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THERMAL GENERATION OF ALPHA-HYDROXY-ORTHOQUINODIMETHANE AND REACTION WITH THE FUMARATE, MALEATE AND ACRYLATE OF S-METHYL LACTATE

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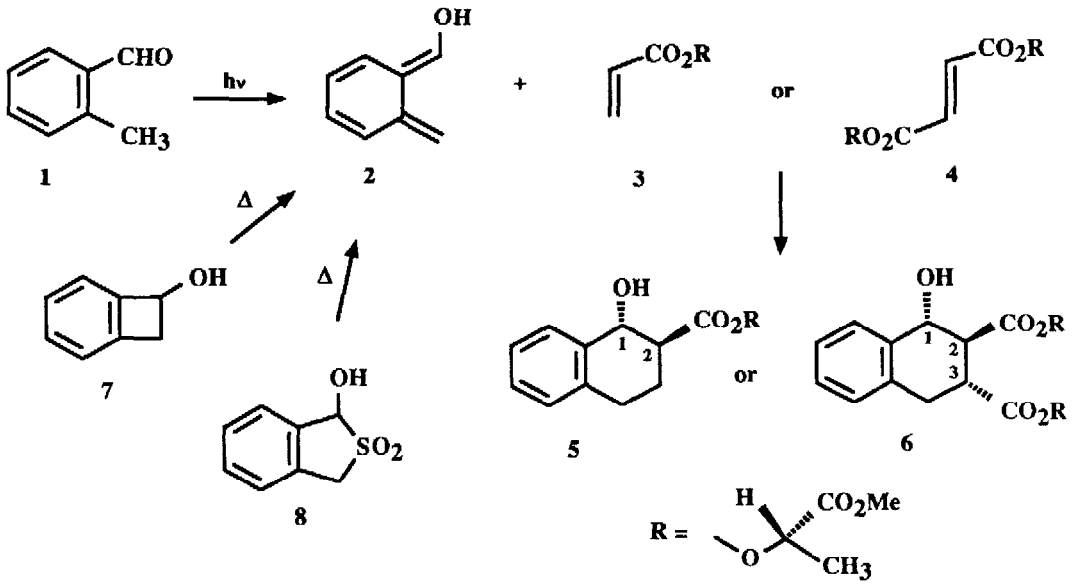
Summary: The thermal generation and reaction of α-hydroxy-o-quinodimethane with the fumarate, maleate and acrylate of S-methyl lactate is described.

In a search for enantioselective routes to aryl tetralin lignans, we have been studying asymmetric Diels-Alder reactions of ortho-quinodimethanes (o-QDMs) and have recently published examples of the highly diastereoselective addition of photochemically produced α-hydroxy-o-QDM (**1** to **2**) to the fumarate and acrylate of S-methyl lactate (**3** and **4**) [1].



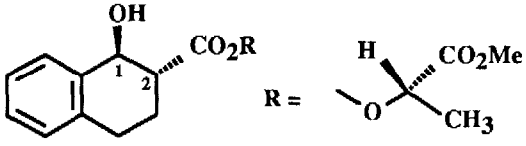
SCHEME 1

The diastereomeric excess (de) for these reactions is >95% and the cycloadducts have a *trans*-1,2 stereochemistry. This stereochemistry is surprising since it is not that predicted from the Alder *endo* rule or that found for the reaction of other dienophiles with α-hydroxy-o-QDMs[2-6]. The lactyl chiral auxiliary controls the stereochemistry at the 2 and 3 positions by directing addition to the *re* face of the dienophile[1,7,8]. While the above reactions will be synthetically useful, there are situations in which the photochemical generation of the o-QDM will be inappropriate

or impossible. For instance, the addition of o-QDMs to dialkyl maleates is complicated by *cis-trans* isomerization of the maleate to fumarate if the o-QDM is generated photochemically. There are also o-alkyl benzaldehydes that do not produce trappable photoenols on irradiation[9]. Generating the α-hydroxy-o-QDM thermally from a suitable precursor would avoid these problems although conditions would have to be found where the high cycloaddition diastereoselectivity (see above) could be maintained. In this communication we describe our investigations of the thermal generation of α-hydroxy-o-QDMs and their reactions with the fumarate, maleate and acrylate of S-methyl lactate.

The α-hydroxy-o-QDM **2**, was prepared by both the known thermolysis of benzocyclobutenol, **7**[10], and by the previously unreported thermolysis of hydroxysulfone **8**[11,12]. The syntheses of the acrylate and fumarate, **3** and **4**, have been described previously[1] and the maleate of S-methyl lactate **11** (see below), was prepared by sensitized photoisomerization of the fumarate (benzophenone, benzene, Pyrex filter, Hanovia 450 watt medium pressure mercury lamp) followed by chromatography on silica gel (hexane/ethyl acetate). The yields of cycloadducts are somewhat dependent on the method by which the α-hydroxy-o-QDM is generated although the diastereoselectivities of the cycloadditions appear to be rather insensitive to the reaction conditions.

Photochemical generation of the o-QDM **2** at room temperature and reaction with acrylate **3** gave exclusively **5** (^{1}H nmr) in 55% yield (after chromatography)[1]. Generating the o-QDM from the benzocyclobutenol **7** at 110-115°C (in toluene) in the presence of **3** (3 equ) and a trace of hydroquinone (2 mg), gave a 73% yield of **5** (after chromatography, 50:50 ethyl acetate-hexane) along with a second isomer **10** (**10**:**5** = 5:95), which could not be purified fully. It was assigned the structure **10** on the basis of its large *trans*-1,2 coupling constant of 9 Hz.



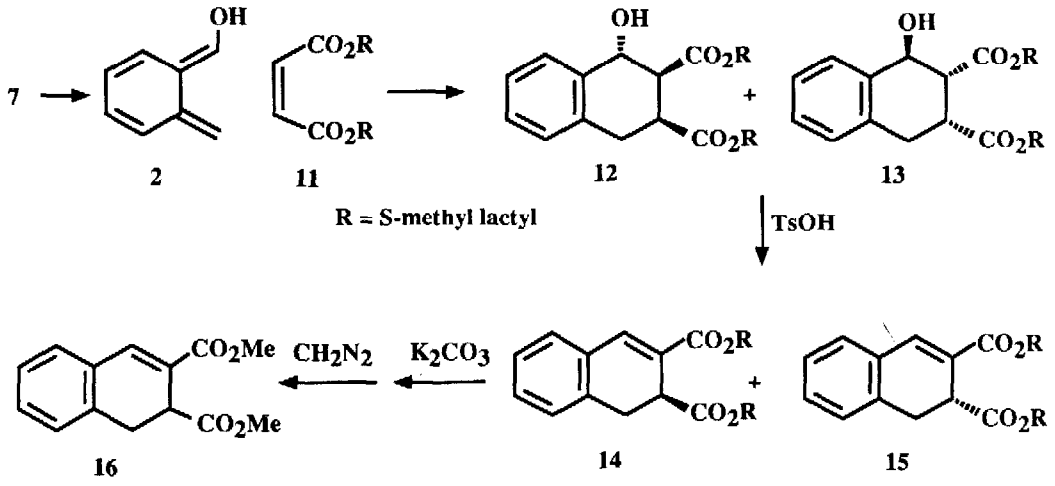
10

Attempted additions to the acrylate **3**, using the hydroxy sulfone **8** as the o-QDM precursor, under a variety of conditions yielded only recovered acrylate and o-methyl benzaldehyde. The presence of sulfur dioxide from the thermolysis of **8** apparently leads to a much shorter lifetime for the o-QDM, probably because of the formation of sulfurous acid due to traces of water, and subsequent acid catalyzed tautomerization of the o-QDM to the aldehyde. Even the presence of ZnO, used successfully previously to scavenge acid in similar reactions[13], did not lead to cycloadduct formation.

Reaction of photochemically formed **2** with the fumarate **4**, gave exclusively **6** in 55% yield (after chromatography)[1]. Thermal generation of **2** from the benzocylobutenol **7** at 110°C and reaction with **4** (2 equ, in toluene in the presence of 3Å molecular sieves) also gave only **6** (no other isomers detectable by ^{1}H nmr) in 55% yield after chromatography (15% ethyl acetate in hexane). The hydroxy sulfone **8** was also an effective source for the o-QDM under the following conditions. To a refluxing solution of the fumarate **4** (292 mg, 1.5 equ) in toluene (3 mL) containing ZnO (50 mg) was added a solution of **8** (124 mg) in methylene chloride (5 mL) over 25 minutes. After refluxing an additional 20 minutes the product was isolated and chromatographed as above to yield

exclusively **6** in 55% yield. Isolation of the cycloadduct **6** from the thermal reactions was much easier than in the previously reported photochemical reaction[1]. This was because the photochemical production of the o-QDM also caused isomerization of the fumarate to the corresponding maleate **11** which was very difficult to separate from the product **6** by chromatography.

The photochemical formation of **2** from 2-methylbenzaldehyde and addition to the maleate of S-methyl lactate, **11**, (in benzene, pyrex filter, 450 watt Hanovia, medium pressure mercury lamp) gave a complicated mixture of cycloadducts. ^{1}H nmr of the crude product revealed the presence of the fumarate **4** and cycloadduct **6**. Control irradiations in the absence of the 2-methylbenzaldehyde indicated that the aldehyde was functioning as a sensitizer for the photochemical *cis-trans* isomerization of the maleate **11** to fumarate **4**. It was therefore impossible to obtain pure maleate adducts with the o-QDM **2** under photochemical conditions since the formation of fumarate led to a mixture of both fumarate and maleate adducts. When the cyclobutenol **7** was heated in the presence of the maleate **11** (as above with fumarate **4**), no isomerization of the maleate occurred and workup gave two cycloadducts in a 70:30 ratio (93% overall yield). Although these adducts were inseparable by chromatography, we were able to tentatively assign structures **12** and **13** to them on the basis of their conversion to **16**[11,14] (by dehydration, hydrolysis and re-esterification). The relative stereochemistry of the 1-hydroxyl and the 3-carboxyl was presumed to be *trans* in both compounds since treatment of the mixture of **12** and **13** with toluene sulfonic acid in methylene chloride at room temperature did not produce a lactone between these two groups. In compound **6**, where the two groups are *cis*, lactone formation occurs readily under such conditions[1]. Under more forcing acid conditions (toluene sulfonic acid in toluene at reflux), an isomeric mixture of alkenes was formed (**14** and **15**, 70:30[15], 91% after chromatography) which when hydrolysed and esterified with diazomethane gave the single known alkene **16**[11,14](70% after chromatography).



All attempts to use the hydroxysulfone **8** as an o-QDM precursor for reaction with maleate **11**, gave only recovered maleate and o-methylbenzaldehyde.

In conclusion, we have demonstrated that the benzocyclobutenol **7** is an excellent source of the intermediate α-hydroxy-o-QDM **2**, giving moderate to high cycloaddition yields with all dienophiles. The very high stereoselectivity and asymmetric induction found previously for the reaction of photochemically produced o-QDM **2** with the fumarate and acrylate of S-methyl lactate[1], is not significantly diminished in the thermal reactions reported here. Unlike the fumarate and acrylate of S-methyl lactate, the maleate of S-methyl lactate does not add to α-hydroxy-o-QDM with high stereoselectivity. Although only *trans*-1,2-adducts are formed, they are formed from addition to both faces of the chiral dienophile. The hydroxysulfone **8** does not appear to be a good α-hydroxy-o-QDM precursor except for the more reactive fumarate **4.**

ACKNOWLEDGMENTS

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15. Using the rotation of **16** to assign the absolute configuration of the major isomer in the isomeric mixtures of **12/13** and **14/15**, was not possible as the chiral center remaining in **16** had been epimerized during the hydrolysis step.

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