Oxidative radical cyclisations for the synthesis of γ-lactones†

Luke H. Powell,[ab] Paul H. Docherty,[ab] David G. Hulcoop,[a] Paul D. Kemmitt[c] and Jonathan W. Burton*[ab]

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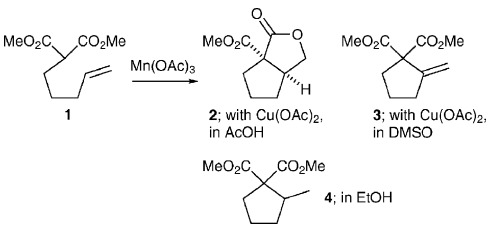
The use of manganese(III) acetate in combination with copper(II) triflate allows the synthesis of [3.3.0]-bicyclic γ-lactones from 4-pentenylmalonates in excellent yields.

Substituted cyclopentanes form the core of many biologically important natural products including the prostaglandins[1] and the brefeldins, and have been used as glycosidase inhibitors,[2] as peptidomimetics[3,4] and as ligands in catalysis.[5] A variety of methodologies have been developed to access these privileged structures,[1,6,7] including diastereoselective radical cyclisations[8] most frequently using the 'tin hydride' method for radical generation and termination with its attendant difficulties of purification and stoichiometric tin waste.[9] We became interested in developing tin-free oxidative radical cyclisations, mediated by manganese(III), for the synthesis of biologically active cyclopentane-containing natural products.[10]

Manganese(III) acetate has emerged as a powerful one-electron oxidant for the generation of electrophilic C-centred radicals from CH-acidic compounds.[11] These educt radicals readily cyclise to form adduct radicals which undergo a variety of termination sequences.[11] Snider and McCarthy have shown that the cyclisation of dimethyl 4-pentenylmalonate **1** in the presence of manganese(III) acetate delivers three different major products depending on the reaction conditions (Scheme 1).[12] Using manganese(III) acetate and copper(II) acetate in acetic acid gives the [3.3.0]-bicyclic γ-lactone **2** in 48% yield along with the methylenecyclopentane **3** (20%).[12–14] Using the same reagents in DMSO provides the methylenecyclopentane **3** in 53% yield whereas using no copper(II) additive and ethanol as solvent gives the methylcyclopentane **4** in 40% yield.[12]

[3.3.0]-Bicyclic γ-lactones such as **2** are attractive intermediates for synthesis as they contain adjacent quaternary and tertiary stereocentres and differentiated oxygen functionality. Herein we report that exposure of 4-pentenylmalonates to manganese(III) acetate and copper(II) triflate gives [3.3.0]-bicyclic γ-lactones in excellent yield. This methodology is showcased in the synthesis of a [5.2.1.0^{1,5}]-tricyclo bis-lactone bearing five contiguous stereocentres, including adjacent quaternary and tertiary stereocentres, which we propose to use in the synthesis of a number of biologically active natural products and analogues.



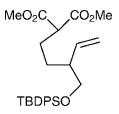
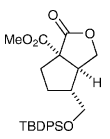
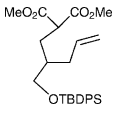
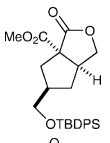
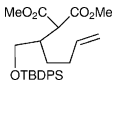
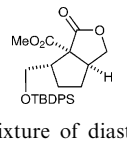
Scheme 1 Cyclisation of dimethyl 4-pentenylmalonate.

We used dimethyl 4-pentenylmalonate **1** to develop an efficient procedure for the synthesis of [3.3.0]-bicyclic γ-lactones. After some optimisation we discovered that exposure of the malonate **1** to two equivalents of manganese(III) acetate, and one equivalent of copper(II) triflate in acetonitrile at reflux delivered the [3.3.0]-bicyclic γ-lactone **2** in excellent yield (Table 1, entry 1).[15] Conducting the reaction in deoxygenated solvent (0.2 M in acetonitrile) is critical for attaining a high yield of the γ-lactone **2**.

The conditions developed for the efficient formation of **2** readily translated to more complex substrates (Table 1).[16,17] Thus, the substituted 4-pentenylmalonate **5** gave the [3.3.0]-bicyclic γ-lactone **6** with good diastereocontrol (dr $>13:1$)[18] in 88% yield (Table 1, entry 2). Similarly, exposure of malonates **7** and **9** to manganese(III) acetate and copper(II) triflate gave the corresponding [3.3.0]-bicyclic γ-lactones **8** and **10** in excellent yields (Table 1, entries 3 and 4).[18]

Slight modification of literature conditions[12] allowed the synthesis of methyl and methylenecyclopentanes from the same

Table 1 Synthesis of [3.3.0]-bicyclic γ-lactones

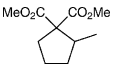
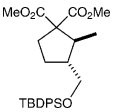
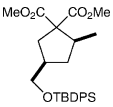
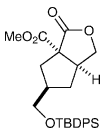
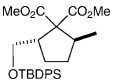
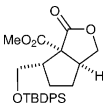
Entry	Substrate		Product		Yield (%)
1		**1**		**2**	92
2		**5**		**6**	88
3		**7**		**8**	92[a]
4		**9**		**10**	90[a]

[a] Combined yield for a 5 : 1 mixture of diastereomers, major diastereomer shown.

[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW*
[b] *Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA. E-mail: jonathan.burton@chem.ox.ac.uk; Fax: +44 1865 285002; Tel: +44 1865 285119*
[c] *AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK SK10 4TF*

† Electronic supplementary information (ESI) available: Experimental procedures and selected NMR spectra. See DOI: 10.1039/b802473a

Table 2 Synthesis of methylcyclopentanes

Entry	Substrate	Conditions	Product(s) (yield, %)		
1	**1**	$Mn(OAc)_3$, 0.02 M, EtOH		**4** (66)	
2	**5**	$Mn(OAc)_3$, 0.02 M, EtOH		**11** (66)	
3	**7**	$Mn(OAc)_3$, 0.02 M, EtOH		**12** (60[a])	 **8** (29)
4	**9**	$Mn(OAc)_3$, 0.02 M, EtOH		**13** (55[a])	 **10** (29)

[a] Combined yield for a *ca.* 3 : 1 mixture of diastereomers.

substrates (Tables 2 and 3). Under reductive conditions (no copper(II) additive, 0.02 M in ethanol) the malonate **1** gave the methylcyclopentane **4** in an improved yield of 66%. Similarly the methylcyclopentane **11** was synthesised with good diastereocontrol (dr > 13 : 1) in 66% yield (Table 2, entry 2). The malonates **7** and **9** gave the corresponding methylcyclopentanes **12** and **13** in 60% and 55% yields respectively as *ca.* 3 : 1 mixtures of diastereomers; with the corresponding γ-lactones **8** and **10** formed as significant by-products.

Treatment of the malonates with manganese(III) acetate and copper(II) acetate in DMSO[12] gave the methylenecyclopentanes (**3**[19] and **14**–**16**) in 50–80% yields (Table 3 entries 1–4).[20] Under these conditions the corresponding γ-lactones were also formed as by-products in varying degrees.

Table 3 Synthesis of methylenecyclopentanes

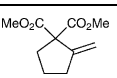
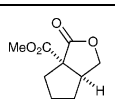
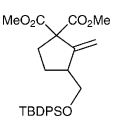
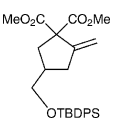
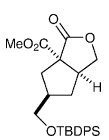
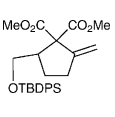
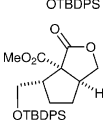
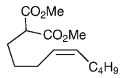
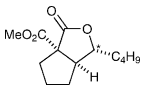
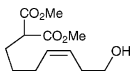
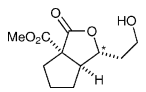
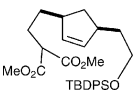
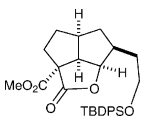
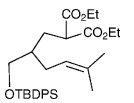
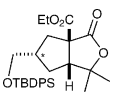
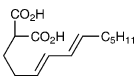
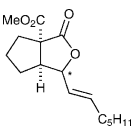
Entry	Substrate	Conditions	Product(s) (yield, %)		
1	**1**	$Mn(OAc)_3$, $Cu(OAc)_2$, 0.2 M, DMSO		**3** (77)	 **2** (7)
2	**5**	$Mn(OAc)_3$, $Cu(OAc)_2$, 0.2 M, DMSO		**14** (71)	
3	**7**	$Mn(OAc)_3$, $Cu(OAc)_2$, 0.2 M, DMSO		**15** (80)	 **8** (13)
4	**9**	$Mn(OAc)_3$, $Cu(OAc)_2$, 0.2 M, DMSO		**16** (50)	 **10** (13)

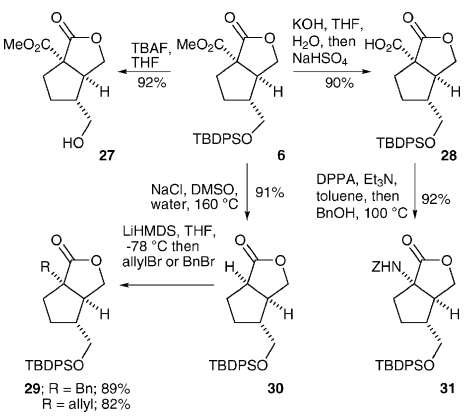
Table 4 Synthesis of bi- and tricyclic γ-lactones

Entry[a]	Substrate		Product[b]		Yield (%)	dr[c]
1		**17**		**18**	58	2 : 1
2		**19**		**20**	76	1.7 : 1
3		**21**		**22**	57	1 : 0
4		**23**		**24**	67	5 : 1
5[d]		**25**		**26**	90	1 : 1

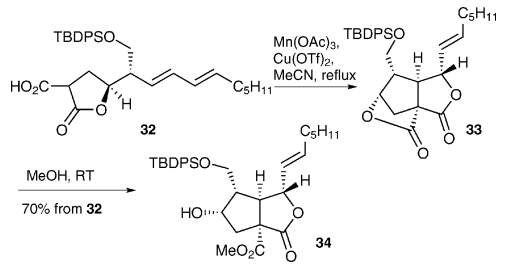
[a] 2 equiv. $Mn(OAc)_3$, 1 equiv. $Cu(OTf)_2$. [b] Isolated as a mixture of diastereomers at the centre marked *, major diastereomer shown. [c] Diastereomeric ratio. [d] The crude product was esterified with $TMSCHN_2$ prior to chromatography.

The formation of [3.3.0]-bicyclic γ-lactones from 1,2-disubstituted alkenes proved possible using our optimised reaction conditions (Table 4).[17] Thus exposure of the linear malonates **17** and **19** to manganese(III) acetate and copper(II) triflate, under our standard reaction conditions, gave the corresponding γ-lactones **18** and **20** (Table 4, entries 1 and 2). Furthermore, cyclisation–lactonisation was possible with cyclic (**21**) and trisubstituted (**23**) alkenes (Table 4, entries 3 and 4). In order to achieve efficient cyclisation–lactonisation with 1,3-diene substrates it proved necessary to use the substituted malonic acid in place of the corresponding dimethyl malonate. Thus, under our standard conditions the malonic acid **25** gave the [3.3.0]-bicyclic γ-lactone **26** in excellent yield after esterification with TMS-diazomethane (Table 4, entry 5).

The γ-lactone products are densely functionalised small molecules which should find great utility in synthesis. For example, the fused bicyclic γ-lactone **6** contains three contiguous stereocentres, one of which is quaternary, differentiated



Scheme 2 Conversions of the [3.3.0]-bicyclic γ-lactone **6**.



Scheme 3 Synthesis of the [3.3.0]-bicyclic γ-lactone **34**.

oxygen-based functionality, and is formed under mild conditions. The utility of this γ-lactone in synthesis is demonstrated by the high yielding conversions shown in Scheme 2. The silicon protecting group is readily removed under standard conditions to give the primary alcohol **27**. Hydrolysis of both the γ-lactone and the methyl ester in **6** followed by re-lactonisation under acidic conditions gave the malonic-lactone half acid **28** in excellent yield. The lactone-acid **28** readily participated in a Curtius rearrangement to give the protected α-amino acid **31**, again in excellent yield. Krapcho decarboxylation of the methyl ester **6** provided the γ-lactone **30** which underwent enolate alkylation to give the benzyl and allyl-substituted γ-lactones **29** with complete diastereocontrol.

Most importantly this methodology has allowed us to synthesise the [5.2.1.0^{1,5}]-tricyclo bis-lactone **33** containing adjacent quaternary and tertiary stereocentres and differentiated oxygen-based functionality in one step from the γ-lactone **32**. Thus, exposure of the γ-lactone **32**[21] to our standard reaction conditions (manganese(III) acetate and copper(II) triflate in acetonitrile under reflux) delivered the [5.2.1.0^{1,5}]-tricyclo bis-lactone **33** with good diastereocontrol (dr $>10:1$) which on exposure to methanol gave the [3.3.0]-bicyclic γ-lactone **34** in good yield.[17] It is noteworthy that the lactones **33** and **34** contain five contiguous stereocentres and that the allylic stereocentre is formed with high diastereocontrol. We are synthesising a range of tricyclic and bicyclic γ-lactones such as **33** and **34** which will serve as key intermediates in the synthesis of biologically relevant targets (Scheme 3).

In summary we have developed an efficient process for the formation of fused bicyclic γ-lactones by the oxidative radical cyclisation of 4-pentenylmalonates. Application of this methodology to the total synthesis of natural products and biologically relevant targets is ongoing in our laboratory, in tandem with efforts to render the above transformations catalytic in metal.

The authors thank the Royal Society (URF to JWB), the EPSRC (EP/C006054/2) and AstraZeneca for financial support.

Notes and references

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13 Snider and McCarthy studied the oxidative radical cyclisation of dimethyl 4-pentenylmalonate **1** in a variety of solvents: see ref. 12.

14 The oxidative cyclisation of dimethyl 4-pentenylmalonate **1** mediated by cerium(IV) ammonium nitrate has been studied. The use of copper(II) nitrate as additive in AcOH gives the γ-lactone **2** in 74% yield, see: E. Baciocchi, A. B. Paolobelli and R. Ruzziconi, *Tetrahedron*, 1992, **48**, 4617.

15 Based on the pioneering work of Kochi on the oxidation of alkyl radicals by copper(II) salts (J. K. Kochi, in *Free Radicals*, ed. J. K. Kochi, Wiley, New York, 1973, vol. 1, pp. 594–623), we have reported that the combination of manganese(III) acetate and copper(II) triflate allows the formation of tethered bicyclic γ-lactones in excellent yields from dimethyl malonates containing a pendent carboxylic acid: D. G. Hulcoop and J. W. Burton, *Chem. Commun.*, 2005, 4687. For other references concerning the use of copper(II) triflate in conjunction with manganese(III) acetate see: A. Toyao, S. Chikaoka, Y. Takeda, O. Tamura, O. Muraoka, G. Tanabe and H. Ishibashi, *Tetrahedron Lett.*, 2001, **42**, 1729; D. G. Hulcoop, H. M. Sheldrake and J. W. Burton, *Org. Biomol. Chem.*, 2004, **2**, 965.

16 Cyclisation of the malonyl radical derivedfrom 4-pentenylmalonate **1** gives a $\approx 9:1$ mixture of the corresponding cyclopentylmethyl radicals and cyclohexyl radicals: see ref. 12. Analysis of the crude reaction mixtures from the cyclisations reported in Table 1 shows $>90\%$ of the product mixture arises from 5-*exo*-trig cyclisation.

17 The stereochemistry of the products was assigned on the basis of ^{1}H NMR NOE experiments.

18 The stereochemical outcome of these reactions is in accord with the Beckwith–Houk model for the 5-*exo*-trig cyclisation of 5-hexenyl radicals see: A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073; A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron Lett.*, 1985, **26**, 373; D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, 1987, **52**, 959.

19 These conditions are the same as those reported by Snider and McCarthy (ref. 12). We have noticed increased yields of products arising from oxidative termination with increased substrate concentration and increased scale of reaction. The different yields of **3** obtained by Snider and McCarthy (ref. 12) and in this work, may be due to different reaction scales.

20 For rationalisation of the different product distributions from the different copper(II) additives see ref. 15. The reason for the solvent effects is not clear (see ref. 12). Cyclisation of 4-pentenylmalonate **5** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in MeCN gives the lactone **6** and the methylenecyclopentane **14** in a 1.5 : 1 ratio, whereas the methylenecyclopentane **14** is the sole product in DMSO. These results are in accord with Snider and McCarthy's study (ref. 12).

21 For an example of the use of malonic hemi acids in manganese(III) mediated reactions see: L. A. Paquette, A. G. Schaefer and J. P. Springer, *Tetrahedron*, 1987, **43**, 5567.