borohydride followed by 3.3 mL of 0.9 N KOH. After 30 min the palladium black was removed by filtration. The organic solution was extracted with 10% HCl, and the aqueous fractions were collected, neutralized, and extracted with ether. The ethereal solution was dried, concentrated, and distilled at 120–122 °C (4 mm) to give 550 mg (68%) of a yellow oil: NMR ($CDCl_3$) $\delta$ 7.35 (m, $J$ = 8 Hz, 4 H), 4.20 (m, 1 H), 2.71 (s, 3 H), 2.45 (s, 3 H); 2.21 (br s, 8 H), 0.95 (d, $J$ = 6 Hz, 3 H); IR (film) 2980, 1610, 1480, 1350 $cm^{-1}$; mass spectrum, $m/e$ 270 ($M^+$). Anal. Calcd for $C_{13}H_{22}N_2O_2S$: C, 57.75; H, 8.20; N, 10.36; S, 11.86. Found: C, 57.76; H, 8.42; N, 10.30; S, 11.90.

**Acknowledgment.** We acknowledge helpful discussions with Professor Robert Holton (Virginia Polytechnic Institute) and Professor Louis Hegedus (Colorado State University). This work was supported by the National Institutes of Health (Grant No. AI-18665). K.A.P. is pleased to acknowledge additional support in the form of a Teacher-Scholar Award from the Camille and Henry Dreyfus Foundation.

**Registry No.** **2a**, 2155-94-4; **2b**, 85151-07-1; **2c**, 24420-11-9; **2d**, 24209-62-9; **2e**, 2520-97-0; **10a**, 3337-93-7; **10b**, 85151-08-2; **10c**, 85151-09-3; **10d**, 85151-10-6; **10e**, 85151-11-7; **11a**, 85151-12-8; **14**, 85151-13-9; **15**, 85151-14-0; LTP, 15525-45-8; $PdCl_2$, 7647-10-1; LiCl, 7447-41-8; $(CH_3CN)_2PdCl_2$, 14592-56-4; potassium phthalimide, 1074-82-4; tetra-*n*-butylammonium phthalimide, 85151-15-1; 1-heptene, 592-76-7.

## Preparation of Methyl Ketones by the Sequential Treatment of Carboxylic Acids with Methyllithium and Chlorotrimethylsilane

George M. Rubottom* and Chong-wan Kim

*Department of Chemistry, University of Idaho, Moscow, Idaho 83843*

*Received August 23, 1982*

One of the major problems associated with the transformation of carboxylic acids 1 into the corresponding methyl ketones 2 using methyllithium has been the co-

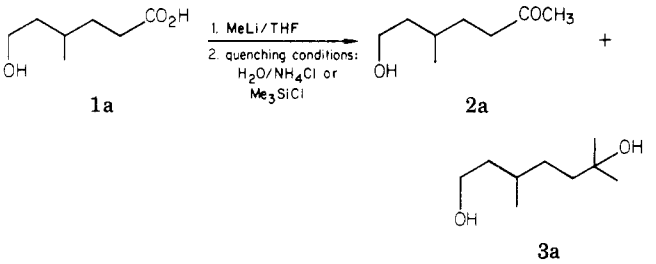
$$\underset{\mathbf{1}}{RCO_2H} \xrightarrow[2.\ H_3O^+]{1.\ MeLi} \underset{\mathbf{2}}{RCOCH_3} + \underset{\mathbf{3}}{RCOH(CH_3)_2}$$

production of unwanted tertiary alcohols **3**.[1] If addition of methyllithium to **1** is slow enough to insure complete conversion of the acid into the lithium carboxylate before carbonyl addition by a second equivalent of methyllithium occurs, then the formation of **3** is thought to result from the slow hydrolysis rate of methyllithium relative to the breakdown of **4** into methyl ketone, thus affording **3** during

$$\underset{\mathbf{4}}{RC(OLi)_2CH_3}$$

the workup procedure.[1] Quenching of the reaction medium by addition to dilute acid with rapid stirring has been one successful method of minimizing production of **3**.[2] The use of theoretical amounts of methyllithium,[3] preformed lithium carboxylates,[4] and THF as solvent to increase carboxylate solubility[5] has also been employed to avoid **3** formation. This last approach is especially useful when the carboxylic acid in question also contains hydroxy functionality.[6] Hydroxy acids necessitate the use of 1 equiv (at least) of methyllithium for each OH group present in the molecule as well.[7] Also, with hydroxy acids, recovery of starting material in addition to **3** can be a problem.[8]

We felt that it might be possible to subvert the production of **3** by using a somewhat different approach, namely, quenching the reaction mixture with a large excess of chlorotrimethylsilane ($Me_3SiCl$). The reaction of $Me_3SiCl$ with any excess methyllithium should be extremely fast, thereby leaving no organometallic to react with ketone **2** in the subsequent aqueous workup step. To test the feasibility of the method, hydroxy acid **1a** was




| | % 2a | % 3a |
|---|---|---|
| $H_2O/NH_4Cl$ | 63 | 37 |
| $Me_3SiCl$ | 91 | 9 |

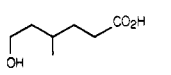
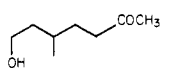
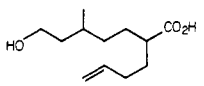
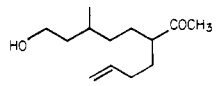
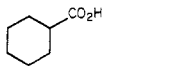
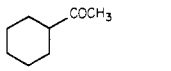
treated with 6.5 equiv of methyllithium at 0 °C. A portion of the resulting mixture was quenched by slow addition to saturated aqueous ammonium chloride with rapid stirring. GC analysis of the resulting mixture revealed a methyl ketone, **2a**, to tertiary alcohol, **3a**, ratio of 63:37. When the remainder of the reaction mixture was quenched with a large excess of $Me_3SiCl$ (ca. 10 equiv) followed by aqueous workup using saturated aqueous ammonium chloride, the ratio of **2a** to **3a** was 91:9.

Encouraged by these preliminary findings, we have tested the method with a number of carboxylic acids and have found the results to be uniformly good. The results of the study are summarized in Table I and deserve some comment. In the cases we studied, the maximum amount of **3** formed was in the range of 10% (see Table I). The method gives excellent yields of pure **2** from hydroxy acids, phenolic acids, alkanoic acids, and aromatic acids. In no case was any trace of starting acid **1** observed upon workup. It is important to note that we made no attempt to minimize the quantities of either methyllithium or $Me_3SiCl$ used. It was our intent to show that methyl ketones can be obtained even when a large excess of methyllithium is employed. It is to be expected that the amount of methyllithium used could be closer to the calculated stoichiometric value for the reagent.[3] This approach, which might well be important for large-scale reactions, would also reduce the amount of $Me_3SiCl$ needed to ensure success. We have not explored the use of any solvent other than THF. One failure of the method was encountered

(1) For a review on the reactions of carboxylic acids with organolithium reagents, see: Jorgenson, M. J. *Org. React. (N.Y.)* **1970**, *18*, 1.
(2) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 943.
(3) See, for instance: van Dorp, D. A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1946**, *65*, 1607; and other references cited in ref 1.
(4) (a) House, H. O.; Bare, T. M. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 775. (b) Levine, R.; Karten, M. J.; Kadunce, W. M. *J. Org. Chem.* **1975**, *40*, 1770.
(5) (a) See, ref 1, p 62, and: Anliker, R.; Müller, M.; Perelman, M.; Wohlfahrt, J.; Heusser, H. *Helv. Chim. Acta* **1959**, *42*, 1071. (b) For an example of the use of DME as solvent, see ref 4a. (c) For an interesting case of the use of hexane as solvent, see: Dalton, J. C.; Chan, H.-F. *Tetrahedron Lett.* **1973**, 3145.
(6) (a) Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1966**, *22*, 3189. (b) Schneider, R. A.; Meinwald, J. *J. Am. Chem. Soc.* **1967**, *89*, 2023.
(7) (a) For the use of 3 equiv of methyllithium with a hydroxy acid, see: Billimoria, J. D.; Maclagan, N. F. *J. Chem. Soc.* **1951**, 3067. (b) For the use of excess methyllithium, see: House, H. O.; Boots, S. G.; Jones, V. K. *J. Org. Chem.* **1965**, *30*, 2519. (c) Heathcock, C. H.; Kelly, T. R. *Tetrahedron* **1968**, *24*, 3753.
(8) (a) Vlad, P. F.; Kryshtal', G. V.; Lazur'evskii, G. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1967**, *37*, 2074. (b) Heusser, H.; Wohlfahrt, J.; Müller, M.; Anliker, R. *Helv. Chim. Acta* **1959**, *42*, 2140.
(9) Nenitzescu, C. D.; Cioranescu, E. *Chem. Ber.* **1936**, *69B*, 1820.

0022-3263/83/1948-1550$01.50/0 

Table I. The Reaction of Carboxylic Acids 1 with MeLi and $Me_3SiCl$

| 1 | 2 | % yield of isolated 2[a] | % of carbinol 3[b] |
|---|---|---|---|
|  1a |  2a | 65 | 9–10 |
|  1b |  2b | 80[c] | |
| *p*-$HOC_6H_4CO_2H$ 1c | *p*-$HOC_6H_4COCH_3$ 2c | 87[d,e] | <5 |
| *m*-$HOC_6H_4CO_2H$ 1d | *m*-$HOC_6H_4COCH_3$ 2d | 94[f,g] | <5 |
| $CH_3(CH_2)_5CO_2H$ 1e | $CH_3(CH_2)_5COCH_3$ 2e | 91[e,h,i] | ca. 8 |
|  1f |  2f | 92[h,j] | 2–3 |
| $C_6H_5CO_2H$ 1g | $C_6H_5COCH_3$ 2g | 97[k] | |
| *p*-$MeOC_6H_4CO_2H$ 1h | *p*-$MeOC_6H_4COCH_3$ 2h | 92[e,h,l] | <3 |

[a] Average yield from two experiments. [b] Value obtained from GC analysis of crude reaction mixture prior to purification of 2. [c] Isolated as the acetate; see Experimental Section. [d] mp 108.5–109.5 °C, crystallization from ether. [e] IR, NMR, and TLC behavior identical with that of authentic sample (Aldrich). [f] mp 94–96 °C, crystallization from chloroform. [g] IR, NMR, and TLC behavior identical with that of authentic sample (Dow). [h] Purified by silica gel chromatography (hexane/ether gradient). [i] GC retention time identical with that of authentic sample (Aldrich). [j] IR, NMR, and GC retention time identical with those of authentic sample prepared by the method of Nenitzescu.[9] [k] 90:10 mixture of 2g and the corresponding carbinol obtained from molecular distillation at 10 mm. [l] mp 36–37 °C.

with the reaction of methyllithium with 2,6-dimethylbenzoic acid. No methyl ketone was produced (NMR) when using the standard conditions noted in the Experimental Section. The deep red–orange color observed during the reaction prior to quenching might indicate that metalation is competing with carbonyl addition. This point was not pursued.

One extension of the method to include the reaction of hexanoic acid (**1i**) with *n*-butyllithium was carried out and a 74% yield of 5-decanone (**5**) resulted. GC analysis of the crude product showed a ketone to carbinol ratio of 90:10, thus giving at least preliminary evidence that the current method should prove to be a general one for the reaction of organolithium reagents with carboxylic acids.

In summary, the sequential treatment of carboxylic acids **1** with methyllithium in THF at 0 °C followed by quenching with $Me_3SiCl$ affords a simple, high-yield method for the synthesis of methyl ketones **2**. Aside from the ease of operation of the method, the amounts of unwanted carbinols **3** produced are minimized with no special precautions being needed.

## Experimental Section

**General Methods.** Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Proton magnetic resonance (NMR) spectra were recorded at 60 MHz on a Varian Anaspect EM 360 spectrometer using chloroform-*d* as solvent and $Me_4Si$ as internal standard. Infrared (IR) spectra were obtained on a Perkin-Elmer 621 grating infrared spectrometer, and low-resolution mass spectra (MS) were obtained on a Hitachi Perkin-Elmer RMU 6E instrument at 15 eV. For column chromatography, Woelm silica gel, 0.032–0.063 mm (ICN Pharmaceuticals GmbH & Co.) was used. TLC analyses were performed on silica gel coated plates, and GC measurements were taken on a 6 ft × 0.25 in. 12.5% Se-52 column (column 1) at the temperature noted. All reactions were carried out under 1 atm of nitrogen, and anhydrous magnesium sulfate was used as drying agent.

**General Method for the Reaction of Carboxylic Acids 1 with Methyllithium, Followed by Treatment with Chlorotrimethylsilane ($Me_3SiCl$).** A stirred solution of 2 mmol of carboxylic acid **1** in 15 mL of dry THF (20 mL for hydroxy acids) was cooled to 0 °C (ice bath) and treated rapidly (ca. 15 s) with 8 mmol (16 mmol for hydroxy acids) of methyllithium (Aldrich, 1.4 M in ether). After 2 h at 0 °C, 5 mL (40 mmol) (7 mL, 55 mmol for hydroxy acids) of freshly distilled $Me_3SiCl$ was rapidly added while stirring continued. The ice bath was then removed and the reaction mixture allowed to come to room temperature at which point 15 mL of 1 N HCl was added, and the resulting two-phase system was stirred at room temperature for 0.5 h. The mixture was then transferred into a separatory funnel and extracted with 25 mL of diethyl ether. The aqueous layer was then extracted with two additional 25-mL portions of diethyl ether, the ethereal layers were combined and washed with 20 mL of water, and the organic layer was dried. Filtration and removal of solvent from the filtrate in vacuo gave crude methyl ketone **2**, which was purified by the appropriate method (see below). The yields cited for pure **2** refer to an average obtained from the results of two runs except in the case of acid **1b** where only one experiment was carried out. Dimethyl carbinols **3** from the reactions of acids **1a**, **1e**, and **1f** were isolated and had physical properties (IR, NMR, MS) consistent with the proposed structures. In the reactions of **1c**, **1d**, **1g**, and **1h**, literature values for **3** were used for comparison in the NMR analyses.

**7-Hydroxy-5-methyl-2-heptanone (2a).** From 0.292 g (2.0 mmol) of 6-hydroxy-4-methylhexanoic acid (**1a**),[10] 16 mmol of methyllithium, 20 mL of THF, and 40 mmol of $Me_3SiCl$ was obtained a 65% yield of 7-hydroxy-5-methyl-2-heptanone (**2a**) (chromatography using a hexane/diethyl ether gradient): $n^{26}_D$ 1.4470 (lit.[11] $n^{20}_D$ 1.4490); IR (neat) 3500, 1720 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.76–0.97 (br d, 3 H), 1.0–1.8 (m, 5 H), 2.05 (s, 3 H), 2.26–2.52 (t, 2 H, $J$ = 6 Hz), 2.83 (br s, 1 H), 3.40–3.68 (t, 3 H, $J$ = 6 Hz); MS, $m/z$ 144 ($M^+$). GC analysis of the crude reaction mixture (160 °C, column 1) showed that 9–10% of the dimethyl carbinol was present.

**Acetate of 3-(3-Butenyl)-8-hydroxy-6-methyl-2-octanone (2b).** From 0.160 g (0.75 mmol) of 2-(3-butenyl)-7-hydroxy-5-methylheptanoic acid (**1b**),[10] 6 mmol of methyllithium, 10 mL of THF, and 24 mmol of $Me_3SiCl$ was obtained crude **2b**. The crude hydroxy ketone was treated with 1 mL of acetic anhydride and 1 mL of pyridine for 8 h, with stirring. After excess acetic anhydride and pyridine were removed in vacuo, the residue was taken up in 50 mL of diethyl ether. The solution was then extracted with 2 × 5 mL of 1.0 N hydrochloric acid and then with 5 mL of water. Drying, filtration, and solvent removal gave crude acetate, which was purified by TLC (Alumina, 40:60 diethyl ether/pentane) to give 0.152 g (80%) of the acetate of **2b** as a colorless oil: IR (neat) 3069, 1741, 1713, 1644 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.79–0.99 (br d, 3 H), 1.0–2.2 (m, 11 H), 2.02 (s, 3 H), 2.12 (s, 3 H), 2.20–2.65 (m, 1 H), 3.90–4.19 (t, 2 H, $J$ = 6 Hz), 4.69–5.12 (m, 2 H), 5.32–6.04 (m, 1 H); MS, $m/z$ 254 ($M^+$). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.88; H, 10.27.

**Methyl Ketones 2c–h.** These compounds had spectral and chromatographic properties identical with those of authentic samples (see Table I).

**5-Decanone (5).** From 0.232 g (2.0 mmol) of hexanoic acid (**1i**), 8 mmol of *n*-butyllithium, 15 mL of THF, and 40 mmol of $Me_3SiCl$ was obtained a 74% yield of pure 5-decanone (**5**) (chromatography using a hexane/diethyl ether gradient). The

(10) The synthesis of this compound will be described elsewhere.
(11) Döring, C.-E.; Hauthal, H. G.; Noglik, H.; Prizkow, W. *J. Prakt. Chem.* **1964**, *24*, 183.

IR [(neat) 1720 $cm^{-1}$], NMR [($CDCl_3$) $\delta$ 2.35 (t, 4 H, $J$ = 7.5 Hz)], and MS [$m/z$ 156 (M+)] are in accord with literature values reported for **5**.[12] GC analysis of the crude reaction mixture revealed the presence of ca. 10% of the di-*n*-butylcarbinol (158 °C, column 1): IR (neat) 3500 $cm^{-1}$; MS, $m/z$ 196 (M - $H_2O$), 157 ($M - C_4H_9$, base peak), 143 (M - $C_5H_{11}$).

**Quenching Experiment for the Reaction of Acid 1a with Methyllithium.** A solution of 0.200 g (1.4 mmol) of **1a** in 20 mL of dry THF was cooled to 0 °C (ice bath) and was treated, with stirring, with 9.0 mmol of methyllithium. With the addition complete (<1 min), the mixture was then stirred at 0 °C for an additional 3 h. At this point, 10 mL of the reaction mixture was removed by syringe and added dropwise to a vigorously stirred solution of 30 mL of saturated aqueous ammonium chloride. Extraction of the resulting mixture with 3 × 20 mL of diethyl ether, drying of the combined ethereal layers, filtration, and solvent removal gave a clear oil that was used for GC analysis (160 °C, column 1). It was determined in this manner that the ratio of ketone **2a** to carbinol **3a** was 63:37. The remainder of the reaction mixture was treated with 2.0 mL (16.0 mmol) of $Me_3SiCl$ by rapid addition. After the solution had been allowed to warm to room temperature (5 min), 10 mL of saturated aqueous ammonium chloride was added in one portion. Workup as described above followed by GC analysis of the crude product (160 °C, column 1) showed a **2a** to **3a** ratio of 91:9. The physical properties of **2a** have been described above. Diol **3a**, obtained by flash chromatography (EtOAC) had the following properties: IR (neat) 3520 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 0.73-.098 (br d, 3 H), 1.12 (s, 6 H), 0.9-1.8 (m, 7 H), 3.08 (br s, 2 H), 3.50-3.75 (t, 2 H, $J$ = 6 Hz); MS, $m/z$ 160 ($M^+$, <1), 159 (M - H), 145 (M - $CH_3$), 142 (M - $H_2O$), 59 (M - $C_6H_{13}O$, base peak). The NMR values cited are in agreement with the partial data given in the literature for 3,6-dimethyl-1,6-heptanediol (**3a**).[13]

**Acknowledgment.** We acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

**Registry No.** **1a**, 56493-06-2; **1b**, 85097-35-4; **1c**, 99-96-7; **1d**, 99-06-9; **1e**, 111-14-8; **1f**, 98-89-5; **1g**, 65-85-0; **1h**, 100-09-4; **1i**, 142-62-1; **2a**, 34221-73-3; **2b**, 85097-36-5; **2c**, 99-93-4; **2d**, 121-71-1; **2e**, 111-13-7; **2f**, 823-76-7; **2g**, 98-86-2; **2h**, 100-06-1; **5**, 820-29-1; MeLi, 917-54-4; $Me_3SiCl$, 75-77-4; *n*-butyllithium, 109-72-8.

(12) Detty, M. R.; Seidler, M. D. *J. Org. Chem.* **1981**, *46*, 1283.

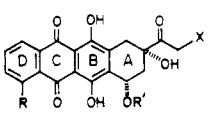
(13) Jakovac, I. J.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165.

# *Communications*

## Synthesis of (±)-4-Demethoxydaunomycinone†

*Summary:* Methods for the preparation of (±)-4-demethoxydaunomycinone from anthraquinone and naphthalene derivatives are described. The difference in the behavior of 1,3-butadienes substituted at the 2-position with 1,3-dithiane and 1,3-dithiolane groupings in the Diels–Alder reaction is discussed.

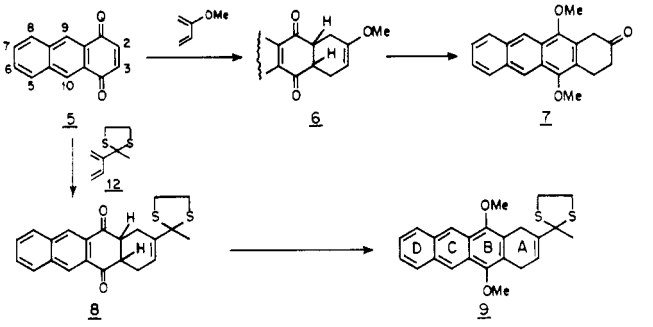
*Sir:* During the past decade, the anthracycline antibiotics such as daunomycin (**1**) and adriamycin (**2**) have emerged



**1**: R = OMe, X = H, R' = Daunosaminyl
**2**: R = OMe, X = OH, R' = Daunosaminyl
**3**: R = X = H, R' = Daunosaminyl
**4**: R = R' = X = H

as the most effective drugs available for the treatment of a broad spectrum of human cancers.[1] Recently it has been shown that 4-demethoxydaunomycin (**3**), a synthetic analogue of **1**, exhibits even greater activity than **1** and is also effective for oral therapy.[2] This has stimulated development of newer methods for the synthesis of 4-demethoxydaunomycinone (**4**),[3] the aglycone of **3**. We report the synthesis of **4** starting from easily available organic intermediates.

Our first attempt was to look into the feasibility of utilizing quinizarine (1,4-dihydroxyanthraquinone) and building the A ring of the anthracyclinone moiety by the Diels–Alder reaction. Many have investigated this approach by first converting quinizarine to quinizarine quinone, which served as the dienophile, but the main limitation was that most of the dienes add preferentially to the "internal" double bond.[4] Although several methods to resolve this difficulty have been devised, including the preparation of a few dienes with substituents that are likely to promote the addition at the "terminal" double bond,[5] the most attractive one is to make use of 1,4-anthraquinone (**5**) in the Diels–Alder (DA) reaction by which any diene can be added to build the tetracyclic system. Further, it



is easy to oxidize the 9,10-positions of the anthracene system to the corresponding anthraquinone derivative. Accordingly, we have shown that DA reaction between **5** (prepared from quinizarine by $NaBH_4$ reduction in AcOH[6]) and 2-methoxy-1,3-butadiene (benzene, 90 °C, 24 h) gave the adduct **6** (96%, mp 192–93 °C), which was converted to the tetracyclic ketone **7** ($Me_2SO_4$, $K_2CO_3$, acetone, reflux followed by acid workup) in 95% yield (mp 142–43 °C).[7]

(1) F. Arcamone, "Doxorubicin-Anticancer Antibiotics", Medicinal Chemistry (Monographs), Academic Press, New York, 1980, Vol. 17.
(2) S. Neidle, *Nature (London)* **268**, 195 (1977).
(3) (a) A. V. Rama Rao, V. H. Deshpande, and N. Laxma Reddy, *Tetrahedron Lett.*, **21**, 2661 (1980). (b) T. R. Kelly, J. Vaya, and L. Ananthasubramanian, *J. Am. Chem. Soc.*, **102**, 5983 (1980), and references cited therein.
(4) T. R. Kelly, *Annu. Rep. Med. Chem.*, **14**, 288 (1979).
(5) M. Chandler and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1007 (1980), and references cited therein.
(6) A. N. Grinev, I. S. Protopov and A. Cherkasova, *J. Org. Chem. USSR (Engl. Transl.)*, **8**, 220 (1972).
(7) G. Venkatswamy, Ph.D. Thesis, University of Poona, 1979. After completing this work, we noticed that a similar approach was used by Gupta et al. (D. N. Gupta, P. Hodge, and N. Khan *J. Chem. Soc., Perkin Trans. 1*, 689 (1981)) for the synthesis of anthracycline analogues.

0022-3263/83/1948-1552$01.50/0 