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A general route to 5-substituted-2-furylacetic acids: a brief synthesis of plakorsin B

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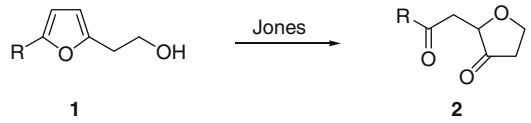
ABSTRACT

3,4-Dihydroxy-5-alkynylcarboxylic acids, readily obtained by the addition of lithium acetylides to α-acetoxysuccinic anhydride followed by reduction and hydrolysis, undergo smooth silver(I)-catalysed 5-*endo*-dig cyclisations and in situ dehydration to give excellent overall yields of 5-substituted-2-furylacetic acids, including the natural metabolite plakorsin B.

In the preceding paper,[1] we reported that 2-furylethanols **1** have a strong tendency to rearrange into the keto-tetrahydrofurans **2**, probably by sequential oxidative ring opening to the corresponding (*Z*)-enediones followed by 5-*exo*-trig Michael-type ring closure, when treated with a variety of oxidising agents, especially the Jones reagent (Scheme 1).

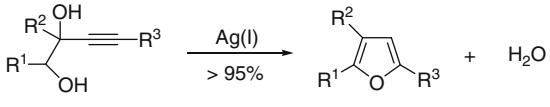
This may account for the fact that the oxidation of 2-furylethanols to the corresponding 2-furylacetic acids is not represented in the current chemical literature. We were therefore left in something of a quandary as to how to apply our very efficient furan synthesis, wherein 3-alkyne-1,2-diols **3** are converted directly into furans **4** and water using heterogeneous silver(I) catalysts (Scheme 2),[2] to the synthesis of naturally occurring 2-furylacetic acids.

Specific examples of interest were the fatty acid derivatives plakorsins A and B **5** (Scheme 3), isolated from the marine sponge, *Plakortis simplex*.[3] While these are simple enough metabolites, they do display some useful cytotoxic activities against various cancer cells lines and, of more chemical interest, are the precursors of the much more densely functionalised metabolite manzamenone A **6**, into which they are converted following sequential oxidative ring opening (the first step in Scheme 1), aldol condensation, dehydrative dimerisation and finally a *retro*-Dieckmann ring closure.[4] Additional members of this complex group of metabolites are members of the pyrrolidine alkaloids, the plakoridines; by a neat piece of logical deduction, it has been proposed that these compounds are all interrelated biosynthetically.[5]



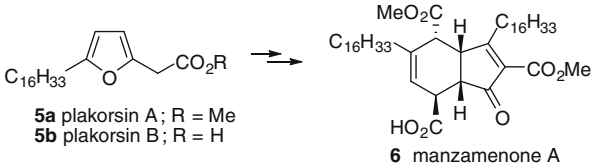
1 **2**

Scheme 1.



3 **4**

Scheme 2.



5a plakorsin A; R = Me
5b plakorsin B; R = H

6 manzamenone A

Scheme 3.

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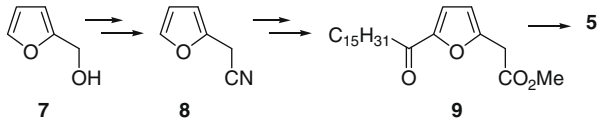


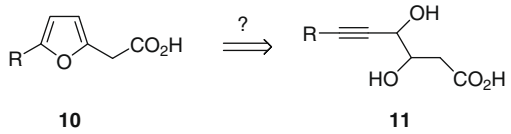
Scheme 4.

The Whitehead group synthesis of the plakorsins **5** occupied their attention for some time. The successful five-step synthesis (Scheme 4) was based on classical steps and consisted of chlorination of very cheap 2-furylmethanol **7** and homologation to the nitrile **8**, hydrolysis to the corresponding methyl ester, introduction of the C_{16} fatty side chain by Friedel–Crafts acylation to give the keto-ester **9** and finally a Wolff–Kishner reduction. Initially, and perhaps unsurprisingly given the sensitive nature of furans in general, this was a rather inefficient synthesis but the group have subsequently achieved remarkable improvements to this by very careful optimisation such that it is now a very effective approach to the plakorsins **5** and, presumably, to many other 5-substituted-2-furylacetic acids in general.[6]

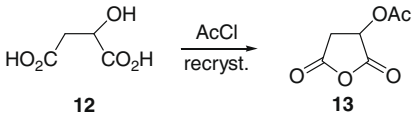
In spite of these improvements, this is still quite a demanding synthesis which utilises a large range of reagents and solvents, so we were still keen to apply our silver(I)-catalysed method and reasoned that, in view of the foregoing problems associated with oxidation chemistry (Scheme 1), a direct approach might be better. We therefore wondered if the generalised 5-substituted-2-furylacetic acids **10** could be obtained from the corresponding dihydroxyalkynoic acids **11**, without interference from the free carboxylic acid group and further of course, if such precursors could be easily synthesised in a general manner (Scheme 5).

Fortunately, the required precursors **11** are available using a one-pot synthesis from α-acetoxysuccinic anhydride **13**, which is readily derived from cheap (DL)-malic acid (hydroxysuccinic acid) **12** by recrystallisation from acetyl chloride (Scheme 6).[7]

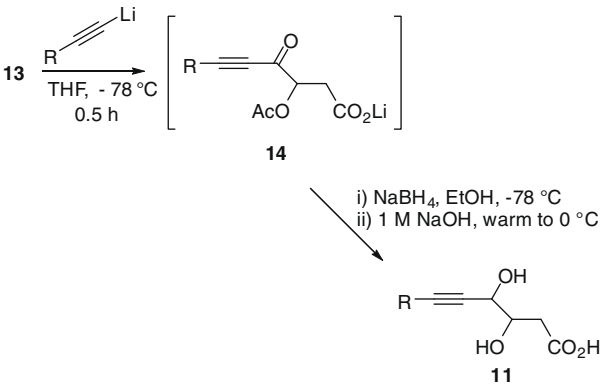
Subsequent addition of a lithio acetylide to the anhydride **13** follows a Bürgi–Dunitz trajectory to give the keto-acetylides **14** (Scheme 7). In our hands, if such a reaction was worked up at this stage, these were the only products (as the free acids), according to ^{1}H NMR analysis, indicating that the attack of the acetylide is extremely regioselective in terms of both the functional group selectivity and the position and angle of attack. Minor constituents of the crude product were the starting acetylide and succinic acid residues, indicating that a side reaction might be deprotonation of the anhydride by the acetylide, however, this did not represent a serious loss. In normal circumstances however, we followed the original Scheme 7 and added ethanolic sodium borohydride to the reaction mixture to reduce the ketone group. This was followed by the addition of aqueous sodium hydroxide to hydrolyse all the esters present after which the mixture was warmed to ambient



Scheme 5.



Scheme 6.



Scheme 7.

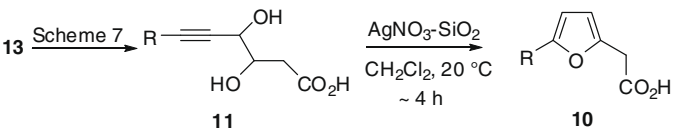
temperature, acidified and the products were extracted into ethyl acetate. The resulting polar dihydroxy acids **11** were obtained in around 60–70% yields and were essentially a clean mixture of diastereoisomers according to ^{1}H NMR analysis and were not further purified beyond drying under high vacuum.

We were delighted to find that subsequent exposure of the dihydroxy acids **11** to 10 mol % of 10% w/w silver(I) nitrate adsorbed on silica gel in dichloromethane generated excellent yields of the desired 2-furylacetic acids **10**.[2] As far as we could judge, these were all well in excess of 90% and hence the overall yields quoted almost entirely reflect the losses at the acetylide addition stage. The results are collected in the Table 1.[8]

It should be noted that these are all unoptimised yields. The method was equally effective for aryl- and alkyl-substituted alkynes and the products (entries 1 and 2) and *tert*-butyldimethylsilyl groups were completely stable to all conditions used (entries 3–5), even when there was a possibility of competing cyclisation of this function onto the alkyne (entry 5). A sensitive citronellyl terpene residue also survived unmolested (entry 6). Finally, the method delivered a decent yield of plakorsin B (entry 7), without the need to modify the reaction conditions in view of the presence of a lengthy alkyl chain.

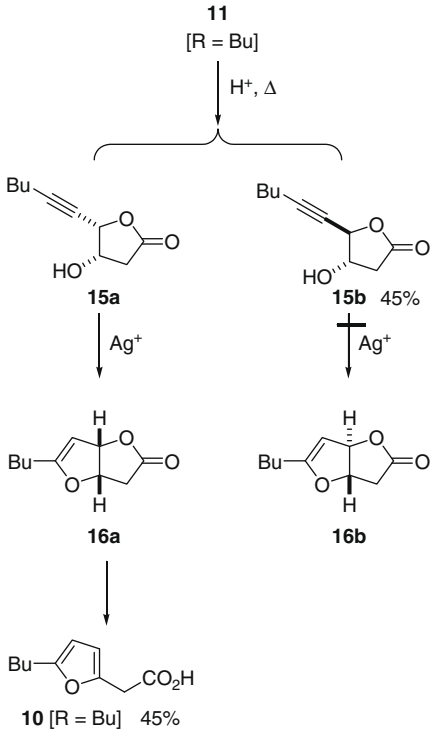
In general, the dihydroxy acids **11** were isolated as 1:1–2:1 mixtures of diastereoisomers; we noticed little difference in the rates at which each underwent cyclisation and dehydration to the furylacetic acids **10**. In an effort to probe this aspect further, the mixture of dihydroxy acids **11** [R = Bu] derived from 1-hexyne was treated with catalytic *p*-toluenesulfonic acid in toluene at 50 °C for two hours,[7] after which we isolated a 51:49 mixture of the two possible lactones **15a**,**b**. When this mixture was treated with 10% w/w sil-

Table 1
The conversion of 3,4-dihydroxy-5-alkynoic acids **11** into 5-substituted-2-furylacetic acids **10** using silver(I) nitrate-SiO_2



Entry	R	Overall yield[a] (%)
1	Ph	85
2	Bu	82
3	$TBSOCH_2$	59
4	$TBSO(CH_2)_2$	67
5	$TBSO(CH_2)_3$	68
6	$Me_2C{:}CH(CH_2)_2CH(Me)(CH_2)_2$	71
7	$Me(CH_2)_{16}$	55

[a] From the anhydride **13**.



Scheme 8.

ver(I) nitrate-silica gel, only one of the diastereoisomeric lactones underwent cyclisation, while the other remained unaltered (Scheme 8).

This must be due to the high degree of strain associated with *trans*-fused 5/5 cyclic systems and hence the isomer **16b** is not formed under these relatively mild conditions. Each compound, **10** [R = Bu] and lactone **15b** was isolated in 45% yield. Clearly, this is mainly of mechanistic interest and does reveal a limitation of this silver-catalysed chemistry, which is not able to trigger cyclisations leading to highly strained systems, although it could prove useful in separating diastereoisomeric mixtures of lactones of type **15**, but obviously somewhat wastefully. It has been established previously that propargylic hydroxy groups assist the binding of silver(I) ions to alkynes.[9] Clearly this is not occurring in the case of cyclisation of the lactone **15a** although its cyclic nature may well be an alternative facilitating feature.

In summary, we contend that the present chemistry represents a rather brief, direct and viable route to 5-substituted-2-furylacetic acids, which should find many applications in the synthesis of these compounds, which are not easy to prepare by the oxidation of the corresponding 2-furylethanols.[10] It is notable that these silver-catalysed cyclisations of 3,4-dihydroxy-5-alkynoic acids **11** were completely regioselective: no products from competing 6-*exo*-dig cyclisations of the carboxylic acid group onto the alkyne were observed. In the case of lower homologues such as (*Z*)-alk-2-en-4-ynoic acids, silver-catalysed 5-*exo*-dig cyclisations of these have long been established as a useful route to ylidenebutenolides.[11] In the current examples, as mentioned above, it seems very likely that the presence of a hydroxy group adjacent to the alkyne assists silver complexation to the latter and hence in accelerating the 5-*endo*-dig process.[12]

Acknowledgements

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