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Unique Michael Addition-Initiated Domino Reaction for the Stereoselective Synthesis of Functionalized Macrolactones from α-Nitroketones in Water†

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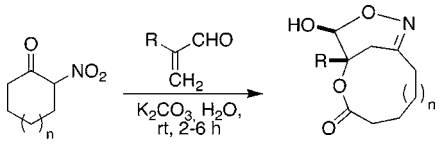
ABSTRACT



n = 2, 3, 5, 7

A unique domino reaction of α-nitrocycloalkanones with α-alkyl α,*β*-unsaturated aldehydes in aqueous base was discovered, leading to the one-pot synthesis of hitherto unknown functionalized, bridged, bicyclic lactones containing 10-, 11-, 13-, and 15-membered rings. The structures of these heterocyclic compounds, containing also an unusual 6-hydroxy-1,2-oxazine ring, were determined by spectral and single-crystal X-ray diffraction studies.

Medium- and large-sized lactones, i.e., those containing 8- to 11-membered rings and higher than 12-membered rings, respectively, have attracted much attention due to their wide range of biological activities. As examples of the first class of compounds, the structures of the fungal phytotoxin pyrenolide A[1] and ferrulactone I, a pheromone of the crusty grain beetle *Cryptolestes ferrugineus*,[2] one of the most common insects that feed on stored grain, are depicted in Figure 1. As just one example of the many biologically relevant macrolactones belonging to the second class, we will mention brefeldin A, a metabolite of the fungus *Eupenicillium brefeldianu* that specifically blocks protein transport from the endoplasmic reticulum to the Golgi apparatus[3] and has therefore become an important tool for cell biologists.

The most obvious approach to macrolactones involves esterification of a suitable *ω*-hydroxy acid or an activated derivative.[4] A systematic comparison of some of these traditional macrolactonization procedures carried out in 1991 showed that they gave only moderate yields and the formation of dimers could not normally be avoided,[5] although subsequent improvements have been made in the case of primary alcohols.[6] Other methods for macrolactone construction involve the formation of single or double carbon−carbon

† This paper is dedicated to Professor Steven V. Ley on the occasion of his 60th birthday.

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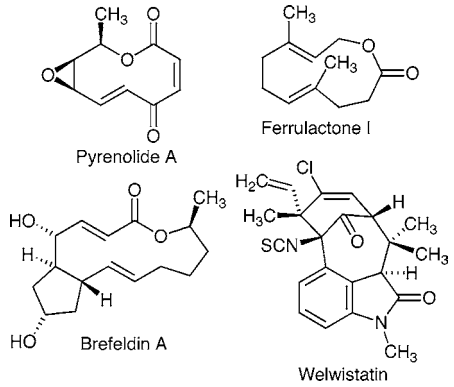
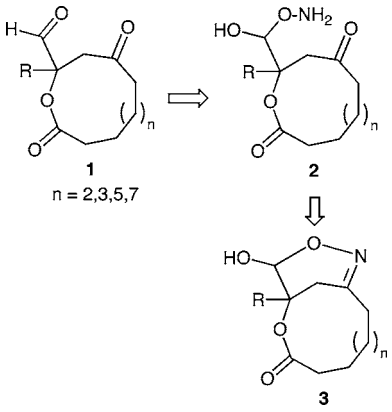


Figure 1. Structures of some natural macrolactones and welwistatin.

bonds by a variety of reactions.[4a,c,7] Generally speaking, routes starting from open-chain precursors have the disadvantage of requiring the use of high-dilution conditions to prevent intermolecular reactions and often lead to inadequate yields, which has prompted the development of methods based on ring expansion[8] that often allow these shortcomings to be overcome.

We present here a novel procedure for the one-pot synthesis of functionalized medium-sized lactones or macrolactones by reaction of cyclic α-nitroketone anions with α-substituted α,*β*-unsaturated aldehydes in aqueous solution, which was discovered in the course of our studies on an approach to analogues of the MDR inhibitor welwistatin (*N*-methylwelwitindolinone C isothiocyanate)[9] based on α-nitroketone chemistry. This reaction led to the isolation of bridged lactones **3**, which can be linked to synthetic intermediates more closely related to natural or unnatural targets with macrolactone structure (compounds **1**) by oxidative cleavage of the C═N bond using one of the many mild methods available for oximes.[10] This would lead to compounds **2** with a ketone carbonyl *γ* to the lactone oxygen and a hemiacetal function, which should spontaneously lose a molecule of hydroxylamine and give an aldehyde group in the α position (Scheme 1).

Scheme 1. Proposed Connection of Bridged Bicyclic Macrolactones **3** and Simple Functionalized Macrolactones



α-Nitroketones are important synthetic intermediates,[11] which have been employed as starting materials in the preparation of building blocks such as nitrocyclohexenes,[12] *ω*-nitro alcohols and spiroketals,[13] *β*-nitro alcohols,[14] *β*-amino alcohols,[15] *ω*-amino acids,[16] α-hydroxyketones,[17] and nitrones,[18] among others.[19] In this context, we have recently shown that α-nitroketones **1** react with unsubstituted α,*β*-unsaturated aldehydes and ketones in water at room temperature, giving the expected Michael adducts,[20] which could also be obtained using dilute potassium carbonate as the reaction medium if the reaction times were kept short enough to prevent opening of the nitroketone moiety by a retro-Claisen-type mechanism. However, in the case of the more hindered α,*β*-unsaturated aldehydes bearing an alkyl group at their α position, the reaction did not take place in the

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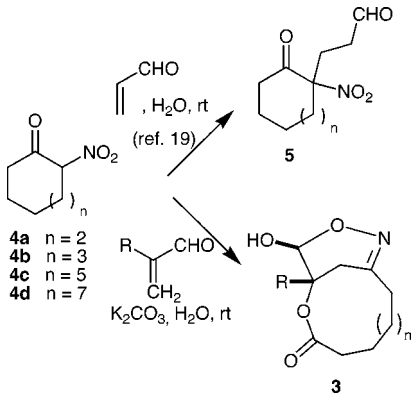
Scheme 2. Reaction of α-Nitroketones with Unsubstituted and 2-Substituted α,β-Unsaturated Aldehydes in Water



absence of catalyst, and addition of base led to an abrupt change in the course of the reaction, since the products were bridged bicyclic lactones **3**[21] bearing an unusual 6-hydroxy-1,2-oxazine ring[22] (Scheme 2). As shown in Table 1, the reaction was very versatile in terms of the size of the starting material, and therefore it could be applied to the fast preparation of functionalized macrolactones of various ring sizes. Although previous work exists on the formation of macrolactones by side chain incorporation in Michael adducts of α-nitroketones,[8a,c,17] the type of rearrangement described here is unprecedented, to our knowledge. Depending on the ring size, compounds **3** were isolated as a mixture of diastereomers or as a single isomer. Prolonged treatment of compound **3d** with base (DBU, THF, rt, 24 h) did not alter the composition of the mixture.

Table 1. Preparation of Bicyclic Lactones **3** from α-Nitroketones

3	*n*	R	time, h	yield, %	ratio of diastereomers
3a	2	CH_3	1	95	4:1
3b	2	C_2H_5	1	89	3:1
3c	2	C_4H_9	1	30	2.5:1
3d	3	CH_3	1.5	51	3:1
3e	3	C_2H_5	1.5	57	4:1
3f	3	C_4H_9	2.5	85	single diastereomer
3g	5	CH_3	2.5	57	single diastereomer
3h	5	C_2H_5	4	66	single diastereomer
3i	5	C_4H_9	6	31	single diastereomer
3j	7	CH_3	5	52	single diastereomer
3k	7	C_2H_5	5	53	single diastereomer
3l	7	C_4H_9	5	28	single diastereomer

(21) **Representative Procedure.** 2-Nitrocycloheptanone (100 mg, 0.64 mmol) was added to a solution of potassium carbonate (45 mg, 0.33 mmol) in water (4 mL). After the mixture was stirred at room temperature for 5 min, 2-ethylacrolein (0.25 mL, 2.17 mmol) was added dropwise, and stirring at room temperature was maintained for 1 h. Filtration of the precipitated white solid gave compound **3b** (136 mg, 89%) as a 3:1 mixture of diastereomers. For spectral data of **3b**, see Supporting Information.

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The structural elucidation of compounds **3** was carried out on **3b**. Combination of combustion microanalysis and mass spectral data showed a molecular formula of $C_{12}H_{19}NO_4$, corresponding to a product arising from addition of the two starting materials. However, spectral data were not compatible with a simple Michael adduct, since the very characteristic IR nitro absorption and ^{13}C NMR ketone or aldehyde carbonyls were absent. On the other hand, spectral data showed the presence of ester and hydroxy groups (signal at 175.3 ppm in ^{13}C NMR and broad singlet at 4.90 ppm in ^{1}H NMR, respectively). Furthermore, duplicate signals in the ^{1}H and ^{13}C NMR spectra suggested the presence of two diastereomers and, hence, of two stereocenters. This observation, together with the rigidity indicated by the appearance of two geminal protons as an AB system, hinted at a bicyclic structure, but complete elucidation was not possible from these data. Fortunately, we were able to obtain single crystals of the major isomer of compound **3b** by recrystallization from water, which allowed its study by X-ray diffraction (Figure 2). This study also allowed us to inequivocally establish the cis arrangement for the hydroxyl and alkyl groups.

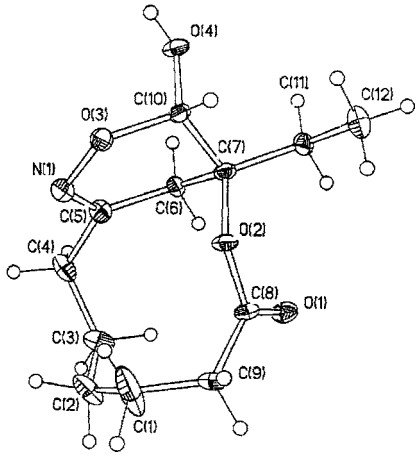

Figure 2. X-ray diffraction structure of compound **3b**.

A mechanism that accounts for the isolation of compounds **3** is summarized in Scheme 3 and involves a unique anionic domino transformation including up to six different reactions in a one-pot process.[23] We propose that anion **II** from the initial Michael addition evolves to **III** through a retro-Claisen-type reaction. Cyclization of **III** by attack of the nitronate oxygen onto the aldehyde group requires the existence of conformation **IIIb**, which would be favored by repulsive interactions between the nitronate and ethyl groups in **IIIa** and would lead to the *N*-oxide **IV**.[24] Elimination of

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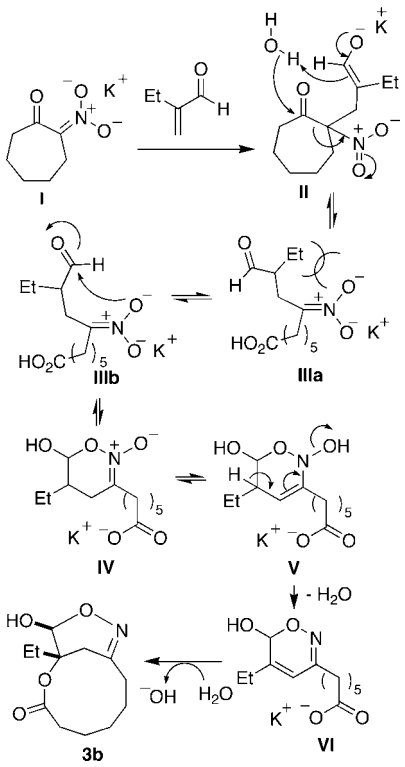
Scheme 3. Proposed Mechanism for the Formation of Lactones **3**



water from its tautomer **V** would give 1,2-oxazine **VI**, and a final intramolecular conjugate addition of the carboxylate group in **VI** onto the α,β-unsaturated imine system contained in the oxazine ring would lead to the observed products **3**, where the nucleophile attacks from the side opposite to the hemiacetalic hydroxyl, which in turn is axial with respect to the oxazine oxygen because of the anomeric effect. Precipitation of compounds **3** from the reaction medium probably helps to drive this series of equilibria to completion with preference to other possible competing reactions. An interesting feature that needs explanation is the pronounced effect of alkyl groups α to carbonyl on the course of the reaction, considering that the reaction between **I** and acrolein leads not to a derivative of **3** but to the Michael adduct for short reaction times[19] and to a retro-Claisen product for a more prolonged treatment. We propose that this difference has its origin in a conformational effect, since the absence of the alkyl side chain R would be expected to lead preferentially to conformer **IIIa**, which is unable to cyclize.

In conclusion, we present a novel, fast, environmentally friendly, and experimentally simple domino reaction that leads to functionalized, bridged, bicyclic lactones containing 10-, 11-, 13-, and 15-membered rings with fair to complete stereocontrol, depending on the ring size. The overall transformation allows the one-pot construction of bridged heterocyclic structures difficult to reach by standard transformations, starting from simple carbocyclic systems. A further advantage of this method is that it allows the easy preparation of strained systems, since medium-sized rings exist in a conformation where the presence of eclipsed C−H bonds leads to ring strain and completely strain-free conformations are not possible for odd-numbered higher macrocycles, in contrast to their even-numbered homologues.[25] It is also interesting to note that compounds **3** can be considered as lactones derived from a tertiary alcohol, which are difficult to make by other methods.[26]

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Supporting Information Available: Representative experimental procedures, characterization data for compounds **3**, X-ray data and CIF file for **3b**, and selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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