SYNTHESIS AND RING CLEAVAGE OF A STERICALLY HINDERED TETRAHYDRO-4H-FURO [2,3-b]PYRAN-2-ONE. A MODEL FOR THE TOTAL SYNTHESIS OF BLEPHAROCALYXIN E

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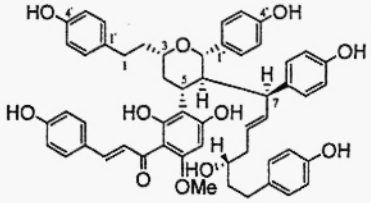
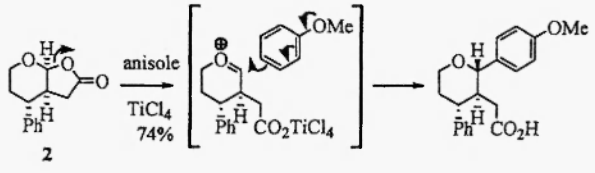
Abstract: A synthesis of 4-(2,4,6-trimethoxyphenyl)-3,4-dihydro-2*H*-pyran from 2,4,6-trimethoxybenzaldehyde is reported. Radical induced cycloaddition of potassium monomethyl malonate (PMMM) to this dihydropyran has been demonstrated to give a bicyclic lactone as a single isomer. Subsequent alpha aryl substitution, ring cleavage, and rearrangement steps provided a *C*-aryl pyranoside derivative which represents a model for the total synthesis of blepharocalyxin E.

Introduction

A number of diarylheptanoid constituents of *Alpinia blepharocalyx* have been isolated and identified by Kadota and coworkers and shown to exhibit significant antiproliferative activity against human fibrosarcoma HT-1080 and murine colon 26-L5 carcinoma cells *in vitro*.[1-3] One of these constituents, blepharocalyxin E **1**, was first reported in 2000.[3] A synthetic plan for this compound was developed by our group which was based on the observation that simple tetrahydro-4H-furo[2,3-b]pyran-2-ones such as compound **2** (Scheme 1) could be cleaved with electron rich aromatic nucleophiles to give *C*-aryl pyranosides as single isomers.[4,5] The generality of this method, however, has not been put to the test. Specifically, the question remained as to whether more complex derivatives of compound **2** bearing bulkier trialkoxyphenyl substitution in place of phenyl could be prepared and ring cleaved with the same efficiency. Given that this would be a requirement for C5-substitution in the natural product **1**, a study was initiated to answer this question.



Blepharocalyxin E **1**



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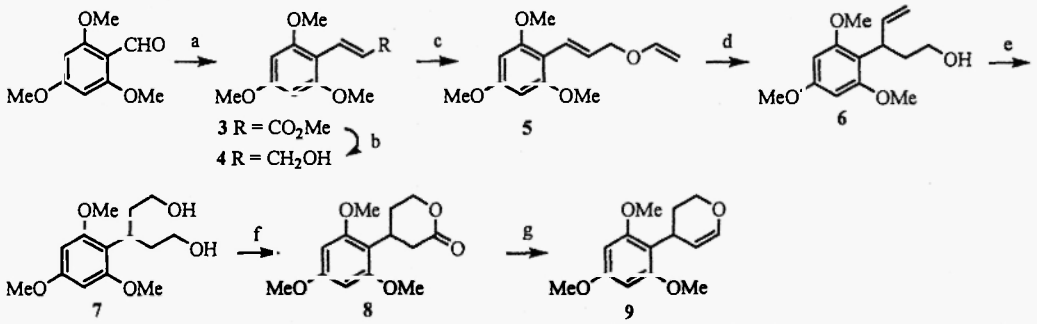
Scheme-1

Results

We have previously reported a route to *exo*-substituted tetrahydro-4H-furo[2,3-b]pyran-2-ones such as compound **2** by radical induced cycloaddition of potassium monomethyl malonate (PMMM) to 4-substituted dihydropyrans.[5] Related reactions had previously been reported independently by the groups of Trogolo[6] and Currie[7], but prior to our work reactions of PMMM with 4-substituted dihydropyrans had not been reported. For our present study we required 4-(2,4,6-trimethoxyphenyl)-

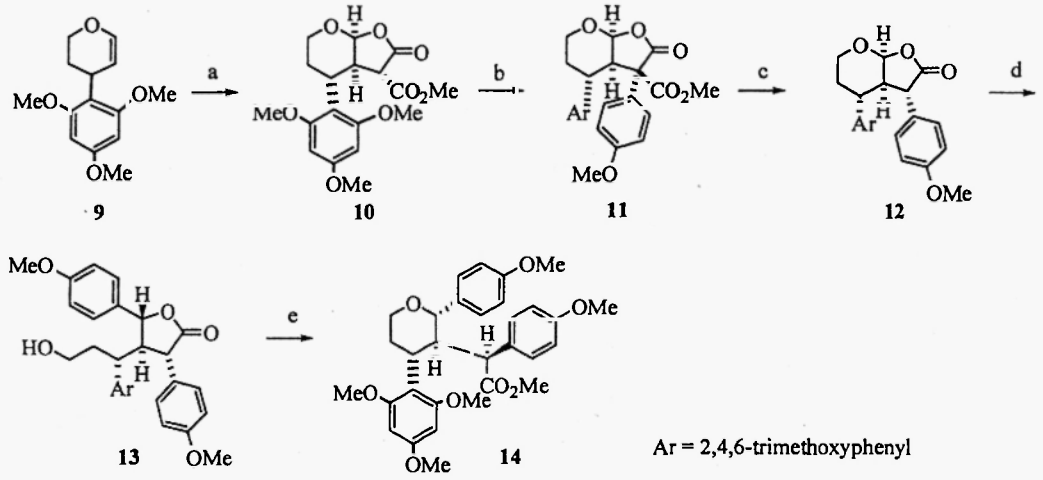
3,4-dihydro-2*H*-pyran **9** (Scheme 2), which had not been reported in the literature. Starting from commercially available 2,4,6-trimethoxybenzaldehyde, conversion to alcohol **4** was achieved in two steps by Horner-Emmons olefination followed by standard reduction of ester **3**. A Claisen rearrangement from vinyl ether **5** provided alcohol **6**, which was converted to dihydropyran **9**, via diol **7** and lactone **8**, in four steps.



[a]Conditions and reagents: (a) $(MeO)_2POCH_2CO_2Me$, LHMDS, 0°C, 2h (98%); (b) DIBAL-H, toluene, 0°C, 3h (94%); (c) CH_2=CHOEt, $Hg(OAc)_2$, reflux 12h (91%); (d) iBu_3Al, CH_2Cl_2, 0°C, 45 min (66%); (e) (i) $BH_3{\cdot}SMe_2$; (ii) NaOH, H_2O_2, THF, 0°C, 3h (98%); (f) PCC, CH_2Cl_2, 4 A° crushed mol. sieves, 0°C – rt, 12h (56%); (g) (i) DIBAL-H, -78°C, 1h (89%); (ii) MsCl, pyridine, 0°C, 2h (64%).

Scheme-2[a]

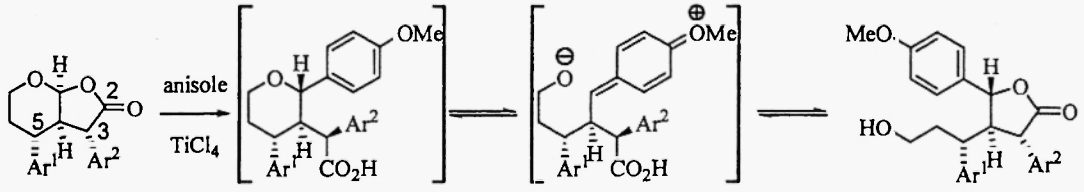
With compound **9** in hand, conversion to bicyclic lactone **10**, as a single isomer in moderate yield, was achieved by reaction with potassium monomethyl malonate in the presence of ceric ammonium nitrate (CAN)[6] (Scheme 3). The stereochemistry of compound **10** was verified by x-ray crystallography. For the alpha-arylation of compound **10**, we turned to the use of aryllead (IV) triacetates, as described by Pinhey[8] and, more recently, Konopelski.[9] Initially this proved to be a little problematic, but was finally solved by treatment of **10** with 4-methoxyphenyllead triacetate in the presence of 1,10-phenanthroline, which gave compound **11** as a single isomer. Numerous conditions were studied for the decarboxylation of intermediate **11**. The best results were found using LiI in DMF, which gave lactone **12** as a 16:1 separable mixture (*exo*:*endo*) of diastereomers. As expected, reaction of lactone **12** with $TiCl_4$ and anisole did not provide the desired product **14**, but instead gave butyrolactone **13**. Fortunately, this rearranged to the methyl ester **14** on exposure to dry methanolic HCl. The stereochemical assignments of compounds **13** and **14** were supported by both 1-D (^1H, ^{13}C)[10] and 2-D (HETCOR) NMR experiments, and by comparison with related derivatives previously prepared in our lab.[4,5]



[a]Conditions and reagents: (a) PMMM, CAN, CH_3CN, rt 45 min (59%); (b) 4-methoxyphenyllead triacetate, 1,10-phenanthroline, $CHCl_3$, reflux 24h (85%); (c) LiI, DMF, reflux 5h (67%); (d) $TiCl_4$, anisole, CH_2Cl_2, -10 to -15°C, 2h (83%); (e) 5% dry HCl, MeOH, rt 5h (94%).

Scheme-3[a]

The formation of compound **13** from intermediate **12** was not unexpected. Earlier work in our lab had shown that alpha-substituted bicyclic lactones give butyrolactone products under these conditions.[4,5] Importantly, compound **13** is believed to arise from equilibration of the first-formed acid **15**, rather than from direct substitution of lactone **12** (Scheme 4). This reasoning is based on the results of ring opening reactions of alpha-unsubstituted derivatives, which give *C*-aryl pyranosides directly (see Scheme 1), coupled with the rationale that the acyl C-O bond in compound **12** is clearly more prone to cleavage than the ether C-O bond. Presumably the rearrangement (**15** → **13**) is driven by the steric interaction between the substituent alpha to the carboxylic acid moiety (Ar^2) and the C2-substituent on the tetrahydropyran ring.



12 **15** **13**

Scheme-4

Conclusions

The formation of an *exo*-substituted tetrahydro-4H-furo[2,3-b]pyran-2-one using the previously reported protocol has been shown to be tolerated by the presence of a bulky 2,4,6-trimethoxyphenyl substituent at the 4-position on the dihydropyran ring. Moreover, subsequent alpha-arylation and ring cleavage reactions of the bicyclic lactone have been shown to proceed without incident. This result bodes well for the total synthesis of blepharocalyxin E and its related analogues using this strategy.

References

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10. Spectral data for compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.12 (d, J=8.8 Hz, 2H), 6.67 (d, J=8.6 Hz, 2H), 6.55 (d, J=8.8 Hz, 2H), 6.46 (d, J=8.8 Hz, 2H), 6.14 (s, 1H), 6.06 (s, 1H), 4.52 (d, J=9.5 Hz, 1H), 3.94 (s, 5H), 3.80 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.64-3.5 (m, 3H), 3.34 (s, 3H), 2.47 (qd, J=12.7, 4.6 Hz, 1H), 1.50 (d(broad), J=11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.3, 159.7, 159.0, 157.6, 133.1, 130.0, 129.76, 129.70, 113.3, 112.7, 112.1, 91.2, 90.5, 83.6, 68.9, 55.5, 55.2, 55.1, 51.4, 51.1, 46.2, 35.5, 31.3; FT-IR ($CHCl_3$): 2946, 2837, 1733, 1608, 1513, 1250, 1153, 1127, 734; R_f: 0.41 (Hexane: EtOAc; 1:1); Melting Point: 130-132°C.

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