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An Asymmetric Diels-Alder Cycloaddition to Alpha-hydroxy-alpha-phenyl-orthoquinodimethane

James L. Charlton*, Shawn Maddaford, Kevin Koh, Serge Boulet and Marilyn H. Saunders

Department of Chemistry, University of Manitoba, Winnipeg, Canada R3T 2N2

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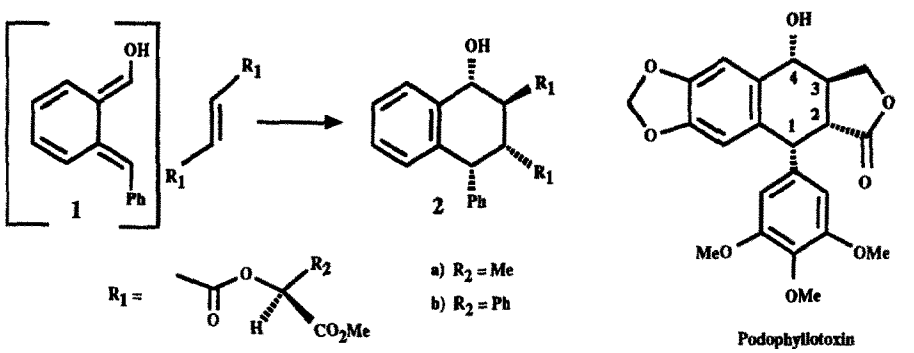
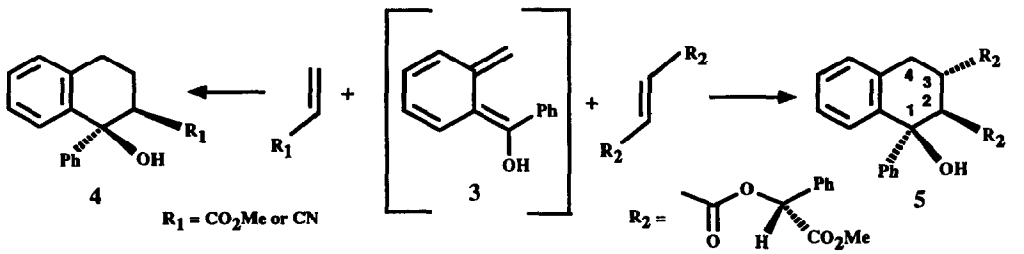
Abstract: The cycloaddition of the fumarate of methyl (R)-mandelate to α-hydroxy-α-phenyl-*o*-quinodimethane **3** gives a single diastereomer in high yield. The absolute stereochemistry of the cycloadduct is established and the potential of the reaction for asymmetric lignan synthesis is discussed.

New methods for the asymmetric synthesis of aryltetralin lignans, particularly those of the podophyllum class have recently been developed.[1-17] Some of these methods depend on asymmetric Diels-Alder reactions of *ortho*-quinodimethanes (*o*-QDMs) to establish the correct absolute and relative stereochemistry for the stereogenic centers of the tetralin ring.[5,7,9,17] In our previous work we have investigated the cycloaddition reactions of α-hydroxy-*o*-QDMs with the fumarate of methyl lactate or methyl mandelate and have found that these reactions yield *exo* cycloadducts with very high diastereoselectivity, as illustrated in the example below.[5,9,18,19]



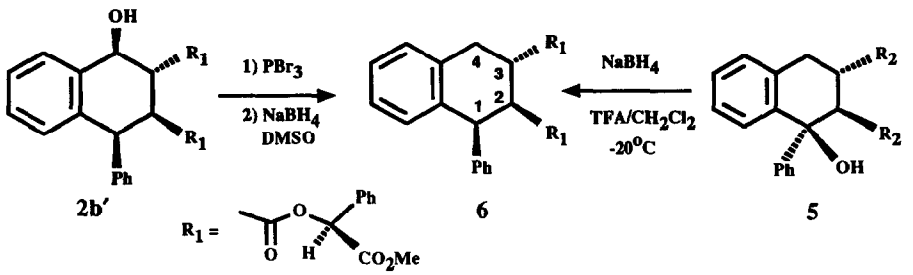
Addition occurs between the *re* face of the (S,S)-dienophile and the *re* face of the *o*-QDM and appears to be controlled by a hydrogen bonding interaction between the *o*-QDM and the dienophile chiral auxiliary.[20] Despite the fact that these reactions generate the correct stereochemistry for the podophyllotoxin skeleton, the *trans*-2-arylbenzocyclobuten-1-ol precursors to *o*-QDM **1** and its analogs tend to be very difficult to prepare.[21,22] While *o*-QDM **1** and its analogs can be prepared photochemically from *o*-benzylbenzaldehydes, this reaction is inefficient or fails in the presence of some dienophiles due to quenching of the triplet aldehyde.[9]

In our search for other diastereoselective routes to the aryltetralin lignans we have investigated the asymmetric cycloaddition of the fumarate of methyl (R)-mandelate to α-phenyl-α-hydroxy-*o*-QDM **3**. The question is whether this reaction will yield *exo* cycloadducts diastereoselectively as did *o*-QDM **1**. Previous studies of Diels-Alder reactions of *o*-QDM **3** with achiral dienophiles[23-26] have shown that *endo* products predominate as given in the example **3** -> **4**.[26]



Heating 1-phenylbenzocyclobutenol[25] at 110°C in toluene to generate **3** in the presence of the fumarate of methyl (R)-mandelate gave a single cycloadduct **5** in 50% isolated yield (flash chromatography on silica; eluent, ethyl acetate/hexanes 35:65). There were no signals in the ^{1}H nmr spectrum of the crude adduct consistent with the presence of other diastereomers of the adduct. The relative stereochemistry of **5** was assigned on the basis of its ^{1}H nmr spectrum ($J_{4a,3}$ = 12.7, $J_{2,3}$ = 9.32) which was consistent with *trans* diaxial protons at the 2 and 3 positions. The large upfield shift of H_8 to 6.79 ppm was indicative of an equatorial phenyl group at position 1 which tentatively fixed the relative stereochemistry at position 1.[27]

The absolute stereochemistry of **5** was established by reduction of **5** to **6** using $NaBH_4$/TFA. The stereochemistry of **6** was assigned partly on the basis of its ^{1}H nmr spectrum ($J_{1,2}$ = 5.6, $J_{2,3}$ = 11.9, $J_{3,4a}$ = 11.5) and also by preparing it by deoxygenation of **2b′**, the enantiomer of **2b** (prepared using the fumarate of methyl (R)-mandelate).[28] The absolute stereochemistry of **2b′** was assigned by analogy to previous examples.[5,9,18,19]



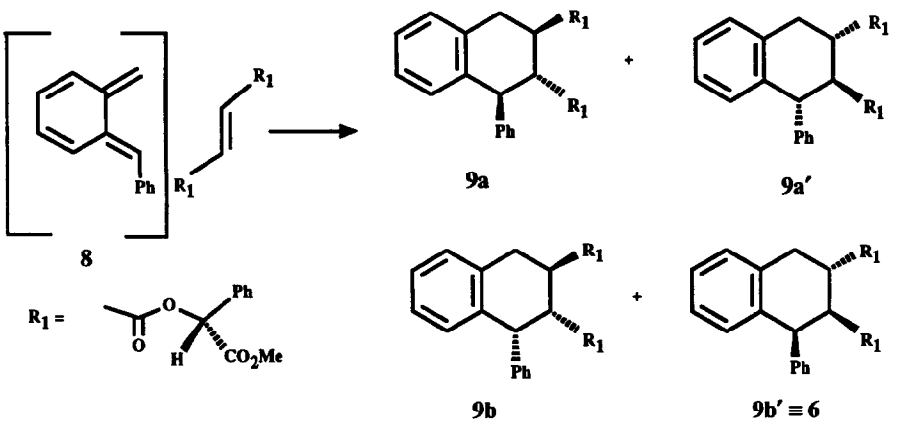
The relative and absolute stereochemistries of **6** and **5** were therefore both established by correlation to **2b′**.

There seems to be no precedent for the complete stereoinversion of a diaryl alcohol on reduction with $NaBH_4$/TFA, as observed on conversion of **5** to **6**. This reaction probably proceeds via the diaryl cation and the selective addition of hydride to one face of the cation must be directed by the neighbouring ester groups.

The question at the outset of this research was whether *o*-QDM **3** would add diastereoselectively to the fumarate of methyl mandelate to give the *exo* adduct as did *o*-QDM **1**. The surprising answer is that the

reaction is very diastereoselective but that the addition is *endo* rather than *exo*, with addition occuring between the *re* face of the (S,S)-dienophile and the *si* face of the *o*-QDM. The stereochemistry of this addition cannot be controlled by a hydrogen bonding interaction (as has been proposed for *o*-QDM 1[20]) as models show that such an interaction for the *endo* transition state is sterically impossible.

In view of the above success, the direct reaction of α-phenyl-*o*-QDM **8**, prepared thermally from 1-phenylbenzocyclobutene[29], with the fumarate was also studied (110°C, toluene). This reaction was unselective giving a mixture of four adducts **9** as evidenced by four doublets in the ^{1}H nmr spectrum between 4.0 and 4.5 ppm. One of the minor isomers was identical to **6**. The major isomers, **9a**, only one of which was characterized, were *exo* isomers as evidenced by their ^{1}H nmr spectra ($J_{1,2}$ = 10.95 and 11.0) as might have been expected from other studies.[30] The fact that **8** reacts with no discrimination at both faces of the fumarate indicates that the facial discrimination observed for reaction with **3** must be very subtly related to the geometry of the *o*-QDM. A complete understanding of the asymmetric control will require further study.



The assumed geometry of *o*-QDMs **1** and **3**, with the hydroxyl group in the E geometry, is based on past experience and torquoselectivity rules recently developed by Houk *et al.*[31]

It is interesting to note that the relative stereochemistry of **6** is identical to that of deoxpodophyllotoxin.[32] It would seem that 1-arylbenzocyclobutenols will be very useful for asymmetric lignan synthesis especially considering their accessibility[25,33] and their stability relative to their *trans*-2-aryl counterparts. Our further work in this area will be reported in the near future.

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