and **4** extruded CF_2: at almost equal rates ($k_2/k_3 = 1.05$).

Our observed activation energy for the geometrical isomerization of **2** (49.7 kcal/mol) can be compared with that for the analogous nonfluorinated molecule (59.1 kcal/mol) which was determined by Flowers and Frey in 1960.[15] It can thus be seen that the presence of the CF_2 group *significantly* facilitates the isomerization process. However it must be emphasized that precise interpretation of these results at this time is premature. There is, as of yet, no experimental evidence as to the mechanism of the cis–trans interconversion, i.e., whether cleavage of bond C_1–C_2 or of bond C_2–C_3 is responsible for the observed isomerization. The earlier mentioned exo-endo epimerizations[10,11] do, of course, provide strong credibility for C_2–C_3 cleavage, but work is currently in progress in our laboratories to fully elucidate the mechanism of the isomerization process.

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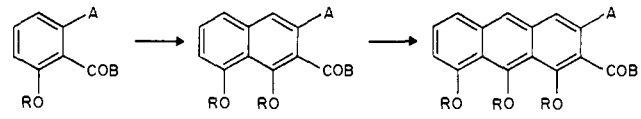
New Synthetic Strategy for the Preparation of Linear Phenolic Natural Products

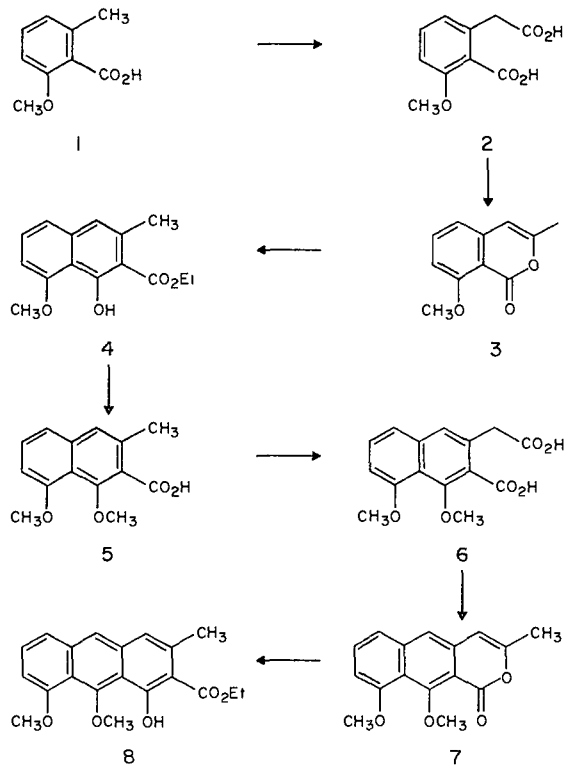
Sir:

We have developed a conceptually simple synthetic strategy which significantly facilitates the preparation of linear polynuclear phenolic systems, a structural feature present in many antiobiotics and other natural products. This strategy, shown in Scheme I, involves repetitive execution[1] of a single regioselective reaction sequence which adds a new phenolic ring to the existing aromatic system in each cycle. To illustrate the versatility of this synthetic strategy, 2-methyl-6-methoxybenzoic acid (**1**) was carried through two cycles yielding the polyfunctionalized anthracenecarboxylic ester **8** (Scheme II).

Scheme I



Scheme II



The aglycone portion of numerous naturally occurring compounds consists of linear tri- and tetracyclic systems with two or more aromatic rings.[2] Many of the parent compounds, such as the anthracyclines adriamycin,[3] daunorubicin,[4] and carminomycin,[5] olivomycins A, B, C, and D,[6] chromomycins A 1–4,[6,7] and aureolic acid,[8] have, in addition to their antibiotic activity, significant anticancer properties. Of these, only daunorubicin[9,10] has been synthesized.

Generally, only three approaches, the use of the Friedel–Crafts acylation,[9,11] variant forms of the Diels–Alder reaction,[12–14] or cyclization of polyketides,[15,16] have been employed to construct linear polynuclear systems. Alternate synthetic methodology is much needed to permit the regioselective preparation of linear phenolic systems not achievable by these other approaches. The described repetitive synthetic strategy and the derived reaction sequence which accomplishes it should be adaptable to a broader range of these systems.

The starting material chosen for the synthesis, 2-methyl-6-methoxybenzoic acid[16] (**1**), was carboxylated on the methyl group by quenching the orange dilithium anion, formed by treatment of **1** with lithium diisopropylamide at −78 °C with dimethyl carbonate. Aqueous workup gave directly homophthalic acid **2**, mp 165–166 °C (lit.[17] mp 165–166 °C), in 90% yield.[18,19] A three-step sequence involving acylation of **2** with acetic anhydride and pyridine, followed by basic hydrolysis with concomitant decarboxylation, and, finally, ring closure of the intermediate using acetic anhydride and perchloric acid yielded isocoumarin (**3**), mp 109 °C (lit.[17] mp 109.5–110.5 °C), in 68% overall yield.[20,21] Slow addition of a dilute benzene solution of ethyl bromoacetate to a refluxing benzene solution of **3** and zinc gave naphthoate **4**, mp 59 °C,

in 73% yield.[22] Methylation of **4** was accomplished using dimethyl sulfate and potassium carbonate; subsequent hydrolysis of the ethyl ester with potassium hydroxide in dimethyl sulfoxide[23] gave naphthoic acid (**5**), mp 149–50 °C.

The ortho disposed carboxyl and methyl functionalities used in the conversion of benzoate system **2** to naphthoate system **5** are retained and permit the annelation sequence to be repeated. Naphthoic acid (**5**), upon treatment with lithium diisopropylamide, was converted to a deep purple dilithium anion which was carboxylated and hydrolyzed to give naphthaleneacetic acid (**6**).[24] The reaction sequence described earlier for conversion of homophthalic acid (**2**) to isocoumarin (**3**) was employed again for the preparation of naphtho[2,3-*c*]pyran (**7**), mp 168–70 °C, in 56% overall yield from naphthoic acid (**5**). Reformatsky reaction on naphtho[2,3-*c*]pyran (**7**), gave 9,10-dimethoxy-1-hydroxy-3-methylanthracenecarboxylic acid (**8**), mp 159–161 °C, which bears a hydroxylation pattern found in naturally occurring linear polynuclear aromatic systems.

Studies to broaden the scope of this approach for synthesis of hydroxylated polynuclear aromatic compounds and to synthesize selected natural products are in progress.

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(24) Compound **6** could not be purified; however, comparison of the relative intensity of the ^{1}H NMR for the aromatic methyl group for the starting material (δ 2.42 ppm) with that for the methylene group of the phenyl acetic acid product (singlet at δ 3.81 ppm) indicated that the conversion of **5** to **6** had occurred in 85–90% yield.

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A Secondary Isotope Effect in the Cysteine-Promoted Dehalogenation of 5-Bromo-2′-deoxyuridine. Evidence for Transient 5,6-Dihydropyrimidine Intermediates

Sir:

There has been long-standing interest in 5-halogenated pyrimidines because of their use as biochemical tools and chemotherapeutic agents.[1,2] The metabolism of 5-bromo- and 5-iodouracils involves their dehalogenation, and numerous model systems have been investigated in attempts to understand the mechanism of these reactions.[3-12] Most studies have centered about the bisulfite mediated halide release and its replacement by proton; the same reaction is prompted by thiols, which is more relevant to enzymic conversions, but less well understood. The proposed mechanism for the thiol mediated dehalogenation of 1-substituted 5-bromouracils is depicted in Scheme I; a similar pathway is believed to exist for dehalogenation of corresponding 5-iodouracils.[10] The initial, and perhaps rate-determining,[9,10] step is believed to involve attack of thiolate at the 6 position of the heterocycle **1** and protonation of C-5 to produce the 5-bromo-6-thiol-5,6-dihydrouracil **2**. Two general pathways have been proposed[9,10,12] to account for subsequent steps leading to the dehalogenated product. The first, E2 Hal, involves abstraction of bromonium (Br^+) ion from **2** to provide intermediate **3** and a sulfenyl halide. The latter would react with a thiol to provide the halide ion and

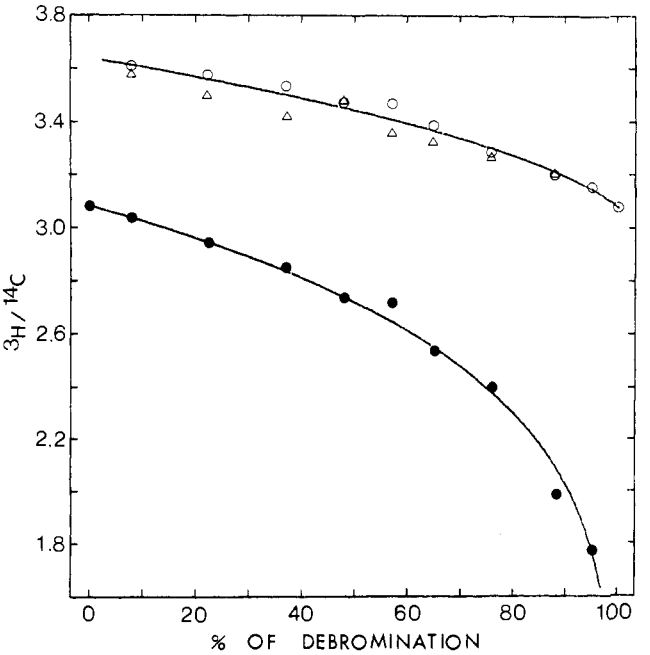

Figure 1. Secondary isotope effect on the cysteine-promoted dehalogenation of BrdUrd. Experimental points refer to the $^3H/^{14}C$ ratio of BrdUrd (●), dUrd (○), and (△) 5-CysdUrd. The lines are theoretical[15] for a secondary isotope effect of $k_T/k_H = 1.18$.