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Studies towards diarylheptanoid synthesis. Part 1: Synthesis and ring cleavage reactions of hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-ones☆

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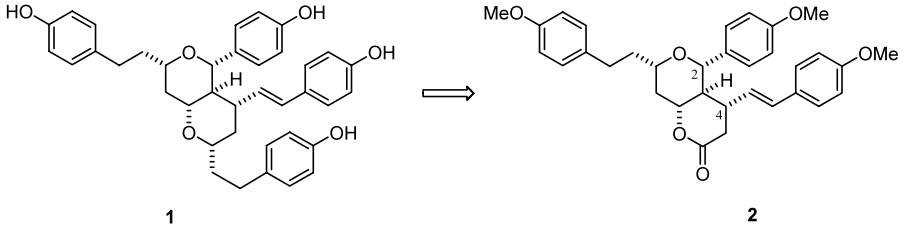
Abstract—Lewis acid promoted anomeric substitution reactions of a stereoselectively prepared hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-one derivative was studied as a model for diarylheptanoid synthesis. Aromatic nucleophiles consistently provided the expected thermodynamic *C*-aryl pyranoside product.

Diarylheptanoids are a class of natural products that are characterized by the presence of two aryl groups separated by seven carbon atoms, with curcumin being the first example to be isolated.[1] Blepharocalyxin D (**1**) is one of several diarylheptanoids recently isolated from *Alpinia blepharocalyx*, which have shown significant in vitro antiproliferative activity against human fibrosarcoma HT-1080 and murine colon 26-L5 carcinoma cells.[2,3] Its structure assignment has so far been based on ^{1}H and ^{13}C NMR spectroscopic data and by comparison with previous isolates of *A. blepharocalyx*.[4] A validation of its structure through synthesis has yet to be reported, and is currently an on-going project in our laboratory.

In our approach to this natural product lactone **2** was considered to be a suitable intermediate target (Scheme 1), a synthesis of which would require the stereocontrolled positioning of a number of prominent fixtures, including the *C*-aryl pyranoside moiety at C-2, as well as the *para*-methoxystyrenyl functionality at C-4. A number of published routes to thermodynamic *C*-aryl pyranosides have involved the addition of an electron-rich aromatic ring to an oxocarbenium ion intermediate.[5] With this idea in mind, a model for the synthesis of lactone **2** was conceived which centered on the use of the hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-one ring system as a pyranosyl donor (Scheme 2). Surprisingly, ring cleavage reactions of this type have seldom been reported.[6] Preliminary studies into the scope of this method therefore seemed justifiable.

Historically, there has been little activity in the synthesis of hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-ones,[7] underscoring the lack of utilization of these structures as synthetic intermediates. Moreover, a route to 4-*endo* derivatives has not been reported, to the best of our knowledge. Compound **9** was chosen for our model



1 2

Scheme 1.

Keywords: blepharocalyxin; diarylheptanoid; oxocarbenium ion; hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-one; *C*-aryl pyranoside.
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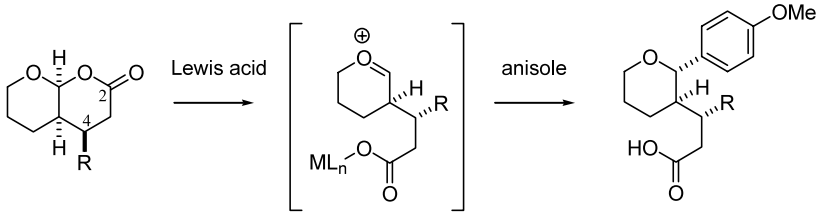
studies, for which synthesis a cycloaddition strategy was employed. Boger[8] and others[9] have reported accelerated and highly stereoselective inverse electron demand hetero Diels–Alder reactions between enol ethers and 1-oxa-1,3-butadienes. Using this methodology, bicyclic structure **4** was formed as a single isomer, after recrystallization, from the cycloaddition of methyl *trans*-4-phenyl-2-oxo-3-butenoate **3** with 2,3-dihydropyran (Scheme 3). The relative stereochemistry of compound **4** was unambiguously assigned by X-ray crystallography. More important, this compound was converted to bicyclic lactone **9** through the series of steps shown. Thus, hydrogenation of compound **4** occurred highly selectively to give ester **5** as a single isomer which was subsequently reduced to alcohol **6** and converted to iodide **7**. Alkene **8**, formed by exposure of compound **7** to sodium hydride in DMF, was not isolated. Instead, the crude material was ozonized without purification to give compound **9**.

Ring cleavage substitution reactions of compound **9** proceeded in highest yield using $TiCl_4$ as Lewis acid in methylene chloride solvent at low temperature (Table 1). Under these conditions acid derivative **10** formed essentially quantitatively on treatment of compound **9** with triethylsilane (entry 1). Not unexpectedly, stereoselectivity with carbon nucleophiles was found to be reagent dependent. Silane-based reagents are known to favor axial attack on the oxocarbenium ion intermediate via a chair-like transition state,[10] and this was indeed found to be the case with 1-phenyl-2-trimethylsilylacetylene. This reagent gave a single diastereomer assigned as compound **11** (entry 2) based on the *cis* coupling constant between ring hydrogens ($J_{2,3}=4.2$ Hz). However, with the more sterically encumbered allyltrimethylsilane (entry 3), a 2:1 mixture of allyl substituted products **12** resulted. This result was not unexpected, as the C3-side chain on the oxocarbenium ion intermediate (see Scheme 2) would provide a steric obstacle to axial attack.[11]

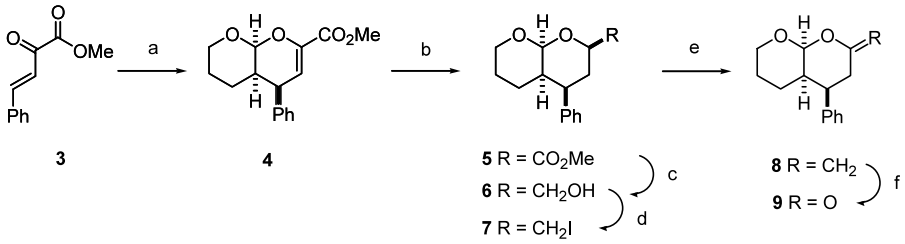
By contrast, and more pertinent to our synthetic goals, reactions with electron rich aromatic nucleophiles were highly stereoselective, giving the predicted *trans* diequatorial product consistent with an equilibration mechanism (Scheme 4).[12] Anisole (entry 4) reacted at the *para*-position only, yielding a single compound identified as structure **13** on the basis of proton NMR ($J_{2,3}=8.7$ Hz) and X-ray crystallography. Unfortunately, replacement of anisole with 4-(trimethylsilyl)-anisole[13] as nucleophile (entry 5) did not result in an increase in the yield of acid **13**.[14] However, efficient substitution was finally realized by replacing anisole with triisopropylsilyloxybenzene (entry 6), which gave compound **14** as a single isomer in 82% yield after chromatography.

In summary, Scheme 2 has been realized and efforts are currently underway to apply this methodology to the synthesis of blepharocalyxin D.

X-Ray crystallographic data: Crystallographic data (excluding structure factors) for structures **4** and **13** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers CCDC 192334 and 208764, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

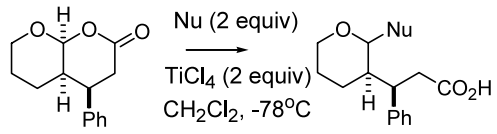


Scheme 2.



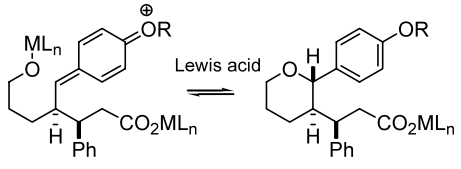
Scheme 3. Synthesis of bicyclic lactone **9**. *Reagents and conditions*: (a) $MeAlCl_2$, DHP, CH_2Cl_2, −78°C (83%); (b) H_2, Pd/C, CH_3OH (99%); (c) $LiAlH_4$, Et_2O (75%); (d) PPh_3, I_2, imidazole, toluene, reflux (70%); (e) NaH, DMF; (f) O_3, CH_2Cl_2, −78°C, then Me_2S (71% from **7**).

Table 1. Reactions of compound **9**



entry	Nu	product(s)	%yield[a]
1	Et_3SiH	**10**	99
2	Ph—≡—$SiMe_3$	**11**[b]	85
3	$SiMe_3$	**12**[c]	96
4	OCH_3	**13**[d]	61
5	OCH_3, $SiMe_3$	**13**[d]	48
6	OTIPS	**14**[e]	82

[a] Yields refer to isolated products.
[b] $J_{2,3}$= 4.2 Hz.
[c] 2:1 diastereomeric mixture, ratio determined by NMR.
[d] $J_{2,3}$= 8.7 Hz.
[e] $J_{2,3}$= 9.1 Hz.



Scheme 4.

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