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Asymmetric synthesis of functionalised cyclopentenones via organocatalysed rearrangement and enzymatic resolution of pyranones

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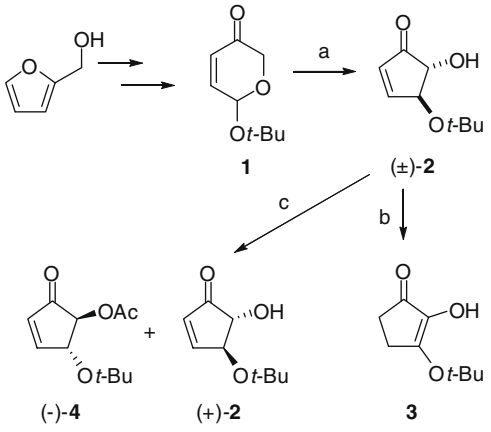
ABSTRACT

A direct asymmetric synthesis of a *trans*-4,5-difunctionalised cyclopentenone derivative has been achieved in 55% yield and 80% ee by organocatalysed rearrangement of a pyranone in *tert*-butanol by DABCO with simultaneous enzymatic resolution.

Functionalised cyclopentenones are versatile precursors for the synthesis of natural products and biologically active molecules,[1,2] including carbocycles.[3] We have developed a convenient synthesis of racemic *trans*-difunctionalised cyclopentenones (±)-**2** from furfuryl alcohol via the key step of rearrangement of the pyranone **1**. The existing protocol requires elevated temperature and an excess of triethylamine (5 equiv), which can lead to the undesirable formation of the isomer **3** if methanol is used as solvent (Scheme 1).[1,2] Further stereoselective transformations, such as conjugate additions, nucleophilic additions, intermolecular cycloaddition, free radical cyclisation and palladium-mediated coupling reactions, on analogues of **2** have been described.[4] Recent efforts aimed at synthesizing (−)-epipentenomycin I have established a chemoenzymatic pathway to the *trans*-difunctionalised cyclopentenone by Pyne *et al.*[5] as well as a more recent asymmetric synthesis by Pohmakotr *et al.* towards the same target molecule.[6] Batey *et al.* have also developed an efficient one-step Lewis acid-catalysed process for the synthesis of a range of racemic *trans*-diamino-cyclopentenones from furfuraldehyde.[7] Since access to enantiomerically pure cyclopentenones is desirable, we also developed an enzymatic resolution of (±)-**2** to afford (−)-**4**, although a large amount of enzyme (3.9 g enzyme/g of (±)-**2**), acylating agent (87 equiv) and long-reaction times (7 days) were required (Scheme 1).[8]

The existing methods for the preparation of enantiomerically pure cyclopentenones have a number of limitations and we therefore sought to improve these protocols. Herein we describe a new, one-pot approach which allows the direct conversion of a pyranone **1** into an enantiomerically pure cyclopentenone (−)-**4** via a sequence involving an organocatalysed rearrangement to give



Scheme 1. Synthesis of enantiomerically pure *trans*-dioxygenated cyclopentenone **2** via a two-step synthesis.[1,4,8] Reagents and conditions: (a) DMF, Et_3N (5 equiv), 80 °C, 24 h, 78%; (b) MeOH, Et_3N (5 equiv), 60 °C, 23 h, 37%; (c) Lipase (Amano PS, 3.9 g enzyme/g of (±)-**2**), vinyl acetate (87 equiv), 40 °C, 7 d, (+)–**2**: 50%, ee ⩾ 95%; (−)–**4**: 45%, ee ⩾ 95%.

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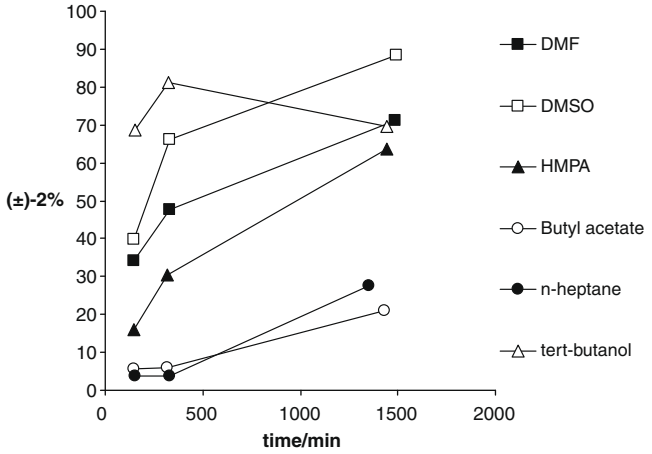
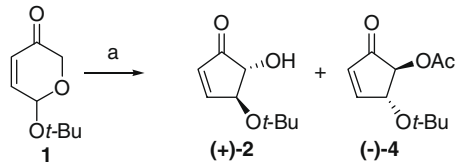


Figure 1. Selected solvent effect on the rearrangement of pyranone **1** to (±)–**2** (70 °C, 0.29 M, Et_3N (5 equiv), determined by GLC using *n*-decane as internal standard).

(±)-**2** followed by enzymatic kinetic resolution. In the context of the present work it is noteworthy that Ramström and co-workers[9] recently described a very elegant combined nitro aldol and enzymatic kinetic resolution protocol.

In order to develop an effective one-pot protocol it was essential to improve the conditions for the isomerisation of the pyranone to the cyclopentenone. The existing conditions required the use of triethylamine (5 equiv) and a prolonged reaction time. Our first objective was to improve these conditions with a view to rendering them compatible with a resolution step. In order to optimize the conditions for the rearrangement of pyranone **1**, a range of solvents were screened at 70 °C in the presence of triethylamine (5 equiv) and each reaction was followed by gas chromatography (GC). A considerable solvent effect can be seen for some representative examples presented in Figure 1.

From Figure 1 it can be seen that the rearrangement proceeds slower for apolar or weakly polar solvents. For more polar aprotic and protic solvents the reaction is faster which is consistent with a proposed mechanism involving an intermediate enol derived from electrocyclic ring opening of **1**, since such an enol would be stabilized in polar protic solvents.[4] It is noteworthy that although the use of these solvents is beneficial, the quantity of (±)-**2** can eventually decrease as a function of reaction time. This can be attributed to decomposition or conversion to the undesired enone **3**. A more detailed study of the effect of solvent, base and temperature was carried out and led us to identify conditions that minimised the formation of **3** and also optimised the formation of (±)-**2**. Selected examples of these studies are presented in Table 1.



Scheme 2. Direct synthesis of enantiomerically pure cyclopentenone (−)–**4** from pyranone **1**: (a) **1** (0.59 mmol) *t*-BuOH (1 mL), DABCO (0.3 equiv), Lipase AK 'Amano' 20 (0.5 mg/mg of **1**), vinyl acetate (5 equiv) 50 °C, 10 d, (+)–**2** and **3** (35%, 91:9 ratio, ee (+)–**2** 11%); (−)–**4**: 55%, ee 80%.

As can be seen from Table 1, the use of a protic solvent to speed up the reaction such as *tert*-butanol was highly beneficial and allowed us to significantly reduce the reaction time (entries 4 and 5). It is also noteworthy that prolonged reaction times led to an undesirable ratio of **2** to **3** with the higher temperature (entry 4). Further studies on the effect of the base also revealed some useful observations. The use of the base DABCO was found to be far more effective than that of triethylamine (80% *vs.* 30% GC yield of (±)-**2** after 20 min) and we were able to reduce the quantity of base from five equivalents in our original procedure, to sub-stoichiometric quantities (10%-15%) (entries 6 and 7). Thus we have developed a new organocatalysed protocol for the isomerisation of (±)-**2** under milder conditions. It is noteworthy that, under these conditions, the quantity of **3** produced is very modest (3%).[10]

These milder conditions for the rearrangement step prompted us to explore the possibility of effecting a combined one-pot sequence of reactions involving organocatalysed rearrangement of pyranone **1** to (±)-**2** followed by *in situ* enzymatic resolution. After screening several enzymes and reaction conditions it was possible to isolate (−)-**4** in 55% yield, ee 80% and a mixture of (+)-**2** and **3** in 35% yield (91:9 ratio, ee (+)-**2** 11%) (Scheme 2).[11] Interestingly, the remaining alcohol (+)-**2** was isolated in low ee which can only be explained by racemisation of the remaining enantiomerically enriched (+)-**2** under the reaction conditions. This may offer the opportunity to further develop this methodology to incorporate a dynamic kinetic resolution (DKR) step with the possibility of improving the conversion further.

In conclusion, we have shown that there is a remarkable solvent effect on the rearrangement of pyranone to cyclopentenone and this has led to a new organocatalysed version of this transformation. The improvement in the conditions resulting from this optimisation study has provided us with the opportunity of developing a combined one-pot sequence involving organocatalysed rearrangement followed by kinetic resolution leading to a convenient asymmetric synthesis of (−)-**4** directly from readily available pyranone **1**. Further work will focus on extending this methodology to other classes of pyranones and towards the possibility of developing a dynamic kinetic resolution approach.

Table 1
Studies on the rearrangement of pyranone **1** to (±)–**2** and **3**

Entry	Solvent	Temp (°C)	Base (equiv)	Reaction time (h)	Yield (±)-**2**, **3**[a]	Ratio (±)–**2**:**3**[b]
1[c]	DMF	80	Et_3N (5)	24	74	91:9
2[c]	DMSO	80	Et_3N (5)	24	22	49:51
3[c]	MeOH	80	Et_3N (5)	24	22	0:100
4[c]	*t*-BuOH	80	Et_3N (5)	48	59	21:79
5[c]	*t*-BuOH	80	Et_3N (5)	5	83	78:22
6[d]	*t*-BuOH	50	DABCO (0.1)	48	77	96:4
7[e]	*t*-BuOH	50	DABCO (0.15)	24	85	97:3

[a] Isolated yield by flash chromatography.
[b] Ratio of (±)–**2**:**3** determined by ^1H NMR.
[c] Reactions were performed using **1** (50 mg/mL).
[d] Reaction was performed using **1** (100 mg/mL).
[e] Reaction was performed using **1** (200 mg/mL).

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10. Rearrangement catalysed by DABCO: To a solution of **1** (200 mg, 1.18 mmol) in *tert*-butanol (1 mL) was added DABCO (19.8 mg, 0.176 mmol). The solution was stirred at 50 °C for 24 h. After cooling the solution, 1 mL of an acetic acid/sodium acetate buffer solution at pH 5 was added to quench the reaction. The organic layer was extracted with CH_2Cl_2 (2 × 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a yellow oil which was purified by chromatography on silica gel with *n*-hexane/ethyl acetate (2:1 v/v) to afford (±)-**2** and **3** in a 97:3 ratio (determined by ^1H NMR) as a yellow low-melting point solid (170 mg, 85%).
11. Direct rearrangement of pyranone **1** to (±)-**2** and enzymatic resolution: To a solution of **1** (100 mg, 0.588 mmol) in *tert*-butanol (1 mL) were added DABCO (19.8 mg, 0.176 mmol), lipase AK 'Amano' 20 (50 mg) and vinyl acetate (0.27 mL, 2.94 mmol). The solution was stirred at 50 °C for 10 d. After cooling the solution was filtered and the solid residue was washed with CH_2Cl_2 (20 mL). The mother liquor was concentrated under reduced pressure to yield a brown oil which was purified by chromatography on silica gel with *n*-hexane/ethyl acetate (3:1 v/v) to afford (−)-**4** as a white low-melting point solid (68 mg, 55%, ee 80%) and (+)-**2** and **3** (32 mg, 35%, ee of (+)-**2** of 11%) in a 91:9 ratio (determined by GLC) as a yellow low melting point solid.