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Stereoselective Approach to *C*-Aryl Pyranoside Synthesis Which Addresses the Problem of C7-Substitution in Blepharocalyxin E

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Abstract: A general route to a series of aryl-substituted pyranoside derivatives has been developed as a model for the synthesis of blepharocalyxin E. Two *exo*-substituted tetrahydro-4*H*-furo[2,3-*b*]pyran-2-one derivatives, **8a** and **8b**, were prepared and treated separately with anisole and phenoxytriisopropylsilane under Lewis acid conditions to effect *C*-aryl pyranoside synthesis. In each case, a γ-lactone was formed, which rearranged to the desired structure on acid treatment. Four compounds (**12**, **14**, **16**, and **18**) were prepared by this route as single isomers in good overall yield.

Interest in the synthesis of diarylheptanoid natural products recently led us to investigate a new strategy in stereocontrolled tetrahydrofuran synthesis, using the tetrahydro-4*H*-furo[2,3-*b*]pyran-2-one framework as a pyranosyl donor (Scheme 1).[1] While this approach was found to be successful with nonaromatic nucleophiles, providing the expected C2-substituted pyranoside products in one step from their bicyclic lactone precursor, an unexpected result was observed when we attempted to prepare *C*-aryl pyranoside **2** directly from compound **1** using anisole as the nucleophile. The only product was γ-lactone **4**, which was reasoned to arise from compound **2** by equilibration. Importantly, on exposure to 5% HCl in MeOH, lactone **4** was cleanly converted to the methyl ester **3** in 90% yield. The C2 equatorial stereochemistry in compound **3**, and presumably intermediate **2**, is believed to be under thermodynamic control, as evidenced by our earlier observation that nonaromatic nucleophiles show a strong kinetic preference for formation of the corresponding *C*-alkyl pyranosides with C2 axial selectivity in these reactions.[1]

We now report that this two-step sequence can be successfully carried out on tetrahydro-4*H*-furo[2,3-*b*]-pyran-2-ones bearing an *exo*-4-alkoxyphenyl substituent at C3. Moreover, the aromatic nucleophile used to effect anomeric substitution in these reactions is not restricted to anisole.

The purpose of this study was to develop a general strategy for accessing the eastern segment of blepharocalyxin E (Figure 1) which incorporates the critical C7 stereocenter. Blepharocalyxin E has been shown to be an inhibitor of human fibrosarcoma HT-1080 and murine colon 26-L5 carcinoma cells in vitro.[2]

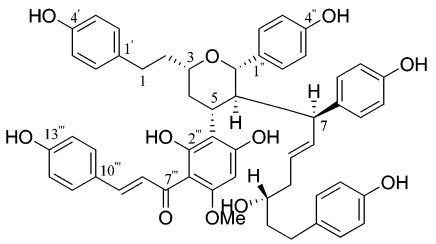
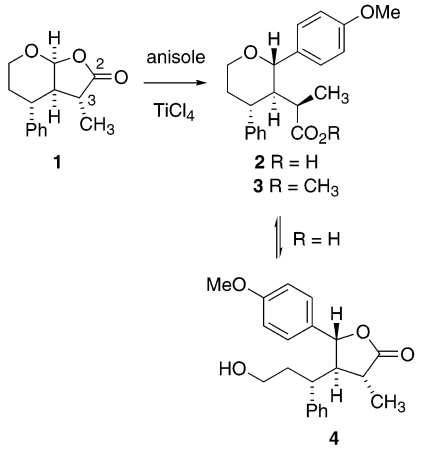


FIGURE 1. Blepharocalyxin E.

SCHEME 1. Novel *C*-Aryl Pyranoside Synthesis



Our study began with the synthesis of bicyclic lactones **8a** and **8b** from the known compound **5** (Scheme 2). We have previously reported the stereoselective synthesis of this ester from 4-phenyl-2,3-dihydropyran.[1] From X-ray data, we were able to determine the vicinal bond angle between protons at C3 and C4 to be 93.3°, which explained why the C3 proton appeared as a singlet in the proton NMR spectrum. Importantly, the lack of multiplicity of this proton in other derivatives became a useful tool for confirming stereochemical assignments (vide infra). Methylation of compound **5** with NaH showed that this bicyclic framework could tolerate a quaternary center at C3. Compound **6** was formed as a single isomer.[3] For C3 arylation of compound **5**, we turned to the use of aryllead(IV) tricarboxylates.[4] High-yielding α arylations of activated methines have been reported using these reagents. Following the published procedure,[5] *p*-methoxyphenyllead triacetate (**9a**) was prepared and reacted with bicyclic lactone **5** under basic conditions. Using DMAP as base, compound **7a** formed as a single isomer, isolated in 85% yield. Formation of compound **8a** from **7a** could be achieved by treatment with NaCl in refluxing wet DMSO,[6] which conditions led to the formation of a separable mixture of the desired

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(1) Cakir, S. P.; Mead, K. T.; Smith, L. T. *Tetrahedron Lett.* **2003**, *44*, 6355−6358.

(2) Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2001**, *24*, 525−528.

(3) The assignment is supported by an X-ray crystallographic structure determination.

(4) For recent examples, see: (a) Konopelski, J. P.; Lin, J.; Wenzel, P. J.; Deng, H.; Elliott, G. I.; Gerstenberger, B. S. *Org. Lett.* **2002**, *4*, 4121−4124. (b) Buston, J. E. H.; Moloney, M. G.; Parry, A. V. L.; Wood, P. *Tetrahedron Lett.* **2002**, *43*, 3407−3409 and references therein.

(5) Collins, D. J.; Cullen, J. D.; Fallon G. D.; Gatehouse, B. M. *Aust. J. Chem.* **1984**, *37*, 2279−2294.

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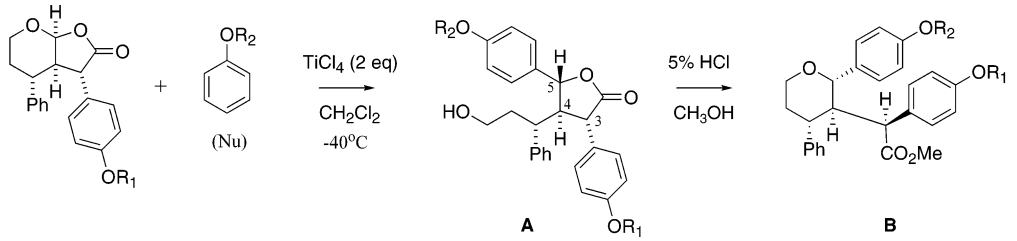
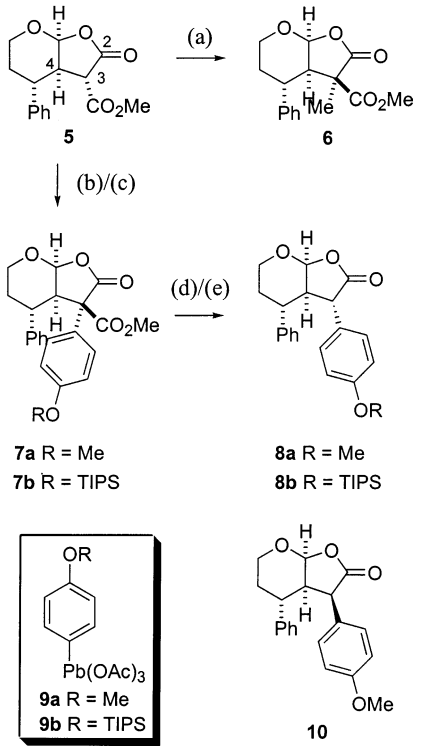
TABLE 1. Reactions of Bicyclic Lactones 8a and 8b with Aromatic Nucleophiles



entry	R_1	R_2	Nu (equiv)	% yield of **A**[a]	A	% yield of **B**[a]	B
1	Me (**8a**)	Me	2	83	**11**	83	**12**
2	Me (**8a**)	Si(Me)$_2$*t*-Bu	2	D[b]		N/A	
3	Me (**8a**)	Si(Ph)$_2$*t*-Bu	3	D[b]		N/A	
4	Me (**8a**)	Si(*i*-Pr)$_3$	3	87	**13**	95	**14**
5	Si(*i*-Pr)$_3$ (**8b**)	Me	3	76	**15**	85	**16**
6	Si(*i*-Pr)$_3$ (**8b**)	Si(*i*-Pr)$_3$	3	80	**17**	73	**18**

[a] Yields refer to purified compounds. [b] Decomposition observed.

SCHEME 2. Synthesis of Derivatives 8a and 8b[a]



[a] Conditions and reagents: (a) NaH, MeI, THF, 0 °C (83%); (b) **9a**, $CHCl_3$, DMAP, reflux (85%, R = Me); (c) **9b**, $CHCl_3$, DMAP, reflux (88%, R = TIPS); (d) NaCl, DMSO, H_2O (81%, R = Me); (e) 1 M KOH, MeOH; 2 N HCl reflux in benzene (45%, R = TIPS).

adduct along with its *endo* diastereomer (**10**)[3] in a ratio of 7.5:1. As expected, the C3 proton in this analogue appeared as a doublet in the NMR spectrum, while the major isomer, compound **8a**, showed a singlet for this proton, supporting its assignment as the corresponding *exo* derivative by analogy with compound **5**.

Following an identical protocol used to prepare compound **7a**, *p*-(triisopropylsilyloxy)phenyllead triacetate (**9b**) was prepared and reacted with compound **5** to give structure **7b**. In this case, however, use of NaCl in refluxing wet DMSO to effect decarboxylation resulted only in product decomposition. Instead, derivative **8b** was prepared as a single isomer, albeit in low yield, by treatment of **7b** with standard hydrolysis conditions.

Reaction of compound **8a** with anisole in the presence of $TiCl_4$ gave the γ-lactone **11** as a single stereoisomer in 83% yield (Table 1, entry 1). The stereochemistry of this product was determined largely by proton NMR. A NOESY cross-peak between protons at C3 and C5 confirmed their *cis* relationship, while the coupling constant between protons at C3 and C4 (10.9 Hz) clearly indicated a *trans* relationship between the substituents at these positions. To our delight, compound **11** rearranged to the pyranoside derivative **12** on exposure to methanolic HCl.

Replacement of anisole with a silyl protected phenol as nucleophile gave mixed results. Use of either *tert*-butyldimethylphenoxysilane (entry 2) or *tert*-butyldiphenylphenoxysilane (entry 3) led only to reagent decomposition under the reaction conditions. In contrast, employment of phenoxytriisopropylsilane gave a clean reaction, providing the γ-lactone **13** in 87% isolated yield as a single isomer (entry 4). Importantly, this compound rearranged to derivative **14** in an impressive 95% yield.

The reactions of compound **8b** with anisole and phenoxytriisopropylsilane paralleled those of structure **8a** (Table 1), giving γ-lactones **15** and **17**, respectively (entries 5 and 6). Moreover, both γ-lactones underwent the desired rearrangement on acid treatment to give *C*-aryl pyranosides **16** and **18**, respectively.

In summary, a stereoselective route to *C*-aryl pyranoside derivatives has been developed which we hope will find application in the synthesis of blepharocalyxin E. Efforts to synthesize this natural product are currently in progress.

Experimental Section

General Procedure for Reactions of 8a and 8b with Aromatic Nucleophiles. To a solution of either **8a** or **8b** (1equiv) in CH_2Cl_2 (0.05 M) were added the nucleophile (3 equiv, unless otherwise indicated) followed by $TiCl_4$ (2 equiv) at −40 °C under argon. The resultant mixture was stirred for the time indicated at the temperature specified, quenched by addition of

(6) Krapcho, A. P.; Jahngen, E. G. E.; Lovey, A. J. *Tetrahedron Lett.* **1974**, 1091−1094.

water at −40 °C, and warmed to room temperature. After the reaction mixture was diluted with CH_2Cl_2, the aqueous layer was separated. The organic phase was washed with brine solution and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the crude product was purified by flash column chromatography.

General Procedure for the Synthesis of *C*-Aryl Pyranosides. To a solution of the γ-lactone in MeOH (c = 0.04 M) was added a solution of freshly prepared anhydrous HCl (5% in MeOH) until the disappearance of γ-lactone was indicated by TLC. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography.

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Supporting Information Available: Experimental procedures and peak listings of all novel compounds, ^1H and ^{13}C NMR spectra of **7a**,**b**, **8a**,**b**, and **10**−**18**, and X-ray crystallographic data for **5**, **6**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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