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C1–C2 cleavage of C1-functionalized 8-oxabicyclo-[3.2.1]-oct-6-en-3-one. Stereoselective preparation of 4-substituted butenolides

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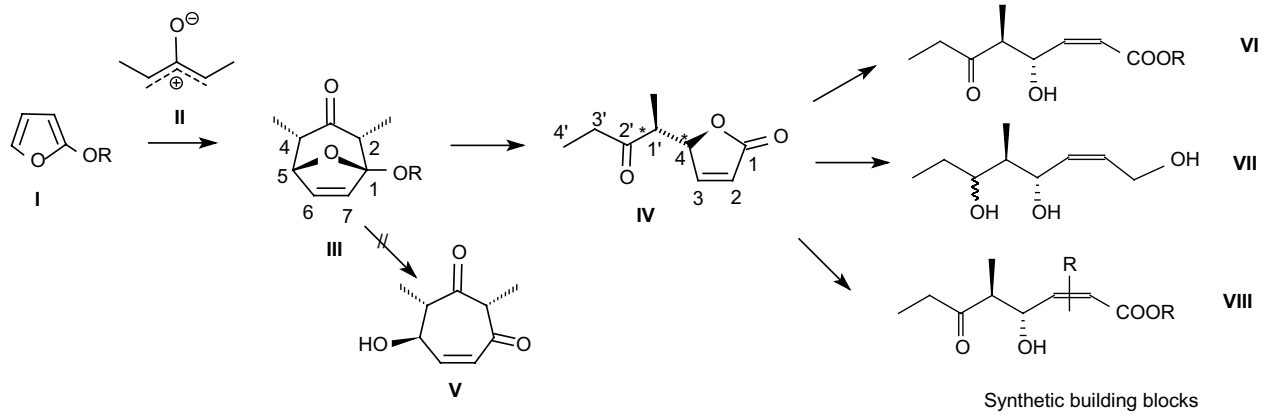
Abstract—Diastereoisomeric epimers at C1′ of 4-(1-methyl-2-oxo-butyl)-2-butenolide, and the corresponding saturated γ-lactones, were synthesized by hydrolysis of 1-methoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one, under acidic conditions. These butenolides are interesting synthetic building blocks, precursors of biologically active natural products like insect pheromones. Their formation could be explained by a cleavage at the C1–C2 bond of the oxabicyclic precursor. On the basis of the experimental data we have proposed a mechanism of hydrolytic cleavage which is formally an intramolecular reverse Dieckmann process.

In the present work we have carried out a study on the hydrolytic cleavage reactions of C1-functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-ones **III** (Scheme 1). These bicycles are prepared by a [4 + 3] cycloaddition reaction between C2-functionalized furans[1] **I** and an oxyallyl cation **II** generated, in situ, from 2,4-dibromo-3-pentanone[2] (Scheme 1). The reason for the use of furans functionalized on C2 as substrates in these cycloaddition reactions is to facilitate the opening of the oxygen bridge of these cycloadducts in order to obtain useful building blocks. This is a methodological advantage with respect to some approaches reported in the literature in which the use of Brönsted or Lewis acids to cleave the oxygen bridge affords complex reaction mixtures and low yields of the desired products.[3] However, there are elegant methods based on S_N2' reactions[4a] for the opening of



Scheme 1. Generation of 4-substituted butenolides, and derived useful synthetic building blocks, from oxabicyclic cycloadducts.

Keywords: [4 + 3] Cycloaddition; Butenolides; 8-Oxabicyclo[3.2.1]oct-6-en-3-one; 1,3-Dicarbonyl systems; Hydrolysis; C–C bond cleavage.
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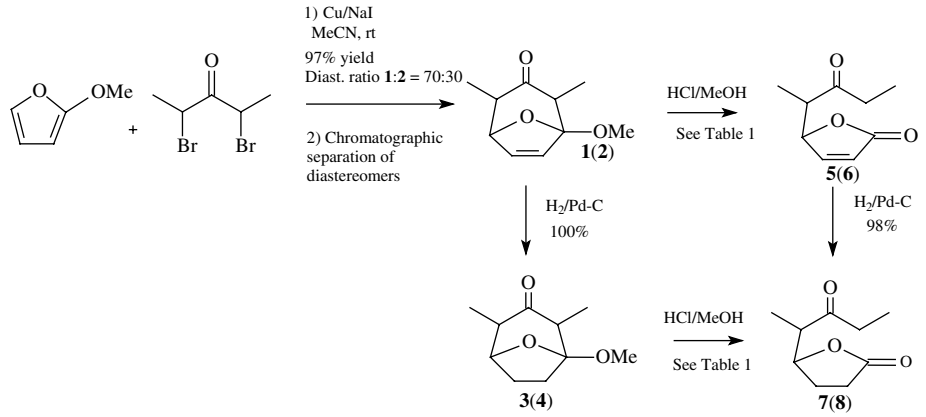


Scheme 2. Synthetic pathway for the preparation of butenolides (**5** and **6**) and γ-lactones (**7** and **8**). See Table 1 for stereochemistry definition of compounds **1**–**8**.

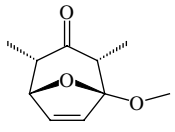
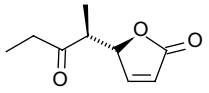
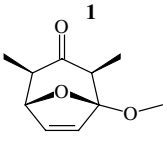
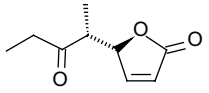
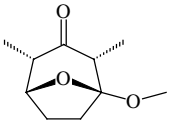
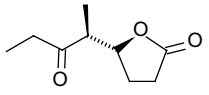
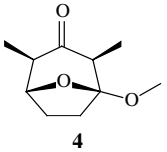
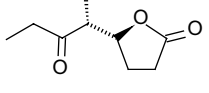
oxabicycles, nonfunctionalized on C1, which afford alkyl-cycloheptene synthons and other substitution models with interest in the synthesis of natural and unnatural products.[4]

The objective of this study is to prepare C4-functionalized butenolides **IV** (Scheme 1), and derived building blocks like **VI**, **VII** and **VIII**, which are synthons of great interest as precursors of biologically active natural products.[5] Substituted butenolides and γ-lactones are important building blocks in natural product synthesis[6] and comprise structural moieties frequently present in insect pheromones,[7] cardenolides,[8] lignans and flavour components.[9] Thus, compounds **5** and **8** could be useful precursors of the insect pheromones eldanolide,[10] serricornin[5a] or stegobinone,[5a] as well as subunits of polyoxygenated natural products such as the antibiotic erythronolide[11] or precursors of key intermediates for antitumour epothilone.[12]

We have obtained these substituted butenolides **IV** from oxabicycles **III** by cleavage of the C1–C2 bond of the cycloadducts under hydrolytic acidic conditions. It is worthwhile to note that no product **V** was observed in the reaction media in any of the evaluated substrates. The present methodology could be an alternative to both the cross-aldol reactions[13] and the nucleophilic additions to oxycarbenium ions[14] for the preparation of such important synthetic building blocks.

Pure diastereoisomeric oxabicycles **1** and **2** were readily available, on 10 g scale, from 2-methoxyfuran and 2, 4-dibromo-3-pentanone by a [4 + 3] cycloaddition reaction.[15] Compounds **3** and **4** were obtained from substrates **1** and

Table 1. Reaction conditions of the hydrolytic cleavage of oxabicyclic substrates, having different configuration on the stereocenters C2 and C4 and different functionality on carbons C6 and C7

Entry	Substrate	Reagent	Molar ratio (substrate/HCl)	Solvent	Reaction time (h)	T (°C)	Yield (%)[a]	Product
1	 **1**	HCl/H_2O	1/14	MeOH	16.0	rt	69	 **5**
2	 **2**	HCl/H_2O	1/15	MeOH	10.0	rt	72	 **6**
3	 **3**	HCl/H_2O	1/23	MeOH	25.0	rt	61	 **7**
4	 **4**	HCl/H_2O	1/23	MeOH	25.0	rt	63	 **8**

[a] On isolated product by column chromatography.

2, respectively, by catalytic hydrogenation on Pd/C with quantitative yield. The hydrolytic opening of the bicyclic compounds **3** and **4** generates the γ-lactones **7** and **8**, respectively, whose structures and properties are identical to those products obtained from **5** and **6**, respectively, by catalytic hydrogenation on Pd/C at room temperature.

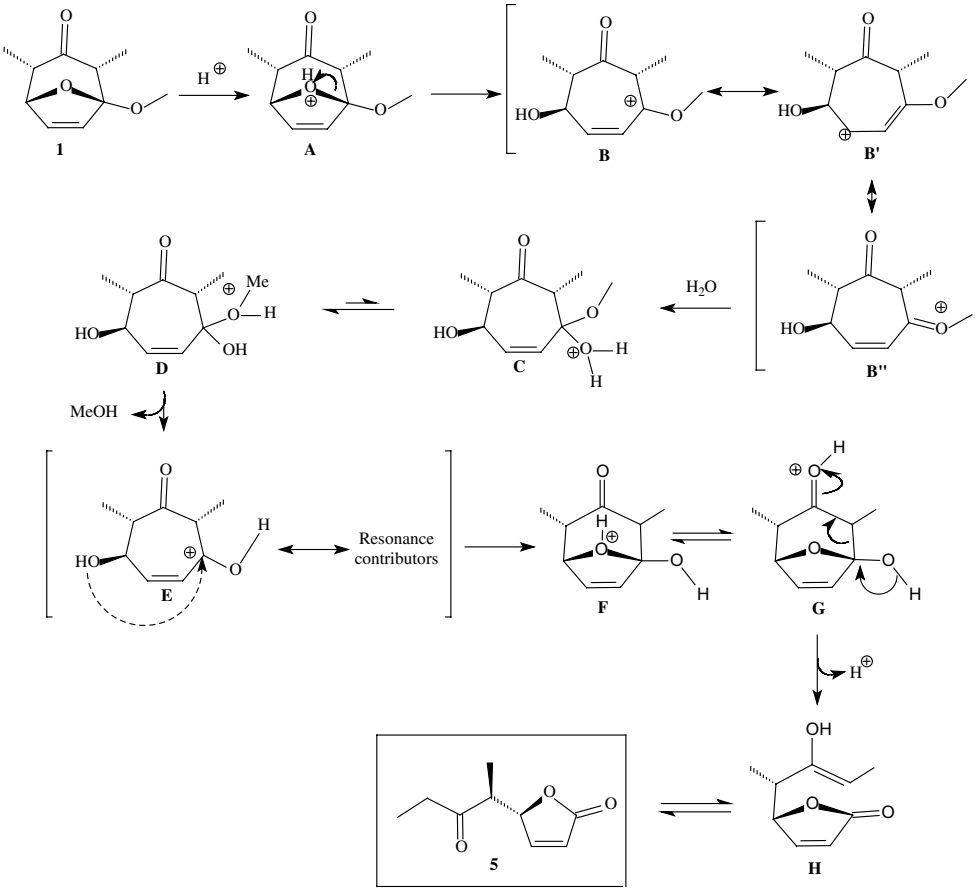
In the present work we have studied the hydrolytic cleavage of four different oxabicycles (Scheme 2), in which we have modified the stereochemistry on C2 and C4 (substrates **1** vs **2**, and **3** vs **4**) and also the presence or not of a double bond between C6 and C7 carbon atoms (substrates **1** and **2** vs **3** and **4**). In all cases we are dealing with 1,3-dicarbonyl systems in which one of the carbonyl groups is masked as a cyclic acetal.

In Table 1 we have quoted the results obtained from the hydrolytic reactions of oxabicycles **1**–**4**. From these data it is possible to conclude that the structure and stereochemistry of substrates do not drastically condition the outcome of the reactions. Indeed, we obtain opening products with similar yield and maintaining the original configuration of stereocenters on C4 and C5 in substrates **1**–**5**, with respect to the stereocenters on C4 and C1′ in the products **5**–**8**, respectively.

The hydrolytic reactions of all substrates have been carried out under similar conditions: using methanol as a solvent and an excess of HCl.[16] In all cases we worked at room temperature. However, the reaction time and the substrate/HCl ratio were different in order to accomplish a complete conversion of all substrates along the optimization process of the reaction.

In Scheme 3, we propose a mechanism for C1–C2 cleavage in substrate **1**. According to the reaction outcome we assume that the opening mechanism for oxabicycles **2**–**4** could be similar to the proposed one. However, it is necessary to take into account that in the case of compounds **3** and **4** it is not possible to stabilize intermediates **B**–**E** by resonance delocalization because they do not have a double bond between C6 and C7. This could be the reason for requiring higher reaction times for these last two compounds. We propose a mechanism involving the following steps: (a) hydrolysis of the cyclic acetal, (b) formation of a cyclic hemiacetal, (c) protonation, under acidic conditions, of this hemiacetal to afford intermediates **F** and **G** and (d) Grob fragmentation[17a] on intermediate **G**, resulting in the cleavage of the C1–C2 bond to generate the butenolides **5**–**8**. Globally this process could be considered as an internal retro-Dieckmann fragmentation.[17b]

There are precedents in the literature on processes of C–C cleavage in 1,3-dicarbonyl compounds. Mahajan[18] observed in cyclohexane-1,3-diones an intramolecular reverse Dieckmann process to generate ketolactones



Scheme 3. Proposed mechanism of C1–C2 cleavage in compound **1**.

under alkaline conditions. A more recent precedent for this type of transformation was described by Barluenga et al.,[19] who observed an unexpected cleavage of a C–C bond in 1-hydroxy-8-oxabicyclo[4.2.1]nonan-3-one, to obtain 2,3-substituted γ-lactones. No further studies were done on this particular work, on either the mechanism or the extension of the methodology to other substrates.

In summary, we have synthesized substituted butenolides **5**–**8**, in moderate yield, by a retro-Dieckmann reaction of cycloadducts **1**–**4**, under acidic conditions.[20] Compounds **5**–**8** are been evaluated in order to know their biological activity in different fields, especially as insect pheromones. On the other hand, we are carrying out additional studies to confirm the proposed hydrolytic mechanism, to optimize the hydrolysis reaction and to find new synthetic applications for compounds **5**–**8**. We are also working on the development of a more general methodology that should allow us to obtain a wide range of 4-substituted butenolides in a diastereo- and enantioselective way, starting from a series of structurally different oxyallyl cations at the level of the [4 + 3] cycloaddition reaction, and we will report the outcome in the near future.

Acknowledgements

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16. Typical reaction procedure for the hydrolytic cleavage of cycloadduct **1**: In a 10 cm^3 round-bottomed flask fitted with a magnetic stirring bar and under nitrogen atmosphere cycloadduct **1** (100 mg, 0.54 mmol) was reacted with a 12% w/w aqueous solution of HCl (2.1 mL) in MeOH as a solvent (2 mL). After 16 h the conversion was complete and the solvent was removed under high vacuum. The residue was redissolved in ether, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness using a rotary evaporator, to obtain a crude product that was purified by flash column chromatography eluting with hexane/AcOEt mixtures of increasing polarity, to isolate 63 mg of pure **5** (69% yield).
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20. All compounds **1**–**8** have been isolated, purified and physically and spectroscopically characterized, including elemental analyses. Also, their relative stereochemistry has been unequivocally established by means of ^1H and ^{13}C NMR correlations.