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Synthesis of bicyclic tetrahydrofurans from linear precursors using manganese(III) acetate†

Anne-Caroline Chany, Léo B. Marx and Jonathan W. Burton*

We have recently developed methodology based on oxidative radical reactions for the synthesis of [3.3.0]-bicyclic lactones containing both cyclopentanes and γ-lactams along with application of this methodology to the synthesis of natural products and complex molecular architectures. Herein we report an extension of this methodology to the synthesis of oxygen heterocycles including bicyclic bis-lactones.

The tetrahydrofuran (THF) moiety is present in a vast array of biologically active natural products including: the polyketides, the acetogenins, halogenated natural products from Laurencia species, and numerous terpenes.[1,2] As a result the development of new methodology for the synthesis of THFs, and related 5-membered oxygen heterocycles, is an on-going and important aspect of modern synthetic organic chemistry.[3] Recently we have developed methodology based on oxidative radical reactions[4] for the synthesis of [3.3.0]-bicyclic lactones containing both cyclopentanes[5] and γ-lactams[6] along with application of this methodology to the synthesis of natural products[6,7] and complex molecular architectures.[8,9] Herein we report an extension of this methodology to the synthesis of 5-membered oxygen heterocycles containing bicyclic bis-lactones with up to four stereocentres. In accord with our previous work,[5,6] we proposed that exposure of substrates such as **1** to a transition metal oxidant could generate the corresponding malonyl radical **2**, which would undergo 5-*exo*-trig cyclisation presumably *via* the pre-transition state assembly **3** in accord with the Beckwith–Houk model of 5-*exo*-trig radical cyclisation, to give the adduct radical **4** (Fig. 1).[10,11] Oxidation of the so formed adduct radical with concomitant C–O bond formation would deliver the dioxocarbenium ion **5** which gives the desired [3.3.0]-bicyclic γ-lactone **6** on hydrolysis. As in our study of the cyclisation of radicals derived from amidomalonates,[6] we were aware that malonyl radicals such as **2** are captodative in nature[12] and, as such might be prone oxidation to the corresponding oxocarbenium ions prior to cyclisation.

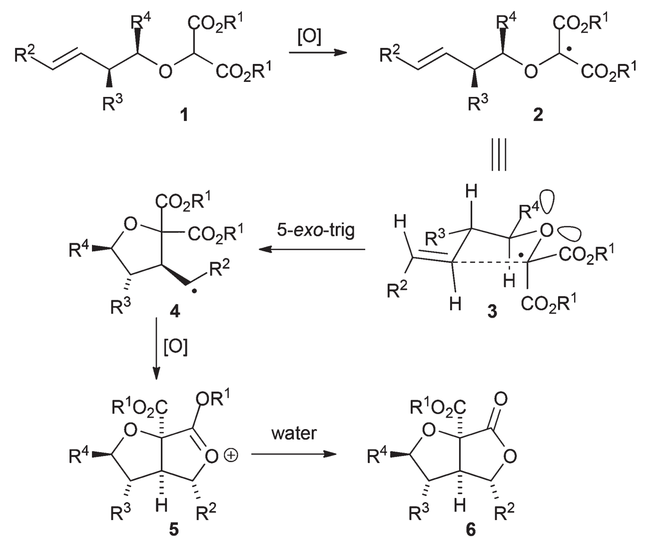


Fig. 1 Proposed mechanism of formation of [3.3.0]-bicyclic γ-lactones.

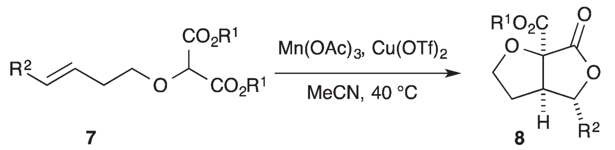
The initial substrates we selected for study were the terminal and phenyl-substituted olefins **7a** and **7c** as we had demonstrated that the corresponding substrates, in the all carbon series, could be successfully converted into [3.3.0]-bicyclic γ-lactones under oxidative conditions.[5,9] These substrates, and all of the substrates in the paper were prepared by O–H insertion into the corresponding diazo-malonates according to the procedure described by Hatakeyama and co-workers (see ESI†).[3d,13]

Exposure of the dimethyl malonate **7a** to two equivalents of the one electron oxidant manganese(III) acetate[14,15] in the presence of one equivalent of copper(II) triflate in acetonitrile at 40 °C, according to our previous work, gave the corresponding [3.3.0]-bicyclic γ-lactone **8a** in 81% yield (Table 1, entry 1).‡ The corresponding di-*tert*-butyl malonate **7b** cyclised with

Department of Chemistry, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: jonathan.burton@chem.ox.ac.uk

†Electronic supplementary information (ESI) available: Experimental details, characterisation data and NMR spectra of new compounds. See DOI: 10.1039/c5ob01091h

Table 1 Initial cyclisation studies



Entry	Substrate	R^1	R^2	Yield (%)	dr
1	**a**	Me	H	81	—
2	**b**	*t*Bu	H	83	—
3	**c**	Me	Ph	92[a]	14 : 1[b]
4	**d**	*t*Bu	Ph	62[a]	16 : 1[b]
5	**e**	Me	Et	50[a]	2 : 1[b]

[a] Combined isolated yield of mixture of diastereomers. [b] Diastereomeric ratio (dr) refers to the mixture of diastereomers at the lactone stereocentre measured from the crude ^{1}H NMR; major diastereomer shown.

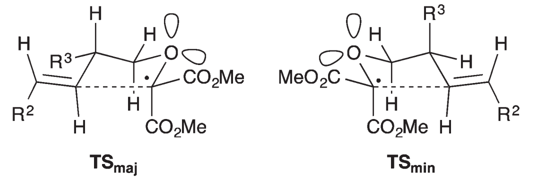


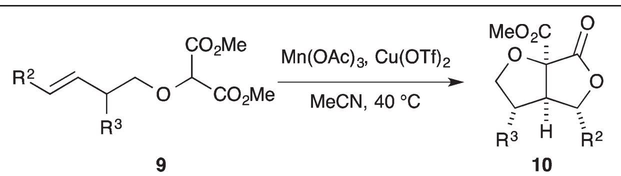
Fig. 2 Plausible pre-transition state assemblies for formation of major and minor diastereomers relating to Table 2.

similar efficiency (Table 1, entry 2). Using the phenyl-substituted alkenes **7c** and **7d** gave the corresponding [3.3.0]-bicyclic lactones **8c** and **8d** in good yield and with high diastereocontrol at the lactone bearing stereocentre (major diastereomer shown, Table 1, entries 3 and 4).§,¶ In keeping with previously reported results in the all carbon series,[5] cyclisation of ethyl-substituted alkene **7e** gave the product **8e** in reduced yield and with lower diastereoselectivity and hence we focussed our attention on substrates bearing a terminal alkene or styrene.

Given the successful cyclisation of substrates **7**, we turned our attention to substrates carrying a substituent at the allylic position (Table 2). With relatively small substituents (**9**, R^3 = Me, CH_2CO_2tBu), the corresponding lactones **10** were formed with moderate diastereocontrol (Table 2, entries 1, 2, 4 and 5).§,¶ In the cyclisation of 5-hexenyl radicals, allylic substituents frequently impart higher levels of diastereocontrol than exhibited above. This is a result of the allylic substituents having a preference for the pseudo-equatorial position in the chair-like transition state so as to minimise both allylic strain and 1,3-diaxial interactions. The modest selectivity exhibited in the cyclisation of substrates **9a,b,d** and **e** is in keeping with the chair-like pre-transition state assembly where R^3 occupies a pseudo-equatorial position (Fig. 2, **TS$_{maj}$**). However the preference for R^3 to occupy a pseudo-equatorial position is determined by allylic strain;[16] if R^3 occupies a pseudo-axial position it would suffer only very minimal 1,3-diaxial interactions with one of the lone pairs of the oxygen atom of the forming THF (**TS$_{min}$**).‖ With much larger substituents (**9c** and **f**), the corresponding lactones **10c,f** were formed with high levels of diastereoselectivity (Table 2, entries 3 and 6). In all cases, the [3.3.0]-bicyclic γ-lactones were formed in synthetically useful yields.

We next moved to investigate cyclisation reactions of homoallylic-substituted substrates **11** (Table 3). Cyclisation of such substrates would give access to THFs carrying 2/5-substituents – positions that are frequently substituted in THF-containing natural products.[1,2] Cyclisation of the substrates **11a–d** (Table 3, entries 1–4) gave the product bicyclic lactones **12a–d** in good yields with pleasing levels of diastereocontrol.§,¶ With the phenyl-substituted alkenes **11e–h** the corresponding products **12e–h** were formed as a mixture of three diastereomers.§ For all the products **12**, the relative configuration of the major

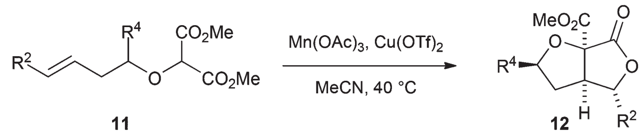
Table 2 Cyclisations with allyl-substituted malonates



Entry	Substrate	R^3	R^2	Yield[a] (%)	dr
1	**a**	Me	H	73	3 : 1[b]
2	**b**	CH_2CO_2tBu	H	76	3.6 : 1[b]
3	**c**	*i*Pr	H	73	22 : 1[b]
4	**d**	Me	Ph	92	4.6 : 1[b]
5	**e**	CH_2CO_2tBu	Ph	69	3.2 : 1[c]
6	**f**	*i*Pr	Ph	92	28 : 1

[a] Combined isolated yield of mixture of diastereomers; major diastereomer shown. [b] Diastereomeric ratio (dr) refers to the mixture of diastereomers at the R^3-bearing sterocentre measured from the crude ^{1}H NMR. [c] Ratio is given as major diastereomer : sum of minor diastereoisomers; detailed dr = 6.7 : 1 : 0.7 : 0.4.

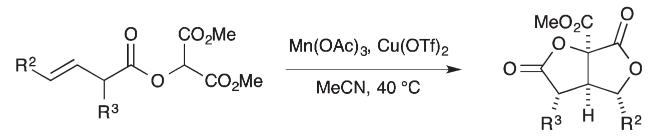
Table 3 Cyclisations with homoallyl-substituted malonates



Entry	Substrate	R^4	R^2	Yield[a] (%)	dr[b]
1	**a**	Me	H	96	6.1 : 1
2	**b**	*i*Pr	H	94	5.7 : 1
3	**c**	Ph	H	80	7.5 : 1
4	**d**	CH=CH$_2$	H	86	5 : 1
5	**e**	Me	Ph	66	2.8 : 1
6	**f**	*i*Pr	Ph	61	3.2 : 1
7	**g**	Ph	Ph	70	2.6 : 1
8	**h**	CH=CH$_2$	Ph	80	2.8 : 1

[a] Combined isolated yield of mixture of diastereomers; major diastereomer shown. [b] Ratio is given as major diastereomer : sum of minor diastereomers.

Table 4 Cyclisations to form bicyclic bis-lactones



13 14

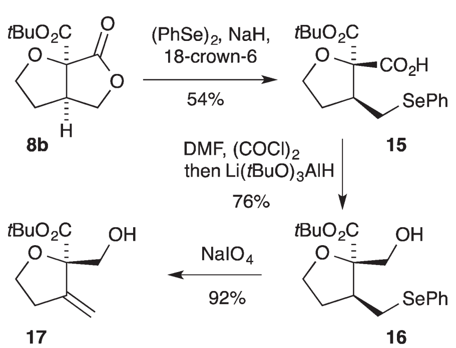
Entry	Substrate	R^3	R^2	Yield[a] (%)	dr[b]
1	**a**	H	H	77	—
2	**b**	*i*Pr	H	73	24 : 1
3	**c**	H	Ph	62	9.6 : 1
4	**d**	*i*Pr	Ph	77	9.6 : 1

[a] Combined isolated yield of mixture of diastereomers >90% pure. [b] Ratio is given as major diastereomer : sum of minor diastereomers.

diastereromer of the products was in keeping with the Beckwith–Houk model[10,11] for 5-hexenyl radical cyclisation. The levels of stereocontrol are in keeping with related cyclisations and examples from our group.[5]

Having investigated the cyclisation of ether substrates we briefly turned to investigate cyclisation of ester substrates **13** (Table 4). Gratifyingly, under our previously optimised conditions efficient cyclisation occurred to give the bicyclic bis-lactones **14** with good levels of diastereocontrol, although it was not always possible to isolate the products in pure form.

Many of the small densely functionalised products formed in the above cyclisation reactions contain differentiated oxygen functional groups which can be independently manipulated (Scheme 1). For example, on treatment of the [3.3.0]-bicyclic γ-lactone **8b** with the phenyl selenide anion[17] the carboxylic acid **15** is formed in 54% yield. Reduction of the carboxylic acid **15** in the presence of the ester could be readily achieved by initial conversion into the corresponding acid chloride followed by treatment with lithium tri-*tert*-butoxyaluminum hydride[18] giving the alcohol **16.** Oxidative elimination from **16** then provided the *exo*-methylene THF **17** bearing full substitution at C-2.



Scheme 1 Synthetic manipulations of lactone **8b**.

Conclusions

In summary, we have reported a mild and operationally simple synthesis of bicyclic THFs and bicyclic bis-lactones in synthetically useful yields and with good levels of diastereocontrol. Application of this methodology to the synthesis of natural products and related targets is on-going.

Acknowledgements

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Notes and references

‡ Control experiments indicated that both manganese(III) acetate and copper(II) triflate were required for efficient product formation – see ESI† for details.

§ In some cases other components were present in the crude reaction mixtures that may be other diastereomers but these components could not be characterised.

¶ The relative configuration of the major diastereomer of the product lactones was assigned on the basis of ^{1}H NMR nOe experiments or by analogy – see ESI† for details. The relative configuration of a small number of the minor diastereomers was also assigned by ^{1}H NMR nOe experiments.

|| Boat-like transition states are also possible.

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