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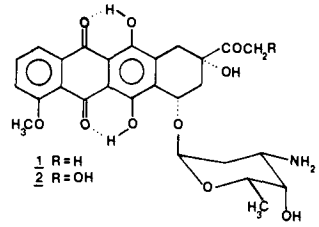
## Anthracyclines and Related Substances. 2. An Efficient and Regiospecific Synthesis of *dl*-7,9-Dideoxydaunomycinone[1]

*Sir:*

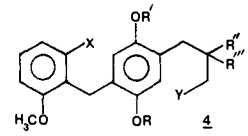
Of the group of compounds that comprise the anthracyclines,[2] two substances, namely daunomycin[3] (**1**) and adriamycin[4] (**2**), have achieved preeminence as antitumor agents, despite the fact that they frequently induce an irreversible cardiomyopathy. This has initiated a search for partially or totally synthetic derivatives that might lack this side effect.[5]




**1** R=H
**2** R=OH

However efforts aimed at the total syntheses of **1** and **2** frequently have been plaqued[6] by the problem of regioisomerism posed by the relationship of the C-4 methoxyl and the substituents on ring A. In cases where this problem has been solved, the methods[7] appear to lack efficiency or alternatively, seem inapplicable to large-scale work. We now describe an efficient synthesis (20% overall yield) of *dl*-7,9-dideoxydaunomycinone (**3**), a compound whose conversion into the aglycones of **1** and **2** is known.[6b,8] The procedure is regiospecific and is adaptable to bulk preparative work.

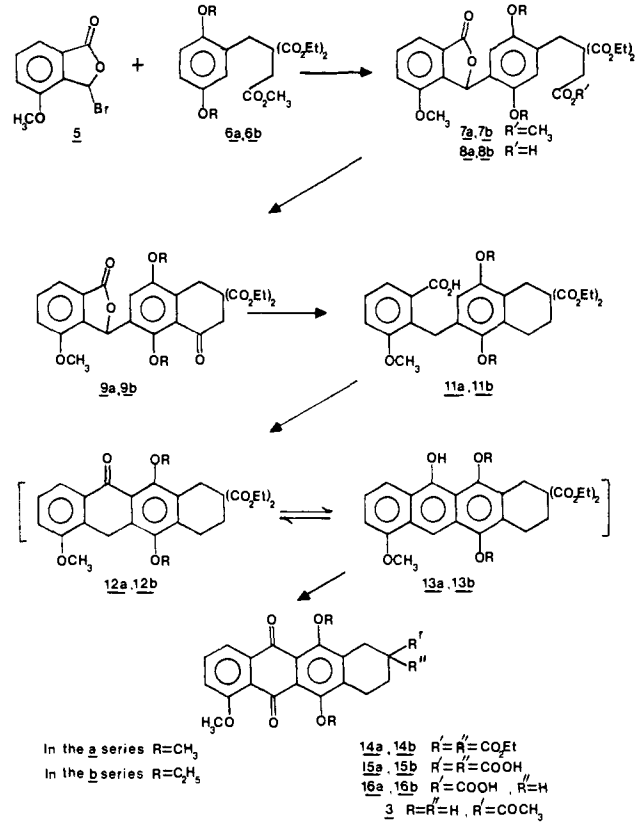
The overall method of construction follows a convergent B + D → BD → ABD → ABCD pattern and called initially for the synthesis of an intermediate belonging to the class represented by **4** (X and Y being suitably functionalized carbon



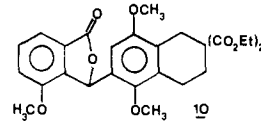

**4**

atoms). The crucial step in the synthesis of molecules of this type is a new Friedel-Crafts *alkylation* which directly introduces a phthalido residue (an inductively deactivating group[9]) into the aromatic nucleus destined to be ring B. In the case under consideration the reaction of 3-bromo-4-methoxyphthalide **5** (obtained almost quantitatively by the action of *N*-bromosuccinimide on 4-methoxyphthalide[10]) with the triester **6a** ($SnCl_4$, $CH_2Cl_2$, 25 °C, 6 h) led to **7a**[11] in 94% yield: mp 135-137 °C. Selective hydrolysis of the terminal methyl ester of **7a** (Scheme I) (1.3 equiv[12] of KOH, THF-$CH_3OH$-

Scheme I




$H_2O$) gave **8a** in 96% yield as needles, mp 105-109 °C, from aqueous methanol. Cyclization[13] ($(CF_3CO)_2O$, $CF_3CO_2H$, 25 °C, 12 h, 91%) of **8a** led to the ketolactone **9a**, mp 149-151 °C. Reduction ($Et_3SiH/CF_3CO_2H$, 25 °C, 48 h) of **9a** initially gives the lactonic tetralin **10**, mp 143 °C, and at 25 °C this can be isolated easily in high (93%) yield. However, after 2 weeks




**10**

at 25 °C or more rapidly (24 h) at 50 °C, the lactone was also reductively cleaved and there was obtained (92%) the dimorphic carboxybenzyltetralin **11a**, mp 117-118 (blades) and 134-136 °C (needles). The cyclization ($(CF_3CO)_2O/CF_3CO_2H$, 25 °C, 30 min, ~88%)) of **11a** occurred with great ease and afforded a tautomeric mixture of the 9-anthrone (**12a**) and the 9-hydroxyanthracene **13a**, in which the latter predominated. Generally these compounds were not isolated. Instead the reaction mixture was diluted with a little water and Jones reagent[14] was added at 0 °C. This led to the quinone **14a**

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(62% from 11a) as yellow needles: mp 124-125 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.2-7.8 (m, 3 H), 4.25 (q, 4 H, $J$ = 7 Hz), 4.05 (s, 3 H), 3.9 (s, 3 H), 3.3 (s, 2 H), 2.9 (t, 2 H, $J$ = 6 Hz), 2.3 (t, 2 H, $J$ = 6 Hz), 1.3 (t, 6 H, $J$ = 7 Hz). The conversion of **14a** into 7,9-dideoxydaunomycinone dimethyl ether (**17a**) was then effected by the following four-part procedure.

Saponification (KOH, aqueous ethanol (1:2), 90 °C, 3 h, 98%) of **14a** led to the diacid **15a** as yellow needles, mp 222-224 °C from $CH_2Cl_2/Et_2O$. This was the decarboxylated ($CH_3CO_2H$, piperidine, 120 °C, 1 h) to give monocarboxylic acid **16a** (85% from **14a**): mp 133.5-135 °C; $^1$H NMR (acetone-$d_6$) $\delta$ 7.6-7.9 (m, 3 H), 4.1 (s, 3 H), 4.0 (s, 6 H), 2.7-3.1 (m, 7 H), ~9 (very br, 1 H). The crude acid chloride derived ($SOCl_2$, $C_6H_6$, 25 °C, 15 h) from **16a** was then treated with lithium dimethylcuprate[15] (THF/$Et_2O$, −78 to 0 °C, 3 h) and afforded 7,9-dideoxydaunomycinone dimethyl ether (**17a**, 80% based on **16a**) as yellow needles: mp 185-186 °C; $^1$H NMR (acetone-$d_6$) $\delta$ 7.6-7.9 (m, 3 H), 4.1 (s, 3 H), 3.9 (s, 6 H), 2.8-3.1 (m, 7 H), 2.3 (s, 3 H).

Selective demethylation of **17a** to give *dl*-7,9-dideoxydaunomycinone (**3**) was possible only by a two-part sequence, namely oxidation[6b,16] ($AgO/HNO_3$, aqueous acetone, 70 °C, 1 h) to the 4,12:6,11-bisquinone, followed by reduction ($Et_2NOH$, EtOAC, 25 °C, 30 min) of the crude product. This afforded **3** in 83% yield after recrystallization from $CH_2Cl_2/Et_2O$: mp 243-245 °C, no depression in melting point when admixed with an authentic sample (mp 243-245 °C); $^1$H NMR ($CDCl_3$) $\delta$ 13.78 (s, 1 H), 13.43 (s, 1 H), 8.1-7.2 (m, 3 H), 2.27 (s, 3 H), 2.15 (m, 1 H), 1.55 (m, 2 H). The NMR, IR (Nujol), visible ($CH_2Cl_2$), and mass spectra were identical with those recorded in the literature[8a] for **3**.

Although the demethylation of **17a** is an efficient process, the initial oxidation is rather vigorous and one could envisage that more delicate molecules may not survive. To avoid this difficulty we have developed an alternative procedure based on the fact that aryl ethyl ethers are more readily cleaved[17] by Lewis acids than the corresponding methyl ethers. Repetition then, of the complete synthetic sequence[18] starting with **6b** produced in comparable yields the corresponding diethoxy homologues **7b** through **17b**. Selective deethylation of **17b** to give **3** was then easily accomplished in one step under mild conditions ($AlCl_3/PhNO_2$, 45 °C, 40 min, 80%).

We believe that the methods presented above, together, constitute a very versatile approach to the anthracyclinones in general. Variations in the substitution patterns of rings A, B, and D and in the nature of the C-9 side chain now seem possible, not only because of the convergent nature of the synthesis and its regiospecificity but also because of the relatively simple nature of the reactions involved. Investigations into the use of these procedures for the synthesis of other classes of anthracyclinones are underway.

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## 2-Hydroperoxyhexafluoro-2-propanol. A Low-Cost, Catalytic Oxidant for Synthesis and a Structural Analogue of Naturally Occurring Flavin Hydroperoxides

*Sir:*

Organic chemists have long been interested in utilizing hydrogen peroxide directly for the epoxidation of simple, unactivated alkenes. Efforts to devise a workable process using $H_2O_2$ to drive the carboxylic acid–peracid exchange have been unsuccessful to date since a strong acid catalyst is required.[1] Transition metal oxides and peroxides achieve a ready equilibrium but are poor oxidants for isolated double bonds.[2] Only recently have the corresponding seleninic–peroxyseleninic acid systems been described as satisfactory alternatives, although they offer little, if any, regio- or stereoselectivity.[3,4]

Since our discovery[5] that peroxytrifluoroacetic acid esterifies alcohols by a Fischer-type mechanism (eq 1), we have been exploring the chemistry of electron-deficient hydroperoxides related to **1**. We now report that 2-hydroperoxyhexafluoro-

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