CYCLOADDITION 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 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. Also of synthetic interest are the ClO-epimers of the aclacinomycins, namely compounds such as mimimycin 4 and other compounds of the bohemic acid complex (e.g., collinemycin) which are derived from the aglycone, 10-epi-e-pyrromycinone 3. Compounds of the two general types are interconvertible by base-catalyzed epimerization at ClO in the respective aglycones. 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.

For several years we have been working on approaches to the anthracyclines based on the use of 6-methoxy-2-pyrone 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. 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 CO2 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\textsuperscript{2b,6} epimerization at C7 would convert 8a into aklavinone 1 while formation of the hydroxy ester from 8b would produce 1-deoxy-c-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.

\[ \text{8a} \quad \text{8b} \quad \Rightarrow 1 - 4 \]

The original work in this area was due to Jones\textsuperscript{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.

\[ \text{9a} \quad \text{9b} \quad \text{10a} \quad \text{10b} \quad \text{11} \]

Conversion of 2-indanone (available in two steps from indene in 72% yield\textsuperscript{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,\textsuperscript{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 1H NMR). We therefore again utilized single crystal x-ray spectroscopy to determine the structure of 17a, and then used similarities in the 1H 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-pyrromycin,11b and auranomycin.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
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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References and Notes


(9) All new compounds exhibited spectroscopic data (200 MHz 1H NMR, 13C NMR, IR, elemental analysis and/or high resolution mass spectroscopy) in full agreement with their proposed structures.


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