

min and was then acidified with 10% aqueous tartaric acid. Isolation of the crude product with ethyl acetate afforded 9 mg of 13-carboxyspiniferin-1 (**60**) as an oil, whose IR and NMR spectra were identical with those recorded above. This unstable compound was used immediately.

The method of Cohen and Schambach²⁸ was employed for the decarboxylation of the furoic acid **60**. A stirred mixture of 8 mg of **60**, 40 mg of 1,10-phenanthroline, and 30 mg of copper(I) oxide in 0.25 mL of distilled quinoline under an argon atmosphere was placed in a preheated (170–180 °C) oil bath. After the mixture was stirred for 5 min, the mixture was cooled and the product was isolated directly by chromatography on silica gel (10% ethyl acetate–hexane) to afford 5 mg of

spiniferin-1 (**1a**), whose IR and NMR spectra were identical with those recorded above.

Acknowledgment. Support from the National Science Foundation (CHE 8020205) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. R.C. is indebted to the National Science Foundation for a predoctoral fellowship. We thank Professor S. D. Burke for his participation in some fruitful and stimulating chalkfest sessions.

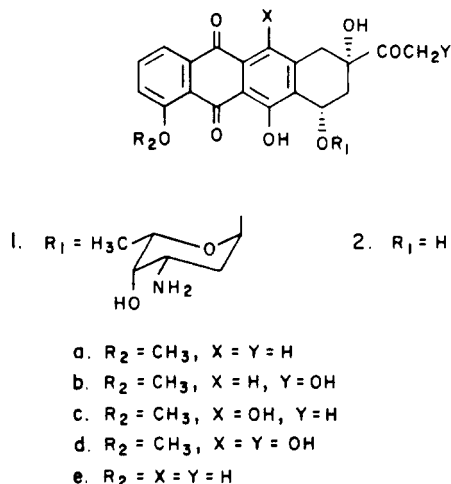
Total Synthesis of 11-Deoxydaunomycinone

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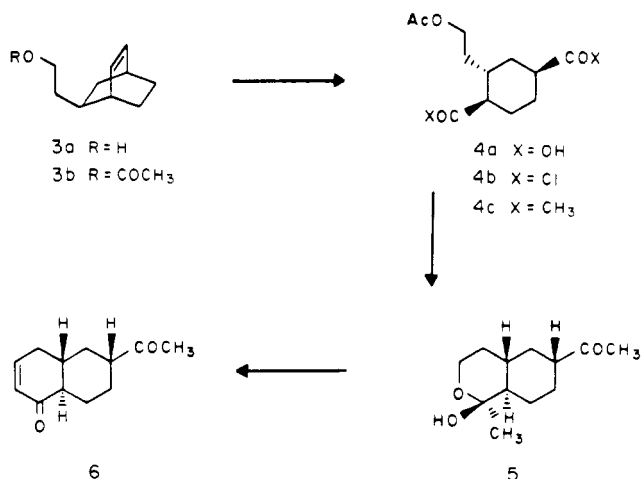
Abstract: An efficient regiospecific synthesis of 11-deoxydaunomycinone (**2a**) is described. Key elements of the synthesis were the use of bicyclooctenol **3a** as a precursor to the acetyl-substituted naphthalenone **6** which served as a synthon for the A and B rings of **2a**. Condensation of **6** with the anion of the methoxy(phenylsulfonyl)isobenzofuranone **7** regiospecifically furnished the tetracyclic product **8**, which was transformed to the tetrahydronaphthacenone **9** in a single step. The eight-step preparation of **9** was achieved in 20% overall yield.

The aklavin type anthracyclines 11-deoxydaunorubicin (**1a**) and 11-deoxyadriamycin (**1b**) possess significant anticancer activity



and are less cardiotoxic² than the clinically important rhodomycins,³ daunorubicin (**1c**) and adriamycin (**1d**). The potential advantages associated with these compounds have prompted interest in their preparations, and several total syntheses of the aglycone fragment **2a**^{4,5} of 11-deoxydaunorubicin (**1a**) and one

Scheme I



of 11-deoxycarminomycinone (**2e**)⁶ have been published.

We report here an efficient and preparatively useful route to the acetyl-substituted naphthalenone **9**, an established⁴ late-stage intermediate to 11-deoxydaunomycinone (**2a**). This reaction sequence has enabled us to perform laboratory preparation of multigram quantities of **9**, with absolute control over the regiochemical integrity, in 20% overall yield from the bicyclooctene **3a**. In addition, only one intermediate required chromatographic purification; the others were purified by either distillation or recrystallization.

Previously, we demonstrated that the A and B rings of 11-deoxyanthracyclines could be introduced as a large single fragment through use of 1(4H)-naphthalenones.⁷ However, the absence of methods for preparing appropriately substituted naphthalenones seriously limited the scope of this strategy. We have now developed a synthesis of the acetyl-substituted naphthalenone **6** that is efficient and permits the practical preparation of the tetracyclic product **9**.

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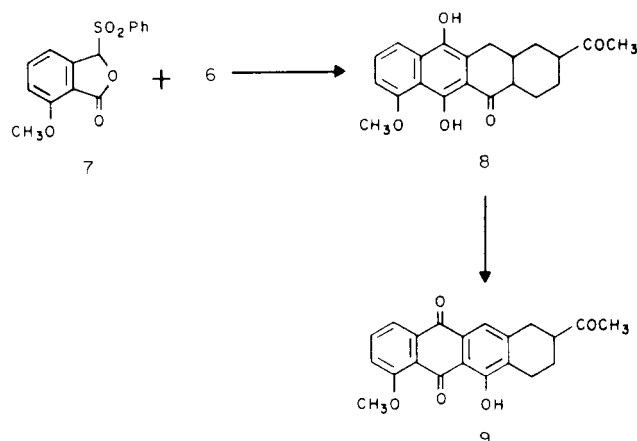
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Scheme II



Antithetic evaluation of **6** led to the novel use, as shown in Scheme I, of the bicyclic alcohol **3a**⁸ as the starting material. The acetate derivative **3b** was oxidized (RuO_4 , NaIO_4 , acetone) to give the dicarboxylic acid **4a** as a viscous syrup in quantitative yield. Treatment of **4a** with thionyl chloride in benzene employing triethylamine as a catalyst gave the acid chloride intermediate **4b**. Because of its anticipated instability, **4b** was not purified but directly reacted with methyl copper⁹ to furnish the diketone **4c** as an oil in 74% overall yield from **4a** after purification by chromatography.

In subsequent work, we chose not to purify **4c** at this point, since its hydrolysis (NaOH , THF, H_2O) gave the lactol **5**, which was readily purified through recrystallization. Oxidation of **5** ($\text{CrO}_3 \cdot 2\text{Py}/\text{CH}_2\text{Cl}_2$)¹⁰ followed by intramolecular cyclization and dehydration of the ketoaldehyde intermediate (HCl , THF) gave the acetyl-substituted naphthalenone **6** in 50% overall yield.

Condensation of **6** with the anion of **7**,^{11,12} as shown in Scheme II, gave the acetyl-substituted tetracyclic product **8** in 96% yield. Heating **8** in DMF under an oxygen atmosphere (2 h) quantitatively furnished the acetyl tetrahydronaphthalenone **9**,¹³ which has been converted in two steps to 11-deoxydaunomycinone **2a** in high yield.⁴ Authentication of **9** was performed with a sample generously supplied by Dr. F. Johnson.

Experimental Section

Melting point were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 621 spectrophotometer and are expressed in reciprocal centimeters. Ultraviolet spectra were run on a Cary 15 (Varian) ultraviolet-visible spectrophotometer and are expressed in nanometers. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a JEOL FX-90Q spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained with a Du Pont Model 21-491B spectrometer at an ionizing voltage of 70 eV. Combustion analyses were performed by Galbraith Laboratories.

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Analytical thin-layer chromatography (TLC) was conducted on 5×10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH). Solvents were reagent grade and were not usually purified prior to use.

2-(2-Acetoxyethyl)bicyclo[2.2.2]oct-5-ene (3b). A mixture of bicyclooctenol **3a** (24.5 g, 161.0 mmol), acetic anhydride (35 mL), and pyridine (70 mL) was stirred at room temperature overnight, then diluted with ether (200 mL), and poured into water (200 mL). The ether layer was separated and successively washed with water (1000 mL), hydrochloric acid (10%, 2×100 mL), and saturated sodium chloride (100 mL). The ether was evaporated and the residue distilled to give 31.0 g (99% yield) of **3b** as a colorless liquid: bp 70 – 72 °C (0.5 mm); ^1H NMR (CDCl_3) δ 6.40–6.0 (m, 2 H), 4.03 (t, $J = 7.0$ Hz, 2 H), 2.60–2.18 (m, 2 H), 2.03 (s, 3 H), 1.84–0.70 (m, 9 H); mass spectrum, m/z 194 (M^+).

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.44; H, 9.30.

2-(2-Acetoxyethyl)cyclohexane-1,4-dicarboxylic Acid (4a). To a solution of the acetate (**3b**) (4.8 g, 24.7 mmol) in acetone (120 mL) was added a solution of sodium metaperiodate (26.5 g, 123.5 mmol) in water (120 mL), followed by ruthenium trichloride hydrate (50 mg). The resulting mixture was stoppered and stirred at room temperature overnight. Isopropanol (5 mL) was added to destroy unreacted oxidizing agent, and after 30 min the solids that were present were removed by filtration through a celite pad. The filtrate was concentrated under reduced pressure to half of its volume. Sodium bicarbonate (5 g) was added, and the water solution was washed with ether (100 mL), which was discarded. To aqueous layer was acidified with concentrated hydrochloric acid (10 mL) and extracted with ethyl acetate (3×200 mL). The combined ethyl acetate extracts were washed with brine (100 mL), dried (MgSO_4), and then evaporated under reduced pressure to give 6.0 g (93% yield) of the diacid (**4a**) as a viscous oil: ^1H NMR (CDCl_3) δ 10.2 (br s, 2 H), 4.15 (t, $J = 7.0$ Hz, 2 H), 2.84–2.48 (m, 2 H), 2.45–1.40 (m, 9 H), 2.08 (s, 3 H); mass spectrum, m/z 258 (M^+). For the purpose of analysis, **4a** was converted to the corresponding lactone through sequential treatment with base and acid: mp 165 – 170 °C.

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_4$: C, 60.59; H, 7.12. Found: C, 60.54; H, 7.22.

2-(2-Acetoxyethyl)cyclohexane-1,4-dicarboxyl Chloride (4b). Thionyl chloride (10 mL) and triethylamine or pyridine (3 drops) were added to a mixture of diacid (**4a**) (6.0 g, 23.3 mmol) in anhydrous benzene (60 mL). The reaction was refluxed for 3 h under a nitrogen atmosphere, then evaporated at reduced pressure to give 6.5 g (95.7% yield) of the diacid chloride (**4b**) as a brown oil that was not further purified but directly used in the next step: ^1H NMR (CDCl_3) δ 4.40–3.95 (m, 2 H), 3.40–1.40 (m, 11 H), 2.08 (s, 3 H); mass spectrum, m/z 295 (M^+).

2-(2-Acetoxyethyl)-1,4-diacetylcyclohexane (4c). To a suspension of dry cuprous iodide (38.6 g, 200.0 mmol) in anhydrous ether (900 mL) at -40 °C under a nitrogen atmosphere was added, with stirring, a solution of methyllithium (143 mL of 1.4 M, 200 mmol), and the mixture was stirred for 15 min. The acid chloride **4b** (13.4 g, 45 mmol) in ether (50 mL) was added dropwise to the methyl copper solution. The reaction mixture was allowed to come to ambient temperature and then quenched with saturated ammonium chloride solution (400 mL). The ether layer was separated, and the aqueous layer was extracted with ether (300 mL). The organic phases were combined, dried (MgSO_4), and evaporated at reduced pressure to give 8.5 g (74% from **3b**) of diketone **4c** as a light yellow oil that was used in the next step without further purification: ^1H NMR δ 4.09 (t, $J = 6$ Hz, 2 H), 3.0–2.64 (m, 2 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 2.04 (s, 3 H), 2.0–1.2 (m, 9 H); mass spectrum, m/z 254 (M^+).

6-Acetyl-1-hydroxy-1-methyl-3,4,4a,5,6,7,8,8a-octahydro-1H-2-benzopyran (5). A solution of sodium hydroxide (4.0 g) in water (60 mL) was slowly added to a solution of (**4c**) (8.5 g, 33.5 mmol) in methanol (60 mL) at room temperature. After 1 h, a TLC showed the reaction was complete. The methanol was evaporated at reduced pressure and the resulting basic aqueous solution was extracted with ether (4×200 mL). The combined ether extracts were washed with brine (50 mL), then dried (MgSO_4), and filtered. Evaporation of the ether at reduced pressure gave a pale yellow solid that was recrystallized from ethyl acetate–hexane to furnish 4.2 g (59.1% yield) of pure alcohol (**3**): mp 115 – 116 °C; ^1H NMR (CDCl_3) δ 4.16–3.50 (m, 3 H), 2.60–2.20 (m, 1 H), 2.14 (s, 3 H), 2.0–1.8 (m, 10 H), 1.39 (s, 3 H); mass spectrum, m/z 212 (M^+).

Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_3$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.50.

6-Acetyl-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (6). To a well-stirred suspension of Collins reagent, prepared from pyridine (27.5 mL, 0.36 mol) and chromium trioxide (18.0 g, 0.18 mol), in methylene

chloride (450 mL) was added a solution of **5** (6.36 g, 30 mmol) in methylene chloride (20 mL). The reaction was stirred at room temperature for 3 h, then diluted with methylene chloride (450 mL). The methylene chloride solution was decanted, and the residue remaining in the flask was washed with additional methylene chloride. The combined organic solutions were filtered through a short column of fluorisil (20 g) to remove colloidal chromates, and the filtrate was evaporated at reduced pressure to furnish 5.4 g (85%) of 2,5-diacetylcyclohexaneacetaldehyde: ^1H NMR (CDCl_3) δ 10.32 (br s, 1 H), 2.64–1.80 (m, 11 H), 2.16 (s, 6 H); mass spectrum, m/z 210 (M^+).

The acetaldehyde intermediate (4.2 g, 20 mmol) was taken up in tetrahydrofuran (200 mL), and water (0.5 mL) and concentrated hydrochloric acid (1.0 mL) were added. The solution was heated at reflux for 5 h, then diluted with water (10 mL), and evaporated at reduced pressure to remove most of the tetrahydrofuran. The residual aqueous solution was extracted with ether (3 \times 200 mL), and the combined ether extracts were successively washed with saturated sodium dicarbonate solution (20 mL) and brine (50 mL), then dried (MgSO_4), and filtered. Evaporation of the ether, chromatography of the residue on silica gel (25 g, CH_2Cl_2), and recrystallization of the eluate from benzene–hexane provided 2.0 g (52%) of pure **6**: mp 86–91 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 7.04–6.78 (m, 1 H), 6.12–5.84 (m, 1 H), 2.60–1.0 (m, 11 H), 2.16 (s, 3 H); mass spectrum, m/z 192 (M^+).

Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.46.

9-Acetyl-5,12-dihydroxy-4-methoxy-6(11H)-hexahydronaphthacene (8). 7-Methoxy-3-(phenylsulfonyl)-1(3H)-isobenzofuranone (**7**) (1.82 g, 6 mmol) was added as a slurry in THF (40 mL) to a magnetically stirred, cold (-78°C) solution of lithium *tert*-butoxide (17.6 mmol) prepared from *n*-butyllithium (17.6 mmol) and *tert*-butyl alcohol (18.0 mmol). The yellow anion solution, still at -78°C , was stirred for 15 min, and then **6** (1.8 g, 0.4 mmol) was added in a single portion. The reaction

was continued at -78°C for 15 min at which point the cooling bath was removed and the reaction was allowed to come to room temperature. The reaction was allowed to stand at room temperature for 1 h and was quenched by addition of hydrochloric acid (2 mL of 6 N), whereupon bright yellow crystals of **8** precipitated. The crystals were collected by filtration and washed with methylene chloride (50 mL) to furnish 2.0 g (93% yield) of pure (**8**): mp 223–226 $^\circ\text{C}$; mass spectrum, m/z 354 (M^+). Compound (**8**) was found to be extremely sensitive to air oxidation, and a satisfactory combustion analysis could not be obtained.

9-Acetyl-6-hydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (9). Oxygen was bubbled through a solution of **8** (4 g, 11 mmol) in DMF (100 mL) at 100°C for 2 h. The oxygen flow was then terminated, and water (20 mL) was added. As the reaction cooled, orange crystals of **9** precipitated, which were collected by filtration, washed with water, and dried to give 3.7 g (94% yield) of pure **9**: mp 222–225 $^\circ\text{C}$ (lit.⁴ mp 223–226 $^\circ\text{C}$), mixture melting point undepressed; ^1H NMR (CDCl_3) δ 13.36 (s, 1 H), 8.08–7.22 (m, 4 H), 4.07 (s, 3 H), 3.30–2.40 (m, 4 H), 2.27 (s, 3 H), 2.27 (m, 1 H), 2.0–1.4 (m, 2 H), mass spectrum, m/z 350 (M^+).

Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{O}_5$: C, 71.99; H, 5.18. Found: C, 71.70; H, 5.30.

Acknowledgment. We thank Dr. Francis Johnson of the State University of New York at Stony Brook for a sample of **9** and the experimental conditions for its transformation to **2a**. This work was generously supported by the National Cancer Institute of the National Institutes of Health (Grant No. CA 18141).

Registry No. **3a**, 86420-17-9; **3b**, 86374-39-2; **4a**, 86391-80-2; **4b**, 86374-40-5; **4c**, 86374-41-6; **5**, 86374-42-7; **6**, 86374-43-8; **7**, 65131-09-1; **8**, 86374-44-9; **9**, 86374-45-0; 2,5-diacetylcyclohexaneacetaldehyde, 86374-46-1; 11-deoxydaunomycinone, 83962-00-9.

Communications to the Editor

Electroorganic Reactions on Organic Electrodes. 3. Electrochemical Asymmetric Oxidation of Phenyl Cyclohexyl Sulfide on Poly(L-valine)-Coated Platinum Electrodes[†]

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As summarized by Tilborg and Smit,¹ some methods for electrochemical asymmetric reduction of prochiral compounds had been reported. Among the methods, the highest optical yield was obtained in the asymmetric reduction in the presence of optically active alkaloids: Kariv and co-workers² reported a high optical yield of 47.5% in the reduction of 2-acetylpyridine to 2-(hydroxymethyl)pyridine in the presence of strychnine. Afterward, Tallec and co-workers³ obtained 44.3% of optical yield in the reduction of 1,1-dibromo-2,2-diphenylcyclopropane to 1-bromo-2,2-diphenylcyclopropane in the presence of emetine.

Recently, Osa and co-workers⁴ have reported a new method for the electrochemical asymmetric reduction: They obtained 2–6% of optical yields in the reduction of 2-hexanone to 2-hexanol

Table I. Electrochemical Asymmetric Oxidation of Phenyl Cyclohexyl Sulfide (**1**) to Phenyl Cyclohexyl Sulfoxide (**2**) on Poly(L-valine)-Coated Platinum Electrodes

type of electrode	2		
	$[\alpha]^{20}_D$ (c)	optical yield, %	chemical yield, %
A ^b	–54.0° (0.7)	28.0	34.0
B ^c	–81.1° (0.3)	40.0	14.5
C ^{d,e}	–106.2° (0.7)	54.0	31.2

^a Measured in acetonitrile. ^b Poly(L-valine) was coated on a bare platinum surface. ^c Poly(L-valine) was coated on the platinum surface precoated with polypyrrole by adsorption. ^d Poly(L-valine) was coated on the platinum surface precoated with polypyrrole anchored covalently. ^e The electrolysis time was 14 h.

using Raney-nickel powder electrodes modified with optically active tartaric acid. More recently, we have found that a poly(L-valine)-coated graphite electrode was effective for the reduction of prochiral olefins.^{5,6} A high optical yield of 43% was obtained in the reduction of 4-methylcoumarin to 4-methyldihydrocoumarin.

On the other hand, a few papers dealing with electrochemical asymmetric oxidation had been published: Low optical yields of 0.3–2.5% were reported in the oxidation of aryl methyl sulfides to the corresponding sulfoxides on electrodes modified chemically with optically active compounds such as phenylalanine methyl ester⁷ and camphoric acid.⁸ In this work, the asymmetric oxi-

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