** (78%, mp 127–128 °C), (ii) oxidation of **12** with pyridinium dichromate in $CH_2Cl_2$ to the aldehyde **13**[19] (84%, mp 115–117 °C), which was identical (IR, $^1H$, NMR, mixture melting point) with an authentic aldehyde[20] obtained from desmosterol THP ether, and (iii) Wittig reaction of the aldehyde **13** with triphenylphosphonium isopropylide[21]

(8) (a) Benn, W. R.; Dodson, R. M. *J. Org. Chem.* **1964**, *29*, 1142. (b) Kessar, S. V.; Rampal, A. L. *Tetrahedron* **1968**, *24*, 887.

(9) The stereochemistry was assigned on the basis of the $^1H$ NMR spectra of **3** and **4** in $CDCl_3$.[8] For **3**: δ 0.89 (3 H, s, 18-H), 1.75 (3 H, d, *J* = 7.3 Hz, 21-H), 5.59 (1 H, q, *J* = 7.3 Hz, 20-H). For **4**: δ 0.76 (3 H, s, 18-H), 1.73 (d, 3 H, *J* = 7.1 Hz, 21-H), 5.33 (m, 20-H, overlapped with 6-H). All $^1H$ NMR spectra described in this report were measured in $CDCl_3$ at 100 MHz.

(10) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. The oxidation of **3** both with pyridinium chlorochromate (PCC) and with pyridinium dichromate (PDC) produced quantitatively a mixture of **5**, **6**, and **i** (2:2:1).



For **5**: IR (KBr) 1723 $cm^{-1}$; $^1H$ NMR δ 1.02 (6 H, s, 18-H and 19-H), 1.78 (3 H, d, *J* = 7.1 Hz, 21-H), 6.35 (1 H, q, *J* = 7.1 Hz, 20-H). For **6**: IR (KBr) 1710 $cm^{-1}$; $^1H$ NMR δ 0.91 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 2.02 (3 H, d, *J* = 7.0 Hz, 21-H), 5.29 (1 H, q, *J* = 7.0 Hz, 20-H).

(11) For **7**: $^1H$ NMR δ 1.04 (3 H, s, 19-H), 1.09 (3 H, s, 18-H), 1.74 (3 H, d, *J* = 7.1 Hz, 21-H), 5.52 (1 H, q, *J* = 7.1 Hz, 20-H), 4.8–5.1 (2 H, m, $CH{=}CH_2$), 5.8 (1 H, m, $CH{=}CH_2$). The $^{13}C$ NMR spectrum of the crude product indicates the presence of a small amount (<5%) of the 16α-hydroxy epimer.

(12) The quasi-equatorial 17β stereochemistry of the side chain in **8** results upon quenching B with water. For **8**: IR ($CHCl_3$) 1732 $cm^{-1}$; $^1H$ NMR δ 0.85 (3 H, s, 18-H), 0.98 (3 H, d, *J* = 6.1 Hz, 21-H), 1.04 (3 H, s, 19-H), 4.7 (1 H, br s, O–CH–O), 4.8–5.1 (2 H, m, or apparent broad singlets at 4.94 and 5.09 with $W_{1/2}$ = 5 and 8 Hz, respectively, 24-H), 5.35 (1 H, br s, 6-H), 5.8 (1 H, m, $W_{1/2}$ = 36 Hz, 23-H).

(13) For some recent work in this area, see: (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Wilson, S. R.; Mao, D. T.; Fernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, 2559. (c) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186. (d) Miyashi, T.; Hazato, A.; Mukai, T. *Ibid.* **1978**, *100*, 1008. (e) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *Ibid.* **1978**, *100*, 2242. (f) Jung, M. E.; Hudspeth, J. P. *Ibid.* **1978**, *100*, 4309. (g) Steigerwald, M.; Goddard, W. A., III; Evans, D. A. *Ibid.* **1979**, *101*, 1994.

(14) Interestingly, the similar treatment of the *Z* isomer of **7** failed to produce any rearranged products presumably due to the quasi-1,3-diaxial interaction between 16-$O^-K^+$ and 20-$CH_3$ (20-$CH_3$/20-H interchanged in A, Scheme I). Instead, this reaction produced a mixture of the enones **5** and **6**.

(15) For **9**: IR ($CHCl_3$) 3460 $cm^{-1}$; $^1H$ NMR δ 0.88 (3 H, s, 18-H), 0.96 (3 H, d, *J* = 7.0 Hz, 21-H), 1.02 (3 H, s, 19-H).

(16) For **10**: IR ($CHCl_3$) 1205, 985 $cm^{-1}$.

(17) For **11**: $^1H$ NMR ($CDCl_3$) δ 0.69 (3 H, s, 18-H), 0.93 (3 H, d, *J* = 6.3 Hz, 21-H), 1.01 (3 H, s, 19-H), 4.85–5.05 (2 H, m, 24-H), 5.8 (1 H, m, 23-H).

(18) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(19) For **13**: IR ($CHCl_3$) 1724 $cm^{-1}$; $^1H$ NMR δ 9.82 (1 H, br s, 24-H).

(20) Craig, I. F.; Boyd, G. S.; Suckling, K. E. *Biochim. Biophys. Acta* **1978**, *508*, 418.

(21) (a) Wechter, W. J. U.S. Patent 3 152 152, Oct 6, 1964; *Chem. Abstr.* **1964**, *61*, 16135g. (b) Wyllie, S. G.; Djerassi, C. *J. Org. Chem.* **1968**, *33*, 305.

followed by the removal of the THP ether to give desmosterol (**1**, 78%).[22] The 20*R* configuration of **1** was confirmed by spectroscopic comparisons with the authentic desmosterol. Desmosterol has been converted into cholesterol and 24,25-epoxy- and 24,25-dihydroxycholesterols (the precursors to the active vitamin D metabolites).[3a]

The approach described herein provides a novel, efficient and totally stereocontrolled steroid side-chain synthesis and can be applied to the steroids with various 24,25-branched side chains from the intermediate olefin **11**.

**Acknowledgment.** We wish to thank the National Institutes of Health, DHEW (Grant No. AI 15664), for their generous support of this work.

**Note Added in Proof.** Since submission of the manuscript, Dr. M. Tanabe of Stanford Research Institute kindly provided us with a preprint of studies on his new approach to the synthesis of sterol side chains: Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862.

(22) Dasgupta, S. K.; Crump, D. R.; Gut, M. *J. Org. Chem.* **1974**, *39*, 1658.

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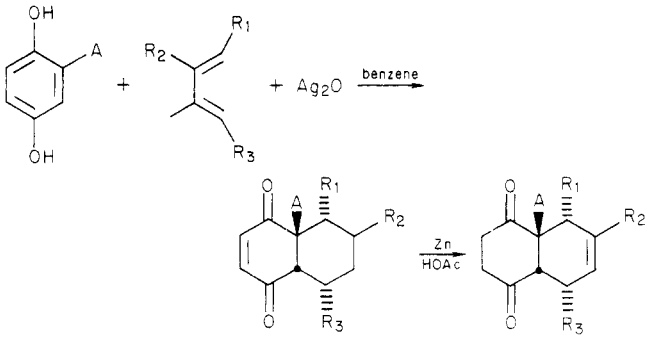
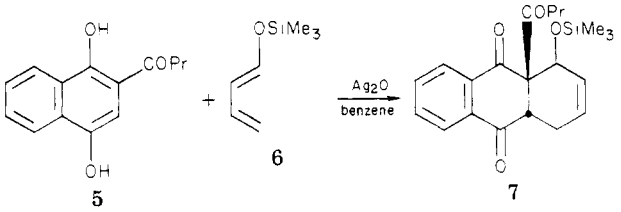
## Diels-Alder Reactions Using In Situ Generated Quinones

*Summary:* High-yield syntheses of Diels-Alder adducts involving dienes and unstable quinones can be effected by generating the quinone in the presence of the diene with silver oxide.

*Sir:* Synthetic studies directed toward the synthesis of antitumor compounds required an efficient preparation of substituted benzoquinones **1a-c** for use in Diels-Alder reactions. A literature search revealed that the sole synthetic method involved silver oxide oxidation of the corresponding hydroquinone.[1] The quinones isolated in low yield by this procedure are rather unstable to both air and water.[2] Although some Diels-Alder reactions had been performed with **1a**,[3] no Diels-Alder reactions of aldehyde **1b** or ketone **1c** have been reported. We wish to communicate a significant modification which permits the high-yield syntheses of Diels-Alder adducts with **1a-c**. It utilizes a one-pot technique wherein the diene, silver oxide, and the requisite hydroquinone are stirred in the absence of light to afford adducts **2a-g** in high yield.[4] The resultant adducts can be reduced with zinc and acetic acid to produce diketone **3**. Epimerization of adducts from (carbomethoxy)benzoquinone can simply be effected by chromatography on alumina.[5] Attempted epimerization of adduct **3e** on alumina led to deformylation. However, epimerization of **3e** could be accomplished with concurrent acetal formation using triethyl orthoformate and *p*-toluenesulfonic acid with a few drops of ethanol. The entries in Table I illustrate the versatility of our procedure. The reaction also works well for naphthoquinones as evidenced by the 77% isolated yield of **7** from ketohydroquinone **5** and diene **6**.




**2** **3**



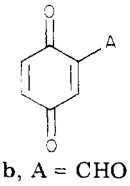

**5** **6** **7**

In a typical experiment, 5 mmol of isoprene, 5 mmol of methyl gentisate, and 10 mL of benzene were placed in a dry, wide-mouth, amber bottle. After the mixture was cooled to ca. 10 °C in an ice bath, 10 mmol of $Ag_2O$ was added at once to the stirred solution. The ice bath was removed and the reaction allowed to stir overnight at room temperature. The reaction was diluted with $Et_2O$ and

**Table I. Diels-Alder Reactions of 1[a]**

| A | $R_1$ | $R_3$ | compd | % yield[b] | compd | % yield[b] | mp, °C |
|---|---|---|---|---|---|---|---|
| $CO_2CH_3$ | $OSiMe_3$ | $CH_3$ | 2a | 96 | 3a | 98 | |
| $CO_2CH_3$ | $CH_2CH_2OCH_2Ph$ | H | 2b | 95 | 3b | 96 | 75-76 |
| $CO_2CH_3$ | H | H | 2c | 100[c] | 3c | 100 | 88-95 |
| $CO_2CH_3$ | $CH_2CO_2Et$ | H | 2d | 98 | 3d | 96 | |
| CHO | $CH_2CO_2Et$ | H | 2e | 94 | 3e | 90 | |
| CHO | $CH_2CH_2OCH_2Ph$ | H | 2f | 97 | 3f | 91 | 94 |
| $COCH_3$ | $CH_2CH_2OCH_2Ph$ | H | 2g | 100 | 3g | 93 | 117 |

[a] $R_2 = CH_3$ for all cases. [b] Isolated yield. Adducts were characterized by IR, NMR, $^{13}C$ NMR, and high-resolution mass spectroscopy and by combustion analysis. [c] Mixture of regioisomers (ratio of expected/unexpected = 70-30).




**1a**, A = $CO_2CH_3$ **b**, A = CHO **c**, A = $C(O)CH_3$

(1) For **1a**, see: Brunner, K. *Monatsh. Chem.* **1913**, *34*, 913. For **1b**, see: Bruce, J. M.; Creed, D. *J. Chem. Soc. C* **1970**, 649. For **1c**, see: Kloetzel, M. C.; Dayton, R. P.; Abadir, B. Y. *J. Org. Chem.* **1955**, *20*, 38.

(2) Cason, J. *Org. React.* **1948**, *4*, 354.

(3) Ansell, M. F.; Culling, G. C.; Nash, B. W.; Wilson, D. A. *Proc. Chem. Soc., London* **1960**, 405. Ansell, M. F.; Lown, J. W.; Turner, D. W.; Wilson, D. A. *J. Chem. Soc.* **1963**, 3036. Ansell, M. F.; Clements, A. H. *J. Chem. Soc. C* **1971**, 269. Goldsmith, D. J.; Srouju, G.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182.

(4) While this work was in progress a brief report of similar methodology for *o*-quinone synthesis was reported: Al-Hamdany, R.; Ali, B. *J. Chem. Soc., Chem. Commun.* **1978**, 397.

(5) Ansell, M. F.; Lown, J. W.; Turner, D. W.; Wilson, D. A. *J. Chem. Soc.* **1963**, 3036.

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