Revisiting the Maitland–Japp reaction. Concise construction of highly functionalised tetrahydropyran-4-ones†

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Application of modern synthetic methods to the Maitland–Japp reaction has provided a one pot, one step procedure for the efficient construction of highly substituted tetrahydropyran-4-ones.

Tetrahydropyran (THP) rings are ubiquitous in the natural product arena, and over the years much effort has been directed towards the development of new strategies for their synthesis.[1] Continued interest in the synthesis of THP containing natural products provided the impetus to initiate a project designed to develop a new and more expedient route to the formation of THP rings. Our attention was attracted to the report published by Maitland and Japp in 1904, which showed that a molecule of pentan-3-one and 2 molecules of benzaldehyde could be condensed in a low yielding process to generate a highly substituted THP ring[2] (Fig. 1). Much later this reaction was found to generate a single diastereomer product.[3] While the original reaction had several drawbacks such as long reaction times, use of excess aqueous reagents, low yields and lack of generality, we were encouraged by its multi-component nature, its diastereoselectivity and the fact that multiple carbon–carbon bond forming reactions were occurring in one pot. We realised that with current synthetic technology it may prove fruitful to revisit this forgotten reaction and to investigate the potential for a version of the Maitland–Japp reaction to be a useful tool in the armory of the synthetic chemist.

As it is desirable to develop a procedure for the synthesis of non-symmetrical tetrahydropyrans, it was decided to move away from a symmetrical ketone based reaction and instead to concentrate on the use of a β-ketoester derivative.[4] In the case of β-ketoester derivatives the difference in reactivity of the α- and γ-positions should allow for the reaction of the β-ketoester derivative with different aldehydes or ketones at the α- and γ-positions. The initial β-ketoester derivative chosen was the bis-trimethylsilyl enol ether of methyl acetoacetate (Chan's diene, **1**).[5] Treatment of **1** with a

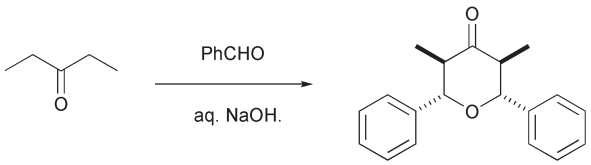

Fig. 1 The Maitland–Japp reaction.

Lewis acid in the presence of an aldehyde should generate aldol product **2**, which could then undergo a Lewis acid catalysed Knoevenagel condensation with a second equivalent of a different aldehyde or ketone to furnish **3**. Finally, a Lewis acid catalysed intramolecular oxy-Michael reaction would deliver tetrahydropyran-4-ones of type **4** (Scheme 1). As there was precedent in the literature for the Lewis acid catalysed versions of all of these processes, it was envisaged that the three individual reactions which make up the synthesis would all follow on from each other in one pot.

The first conditions examined used $TiCl_4$ as the Lewis acid as this has been shown to promote both Mukaiyama aldol reactions[6] and Knoevenagel condensations.[7] When isobutyraldehyde was treated with $TiCl_4$ and **1** at −78 °C, smooth conversion to the aldol product was observed. Addition of *n*-butanal to the reaction mixture at this time and warming the reaction to room temperature led to the very slow formation of tetrahydropyrans **5a** and **6a**. It was found that the rate of the tandem Knoevenagel–Michael reaction could be increased dramatically if TFA was added to the reaction before the addition of *n*-butanal. This increase in rate presumably arose from the acid catalysed removal of the silyl ethers initially formed in the Mukaiyama aldol reaction. In this manner tetrahydropyrans **5a** and **6a** were generated in a 1 : 1 ratio in an excellent 98% yield. However, when $Yb(OTf)_3$ was used as the Lewis acid it was discovered that the diastereoselectivity of the reaction favored the formation of **5a** over **6a**, in an excellent 91% yield (Table 1).[8] Encouraged by this success a range of different aldehyde partners were investigated with each Lewis acid (Table 1).

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b416247a/

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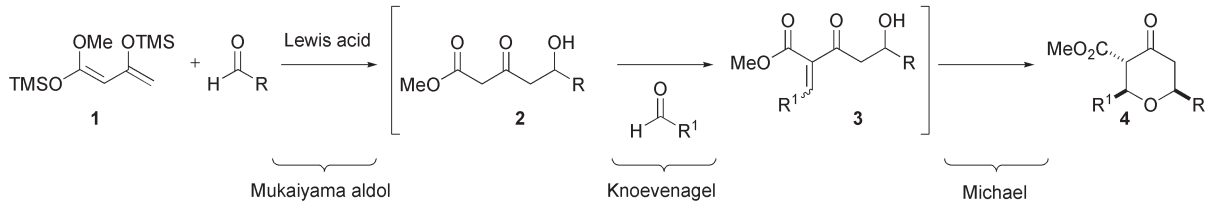
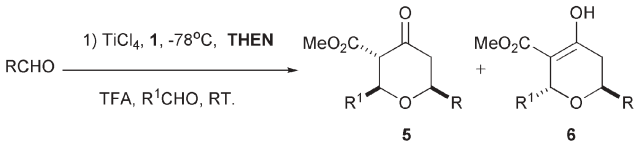


Scheme 1 Strategy for the synthesis of highly functionalised tetrahydropyran-4-ones.

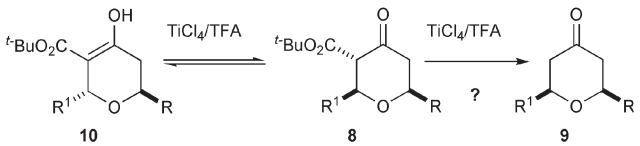
Table 1 One pot formation of tetrahydropyran-4-ones



	R	R^1	$TiCl_4$ Yield (%)	$TiCl_4$ Ratio **5** : **6**	$Yb(OTf)_3$ Yield (%)	$Yb(OTf)_3$ Ratio **5** : **6**
a	^{i}Pr	Pr	98	1 : 1	91	10 : 1
b	Ph	Ph	98	1 : 3	98	2.5 : 1
c	^{i}Pr	$(CH_2)_2CH{=}CH_2$	88	1 : 4	93	2 : 1
d	Pr	CH_2OBn	88	1 : 1	81	6 : 1
e	Ph	4-$MeOC_6H_4$	93	1 : 3	91	2 : 1
f	Ph	^{i}Pr	80	1 : 0	75	1 : 0
g	Cyhx	Ph	74	1 : 2	86	11 : 1
h	^{i}Pr	Ph	82	1 : 3	80	2.5 : 1

As can be seen from Table 1, a wide range of structurally different aldehydes can be incorporated in either the 2 or 6 position of the products, and the yields of the tetrahydropyran-4-ones range from good to excellent. Of particular interest is the significant change in the diastereoselectivity of the reaction when the Lewis acid was changed from $TiCl_4$ to $Yb(OTf)_3$. In general, use of $TiCl_4$ tended to favor the formation of the 2,6-*trans* diastereomer **6**, while use of $Yb(OTf)_3$ favored the formation of the 2,6-*cis* diastereomer **5**. It is rationalised that the 2,6-*cis*-diastereomer exists as the keto-tautomer as this obviates a large eclipsing interaction between the C5-ester group and the C6-substituent which would be present in the enol-tautomer. The 2,6-*trans*-diastereomer exists as the enol-tautomer as the hydrogen bond formed between the enol proton and the carbonyl of the adjacent ester compensates for placing the C6-substituent in a pseudo-axial position. A possible explanation for this change in diastereoselectivity with different Lewis acids is that the stoichiometric amount of $TiCl_4$ in solution is chelated by the enol form of the *trans*-diastereomer. However, $Yb(OTf)_3$ is much less soluble in CH_2Cl_2 and therefore present in solution in much smaller amounts. This has the effect that much less of the product is chelated with the Lewis acid and so exists as the *cis*-diastereomer in the keto form, where all the substituents are equatorial.

Exploration into the nature of the diastereoselection showed that in the case of both Lewis acids the reaction was under thermodynamic control. When separate samples of **5b** and **6b** were resubmitted to the reaction conditions in the presence of $TiCl_4$ for 18 h an identical 1 : 3 mixture of **5b** and **6b** resulted in both cases. However, when this equilibration was carried out at −78 °C for 18 h, rather than at room temperature, the ratio of **5b** to **6b** was found to be reversed at 3 : 1. Interestingly, when the formation reaction was repeated with $TiCl_4$ and held at 0 °C, then worked-up within 2 minutes of the addition of the second aldehyde, **5b** was formed exclusively, implying that, under these conditions, **5b** is the kinetic product and **6b** is the thermodynamic one. In the case of the $Yb(OTf)_3$ promoted reaction, separate samples of **5b** and **6b** were resubmitted to the reaction conditions and after 18 h were found to have equilibrated to identical 2.5 : 1 mixtures of **5b** to **6b**. This shows that the $Yb(OTf)_3$ promoted reaction is also under thermodynamic control. In all cases there was no loss of material from these equilibration studies.



Scheme 2 The decarboxylative Maitland–Japp reaction.

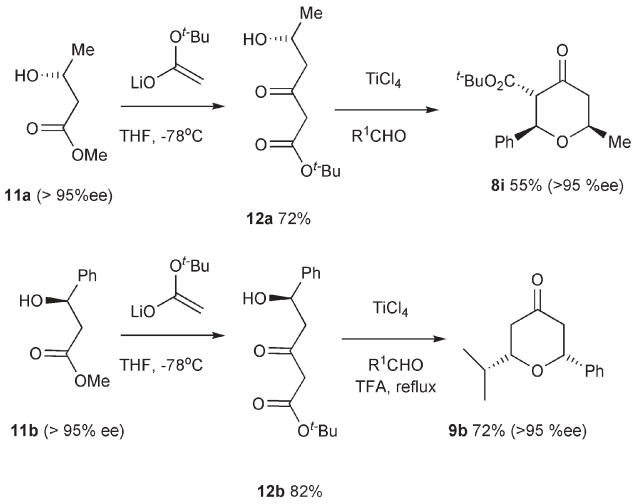
As the 2,6-*cis* and 2,6-*trans* diastereomers were in equilibrium with one another diene **1** was changed for the bis-trimethylsilyl enol ether of *tert*-butyl acetoacetate **7**, in an attempt to initiate *in situ* Lewis acid catalysed decarboxylation of the 2,6-*cis*-tetrahydropyran-4-one **8** which existed as the keto tautomer, and thus drive the equilibrium over to the 2,6-*cis* compound **9**. It was rationalised that as the 2,6-*trans* diastereomer **10** existed as the enol tautomer decarboxylation would not be possible (Scheme 2).

As can be seen from Table 2, *in situ* decarboxylation did not occur under the reaction conditions which instead furnished excellent yields of mixtures of **8** and **10** with **8**, the 2,6-*cis*-tetrahydropyran-4-one, predominating. This *cis* selectivity is the complete reverse of the selectivity obtained when the reaction was run under identical conditions using Chan's diene **1** (Table 1).

It is also possible to construct enantiomerically pure tetrahydropyran-4-ones as there is no erosion of the enantiomeric excess of the δ-hydroxy β-ketoesters **12** under the cyclisation reaction conditions (Scheme 3). Enantiomerically pure β-hydroxy esters **11a/b** are available commercially and were homologated *via* a standard Claisen condensation reaction[9] to yield **12a/b**. δ-Hydroxy β-ketoesters **12a/b** were subjected to our $TiCl_4$ promoted tandem Knoevenagel/oxy-Michael reaction and yielded **8i** and **8f** respectively; pyranone **8f** was then decarboxylated *in situ* by further

Table 2 Use of bis-trimethylsilyl enol ether of *tert*-butyl acetoacetate in the Maitland–Japp reaction

	R	R^1	Yield (%)	Ratio **8** : **10**
a	^{i}Pr	Pr	92	14 : 1
b	Ph	Ph	98	4 : 1
c	^{i}Pr	$(CH_2)_2C{=}CH_2$	91	2 : 1



Scheme 3 Construction of single enantiomers.

addition of 10 equiv. of TFA and heating to provide **9b**. Analysis of the enantiomeric excesses by chiral ^{1}H NMR shift reagent showed that both **8i** and **9b** were single enantiomers, proving that the enantiomeric integrity of the δ-hydroxy β-ketoesters **12** or the pyran products **8** and **9** are not eroded by the Maitland–Japp reaction conditions.[10]

In summary, we have developed an efficient one pot, multi-component and diastereoselective synthesis of highly functionalised tetrahydropyran-4-ones and have shown that it can be used to prepare 2,6-*cis*-disubstituted tetrahydropyran-4-ones in enantiomerically pure form. We are now investigating the possibility of installing the hydroxyl stereocentre *via* a catalytic asymmetric aldol reaction in the same pot as the subsequent Knoevenagel/oxy-Michael reactions.‡

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Notes and references

‡ Diffraction data were acquired on a Bruker SMART1000 (**5b**) or a Bruker SMART APEX (**6b**) CCD area detector diffractometer equipped with an Oxford Cryosystems open-flow cryostat operating at 150 K. The structures were solved by direct methods and refined by full-matrix least-squares on F^2. Crystal data for **5b**. $C_{19}H_{18}O_4$, M = 310.33, monoclinic, a = 13.0132(10), b = 8.6004(7), c = 14.1620(11) Å, β = 91.558(2)°, V = 1584.4(2) Å^3, T = 150(2) K, Z = 4, D_x = 1.301 g cm^{-3}. Final R_1 [2746 $F > 4\sigma(F)$] = 0.0375, wR_2 [all 3656 F^2] = 0.105. Crystal data for **6b**. $C_{19}H_{18}O_4$, M = 310.33, triclinic, a = 5.5429(5), b = 9.5351(8), c = 15.1955(13) Å, α = 82.937(2), β = 85.273(2), γ = 77.190(2)°, V = 775.9(2) Å^3, T = 150(2) K, Z = 2, D_x = 1.328 g cm^{-3}. Final R_1 [2913 $F > 4\sigma(F)$] = 0.0401, wR_2 [all 3507 F^2] = 0.111. CCDC 250776–250777. See http://www.rsc.org/suppdata/cc/b4/b416247a/ for crystallographic data in .cif or other electronic format.

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8 On the basis of ^{1}H NMR studies **6** was initially assigned as the enol-form of **5**. This mis-assignment was corrected when crystals of **5b** and **6b** suitable for X-ray analysis were obtained. Single crystal X-ray analysis also confirmed the structures of the other tetrahydropyran-4-ones synthesized.
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10 See supporting information for details.