PREPARATION AND CYCLOADDITION OF FUNCTIONALIZED 4,6-DIALKYLPYRONE-5-CARBOXYLATES. SYNTHESIS OF BICYCLIC LACTONES AND SUBSTITUTED BENZOATES[1]

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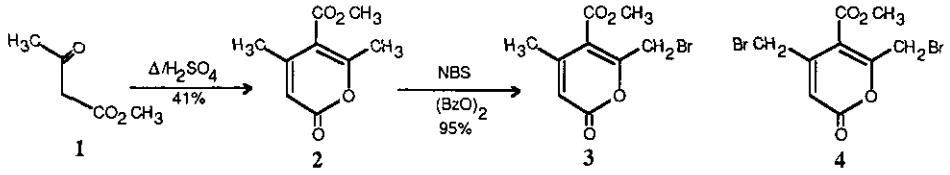
Abstract - Several alkyl pyrone-5-carboxylates (coumalates) with alkyl and functionalized alkyl substituents at C4 and C6 have been prepared by a general route; their cycloadditions with electron-rich olefins have been carried out to provide aromatic and non-aromatic products, of potential value for natural products synthesis.

In 1969 Behringer reported the thermal cycloaddition of alkyl coumalates with electron-rich olefins such as ketene acetals and enol ethers to give substituted benzoates via loss of CO_2 and alcohol from the initial cycloadduct.[2] Only with unsubstituted coumalates could the initial adduct be isolated. Since then, several other groups have utilized pyrone-3- and -5-carboxylates as dienes in cycloadditions with electron-rich olefins.[3] In order to be of general value for use in natural products synthesis, however, two further accomplishments are necessary, namely: the development of a) general methods for the preparation of functionalized substituted pyrone carboxylates and b) general procedures for the preparation of the initial bicyclic lactone cycloadducts without extensive aromatization. We now report the successful achievement of those two goals.

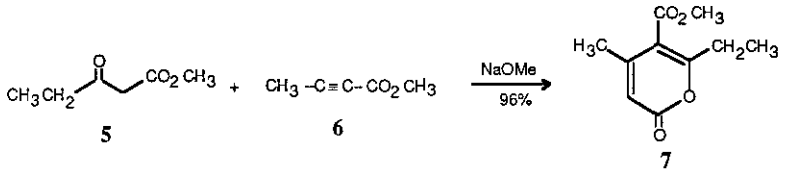
a) Preparation of Functionalized Substituted Pyrone-5-carboxylates (Coumalates).

Pyrone-5-carboxylates which are symmetrically substituted in the 4- and 6-positions are formed most easily by the acid-catalyzed condensation of β-keto esters.[4] Unsymmetrical coumalates have been prepared by the reaction of β-keto ester enolates with acetylenic esters.[5] We have used both of these routes to prepare functionalized coumalates as follows. Sulfuric acid promoted self-condensation of methyl acetoacetate **1** afforded methyl 4,6-dimethylpyrone-5-carboxylate **2** in 41% yield.[6] Bromination of **2** with NBS furnished in 95% yield the 6-bromomethyl compound **3** with none of the 4-bromomethyl isomer **4** being produced. Since 4-substituted coumalates were desired for a potential synthesis of anthracyclines, we investigated other routes to these compounds. Condensation of methyl 3-oxopentanoate **5** (prepared by methylation of the dianion of **1** in 81% yield or in 80% yield by acylation of Meldrum's acid followed by cleavage with methanol)

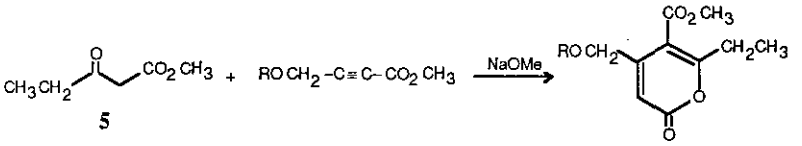


1 2 3 4

with methyl butynoate **6** in the presence of sodium methoxide produced the unsymmetrical pyrone **7** in 96% yield. The use of functionalized butynoates allowed for the preparation of functionalized pyrones in this reaction, albeit in fair yield. Thus, condensation of methyl 4-methoxybutynoate **8a** (prepared by carbomethoxylation of methyl propargyl ether) with **5** afforded the 4-methoxymethyl-pyrone **9a** in 33% yield. The identical reaction pathway using 4-(methoxymethoxy)butynoate **8b** gave the analogous pyrone **9b** in 22% yield. A highly desirable intermediate for use in synthesis was



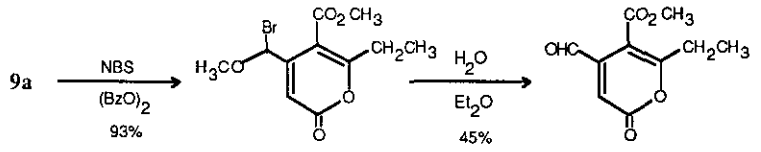
5 6 7



5 8a R = Me 33% 9a
8b R = MeOCH2 22% 9b

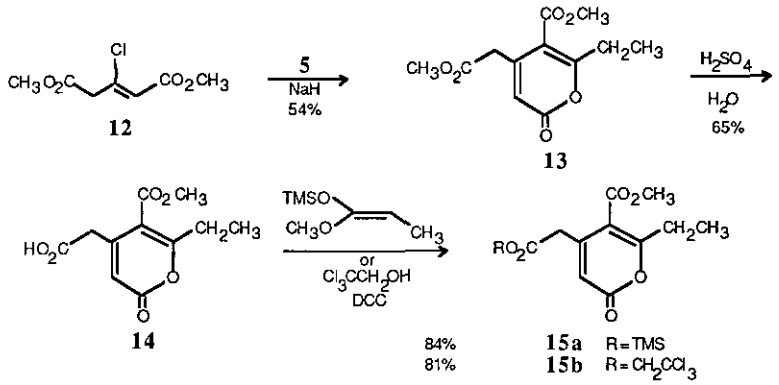
the 4-formyl-pyrone **10**, since it might permit the coupling of the pyrone ring to other molecular units via nucleophilic addition. We hope to prepare **10** from **9a** by selective free-radical bromination, postulating that the methoxy substituent on the C4 methylene unit would overcome the system's basic preference for stabilization of a radical at C6 (cf. bromination of **2** to give **3**). In the event, bromination of **9a** proceeded cleanly to give the α-bromoether **11** in excellent yield. This very moisture-sensitive compound was immediately hydrolyzed by stirring with wet diethyl ether to produce **10** in 45% yield. We have not yet examined nucleophilic additions to **10**.

Derivatives of this pyrone system that might be used as nucleophiles were also desirable as potential intermediates in an approach to the anthracyclines. These were prepared by a

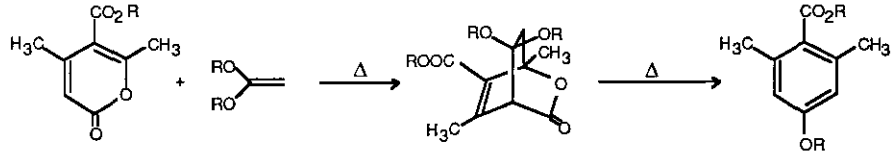


11 10

modification of this general route.[7] Condensation of **5** with dimethyl β-chloroglutaconate **12** (the mixture of isomers produced from treatment of dimethyl 3-oxopentanedioate with PCl_5 and subsequent remethylation[8]) with sodium hydride as base afforded the diester **13** in 54% yield. Selective hydrolysis of the less hindered ester gave the acid **14** in 65% yield along with 25% recovered starting material. The acid **14** could be converted easily into the mixed diesters **15a** or **15b** in 84% and 81% yield, respectively.



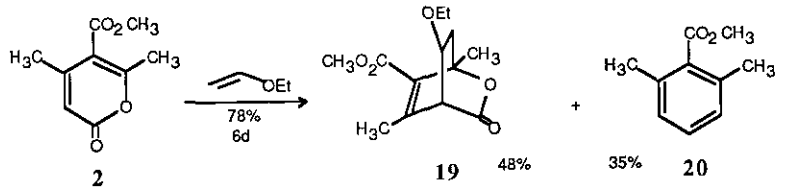
b) Cycloadditions of the Coumalates and Further Reactions. Having developed general methods for the preparation of 4,6-disubstituted coumalates, we next examined their utility in cycloadditions. Behringer reported that the ethyl ester **2'** analogous to **2**, reacted with diethyl ketene acetal **16a** in refluxing toluene for 15h to give a 73% yield (based on unrecovered ester) of the substituted benzoate **18a** presumably via the intermediacy of the bicyclic lactone **17a** which lost CO_2 and ethanol at this temperature. We found that the methyl analogue **2** reacted with dimethyl ketene acetal **16b** in refluxing benzene (82°C) for 24h to give a 63% yield of **18b** along with 10% of the desired bicyclic lactone **17b**. Lowering the reaction temperature to 78°C for 24h allowed the isolation of the desired adduct **17b** in 62% yield with none of the aromatic product **18b** being formed at this temperature. At reaction temperature below 75°C, the cycloaddition occurs only very slowly, thus indicating that the clean formation of the desired bicyclic intermediate is



2' R=Et **2** R=Me **16a** R=Et **16b** R=Me **17a** **17b** **18a** **18b**

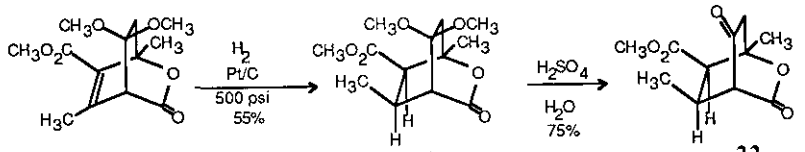
limited to a very narrow temperature range. Also in contrast to Behringer's results, we were able to obtain the bicyclic lactone **19** from the reaction of **2** with ethyl vinyl ether (6 days at 78°C) in 48% yield along with 35% of the aromatic ester **20**. The lactone **19**, isolated as a mixture of

stereoisomers, is unstable at 25°C and slowly decomposes into **20** over several days.



2 **19** 48% 35% **20**

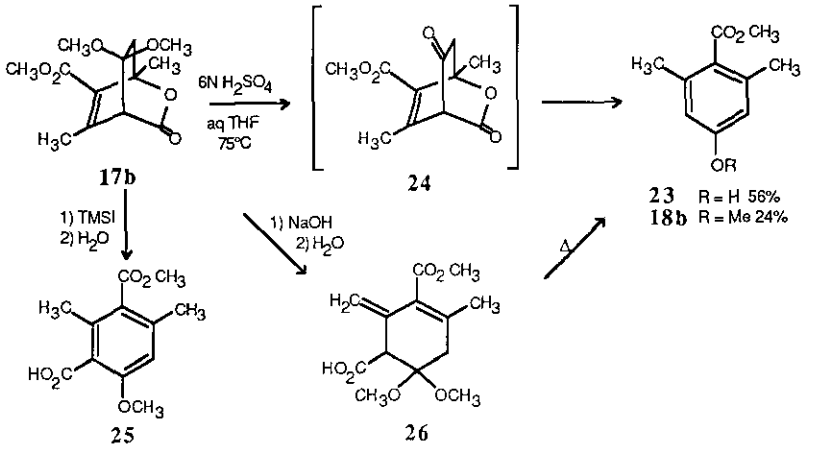
The bicyclic lactone **17b** could be converted into further products. Catalytic hydrogenation of the hindered electron-poor olefin of **17b** proved difficult but could be accomplished under forcing conditions (5% Pt/C, 500 psi H_2, 14d) to give after chromatography a single isomer as the major product in 55% yield. The structure **21** has been assigned to this compound on the basis that the hydrogenation would occur from the less hindered face (syn to the lactone bridge) rather than the more hindered one (syn to the ketal-bearing bridge). The ketal of **21** could be readily hydrolyzed (6N H_2SO_4, 2h, 25°C) to give in 75% yield the keto lactone **22**, which has the correct stereochemistry and certain functionality to perhaps serve as a precursor to the A ring of the aclacinomycin class of the anthracyclines with ethyl at C5 instead of methyl and a naphthylmethyl group at C4 instead of methyl.[9]



17b **21** **22**

Hydrolysis of the olefinic bicyclic lactone **17b** was considerably more difficult (6N H_2SO_4, aq THF, 75°C, 24h) and could not be achieved without loss of carbon dioxide to give the phenol **23** in 56% yield and anisole **18b** in 38% yield. Separate experiments showed that **23** was not formed from **18b** under these conditions, thus indicating that some hydrolysis of **17b** to the desired keto lactone **24** had occurred but that enolization and loss of CO_2 were too fast under these conditions to allow for its isolation and **23** was produced instead. Finally other interesting transformations of **17b** are also possible. Treatment of **17b** at 25°C with TMSI, a reagent known to cleave dimethyl ketals,[10] gave an excellent yield of the pentasubstituted benzene, the isophthalic acid derivative **25**, in which only one of the two acid functionalities is protected as the ester. This reaction presumably proceeds by opening of the lactone with TMSI to the dienic silyl ester which loses methanol to give **25** after workup. Interestingly, treatment of **17b** under basic conditions - sodium hydroxide in methanol at 25°C - produces a different carboxylic acid **26** in quantitative yield. Presumably proton abstraction from the acidic Y-position of the α,β-unsaturated ester sets the stage for a vinylogous β-elimination of the lactone bridge to afford the observed product after

protonation. Consistent with its structure, the acid **26** was converted via decarboxylative elimination into **18b** upon heating at 120°C.



Thus we have developed general routes to substituted coumalates and effected their simple cycloadditions to give bicyclic lactones. Moreover, we have been able to carry out further reactions on these initial adducts to produce both aromatic and non-aromatic compounds of potential use in synthesis.

ACKNOWLEDGEMENT

We thank the National Institutes of Health (CA-21968 and GM-31349) for financial support.

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Received, 27th May, 1986