Synthesis of fused tricyclic γ-lactones mediated by manganese(III) acetate†

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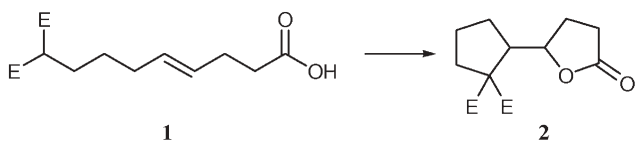
Exposure of cyclic alkenes bearing a carboxylic acid and a malonate group to manganese(III) acetate and an appropriate copper(II) salt provides the corresponding tricyclic γ-lactones in good yield.

The use of manganese(III) acetate as a mild one-electron oxidant for organic synthesis has been widely-developed by Snider and others[1] since its introduction as a reagent for the formation of γ-lactones from alkenes and acetic acid.[2] We recently reported the use of manganese(III) acetate for the one-step formation of carbocycles linked to cyclic ethers from acyclic malonates.[3] One drawback of this method was that the yield of the cyclic ether was modest because a number of side-products were often formed. Herein we describe an extension of our methodology to a high yielding synthesis of tricyclic γ-lactones; structural motifs which are represented in over 700 natural products and biologically-active compounds.

The initial aim of this study was to define conditions which would allow the formation of the tethered bicyclic lactones **2** from the linear precursor **1** (Scheme 1, Table 1).‡ Surprisingly, exposure of **1** to manganese(III) acetate in acetonitrile under reflux resulted in no conversion. Conducting the reaction in the presence of sodium carbonate provided the desired lactones **2** in low yield (19%). Omitting the base and performing the reaction in ethanol improved the yield of **2** to 44% (Table 1, entry 3), with a further improvement in yield being achieved by conducting the reaction in acetic acid (Table 1, entry 4). We next turned to the use of copper(II) additives to help mediate the desired process. Copper(II) acetate has been widely-used in manganese(III) acetate mediated reactions to convert adduct radicals into alkenes.[1] Exposure of **1** to manganese(III) acetate and copper(II) acetate in acetonitrile under reflux provided the desired lactone in 33% yield, along with recovered starting material (44%) and a mixture of alkene products. Based on the pioneering work of Kochi,[4] we have introduced the use of copper(II) salts bearing highly stabilised anions[3] (*e.g.* $Cu(OTf)_2$ and $Cu(BF_4)_2$), in conjunction with manganese(III) acetate, to promote the formation of oxidative substitution products in preference to products arising from oxidative elimination (β-hydride elimination).§ Exposure of the acid **1** to manganese(III) acetate and 1 equiv. of copper(II) triflate in acetonitrile provided the desired lactones **2** in quantitative yield as a 1 : 1 mixture of diastereomers (Table 1, entry 7). Reducing the amount of copper(II) triflate to 0.5 equiv. still provided the lactones **2** in quantitative yield, however further reducing the quantity of the additive to 0.1 equiv. resulted in a marked decrease in the product yield (Table 1, entry 8). Having optimised the conditions for the formation of the bicyclic lactones **2** from the acid **1**, we applied these conditions to a range of cyclic alkenes¶ to provide tricyclic γ-lactones in good to excellent yields (Table 2).



1 **2**

Scheme 1 Reagents and conditions: see Table 1; E = CO_2Me.

The cyclisation of the acid **3** provided a challenging test for our methodology. Pleasingly, exposure of **3** to our optimised conditions provided the all *cis*-substituted tricyclic γ-lactone **4a** in good yield‖ (Table 2, entry 1). The formation of the γ-lactone **4a** is noteworthy as both new bonds are formed on the most sterically-hindered face of the molecule. Also isolated from this reaction was the bicyclic alkene **20** (Scheme 2, $n = 1$) (28%).** The *trans*-disubstituted cyclopentene **5** cyclised in a similar manner to provide the *cis-trans-cis* tricyclic γ-lactone **6a**, again in good yield (Table 2, entry 2). The lactone **6a** provided crystals suitable for X-ray analysis, which allowed full stereochemical assignment. (Fig. 1).†† Use of the homologous cyclisation substrate **7** provided the desired γ-lactones **8**‖ in excellent combined yield (82%) as a 1 : 1 mixture of epimers at the oxygen-bearing stereocentre (Table 2, entry 3). Cyclisation of the *trans*-disubstituted cyclohexene **9** provided the desired *cis-trans-cis* tricyclic γ-lactone **10a**‖ as a single diastereomer in 94% yield (Table 2, entry 4). With the 7-membered ring substrates **11** and **13**, the flexibility of the ring system allows access to a variety of low energy conformers. Nevertheless, the *trans*-disubstituted substrate **11** provided the corresponding *cis-trans-cis*-tricyclic γ-lactone **12a**‡‡

Table 1 Cyclisation of the acid **1**

Entry[a]	Solvent	Additive[b]	Yield (%)
1	MeCN	—	trace
2	MeCN	Na_2CO_3	19
3	EtOH	—	44
4	AcOH[c]	—	50
5	MeCN	$Cu(OAc)_2$	33
6	MeCN	$CuSO_4$	29
7	MeCN	$Cu(OTf)_2$[d]	quant.
8	MeCN	$Cu(OTf)_2$[e]	58

[a] All reactions conducted with 2 equiv. of $Mn(OAc)_3$ under reflux. [b] 1 equiv. of additive was used. [c] Reaction conducted at 80 °C. [d] Similar results were obtained with $Cu(BF_4)_2$ as the additive. [e] 0.1 equiv. of additive was used.

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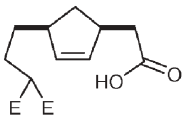
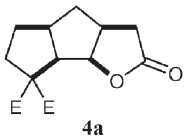
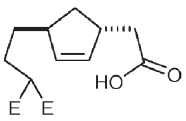
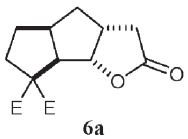
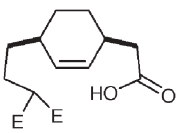
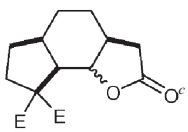
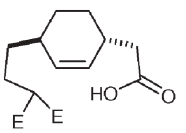
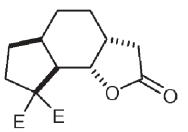
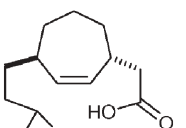
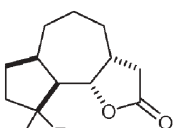
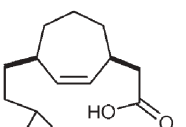
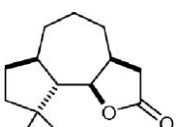
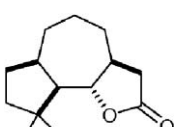
† Electronic supplementary information (ESI) available: Experimental procedure and characterisation data of the compounds prepared. See http://dx.doi.org/10.1039/b508529b

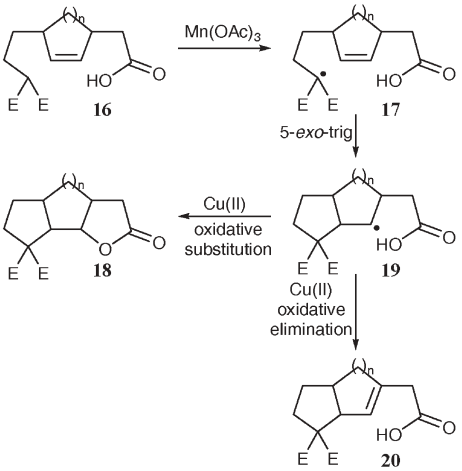
Table 2 Synthesis of fused tricyclic γ-lactones

Entry[a,b]	Substrate	Product	Yield (%)
1	 **3**	 **4a**	72
2	 **5**	 **6a**	71
3	 **7**	 **8**	82
4	 **9**	 **10a**	94
5	 **11**	 **12a**	86
6	 **13**	 **14a**  **15a**	52 23

[a] All reactions were conducted using 2 equiv. of $Mn(OAc)_3$ and 1 equiv. of either $Cu(OTf)_2$ or $Cu(BF_4)_2$ in MeCN under reflux. [b] E = CO_2Me. [c] Formed as a 1 : 1 mixture of epimers.

as a single diastereomer in excellent yield (Table 2, entry 5). Cyclisation of the *cis*-disubstituted cycloheptene **13** provided the desired tricyclic γ-lactones **14a** and **15a** as a 2 : 1 mixture of diastereomers‡‡ (Table 2, entry 6).

The mechanism of these reactions most probably involves the formation of an electrophilic *C*-centred malonyl radical[1] **17** (Scheme 2) which undergoes 5-*exo*-trig cyclisation onto the pendant alkene, generating a secondary adduct radical **19**. A copper(II) mediated oxidative C–O bond formation then occurs presumably *via* an organocopper(III) intermediate,[8] which suffers oxidative substitution from the pendant carboxylic acid to deliver product **18**. Alternatively, the adduct radical **19** can undergo oxidative elimination (β-hydride elimination) from the same organocopper(III) intermediate to deliver alkene **20**. According to this mechanistic scheme, formation of the terminal cyclopentane



Scheme 2 Proposed cyclisation mechanism; n = 1, 2 or 3.

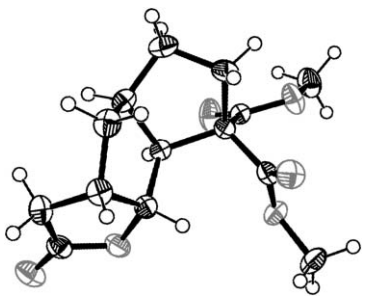
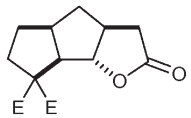
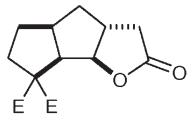
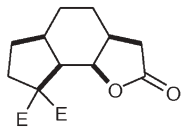
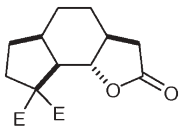
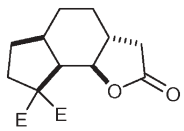
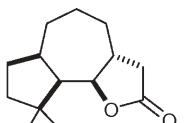
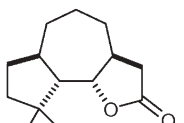
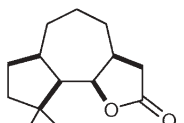


Fig. 1 X-ray crystal structure of the γ-lactone **6a**.

precedes γ-lactone formation, hence with substrates **3**, **5**, **7** and **9**, the products invariably contain a terminal carbocycle, *cis*-fused to the central ring, in accordance with a large body of literature for 5-*exo*-trig radical cyclisations onto cyclopentenes and cyclohexenes.[9] Again, in agreement with literature precedent, the cyclisation of the malonyl radical onto a conformationally more flexible cycloheptene may occur to give a *cis* or *trans*-ring fusion.§§[11,12]

The formation of the γ-lactone occurs from the [*n*.3.0]-bicyclic adduct radical **19** (Scheme 2). In general, the γ-lactone is formed *cis*-fused to the central carbocycle. However, the γ-lactones **8** are formed as a 1 : 1 mixture of epimers at the oxygen-bearing stereocentre, and the 7-membered substrate **13** yields both *cis* and *trans*-fused γ-lactone products **14a** and **15a**. Each of the γ-lactone products (and epimers at the C–O stereocentre) were molecular modelled (Table 3).¶¶ In every case, the molecular modelling results were in accordance with our experimental results, *viz.* the γ-lactone formed experimentally was the lowest energy γ-lactone epimer found computationally.‖‖ The γ-lactones **8** were formed as a 1 : 1 mixture of epimers at the C–O stereocentre, which is also in accord with the results from molecular modelling, with the lowest energy conformations for the γ-lactones **8** being within 0.2 kJ mol^{-1} (Table 3, entry 3). It is not at all surprising that with substrates **5** and **9**, the tricyclic products **6a** and **10a** contain a *cis*-fused γ-lactone. What is more interesting is that with both the sterically more encumbered substrates **3** and **7**, and the conformationally more flexible substrates **11** and **13**, the molecular modelling and the experimental results are in complete agreement. Thus, it may well prove possible to use molecular modelling as a predictive tool

Table 3 Molecular modelling of the γ-lactones

Entry	γ-Lactone B	γ-Lactone A	$E_B - E_A$/kJ mol^{-1} [a]
1	 **4b**	**4a**	35.9
2	 **6b**	**6a**	50.5
3	 **8b**	 **8a**	<0.2
4	 **10b**	**10a**	14.1
5	 **12b**	**12a**	8.4
6	 **14b**	**14a**	9.5
7	 **15b**	**15a**	17.9

[a] Difference in energy of the global minima of lactones A and B.

for determining the likely stereochemical outcome of both the initial cyclopentane formation§§ and the γ-lactone formation in cyclisation reactions of more complex substrates.

In summary, we have reported a mild and efficient synthesis of fused tricyclic γ-lactones, mediated by manganese(III) and copper(II), with the stereochemistry of the products being readily predicted by molecular modelling. The application of this methodology to total synthesis, as well as extending the methodology to encompass the synthesis of a variety of bi- and tricyclic heterocycles, is ongoing.

We thank Dr J. E. Davies for solving the X-ray structure of **6a**, Dr J. M. Goodman for advice and help with molecular modelling, the Royal Society for the award of a University Research Fellowship (JWB) and the EPSRC for funding, including financial assistance towards the purchase of the Nonius CCD diffractometer. AstraZeneca UK are gratefully acknowledged for some unrestricted funds.

Notes and references

‡ All new compounds exhibited satisfactory spectroscopic and exact mass data.†

§ Copper(II) triflate has previously been used in conjunction with manganese(III) acetate (ref. 5).

¶ The cyclohexene and cycloheptene cyclisation substrates were synthesised from 1,3-cyclohexadiene and 1,3-cycloheptadiene respectively, using the 1,4-oxidation methodology developed by Bäckvall as a key step (ref. 6). Full details of the preparation of all the substrates will be reported in due course.

‖ The stereochemistry was proven by ^{1}H NMR NOE analysis.

** The lactone **4a** is not formed from alkene **20** (n = 1) under the reaction conditions.

†† Crystal data for **6a**: $C_{14}H_{18}O_6$, M = 282.28, monoclinic, space group $P2_1/n$ (no. 14), a = 7.6093(2), b = 12.2244(3), c = 14.2977(4) Å, β = 93.281(1)°, U = 1327.8(1) Å^3, Z = 4, μ(Mo-Kα) = 0.111 mm^{-1}, 11938 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3033 unique (R_{int} = 0.036), R_1 = 0.047, wR_2 = 0.113 [$I>2\sigma(I)$]. The structure was solved with SHELXS-97 and refined with SHELXL-97 (ref. 7). CCDC 277611. See http://dx.doi.org/10.1039/b508529b for crystallographic data in CIF or other electronic format.

‡‡ The structure was determined by a combination of ^{1}H NMR coupling constant and NOE analysis, and molecular modelling.

§§ Transition state modelling, using Houk's force field for intramolecular radical additions, is in good agreement with the experimental results for the stereochemistry of the cyclopentanes formed by 5-*exo*-trig cyclisation from substrates **11** and **13** (ref. 10).

¶¶ The global minima were found by conducting a Monte Carlo conformational search (ref. 13) using the MM2* force field (ref. 14), as implemented in MacroModel v 8.0. MacroModel is available from Schrödinger (http://www.schrodinger.com).

‖‖ The γ-lactone stereoisomers do not interconvert under the reaction conditions, and the lactone-forming reactions are therefore kinetically controlled. Nevertheless, the specific lactone C–O diastereomer formed correlates with the lowest energy diastereomer found from molecular modelling.

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