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Diastereoselective Synthesis of Highly Substituted Tetrahydropyran-4-ones

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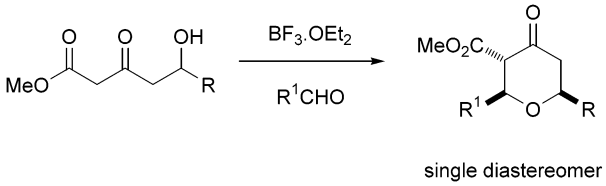
ABSTRACT

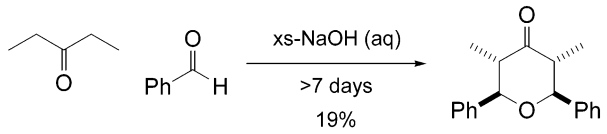


Aldol reactions of β-ketoesters with aldehydes followed by a tandem Knoevenagel condensation, with a further equivalent of aldehyde, and intramolecular Michael addition produces single diastereomers of highly substituted tetrahydropyran-4-ones.

Tetrahydropyran (THP) rings are ubiquitous in the natural product arena, and over the years many methods have been developed for their construction. Some of the most widely used methods are intramolecular epoxide opening, manipulation of carbohydrates,[1] hetero- Diels−Alder cyclizations,[2,3] Prins reactions,[4] and intramolecular Michael reactions.[5] However, all of these procedures have drawbacks: for example, the regiochemistry of epoxide opening, the many protecting group manipulations and functional group interconversions inherent in starting from a carbohydrate, restriction to the use of *E*,*E*-dienes and activated aldehydes in the hetero-Diels−Alder approach,[3] the need for single double bond isomers of homoallylic alcohols[4] and product scrambling in the Prins reaction,[6] and finally the reliance on phenols in the Michael reaction.[5]

Our interest in the formation of THP rings arose from the reports of Maitland and Japp[7] and later Cornubert and Robinet,[8] who showed that a ketone and 2 molecules of aldehyde could be condensed in a low- yielding process to generate substituted THP rings. Much later both of these reactions were found to generate single diasteromers of the THP products (Scheme 1).[9,10] We realized that with current synthetic technology it may be fruitful to revisit these forgotten reactions. In this letter we wish to communicate

Scheme 1. The Maitland−Japp Reaction



(1) Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Baldwin, J. E., Ed.; Pergamon: Oxford, UK, 1983.
(2) For a treatise on the Hetero Diels−Alder reaction see: Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.
(3) For recent examples of asymmetric intermolecular reactions see: Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398. Johannsen, M.; Jorgensen, K A. *J. Org. Chem.* **1995**, *60*, 5757. Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.
(4) For several recent examples see: Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. For a review see: Adams, D. R.; Bhaynagar *Synthesis* **1977**, 661.
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(7) Japp, F. R.; Maitland, W. *J. Chem. Soc.* **1904**, *85*, 1473.
(8) Cornubert, R.; Robinet, P. *Bull. Chim. Soc. Fr.* **1934**, 90.
(9) Sivakumar, R.; Satyamurthy, N.; Ramalingam. K.; O'Donnell, D. J.; Ramarajan, K.; Berlin, K. D. *J. Org. Chem.* **1979**, *44*, 1559.
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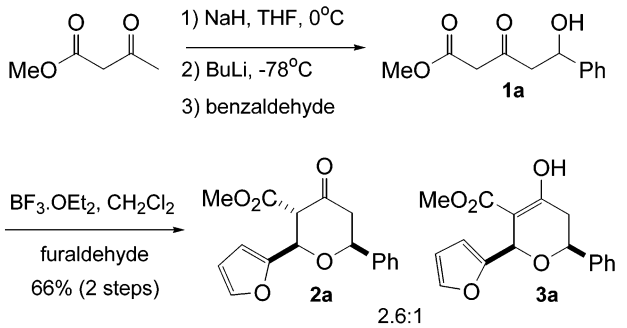
our attempts at developing an alternative, yet complementary, diastereoselective method for the synthesis of THP rings, based on the Maitland−Japp reaction,[7] starting from commercial or readily available starting materials.

To widen the scope of the reaction and enable the installation of different substituents in the 2 and 6 positions of the THP ring, we decided to move away from ketones such as pentan-2-one and, instead, investigate the use of dienolates of β-ketoesters. The marked difference in the reactivity of the two enolate carbons[11,12] should enable the selective incorporation of different aldehydes, thus providing THP rings with different substituents in the 2 and 6 positions.

Methyl acetoacetate was treated with NaH in THF at 0 °C and then with BuLi at −78 °C. The resulting dianion was then treated with 1 equiv of benzaldehyde and the resulting aldol product isolated (**1a**, Scheme 2). If we were

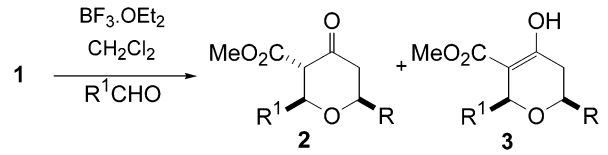
Scheme 2



to generate THP rings we would now have to develop a tandem Knoevenagel−Michael reaction. We rationalized that as both reactions have been promoted by Lewis acids,[5,12] simply mixing the aldol product with a second aldehyde in the presence of $BF_3{\cdot}OEt_2$ might be successful. As retro-Michael reactions have hampered the formation of THP rings in nonphenolic systems,[5] we were optimistic that the relative pK_a values of the starting hydroxyl proton and the β-ketoester proton in the THP product would favor Michael cyclization and drive the equilibrium over to THP products. Indeed, when aldol product **1a** was subjected to $BF_3{\cdot}OEt_2$ in the presence of furaldehyde in CH_2Cl_2, the THP ring was formed rapidly as a mixture of keto and enol tautomers in 66% yield over the two steps. Gratifyingly, only one diastereomer could be detected in the ^{1}H NMR of the crude reaction mixture. This diastereomer was identified as the C2−C6 cis, C5−C6 trans isomer, implying that the reaction was under thermodynamic control.

We next investigated the scope of the pyran forming reaction by surveying a number of different aldehydes in both the initial aldol and the $BF_3{\cdot}OEt_2$ promoted reactions. These results are summarized in Table 1. As can be seen,

Table 1.



1	R	R^1	yield (%)[a]	ratio[b] 2/3
b	hexyl	Ph	80	1:2
c	hexyl	Pr	80	12:1
d	*i*-Pr	Pr	55	1:1
e	*i*-Pr	hexyl	55	1:1.4
f	Ph	Pr	78	only keto
g	Ph	Ph	68	only keto

[a] Isolated yields after flash column chromatography, calculated over two steps from methyl acetoacetate. [b] ^{1}H NMR (400 MHz).

aryl, alkyl, and branched alkyl aldehydes can all be used in either position without any reduction in diastereoselectivity or yield.

It is of interest that the keto and enol tautomers (**2** and **3**) could be isolated by careful flash column chromatography. In these cases it was found that upon standing in $CHCl_3$ the enol tautomer would slowly convert to the keto tautomer. Under identical conditions the keto tautomer was unaffected. This can be explained when one considers that the ^{1}H NMR spectra for the keto tautomers indicate that they exist in a boat conformation, and hence there is little overlap between C5−H5β σ-bonding orbital and the C=O π^* orbital. The boat conformation is evident from a W-coupling between H3β and H5β of 0.8 Hz, and from the gradient nOe enhancements of the THP ring protons (Figure 1). It is

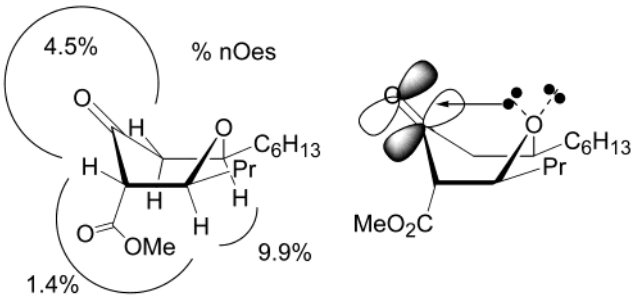


Figure 1.

possible that this boat conformation is stabilized relative to the chair conformation by the donation of a lone pair of the ring oxygen into the C=O π^* orbital.

It has also proved possible to use cyclohexanone in the Knoevenagel/Michael reaction to gain access to spiro-fused THP products such as **4** in an unoptimized 48% yield over the two steps (Scheme 3). Additionally, when the dianion of methyl propionyl acetate was treated with isobutanal and the product subjected to the $BF_3{\cdot}OEt_2$ conditions, pyran **5**

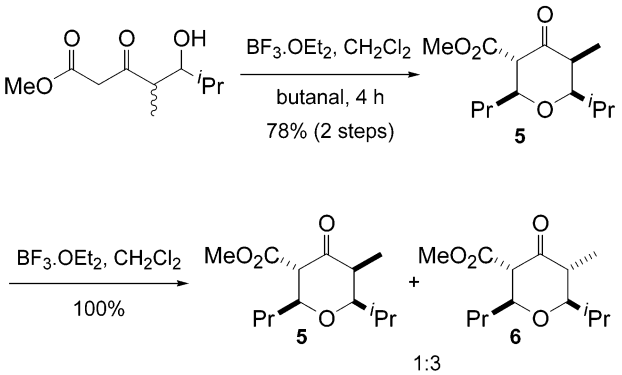
(11) For the pioneering work of Weiler see: Huckin, S. N.; Weiler, L. *Tetrahedron Lett.* **1971**, *50*, 4835. Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157.

(12) For a review see: Jones, G. *Org. React.* **1967**, *15*, 204.

Scheme 3

was formed rapidly in 78% yield. Extended reaction times or resubmission of **5** to the reaction conditions resulted in the partial epimerisation of the C3 position to generate quantitatively a 1:3 ratio of pyrans **5** and **6** (Scheme 4). This

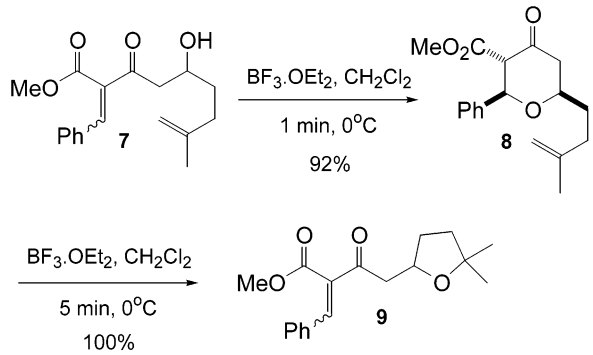
Scheme 4



result can be rationalized if the reaction is assumed to be under thermodynamic control. The initial Knoevenagel reaction generated a mixture of *E* and *Z* double bond isomers. Each of these isomers undergoes rapid Michael/retro-Michael reaction via the appropriate enol to place both the C2 and C6 THP substituents equatorial, regardless of the original double bond geometry. Enolization of the C3 position under the reaction conditions ultimately results in the formation of the more stable diastereomer.

Further evidence to support this hypothesis was obtained by the synthesis of Michael precursor **7**, with pendant unsaturation, as a 1:1 mixture of *E/Z* double bond isomers,

Scheme 5



via standard Knoevenagel conditions reported by Tietze[13] (Scheme 5). When **7** was submitted to the $BF_3{\cdot}OEt_2$ conditions it was rapidly converted (~1 min) to THP **8**, which was isolated as a single diastereomer in 92% yield. When **8** was resubjected to the reaction conditions it was found to be converted to furan **9**. This presumably occurs via retro-Michael reaction followed by cyclization onto the unactivated double bond. As the Lewis acid mediated cyclization of alcohols onto unactivated double bonds is somewhat rare, we believe that this cyclization is promoted by trace amounts of HF present in the $BF_3{\cdot}OEt_2$ solution.

In summary, we have developed a general and convergent diastereoselective synthesis of highly substituted THP rings from readily available starting materials. We are now actively engaged in the attempt to include the initial aldol reaction in the same pot as the tandem Knoevenagel/Michael reactions and in the possibility of making this THP forming procedure enantioselective. These results will be reported in due course.

Acknowledgment. We thank the EPSRC and the University of Nottingham (DTA studentship to W.H.C.M) for financial support.

Supporting Information Available: Experimental details for the pyran-4-one forming reaction and representative examples of spectroscopic data (compounds **2b**, **3b**, and **2f**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182.