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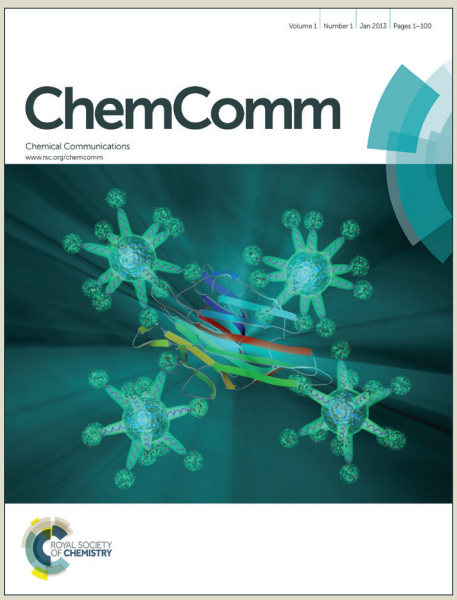

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An Organocatalytic One-pot Cascade Incorporating the Achmatowicz Reaction Affording 3-Pyrone Derivatives

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The development of an organocatalytic one-pot cascade for the annulation of simple starting materials: α,β-unsaturated aldehydes, hydrogen peroxide, β-carbonyl compounds and NBS to furnish optically active 3-pyrones in good yield and with excellent enantioselectivity is presented. Further diversification of the obtained products is demonstrated by selective reductive transformations.

Owing to their potential as orthogonally functionalised building blocks, 3-pyrones are widespread intermediates in the synthesis of complex natural products.[1-4] The application of 3-pyrones in diversity-oriented synthesis and in organometallic enantiomeric scaffolding has also been demonstrated.[5,6] In addition to their usefulness as reactive intermediates, derivatives of 3-pyrone can also be found in naturally occurring compounds. These include the sugar L-Aculose, which is a common constituent of the carbohydrate side chain in Saquamycins and Moromycins,[7] the cellulose pyrolysis product (–)-Levoglucosenone,[8] and the recently isolated apotirucallane (+)-Trichostemonate (Fig. 1).[9]

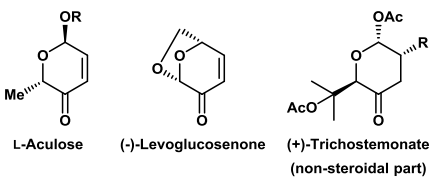


Fig. 1 Naturally occurring 3-pyrone derivatives.

Numerous routes for the formation of 3-pyrones have been demonstrated, among which the Achmatowicz reaction stands out as one of the most successful (Fig. 2, a).[10] This reaction, which allows for the formation of multi-substituted products from hydroxyalkyl substituted furans, has been widely studied, and various modifications of the original conditions have been demonstrated, including stereoselective methodologies for the formation of optically active products. The stereocontrol has been achieved in various ways; *e.g.* by formation of the starting material via enantioselective hydrogenation or alkylation of the parent carbonyl substituted furan, by chiral resolution of the starting material or by application of enantioselective oxidation conditions such as the Sharpless epoxidation or dihydroxylation.[4,11-13] While these strategies allow for the formation of the target 3-pyrones in high yield and enantioselectivity, they are limited by the availability of appropriate furan starting materials. An enantioselective procedure for the direct formation of 3-pyrones from acyclic starting materials would therefore be of major interest (Fig. 2, b).

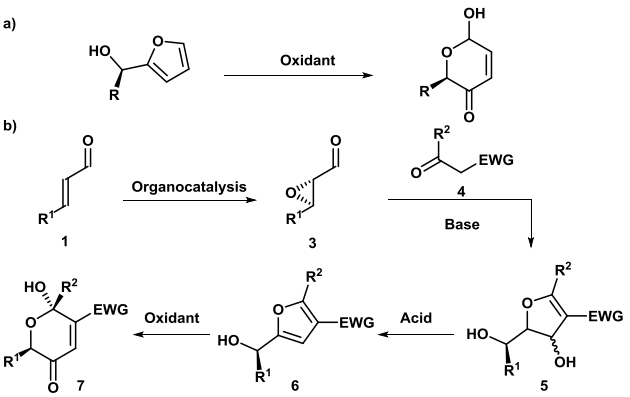


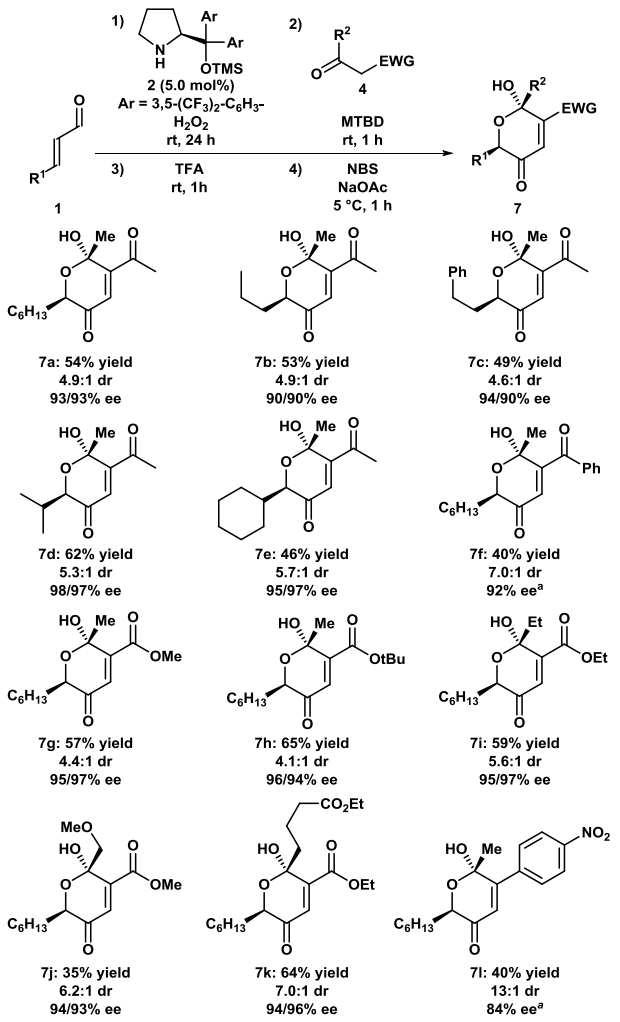
Fig. 2 a) The Achmatowicz reaction. b) Envisioned one-pot formation of 3-pyrones from acyclic starting materials.

The application of asymmetric organocatalytic reactions in one-pot strategies has recently been demonstrated as a powerful tool for the direct formation of chiral heteroaromatic compounds and their derivatives.[14] One-pot methodologies allow newly formed reactive intermediates to be incorporated in a reaction cascade, thereby avoiding their purification and the time and material costs associated therewith. Additionally, complicated structures can be assembled from simple starting materials without the use of protecting group strategies and other means necessary for successful stepwise synthesis. As a result, the development of new one-pot methodologies is a rapidly expanding field in organic synthesis.[15] It was therefore envisioned that multi-substituted 3-pyrones could be obtained via an organocatalytic one-pot cascade reaction, forming the hydroxy substituted furans needed for the final Achmatowicz step *in situ*.[16]

Initial investigations revealed that furans **6**, formed via an asymmetric organocatalytic epoxidation of nonenal **1** followed by cyclisation with 2,4-pentanedione **4** and subsequent CSA catalysed aromatisation, could serve as substrates for the Achmatowicz reaction when *m*-CPBA was used as oxidant. When the reaction sequence was performed in toluene, the entire cascade could, as envisioned, be completed under one-pot conditions, without isolation of any intermediates. Through a screening of oxidants (see SI), NBS with addition of water was found to be a superior alternative to *m*-CPBA. Furthermore, the

chiral CSA was found to be replaceable with TFA. Notably, the observed diastereomeric ratio is under thermodynamic control, underlined by the observation of minor amounts of the open chain triketone as well as inseparability of the diasteromeric hemi-ketals. As such the diastereomeric ratio was not significantly affected by either change of reaction conditions or choice of solvent.

With the optimised one-pot cascade established, investigations were directed towards the scope of the reaction (Scheme 1). Incorporation of various alkyl substituents in the 2-position of the 3-pyrone products (originating from **1**) was carried out, successfully demonstrating incorporation of primary alkyl groups (**7a**–**c**), a secondary alkyl group (**7d**) and a cyclohexyl group (**7e**), all in good yields and excellent enantioselectivities. The scope is limited by the variety of reaction conditions which the aldehyde derived substituent has to sustain; unsatisfactory results were obtained for α,β-unsaturated aldehydes carrying conjugated substituents such as an ester or phenyl, as well as unsaturated alkyl chains.



Scheme 1 Formation of chiral 3-pyrones. Major diastereomer depicted. See SI for details. [a]ee of minor diastereomer could not be established.

Variation of the substituent at the 5- and 6- position of the 3-pyrone products was demonstrated through the application of a selection of β-carbonyl compounds **4**. An unsymmetric diketone was successfully incorporated giving rise to the product in acceptable yield and excellent enantiomeric excess, interestingly as a single regioisomer (**7f**) despite the observation of a mixture of regioisomeric furan intermediates, supporting thermodynamic control of the hemi-ketal ring closure. Ester substituted products were synthesised in improved yields at the expense of slightly lowered diasteroselectivities, but with maintained enantioselectivity (**7g**,**h**).

The substituent at the anomeric centre was successfully varied through the incorporation of commercial β-keto esters, giving rise to the products in good yields and excellent enantioselectivities (**7i**–**k**). The improved diastereoselectivity observed for these substrates can be attributed to the preference for pseudo equatorial positioning of the larger substituents, adding to the generally observed anomeric effect. Finally, replacement of one of the carbonyl groups for an electron-poor aromatic ring was demonstrated to be possible, affording the desired product with high diastereoselectivity, however in slightly decreased yield and enantiomeric excess (**7l**). An important limitation to the nucleophile scope was found to be the inability of furans derived from cyclic 1,3-diketones to undergo the Achmatowicz reaction.

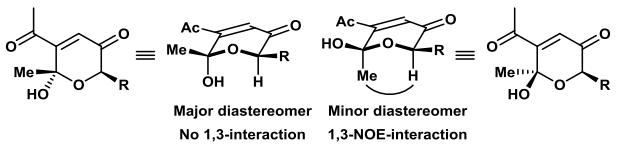
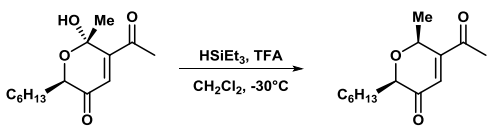


Fig. 3 Determination of relative stereochemistry.

The relative stereochemistry of the two diastereomers of product **7a** was established by NOESY (Fig. 3), from which it was evident that the anomeric effect allows the diastereomer with the hydroxy group pseudo-axial to form as the major product.

The absolute stereochemistry of the products **7** follows from the stereospecificity of the Achmatowicz reaction,[10] as the absolute stereochemistry of the intermediary furans is known.[16] The enantioselectivity originates from the well-studied organocatalytic epoxidation reaction.[17]

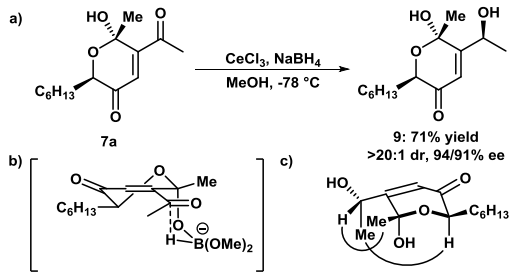
Having established the substituent scope of the reaction, our attention turned towards selective reductive transformations of the obtained products. This constituted a major challenge, as the products contain four possible candidates for reduction, thus careful selection of reaction conditions would be crucial for success. The Kishi reduction is a well-described silane-mediated reduction of hemi-acetals to their corresponding ethers, and we envisioned it would be sufficiently mild to afford selective reduction in our system.[13,18] Delightfully, the unoptimised reaction proved successful, forming the desired dehydroxy product **8** in moderate yield, with conserved enantioenrichment and improved diastereomeric control (Scheme 2).



Scheme 2 Selective Kishi reduction of hemi-ketal.

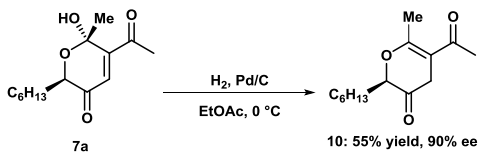
Next, investigations focused on the regioselective reduction of

the ketone functionality, and Luche conditions, which are known to reduce unsaturated ketones in a 1,2-selective manner, stood forward as the method of choice.[19]



Scheme 3 Selective Luche reduction of the exocyclic ketone. a) Reaction conditions. b) Tethered reaction intermediate. c) Notable observed NOEs.

Interestingly, the exocyclic ketone was selectively reduced (Scheme 3, a). To rationalise the formation of the product **9** as exclusively one diasteroisomer, it is important to consider that cerium catalyses the exchange of hydride with alcohols in the reduction agent. We suggest that this allows the neighbouring axial hydroxy group in **7a** to direct the reducing agent in a tethered fashion (Scheme 3, b). Dictated by the Bürgi-Dunitz trajectory, the product **9** can then exclusively be formed from the major diastereomer of **7a**, thereby giving rise to the observed complete diastereoselectivity. The relative stereochemistry of the product was confirmed by NOESY (Scheme 3, c).



Scheme 4 Selective hydrogenation / elimination.

To selectively modify the final main functionality of the 3-pyrone, hydrogenation of the C-C-double bond was attempted. The reaction was unsuccessful in methanol, but proceeded smoothly in ethyl acetate. Interestingly, elimination immediately followed, affording the product **10** in moderate yield under unoptimised conditions, and with preserved enantiomeric excess (Scheme 4). Attempts to avoid the elimination were unsuccessful, suggesting high thermodynamic stability of the tetra-substituted olefin.

Conclusions

Results outlining the development of a new organocatalytic one-pot reaction cascade for the annulation of chiral 3-pyrone derivatives in good yields and excellent enantiomeric excesses have been presented. A wide selection of functional groups has successfully been incorporated in the products to demonstrate the scope of the methodology. Finally, selective reduction of each of the three main functionalities of the obtained 3-pyrone ring systems have been conducted, in all cases affording the desired products regio- and stereoselectively in good yield.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, analytical data for full characterisation and NMR spectra. See DOI: 10.1039/b000000x/

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