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Synthesis of homoallylic oxygenated α-methylene-γ-butyrolactones: a model for preparing biologically active natural lactones

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ABSTRACT

In this Letter we describe a 12% overall yield synthesis of a model for homoallylic oxygenated α-methylene-γ-butyrolactones with relative stereochemistry defined by selective hydrogenation with Rh/Al_2O_3. The synthesis was realized in 9 steps involving simple reactions.

The group of organic functions described as 'α-methylene-γ-butyrolactone', which occurs in many terpenic natural products, has been recognized as responsible for a large number of biological activities due to their ability to accept Michael addition of nucleophilic enzymes to the conjugated system.[1] As a consequence, an expressive number of original papers and reviews about synthesis of these lactonic moieties have been produced in the last decades.[2]

There is, however, a particular case that has not received as much attention as it deserves: the homoallylic oxygenated α-methylene-γ-butyrolactones. Occurring in many natural products, as shown by examples in Figure 1, this group brings some characteristic challenges to the synthetic work, which is the subject of this Letter.[3]

Our synthetic strategy is based on the short retrosynthetic analysis shown in Scheme 1.

The two oxygenated functions symmetrically distributed on each side of the isopropenylic acidic substituent could come from a β-diketone system, which could also be used to introduce the acidic substituent in the system through the easily formed enolate.

The regiochemistry of the lactone formation and the relative stereochemistry of the three stereogenic centers are the main problems in this type of synthesis.[4] There are no simple solutions because the natural diversity is large: we can find examples of natural lactones for virtually all possible combinations of regio- and stereoisomers. The method described here, summarized in Scheme 2, can produce the lactones with the relative stereochemistry of the examples shown in Figure 1; as we are presently investigating, it can also be modified to give different relative configurations.

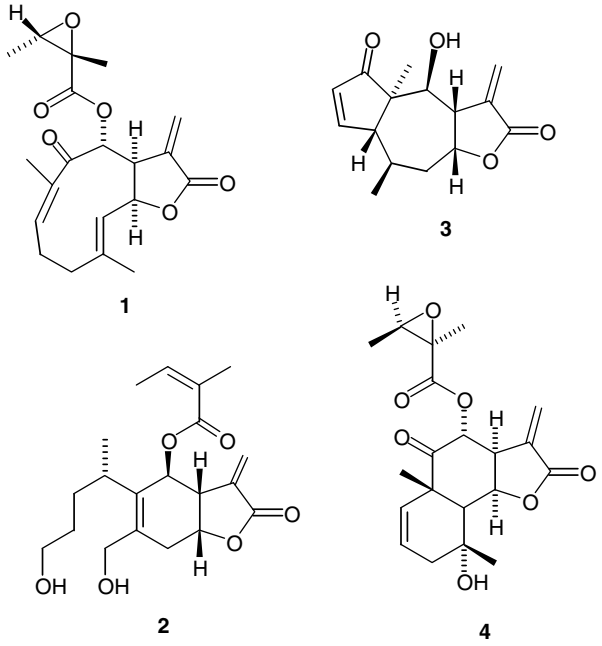

Figure 1. Examples of natural homoallylic oxygenated α-methylene-γ-butyrolactones: 8α-(2′*S*,3′*S*-epoxy-2′-methylbutyryloxy)-9-oxogermacra-4*E*,1(10)*E*-dien-6β,12-olide (**1**),[3] eriolangin (**2**),[4] helenalin (**3**),[5] 8α-(2′*R*,3′*R*-epoxy-2′-methylbutyryloxy)-4α-hydroxy-9-oxo-5β*H*-eudesm-1*Z*,11(13)-dien-6β,12-olide (**4**).

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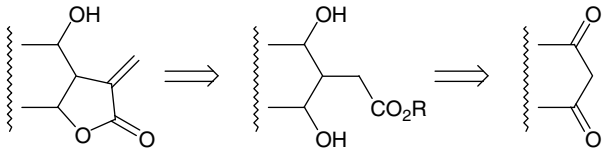
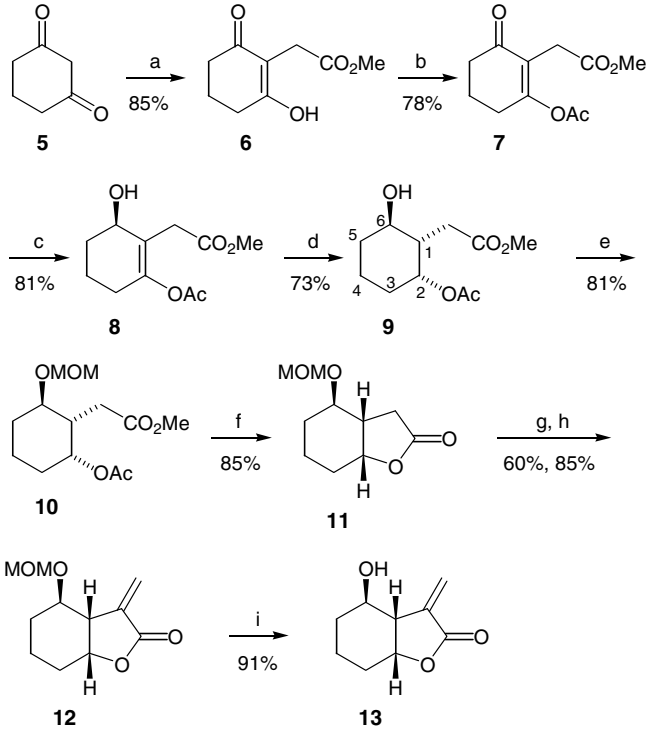


Scheme 1. Retrosynthetic analysis.



Scheme 2. Summary of the synthetic steps. Reagents and conditions: (a) MeONa, $BrCH_2CO_2Me$; (b) Ac_2O/Pyr, DMAP; (c) $NaBH_4$, $CeCl_3.7H_2O$; (d) H_2/5% Rh on alumina; (e) MOMCl, CH_2Cl_2; (f) K_2CO_3, MeOH; (g) LDA/$Me_2N^+ = CH_2I^-$, THF; (h) (1) MeI/MeOH; (2) K_2CO_3; (i) PTSA/MeOH.

In the first step, the enolate of 1,3-cyclohexanedione was used to make a simple nucleophilic substitution on methyl bromoacetate.[6] Direct reduction of **6** could not be easily effected with $NaBH_4$, but the corresponding enol acetate **7** gave good yield of the reduced material **8** when treated with $NaBH_4/CeCl_3$.[7]

The hydrogenation of **8** is the step that defines the relative stereochemistry of the three substituents of the cyclohexane ring. The use of Pd catalysts gave large amounts of hydrogenolysis products, but Rh/Al_2O_3 at 6 atm/room temperature gave good results.[8] As expected, the addition of the two hydrogen atoms occurred in a *cis* manner, from the same face of the OH group, thus resulting in product **9**.

The relative stereochemistry of product **9** could be determined by NMR analysis. By carefully comparing ^1H, ^{13}C, DEPT-135, *g*HMQC, and *g*HMBC data we can unequivocally assign the ^1H NMR signals to H6, H1, and H2. From the signal of H6, a double triplet with two J_{aa} (10.2 Hz) values, we can conclude that both H6 and H1 are in axial positions. The signal of H2, on the other hand, has only small values of *J*, showing that H2 must be equatorial.

Confirming these conclusions, a conformational search carried on with molecular mechanics programs[9] has shown that the ring conformation depicted in Figure 2 is more stable than the other

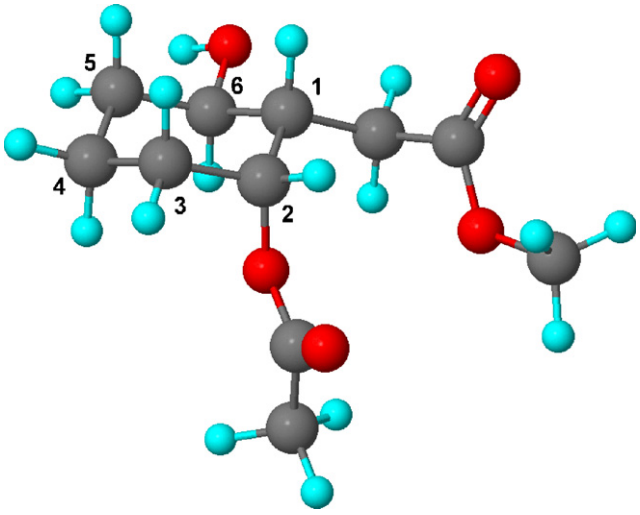


Figure 2. A stable conformation of compound **9**.

chair by over 2 kcal/mol. The calculated (Boltzmann averaged considering all found conformations) coupling constants for H6 were 10.9, 10.3, and 4.7 Hz, which are in good agreement with the experimental values of 10.2, 10.2, and 4.1 Hz.

The transformation of **9** into the lactone **11** was accomplished through two simple steps: protection of the alcohol function as methoxymethyl ether[10] followed by basic hydrolysis of the ester functions.[11] Finally, the methylene group was introduced in the lactone ring by the sequence developed by Danishefsky et al.[12] using Eschenmoser's salt.

This 12% overall yield synthesis represents a versatile approach to the preparation of homoallylic oxygenated α-methylene-γ-butyrolactones with clearly defined relative stereochemistry.

Acknowledgments

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Supplementary data

Supplementary data (experimental section, ^1H and ^{13}C NMR spectra, including 2D spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.099.

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