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CYCLOADDITIONS OF BENZOPYRONES: RAPID ACCESS TO BICYCLIC AB-RING ANALOGUES OF ANTHRACYCLINES

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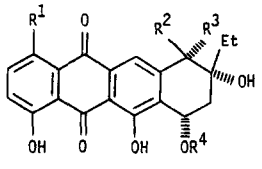
Summary: Cycloaddition of the benzopyrone **10b** with 1,1-disubstituted alkenes **12**, **14**, and **16** produces fair yields of the lactones **13**, **15**, and **17**, AB-ring analogues of the anthracyclines.

A large amount of synthetic work has been directed recently[2] at the total synthesis of aklavinone **1**, the aglycone of the clinically important antitumor antibiotic aclacinomycin A, **2**, which has resulted in six total syntheses.[3] Also of synthetic interest are the C10-epimers of the aclacinomycins, namely compounds such as mimimycin **4** and other compounds of the bohemic acid complex[4] (e.g., collinemycin) which are derived from the aglycone, 10-epi-ε-pyrromycinone **3**. Compounds of the two general types are interconvertible by base-catalyzed epimerization at C10 in the respective aglycones.[2b,4] We now report a new method for the rapid production of bicyclic A,B-ring analogues of these compounds from readily available starting materials in only a few steps.

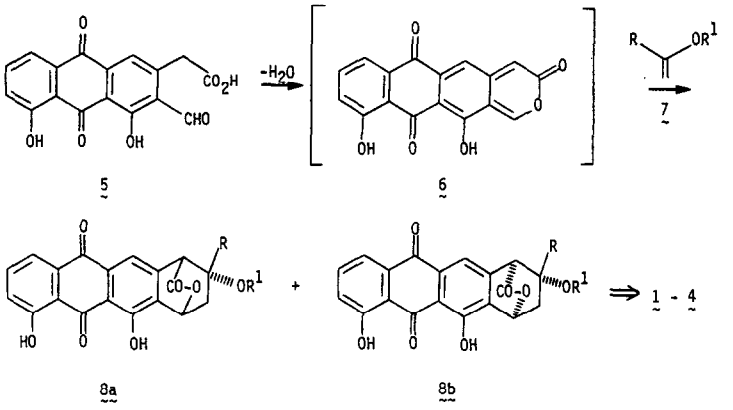


	R^1	R^2	R^3	R^4
1	H	CO_2Me	H	H
2	H	CO_2Me	H	Rh—DF—Cin
3	OH	H	CO_2Me	H
4	OH	H	CO_2Me	Rh—DF—DF

Rh = α-rhodosamine DF = 2-deoxy-L-fucose
Cin = cinerulose A

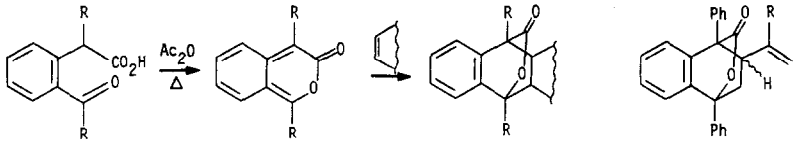
For several years we have been working on approaches to the anthracyclines based on the use of 6-methoxy-2-pyrones as dienes in Diels-Alder cycloadditions with quinones for the preparation of the tetracyclic ring system in which bonds C5a-C6 and C11-C11a are formed in the key constructive step.[5] We were interested in the possibility of a somewhat similar approach using a pyrone lacking the 6-alkoxy group as a diene for the construction of the A-ring with all the required functionality in place. For example, dehydration of 7-formyl-4,6-dihydroxy-anthraquinone-8-acetic acid **5** might proceed with loss of aromaticity in the benzene ring to produce the benzopyrone derivative **6**. This compound is essentially an ortho-quinodimethane bridged by CO_2 and thus should

be highly reactive toward cycloaddition with simple olefins. In particular a 1,1-disubstituted olefin **7** should add regiospecifically (due to stabilization of zwitterionic-like character in the transition state) to give the desired regioisomers **8ab** as a mixture of stereoisomers. Opening of the lactone to the hydroxy ester followed by known[2b,6] epimerization at C7 would convert **8a** into aklavinone **1** while formation of the hydroxy ester from **8b** would produce 1-deoxy-ε-pyrromycinone (analogous to **3**) which could be epimerized at C10 to also give **1**. Thus this route seemed to offer a rapid route to the functionalized A ring and we decided to test it in a model system.



5 **6** **8a** **8b**

The original work in this area was due to Jones[7] who showed that (2-benzoylphenyl)phenylacetic acid **9a** could be dehydrated to 1,4-diphenyl-3H-2-benzopyran-3-one **10a**, an isolable crystalline compound. The unsubstituted compound **10b** could also be prepared from **9b** but was too reactive to be isolated. Both compounds underwent Diels-Alder reactions when generated in the presence of dienophiles to give bicyclic lactones with either endo or exo-specificity depending on the system. With isoprene and butadiene the diphenyl pyrone **10a** gave mainly the regioisomer **11** as a mixture of stereoisomers.

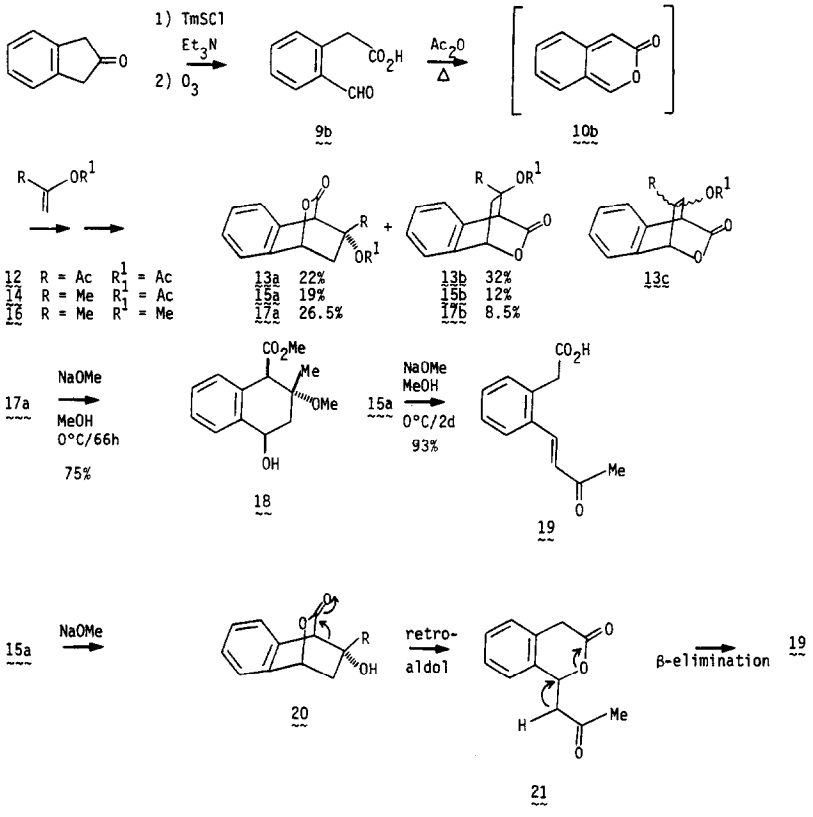


9a R = Ph **9b** R = H **10a** **10b** **11** R = H, Me

Conversion of 2-indanone (available in two steps from indene in 72% yield[8]) via ozonolysis of its trimethylsilyl enol ether into 2-formylphenylacetic acid **9b** was straightforward. Dehydration of **9b** in refluxing acetic anhydride in the presence of various olefins produced the desired regiochemically pure bicyclic lactones. Use of a slight excess of the enol acetate of biacetyl **12** produced a 54% yield of two compounds,[10] **13a** (slightly yellow oil, 22%) and **13b** (colorless crystals, mp 191.5-192.5°, 32%) shown by high field NMR to be stereoisomers with the desired regiochemistry. That the major compound was the product with acetate syn to the lactone bridge, **13b**,

was determined by a single crystal x-ray analysis. Under these conditions the reaction was regiospecific. However under more vigorous conditions (12 hr, 95°C), a small amount of the regioisomer **13c** (colorless oil, 5%) was produced along with **13a** (26%) and **13b** (20%).

Several other commercially available olefins could be used in this cycloaddition process. For example, isopropenyl acetate **14** gave a 31% yield of a 1.5:1 mixture of the two stereoisomers **15a** (colorless crystals, mp 72-4°C, 19%) and **15b** (colorless crystals, mp 95-8°C, 12%).



Isopropenyl methyl ether **16** afforded a 35% yield of an approximately 3:1 mixture of stereoisomers, **17a** (colorless crystals, mp 104-105.5°C, 26.5%) and **17b** (colorless, 8.5%). We have not yet really tried to improve the yields in this cycloaddition process. The assignment of structure for compounds **15ab** and **17ab** was impossible by simple spectroscopic means (e.g., high field ^{1}H NMR). We therefore again utilized single crystal x-ray spectroscopy to determine the structure of **17a**, and then used similarities in the ^{1}H NMR data to assign the structure of **15a**.

To demonstrate the potential utility of these bicyclic lactones for the synthesis of the A-ring of anthracyclines, we subjected the methyl ether **17a** to basic methanolysis to produce the hydroxy ester **18** in 75% yield. This compound is an analogue of the anthracycline antitumor antibiotics having a β-methyl group at C9 (e.g., nogalamycin,[11] ε_1-pyrromycin,[11b] and auramycin.[11c] This base-catalyzed methanolysis could not be successfully applied to the acetate **15a** however. Treatment of **15a** under identical conditions produced an excellent yield of the acid **19**

[colorless oil, 93%: ^{1}H NMR δ 8.32 (1H, bs), 7.96 (1H, d, J = 17 Hz), 7.3-7.8 (4H, m), 6.69 (1H, d, J = 17 Hz), 3.82 (2H, s), 2.40 (3H, s). IR ($CDCl_3$) 3300-2800, 1735-1700, 1675, 1610, 1365, 1265, 1075 cm^{-1}]. The clean formation of the acid (and the absence of the corresponding methyl ester) implies that the tertiary acetate is methanolized faster than the lactone to produce the alcohol **20**. This alcohol can then undergo a base-catalyzed retro-aldol reaction to give the keto lactone **21** which then suffers β-elimination to give **19**.

We are currently attempting to prepare the aldehyde acid **5** and apply this route to the synthesis of the natural anthracyclines.

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