tography was conducted on the previously described system which now uses a Crane 202-C-50-43-5M ChemPump, a somewhat modified solvent-recovery system, and a sample injector comprised of a reservoir which gravity feeds sample into a loop through electrically operated solenoid valves.

Preparation of the Chiral Adsorbent 1. To a slurry of 900 g of γ-aminopropyl-silanized 40-μm irregular silica in 1 L of THF was added a THF solution of 250 g of (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine (**2**) in 1 L of THF. After overnight stirring, the adsorbent was isolated by filtration and washed with THF and with CH_2Ch_2.

Anal. Found: C, 15.18; H, 1.97; N, 4.16; Si, 33.27. Calcd for 0.69 mol of chiral sites/g of support (based on C) and 0.70 mol of chiral sites/g of support (based on N).

Resolution of Racemates. The adsorbent was dry packed into a 2 in. × 30 in. stainless-steel column. Chromatographic resolutions were performed on an automated system by using hexane containing varying amounts of 2-propanol as a mobile phase. The racemic solutes were injected as CH_2Cl_2 solutions. Enantiomeric purity assays were performed directly on chromatographic fractions. The high-R_f and low-R_f enantiomers of several of the solutes were once recrystallized after resolution and found to have the following properties.

3-(2,6-Dimethylnaphth-1-yl)-3-methylphthalide (3). High-R_f enantiomer: mp 119–120 °C; $[\alpha]_D$ −474.9° (*c* 1.60, $CHCl_3$). Low-R_f enantiomer: mp 118–119 °C; $[\alpha]_D$ +460.0° (*c* 1.58, $CHCl_3$).

5-(1-Naphthyl)-5-(4-pentenyl)hydantoin (4a). High-R_f enantiomer: mp 199.5–200 °C; $[\alpha]_D$ −7.9° (*c* 1.45, EtOAc).

5-(1-Naphthyl)-5-methylhydantoin (4b). High-R_f enantiomer: mp 250 °C; $[\alpha]_D$ −84.2° (*c* 0.89, THF). Low-R_f enantiomer: mp 260 °C; $[\alpha]_D$ +83.9° (*c* 0.67, THF).

2′-Methoxy-2-hydroxy-1,1′-binaphthyl (5). High-R_f enantiomer: mp 107–110 °C; $[\alpha]_D$ −49.1° (*c* 1.54, $CHCl_3$). Low-R_f enantiomer: mp 108–112 °C; $[\alpha]_D$ +47.7° (*c* 0.94, $CHCl_3$).

2,2,2-Trifluoro-1-(10-methylanthr-9-yl)ethanol (6). High-R_f enantiomer: mp 138–139 °C; $[\alpha]_D$ −38.1 (*c* 1.81, EtOH). Low R_f enantiomer: mp 135–137 °C; $[\alpha]_D$ +32.5° (*c* 1.08, EtOH).

***n*-Butyl 10-(Chloromethyl)anthr-9-yl Sulfoxide (7).** High-R_f enantiomer: mp 108–111 °C; $[\alpha]_D$ −132.8° (*c* 2.14, $CHCl_3$). Low R_f enantiomer: mp 109–111 °C; $[\alpha]_D$ +127.0° (*c* 0.60, $CHCl_3$).

3-*p*-Anisyl-2-pyrrolidinone (8). High-R_f enantiomer: mp 82–83 °C; $[\alpha]_D$ −27.9° (*c* 1.89, $CHCl_3$). Low-R_f enantiomer: mp 82–83 °C; $[\alpha]_D$ +29.4° (*c* 3.08, $CHCl_3$).

2,2,2-Trifluoro-1-(9-anthryl)ethanol (9a). High-R_f enantiomer: mp 129–130 °C; $[\alpha]_D$ −30.1° (*c* 2.2, $CHCl_3$). Low-R_f enantiomer: mp 131–132 °C; $[\alpha]_D$ +30.0° (*c* 3.1, $CHCl_3$).

Acknowledgment. This work has been funded by the National Science Foundation. We are grateful to the J. T. Baker Chemical Co. for a gift of γ-aminopropyl-silanized silica and to the Kay-Fries Co. for gifts of (*R*)-phenylglycine and triethoxy(γ-aminopropyl)silane. Phthalide **3** and hydantoin **4a** were prepared by Thomas Sowin and Myung Ho Hyun, respectively.

Registry No. (*R*)-**2**, 74927-72-3; (±)-**3**, 82752-65-6; (+)-**3**, 82752-70-3; (−)-**3**, 82752-71-4; (±)-**4a**, 82752-66-7; (+)-**4a**, 82752-72-5; (−)-**4a**, 82752-73-6; (±)-**4b**, 82752-67-8; (+)-**4b**, 82752-74-7; (−)-**4b**, 82752-75-8; (±)-**5**, 35193-70-5; (+)-**5**, 79547-82-3; (−)-**5**, 35193-69-2; (±)-**6**, 74958-72-8; (+)-**6**, 63017-54-9; (1)-**6**, 53282-95-4; (±)-**7**, 82752-68-9; (+)-**7**, 82752-76-9; (−)-**7**, 82752-77-0; (*u*)-**8**, 82752-69-0; (+)-**8**, 82752-78-1; (−)-**8**, 82752-79-2; (±)-**9a**, 60686-64-8; (+)-**9a**, 60646-30-2; (−)-**9a**, 53531-34-3; (±)-**9b**, 77495-10-4; (+)-**9b**, 82752-80-5; (−)-**9b**, 82752-81-6.

α-Nitro Ketones and Esters from Acylimidazoles

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The anion of 2-(2-nitroethyl)-1,3-dioxolane (**4**), prepared from the corresponding 2-bromo compound (**3**), undergoes condensation with acylimidazoles to give the 3-nitro-4-oxobutanal acetals (**9**), which can serve as valuable polyfunctional intermediates. Condensation with 1-(methoxyoxalyl)imidazole gives the tetrafunctionalized methyl 4-(1,3-dioxolan-2-yl)-3-nitro-2-oxobutanoate (**13**), which, however, decomposed on attempted deprotection of the ester function. The syntheses in excellent yields of simple α-nitro ketones and α-nitro esters from acylimidazoles and nitroethane and 2-nitropropane are also described.

Aliphatic nitro compounds are valuable synthetic intermediates;[1] however, their full potential has not been realized because of the limited availability of satisfactory synthetic methods involving carbon–carbon bond-forming reactions of such nitro compounds. A major reason for this has been the propensity of aliphatic nitro compounds to undergo oxygen alkylation and acylation in preference to carbon alkylation[2] and acylation.[3,4] This has been overcome in an important way by the double deprotonated intermediates introduced by Seebach et al.,[5] but again this technique is not as widely applicable as one might wish. The mechanism of carbon alkylation of nitro compounds has been studied extensively.[3-9] The factors influencing the oxygen vs. carbon alkylation of ambident anions has been reviewed by le Noble.[10]

A significant improvement on the C-acylation of nitromethane anion was introduced by Baker and Putt,[4] by the use of highly reactive acylimidazoles as the acylating agents; however, this method was not extended to other aliphatic nitro compounds. We had made use of acylimidazoles in the synthesis of α-keto esters[11,12] and sought

(1) D. Seebach, E. W. Calvin, F. Lehr, and T. Weller, *Chimia*, **33**, 1 (1979).
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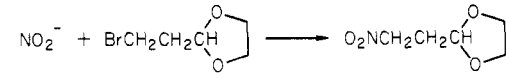
Table I. Reaction of 2-(2-Bromoethyl)-1,3-dioxolane with Nitrite under Various Conditions



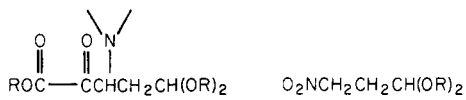
3 4

reaction conditions	% yield of 4
$NaNO_2/Me_2SO$, room temp, 12 h	35
$NaNO_2$/DMF/urea, room temp, 12 h	36
KNO_2/Me_2SO/18-crown-6, room temp, 18 h	37
$AgNO_2/Et_2O$, 35 °C, 4 days	47
$NaNO_2/Me_2SO$/phloroglucinol, room temp, 18 h	51
Amberlite IRA-900, NO_2 form, benzene, room temp, 36 h	82[a]

[a] This isolated yield was obtained on a small-scale trial. When done with a 10-g amount of 3, a 76% yield was obtained, and on a 53-g scale, a 60% yield.

an extension of this to the acylation of further functionalized nitro compounds.

Our target was the tetrafunctionalized structure shown in 1; i.e., a keto ester having a nitrogen functionality in the

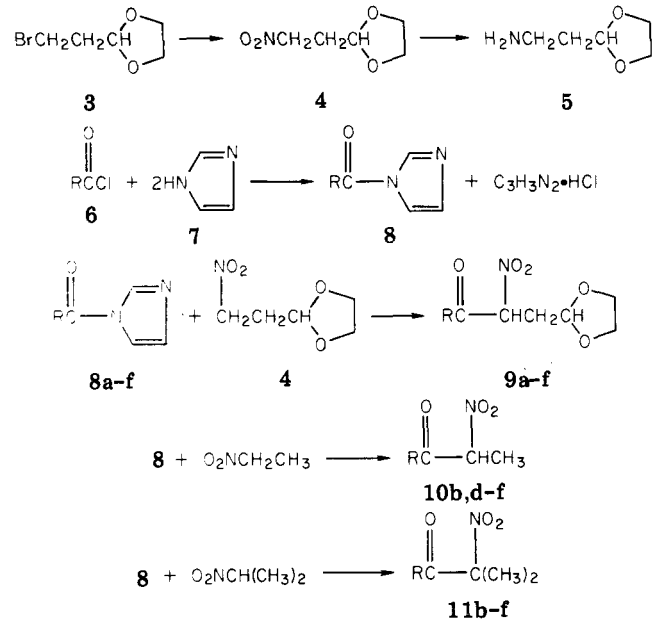


1 2

α position and a protected aldehyde in the γ position. We speculate[12] that such a compound could serve as a convenient proheterocyclic moiety in a synthesis of capreomycidine[13] and for elaboration of the guanidinium ring in a convergent synthesis of tetrodotoxin.

A possible route to 1 would be by the acylation of the nitro carbanion derived from 2. We have synthesized (alkoxyoxalyl)imidazoles from their respective alkoxyoxalyl chlorides[11] so that this approach appeared feasible. The synthesis of the protected nitro aldehyde 2 was originally attempted by condensation of α-bromoacetaldehyde diethyl acetal with the dianion of nitromethane[5] under a variety of conditions; in no case could the desired product be detected. We therefore undertook a study of the conversion of the readily available 2-(2-bromoethyl)-1,3-dioxolane[14] (3) to the corresponding nitro compound 4 (Scheme I). As shown in Table I, the yields were barely satisfactory with use of sodium, potassium or silver nitrites in various solvents and in the presence of additives that have been helpful in other cases,[7,9,10] i.e., urea, phloroglucinol, and the cyclic polyether chelating agent, 18-crown-6.[15] The yield became quite respectable (up to 82%), however, when the nitrite anion was bound to a macroporous quaternary ammonium Amberlite resin (Amberlite IRA 900), according to a method reported by Gelbard and Colonna.[16] The protected β-nitro aldehyde 4 is, therefore, a reasonable synthon for the β-aminopropionaldehyde moiety. For example, it is readily reduced to the corresponding amine 5, which is a convenient alternative to the corresponding diethyl acetal.[13,17] More-

Scheme I[a]



[a] a, R = CH_3; b, R = C_6H_5; c, R = p-BrC_6H_4; d, R = p-$NO_2C_6H_4$; e, R = CH_3O; f, R = C_2H_5O

over, it is activated in the position α to the nitro group for further substitution.

Acylations of 2-(2-nitroethyl)-1,3-dioxolane (4) with acylimidazoles, 8, were studied under a variety of conditions: sodium hydride in tetrahydrofuran (THF), sodium hydride in THF–hexamethylphosphoramide (THF–HMPA mixtures), lithium hydride in THF, and potassium hydride in THF. These attempts either gave no product or a product in low yield that was difficult to purify. The difficulty appeared to be the virtual insolubility of the sodium, lithium, or potassium salts in these solvents. This problem was completely overcome by using the general Kornblum[7] procedure in which the lithium salt is prepared and stored in the dry form. A Me_2SO solution of the lithium salt was cooled to incipient crystallization at which point a Me_2SO solution of the acylimidazole 8 was added. The isolated yields were excellent (85–95%) as shown in Table II, **9a–f**. Purification was not always simple but was achieved in most cases by either distillation of the lower boiling products, crystallizations of the solids, or chromatogrpahy on cellulose (which was of limited utility); some compounds, however, decomposed upon attempted purification by these methods.

The further generality of this reaction procedure in Me_2SO solvent was investigated by examining the reactions of the lithium salts of nitroethane and 2-nitropropane. Nitroethane gave the desired products in excellent isolated yields (90–92%, Table II, **10b–10f**). However, with 2-nitropropane the yields were 23–34% (Table II, **11b–11e**), presumably because of the lower reactivity of the tertiary carbanion and/or a greater amount of O-acylation. These acylation products were easily isolated and purified by chromatography even though they were formed in low yield.

Since the acyl group in these reactions can be aliphatic or aromatic, this general procedure can serve to form a very large variety of α-nitro ketones. Furthermore, since the acylating agent can also be a formylimidazole ester, as shown in **8e** and **8f**, a variety of α-nitro esters, such as **9e**,

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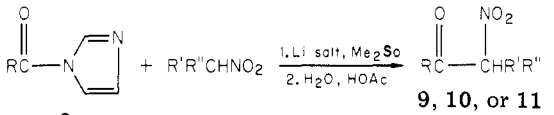
Table II. Properties and Yields of α-Nitro Ketones[a] and Esters[b]



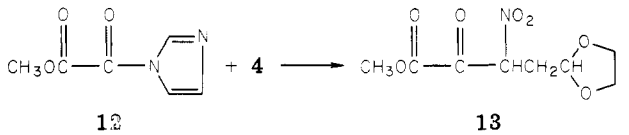
8 9, 10, or 11

product	substituent R	substituent R'[d]	substituent R''	% yield[c]	bp/pressure °C/torr	mp, °C	^{1}H NMR[m]
9a	CH_3	$CH_2CH(OCH_2)_2$	H	85	55/0.2		2.38 (s, 3 H), 2.38-3.10 (2 H, J = 8, J' = 3)
9b	C_6H_5	$CH_2CH(OCH_2)_2$	H	95	dec		2.55, 2.98 (ddq, 2 H, J = 15.6), 4.0-3.8 (m, 4 H), 5.05 (dt, 1 H, J = 2.9, J' = 3.5), 6.38 (dd, 1 H, J = 8.5, J' = 3.9), 7.66-7.45 (m, 3 H), 8.08-7.96 (m, 2 H)
9c	p-BrC_6H_4	$CH_2CH(OCH_2)_2$	H	91		93[e]	2.50, 2.31 (ddq, 2 H, J = 15), 4.0-3.8 (m, 4 H), 5.05 (dd, 1 H, J = 3.0, J' = 3.5), 6.35 (dd, 1 H, J = 8.3, J' = 4.0), 7.90, 7.58 (AA'B'B q, 4 H, J = 9)
9e	CH_3O	$CH_2CH(OCH_2)_2$	H	92	45/0.1		2.83, 2.58 (ddq, 2 H, J = 15), 3.84 (s, 3 H), 4.07-3.77 (m, 4 H), 5.05 (dd, 1 H, J = J' = 3.4), 5.39 (dd, 1 H, J = 4.8, J' = 8.6)
9f	C_2H_5O	$CH_2CH(OCH_2)_2$	H	91	55/0.05		1.29 (t, 3 H, J = 7.2), 2.80, 2.54 (ddq, 2 H, J = 15.2), 4.05-3.75 (m, 4 H), 4.27 (q, 2 H), 5.03 (dd, 1 H, J = J' = 3.4), 5.33 (dd, 1 H, J = 4.8, J' = 8.7)
10b	C_6H_5	CH_3	H	92	70/1[f]		
10d	p-$NO_2C_6H_4$	CH_3	H	90		71[g]	1.86 (d, 3 H, J = 7.0), 6.15 (q, 1 H), 8.12, 8.35 (AA'BB' q, 4 H, $J_{AB'}$ = $J_{A'B'}$ = 9.0, $J_{AA'}$ = $J_{BB'}$ = 2.0)
10e	CH_3O	CH_3	H	91	75/5[h]		
10f	C_2H_5O	CH_3	H	90	78/10[i]		
11b	C_6H_5	CH_3	CH_3	30	oil[j]		2.11 (s, 6 H), 8.15-8.00 (m, 2 H), 7.60-7.25 (m, 3 H)
11c	p-BrC_6H_4	CH_3	CH_3	32		104[j]	2.13 (s, 6 H), 7.93, 7.61 (AA'BB' q, 4 H, J = 8)
11d	p-$NO_2C_6H_4$	CH_3	CH_3	23		147[k,e]	2.16 (s, 6 H), 8.32, 8.24 (AA'BB' q, 4 H, J = 9)
11e	CH_3O	CH_3	CH_3	34	80/15[l]		

[a] All new compounds recorded in this table gave satisfactory analysis, i.e., within 0.4% of the calculated value for C, H, N, or halogen. [b] Ketones **9a-c, 10b, 10d, 11b-d**; esters **9e, 9f, 10e, 10f,** and **11e**. [c] Isolated yields in all cases. [d] The symbol $CH(OCH_2)_2$ represents the 1,3-dioxolan-2-yl group (ethylene acetal group). [e] Crystallized from ether. [f] See ref 23. [g] Crystallized from petroleum ether. Methyl p-nitrobenzoate was isolated when pure 10d was crystallized from methanol. [h] See ref 24. [i] See ref 22. [j] Purified by TLC (10% EtOAc/90% C_6H_6) and crystallized from hexane. [k] Purified by TLC (10% EtOAc/90% C_6H_6) and crystallized from ether. [l] Purified by TLC (5% Et_2O/petroleum ether). [m] δ ($CDCl_3$, Me_4Si), J values in hertz.

9f, 10e, 10f, and **11e** can be synthesized as well. These reactions are summarized in Table II.

We expected that the lithium salt of **4** would react with 1-(methoxyoxalyl)imidazole[11] (**12**) to give the desired product **13** when treated according to this successful



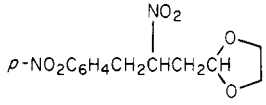
12 13

procedure. Although it was evident that the lithium salt was rapidly consumed, as observed by analysis of NMR spectra during the course of the reaction, nevertheless, the nitro compound was recovered unchanged. However, it was found that C-acylation did proceed when the sodium salt of **4**, made with sodium hydride in THF, was treated with 1-(methoxyoxalyl)imidozale (**12**) at reflux. The crude sodium salt of methyl 4-(1,3-dioxolan-2-yl)-3-nitro-2-oxobutanoate (**13**) was obtained in 39% yield. This crude dried material darkened over a period of a few days. The free ester (**13**) was obtained as a yellow oil (24% yield), which could not be distilled. The ethyl ester corresponding to **13** was obtained similarly but showed some decomposition on distillation. The *tert*-butyl ester did not form an insoluble sodium salt and therefore could not be separated readily from unreacted starting material. The free ester decomposed on attempted distillation or in the presence of acid, base, or silica gel.

Attempted aldehyde condensatons of the methyl ester **13** led to its decomposition into the starting nitro compound **4**, carbon dioxide, and carbon monoxide. We were unable to obtain the free acid of **13** nor were we able to carry out transesterifications on it.[12] In view of the low yield of **13**, and our inability to utilize it, we have abandoned further studies on its reactions.

We investigated treatment of nitro acetal **4** with *p*-nitrobenzyl chloride, which should be a reaction proceeding by the Kornblum $S_{RN}1$ mechanism. The expected product **14** was obtained in 68% yield along with four minor products which were separable by chromatography. These were identified by NMR as the following: the ketone 1-(1,3-dioxolan-2-yl)-3-(*p*-nitrophenyl)-2-propanone (**15**, 11%), two oximes *syn*- and *anti*-**16** (5% each) and the isoxazole 3-(*p*-nitrobenzyl)-5-(2-hydroxyethoxy)isoxazole (**17**, 5%). These minor products appear to be derived from **14** by conversion of the nitro function to an oximino group.

An attempt was made to prepare 2-(2-chloro-2-nitroethyl)-1,3-dioxolane, which might be used in chlorine displacement reactions. However, chlorination of **4** gave a dichloro product, presumably 2-(2-nitro-1,2-dichloroethyl)-1,3-dioxolane (**18**). This product contained im-



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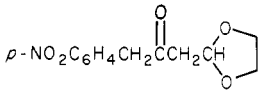

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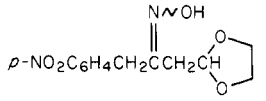
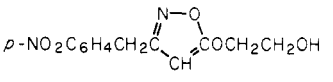


syn- and *anti*-16



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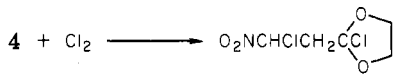
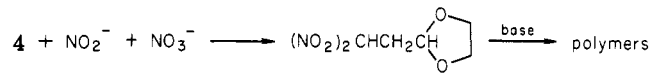
purities that were not removed by distillation and it was unstable to chromatography.



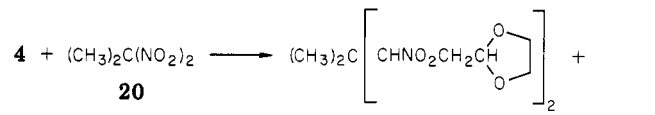
18

With use of the oxidative nitration method of Kaplan and Schechter,[18] the 2,2-dinitro compound **19** was prepared by the sequential treatment of **4** with sodium hydroxide, sodium nitrite, and silver nitrate. Since attempts to prepare the anion of **19** yielded insoluble polymers, this method was of no synthetic value.



19

Finally, the reaction of **4** with 2,2-dinitropropane (**20**) was studied. Both nitro groups were displaced with the formation of *meso*-4,4-dimethyl-3,5-dinitroheptanedial diethylene acetal (**21**, 22%); symmetry of the NMR spectrum requires assignments of a *meso* structure. A related product (38% yield based on the molecular formula $C_{13}H_{21}NO_6$) appears to be derived from **21** by the loss of the elements HNO_2. Its structure, however, was not established.



20 21

$C_{13}H_{21}O_6N$

22

Experimental Section

Tetrahydrofuran (THF), dried by refluxing over benzophenone ketyl, was distilled immediately before use. Dimethyl sulfoxide (Me_2SO) was refluxed over calcium hydride and stored over A_4 molecular sieves. The acid chlorides were commercial samples and were distilled or recrystallized before use. 2-(2-Bromoethyl)-1,3-dioxolane (**3**) was synthesized by the method of Büchi and Wüest[14] and 2,2-dinitropropane according to Kaplan and Schechter.[18]

Uncorrected melting points were determined on a "Meltemp" aluminum block apparatus. IR spectra were obtained on a Perkin-Elmer 237B instrument, NMR spectra on a Varian XL-100 instrument, and mass spectra on a Mat-44 instrument at 70 eV. NMR chemical shift data are recorded in δ, parts per million downfield from internal tetramethylsilane (Me_4Si). Coupling constants are in hertz (Hz) and splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, unresolved multiplet; dd, doublet of doublets; dq, doublet of quartets (eight signals); ddq, doublet of double quartets (16 signals). Microanalyses (C, H, and N) were carried out by E. Meier of the Stanford University Chemistry Department, Microanalytical Laboratories.

2-(2-Nitroethyl)-1,3-dioxolane (4). Amberlite IR-900 (Rohm and Haas) in the chloride form was converted to the nitrite form according to the literature[16] by passing a sodium nitrite solution through the resin column until no more Cl^- was displaced as detected by silver ion. The column was then washed successively with anhydrous ethanol, ethanol/benzene, and benzene followed by drying at 0.5 torr for 8 h. Titration of the amount of sodium nitrite displaced from the column by sodium chloride, using 0.1 N HCl and methyl orange indicator, gave a value of 1.6 mmol of bound nitrite/g of dry resin. This resin in the nitrite form (100 g) was added to 2-(2-bromoethyl)-1,3-dioxolane[14] (**3**, 10 g) in benzene (1 L) and the resulting slurry stirred at ca. 20 °C for 36 h. The resin was removed and washed with benzene; the combined benzene solutions were evaporated under reduced pressure to give a yellow liquid, which was purified by distillation to afford 2-(2-nitroethyl)-1,3-dioxolane (**4**, 6.2g, 76%), bp 68 °C (0.25 torr), as a colorless liquid: NMR ($CDCl_3$) δ 2.35 (d of t, 2 H, J_1 = 4 Hz, J_2 = 7 Hz), 3.85 (m, 4 H), 4.40 (t, 2 H, J = 7 Hz), 4.95 (t, 1 H, J = 4 Hz), identical with a sample from a previous trial that was analyzed. Anal. Calcd for $C_5H_9NO_4$: C, 40.80; H, 6.16; N, 9.51. Found: C, 40.99; H, 6.19; N, 9.12. A run carried out on a 0.35-g scale of bromide gave an 82% yield, while another run on a 53-g scale of bromide gave a 60% yield.[12]

2-(2-Aminoethyl)-1,3-dioxolane (5). 2-(2-Nitroethyl)-1,3-dioxolane (**4**; 5.0 g, 34 mmol) in ethanol (30 mL, 95%) was reduced in a Parr apparatus at 57 psi in the presence of prereduced PtO_2 catalyst (55 mg) to give the amine **5** (2.87 g, 72%): bp 93 °C (3.5 torr); NMR ($CDCl_3$) δ 1.60 (s, 2 H), 1.80 (m, 1 H), 2.85 (t, 2 H), 3.90 (m, 4 H), 4.90 (t, 1 H); IR (neat) 3150–3375 (NH_2) cm^{-1}. This compound presumably has been made before, but the original patent is unavailable[26] to us. The corresponding diethyl acetal is well-known.[13,17,19]

2-(2-Guanidinoethyl)-1,3-dioxolane Picrate. The amine (1.0 g, 8.5 mmol in 5 mL of H_2O) was treated with *S*-methylisothiourea sulfate (2.13 g, 7.65 mmol in 8 mL of H_2O). The solution was neutralized with NaOH (7.65 mmol) and stirred for 3 days at room temperature. The addition of picric acid solution gave a precipitate, which was crystallized from water (100 mL) to give large yellow needles (0.94 g, mp 153–154 °C). This compound correspnds to the diethyl acetal previously prepared.[17] The NMR and IR spectra were compatible with this structure. Anal Calcd $C_{12}H_{10}N_6O_9$: C, 37.08; H, 4.15; N, 21.72. Found: C, 37.05; H, 4.26; N, 21.44.

Cyclization according to the conditions of Suzuki et al.[17] gave 2-amino-4-hydroxytetrahydropyrimidine picrate with the reported melting point and with compatible NMR and IR spectra.[12]

Reactions of Acylimidazoles with Lithium Salts of Nitroalkanes in Me_2SO. General Procedure. The imidazoles **8a–8f**, were prepared from imidazole (**7**) and the appropriate acid chloride **6**, in THF.[20] Imidazole (2 equiv) in THF was added dropwise to a stirred solution of the acid chloride **6** in THF at 0 °C and the mixture was stirred for 18 h at room temperature.[20] The solid was quickly removed by filtration and the filtrate was concentrated under reduced pressure to give the residual acylimidazole **8** or **12**. The lithium salts of 2-(2-nitroethyl)-1,3-dioxolane (**4**), nitroethane, and 2-nitropropane were prepared according to the Kornblum procedure.[7]

The lithium salt (0.5 g) was dissolved in Me_2SO (15 mL) under an inert atmosphere, and the resulting solution was coooled to incipient crystallization of the solvent. Acylimidazole (1 equiv) in Me_2SO (5 mL) was then added, and the resulting solution was stirred for 36 h at room temperature, after which it was poured into an ice slurry containing glacial actic acid (1 equiv). The aqueous mixture was extracted with ethyl acetate or dichloromethane (4 × 100 mL); the organic extracts were washed with water (3 × 50 mL) and brine (100 mL) and dried ($MgSO_4$), and the solvent was removed. The crude products were purified by distillation, crystallization, or chromotography, as outlined in the individual cases in Table II.

Methyl 4-(1,3-Dioxolan-2-yl)-3-nitro-2-oxobutanoate (13). Sodium hydride (2.7 g, 60% in oil) was freed from oil by washing with cyclohexane and added to THF (60 mL) containing 2-(2-

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nitroethyl)-1,3-dioxolane (4, 10 g). 1-(Methoxyoxalyl) imidazole[11] (10.3 g) in THF (40 mL) was added dropwise with stirring. After 1 h at 20 °C, the mixture was cautiously heated to reflux. After 18 h at reflux the cooled mixture was filtered and the precipitate of sodium salt washed (CH_2Cl_2) and dried in vacuum to give a tan powder (6 g, 39% crude yield),which turned dark on standing for several days. A 2.0-g sample was dissolved in ice water (10 mL) and 1 M HCl (7.8 mL) added. The solution was extracted with ethyl acetate, the extracts were washed (water and brine) and dried ($MgSO_4$), and the solvent was removed to give **13** (1.3 g, 24%) as a pale-yellow liquid: NMR ($CDCl_3$) δ 2.80 (dd, 2 H, J_1 = 3 Hz, J_2 = 7 Hz), 3.80 (, 4 H), 3.90 (s, 3 H), 5.00 (t, 1 H, J = 3 Hz), 5.80 (t, 1 H, J = 7 Hz). Anal. Calcd for $C_8H_{11}NO_7$: C, 41.2; H, 4.8; N, 6.0. Found: C, 40.9; H, 5.1; N, 5.8. The ethyl and *tert*-butyl ester analogues were prepared similarly but were not obtained analytically pure. The ethyl ester partially decomposes on distillation and the *tert*-butyl ester sodium salt was soluble and thus it could not be separated from unreacted starting material.

Other Reactions of 2-(2-Nitroethyl)-1,3-dioxolane (4). a. Reacton of 4 with *p*-Nitrobenzyl Chloride. When *p*-nitrobenzyl chloride was added to the lithium salt of 4 according to the general procedure, the solution assumed an intense red color. After 3 h at 20 °C, TLC analysis indicated that the *p*-nitrobenzyl chloride had been consumed. Isolation of the resulting oil by the general procedure, followed by separation (Analtech 1-mm silica plates, 20% EtOAc–80% C_6H_6) gave five purified products listed as follows in the order of their increasing polarities.

i. 1-(1,3-Dioxolan-2-yl)-2-nitro-3-(*p*-nitrophenyl)propane (14) was obtained as pale-yellow plates from methanol (0.63 g, 68%): mp 108 °C; NMR ($CDCl_3$) δ 2.11, 2.62 (ddq, 2 H, J_{AB} = 15 Hz, J = 3.5,4, 9, 5 Hz), 3.22, 3.35 (dq, 2 H, J_{AB} = 14.5 Hz, J = 8.5, 6.0 Hz), 3.70–4.15 (m, 4 H), 4.5–5.2 (m, 2 H), 7.35, 8.18 (AA′BB′ q, J_{AB} = 8.8 Hz, $J_{AA'}$ = 2 Hz); IR (Nujol) 1550, 1515, 1350 cm^{-1}; mass spectrum, m/e 281 (M^+ – 1). Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.1; H, 5.0; N, 9.9. Found: C, 51.2; H, 4.9; N, 9.7.

ii. 1-(1,3-Dioxolan-2-yl)-3-(*p*-nitrophenyl)-2-propanone (15) was obtained as white needles from methanol (90 mg, 11%): mp 78 °C; NMR ($CDCl_3$) δ 2.86 (d, 2 H, J = 4.9 Hz), 3.92 (s, 2 H), 3.75–4.10 (m, 4 H), 5.22 (t, 1 H), 7.37, 8.19 (AA′BB′ q, 4 H, J = 8.8 Hz); IR (Nujol) 1705, 1507 cm^{-1}; mass spectrum, m/e 251 (M^+). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.4; H, 5.2; N, 5.6. Found: C, 57.2; H, 5.2; N, 5.5.

iii. *syn*-1-(1,3-Dioxolan-2-yl)-3-(*p*-nitrophenyl)-2-propanone oxime (*syn*-**16**) was obtained as yellow needles from petroleum ether (43 mg, 5%): mp 110–112 °C; NMR ($CDCl_3$) δ 2.68 (d, 2 H, J = 4.9 Hz), 3.72 (s, 2 H), 3.75–4.00 (m, 4 H), 5.13 (t, 1 H), 7.40, 8.17 (AA′BB′ q, 4 H, J_{AB} = 8.7 Hz, $J_{AA'}$ = 2.2 Hz), 8.5–7.75 (br s, OH); IR (Nujol) 3350, 1605, 1510, 1355 cm^{-1}; mass spectrum, m/e 265 (M^+). This syn configuration is assigned on the basis of analyses of these NMR data.[25]

iv. *anti*-1-(1,3-Dioxolan-2-yl)-3-(*p*-nitrophenyl)-2-propanone oxime (*anti*-**16**) was obtained as yellow needles from petroleum ehter (42 mg, 5%): mp 101–103 °C; NMR ($CDCl_3$) δ 2.52 (d, 2 H, J = 4.7 Hz), 3.93 (s, 2 H), 3.82–5.09 (m, 4 H), 5.05 (t, 1 H), 7.43, 8.16 (AA′BB′ q, 4 H, J_{AB} = 8.7, $J_{AA'}$ = 2.1 Hz), 8.00–8.75 (br s, 1 H); IR (Nujol) 3350, 1605, 1510 cm^{-1}; mass spectrum, m/e 265 (M^+). The anti configuraton is assigned on the basis of analysis of the NMR data.[25]

v. 3-(*p*-Nitrobenzyl)-5-(2-hydroxyethoxy)isoxazole (17) was obtained as yellow needles from ether (43 mg, 5%): mp 127–128 °C; NMR ($CDCl_3$) δ 2.03 (br t, 1 H), 3.93–4.00 (m, 4 H), 4.22–4.31 (m, 2 H), 5.03 (s, 1 H), 7.43, 8.18 (AA′BB′ q, 4 H, J_{AB} = 8.7, $J_{AA'}$ = 1.9 Hz); IR (Nujol) 3400, 1605, 1525, 1350 cm^{-1}; mass spectrum, m/e 264 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.6; H, 4.6; N, 10.6. Found: C, 54.5; H, 4.7; N, 10.4.

b. With 2,2-Dinitropropane (19). The lithium salt of 4 (1 g) was dissolved in Me_2SO under an inert atmosphere and then cooled to incipient crystallization. 2,2-Dinitropropane (0.44 g) in Me_2SO (2 mL) was then added and the solution was stirred for 16 h at 30–38 °C. The reaction could not be followed successfully by chromatography. The solution was then diluted with ice water (300 mL) and extracted with ethyl acetate (4 × 200 mL). The extracts were washed with water (2 × 50 mL) and brine (100 mL) dried ($MgSO_4$), and the solvent was removed. The crude product was purified by chromatography (60% ether/heptane to give two major products: (i) *meso*-4,4-dimethyl-3,5-dinitroheptanedial diethylene acetal (**21**). The compound was further purified by TLC (75% benzene/25% ethyl acetate and then recrystallized from methanol to give white needles (0.24 g, 21%): mp 97–98 °C; NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.16 (s, 3 H), 2.00–2.35 (ddq, 4 H, J_{AB} = 15 Hz), 3.82–3.99 (m, 8 H), 4.61 (dd, 2 H, J = 1.5, 10.8 Hz), 4.97 (dt, 2 H, J_1 = J_2 = 3.7 Hz); mass spectrum, m/e 333 (M^+ – 1). Anal. Calcd for $C_{13}H_{22}N_2O_8$: C, 46.7; H, 6.6; N, 8.4. Found: C, 46.6; H, 6.6; N, 8.4.

ii. An unidentifiable oil (**22**) was repurified by TLC (benzene); analysis of its NMR showed that it was structurally related to **21**, but differed by loss of the elements of HNO_2 (38% yield based on its empirical formula): NMR ($CDCl_3$) δ 1.09 (s, 3 H), 1.19 (s, 3 H), 1.76, 2.09 (ddq, 2 H, J_{AB} = 14.2 Hz), 2.59 (d, 2 H, J = 5 Hz), 3.75–4.07 (m, 8 H), 4.38 (dd, 1 H, J = 3.0, 9.9 Hz), 4.99 (dd, 1 H, J = 2.9, 6.9 Hz), 5.20 (t, 1 H, J = 5.0 Hz); IR (liquid film) 3500, 1625, 1125, 1010 cm^{-1}; mass spectrum, m/e 287 (M^+). Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.4; H, 7.3; N, 4.9. Found: C, 54.2; H, 7.3; N, 4.8.

c. Nitration To Yield 1-(2,2-Dinitroethyl)-1,3-dioxolane (19). An emulsion formed from the nitro acetal 4 (0.5 g), sodium nitrite (0.07 g), and NaOH (0.15 g) in water (20 mL) was poured into a stirred mixture of silver nitrate (1.2 g in 10 mL of water) and ether (20 mL) at 0 °C. A black solid formed immediately but there was no noticeable rise in temperature. The mixture was stirred at 0 °C for 1 h and then at room temperature for a further 2 h. The precipitate was removed by filtration and washed with ether, the ether layer dried ($MgSO_4$), and the solvent removed to give a yellow oil, which was purified by distillation to give the product (**19**) as a colorless liquid (302 mg, 46%): bp 40 °C (0.01 mm); NMR ($CDCl_3$) δ 3.05 (dd, 2 H), 3.86–4.03 (m, 4 H), 5.11 (t, 1 H, J = 3.0 Hz), 6.39 (t, 1 H, J = 6.5 Hz); mass spectrum, m/e 191 (M^+ – 1). Anal. Calcd for $C_5H_8N_2O_6$: C, 31.3; H, 4.2; N, 14.6. Found: C, 31.3; H, 4.2; N, 14.4.

d. Chlorination of 4. The reaction was maintained at 4–5 °C. Nitro acetal 4 (2.0 g) was added with vigorous stirring to commercial bleach (27 mL, 5.25% NaOCl). Sodium hydroxide (0.28 g in 5 mL) was added dropwise and the stirring continued for 2 h. The mixture was extracted with ether (3 × 150 mL), and the extracts were washed with water (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated to give a yellow oil, which was purified by distillation to give crude 2-(2-chloro-2-nitroethyl)-2-chloro-1,3-dioxolane (2.4 g, 82%): bp 130 °C (0.5 torr) as a colorless liquid; NMR ($CDCl_3$) δ 3.10 (d,2 H, J = 5 H); 3.8–4.0 (m, 4 H), 5.24 (t, 1 H). This material gave the expected parent ion peaks (M^+ 215, 219) but was impure, as shown by microanalysis, which was low in chlorine, and by peaks in the NMR that indicated an olefin impurity. Further distillation and a treatment with aqueous alkali gave increased amounts of the olefin impurity.

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Registry No. 3, 18742-02-4; **4**, 82891-99-4; 4·Li, 82902-22-5; **5**, 5754-35-8; **6a**, 75-36-5; **6b**, 98-88-4; **6c**, 586-75-4; **6d**, 122-04-3; **6e**, 79-22-1; **6f**, 541-41-3; **7**, 288-32-4; **8a**, 2466-76-4; **8b**, 10364-94-0; **8c**, 82892-00-0; **8d**, 10364-96-2; **8e**, 61985-23-7; **8f**, 19213-72-0; **9a**, 82892-01-1; **9b**, 82892-02-2; **9c**, 82892-03-3; **9d**, 82892-04-4; **9e**, 82892-05-5; **10b**, 14897-67-7; **10d**, 74261-46-4; **10e**, 6118-50-9; **10f**,

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Development of a Strategy for Convergent Total Synthesis of the Aureolic Acid Antitumor Antibiotics[1,2]

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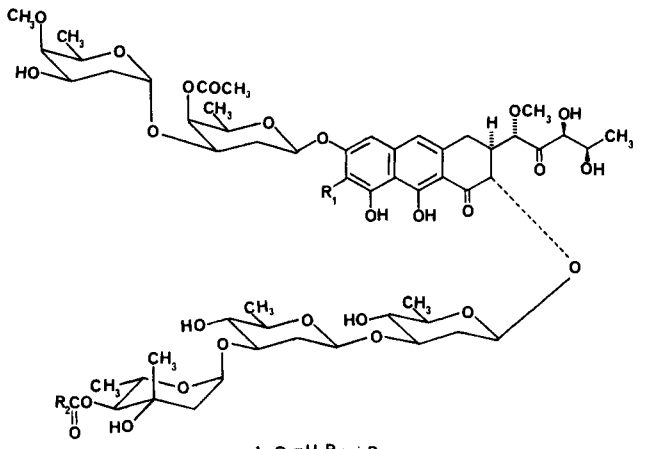
It has been found that condensation of an *o*-toluate carbanion with a 3-alkoxycyclohexen-2-one will produce the dihydroanthracenone system found in olivin (**3**) and chromomycinone (**4**), the aglycons of the aureolic acids. Several examples of this reaction are described, leading to synthesis of model aromatic systems **17**, **18**, **21**, **23**, **24**, and **26**. A route to compound **34**, having the complete carbon framework and most of the functionality of olivin, has been developed which uses the above type of condensation as the critical step.

The aureolic acids are a class of structurally related compounds produced by several varieties of *Streptomyces* and *Actinomyces*.[3,4] A few of these metabolites such as olivomycin A (**1**) and chromomycin A_3 (**2**), are clinically

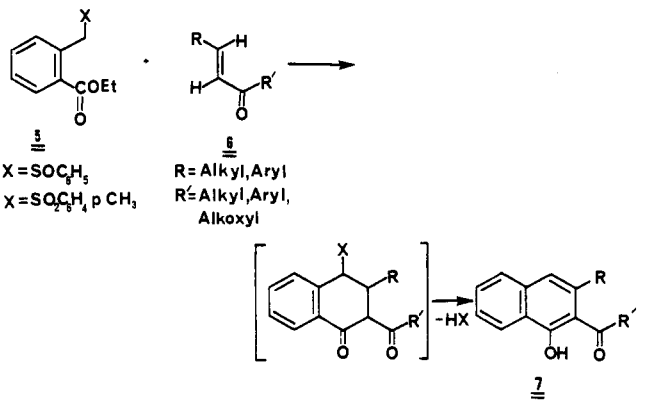


1 R_1=H, R_2= *i*-Pr
2 R_1=CH_3, R_2=CH_3

effective antitumor agents. Aureolic acid itself (also known as mithramycin) has been approved in the United States for treatment of testicular cancers.[5] However, these compounds have not found wide applicability in chemotherapy due to their high toxicities, although an attempt has been made recently to produce semisynthetic analogues of **1** having more favorable therapeutic properties.[4b]

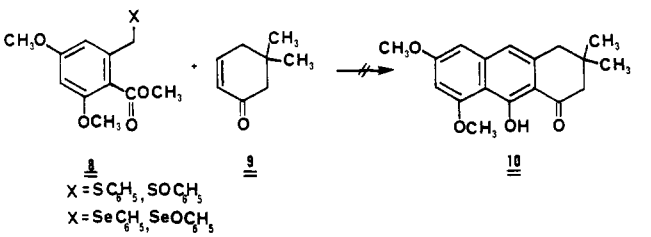
From a structural standpoint, the aureolic acids are all comprised of a complex tricyclic aglycon attached to disaccharide and trisaccharide moieties. The compounds in the olivomycin subgroup of aureolic acids all contain olivin (**3**)[6] as the aglycon. Metabolites designated as chromomycins have chromomycinone (**4**)[7] as the aglycon unit. Mithramycin also contains chromomycinone but is distinct

Scheme I

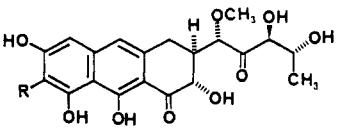


5 X=SOC_6H_5, X=$SO_2C_6H_4$ p CH_3
6 R=Alkyl,Aryl; R'=Alkyl,Aryl, Alkoxyl
7

Scheme II



8 X=SC_6H_5, SOC_6H_5; X=SeC_6H_5, $SeOC_6H_5$
9
10



3 R=H
4 R=CH_3

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