Synthesis of Novel 6-Deoxyanthracyclines

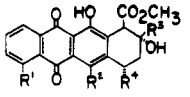
George A. Kraus* and Michael D. Hagen

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received January 21, 1985

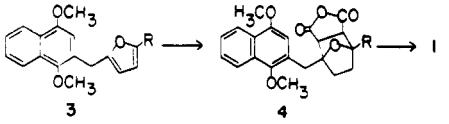
An extremely direct route to the 6-deoxyanthracycline skeleton is described. The initial route to quinone **10** failed due to an unexpected complication in the AgO demethylation step. However, starting from 2-bromo-1,4-dimethoxynaphthalene, furan **17** could be prepared in two steps. Furan **17** was then converted into anthraquinone **19** in five steps. The eight-step route proceeds in 9% overall yield.

The outstanding chemotherapeutic activity exhibited by adriamycin has prompted an extensive search for anthracyclines which do not possess the severe and cumulative dose-dependent cardiotoxicity of adriamycin. This search has led to the deoxyanthracycline aclacinomycin.[1] Through modification of existing anthracyclines and independent synthesis, the relationships between structure and activity of over 61 anthracyclines have been studied.[2] Of significance to synthetic planning is that replacement of the C-4 (anthracycline numbering) hydroxyl group by a hydrogen atom does not materially affect the biological activity. Additionally, variation of the side chain at C-9 has only a small influence on cytotoxicity. The recent discovery by Pence[3] that certain 6-deoxyanthracyclines showed the same cytotoxicity on HeLa cells (ID_{50} = 17 ng/mL) as daunorubicin is certain to stimulate further research into this subset of anthracyclines. Boeckman,[4] Gesson,[5] and Swenton[6] have also reported syntheses of 6-deoxyanthracyclines. We have demonstrated that anthracycline precursors can be efficiently constructed by way of a sequential Diels–Alder/Friedel–Crafts pathway.[7]



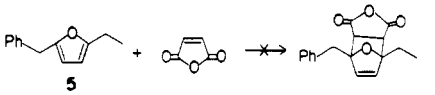
1: $R^1=R^3=R^4=H$, $R^2=OH$
2: $R^1=R^3=H$, $R^2=R^4=OH$

The pathway began with **3** (R = H) which was transformed into **4** (R = H). Anhydride **4** was then converted into **1** in five steps.[8] However, direct modification of the aforementioned route (e.g., using **3** (R = Et) to prepare **4**



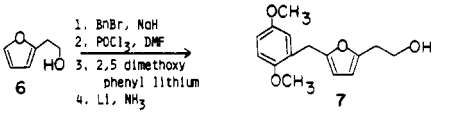
3 **4**

(R = Et) would create significant problems. The methanolysis of anhydride **4** (R = Et) would undoubtedly be less selective then for **4** (R = H). Moreover, the Diels–Alder reaction needed to construct **4** might now proceed in reduced yield. This latter concern was supported by the literature precedent[9] and was addressed first. Furan **5**,



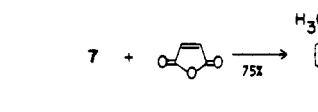
5

available from 2-ethylfuran by the method of Hall and co-workers,[10] did not afford an adduct when reacted with maleic anhydride under reaction conditions that readily generated adducts from **3** (R = H). Hydroxyfuran **7** was next synthesized by the sequence illustrated in eq 1.

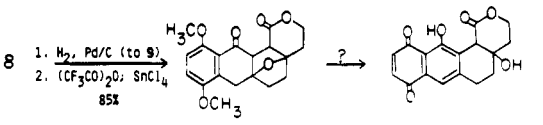


6 **7** (1)

Benzylation of 2-(2-hydroxyethyl)furan[11] followed by a Vilsmeier reaction afforded an aldehyde which was treated with 2,5-(dimethoxyphenyl)lithium[7] and then lithium in ammonia to produce furan **7**. Since many Diels–Alder reactions of maleic anhydride with furans are reversible, we reasoned that the alcohol could react with the adduct to form a lactone acid.[12] Alternatively, the alcohol could react with maleic anhydride and then intramolecularly cyclize to **8**. In practice, the reaction of **7** with maleic anhydride gave lactone acid **8** along with a minor byproduct which was the ester acid from maleic anhydride and **7**. This ester acid could *not* be induced to cyclize to **8** and was hydrolyzed back to **7** with LiOH in CH_3OH. Adduct **8** was reduced to **9** with hydrogen and palladium-on-carbon to prevent undesired side reactions during the Friedel–Crafts cyclization step. Surprisingly, attempted cyclization using trifluoroacetic anhydride afforded only a mixed anhydride. Prolonged reaction times led to decomposition. However, treatment of the mixed anhydride formed in situ with trifluoroacetic anhydride with tin tetrachloride produced keto lactone **11** in 85% yield. Presumably the in-



7 **8**

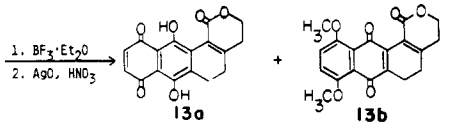


11 **10**

(1) Oki, T.; Matsuzawa, Y.; Yoshimot, A.; Numata, K.; Kitamura, I.; Huri, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Naganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1975**, *28*, 830.
(2) El Khadem, H. S. "Anthracycline Antibiotics"; Academic Press: New York, 1982.
(3) Penco, S.; Angelucci, F.; Arcamone, F.; Ballabio, M.; Barchielli, G.; Francheski, G.; Franchi, G.; Surata, A.; Vanolti, E. *J. Org. Chem.* **1983**, *48*, 405.
(4) Boeckman, R. K.; Sum, F. W. *J. Am. Chem. Soc.* **1982**, *104*, 4604.
(5) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1981**, 1337.
(6) Anderson, D. K.; Coburn, C. E.; Haag, A. P.; Swenton, J. S. *Tetrahedron Lett.* **1983**, 1329.
(7) Kraus, G. A.; Hagen, M. D. *J. Org. Chem.* **1983**, *48*, 3265.
(8) The steps involved methanolysis (CH_3OH, 60 °C), cyclization (TFAA, CH_2Cl_2), trifluoroacetate hydrolysis (KCN, CH_3OH), oxidative demethylation ($Tl(NO_3)_3$), and quinone formation (AgO).
(9) Lee, M. W.; Herndon, W. C. *J. Org. Chem.* **1978**, *43*, 518.
(10) Zilenovski, J. S. R.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 1159 and references therein.
(11) See: E. D.; Plucker, J., III. *j. Am. Chem. Soc.* **1941**, *63*, 206. It is also available from 2-lithiofuran and ethylene oxide at 0 °C in ether.
(12) Imagawa, T.; Nakagawa, T.; Matsuura, K.; Akiyama, T.; Kawanishi, M. *Chem. Lett.* **1981**, 903.

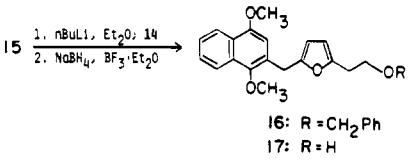
0022-3263/85/1950-3252$01.50/0

ductive effect of the lactone necessitated the more vigorous reaction conditions. With **11** in hand, the plan centered around the preparation of **10** by aromatization and oxidation followed by a Diels–Alder reaction of its O-acetyl derivative with an alkoxy diene. Boeckman and others have elegantly demonstrated the regioselectivity of various 5-hydroxynaphthoquinones with dienes.[13] Unfortunately, aromatization of **11** produced only an α,β-unsaturated lactone **12**. Kende has shown, however, that the hydroxyl group can be reintroduced by epoxidation and reduction.[14] Oxidative demethylation furnished a mixture of quinones, **13a** and **13b**. Variation of the reaction temperature and

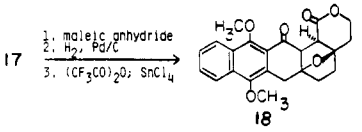


the number of equivalents of freshly prepared AgO did not change the ratio of **13a** to **13b** nor did it afford any precursor to 6-deoxyanthracyclines. The oxidation of **11** did yield an unstable ketoquinone that gave a mixture of products on treatment with 1-acetoxybutadiene.

In view of the problems associated with the silver oxide oxidation,[15] the synthesis of **17** was undertaken. 2-Bromo-1,4-dimethoxynaphthalene (**15**) was treated with *n*-BuLi followed by 5-[2-(benzyloxy)ethyl]-2-furaldehyde (**14**) to yield **16**. Debenzylation (H_2, Pd/C) produced

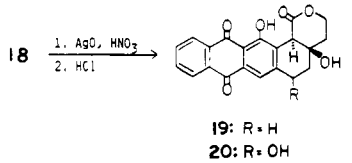


alcohol **17**. This was subjected to the sequential Diels–Alder/Friedel–Crafts protocol afforded keto lactone **18** in 58% overall yield from **17**. The 300-MHz NMR of **18** indicated a mixture of diastereomers in a ratio of approximately 10:1. The major isomer was isolated by re-



crystallization and its structure determined by X-ray spectroscopy. The relative stereochemistry as depicted above has the ether bridge trans to the hydrogen atom α to the lactone carbonyl.

In contrast to keto lactone **11**, aromatization of **18** with boron trifluoride etherate gave a mixture of products. Tin tetrachloride and titanium tetrachloride produced similar results. Oxidative demethylation generated an unstable



keto quinone, which when dissolved in deuterated chloroform produced a red precipitate. This precipitate was shown to be anthraquinone **19**. Treatment of the unpurified ketoquinone with a catalytic amount of concentrated hydrochloric acid also precipitated anthraquinone **19**.

Anthraquinone **19** is available from **15** in eight steps in 9% overall yield. This route constitutes a direct entry to 6-deoxyanthracyclines containing a novel δ-lactone subunit. Testing results on this conformationally restricted anthracycline and its 7-hydroxy counterpart **20** will provide interesting new structure–activity information.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran and diethyl ether were distilled from lithium aluminium hydride prior to usage. Dichloromethane was distilled from phosphorus pentoxide. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or Acculab 2 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High-field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a JOEL FX-90Q or Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High-resolution mass spectra were recorded on a AEI-MS 902 high-resolution mass spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

2-[2-(Benzyloxy)ethyl]furan. To a suspension of sodium hydride (4.30 g, 179 mmol) in 80 mL of THF at 0 °C was added **6** (11.91 g, 106 mmol) in 40 mL of THF. After the mixture was stirred for 30 min, benzyl bromide (12.8 mL, 108 mmol) was added dropwise. The reaction mixture was stirred for 12 h and was then poured into ice water. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Distillation afforded 19.70 g (92%): bp 100 °C, (4 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.94 (t, 2 H, J = 7 Hz), 3.73 (t, 2 H, J = 7 Hz), 4.53 (s, 2 H), 6.06 (d, 1 H, J = 4 Hz), 6.22–6.34 (m, 1 H), 7.29 (s, 6 H); ^{13}C NMR 28.87, 68.28, 72.83, 105.87, 110.16, 127.52, 128.30, 138.32, 140.99, 153.02 ppm; IR (film) 3010, 2940, 1590, 1495, 1443, 1355, 1135, 1090, 995, 720 cm^{-1}.

5-[2-(Benzyloxy)ethyl]-2-furancarboxaldehyde (14). To a solution of *N,N*-dimethylformamide (3.87 mL, 50 mmol) in 10 mL of 1,2-dichloroethane at 0 °C was added phosphorus oxychloride (4.60 mL, 49.5 mmol). After the mixture was stirred for 20 min (10.0 g, 49.5 mmol) in 10 mL of 1,2-dichloroethane was added. The reaction mixture was stirred for 1 h at 0 °C and then 4 h at room temperature. The reaction mixture was then poured into ice water and was neutralized with sodium carbonate. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Chromatography on silica gel using 2:1 hexane/ether as solvent yielded 9.80 g (86%) of **14** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.98 (t, 2 H, J = 7 Hz), 3.73 (t, 2 H, J = 7 Hz), 4.48 (s, 2 H), 6.27 (d, 1 H, J = 4 Hz), 7.12 (d, 1 H, J = 4 Hz), 7.25 (s, 5 H), 9.50 (s, 1 H); ^{13}C NMR 29.20, 67.18, 72.96, 109.71, 114.84, 122.97, 127.52, 128.30, 137.93, 151.98, 160.56, 173.82 ppm; IR (film) 2880, 1680, 1520, 1400, 1365, 1285, 1200, 1100, 1025, 800, 750, 700 cm^{-1}; high-resolution mass spectrum for $C_{14}H_{14}O_3$ requires 230.09490, measured 230.09423.

2-[(2,5-Dimethoxyphenyl)methyl]-5-(2-hydroxyethyl)-furan (7). With the tandem alkylation–reduction procedure developed in ref 7 a mixture was obtained from *p*-dimethoxybenzene (2.76 g, 20 mmol), aldehyde **14** (4.68 g, 20 mmol), and lithium wire (46 mmol).

Resubmitting the mixture to the reduction conditions (2 equiv of lithium, 15 min) afforded **7**. Chromatography on silica gel using 2:1 hexane/ethyl acetate provided a 63% yield of **7** as a colorless oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.88 (br s, 1 H), 2.83 (t, 2 H, J = 6.5 Hz), 3.72 (s, 3 H), 3.77 (s, 3 H), 3.82 (t, 2 H, J = 6.5 Hz), 3.90 (s, 2 H), 5.88 (d, 1 H, J = 3 Hz), 5.98 (d, 1 H, J = 3 Hz),

(13) Boeckman, R. K.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.
(14) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247.
(15) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227. No similar abnormal oxidations have been reported.
(16) Pettit, G. R.; Green, B.; Dunn, G. L.; Hufer, P.; Evers, W. J. *Can. J. Chem.* **1966**, *44*, 1283. We thank John Walling for bringing this reference to our attention.

6.69–6.80 (m, 3 H); ^{13}C NMR 28.48, 31.67, 55.54, 56.12, 61.00, 106.78, 106.97, 111.72, 116.40, 128.04, 151.59, 153.02, 153.60 ppm. IR (film) 3640–3180 (br), 2950, 2840, 1500, 1220, 1045, 900, 720 cm^{-1}; high-resolution mass spectrum for $C_{15}H_{18}O_4$ requires 262.12051, found 262.12040.

7-Carboxy-8-[(2,5-dimethoxyphenyl)methyl]-4,11-dioxatricyclo[6.2.1.0^{1,6}]undecan-5-one (9). Cycloaddition of **7** (1.23 g, 4.69 mmol) with maleic anhydride (0.46 g, 4.70 mmol) was accomplished with the procedure developed for in ref 7. After being stirred for 3 days, the reaction mixture was filtered and washed with cold ether to yield 1.29 g (75%) of crude **8**.

With the procedure developed in ref 7, the crude adduct **8** (1.29 g, 3.58 mmol) in 75 mL of THF was hydrogenated to afford **9**. Recrystallization from acetone yielded 1.03 g (80%) of **9** (mp 256–257 °C). The overall yield of **9** from **7** was 60%. Due to the insolubility of acid **9** it was esterified with diazomethane and was characterized as the methyl ester: mp 170–171 °C; 300-MHz ^1H NMR ($CDCl_3$) δ 1.50–1.71 (m, 4 H), 2.08–2.22 (m, 2 H), 2.90 (d, 1 H, J = 14.3 Hz), 2.95 (d, 1 H, J = 9.4 Hz), 3.25 (d, 1 H, J = 14.3 Hz), 3.47 (d, 1 H, J = 9.4 Hz), 3.73 (s, 3 H), 3.76 and 3.77 (2 s, 6 H), 4.39–4.44 (m, 1 H, 4.79–4.82 (m, 1 H), 6.75–6.80 (m, 2 H), 6.92 (d, 1 H, J = 3 Hz). ^{13}C NMR 20.10, 30.48, 32.24, 36.17, 51.34, 51.87, 55.65, 55.88, 58.82, 66.00, 82.05, 88.26, 111.27, 112.46, 117.78, 125.95, 151.78, 153.20, 171.36, 171.50 ppm; IR ($CDCl_3$) 2980, 2860, 1735, 1720 (sh), 1505, 1470, 1435, 1365, 1270, 1230, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.12. Found: C, 62.95; H, 6.11.

8,11-Dimethoxy-1,12-dioxo-2-oxa-1,2,3,4,4a,5,6,6a,7,12,-12a,12b-dodecahydro-4a,6a-epoxybenz[*a*]anthracene (11). To a suspension of **9** (0.526 g, 1.45 mmol) in 14 mL of dichloromethane at 0 °C was added trifluoroacetic anhydride (0.43 mL, 3.04 mmol). The mixture was stirred for 30 min. Tin tetrachloride (0.51 mL, 4.36 mmol) was added at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then for 5 h at room temperature. The reaction mixture was poured into ice water and was extracted with dichloromethane. The extracts were combined, washed with brine, dried, and concentrated in vacuo. The residue was dissolved in chloroform and was filtered through silica gel to afford 0.424 g (85%) of **11**: mp 230–233 °C; 300-MHz ^1H NMR ($CDCl_3$) δ 1.60–1.73 (m, 2 H), 1.97–2.20 (m, 4 H), 2.88 (d, 1 H, J 7.8 Hz), 3.21 (d, 1 H, J = 20 Hz), 3.38 (d, 1 H, J = 20 Hz), 3.62 (d, 1 H, J = 7.8 Hz), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.30–4.38 (m, 2 H), 6.78 (d, 1 H, J = 9 Hz), 6.95 (d, 1 H, J = 9 Hz); ^{13}C NMR 28.26, 28.73, 35.65, 36.50, 48.01, 55.88, 56.32, 61.16, 65.25, 84,23, 85.23, 110.18, 114.64, 122.60, 129.11, 149.94, 152.59, 172.40, 194.85 ppm; IR ($CDCl_3$) 2950, 1700, 1590, 1475, 1385, 1260, 1235, 1080, 970 cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 64.96; H, 5.94.

8,11-Dimethoxy-12-hydroxy-2-oxa-1-oxo-1,2,3,4,5,6-hexahydrobenz[*a*]anthracene 12. To a solution of **11** (0.226 g, 0.66 mmol) in 5 mL of dichloromethane at 0 °C was added boron trifluoride etherate (0.09 mL, 0.73 mmol). The reaction mixture was stirred for 20 h at room temperature and was then poured into ice water. The aqueous phase was extracted with dichloromethane. The extracts were combined, washed with water, dried, and concentrated in vacuo. Chromatography on silica gel using 2:1 chloroform/hexane as solvent afforded 0.144 g (67%) of **12**: mp 155–158 °C; 300-MHz ^1H NMR ($CDCl_3$) δ 2.36 (t, 2 H, J = 7 Hz), 2.57 (t, 2 H, J = 7 Hz), 2.81 (t, 2 H, J = 7 Hz), 3.87 (s, 3 H), 3.92 (s, 3 H), 4.37 (t, 2 H, J = 7 Hz), 6.56 (s, 2 H), 7.47 (s, 1 H), 9.94 (s, 1 H); ^{13}C NMR 28.75, 29.05, 30.17, 55.63, 56.15, 64.96, 103.15, 103.60, 110.44, 113.97, 115.06, 124.15, 127.22, 136.77, 149.58, 149.77, 150.36, 154.13, 162.21 ppm; IR ($CDCl_3$) 3350, 3060, 2945, 1720, 1610, 1500, 1360, 1145, 1100, 1070 cm^{-1}; MS, m/e 326, 311, 296, 282, 267, 253. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.05; H, 5.60.

General Procedure for Oxidative Demethylation of *p*-Dimethoxyaryl Ethers. To a mixture of the dimethoxyaryl ether (1 mmol) and silver(II) oxide (4 mmol) in 10 mL of THF was added 6 N HNO_3 (1.0 mL). The reaction mixture was stirred for 5 min and was then poured into water. The aqueous phase was extracted with chloroform. The extracts were combined, washed with water, dried, and concentrated in vacuo.

Quinones 13a and 13b: ^1H NMR ($CDCl_3$) δ 2.46–2.88 (m), 3.95 (s), 4.49 (t, J = 6 Hz), 7.27 (d, J = 3 Hz), 12.26 (s), 12.50 (s); IR ($CDCl_3$) 3400–3000 (br), 2940, 1720, 1600, 1445, 1390, 1255, 1205, 1145 cm^{-1}; MS, m/e 340, 310.

2-[2-(Benzyloxy)ethyl]-5-[(1,4-dimethoxy-2-naphthalenyl)methyl]furan (16). To a solution of 2-bromo-1,4-dimethoxynaphthalene (**15**) (3.60 g, 13.5 mmol) in 15 mL of ether at −78 °C was added *n*-butyllithium (14.0 mmol). After the mixture was stirred for 10 min, aldehyde **14** (3.10 g, 13.5 mmol) in 20 mL of ether was added. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min. The reaction mixture was then poured into water and was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. The crude alcohol was dissolved in 20 mL of THF and was added to a solution of sodium borohydride (1.02 g, 27 mmol) in 20 mL of distilled diglyme at 0 °C. Boron trifluoride etherate (8.3 mL, 67 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred for 10 h and was then carefully quenched with water at 0 °C. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Chromatography on silica gel using 8:1 hexane/ether afforded 2.98 g (55%) of **16** as a colorless oil: 300 MHz ^1H NMR ($CDCl_3$) δ 2.92 (t, 2 H, J = 6.2 Hz), 3.71 (t, 2 H, J = 6.2 Hz), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.12 (s, 2 H), 4.50 (s, 2 H), 5.91 (d, 1 H, J = 3 Hz), 5.99 (d, 1 H, J = 3 Hz), 6.64 (s, 1 H), 7.30 (s, 5 H), 7.42–7.57 (m, 2 H), 8.04 (d, 1 H, J = 8 Hz), 8.21 (d, 1 H, J = 8 Hz). ^{13}C NMR 28.66, 29.05, 55.64, 62.35, 68.45, 72.95, 105.72, 106.67, 106.96, 121.90, 122.32. 125.08, 125.84, 125.98, 126.44, 126.53. 127.59, 128.37, 128.62, 138.31, 147.07, 151.83, 152.96 ppm; IR film (3050, 2940, 2860, 1600, 1460, 1365, 1260, 1220, 1085, 1000, 750 cm^{-1}; high-resolution mass spectrum for $C_{26}H_{26}O_4$ requires 402.18312, measured 402.18256.

2-[(1,4-Dimethoxy-2-naphthalenyl)methyl]-5-(2-hydroxyethyl)furan (17). To a suspension of activated 10% Pd/C (0.22 g) in 10 mL of ethanol under a hydrogen atmosphere was added **16** (2.25 g, 5.60 mmol) in 20 mL of ethanol. The reaction mixture was stirred for 8 h, filtered through Celite, and concentrated in vacuo. Chromatography on silica gel using 1:1 hexane/ether yielded 1.62 g (93%) of **17** as a colorless oil: 300-MHz ^1H NMR ($CDCl_3$) δ 1.65 (br, s, 1 H), 2.85 (t, 2 H, J = 6.2 Hz), 3.83 (t, 2 H, J = 6.2 Hz), 2.89 (s, 3 H), 3.93 (s, 3 H), 4.13 (s, 2 H), 5.91 (d, 1 H, J = 3 Hz), 6.00 (d, 1 H, J = 3 Hz), 6.63 (s, 1 H), 7.45–7.53 (m, 2 H), 8.04 (d, 1 H, J = 8 Hz), 8.20 (d, 1 H, J = 8 Hz). ^{13}C NMR 28.76, 31.77, 55.68, 61.21, 62.35, 105.63, 106.96, 107.28, 121.89, 122.27, 122.34, 125.14, 125.80, 126.60, 128.64, 147.11, 151.59, 151.87, 153.51 ppm; IR (film) 3700–3200 (br), 2960, 1600, 1560, 1375, 1265, 1220, 1090, 1000 cm^{-1}; high-resolution mass spectrum for $C_{19}H_{20}O_4$ requires 312.13616, measured 312.13541.

7-Carboxy-8-[(1,4-dimethoxy-2-naphthalenyl)methyl]-4,11-dioxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one. Cycloaddition of **17** (1.50 g, 4.80 mmol) with maleic anhydride (0.47 g, 4.80 mmol) was accomplished using the procedure developed for **7**. After the mixture was stirred for 4 days, the yellow gel was dissolved in ether. With rapid stirring, hexane was added dropwise. The solid was filtered and washed with cold ether to yield 1.20 g (60%): 300-MHz ^1H NMR ($CDCl_3$) δ 2.32–2.44 (m, 2 H), 2.87 (d, 1 H, J = 8.7 Hz), 3.28 (d, 1 H, J = 8.7 Hz), 3.30 (d, 1 H, J = 14.4 Hz), 3.65 (d, 1 H, J = 14.4 Hz), 4.43–4.51 (m, 1 H), 4.73–4.82 (m, 1 H), 6.21 (d, 1 H, J = 5.7 Hz), 2.26 (d, 1 H, J = 5.7 Hz), 6.79 (s, 1 H), 7.42–7.54 (m, 2 H), 8.02 (d, 1 H, J = 8.4 Hz), 8.19 (d, 1 H, J = 8.4 Hz).

The filtrate was concentrated in vacuo. The residue (0.71 g) was dissolved in 20 mL of methanol. After the addition of lithium hydroxide (0.30 g), the solution was refluxed for 12 h. The solution was then concentrated and diluted with water. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Chromatography on silica gel using 1:1 hexane/ether afforded 0.37 g of **17**.

7-Carboxy-8-[(1,4-dimethoxy-2-naphthalenyl)methyl]-4,11-dioxatricyclo[6.2.1.0^{1,6}]undecan-9-one. With the procedure developed for **9**, the crude adduct (1.20 g, 2.93 mmol) in 30 mL of acetone was hydrogenated to afford 1.14 g (95%) (mp 138–145 °C) as a mixture of diastereomers: 300-MHz ^1H NMR (CDCl3) δ 1.47–1.61 (m, 4 H), 2.14–2.22 (m, 2 H), 3.02 (d, 1 H, J = 9.2 Hz), 3.30 (d, 1 H, J = 14 Hz), 3.45 (d, 1 H, J = 14 Hz), 3.55 (d, 1 H, j = 9.2 Hz), 3.85 (s, 3 H), 3.95 (s, 3 H), 4.41–4.45 (m, 1 H), 4.80–4.84 (m, 1 H), 6.90 (s, 1 H), 7.45–7.54 (m, 2 H), 8.01 (d, 1 H, J = 7.9

Hz), 8.20 (d, 1 H, J = 7.9 Hz); ^{13}C NMR 28.06, 31.00, 32.42, 36.14, 51.19, 55.68, 58.90, 61.99, 65.82, 66.15, 82.29, 88.50, 106.70, 121.87, 122.20, 124.75, 125.05, 125.81, 126.37, 128.20, 147.51, 151.36, 172.40, 174.52 ppm; IR ($CDCl_3$) 3400–2820 (br), 1730, 1600, 1465, 1372, 1265, 1230, 1160, 1090 cm^{-1}. Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 64.70; H, 6.50.

8,13-Dimethoxy-1,14-dioxo-2-oxa-1,2,3,4,4a,5,6,6a,7,14,14a,14b-dodecahydro-4a,6a-epoxybenzo[*a*]naphthacene 18. With the procedure developed for 11, acid (0.627 g, 1.52 mmol) was converted to keto lactone 18. Recrystallization from acetone/hexane afforded 0.45 g (75%) of 18: mp 208–210 °C; 300-MHz ^{1}H NMR ($CDCl_3$) δ 2.05–2.19 (m, 4 H), 3.02 (d, 1 H, J = 8 Hz), 3.46 (d, 1 H, J = 18.9 Hz), 3.65 (d, 1 H, J = 18.9 Hz), 3.66 (d, 1 H, J = 8 Hz), 3.92 (s, 3 H), 3.98 (s, 3 H), 4.32–4.36 (m, 2 H), 7.52 (t, 1 H, J = 7 Hz), 7.61 (t, 1 H, J = 7 Hz), 8.04 (d, 1 H, J = 8.2 Hz), 8.27 (d, 1 H, J = 8.2 Hz); ^{13}C NMR 28.20, 28.75, 35.98, 36.54, 49.34, 61.20, 61.37, 63.95, 65.42. 84.26, 85.49, 121.78, 122.01, 124.61, 125.68, 126.20, 128.53, 128.60, 130.89, 148.42, 153.82, 171.50, 195.44 ppm; IR ($CDCl_3$) 2960, 1715, 1615, 1450, 1375, 1340, 1270, 1080, 1035 cm^{-1}. Anal. Calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 69.90; H, 5.69.

4a,14-Dihydroxy-2-oxa-1,8,13-trioxo-1,2,3,4,4a,5,6,8,13,14b-decahydrobenzo[*a*]naphthacene (19). With the general oxidative demethylation procedure, keto lactone 18 (0.083 g, 0.21 mmol) was oxidized to quinone. The crude quinone was dissolved in 5 mL of acetone. After the addition of concentrated HCl (1 drop), the reaction mixture was stirred for 20 h. The yellow precipitate was filtered and washed with cold acetone to afford 0.023 g (30%) of 19 (mp 263–268 °C) as a mixture of diastereomers: 300-MHz ^{1}H NMR (Me_2SO-d_6) δ 1.99–2.48 (m, 4 H), 4.19 and 5.12 (2 s, 1 H), 4.43–4.64 (m, 2 H), 7.53 (s, 1 H), 7.92–7.98 (m, 2 H), 8.18–8.26 (m, 2 H), 13.01 (s, 1 H); MS, m/e 364, 346, 316, 302, 292, 275, 263; high-resolution mass spectrum for $C_{21}H_{16}O_6$ requires 364.0947; found 364.0960; FT IR (KBr) 3500, 1749, 1674, 1630, 1589, 1380, 1337, 1276, 1213, 1176, 1056, 1020, 943, 790, 717 cm^{-1}.

Acknowledgment. We thank the National Institutes of Health for generous financial support. We thank Dr. R. A. Jacobson and Jim Benson for the X-ray structure determination.

Generation of (1-Alkoxycyclopropyl)lithium Reagents

Robert C. Gadwood,* Mark R. Rubino, Sridhar C. Nagarajan, and Suzanne T. Michel

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received January 9, 1985

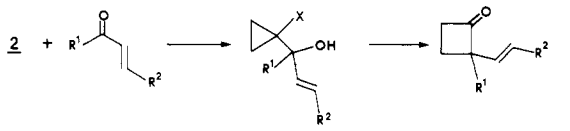
Various approaches to the generation of (1-alkoxycyclopropyl)lithium reagents were investigated. The syntheses of [1-(methoxymethoxy)cyclopropyl]tri-*n*-butylstannane, cyclopropyl 2,4,6-triisopropylbenzoate, and 1-bromo-1-ethoxycyclopropane were carried out and their conversions to the corresponding organolithium species were studied. The most convenient preparative-scale precursor of a (1-alkoxycyclopropyl)lithium reagent was found to be 1-bromo-1-ethoxycyclopropane.

Organometallic compounds bearing α-heteroatoms occupy a central position in synthetic organic chemistry, serving as nucleophilic latent precursors of a variety of functional groups. A large number of α-hetero-substituted organometallic reagents are known, with the most common being α-lithiated ethers, sulfides, selenides, silanes, phosphoranes, and alkyl halides (1, X = OR, SR, SeR, SiR_3, PR_2, Br, etc.).[1] The α-hetero-substituted cyclo-

1 2

propyllithium compounds (2) comprise a particularly interesting subclass of this family of organometallic reagents, since they play a key role in strategies developed for the synthesis of cyclobutanes[2,3] and cyclopentanes.[4]

In connection with a number of ongoing research projects in our group, we needed to prepare a variety of 2-alkenylcyclobutanones. Among all the known methods for the synthesis of cyclobutanones, the most convenient for our needs appeared to be the addition of an α-hetero-substituted cyclopropyllithium reagent to an enone or enal, followed by rearrangement of the adduct to a cyclobutanone (eq 1). Unfortunately, all of the available α-



(1)

hetero-substituted cyclopropyllithium reagents suffer from some drawback. Problems with available reagents include failure to afford cyclobutanones from aldehydes,[5] formation of byproducts in the rearrangement step,[6] or conjugate addition to enones.[7]

The best currently available reagent of this type is (1-methoxycyclopropyl)lithium (4),[3] which cleanly undergoes 1,2-addition to enones to afford adducts which can be rearranged to 2-alkenylcyclobutanones in high yield under mild conditions. Generation of (1-methoxycyclopropyl)-lithium is accomplished by reductive desulfurization[8] of

(1) For excellent reviews of this area, see: (a) Petersen, D. J. *Organomet. Chem. Rev., Sect. A* **1972**, *7*, 295. (b) Krief, A. *Tetrahedon* **1980**, *36*, 2531. (c) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

(2) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321. Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, M. J. *Ibid.* **1977**, *99*, 3080. Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *Ibid.* **1977**, *99*, 3088. Halazy, S.; Lucchetti, J.; Krief, A. *Tetrahedron Lett.* **1978**, 3971. Halazy, S.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1136.

(3) Matz, J. R.; Cohen, T. *Tetrahedron Lett.* **1981**, *22*, 2459.

(4) Trost, B. M.; Scudder, P. H. *J. Org. Chem.* **1981**, *46*, 506. Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328. Trost, B. M.; Bogdanowicz, M. J. *Ibid.* **1973**, *95*, 289, 5311. Paquette, L. A.; Horn, K. A.; Wells, G. J. *Tetrahedron Lett.* **1982**, *23*, 259. Paquette, L. A.; Wells, G. J.; Horn, K. A.; Yan, T.-H. *Ibid.* **1982**, *23*, 263.

(5) Hiyama, J.; Takehara, S.; Kitatani, K.; Nozaki, H. *Tetrahedron Lett.* **1974**, 3295. Braun, M.; Dammann, R.; Seebach, D. *Chem. Ber.* **1975**, *108*, 2368.

(6) (a) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910. (b) Gadwood, R. C. *Tetrahedron Lett.* **1984**, *25*, 5851.

(7) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5311, 5321.

0022-3263/85/1950-3255$01.50/0