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C_2-Symmetric enantiopure *bis*-α,β-butenolides as diastereoselective substrates in ethylene photocycloaddition

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Abstract. Several C_2-symmetric *bis*-α,β-butenolides have been synthesised starting from D-mannitol. Their [2+2]-photocycloaddition to ethylene has been studied as a model reaction to evaluate the influence of the protecting groups of the central diol system on the facial diastereoselectivity. The trimethylsilyl derivative shows the highest selectivity. The *bis*-cyclobutane containing products have been converted into the enantiopure adducts of γ-hydroxymethyl-α,β-butenolide and ethylene.

Keywords: Stereocontrol; furanones; cycloadditions

The use of natural, easily-available compounds with C_2-symmetry as starting materials for the preparation of valuable enantiopure products is extremely attractive. In a strategy based on a two-directional synthesis with simultaneous homologation of both ends of the initial chain, the sense of chirality in the formation of new stereogenic centres may proceed with substrate control.[1] γ-Hydroxymethyl-α,β-butenolide derivatives, **1**, have been extensively employed as chiral scaffolds in the enantioselective synthesis of many biologically important products.[2] Compounds **1** may be conveniently prepared from D-mannitol through sequences involving an oxidative cleavage step that yields a protected D-glyceraldehyde.[3] The many synthetic applications of **1** include the addition of different species to the carbon-carbon double-bond with the concomitant formation of new stereogenic centres, this can be accomplished with variable degrees of success (Scheme 1). We thought that perhaps the use of C_2-symmetric analogues of **1**, *i.e.* **2**, may improve the facial selectivity of the addition of external reagents, should a favourable combination of steric and electronic factors increase the accessibility of one of the pair of homotopic diastereofaces of the olefin. After the addition, symmetric cleavage of the products would give the formal adducts of **1**. The [2+2] photocycloaddition of ethylene to lactones **1** was previously investigated;[4] we have now prepared several C_2-*bis*-butenolides of type **2** and performed the same cycloaddition. Preliminary results of this study are described herein.

The *bis*-epoxides **3a-d** were prepared from D-mannitol following described methodologies.[5] We decided to investigate their conversion into the corresponding *bis*-α,β-butenolides **2a-d**, with the simultaneous formation of the two equivalent lactones, through the procedure outlined in Scheme 2 that works well for the synthesis of simple γ-heteromethyl-α,β-butenolides.[6] *Bis*-epoxide **3a**, lacking the protected diol unit, was used

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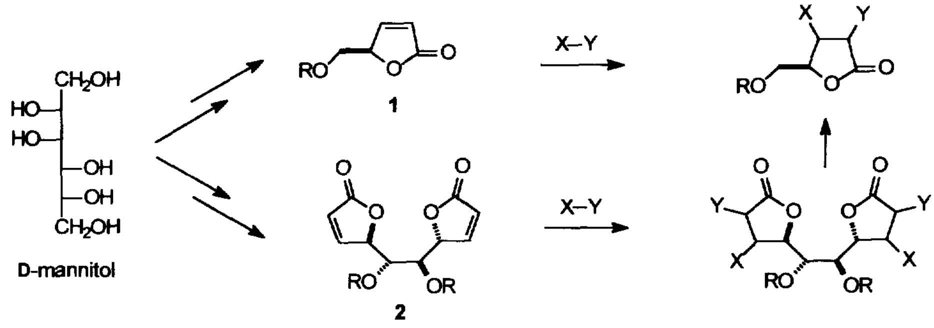
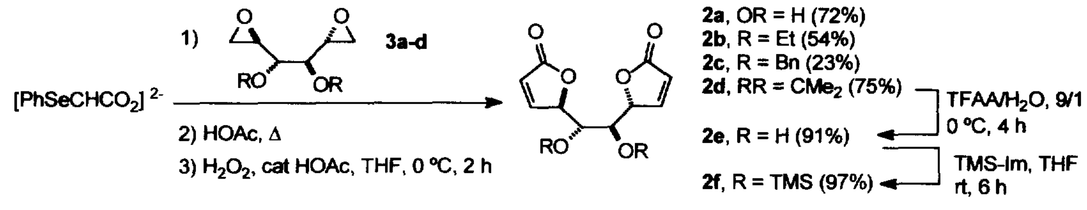


Scheme 1

to optimise the reaction conditions. Among the rest of the substrates, the isopropylidene derivative **2d** was obtained with the highest yield (75% from **3d**). Hydrolysis of **2d** gave the unprotected *bis*-lactone **2e**, which was converted into the disilyl derivative **2f**. Attempts to improve the synthesis of **2b-c** through alkylation of **2e** were unsuccessful.

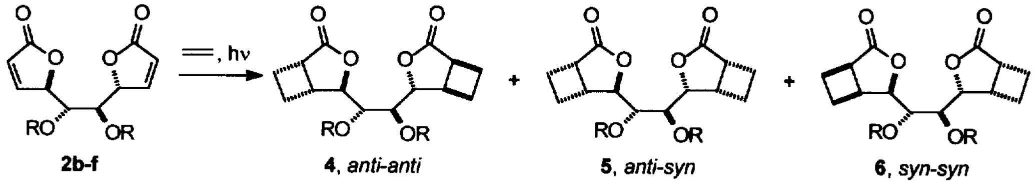


Scheme 2

The *bis*-butenolides **2b-f** were irradiated in a solution of acetone saturated with ethylene in a pyrex vessel with a medium pressure 125 W mercury lamp at -78 °C, following the conversion by ^{1}H NMR analysis of aliquot samples (Scheme 3). The results of the photochemical reactions are collected in Table 1. The diethyl and dibenzyl *bis*-lactones, **2b** and **2c**, gave very complex reaction crudes, where the *bis*-cyclobutane adducts were only minor products, but the other substrates, **2d-f**, yielded mixtures of the expected cycloadducts in very good yields. In all the cases the major product was the *anti-anti* isomer, **4**, followed by the *anti-syn*, **5**, and only for the unprotected diol we were able to detect the *syn-syn* isomer, **6e**. The overall antifacial selectivity for the disilyl derivative **2f** is higher than 98%. In additions to acyclic C_2-*bis*-allylic disilylated diols the control of the facial selectivity has been attributed to the tendency of the bulky trialkylsilyl groups to adopt an antiperiplanar arrangement.[7] In the dioxolanic substrate **2d** the dihedral angle defined by the two central oxygen atoms is constricted by the ring and the conformational preference of the free diol **2e** is probably determined by the formation of intramolecular hydrogen bonds.

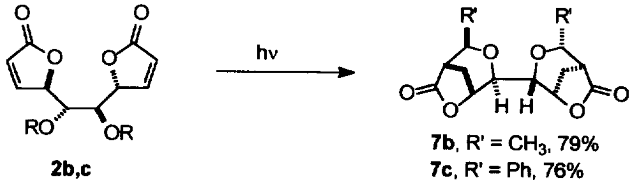
Table 1. Photochemical reactions of *bis*-butenolides **2b-f** with ethylene.

bis-butenolide	Global Yield	**4**, *anti-anti*	**5**, *anti-syn*	**6**, *syn-syn*	**7**	mixed adducts
2b	80%	30%	10%	-	30%	10%
2c	75%	5%	-	-	23%	47%
2d	65%	51%	14%	-	-	-
2e	90%	44%	38%	8%	-	-
2f	85%	83%	2%	-	-	-

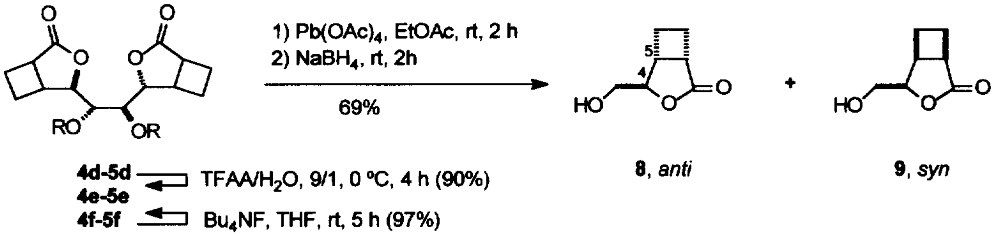


Scheme 3

All the *bis*-lactones were also irradiated under the same conditions but in the absence of ethylene. Substrates **2d-f** underwent only slow decomposition to unidentified products, but **2b** and **2c** were cleanly converted into the corresponding *bis*-pyrans **7b** and **7c** in very high yields (Scheme 4). The photochemical formation of a pyran had previously been observed in the *mono*-butenolide analogue of the benzyl derivative **2c**.[4] The isolation of **7b** illustrates that this transformation may be extended to substituents other than benzyl, in spite of the lower stability of the intermediate radical presumably formed. The stereochemistry of **7b** was established by X-ray analysis, demonstrating the stereospecificity of the cyclization. The isolation and characterisation of these *bis*-pyrans allowed us to recognise the mixed cyclobutane-pyran adducts contained in the reaction products of the previous irradiations of **2b** and **2c** in the presence of ethylene.



Scheme 4



Scheme 5

Next, the mixtures of *bis*-cyclobutane adducts **4d-5d** and **4f-5f** were hydrolysed to the diols **4e-5e** which were cleaved by consecutive treatment with $Pb(OAc)_4$ and $NaBH_4$ to give **8** and **9** in 69% overall yield (Scheme 5). In this way, the formal [2+2] cycloadducts of (*R*)-γ-hydroxymethyl-α,β-butenolide, **1** (R=H), and ethylene were obtained. The value of the coupling constant $J_{4,5}$ is 1.5 Hz for the major *anti* adduct **8**, according to an almost orthogonal arrangement of H_4 and H_5, and 5.1 Hz for the minor *syn* adduct **9**, in agreement with their *cis* relationship.[4] Compound **8** has the specific rotation $[\alpha]_D=+49$ (*c* 1.60, $CHCl_3$). If the complete sequence is applied to the *bis*-butenolide **2f**, the *anti* isomer **8** is obtained with more than 98% facial selectivity.

In summary, our strategy based on the two-directional synthesis of C_2-*bis*-α,β-butenolides starting from D-mannitol, with the aim of improving the diastereofacial selectivity of the substrate, has proven to be very effective when applied to the cycloaddition reaction with ethylene. Work is in progress to use it in the synthesis of interesting target molecules.

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