Cycloadducts Synthesis and Relative Stereochemistry Determined by NMR and DFT-GIAO calculations

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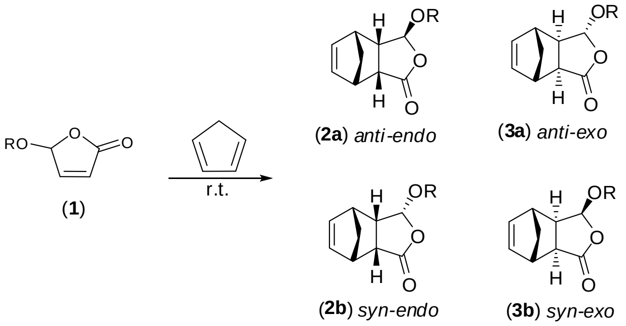
INTRODUCTION

The isobenzofuran-1(*3H*)-ones (or phthalides) and dihydro, tetrahydro, and hexahydro derivatives are a group of secondary metabolites mostly produced by several genera of the family Apiaceae[1]. These bicyclic γ-lactones have been studied because of their wide range of bioactivities[2].In our work, the Diels-Alder reaction was chosen as the key step to obtain tetrahydroisobenzofuran-1(*3H*)-ones derivatives from C-5 substituted butenolides, since α,β-unsaturated γ-lactones act as excellent dienophiles in cycloaddition reactions with dienes[3].

RESULTS AND DISCUSSION

For the reaction between generic lactone **1** and cyclopentadiene (Cp) only the adducts *anti-endo* **2a** and *anti-exo* **3a**, should be formed (Scheme 1)[4]. However, the adduct *syn-endo* **2b** was also isolated for lactone **1c** (Table 1).



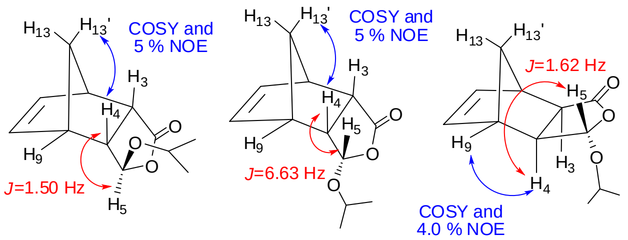
Scheme 1. Possible adducts (enantiomers are not represented) for the DA reaction between C-5 substituted butenolides and cyclopentadiene.

Table 1. Reactions of lactones **1a-c** with cyclopentadiene

Lactone: -OR group	Reaction conditions[a]	Yield (%)[b]	Adduct ratio[c]		
			Anti-endo **2a**	*Anti-exo* **3a**	*Syn-endo* **2b**
1a: OAc	A	98	95	5	-
1b: OH	B	96	97	3	-
1c: OiPr	C	91	83	9	8

[a] A: 3.4 eq.of Cp, 20h; B: 2.4 eq., DCM, 20h; C: 4.3 eq., 96h.
[b] Combined yield of pure products after chromatography.
[c] (%) Determined by CG/MS.

The relative stereochemistry of the products was established by NMR experiments (Fig.1) and DFT calculations. In adducts from lactone **1c**, for example, the COSY presented a cross correlation signal of H-13´ with H-3 and H-4 for the *endo* adducts. Moreover, a NOE enhancement of 5% was observed on H4 from H13' on *syn-endo* and *anti-endo* isomers, while this effect has not been observed in *anti-exo*. A NOE enhancement of 4,0% was observed on H-9 by irradiating H-4 on *anti-exo*.



(**2ac**) *anti-endo* (**2bc**) *syn-endo* (**3ac**) *anti-exo*

Figure 1. Representation of positive NOE interactions, COSY correlations and coupling constants for butenolide **1c** cycloadducts.

On the ^{1}H NMR spectra were observed coupling constants between H-4 and H-5 of 1.62 Hz for *anti-exo* adduct and 1.50 Hz for *anti-endo* adduct whereas for the *syn* isomer, this constant is 6.63 Hz. The unequivocally assignment of all ^{1}H and ^{13}C signals were possible with the assistance of HETCOR experiments and DFT-GIAO calculations.

CONCLUSION

The DA reactions with C-5 substituted α,β-unsaturated γ-lactones and cyclopentadiene was successfully employed to synthesize seven analogues of tetrahydroisobenzofuran-1(*3H*)-ones which were structurally elucidated by NMR techniques and DFT calculations.

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