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A Maitland–Japp inspired synthesis of dihydropyran-4-ones and their stereoselective conversion to functionalised tetrahydropyran-4-ones†

Paul A. Clarke,* Philip B. Sellars and Nadiah Mad Nasir

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The Maitland–Japp reaction has been extended to the synthesis of highly functionalised dihydropyran-4-ones. These dihydropyran-4-ones can in turn be converted stereoselectively into tetrahydropyran-4-ones with tertiary and quaternary stereocentres *via* the one-pot addition of hydride or carbon nucleophiles and trapping with carbon electrophiles. The utility of this method is demonstrated by providing access to the functionalised tetrahydropyran units present in a component of the Civet fragrance and the anticancer polyketide lasonolide A.

Introduction

Tetrahydropyran (THP) containing natural products, such as (−)-centrolobine, (+)-phorboxazole A and B, (−)-lasonolide A, and Civet cat secretion (Fig. 1), are an important class of synthetic targets because of their challenging architectural features, their biological activities and their limited availability from natural sources. In the cases of (−)-centrolobine, (+)-phorboxazole A and B, and (−)-lasonolide A, each has potent activity against a human disease, with (−)-centrolobine showing activity against the parasite responsible for leishmaniasis[1] and the phorboxazoles and lasonolide A showing potent anticancer activity.[2,3] As such, these molecules have the potential to become the next generation of therapeutic agents if enough material can be provided to complete the required biological studies and satisfy the supply problem. The challenging molecular architectures of these compounds, coupled with their biological activities, have prompted many groups around the world to embark upon research programs aimed at the development of new methods for the construction of the tetrahydropyran rings found within them.[4] There have been significant developments in the formation of tetrahydropyrans by the Prins reaction[5] and the hetero-Diels–Alder reaction,[6] and these strategies have been applied with varying degrees of success to the synthesis of tetrahydropyran-containing natural products including (−)-centrolobine, (+)-phorboxazole A and B, and (−)-lasonolide A.[4]

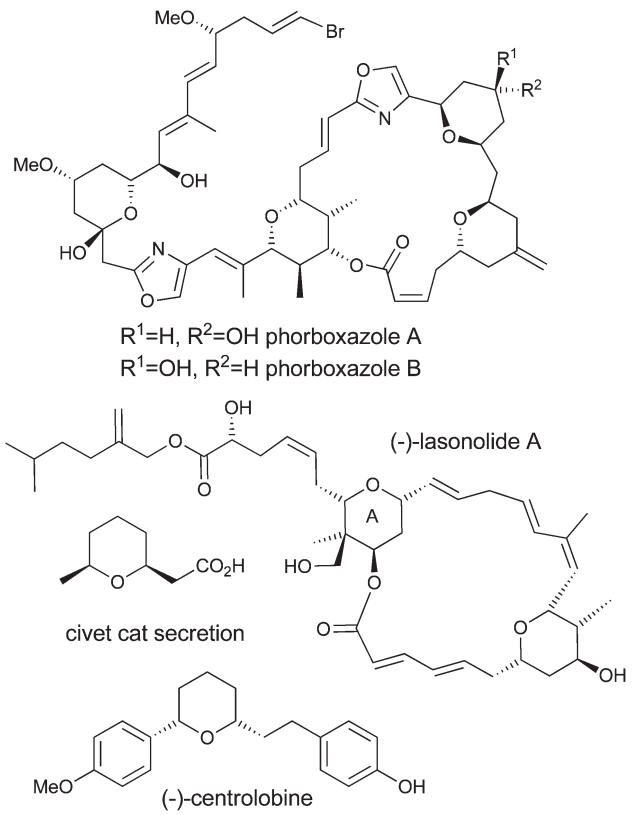

Fig. 1 Tetrahydropyran containing natural products.

Over the last few years we have been interested in developing new methods for the synthesis of functionalised tetrahydropyran-4-ones[7] and the application of these methods to the total synthesis of tetrahydropyran containing natural pro-

Department of Chemistry, University of York, Heslington, York, North Yorkshire YO10 5DD, UK. E-mail: paul.clarke@york.ac.uk; Fax: +44 (0)1904 322516; Tel: +44 (0)1904 322614

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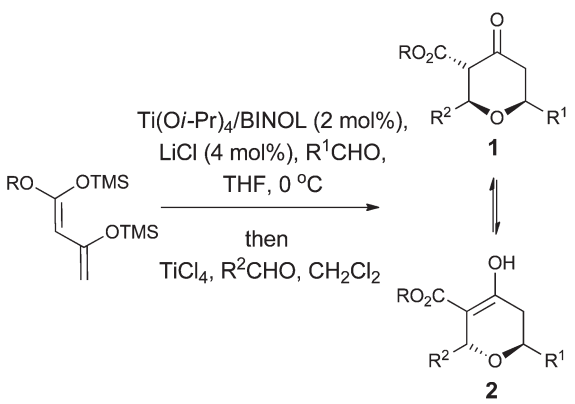
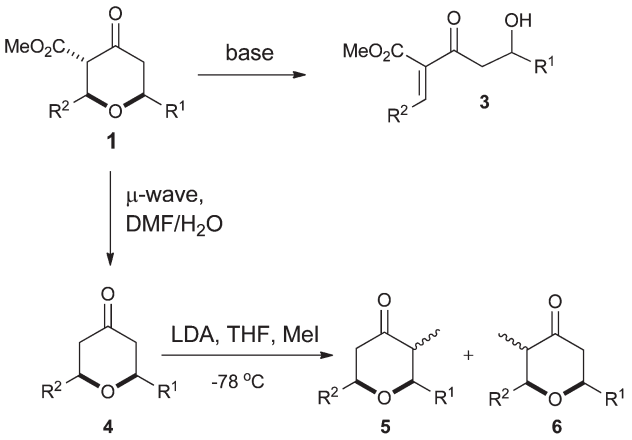
ducts such as (−)-centrolobine[8] and (+)-phorboxazole B.[9,10] Our work in this area focused on updating the venerable Maitland–Japp reaction,[11] initially as a two-pot process involving the addition of the Weiler dianion to an aldehyde in the first step, to be followed by the Lewis acid catalysed Knoevenagel reaction and oxy-Michael cyclisation in the second step.[12] This in turn led to the development of a one-pot procedure. When Chan's diene was used as the nucleophile, we found that we could effect a Lewis acid catalysed Mukaiyama aldol reaction and follow it with the Knoevenagel reaction and oxy-Michael cyclisation, without the need for isolation of the intermediate δ-hydroxy-β-ketoester adduct. This generated mixtures of 2,6-*cis* and 2,6-*trans*-tetrahydropyran-4-ones in good yields.[13] Later we replaced Chan's diene with diketene and made the reaction pot, atom and step economic (PASE),[14] as well as asymmetric.[14,15]

However, despite the utility of the Chan's diene and diketene versions of the Maitland–Japp reaction, it became apparent that there were a number of difficulties associated with them. Of primary concern was the formation of mixtures of the 2,6-*cis* and 2,6-*trans* diastereomers **1** and **2**, which interconverted under the reaction conditions (Scheme 1).[13b] While these diastereomers could be separated *via* flash column chromatography and re-equilibrated to give the desired diastereomer, such a procedure was not ideal. Of secondary concern was the inherent difficulty in functionalising either the 3- or 5-positions of the tetrahydropyran-4-one ring. Treating the tetrahydropyran-4-one products with a base resulted in a retro-Michael reaction affording **3**;[8] furthermore, after decarboxylation, it proved impossible to control the regioselectivity of enolate formation in the resulting decarboxylated tetrahydropyran-4-one **4** and hence formation of products **5** and **6** (Scheme 2). As such, the tetrahydropyran-4-one products from the Maitland–Japp reaction cannot be readily converted into the tetrahydropyrans found in the C20–C32 fragment of the phorboxazoles[16] or the A-ring of lasonolide A.

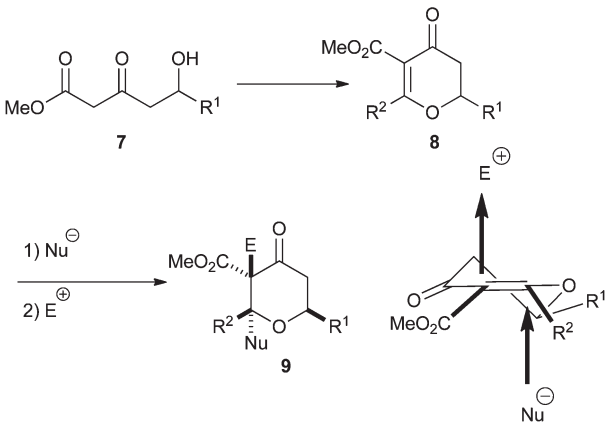
In order to overcome these problems we considered the possibility of developing a procedure to generate dihydropyran-4-ones **8**, which would be more amenable to further functionalisation. Conjugate addition of a nucleophile to the double bond of the dihydropyran-4-one would generate an enolate which we hoped we could trap with an appropriate electrophile, thus generating a quaternary stereocentre. If the nucleophile was a hydride, then the resulting tetrahydropyran-4-one **9** would have the 2,6-*cis* relationship, and if the nucleophile was an organometallic reagent the resulting tetrahydropyran-4-one would have a tertiary stereocentre at C2 (Scheme 3). This paper builds on our earlier communication and fully details our studies in this area.[17]



Scheme 1 The Maitland–Japp reaction.



Scheme 2 Problems of functionalising Maitland–Japp products.



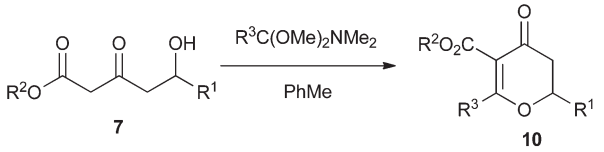
Scheme 3 Proposed dihydropyran route.

Results and discussion

Formation of dihydropyran-4-ones

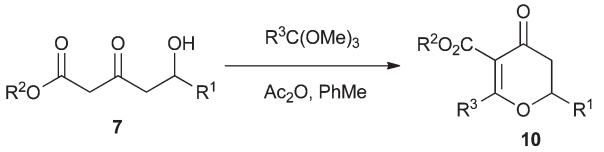
Our initial investigations focused on modifying the Maitland–Japp cyclisation to produce dihydropyran-4-ones **10**. We achieved this by replacing the second aldehyde in the Maitland–Japp reaction sequence with the dimethyl acetal of a *N*,*N*-dimethyl amide (Table 1).[17]

Table 1 Synthesis of dihydropyran-4-ones using orthoamides



DHP (**10**)	R^1	R^2	R^3	Yield (%)
a	Ph	Me	Me	60
b	Et	Me	Me	71
c	Pr	Me	Me	70
d	i-Pr	Me	Me	70
e	2-Furyl	Me	Me	40
f	CH_2OBn	Me	Me	61
g	CH_2CH_2OBn	Me	Me	72
h	Ph	i-Pr	Me	62
i	Cy-hex	i-Pr	Me	81
j	Pr	i-Pr	Me	78
k	$CH{=}CHCH_3$	i-Pr	Me	69
l	Pr	i-Pr	Ph	68
m	$CH{=}CHCH_3$	i-Pr	Ph	56
n	i-Pr	i-Pr	Ph	53
o	CH_2CH_2OBn	Me	Ph	41
p	Cy-hex	Me	Ph	33

Table 2 Synthesis of dihydropyran-4-ones using orthoesters



DHP (**10**)	R^1	R^2	R^3	Yield (%)
c[a]	Pr	Me	Me	56
d[b]	i-Pr	Me	Me	32
e[b]	2-Furyl	Me	Me	34
i[a]	Cy-hex	i-Pr	Me	59
j[a]	Pr	i-Pr	Me	56
q[a]	Pr	Me	Bu	53
r[a]	i-Pr	Me	Bu	39
s[b]	Ph	Me	Bu	80
t[b]	CH_2OBn	Me	Bu	70

[a] 10 equiv. of orthoester used. Heated under reflux. [b] 2 equiv. of orthoester used. Microwave heating.

As can be seen from Table 1, a wide range of δ-hydroxy-β-ketoesters **7** can be reacted with the dimethyl acetals of *N*,*N*-dimethyl acetamide or benzamide to generate dihydropyran-4-ones **10** in good to excellent yields. However, the scope of this approach is limited by the commercial availability and synthetic accessibility of such orthoamides. While the dimethyl acetal of *N*,*N*-dimethyl acetamide was commercially available, the corresponding dimethyl acetal of *N*,*N*-dimethyl benzamide required a two-step synthesis. This involved first reacting the *N*,*N*-dimethyl benzamide with dimethyl sulfate and then treating the resulting product with NaOMe in methanol.[18] Thus, while unfunctionalised alkyl and aryl dimethyl acetals of *N*,*N*-dimethyl amides can be formed, this procedure cannot be used for any amides containing either Lewis acid or base sensitive functional groups.

In order to overcome this problem, we studied the use of orthoesters, which are more easily accessible than their orthoamide counterparts. We selected two commercially available orthoesters to study: trimethyl orthoacetate and trimethyl orthovalerate (Table 2). However, it is worth noting that functionalised orthoesters can be synthesised in two steps from the appropriate nitrile.[19]

We found that these orthoester Maitland–Japp reactions required heating under reflux, the presence of acetic anhydride as a dehydrating agent and a large excess of orthoester in order to achieve completion. However, the large excess of orthoester caused problems in the isolation of the dihydropyran-4-one products **10**. We therefore investigated the use of microwave heating,[20] which enabled us to reduce the amount of orthoester to only 2 equiv. and still maintain reasonable yields. Microwave heating also reduced the reaction time from hours to a matter of minutes.

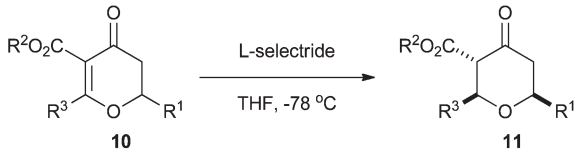
Conversion of dihydropyran-4-ones to 2,6-*cis*-tetrahydropyran-4-ones

Having developed the Maitland–Japp cyclisation to form dihydropyran-4-ones **10**, we turned our attention to reduction of the double bond to form tetrahydropyran-4-ones **11**. We predicted that addition of a hydride to the double bond would occur from a pseudo-axial trajectory, thus generating the 2,6-*cis*-tetrahydropyran-4-one stereoselectively. A number of reducing agents were investigated, with L-Selectride® proving to be the best. Treatment of dihydropyran-4-ones **10** with L-Selectride® delivered tetrahydropyran-4-ones **11** as the sole products as mixtures of ketone and enol tautomers with excellent 2,6-*cis*-diastereoselectivity (Table 3).[17]

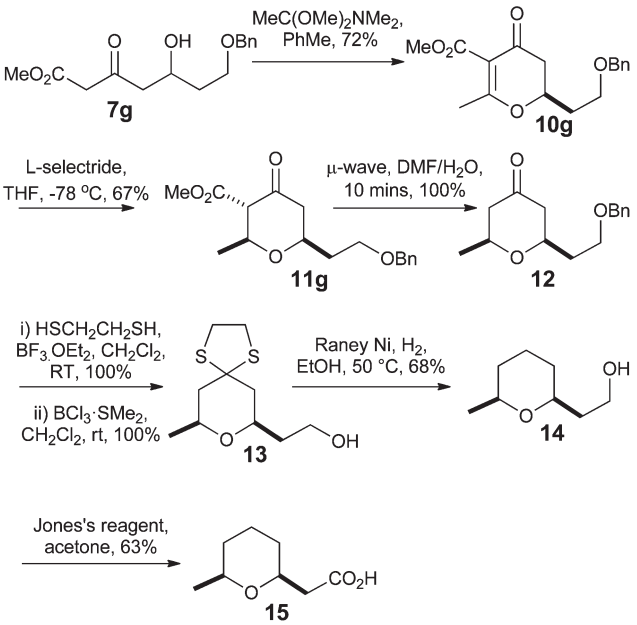
In the case of the 2-methyl tetrahydropyran-4-ones **11a–k** a trace amount of the 2,6-*trans*-tetrahydropyran-4-one was formed, although this could be separated from the major 2,6-*cis*-product by flash column chromatography using cyclohexane–ethyl acetate mixtures. We believe that the 2,6-*trans* products arose from a retro-Michael/Michael equilibration, rather than from pseudo-equatorial addition of a hydride. Indeed, we have seen this equilibration in these tetrahydropyran-4-ones previously, especially under Lewis or Brønsted acid conditions.[13] With larger C2 substituents, the 2,6-*trans*-tetrahydropyran-4-ones were not observed; the 2-butyl tetrahydropyran-4-ones **11q** and **11r** were formed solely as the ketone tautomer. Interestingly, the 2-phenyl tetrahydropyran-4-ones **11l** and **11m** were formed exclusively as the enol tautomer.

The structures of the 2,6-*cis* ketone tautomers were elucidated by analysis of the coupling constants in ^{1}H NMR and nOe studies. Coupling constants of about 10 Hz were observed between H2/H3 and $H5_{ax}$/H6, indicating that the two pairs had *trans*-diaxial relationships and thus all of the protons occupied axial positions. Positive nOe correlations between H2 and H6 of 1.7–2.6% confirmed the 2,6-*cis* relationship. The 2,6-*cis* enol

Table 3 Synthesis of 2,6-*cis*-tetrahydropyran-4-ones from dihydropyran-4-ones by L-Selectride® reduction



THP (**11**)	R^1	R^2	R^3	Keto : enol	Yield (%)
a	Ph	Me	Me	1 : 0.34	69
b	Et	Me	Me	1 : 0.10	54
c	Pr	Me	Me	1 : 0.13	61
d	i-Pr	Me	Me	1 : 0.13	67
e	2-Furyl	Me	Me	1 : 0.20	84
f	CH_2OBn	Me	Me	1 : 0.15	62
g	CH_2CH_2OBn	Me	Me	1 : 0.19	67
h	Ph	i-Pr	Me	1 : 0	79
k	$CH{=}CHCH_3$	i-Pr	Me	1 : 0.15	51
q	Pr	Me	Bu	1 : 0	65
r	i-Pr	Me	Bu	1 : 0	60
l	Pr	i-Pr	Ph	0 : 1	63
m	$CH{=}CHCH_3$	i-Pr	Ph	0 : 1	73



Scheme 4 Synthesis of Civet.

stereochemistry was also confirmed by positive nOe correlations between H2 and H6 of around 1.0–1.5%.

Synthesis of a constituent of Civet cat secretion

Having developed methods for the synthesis of dihydropyran-4-ones **10** and for their conversion to 2,6-*cis*-tetrahydropyran-4-ones **11**, we looked to apply them to the synthesis of the small 2,6-*cis*-tetrahydropyran natural product that is found in the glandular secretions of the Civet cat (*Viverra civetta*) and is used in the fragrance industry.[21]

Our synthesis began with the Maitland–Japp formation of dihydropyran-4-one **10g** in 72% yield using the orthoamide procedure. This was then treated with L-Selectride® to furnish the 2,6-*cis*-tetrahydropyran-4-one **11g** in 67% yield in a 1 : 0.19 ratio of ketone and enol tautomers. Microwave mediated decarboxylation in wet DMF provided 2,6-*cis*-tetrahydropyran-4-one **12** quantitatively. Tetrahydropyran-4-one **12** was converted into tetrahydropyran **13**, quantitatively, by formation of the dithiolane and removal of the benzyl group with $BCl_3{\cdot}SMe_2$ in CH_2Cl_2. Reduction of the dithiolane with RANEY® Ni and H_2 gave alcohol **14** in 68% yield. Alcohol **14** was then oxidized with Jones reagent to give the carboxylic acid in 63% yield, thus completing the total synthesis of the Civet cat secretion natural product **15** in 7 steps (Scheme 4).

Synthesis of tetrahydropyran-4-ones with quaternary stereocentres

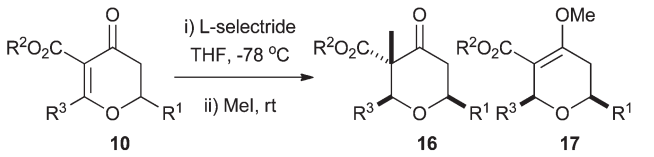
As the addition of L-Selectride® to dihydropyran-4-ones **10** generated an enolate, we wondered whether it would be possible to trap the enolate with a carbon electrophile. We envisaged that the enolate trapping should occur *anti* to the incoming hydride nucleophile; thus if MeI were used as an electrophile this should lead to structures containing the substitution found on the A-ring of (−)-lasonolide A, specifically the quaternary stereocentre. L-Selectride® was added to a solution of the dihydropyran-4-ones **10** in THF at −78 °C and after an hour MeI was introduced and the reaction was warmed to room temperature.

The desired 2,6-*cis*-tetrahydropyran-4-ones **16** were formed in moderate to good yields with alkylation at C3 and with the methyl substituent in an axial position (Table 4). The exceptions to this were dihydropyran-4-ones **10l** and **10m** where R^3 was a phenyl group. In these cases alkylation occurred on the C4 oxygen to give enol ethers **17l** and **17m**. The 2,6-*cis* stereochemistry was again confirmed by *trans*-diaxial couplings between $H5_{ax}$ and H6 of around 11.0–12.0 Hz and positive nOe correlations between H2 and H6 of 2.8%. Positive nOe correlations between $H5_{ax}$ and the C3 methyl substituent of 1.2% showed that the methyl quench occurred from the expected pseudo-axial trajectory, *anti* to the addition of a hydride.

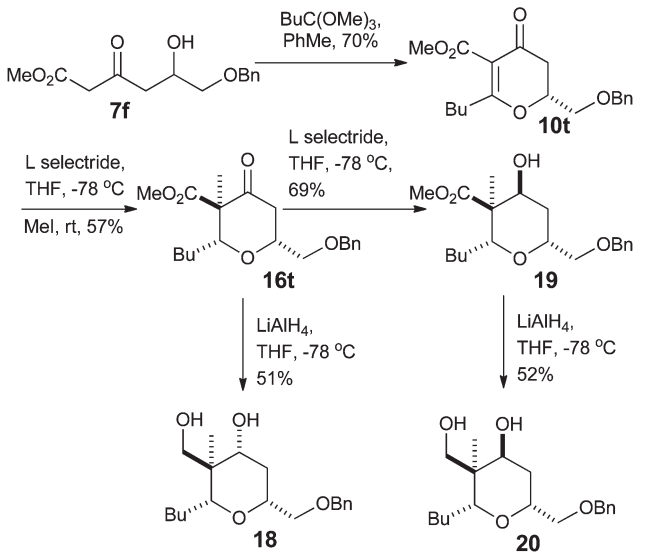
Synthesis of the tetrahydropyran A-ring of lasonolide A

With a procedure in place for the alkylation of the C3 position we could focus on completing a synthesis of a model A-ring of lasonolide A (Scheme 5).[22] Tetrahydropyran **16t** with the quaternary stereocentre at C3 was treated with an excess of $LiAlH_4$ in THF to reduce both the ketone and ester functional groups. This furnished diol **18**, where a hydride had been delivered to the ketone in a pseudo-axial manner to generate the equatorial alcohol. The stereochemistry of the new alcohol was confirmed by analysis of the coupling constants that H4 had with both $H5_{ax}$ and $H5_{eq}$. The coupling constant between H4 and $H5_{ax}$ was 12.0 Hz, indicating a *trans*-diaxial relationship, while that between H4 and $H5_{eq}$ was only 4.8 Hz (Fig. 2). Reduction of **16t** with L-Selectride® in THF resulted in the formation of **19**,

Table 4 Synthesis of 2,6-*cis*-tetrahydropyran-4-ones with a quaternary C3 stereocentre



THP (**16**/**17**)	R^1	R^2	R^3	Ratio (**16** : **17**)	Yield (%)
a	Ph	Me	Me	1 : 0	61
b	Pr	Me	Me	1 : 0	35
d	i-Pr	Me	Me	1 : 0	47
e	2-Furyl	Me	Me	1 : 0	49
f	CH_2OBn	Me	Me	1 : 0	61
j	Pr	i-Pr	Me	1 : 0	62
r	i-Pr	Me	Bu	1 : 0	41
t	CH_2OBn	Me	Bu	1 : 0	57
l	Pr	i-Pr	Ph	0 : 1	72
m	$CH{=}CHCH_3$	i-Pr	Ph	0 : 1	46



Scheme 5 Synthesis of a model A-ring of lasonolide A.

where delivery of a hydride occurred from the pseudo-equatorial trajectory placing the hydroxyl group in an axial position. Once again, ^{1}H NMR coupling constants confirmed the stereochemistry. Now H4 had a coupling constant of 2.7 Hz to $H5_{ax}$ and 5.7 Hz to $H5_{eq}$, indicating that H4 was indeed equatorial (Fig. 2). Treatment of **19** with $LiAlH_4$ reduced the ester to the primary alcohol, thus generating tetrahydropyranol **20**, which has the substitution and relative configuration present in the A-ring of lasonolide A.

Synthesis of 2,2,6-substituted tetrahydropyran-4-ones from dihydropyran-4-ones

We next turned our attention to extending the scope of the nucleophile we could employ in the conjugate addition reaction. Gilman cuprates had been previously reported in the conjugate addition reaction to dihydropyran-4-ones.[23] In addition to these we extended the scope of the investigation to other nucleophiles (Table 5).

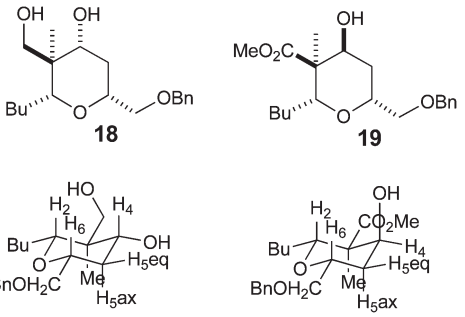
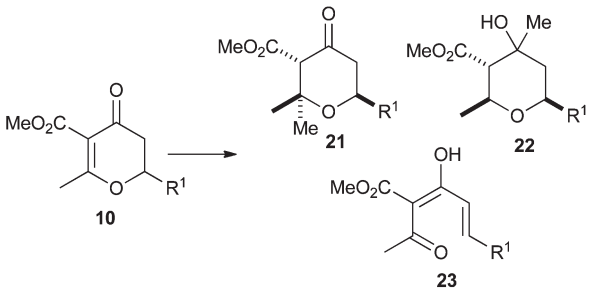


Fig. 2 Conformations and stereochemistry of **18** and **19**.

Table 5 Investigation of carbon nucleophiles

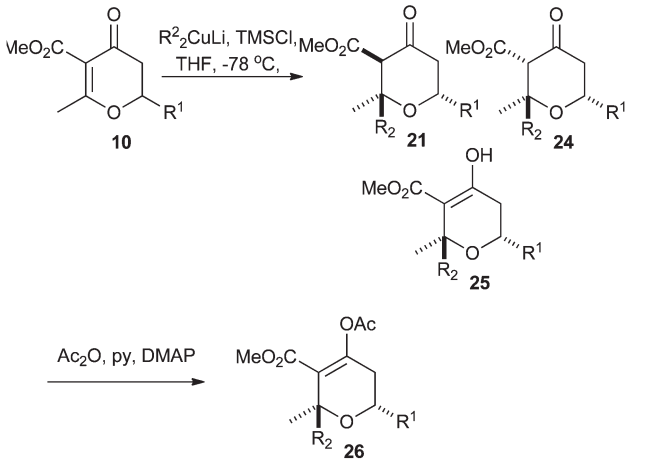


			Yield (%)			
Entry	Nucleophile	Additive	**10**	**21**	**22**	**23**
1	MeMgBr	None	33	17	15	0
2	MeMgBr	$CuBr_2{\cdot}SMe_2$	0	68	9	20
3	Me_2CuLi	None	0	49	0	14
4	Me_2CuLi	TMSCl	0	70	4	8
5	(2-Th)Cu(CN)$MeLi_2$	None	0	44	32	5

As can be seen from Table 5, when MeMgBr was used, the reaction generated essentially equal amounts of the 1,4- and 1,2-addition products **21** and **22**. The inclusion of a $CuBr_2{\cdot}SMe_2$ additive did bias this in favour of the 1,4-addition product **21**, but also resulted in the formation of **23** which presumably arose from an elimination reaction. Gilman cuprate (Me_2CuLi) also resulted in both 1,4-addition and elimination products. However, when TMSCl was added to the reaction,[24] an increase in rate and selectivity for the 1,4-addition product **21** was seen. Finally, the use of a higher order cuprate was investigated but this did not lead to any further improvements and actually gave a sizable amount of the 1,2-addition product **22**. As a result of these studies we opted for the use of Gilman cuprates.

We chose to investigate the reactions of Me_2CuLi, Bu_2CuLi, $(H_2C{=}CH)_2CuLi$ and Ph_2CuLi with a representative number of dihydropyran-4-ones **10** (Table 6).

Table 6 Formation of 2,2,6-substituted tetrahydropyran-4-ones from dihydropyran-4-ones by conjugate addition



THP	R^1	R^2	Ratio **21 : 24 : 25**	Overall yield (%)	Yield (%) **26**
a	Ph	Me	3.3 : 1.0 : 6.7	75	89
b	Pr	Me	2.4 : 1.0 : 3.0	65	74
c	i-Pr	Me	2.1 : 1.0 : 3.0	60	59
d	2-Furyl	Me	2.4 : 1.0 : 3.7	27	73
e	CH_2OBn	Me	2.3 : 1.0 : 2.3	69	92
f	CH_2CH_2OBn	Me	2.4 : 1.0 : 4.2	58	86
g	Ph	Bu	0.9 : 1.0 : 6.3	67	85
h	Pr	Bu	2.0 : 1.0 : 5.9	75	63
i	Ph	$CH{=}CH_2$	0.1 : 0.1 : 1.0	59	90
j	Pr	$CH{=}CH_2$	0.1 : 0.1 : 1.0	52	77
k	i-Pr	$CH{=}CH_2$	0.1 : 0.1 : 1.0	59	69
l	2-Furyl	$CH{=}CH_2$	0.1 : 0.1 : 1.0	60	90
m	CH_2OBn	$CH{=}CH_2$	0.1 : 0.1 : 1.0	76	85
n	CH_2CH_2OBn	$CH{=}CH_2$	0.1 : 0.1 : 1.0	47	100
o	Ph	Ph	0.0 : 0.0 : 1.0	85	—
p	Pr	Ph	0.0 : 0.0 : 1.0	67	—
q	i-Pr	Ph	0.0 : 0.0 : 1.0	67	—
r	2-Furyl	Ph	0.0 : 0.0 : 1.0	61	—
s	CH_2OBn	Ph	0.0 : 0.0 : 1.0	75	—

The Gilman cuprates all added from a pseudo-axial trajectory to form products with a 2,6-*cis* relationship between the new C2 substituent and H6, which was shown by positive nOe correlations of 4% in the case of the butyl, vinyl and phenyl substituents. Interestingly the tetrahydropyran-4-ones were actually formed as mixtures of three tautomers: the enol tautomer **25** and two ketone tautomers **21** and **24** which resulted from protonation of the intermediate enolate from either face. The product of the pseudo-axial protonation **21** had a positive nOe correlation of 1.6% between H3 and $H5_{ax}$, confirming the stereochemistry, whilst in the product of pseudo-equatorial protonation, $H5_{ax}$ was shifted about 0.5 ppm downfield in ^{1}H NMR due to an interaction with the nearby axial ester substituent (Fig. 3). When Ph_2CuLi was used as the nucleophile the enol-tautomer **25** was the only product. Where mixtures of tautomers occurred they could be converted into single enol acetate products **26** in good yields by treatment with acetic anhydride in pyridine at 40 °C. This conversion provided

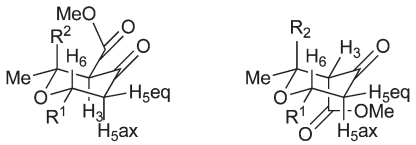


Fig. 3 Conformation and stereochemistry of **21** and **24**.

further support for our assignment of these 1,4-addition products as compounds **21**, **24** and **25**.

Conclusions

We have developed a new modification of the Maitland–Japp reaction using orthoamides and orthoesters, which provides access to a range of dihydropyran-4-ones **10** in good yields. These dihydropyran-4-ones **10** can be converted to 2,6-*cis* tetrahydropyran-4-ones **11** by the stereoselective addition of L-Selectride®. The intermediate enolate resulting from this addition can be trapped stereoselectively with either a proton or MeI to form tetrahydropyran-4-ones with a quaternary stereocentre at C3 **16**. The utility of these procedures was demonstrated by their use in the total synthesis of a constituent of the Civet cat secretion and for the synthesis of a model A-ring of lasonolide A. Treatment of the dihydropyran-4-ones **10** with a Gilman cuprate has led to the development of a procedure for the stereoselective formation of tetrahydropyran-4-ones **25** that are doubly substituted at the C2 position. Hence, we have overcome the difficulties inherent in the functionalisation of 2,6-*cis*-tetrahydropyran-4-one products of the Maitland–Japp reaction **1**, and provided a route to the stereoselective construction of highly functionalised tetrahydropyran rings.

Experimental

General methods

For general experimental details, including information on solvent purification and the spectrometers used in this research, as well as for procedures and spectroscopic and crystallographic data not reported below, see ESI.†

General procedure for the synthesis of 2-methyl dihydropyrans

N,*N*-Dimethylacetamide dimethyl acetal (0.16 mL, 1.08 mmol) was added to a stirred solution of δ-hydroxy-β-ketoester (0.54 mmol) in dry toluene (4 mL) at room temperature. The solution was stirred at room temperature and monitored by TLC. Upon completion of the reaction, the solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether–ethyl acetate) afforded the product.

Methyl 2-methyl-4-oxo-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate (10a). Pale yellow solid; Mp: 102.0–103.6 °C. ν_{max} 2924, 2852, 1729, 1661, 1577, 1430, 1392, 1336, 1186, 1164, 1081,

1047 cm^{-1}; δ_H (400 MHz, C_6D_6) 7.08–7.01 (3H, m), 6.90–6.88 (2H, m), 4.58 (1H, dd, J = 14.0, 3.7 Hz), 3.56 (3H, s), 2.29 (1H, dd, J = 16.5, 14.0 Hz), 2.20 (1H, dd, J = 16.5, 3.7 Hz) and 1.91 (3H, s) ppm; δ_C (100 MHz, C_6D_6) 185.8, 174.5, 165.7, 137.3, 128.1, 128.0, 113.0, 79.9, 51.0, 41.7 and 18.9 ppm; m/z (ESI+) 269 $(M + Na)^+$, 247 $(M + H)^+$, 215 $(M - CH_3OH)^+$. (Found 247.0958 $(M + H)^+$. $C_{14}H_{15}O_4$ requires 247.0965.) Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.74. Found C, 67.93; H, 5.99.

General procedure for L-Selectride® reduction of dihydropyran-4-ones with methyl iodide quench

A 1.0 M solution of L-Selectride® in THF (0.04 mL, 0.04 mmol) was added to a stirred solution of DHP (0.04 mmol) in THF (1 mL) at −78 °C. The mixture was stirred for 1 hour, after which time iodomethane (0.4 mmol) was added. The reaction mixture was stirred at room temperature until completion, when it was partitioned between Et_2O (10 mL) and sat. aq. $NHCl_4$ (10 mL). The aqueous layer was washed with Et_2O (10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–ethyl acetate) afforded the product.

Methyl 2,3-dimethyl-4-oxo-6-phenyl-tetrahydro-2*H*-pyran-3-carboxylate (16a). Oil; ν_{max} (film) 3017, 2986, 2940, 2906, 1717, 1686, 1584, 1474, 1429, 1354, 1326, 1291, 1250, 1081 cm^{-1}; nOe: H2–H6 2.3%, $H5_{ax}$–H10 0.8%, H7–H10 0.7%; δ_H (400 MHz, $CDCl_3$) 7.40–7.30 (5H, m), 4.78 (1H, dd, J = 11.9, 3.1 Hz), 4.41 (1H, q, J = 6.1 Hz), 3.81 (3H, s), 2.74 (1H, dd, J = 15.0, 11.9 Hz), 2.57 (1H, dd, J = 15.0, 3.1 Hz), 1.49 (3H, s) and 1.25 (3H, d, J = 6.1 Hz) ppm; δ_C (100 MHz, $CDCl_3$) 205.9, 171.3, 140.4, 128.7, 128.2, 125.6, 78.3, 76.6, 62.3, 52.3, 45.0, 16.1 and 13.8 ppm; m/z (ESI+) 317, 285 $(M + Na)^+$ (found 285.1094 $(M + Na)^+$. $C_{15}H_{18}NaO_4$ requires 285.1097).

General procedure for Gilman cuprate addition to dihydropyran-4-ones

An organolithium solution (0.41 mmol) was added to a suspension of copper iodide (38.7 mg, 0.20 mmol) in THF (1.17 mL) at 0 °C. The mixture was stirred at this temperature for 20 minutes and then cooled to −78 °C. Addition of TMSCl (0.08 mL, 0.64 mmol) was followed by addition of DHP (0.13 mmol) in THF (1.17 mL) at −78 °C. The reaction mixture was stirred at this temperature for 4 hours, then quenched with sat. aq. NH_4Cl (1 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (petroleum ether–ethyl acetate) afforded the products.

Methyl 4-hydroxy-2,2-dimethyl-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate (25a). Oil ($keto_{eq}$: enol : $keto_{ax}$ 3.3 : 6.7 : 1); ν_{max} (film) 3016, 2985, 2930, 2889, 1723, 1692, 1619, 1582, 1418, 1356, 1317, 1257, 1200, 1111, 1048 cm^{-1}; δ_H (400 MHz, C_6D_6) 13.27 (1H, s), 7.80–7.00 (5H, m), 7.80–7.00 (5H, m, $keto_{eq}$), 7.80–7.00 (5H, m, $keto_{ax}$), 4.64–4.59 (1H, m, $keto_{eq}$), 4.64–4.59 (1H, m, $keto_{ax}$), 4.57 (1H, dd, J = 10.7, 2.9 Hz), 3.47 (1H, s, $keto_{eq}$), 3.39 (3H, m, $keto_{eq}$), 3.38 (1H, m, $keto_{ax}$), 3.27 (1H, s, $keto_{ax}$), 3.26 (3H, s), 3.19 (3H, s, $keto_{ax}$), 2.46 (1H, dd, J = 17.4, 10.7 Hz), 2.44 (1H, m, $keto_{ax}$), 2.35–2.30 (1H, m), 2.35–2.30 (1H, m, $keto_{eq}$), 2.02 (1H, dd, J = 13.7, 10.7 Hz, $keto_{eq}$), 1.62 (3H, s), 1.47 (3H, s), 1.45 (3H, s, $keto_{eq}$), 1.35 (3H, s, $keto_{eq}$), 1.23 (3H, s, $keto_{ax}$) and 0.90 (3H, s, $keto_{ax}$) ppm; δ_C (100 MHz, C_6D_6) 201.9 ($keto_{ax}$), 200.8 ($keto_{eq}$), 172.3, 171.8, 168.1 ($keto_{eq}$), 168.0 ($keto_{ax}$), 142.1, 141.6, 128.7, 128.6, 128.5, 127.9, 127.7, 126.6, 126.2, 126.0, 105.1, 77.6, 76.4, 74.0, 73.4, 72.7 ($keto_{eq}$), 68.6, 67.0 ($keto_{eq}$), 66.0 ($keto_{ax}$), 53.2 ($keto_{ax}$), 51.5 ($keto_{eq}$), 51.0, 48.8 ($keto_{eq}$), 47.3 ($keto_{ax}$), 37.6, 29.8, 29.3 ($keto_{eq}$), 27.7 ($keto_{ax}$), 25.8, 24.7 ($keto_{ax}$) and 21.5 ($keto_{eq}$) ppm; m/z (ESI+) 285 $(M + Na)^+$ (Found 285.1092 $(M + Na)^+$. $C_{15}H_{18}NaO_4$ requires 285.1097).

General procedure for acylation of tetrahydropyrans

The THP mixture (0.03 mmol), acetic anhydride (0.1 mL, 0.1 mmol) and DMAP (cat.) were stirred in pyridine (0.47 mL) at 40 °C for 40 minutes. The mixture was cooled to rt, concentrated *in vacuo*, and then partitioned between Et_2O (30 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (petroleum ether–diethyl ether) gave the product.

Methyl 4-acetoxy-2,2-dimethyl-6-phenyl-5,6-dihydro-2*H*-pyran-3-carboxylate (26a). Oil; ν_{max} (film) 2933, 2885, 1739, 1694, 1413, 1344, 1223, 1190, 1172, 1155, 1042 cm^{-1}; δ_H (400 MHz, C_6D_6) 7.26–7.24 (2H, m), 7.17–7.10 (2H, m), 7.05 (1H, m), 4.72 (1H, dd, J = 10.6, 3.3 Hz), 3.33 (3H, s), 2.63 (1H, dd, J = 17.2, 10.6 Hz), 2.14 (1H, dd, J = 17.2, 3.3 Hz), 1.75 (3H, s), 1.63 (3H, s) and 1.62 (3H, s) ppm; δ_C (100 MHz, C_6D_6) 167.6, 165.5, 150.9, 141.9, 128.5, 127.9, 126.3, 126.0, 75.2, 69.8, 51.2, 36.8, 28.7, 26.0 and 20.4 ppm; m/z (ESI+) 327 $(M + Na)^+$ (Found 327.1197 $(M + Na)^+$. $C_{17}H_{20}NaO_5$ requires 327.1203).

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