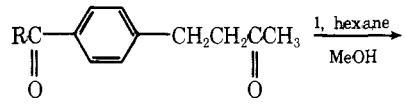
results to an intramolecular situation is demonstrated in eq 5.



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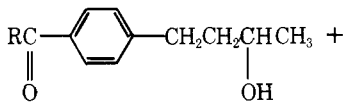

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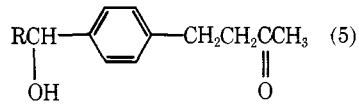

(5)

5

Isolated Yield of Ketol 4:5

3a,	R = Ph	77%	~100:0
b,	R = *i*-Pr	69%	>99:<1
c,	R = *n*-Pr	59%	97:3
d,	R = Et	57%	90:10
e,	R = Me	60%	83:17

A representative example is the regioselective reduction of 4-(*p*-benzoylphenyl)-2-butanone (**3a**). A mixture of the diketone (10 mmol, 2.53 g), MeOH (11 mmol, 0.36 g), and **1** (20 mmol) in 20 ml of hexane was stirred at room temperature for 2.5 h. Water was added, and the reaction mixture was oxidized with air and extracted with ether. The extract was dried over anhydrous K_2CO_3 and concentrated. Kügelrohr distillation gave 4-(*p*-benzoylphenyl)-2-butanol, 1.96 g, 77%; 2,4-dinitrophenylhydrazone, mp 148–151 °C (lit. 155–157 °C).[12]

It is often required to reduce specific functional groups in a stereo-, chemo-, or regioselective manner. Successful approaches to such reductions have hitherto involved modification of the borohydride or aluminohydride anion by the replacement of hydrogen with sterically bulky substituents or electron-withdrawing groups.[2,5] The present development, therefore, provides an entirely new approach to this problem.

References and Notes

(1) In this manuscript the commonly used term, "selective reduction",[2] is for convenience divided into three categories: stereo-, chemo-, and regioselective reductions. The terms chemo-[3] and regioselectivities[4] seem to be used for describing the differentiation of targets in a given structural unit, namely, intramolecular discrimination. However, here, these terms are also used for such intermolecular discrimination as in eq 2 and 3.

(2) For reviews of selective reduction, see (a) R. L. Augustine, "Reduction", Marcel Dekker, New York, N.Y., 1968; (b) H. O. House, "Modern Synthetic Reactions", 2nd ed, W.A. Benjamin, New York, N.Y., 1972; (c) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972.

(3) B. M. Trost and T. N. Satzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973).

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(5) For the well-known selective reducing agents, see ref 2. Recently developed agents for selective reduction of carbonyl groups are as follows: Brown's reagents, (a) H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970); (b) H. C. Brown and S. Krishnamurthy, *ibid.*, **94**, 7159 (1972); (c) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **40**, 1864 (1975); Corey's reagent, (d) E. J. Corey and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 7319 (1971); Lalancette's reagent, (e) J. M. Lalancette, A. Freche, J. R. Brindle, and M. Laliberte, *Synthesis*, 562 (1972); Hutchins' reagent, (f) R. O. Hutchins and D. Kandasamy, *J. Am. Chem. Soc.*, **95**, 6131 (1973); Hooz's reagent, (g) J. Hooz, S. Akiyama, F. J. Ceder, M. J. Bennett, and R. M. Tuggle, *ibid.*, **96**, 274 (1974); copper "ate" complexes, (h) R. K. Boeckman, Jr., and R. Michalak, *ibid.*, **96**, 1623 (1974); (i) S. Masamune, G. S. Bates, and P. E. Georghiou, *ibid.*, **96**, 3686 (1974); $NaBH_3CN$, (j) C. F. Lane, *Synthesis*, 135 (1975).

(6) Y. Yamamoto, H. Toi, S.-I. Murahashi, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 2558 (1975).

(7) If equimolar amounts of reagent were employed (ketone:**1**:MeOH = 1:1:1), both the conversion and selectivity achieved were somewhat low.

(8) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).

(9) It is anticipated that the decomposition of **2** into lithium alkoxide and trialkylborane is relatively sluggish in the absence of MeOH, permitting the hydride transfer. However, there is also the possibility that methanol is protonating reactive intermediates. For such alkoxyalkyl "ate" complexes, see G. W. Kramer and H. C. Brown, *J. Organomet. Chem.*, **73**, 1 (1974). When the reduction was complete, oxidation of the reaction mixture produced RR'CHOH, *n*-BuOH, and bicyclo[3.3.0]octan-1-ol along with small amounts of cyclooctanone.

(10) Even highly hindered borohydrides, such as lithium perhydro-9b-borophenalylhydride[5a] and Li(*sec*-Bu)$_3$BH,[5b] reduce 2-methylcyclohexanone quantitatively in 1 h at 0°.

(11) Cyclohexanone was preferentially reduced in the presence of benzyl chloride.[6] With some ketones or aldehydes, the corresponding aldol condensation products were also formed. Here also, the selectivity is low in the absence of methanol. The reaction with 1,3-dicarbonyl compounds resulted in the formation of complex mixtures.

(12) P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.*, **85**, 2236 (1963).

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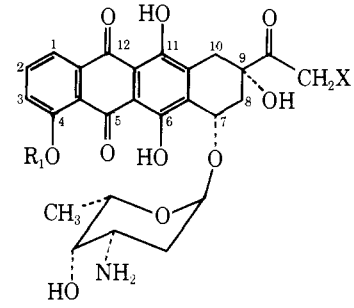
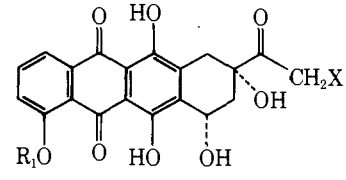
Total Synthesis of (±)-Daunomycinone and (±)-Carminomycinone

Sir:

The anthracycline antibiotics daunorubicin[1] (**1**), adriamycin[2] (**2**), and carminomycin[3] (cf. carminomycin-I, **3**)[4] are effective antineoplastic agents against a variety of experimental tumors and in certain types of human cancer. Chemotherapy employing anthracyclines **1** and **2** is known to be hampered by dose-related cardiotoxic effects,[5] so that there is great current interest in natural or synthetic sources of related compounds having improved therapeutic indices.



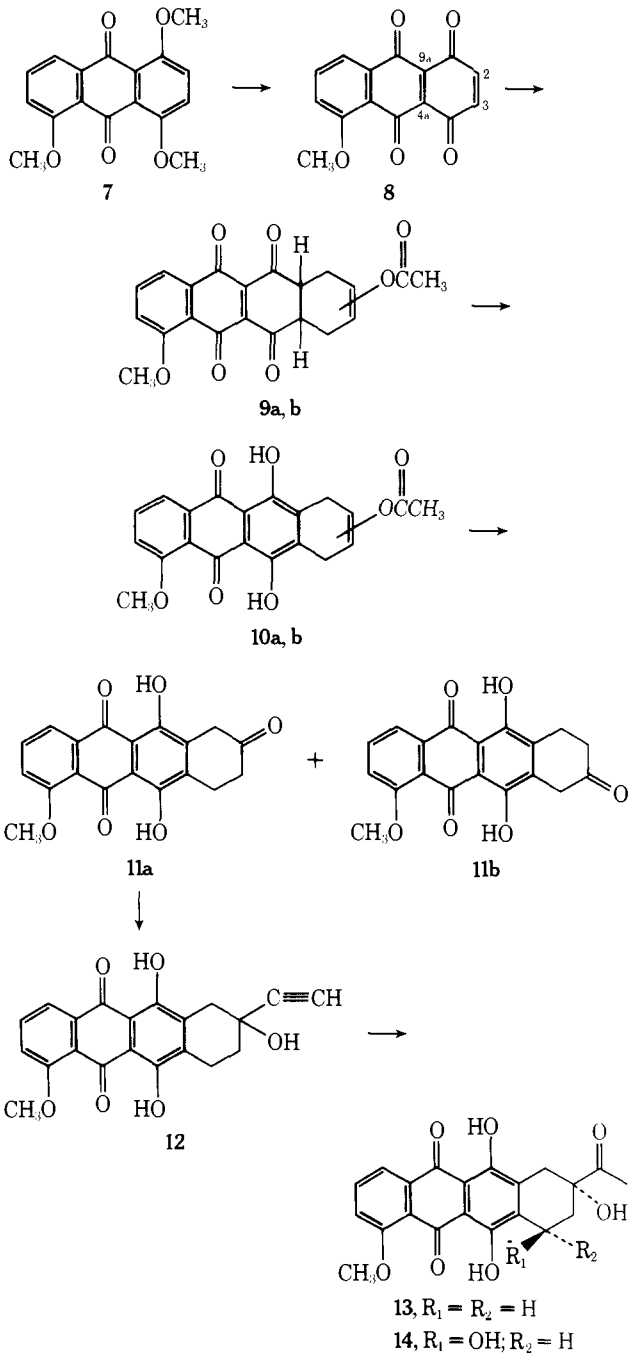
1, $R_1 = CH_3$; X = H
2, $R_1 = CH_3$; X = OH
3, R_1 = H; X = H



4, $R_1 = CH_3$; X = H
5, $R_1 = CH_3$; X = OH
6, R_1 = H; X = H

Wong has reported a synthesis of (±)-daunomycinone (**4**) by a 22-step procedure starting from 2,5-dimethoxybenzaldehyde.[6] Two syntheses of natural L-daunosamine have been described,[7] and the coupling of a protected L-daunosamine with daunomycinone to give natural daunorubicin has been achieved in good yield.[8] To date, however, no practical route for the large scale preparation of the agly-

Scheme I



cones of these antibiotics appears to be available. We now report a general method for the efficient total synthesis of the compounds (±)-daunomycinone (**4**) and (±)-carminomycinone (**6**). Since conversions of daunomycinone (**4**) to adriamycinone (**5**) and of daunorubicin (**1**) to adriamycin (**2**) have been described,[9] this new route appears to offer practical access to all three of the above aglycones and their fully active L-daunosamine glycosides.

Our synthesis (Scheme I) proceeds from the highly reactive key intermediate 5-methoxy-1,4,9,10-anthradiquinone (**8**),[10] mp 252–253 °C (ir (KBr) 1683, 1653 cm^{-1}; NMR ($CDCl_3$) δ 7.85–7.25 (m, 3 H), 6.88 (s, 2 H), 3.99 (s, 3 H)), itself available in 98% yield by silver(II) oxide demethylation[11] (4 equiv of AgO, 50°, acetone, dilute HNO_3, 10 min) of the readily accessible 1,4,5-trimethoxyanthraquinone (**7**).[12] Like the desmethoxy counterpart studied by Inhoffen,[13] diquinone **8** is a bifunctional dienophile which can undergo initial Diels–Alder addition at the internal (4a, 9a) or terminal (2, 3) double bond. Both analogy[13,14] and Hückel perturbation MO calculations[15] suggest that internal addition will be favored by electron-rich dienes, terminal addition more probable for slightly electron-poor or unsubstituted dienes. Thus 2-ethoxybutadiene selectively adds to the internal double bond of **8**, whereas 1,3-butadiene itself and, more interestingly, 2-acetoxybutadiene add predominantly to the terminal double bond.

Diels–Alder addition of 2-acetoxybutadiene to diquinone **8** (3 equiv of diene, AcOH, 25°, 4 days) yields 71% of a precipitate, mp 165–169 °C, (δ 5.4, m, 1 H) consisting of the adducts **9a** and **9b** in 1:1 regioisomeric ratio. Anhydrous sodium acetate in acetic acid (reflux, 2 min) quantitatively converts these adducts to the corresponding red anthraquinone tautomers **10a** and **10b,** mp 222–226 °C. Cleavage of the enol acetate function was achieved in 85% yield (EtOH, 6 N HCl, reflux, 6 h) to produce the mixture of ketones **11a** and **11b** as a dark red solid: mp 230–234 °C dec; ir 1720, 1618 cm^{-1}. Alternatively these ketones could be formed directly from adducts **9** in comparable yield in refluxing ethanol containing a few percent 6 N HCl. Trituration of the ketones **11a** and **11b** with hot ethanol, or recrystallization from pyridine, led to a single ketone, mp 248–250 °C dec, identified as the isomer **11a** by TLC and NMR comparison (δ 13.81, 13.30 (s, 1 H ea, ArOH), 4.10 (s, 3 H, OCH_3), 3.63 (s, 2 H), 3.27 (t, 2 H), 2.66 (t, 2 H)) with a sample prepared by side-chain degradation of 7-deoxy-13-daunomycinol derived from natural daunorubicin.[16]

Reaction of ketone **11a** in dry tetrahydrofuran with a tenfold excess of ethynylmagnesium bromide (room temperature, 16 h) followed by workup with saturated ammonium chloride solution gave 52% of the ethynylcarbinol **12,** (nmr δ 13.88 (s, 1 H), 13.48 (s, 1 H), 8.0–7.2 (m, 3 H), 4.08 (s, 3 H), 3.2–2.9 (m, 4 H), 2.52 (s, 1 H), 2.0–2.2 (m, 2 H)) which was transformed with yellow mercuric oxide in dilute sulfuric acid (3 M, 70°, 4 h) to (±)-7-deoxydaunomycinone (**13**) in 40% yield. The solution ir, uv, NMR, MS, and chromatographic properties of this material were identical with those of an authentic sample of 7-deoxydaunomycinone from hydrogenolysis (5% Pd–C, EtOH) of (+)-daunomycinone (**4**).

Racemic 7-deoxydaunomycinone (**13**) was dissolved in a large volume of carbon tetrachloride, N_2 bubbled through the liquid, and a three- to fivefold excess of bromine (0.1 M in CCl_4) very slowly added while irradiating the reaction with a sunlamp. Under these conditions enol bromination at C-14 is suppressed and the product is that of free radical bromination at C-7. Hydrolysis of this very labile bromine was achieved by chromatography on moist silica gel plates to give a ca. 5:2:1 mixture of (±)-7-epidaunomycinone (**14**) (NMR 14.35 and 13.27 (s, 1 H ea), 8.06–7.33 (m, 3 H), 5.35 (m, 1 H, $\nu_{1/2}$ = 17 Hz), 4.08 (s, 3 H), 3.00 (m, 2 H), 2.40 (s, 3 H); R_f = 0.08),[17] (±)-daunomycinone (R_f = 0.14),[17] and recovered 7-deoxy compound. The 7-epidaunomycinone fraction was epimerized by dissolving in trifluoroacetic acid (25°, 2 h), aqueous workup, and silica gel chromatography as above to give (±)-daunomycinone (**4**) in 76% yield. Our synthetic (±)-**4** (ca. 50% yield from **13**) was identical in all relevant respects (ms, NMR, TLC) with (+)-**4** from hydrolysis of natural daunorubicin (**1**).

(+)-Carminomycinone (**6**) can be obtained in nearly quantitative yield by O-demethylation of a dilute solution of (+)-**4** in benzene with excess anhydrous aluminum chloride (room temperature, 16 h); synthetic (±)-**4** similarly gives (±)-carminomycinone[18] (R_f = 0.16).[17] Our samples of **6** were identical by uv, MS, TLC, and HPLC with an authentic sample from natural carminomycin. The above seven-step sequence makes available ca. 3 g of (±)-daunomycinone (**4**) from 100 g of diquinone **8**; (±)-carminomycinone

(6) is accessible in similar yield. The utility of our synthesis for the preparation of known as well as novel anthracycline antitumor agents is under investigation.

Acknowledgment. We are grateful to Drs. D. Henry and T. Smith (Stanford Research Institute) for valuable discussions and reference samples, to Dr. H. B. Wood, Jr. (National Cancer Institute), for 3-methoxyphthalic anhydride, to Dr. M. Wall (Research Triangle Institute) for a reference sample of carminomycinone, and Dr. J. Airey and Mr. E. Hume (Rochester) for preparation of intermediates. Partial support of this work is by Grant CA-11326 from the National Cancer Institute (U.S. Public Health Service), by a faculty grant from the Hoffmann-La Roche Co., and by the University of Rochester.

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(8) E. M. Acton, A. N. Fujiwara, and D. W. Henry, *J. Med. Chem.*, **17**, 659 (1974).
(9) F. Arcamone, W. Barbieri, G. Franceschi, and S. Penco, *Chim. Ind. (Milan)*, **51**, 834 (1969); F. Arcamone, G. Franceschi and S. Penco, U.S. Patent 3 803 124, April 9, 1974.
(10) All new compounds gave combustion analyses and/or mass spectra and NMR spectra consistent with the reported structures. Unless otherwise specified, ir and NMR (δ) were in $CDCl_3$ solution, and melting points were uncorrected.
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(12) L. A. Wiles and L. C. Thomas, *J. Chem. Soc.*, 4811 (1956). A convenient alternative synthesis of **7** from 3-methoxyphthalic anhydride and *p*-dimethoxybenzene ($AlCl_3$ in $C_6H_5NO_2$, then H_2SO_4) proceeds in satisfactory yield.
(13) H. H. Inhoffen, H. Muxfeldt, V. Koppe, and J. Heimann-Trosien, *Chem. Ber.*, **90**, 1448 (1957).
(14) Cf. J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).
(15) Cf. R. Sustmann, *Tetrahedron Lett.*, 2717 (1971). We thank Mr. D. Curran for performing these calculations.
(16) See T. Smith, A. Fujiwara, W. Lee, and D. Henry, *J. Am. Chem. Soc.*, following paper in this issue.
(17) R_f values were measured on plates (Analtech) coated with silica gel GF (250 μm) and eluted with 3% (v/v) methanol in methylene chloride; daunomycinone had reference $R_f \approx 0.14$.
(18) A 100-MHz Fourier transform proton NMR spectrum ($CDCl_3$, δ) showed signals at 13.47, 12.96, 12.17 (s, 1 H ea), 7.94–7.25 (m, 3 H), 5.31 (br s, 1 H, $\nu_{1/2} = 8$ Hz), 3.05 (q, 2 H), 2.43 (s, 3 H), 2.27 (m, 2 H).

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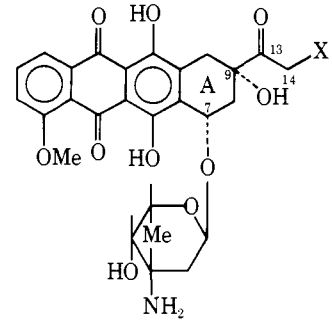
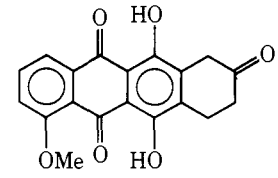
Synthetic Approaches to Adriamycin. Degradation of Daunorubicin to Nonasymmetric Tetracyclic Ketone and Refunctionalization of the A-Ring to Adriamycin

Sir:

The anthracycline antibiotics daunorubicin (**1**) and adriamycin (**2**) are clinically useful antineoplastic agents with adriamycin having an especially broad spectrum of activity.[1] Due to their potent biological activity there is considerable interest in their synthesis.[2] As part of our efforts in developing a practical total synthesis of these agents, we report the preparation of the tetracyclic ketone **3**, a key intermediate in our proposed total synthesis, via a three-step



1, X = H
2, X = OH



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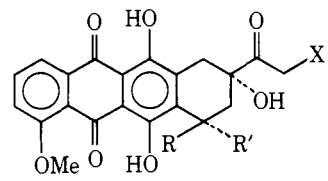
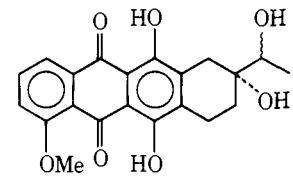
degradation of **1** and its elaboration to adriamycin (**2**) and the new aglycone 7-epidaunomycinone (**4**).





4, X = R′ = H; R = OH
5, X = R′ = R = H
14, X = R = H; R′ = OH
15, X = R′ = OH; R = H
16, X = $OC(C_6H_5)_2$-*p*-$OMeC_6H_4$; R′ = OH; R = H

6

Reductive cleavage (2 equiv of $Na_2S_2O_4$, $NaHCO_3$, aqueous THF/MeOH, 23°, 15 min) of **1** afforded the previously reported[3] 7-deoxydaunomycinone (**5**) in quantitative yield. The 9-acetyl group was reduced (4 equiv of $LiAlH(Ot\text{-}Bu)_3$), THF, 23°, 44 h, 80%) to afford the diol **6**.[4] Oxidative cleavage of **6** (2.1 equiv of $NaIO_4$, THF/aqueous MeOH, 16 h, 23°) produced the ketone **3** (ir_{Nujol} 5.82 (C=O), 6.15, 6.35 (chelated quinone) μ; ^1H NMR 100-MHz $CDCl_3$ δ 2.64 (t, 2 H, 8-H_2), 3.25 (t, 2 H, 7-H_2), 3.63 (s, 2 H, 10-H_2), 4.09 (s, 3 H, $-OCH_3$), 7.38 (dd, 1 H, J = 8 and J = 1 Hz, 3-H), 7.77 (t, 1 H, J = 8 Hz, 2-H), 8.04 (dd, 1 H, J = 8 and J = 1 Hz, 1-H), 13.30 (s, 1 H, phenolic OH), 13.80 (s, 1 H, phenolic OH); MS 12 eV, *m/e* 338 M^+) in 99% yield with 71% conversion of **6.** The product and unreacted starting material could be readily separated and recovered by silica gel chromatography.

Several synthetic methods for the elaboration of the dihydroxy acetone side chain were investigated during model studies on 5,8-dimethoxy-2-tetralone.[5] The most efficient method in our hands was the addition of methylmagnesium iodide to a protected cyanohydrin followed by acid workup.[6]

Cyanohydrin **7** was prepared in 77% yield by addition of HCN (KCN, HOAc, EtOH/$CHCl_3$, 0–23°, 5 h) to **3.** The tetrahydropyranyl ether **8** (dihydropyran, concentrated HCl (catalyst), THF, reflux, 5 h, 90%) was treated with methylmagnesium iodide (30 equiv, THF, 55°, 14 h) followed by acid hydrolysis (60% HOAc, 90°, 1 h) to afford (±)-7-deoxydaunomycinone (**9**), having spectral (ir, ^1H NMR, MS) properties identical with the degradation product **5** in 45% yield.

Functionalization of the 7-position was achieved by a modification of the procedure developed by Goodman et al.[7] Benzylic bromination of **5** afforded, besides the bromide