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Diastereoselective Synthesis of Fused Lactone-Pyrrolidinones; Application to a Formal Synthesis of (−)-Salinosporamide A

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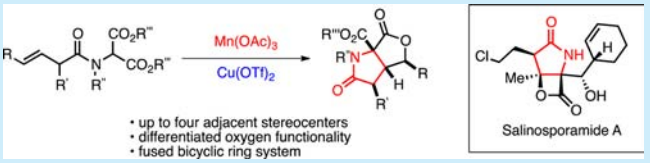
Supporting Information

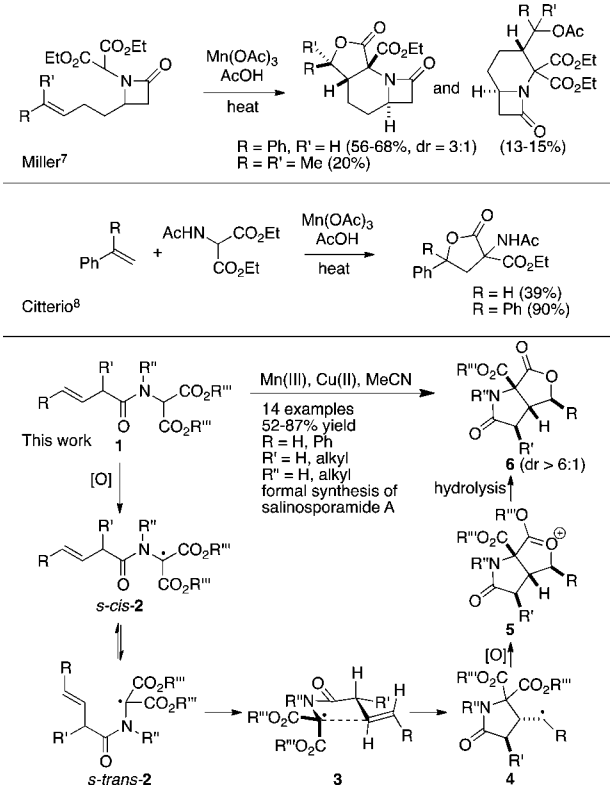
ABSTRACT: A mild, diastereoselective synthesis of fused lactone-pyrrolidinones using an oxidative radical cyclization is reported. The methodology is demonstrated in a formal synthesis of (−)-salinosporamide A.



The development of new methodology for the rapid generation of molecular complexity from relatively simple starting materials is a continuing goal of modern target-oriented synthesis. Within this arena, oxidative radical reactions have emerged as powerful processes for the mild formation of carbon−carbon and carbon−heteroatom bonds with control over multiple stereocenters.[1] In these reactions, substrate prefunctionalization is frequently not required, and the product generally ends up at a higher oxidation level than the substrate thus providing a handle for subsequent synthetic manipulation. Manganese(III) acetate is a mild, economical, and relatively nontoxic reagent for the formation of electron-deficient C-centered radicals from malonates and related CH-acidic compounds and has found wide use in organic synthesis in both method development and in the total synthesis of complex natural products.[2] Recently we reported an efficient synthesis of a number of [3.3.0]-bicyclic γ-lactones from variously substituted 4-pentenyl malonates[3] along with application of this methodology to a diastereoselective synthesis of a cyclopentane-containing natural product.[4] Herein, we report the extension of this methodology to an efficient, diastereoselective synthesis of fused lactone-pyrrolidinones from acyclic precursors. These bicyclic products contain multiple adjacent stereocenters and differentiated oxygen functionality and are formed in good yields under mild conditions.[5] Application of this methodology to the formal synthesis of the potent proteasome inhibitor (−)-salinosporamide A[6] is also reported.

Precedent for the proposed transformation comes from the groups of Miller[7] and Citterio.[8] The Miller group synthesized two tricyclic γ-lactones by the cyclization of α-amido malonates in the presence of manganese(III) acetate, and Citterio reported related reactions between α-amido malonates and alkenes for the formation of two γ-lactones and numerous other products. We aimed to extend these results to a mild and general diastereocontrolled synthesis of [3.3.0]-bicyclic γ-lactones bearing a variety of substituents (Scheme 1).

Scheme 1. Cyclization Precedent from Miller[7] and Citterio[8] with Relation to Current Work



The mechanism of the proposed reaction most likely involves single electron oxidation of the substrate **1** in the presence of manganese(III) acetate to deliver the corresponding α-

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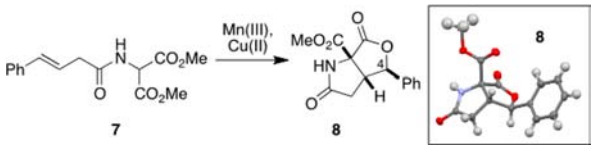
amidomalonyl radical **2**.[9] Cyclization of the α-amidomalonyl radical **2** may occur stereoselectively, via pretransition state assembly **3**,[10] to give the adduct radical **4**, which after further single electron oxidation and trapping by the adjacent oxygen atom would give oxocarbenium ion **5**. Hydrolysis of **5** would give the desired fused lactone-pyrrolidinones **6**. We were mindful that the α-amidomalonyl radical **2** would likely exist as a mixture of *s-cis* and *s-trans* rotamers and that cyclization would be geometrically possible only from the *s-trans* conformer; hence, efficient interconversion of the two rotameric forms would be a prerequisite for efficient cyclization.[11] We have previously used copper(II) triflate as an additive in manganese(III) acetate mediated cyclization reactions to promote γ-lactone formation[3] and therefore elected to use the amide **7** as our test substrate with copper(II) triflate as additive.[12]

Initial scoping reactions indicated that the lactone-pyrrolidinone **8** was formed in highest yield from the amidomalonate **7** using manganese(III) acetate and copper(II) triflate under relatively dilute reaction conditions, contrary to what we had observed in the all-carbon series (Table 1, entry 1).[3a,4,13] The

Table 1. Optimization and Single Crystal X-ray Diffraction Structure of 8[14]



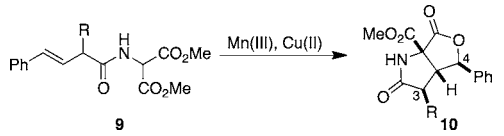
entry[a]	*t* (°C)	yield (%)[b]	dr[c]
1	80	82	6:1
2	40	73	8:1
3	25	72	14:1

[a]Reaction conditions: manganese(III) acetate (2 equiv), copper(II) triflate (1 equiv) in MeCN and 0.05 M substrate concentration for 5 h; control experiments can be found in the Supporting Information. [b]Yield for mixture of diastereomers. [c]The diastereomeric ratio (dr) refers to the mixture of diastereomers formed at C-4.

diastereocontrol was improved by conducting the reactions at lower temperature, with the highest diastereocontrol being observed at 25 °C, which gave the product in 72% yield as a 14:1 mixture of diastereomers at C-4 (Table 1, entry 3). The structure of the major diastereomer of **8** was confirmed by single crystal X-ray diffraction studies.[14]

Next we turned our attention to the cyclization of substituted substrates **9**, with a view to the substituent acting as a control element for the formation of two further stereocenters in the product lactone-pyrrolidinone **10** (Table 2). Gratifyingly, α-substituted amides **9** gave the highly substituted lactone-pyrrolidinones **10** with good yields and stereoselectivities (Table 2).[15] The methyl-substituted substrate **9a** was found to cyclize in excellent yield to give the lactone-pyrrolidinone **10a** as a 6.6:1 mixture of C-3 epimers (Table 2, entry 1).[13] Three further substrates **9b–d** with saturated alkyl side chains were found to cyclize similarly (Table 2, entries 2–4).[13] A range of unsaturated side chains were also found to direct the stereochemical outcome of the cyclization with high levels of stereocontrol, affording lactone pyrrolidinones functionalized with propargyl, allyl, benzyl, and benzyloxyethyl groups (Table 2, entries 5–8).[13] In all cases, the major diastereomer formed is in accord with cyclization via the chairlike Beckwith–Houk transition state (see

Table 2. Cyclization of α-Substituted Substrates[13]



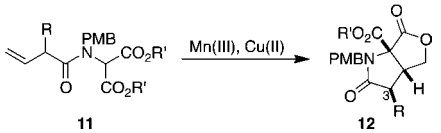
entry[a]	substrate **9**	R	**10**, yield (%)[b]	dr[c]
1	**a**	Me	84	6.6:1
2	**b**	Et	76	10.4:1
3	**c**	*i*-Pr	81	>25:1
4	**d**	*n*-Bu	65	8.4:1
5	**e**	$CH_2C{\equiv}CH$	76	18:1
6	**f**	Allyl	74	19:1
7	**g**	Bn	87	11:1
8	**h**	$(CH_2)_2OBn$	70	25:1

[a]Reaction conditions: manganese(III) acetate (2 equiv), copper(II) triflate (1 equiv) in MeCN at 25 °C for 4 h; yields and diastereomeric ratios for reactions conducted at 40 and 80 °C can be found in the Supporting Information. [b]Yield for mixture of diastereomers. [c]The diastereomeric ratio (dr) refers to the mixture of diastereomers formed at C-3.[15]

pretransition state assembly **3**)[10] with the α-amido substituent occupying a pseudo-equatorial position.[16]

The success of these cyclization reactions is likely in part due to the adduct radical (**4**) being benzylic. Indeed, cyclization of the terminal alkene substrate **1** (R, R′, R″ = H) was initially found to be highly capricious with the corresponding lactone pyrrolidinone **6** (R, R′, R″ = H) being isolated in highly variable yield (~20–70%). However, we found that the *N*-PMB-protected substrates **11** gave the corresponding lactone-pyrrolidinones **12** that were isolated with synthetically useful yields and with high diastereoselectivities (Table 3). The success of these cyclizations may be related to the increased proportion of the *s-trans* radical corresponding to *s-trans* **2** with tertiary amide substrates compared with secondary amide substrates.

Table 3. Cyclization of Terminal Olefin Substrates[13]



entry[a]	substrate **11**	R	R′	**12**, yield (%)[b]
1	**a**	H	Me	74
2	**b**	H	Et	48
3	**c**	H	*t*-Bu	75
4	**d**	Bn	*t*-Bu	52[c]
5[d,e]	**e**	allyl	*t*-Bu	43
6[d,f]	**e**	allyl	*t*-Bu	65
7[d,g]	**e**	allyl	*t*-Bu	10

[a]Reaction conditions: manganese(III) acetate (2 equiv), copper(II) triflate (1 equiv) in MeCN at 40 °C for 2 h; yields for reactions conducted at 25 and 80 °C, along with control experiments, can be found in the Supporting Information. [b]The products were isolated with >15:1 dr; it was not possible accurately to measure the diastereomeric ratio from the crude reaction mixture. [c]A [4.3.0]-bicyclic lactam corresponding to (−)-**16** was also isolated. [d]Enantiopure starting material was used. [e](−)-**16** was also isolated in 26% yield. [f]2 equiv of copper(II) triflate was used, and (−)-**16** was also isolated in 19% yield. [g]0.1 equiv of copper(II) triflate was used, and (−)-**16** was also isolated in 79% yield.

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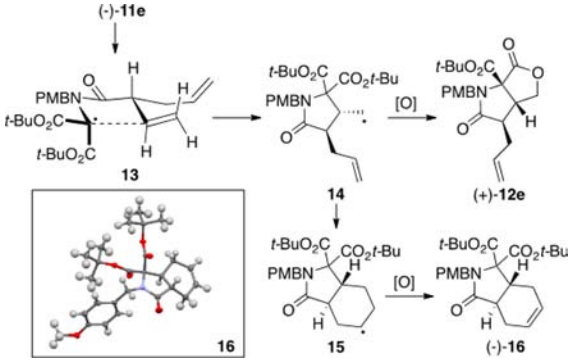
A range of dialkyl malonates were tolerated,[17] and substrates bearing unsaturated side chains gave the corresponding lactone-pyrrolidinones with high levels of diastereocontrol (Table 3, entries 3−5). Cyclization of the allyl-substituted amide (−)-**11e** with 2 equiv of manganese(III) acetate and 1 equiv of copper(II) triflate gave the desired lactone-pyrrolidinone (+)-**12e** in 43% yield along with the *trans*-fused [4.3.0]-bicyclic alkene (−)-**16** in 26% yield, the structure of which was confirmed by single crystal X-ray diffraction studies (Scheme 2).[14] The lactone-pyrrolidinone (+)-**12e** could be isolated in 65% yield by increasing the copper loading to 2 equiv, with the cyclohexene being formed in 19% yield (Table 3, entry 6). Conversely reducing the copper loading to 0.1 equiv gave the cyclohexene in 79% yield along with 9% of the lactone (+)-**12e** (Table 3, entry 7). The *trans*-fused [4.3.0]-bicyclic alkene (−)-**16** is most likely formed from the initial adduct radical **14**, which may arise from pretransition state assembly **13** (Scheme 2).[10] Further 6-*endo*-*trig* cyclization can occur, followed by oxidation of the second adduct radical **15** by copper(II) to give the *trans*-fused bicyclic cyclohexene (−)-**16**. Alternatively, the initially formed adduct radical **14** can be directly oxidized by copper(II) to give the lactone-pyrrolidinone (+)-**12e**; this is the major pathway at higher concentrations of copper(II).

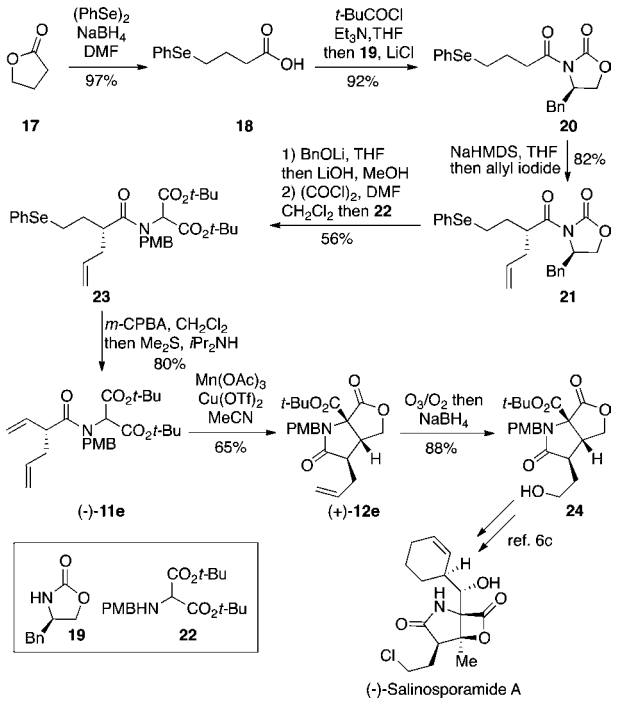
Scheme 2. Proposed Mechanism of Formation of (+)-12e and (−)-16 with the Structure of 16 from Single Crystal X-ray Diffraction Studies[14]



The synthetic utility of the developed methodology was demonstrated by the enantioselective synthesis of the lactone-pyrrolidinone **24**, an intermediate in Danishefsky's synthesis of the proteasome inhibitor (−)-salinosporamide A (Scheme 3).[6d] The known carboxylic acid **18**[18] was readily prepared and converted into the allyl-substituted oxazolidinone **21** using an Evans asymmetric alkylation.[19] Hydrolysis of the chiral auxiliary in **21** required initial conversion into the corresponding benzyl ester followed by *in situ* hydrolysis to the carboxylic acid so as to avoid *endo* cleavage of the oxazolidinone.[19] The carboxylic acid was coupled with the amino malonate **22** under Schotten−Baumann conditions to give the amide **23**.[6f] Oxidative elimination of the selenide in amide **23** gave the enantioenriched cyclization substrate (−)-**11e**. Cyclization of malonate (−)-**11e** gave the required bicyclic γ-lactone (+)-**12e** in 65% yield, which was subjected to ozonolysis with a reductive workup to afford alcohol **24**.[6d,20] The advanced intermediate **24** en route to salinosporamide A was prepared in 8 steps and 19% overall yield from γ-butyrolactone **17**.[21]

In summary, we have successfully developed a mild methodology for the synthesis of a range of fused bicyclic lactone-pyrrolidinones with good diastereocontrol in the key cyclization step. The methodology has been applied to the enantioselective formal synthesis of (−)-salinosporamide A.

Scheme 3. Formal Synthesis of (−)-Salinosporamide A



■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) As well as restricted rotation around the C−N acyl (peptide) bond, rotation may also expected be restricted around the C−N alkyl bond owing to overlap of the SOMO and the *N*-lone pair. For calculation of some barriers to rotation in related systems, see: MacInnes, I.; Walton, J. C.; Nonhebeal, D. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1789−1794.

(12) Citterio found that the diethyl analogue of **7** underwent oxidative radical cyclisation with manganese(III) acetate in acetic acid to give a cyclized benzylic acetate and not a [3.3.0]-bicyclic γ-lactone.

(13) The relative configuration of the products was assigned on the basis of ^{1}H NMR NOE experiments or by analogy (see Supporting Information).

(14) Low temperature, single crystal diffraction data for **8** were collected using a Nonius KCCD diffractometer [Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326] and for **16** on I19 (EH1) at the Diamond Light Source, Harwell [Nowell, H.; Barnett, S. A.; Christensen, K. E.; Teat, S. J.; Allan, D. R. *J. Synchrotron Radiat.* **2012**, *19*, 435−441]. The structures were solved using SuperFlip [Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, *40*, 786−790] and refined within the CRYSTALS suite [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487; Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100−1107; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2011**, *44*, 1017−1022]. Full refinement details are given in the Supporting Information (CIF). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 993331 and CCDC 993332) and can be obtained via http://www.ccdc.cam.ac.uk/data_request/cif. The structure of **16** was determined from a sample of racemic **16** prepared in initial studies; the racemic sample of **16** crystallized as a conglomerate.

(15) The diastereoselectivities are measured from the crude reaction mixture. In some cases other components were present in the crude reaction mixture that may be other diastereomers, but these components could not be characterized.

(16) For *N*-protecting group-dependent diastereoselective cyclizations of α-amido radicals, see: Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464−470.

(17) The ethyl ester **11b** routinely gave inferior yields of lactone **12b** when compared with the corresponding methyl or *tert*-butyl ester substrates **11a** and **11c**. This may be related to the ease of formation/hydrolysis of the presumed oxocarbenium ion related to **5**; however, both Citterio[8] and Miller[7] achieved efficient lactonisation with diethyl malonate derived substrates.

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(20) Our synthetic material matched the literature data very well except that there was a small discrepancy in the ^{13}C NMR resonance of the carbon adjacent to the hydroxyl group, most likely the result of a solvation effect. We therefore converted **24** into the corresponding benzyl ether, which was an excellent match with the literature data.[6d] The optical purity our synthetic **24** was shown to be >95% ee by chiral HPLC. See Supporting Information for details.

(21) The lactone-pyrrolidinone **24** was previously prepared in 12 steps and 14% overall yield from (2*S*,5*R*)-2-phenyl-1-aza-3-oxabicyclo[3.3.0]oct-6-en-8-one, which can itself be prepared from (*S*)-pyroglutamic acid.[6d]