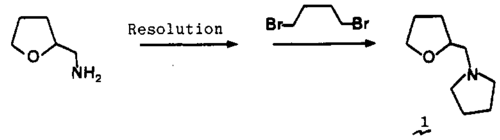

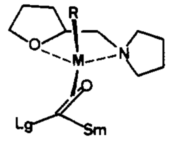

Figure 1.

Table I

$$\mathrm{PhCHO}\ \xrightarrow[\text{2. }H_2O]{\text{1. RM}}\ \mathrm{Ph}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{HR}$$

RM	time, h/ temp, °C	solvent	% yield chem-ical	opti-cal
MeLi	1.5/-78	pentane	38	19
n-BuLi	1.5/-78	pentane	36	17
MeMgCl	14/25	ether	18	0

Table II

$$\mathrm{PhCOCH_3}\ \xrightarrow[\text{2. }H_2O]{\text{1. }[H^-]}\ \mathrm{Ph}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{HCH_3}$$

$[H^-]$	time, h/ temp, °C	solvent	% yield chem-ical	opti-cal
$LiAlH_4$	2/-78	pentane	56	3
$LiAlH_4$		ether	52	2
$LiBH_4$	2/reflux	THF	51	15
$NaBH_4$	23/reflux	THF	52	3

However, we were unable to find a convenient system for the direct resolution of 1.

A number of systems involving nucleophilic addition to the carbonyl groups of benzaldehyde and acetophenone was examined, and these results are summarized in Tables I and II. In all cases, a slight excess (~20%) of the ligand 1 relative to the metal was employed. In the case of both methyllithium and methylmagnessium chloride, the use of nonether solvents led to the relatively rapid reaction between the ligand and the nucleophile (the yields reported are for highly purified material and do not represent the true level of conversion). It is interesting to note that, in contrast to the results with the ligand system described by Mukaiyama, no overall enantioselectivity was observed with magnesium as the cation. Relatively little induction was also obtained with sodium as the counterion and with the relatively more reactive lithium aluminum hydride.

Experimental Section

All reagents were commercial materials and were used without further purification except for ether solvents which were obtained immediately prior to use by distillation from blue solutions of the anion radical from benzophenone and sodium. Melting and boiling points are uncorrected. Varian HA-100 and FT-80 spectrometers were used to obtain ^1H and ^{13}C spectra with tetramethylsilane as internal standard. Optical rotations were obtained by using a Perkin-Elmer 141 polarimeter, and all samples measured were homogeneous by spectral and GLC (SE-30 and/or Carbowax 20M) analyses. Elemental analysis was performed by Chemalytics, Tempe, Az. HPLC refers to the use of two 0.95 × 60 cm columns packed with Porasil A.

(−)-*N*-(Tetrahydrofurfur-2-yl)methylpyrrolidine (1). Resolution of tetrahydrofurfurylamine was carried out by repeated crystallization of the tartartic acid salt according to the literature procedure.[5] Five recrystallizations afforded 72% (based on one enantiomer) of the salt with mp 96–98.5 °C. The free base obtained from this salt after distillation [bp 60 °C (15 mm)] had $[\alpha]^{25}_D$ −8.69° (H_2O) (lit.[5] $[\alpha]^{27}_D$ −8.57°).

The amine obtained above (11.3 g, 0.11 mol) was added dropwise to a refluxing solution of 26.4 g (0.12 mol) of 1,4-dibromobutane and 31.6 g (0.25 mol) of *N,N*-diisopropylethylamine in 250 mL of THF. After 48 h at reflux, the reaction was cooled and then extracted with 350 mL of 6 N aqueous sodium hydroxide. The aqueous layer was extracted with three 500-mL portions of ether and the combined organic layers were dried and concentrated in vacuo. The crude oil was fractionated by distillation to afford 4.0 g (23%) of 1: bp 90 °C (15 mm); $[\alpha]^{25}_D$ −61.7° (*c* 4.1, 0.67 N aqueous HCl); ^{13}C NMR (acetone-d_6) δ 78.0, 67.8, 61.1, 54.8, 30.3, 25.6, 23.6. Anal. Calcd for $C_9H_{17}NO$: C, 69.68; H, 10.97; N, 9.03. Found: C, 69.52; H, 10.71; N, 9.00.

Representative Procedure for Addition of Alkyllithium to Benzaldehyde in the Presence of 1. To a solution of 250 mg (1.61 mmol, 1.2 equiv) of 1 in 10 mL of pentane under nitrogen at −78 °C was added 1.34 mmol (by titration) of *n*-butyllithium solution in pentane. The solution was stirred at −78 °C for 1 h. A solution of 129 mg (1.22 mmol, 0.9 equiv) of benzaldehyde in 2 mL of pentane was introduced dropwise via syringe. The reaction was quenched after 1.5 h at low temperature by the addition of 0.25 mL of methanol. The reaction solution was diluted with ether and extracted with 15 mL of saturated aqueous ammonium chloride. Concentration gave an oil that was further purified by HPLC (2:1 hexane–ethyl acetate, $k' = 2$) to afford 71 mg (36%) of 1-phenyl-1-butanol, $[\alpha]^{25}_D$ +5.42° (*c* 3, benzene) [lit.[6] $[\alpha]^{24}_D$ 31.3° (benzene)].

For 1-phenylethanol obtained by the addition of methyllithium to benzaldehyde: $[\alpha]^{25}_D$ +9.69° (*c* 3, toluene) [lit.[7] $[\alpha]_D$ 50.6 (*c* 3, toluene)]; HPLC $k' = 2.5$, 2:1 hexane–ethyl acetate.

Reduction of Acetophenone with $LiBH_4$ in the Presence of 1. To a solution of 38 mg (1.66 mmol) of lithium borohydride in 6 mL of THF at −78 °C under nitrogen was added 344 mg (2.2 mmol) of 1 in 1 mL of THF. After 1 h, 199 mg (1.66 mmol of acetophenone in 2 mL of THF was added dropwise. The solution was warmed slowly to room temperature and then heated at reflux for 2 h. The product, 103 mg (51%) of 1-phenylethanol, was isolated as described above, $[\alpha]^{25}_D$ −7.48° (*c* 2.1, toluene).

Acknowledgment. We are grateful to the Robert A. Welch Foundation (Grant No. F-626) and the donors of the Petroleum Research Fund (Grant No. 9275-AC), administered by the American Chemical Society, for financial support of this research.

Registry No. (−)-1, 77224-35-2; (−)-tetrahydrofurfurylamine D-tartrate, 33002-00-5; (−)-tetrahydrofurfurylamine, 7202-43-9; 1,4-dibromobutane, 110-52-1; benzaldehyde, 100-52-7; (+)-1-phenyl-1-butanol, 22144-60-1; (+)-1-phenylethanol, 1517-69-7; acetophenone, 98-86-2; (−)-1-phenylethanol, 1445-91-6.

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[6] Leven, P. A.; Marker, R. E. *J. Biol. Chem.* **1932**, *97*, 379.

[7] Doering, W. von E.; Aschner, T. C. *J. Am. Chem. Soc.* **1949**, *71*, 838.

Regiospecific Total Synthesis of (±)-11-Deoxycarminomycinone

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Received December 30, 1980

The recent discovery of naturally occurring antitumor anthracyclines related to 11-deoxydaunorubicin (1)[1] and the favorable spectrum of antitumor activity and reduced

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[1] Arcamone, F.; Cassinelli, G.; Dimatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462–1463.

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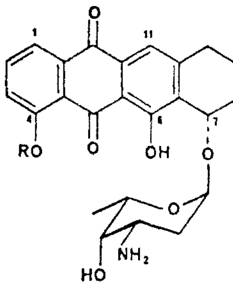
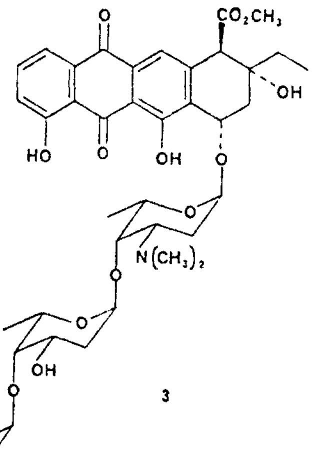


1 R = CH_3

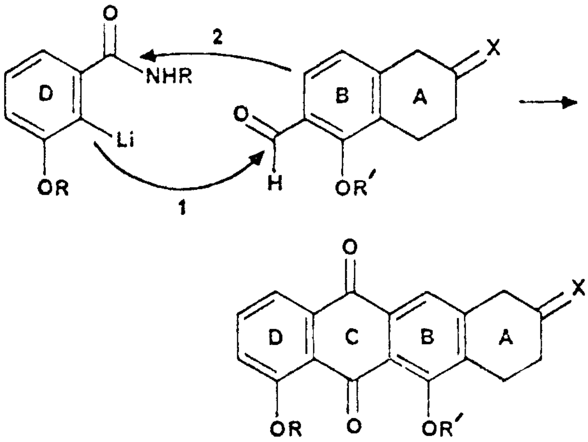
2 R = H



3

toxicity reported for aclacinomycin A (3)[2] have led to urgent interest in the total synthesis of 11-deoxyanthracyclinones.[3] We describe here the total synthesis of one member of this class, the aglycon of 11-deoxycarminomycin (2), by a sequence that could be a useful prototype for other syntheses in this series.

Our convergent general strategy is summarized by eq 1, in which a preformed A–B bicyclic synthon is condensed with a D-ring unit sequentially to form first bond 1 and then bond 2, thus generating the C ring.



(1)

In the present instance, the requisite A–B synthon 12 was prepared from the readily available tetralone[4] in seven steps with a 37% overall yield according to Scheme I. Treatment of ketone 4 with ethylene glycol and *p*-TSA in refluxing benzene gave ketal 5. Nucleophilic demethylation of 5 with sodium thioethoxide in DMF[5] gave phenol 6, which was alkylated with allyl bromide and sodium methoxide to give ether 7. Claisen rearrangement of 7 at 175 °C in *N*,*N*-dimethylaniline followed by methylation with iodomethane and sodium hydride gave in 75% yield the 6-allyl methyl ether 8, which was readily separated by silica gel chromatography from the 8-allyl isomer 9 (15%). Prototropic isomerization of ether 8 with catalytic potassium *tert*-butoxide in refluxing *tert*-butyl alcohol followed by reketalization of the accompanying enol ether byproduct 10 gave the conjugated olefin 11 in 97% yield from 8. Ozonolysis of 11 in dichloromethane at −78 °C followed by ozonide reduction gave, cleanly, the desired methoxy aldehyde 12.

Condensation of dilithio-3-methoxybenzanilide 13, prepared by treatment of the anilide with 2 equiv of *n*-butyllithium and TMEDA in THF at −10 °C, with methoxyaldehyde 12 at −78 to +25 °C according to the model studies of Baldwin and Bair[6] gave on acidic workup and partial reketalization the crystalline phthalide 14 in 73% yield. Reduction of 14 with a vigorously stirred suspension of activated zinc dust in refluxing 2 N aqueous potassium hydroxide[7] gave acid 15 in ca. 95% yield. Cyclization of 15 with trifluoroacetic acid and trifluoroacetic anhydride in dichloromethane at −10 °C produced in 83% yield anthrone 16, which was oxidized with chromium trioxide in acetic acid to quinone 17 in 82% yield. Ketal cleavage with trifluoroacetic acid and aqueous hydrochloric acid followed by demethylation with aluminum chloride in dichloromethane gave the tetracyclic 11-deoxy ketone 18 in 90% yield. Ketone 18 prepared by this sequence (Scheme II) was identical in all respects with a sample independently synthesized by Gesson using an alternative approach.[8]

Ethynylation of the C-9 carbonyl of ketone 18 with excess ethynylmagnesium bromide in THF at −25 °C gave ethynyl carbinol 19 in 25% yield plus a 57% yield of recovered 18;[9] ketone 18 was recycled after separation from 19 by silica gel chromatography. Acetoxy ketone 20 was prepared in 90% yield by treatment of carbinol 19 with mercuric acetate in ethyl acetate, followed by a hydrogen sulfide workup (Scheme III). Regiospecific bromination of 20 with bromine and AIBN in refluxing carbon tetrachloride followed by solvolysis of the resulting benzylic bromide in 1:1 aqueous $NaHCO_3$–THF gave after silica gel chromatography mainly (±)-9-*O*-acetyl-11-deoxycarminomycinone (21) in 38% yield, accompanied by lesser amounts of the C-7 β epimer and unidentified byproducts. Mild deacetylation of 21 with aqueous potassium carbonate in methanol gave the new aglycon (±)-11-deoxycarminomycinone (22). The TLC properties of synthetic (±)-22 and its high-resolution mass spectrum, mass spectrometric fragmentation pattern, UV spectrum, and 400-MHz Fourier transform ^1H NMR spectrum were all identical with those measured for a sample of 11-deoxycarminomycinone prepared at Farmitalia by aluminum chloride demethylation of natural 11-deoxydaunomycinone.

In its present form our synthesis is a completely regiospecific 15-step sequence to (±)-11-deoxycarminomycinone from tetralone 4. More convergent variants of the strategy leading both to (±)-11-deoxydaunomycinone and to (±)-aklavinone are in progress.

Experimental Section

General Methods. The solvents were dried as follows: benzene from sodium; *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA) and *tert*-butyl alcohol from calcium hydride; THF from sodium–

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[2] (a) Oki, T.; Kitamura, I.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, T.; Yoshimoto, A.; Inui, T. *J. Antibiot.* **1979**, *32*, 801–819. (b) Hori, S.; Shirai, M.; Hirano, S.; Oki, T.; Inui, T.; Tsukagoshi, S.; Ishizuka, M.; Takeuchi, T.; Umezawa, H. *Gann* **1977**, *68*, 685–690.

[3] (a) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561–1563. (b) Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, 811–814.

[4] Cornforth, J. W.; Robinson, R. *J. Chem. Soc.* **1949**, 1855–1865.

[5] Feutrill, G. I; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719–1929.

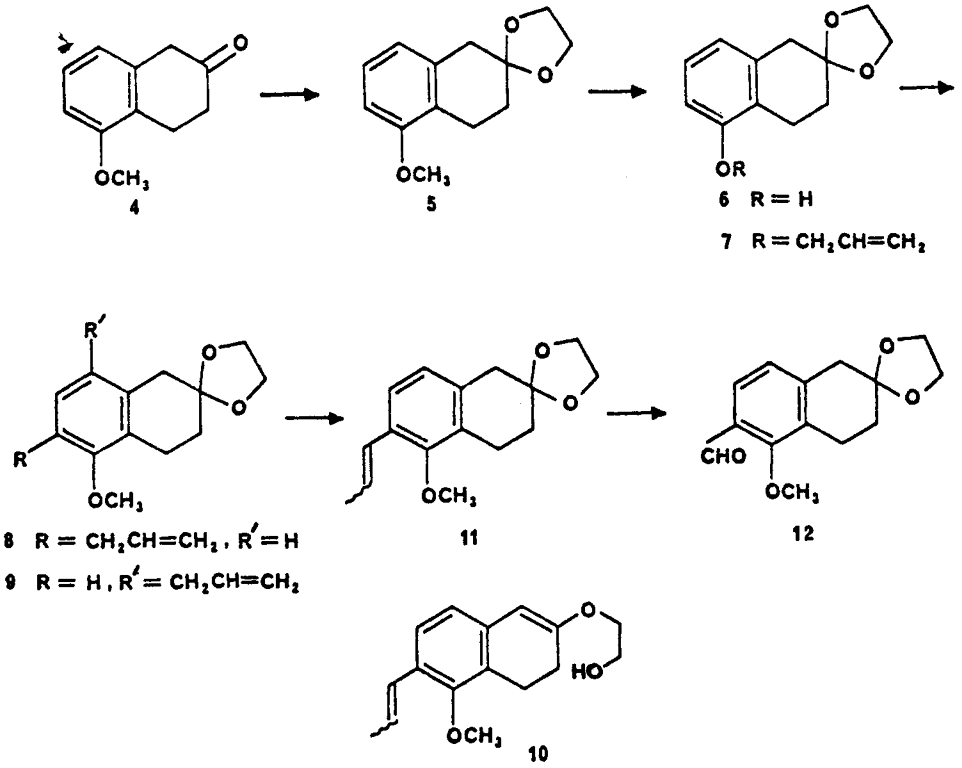
[6] Baldwin, J. E.; Bair, K. W. *Tetrahedron Lett.* **1978**, 2559–2562. For related reactions see: Forbes, I.; Pratt, R. A.; Raphael, R. A. *Ibid.* **1978**, 3965–3966; Osmond de Silva, S.; Snieckus, V. *Ibid.* **1978**, 5103–5106.

[7] Newman, M. S.; Sankoran, V.; Olson, P. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237–3242.

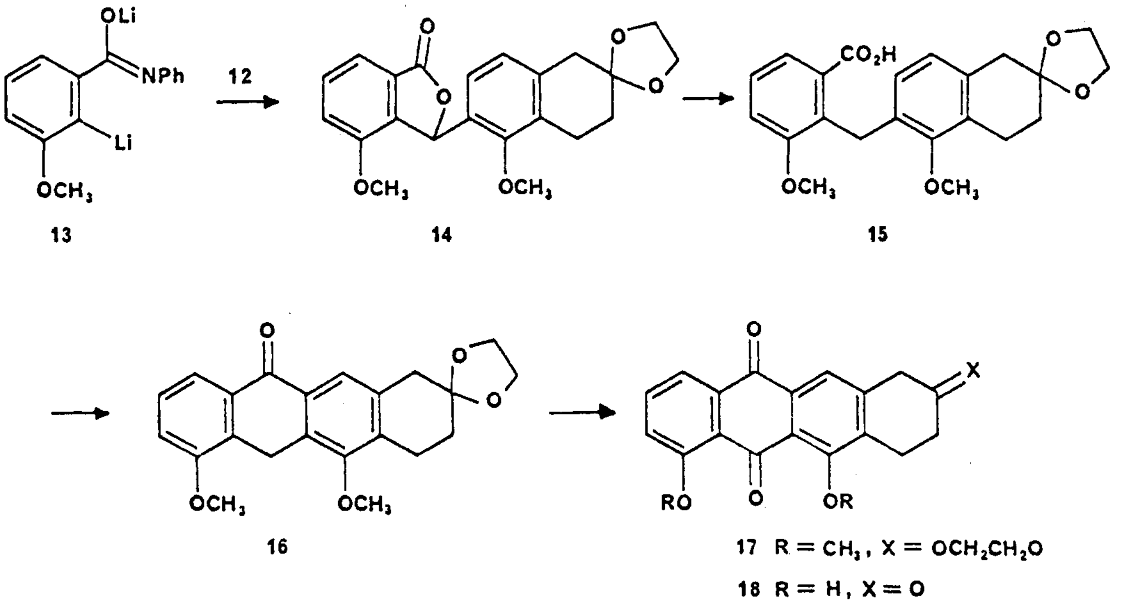
[8] Gesson, J. P.; Jacquesy, J. C; Mondon, M. *Tetrahedron Lett.* **1980**, 3351–3354.

[9] The yield of 19 is optimized; use of higher reaction temperatures (to reduce the relative amount of enolate formation vs. nucleophilic attack at C-9) or other acetylene nucleophiles (lithium acetylide, lithium acetylide–ethylenediamine complex) consistently gave much lower yields.

Scheme I



Scheme II



benzophenone ketyl; DMF, dichloromethane, and ethyl acetate were stored over activated 4-Å molecular sieves. All other solvents and reagents were ACS reagent grade.

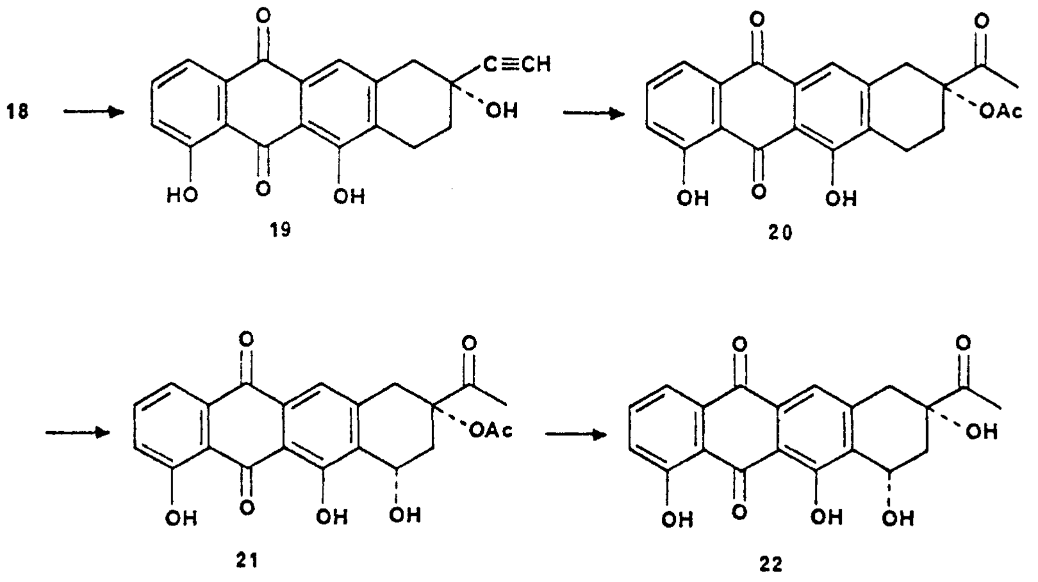
All melting points are uncorrected. ^{1}H NMR spectra were recorded on either a JEOL-MH 100, JEOL JNM-PS FT-100, or Bruker FT-400 instrument using tetramethylsilane as an internal standard. Infrared spectra were run on a Perkin-Elmer 467. Mass spectra were recorded on a Du Pont 21-490B instrument. Ultraviolet spectra were run on a Hitachi Perkin-Elmer 200 instrument. Analyses were performed by Spang, Galbraith, and Instranal Laboratories.

2,2-(Ethylenedioxy)-5-methoxytetralin (5). A mixture of 5-methoxy-2-tetralone (4; 4.32 g, 24.5 mmol), ethylene glycol (5 mL), *p*-toluenesulfonic acid monohydrate (*p*-TSA, 0.020 g), and benzene (70 mL) was heated at reflux overnight with protection from moisture by a calcium sulfate drying tube. Water generated during the reaction was removed by means of a Dean–Stark trap. The mixture was poured into saturated sodium bicarbonate solution and the aqueous layer was extracted twice with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to leave a yellow solid, which was recrystallized from ether–pentane to give 5 as white needles: 4.25 g (79%); mp 84.5–85 °C; ^{1}H NMR ($CDCl_3$) δ 1.87 (t, 2 H, J = 7 Hz), 2.85 (t, 2 H, J = 7 Hz), 2.93 (s, 2 H), 3.72 (s, 3 H), 3.92 (s, 4 H), 6.62 (d, 2 H, J = 8 Hz), 7.05 (t, 1 H, J = 8 Hz); IR ($CHCl_3$) 2950, 1590, 1475 cm^{-1}; mass spectrum, *m/e* (relative intensity) 220 ($M^{+\cdot}$, 100), 206, 134.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 71.05; H, 7.47.

2,2-(Ethylenedioxy)-5-(allyloxy)tetralin (7). According to the general procedure of Feutrill and Mirrington,[5] a solution of sodium thioethoxide, prepared from sodium hydride (60% dispersion in mineral oil, washed with hexane; 7.0 g, 0.175 mol) and ethanethiol (14.0 mL, 0.19 mol), and ketal 5 (11.0 g, 0.050 mol) in DMF (160 mL) was heated under nitrogen at 155 °C for 4 h. The resulting red solution was cooled in an ice bath and then

Scheme III



poured into a cold mixture of ether and saturated ammonium chloride solution. After acidification to pH 2 with hydrochloric acid, the aqueous layer was extracted with ether (3×) and the combined organic layers were washed with water (6×) and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to leave a pale yellow solid. The residue was dissolved in DMF (25 mL) and added dropwise over 15 min to a cold (0 °C) suspension of sodium methoxide (3.40 g, 60 mmol) in DMF (90 mL) to form a thick, off-white suspension. After 20 min, allyl bromide (6.5 mL, 75 mmol) was added dropwise over 5 min to give a pale brown solution which was stirred at 25 °C overnight. The mixture was then partitioned between ether and half-saturated ammonium chloride solution, and the organic layers were washed with water (6×), 1.0 M sodium hydroxide solution, and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to leave a yellow solid. Recrystallization from ether–pentane gave **7** as colorless needles: 9.52 g (77.5%); mp 48.0–49.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (t, 2 H, J = 7 Hz), 2.86–3.04 (m, 4 H), 4.00 (s, 4 H), 4.50 (br d, 2 H, J = 6 Hz), 5.20–5.50 (m, 2 H), 5.88–6.26 (m, 1 H), 6.66 (d, 2 H, J = 8 Hz), 7.03 (t, 1 H, J = 8 Hz); IR (neat) 1650, 1590, 1110 cm^{-1}; mass spectrum, m/e (relative intensity) 246 ($M^{+}\cdot$, 100), 231, 204, 145. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.36. Found: C, 73.06; H, 7.27.

2,2-(Ethylenedioxy)-6-allyl-5-methoxytetralin (8). A solution of allyl ether **7** (3.10 g, 1.26 mmol) in *N,N*-dimethylaniline (11 mL) was heated under nitrogen at 175 °C for 43 h, cooled, and poured into ether. The solution was washed with 5% hydrochloric acid (4×) and brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The residual red oil was dissolved in DMF (5 mL) and added dropwise over 10 min to a cold (0 °C) suspension of sodium hydride (50% dispersion in mineral oil, washed with hexane; 0.675 g, 14.1 mmol) in DMF (45 mL) under nitrogen. After 30 min, iodomethane (1.25 mL, 20.0 mmol) was added in one portion, and the resulting brown suspension was stirred at 25 °C for 4 h. The mixture was then poured into half-saturated ammonium chloride solution and extracted with ether (4×). The combined organic layers were washed exhaustively with water and once with brine, dried over $MgSO_4$, and concentrated by rotary evaporation to leave a pale yellow oil. Chromatography (SiO_2, medium pressure, 9% ether–hexane) gave **8** as a colorless oil (2.47 g, 75%) accompanied by 2,2-(ethylenedioxy)-8-allyl-5-methoxytetralin (**9**, 15%). Spectral data for **8**: ^{1}H NMR ($CDCl_3$) δ 1.90 (t, 2 H, J = 7 Hz), 2.88–3.08 (m, 4 H), 3.39 (br d, 2 H, J = 7 Hz), 3.70 (s, 3 H), 4.00 (s, 4 H), 4.92–5.20 (m, 2 H), 5.74–6.16 (m, 1 H), 6.75 (d, 1 H, J = 8 Hz), 6.95 (d, 1 H, J = 8 Hz); IR (neat) 1645, 1100 cm^{-1}; mass spectrum, m/e (relative intensity) 260 ($M^{+}\cdot$, 100), 245, 231, 174. Spectral data for **9**: ^{1}H NMR ($CDCl_3$) δ 1.86 (t, 2 H, J = 7 Hz), 2.72–3.04 (m, 4 H), 3.24 (br d, 2 H, J = 7 Hz), 3.75 (s, 3 H), 3.96 (s, 4 H), 4.80–5.16 (m, 2 H), 5.72–6.12 (m, 1 H), 6.60 (d, 1 H, J = 8 Hz), 6.93 (d, 1 H, J = 8 Hz); IR (neat) 2950, 1640, 1590, 1270 cm^{-1}; mass spectrum, m/e (relative intensity) 260 ($M^{+}\cdot$), 245 (100), 154.

Anal. Calcd for $C_{16}H_{20}O_3$ (**8**): C, 73.82; H, 7.74. Found: C, 73.88; H, 8.06.

2,2-(Ethylenedioxy)-5-methoxy-6-propenyltetralin (11). A solution of ketal **8** (2.26 g, 8.70 mmol) and potassium *tert*-butoxide (0.293 g, 2.61 mmol) in *tert*-butyl alcohol (30 mL) was heated at reflux under nitrogen for 8.5 h. The mixture was poured into half-saturated ammonium chloride solution and extracted with ether (3×). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to leave a colorless oil which showed two spots by analytical TLC (SiO_2, R_f 0.50 and 0.15, 25% ether–hexane). The residue was combined with benzene (50 mL), *p*-TSA (0.020 g), and ethylene glycol (2 mL) and heated at reflux for 5 h with removal of water by a Dean–Stark trap. The reaction mixture was then treated as described for **5** to give **11** as a white solid: 2.20 g (97%); mp 59–60 °C (from ether–pentane); ^{1}H NMR ($CDCl_3$) δ 1.76–1.94 (m, 5 H), 2.84–3.08 (m, 4 H), 3.70 (s, 3 H), 4.00 (s, 4 H), 5.90–6.40 (m, 1 H), 6.48–6.84 (m, 2 H), 7.24 (d, 1 H, J = 8 Hz); IR (neat) 2950, 1610, 1575, 1110 cm^{-1}; mass spectrum, m/e (relative intensity) 260 ($M^{+}\cdot$, 100), 245, 230.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.75; H, 7.78.

Column chromatography (SiO_2, 10–50% ether–hexane) prior to recyclization of the ketal provided a sample of the lower R_f fraction, which was identified by spectral analysis as 2-(2-hydroxyethyl)-5-methoxy-6-propenyl-3,4-dihydronaphthalene **10** (mp 71–75 °C): ^{1}H NMR ($CDCl_3$) δ 1.88 (d, 3 H, J = 7 Hz), 2.32 (br s, 1 H), 2.38 (t, 2 H, J = 7 Hz), 2.91 (t, 2 H, J = 7 Hz), 3.63 (s, 3 H), 3.86 (br s, 4 H), 5.44 (s, 1 H), 6.10 (dd, 1 H, J = 15, 7 Hz), 6.57 (d, 1 H, J = 15 Hz), 6.62 (d, 1 H, J = 8 Hz), 7.14 (d, 1 H, J = 8 Hz); IR (neat) 3420, 2950, 1640 cm^{-1}; mass spectrum, m/e (relative intensity) 260 ($M^{+}\cdot$, 100), 216, 185.

2,2-(Ethylenedioxy)-5-methoxy-1*H*-3,4-dihydronaphthalene-6-carboxaldehyde (12). Ozone (2–3% in oxygen) was introduced by means of a gas-dispersion tube into a solution of **11** (2.45 g, 9.42 mmol) in dichloromethane (120 mL) at −78 °C until the blue color persisted (ca. 2 h). Excess ozone was removed by flushing with nitrogen at −78 °C. Dimethyl sulfide (5 mL) was then added and the solution allowed to warm to 25 °C over 2 h. After concentration by rotary evaporation, the residue was combined with 10% aqueous potassium iodide solution (100 mL) and THF (150 mL) and stirred vigorously overnight. The red solution was saturated with sodium chloride and extracted twice with ether. The combined organic layers were washed with sodium thiosulfate solution, water, and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to leave a yellow oil. Column chromatography (SiO_2, medium pressure, 7% acetone–hexane) gave aldehyde **12** as white cubes: 1.81 g (82%); mp 58–60 °C (from ether–pentane); ^{1}H NMR ($CDCl_3$) 1.92 (t, 2 H, J = 7 Hz), 2.88–3.08 (m, 4 H), 3.86 (s, 3 H), 4.02 (s, 4 H), 6.91 (d, 1 H, J = 8 Hz), 7.60

(d, 1 H, J = 8 Hz), 10.30 (s, 1 H); IR (neat) 2740, 1690, 1575 cm^{-1}; mass spectrum, m/e (relative intensity) 248 (M$^{+}\cdot$, 100), 233, 220, 205, 189.

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.73; H, 6.54.

Phthalide 14. According to the procedure of Baldwin and Bair,[6] the dilithio derivative of 3-methoxybenzanilide was prepared by the addition of n-BuLi (1.50 M in hexane, 5.85 mL, 8.80 mmol) to a solution of 3-methoxybenzanilide (1.00 g, 4.4 mmol) and TMEDA (1.35 mL, 8.8 mmol) in THF (30 mL) at −78 °C under nitrogen. After being stirred for 30 min at −78 °C, the reaction mixture was warmed to −10 °C, with formation of a white precipitate. After 5 h at −10 °C, the suspension was recooled to −78 °C and aldehyde **12** (1.04 g, 4.2 mmol) in THF (35 mL) was added dropwise over 1 h. The resulting yellow suspension was stirred for 4 h at −78 °C and then allowed to warm to 25 °C overnight. The orange solution was poured into 10% hydrochloric acid, and the mixture was stirred for 1.5 h. After saturation with salt, the mixture was extracted twice with ether, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The residue was mixed with benzene (60 mL), p-TSA (0.020 g), and ethylene glycol (4 mL) and heated at reflux for 5 h, with removal of water by a Dean–Stark trap. The reaction mixture was then treated as described for **5** to give a yellow oil which, on trituration with ether–pentane, gave phthalide **14** as off-white needles: 1.17 g (73%); mp 182–183 °C (from ether–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 1.92 (t, 2 H, J = 7 Hz), 2.88–3.12 (m, 4 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 4.00 (s, 4 H), 6.52 (d, 1 H, J = 8 Hz), 6.70 (d, 1 H, J = 8 Hz), 6.72 (s, 1 H), 7.00–7.20 (m, 1 H), 7.44–7.60 (m, 2 H); IR ($CHCl_3$) 1770, 1500, 1210 cm^{-1}; mass spectrum, m/e (relative intensity) 382 (M$^{+}\cdot$, 100), 367, 293, 231.

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.09; H, 5.72.

5,7-Dimethoxy-2,2-(ethylenedioxy)-1,3,4,6-tetrahydronaphthacen-11-one (16). According to a general procedure,[7] a suspension of phthalide **14** (0.60 g, 1.57 mmol), zinc dust (10 g), $CuSO_4 \cdot 5H_2O$ (0.30 g), and pyridine (2 mL) in 10% aqueous potassium hydroxide solution (50 mL) was stirred vigorously and heated at reflux for 2 days. After the solids were removed by centrifugation, the supernatant was washed with ether. An ice-cold mixture of the aqueous phase and chloroform was then acidified to pH 2 with concentrated hydrochloric acid, and the aqueous phase was extracted twice with chloroform. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated by rotary evaporation to leave an orange oil which showed phthalide **14** and acid **15** by analytical TLC (SiO_2, 25% acetone–hexane, R_f 0.5 and 0.2–0.4, respectively). Acid **15** was separated from starting material and other contaminants by extraction into 5% sodium carbonate solution, followed by careful reacidification and extraction into chloroform. Concentration of the organic phase left acid **15** as an unstable white foamy solid (0.575 g, 95%; mp 55–60 °C) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.88 (t, 2 H, J = 7 Hz), 2.80–3.08 (m, 4 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 3.98 (s, 4 H), 4.40 (s, 2 H), 6.40 (d, 1 H, J = 8 Hz), 6.56 (d, 1 H, J = 8 Hz), 6.98 (d, 1 H, J = 8 Hz), 7.28 (t, 1 H, J = 8 Hz), 7.56 (d, 1 H, J = 8 Hz), 11.04 (br s, 1 H); IR ($CHCl_3$) 3000, 1700, 1270 cm^{-1}; mass spectrum, m/e (relative intensity) 384 (M$^{+}\cdot$), 366, 353, 119 (100), 117 (100).

To a cold (−15 °C) solution of acid **15** (0.45 g, 1.17 mmol) in dichloromethane (40 mL) were added sequentially trifluoroacetic anhydride (0.5 mL) and trifluoroacetic acid (0.5 mL) under nitrogen. The pale brown solution was stirred for 1 h at −10 °C and 1 h at 0 °C and then poured into cold saturated sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was triturated with cold ether to give anthrone **16** as shiny white plates: 0.36 g (83%); mp 198–200 °C (from ether–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 1.98 (t, 2 H, J = 7 Hz), 3.10 (m, 4 H), 3.90 (s, 3 H), 3.96 (s, 3 H), 4.08 (s, 4 H), 4.11 (s, 2 H), 7.08 (d, 1 H, J = 8 Hz), 7.40 (t, 1 H, J = 8 Hz), 7.88 (s, 1 H), 7.96 (d, 1 H, J = 8 Hz); IR ($CHCl_3$) 1660, 1585, 1320 cm^{-1}; mass spectrum, m/e (relative intensity) 366 (M$^{+}\cdot$, 100), 351, 322, 280.

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found: C, 72.18; H, 6.21.

5,7-Dimethoxy-2,2-(ethylenedioxy)-1*H*-3,4-dihydronaphthacene-6,11-dione (17). Chromium trioxide (0.31 g, 3.1 mmol) was added to a solution of anthrone **16** (0.30 g, 0.82 mmol) in glacial acetic acid (28 mL), and the resulting green suspension was stirred at 25 °C for 7 h and then concentrated by rotary evaporation. The residue was partitioned between chloroform and 5% sodium carbonate solution, and the aqueous phase was extracted twice with chloroform. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated by rotary evaporation to leave a brown semisolid which was filtered through SiO_2 (1% methanol–dichloromethane) to give quinone **17** as shiny orange needles after recrystallization from methanol: 0.26 g (82%); mp 188.5–191 °C; ^{1}H NMR ($CDCl_3$) δ 1.96 (t, 2 H, J = 7 Hz), 3.08 (m, 4 H), 3.95 (s, 3 H), 3.99 (s, 3 H), 4.04 (s, 4 H), 7.27 (d, 1 H, J = 8 Hz), 7.60 (t, 1 H, J = 8 Hz), 7.70 (s, 1 H), 7.81 (d, 1 H, J = 8 Hz); IR ($CHCl_3$) 1670, 1586, 1275 cm^{-1}; mass spectrum, m/e (relative intensity) 380 (M$^{+}\cdot$), 365, 351, 293 (100).

Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.35; H, 5.30.

5,7-Dihydroxy-1*H*-3,4-dihydronaphthacene-6,11-dione (18). A solution of quinone **17** (0.23 g, 0.61 mmol) in trifluoroacetic acid (8 mL) and 10% hydrochloric acid (5 mL) was stirred at 25 °C for 3 h and then partitioned between water and chloroform. The aqueous phase was extracted with chloroform, and the combined organic phases were washed with water and brine, dried over Na_2SO_4, and concentrated by rotary evaporation to give a yellow solid which showed one spot by analytical TLC (SiO_2, 3% methanol–dichloromethane). The product was dissolved in dichloromethane (200 mL) and aluminum chloride (0.81 g, 6.1 mmol) was added in one portion. The blue suspension was stirred overnight and then partitioned between ether and saturated oxalic acid solution. After the two-phase mixture had been stirred vigorously for 30 min, the aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution, water, and brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was dissolved in dichloromethane and passed through a short column of silica gel, eluting with 0–1% methanol–dichloromethane, to give quinone **18** as an orange powder: 0.17 g (90%); mp 242 °C dec (from chloroform–methanol) (lit. [8] mp 245–247 °C); ^{1}H NMR ($CDCl_3$) δ 2.60 (t, 2 H, J = 7 Hz), 3.24 (t, 2 H, J = 7 Hz), 3.70 (s, 2 H), 7.25 (d, 1 H, J = 7 Hz), 7.56 (s, 1 H), 7.68 (t, 1 H, J = 7 Hz), 7.78 (d, 1 H, J = 7 Hz); IR (KBr) 3000, 1725, 1665, 1615, 1290 cm^{-1}; mass spectrum, m/e (relative intensity) 308 (M$^{+}\cdot$), 280, 266 (100); UV (95% EtOH) λ_{max} 228 nm (log ϵ 4.23), 261 (415), 290 (3.76), 434 (3.83).

Anal. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92. Found: C, 69.86; H, 3.91.

2-Ethynyl-2,5,7-trihydroxy-1*H*-3,4-dihydronaphthacene-6,11-dione (19). The title compound was prepared according to a general procedure. Acetylene, purified by passage through dry ice–acetone and sulfuric acid traps, was bubbled rapidly through THF (30 mL) for 1 h. Ethylmagnesium bromide (3 M solution in ether, 0.7 mL, 2.1 mmol) was then added and the passage of acetylene continued for 2 h. After the reaction mixture had been cooled to −25 °C, a solution of quinone **18** (0.037 g, 0.12 mmol) in THF (16 mL) was added dropwise over 5 min to give a deep red solution. Passage of acetylene through the cold solution was continued for 1 h, and the mixture was then stirred at −25 °C for an additional 2.5 h under nitrogen. The mixture was poured into cold saturated ammonium chloride solution and extracted twice with dichloromethane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated by rotary evaporation. Preparative layer chromatography of the residue (SiO_2, 3% methanol–dichloromethane) gave starting quinone **18** (0.021 g, 57%) and ethynyl quinone **19** [0.010 g (25%); mp 260 °C (from chloroform–methanol)] as orange powders. Spectral data for **19**: ^{1}H NMR (FT-100, $CDCl_3$) δ 2.19 (t, 2 H, J = 7 Hz), 2.50 (s, 1 H), 3.03 (t, 2 H, J = 7 Hz), 3.11 (AB q, 1 H, J = 18 Hz), 3.35 (AB q, 1 H, J = 18 Hz), 7.30 (d, 1 H, J = 7 Hz), 7.57 (s, 1 H), 7.67 (t, 1 H, J = 7 Hz), 7.83 (d, 1 H, J = 7 Hz), 12.13 (s, 1 H), 12.48 (s, 1 H); IR (KBr) 1665, 1620, 1290 cm^{-1}; mass spectrum, m/e (relative intensity) 334 (M$^{+}\cdot$), 316 (100), 266; UV

(95% EtOH) λ_{max} 228 nm (log ε 4.44), 261 (4.37), 291 (3.91), 434 (4.04); high-resolution mass spectral mol wt calcd for $C_{20}H_{14}O_5$ 334.0841, found 334.0837.

2-Acetyl-2-acetoxy-5,7-dihydroxy-1*H*-3,4-dihydronaphthacene-6,11-dione (7,11-Dideoxy-9-*O*-acetylcarminomycinone, 20). To a solution of acetylenic alcohol **19** (0.100 g, 0.30 mmol) in ethyl acetate (180 mL) was added mercuric acetate (1.00 g, 3.10 mmol). The resulting orange suspension was stirred overnight under nitrogen. Hydrogen sulfide gas was then bubbled through the mixture for 7 min, with formation of a black precipitate which was removed by filtration through Celite. The filtrate was washed sequentially with saturated sodium bicarbonate solution, water, and brine, dried over Na_2SO_4, and concentrated by rotary evaporation. Preparative layer chromatography (elution with 3% methanol–dichloromethane) gave acetate **20**: 0.103 g (85%); mp 238–240 °C (from pentane-chloroform); orange powder; ^{1}H NMR (FT-100, $CDCl_3$) δ 2.06 (s, 3 H), 2.14–2.39 (m, 2 H), 2.20 (s, 3 H), 2.94 (m, 2 H), 3.21 (AB q, 1 H, J = 18 Hz), 3.49 (AB q, 1 H, J = 18 Hz), 7.29 (dd, 1 H, J = 7, 2 Hz), 7.60 (s, 1 H), 7.67 (t, 1 H, J = 7 Hz), 7.83 (dd, 1 H, J = 7, 2 Hz), 12.10 (s, 1 H), 12.48 (s, 1 H); IR (CH_2Cl_2) 3050, 1740, 1725, 1670, 1625, 1260 cm^{-1}; mass spectrum, m/e (relative intensity) 394 ($M^{+}\cdot$), 334 (100), 309, 291; UV (95% EtOH) λ_{max} 228 nm (log ε 4.50), 261 (4.42), 290 (3.94), 432 (4.06).

(±)-11-Deoxycarminomycinone (22). Nitrogen was bubbled through a mixture of acetate **20** (0.025 g, 0.065 mmol) in carbon tetrachloride (100 mL) for 15 min. After the solution had been heated to reflux, bromine (0.1 M in CCl_4, 1.0 mL, 1.0 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.003 g) were added, and the solution was heated at reflux under nitrogen flow for 20 min. When analytical TLC (SiO_2, 3% methanol–dichloromethane) showed the presence of starting material, additional aliquots of bromine solution (1.0 mL) and AIBN (0.003 g) were added, and reflux was continued for 20 min. The mixture was then washed with sodium bisulfite solution and brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was stirred with THF (25 mL) and saturated sodium bicarbonate solution (25 mL) for 1 h. After acidification with oxalic acid, the aqueous layer was extracted twice with chloroform, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. Preparative layer chromatography of the residue (SiO_2, 3% methanol–dichloromethane) gave 9-*O*-acetyl-11-deoxycarminomycinone (**21**; 0.010 g, 38%) plus a mixture of **21** and the 7-epi isomer (0.005 g). Spectra data for **21**: ^{1}H NMR (FT-400, $CDCl_3$) δ 2.03 (s, 3 H), 2.25 (s, 3 H), 2.34 (dd, 1 H, J = 15, 6.4 Hz), 2.86 (dt, 1 H, J = 15, 2 Hz), 3.11 (d, 1 H, J = 18 Hz), 3.16 (d, 1 H, J = 4.4 Hz), 3.29 (dd, 1 H, J = 18, 2 Hz), 5.28 (m, 1 H, $v_{1/2}$ = 14 Hz), 7.33 (dd, 1 H, J = 8, 1.5 Hz), 7.66 (s, 1 H), 7.76 (t, 1 H, J = 8 Hz), 7.85 (dd, 1 H, J = 8, 1.5 Hz), 12.02 (s, 1 H), 12.77 (s, 1 H); mass spectrum, m/e (relative intensity) 350, 332 (100), 317, 289, 279 (no $M^{+}\cdot$).

To a solution of acetate **21** (0.010 g, 0.024 mmol) in methanol (35 mL) under nitrogen was added saturated aqueous potassium carbonate solution (0.3 mL). After 2 h at 25 °C, the red solution was acidified with aqueous oxalic acid and partitioned between water and chloroform. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated by rotary evaporation. Preparative layer chromatography of the combined reaction mixtures (from 0.015 g of **21**; 3.5% methanol–dichloromethane) gave (±)-11-deoxycarminomycinone (**22**; 0.005 g, 37%) along with an unidentified yellow solid (0.006 g). Spectral data for **22**: ^{1}H NMR (FT-400, $CDCl_3$) δ 2.21 (dd, 1 H, J = 14, 5 Hz), 2.38 (dt, 1 H, J = 14, 2 Hz), 2.43 (s, 3 H), 3.02 (dd, 1 H, J = 20, 2 Hz), 3.29 (d, 1 H, J = 20 Hz), 3.65 (m, 1 H), 4.59 (s, 1 H), 5.36 (br t, 1 H, $v_{1/2}$ = 12 Hz), 7.32 (d, 1 H, J = 8 Hz), 7.67 (s, 1 H), 7.71 (t, 1 H, J = 8 Hz), 7.85 (d, 1 H, J = 8 Hz), 12.04 (s, 1 H), 12.75 (s, 1 H); IR (KBr) 1710, 1675, 1625, 1280 cm^{-1}; mass spectrum, m/e (relative intensity) 368 ($M^{+}\cdot$), 350, 332, 307 (100), 279; UV (95% EtOH) λ_{max} 228 nm (log ε 4.33), 259 (4.15), 286 (3.76), 433 (3.80); high-resolution mass spectral mol wt calcd for $C_{20}H_{16}O_7$ 368.0896, found 368.0908.

Acknowledgment. We are grateful to Professor Federico Arcamone (Farmitalia Carlo-Erba) and to Dr. Jean-Pierre Gesson (University of Poitiers) for providing valuable references samples and thank Mr. J. Rizzi for helpful discussions. Partial support of this work by Grant CA 11326 from the National Cancer Institute, USPHS, is grateful acknowledged.

Registry No. 4, 32940-15-1; 5, 32940-19-5; 7, 77305-93-2; 8, 77305-94-3; 9, 77305-95-4; 10, 77305-96-5; 11, 77305-97-6; 12, 77305-98-7; 13, 77305-99-8; (±)-14, 77306-00-4; 15, 77306-01-5; 16, 77306-02-6; 17, 77306-03-7; 18, 77219-83-1; (±)-19, 77306-04-8; (±)-20, 77306-05-9; (±)-21, 77306-06-0; (±)-22, 77397-59-2.

Formation of Olefins in the Pyrolysis of N,N-Disubstituted Carbamates[1]

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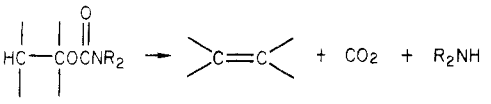
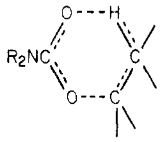
Received October 7, 1980

N,N-Disubstituted carbamates have been shown[2-8] to give alkenes, amine, and carbon dioxide upon heating.



$$\mathrm{HC{-}COCNR_2} \rightarrow \mathrm{>C{=}C<} + \mathrm{CO_2} + \mathrm{R_2NH}$$

Kinetic studies[3b,4,6-8] indicate first-order decomposition of such carbamates and support a concerted mechanism with a transition state such as that given below. This mechanism predicts a stereospecific syn elimination and the exclusive formation of terminal olefins from carbamates of primary alcohols. We have confirmed these predictions in the pyrolysis of *N*,*N*-dimethyl- and *N*,*N*-diphenylcarbamates. We have also established reaction conditions appropriate for the utilization of this reaction in the synthesis of olefins.



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(1) This work was supported by National Science Foundation Grant GY-5578 and by a grant from the Research and Scholarly Development Committee of Grand Valley State Colleges.

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0022-3263/81/1946-2804$01.25/0 © 1981 American Chemical Society