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SYNTHETIC STUDIES ON ARENE-OLEFIN CYCLOADDITIONS. XII. TOTAL SYNTHESIS OF (±)-SUBERGORGIC ACID

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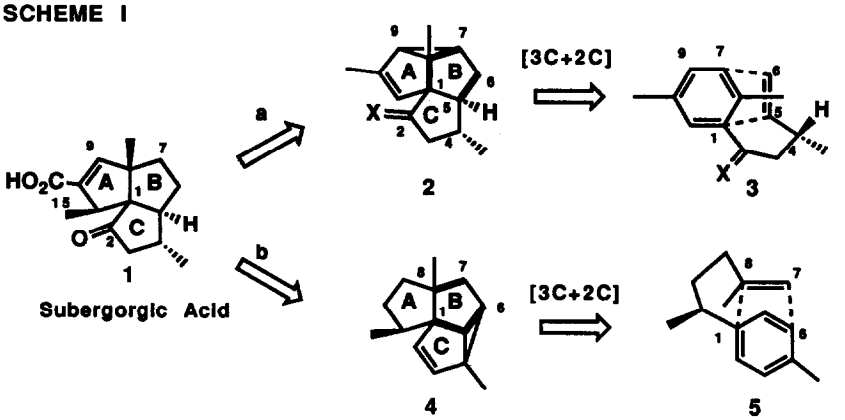
Summary: A total synthesis of (±)-subergorgic acid is described that is based on the arene alkene cycloaddition of a benzylic ketal and additionally features a free radical addition to a vinylcyclopropane as a method for cycloadduct modification.

The arene-alkene photocycloaddition has proven to be a remarkably effective and versatile process for complex molecule synthesis, providing concise, practical access to a wide range of structural motifs.[1] Our continuing interest in elucidating the factors that influence the selectivity of these reactions and in expanding the methodology for cycloadduct modification has led to the current synthesis of the cardiotoxic triquinane subergorgic acid (1).[2] This synthesis establishes the utility of benzylic ketals in the photocycloaddition, an important prerequisite for achieving one type of asymmetric control in these reactions, and it adds a new process to our previously disclosed methodology for free radical additions to vinyl cyclopropanes.[1]

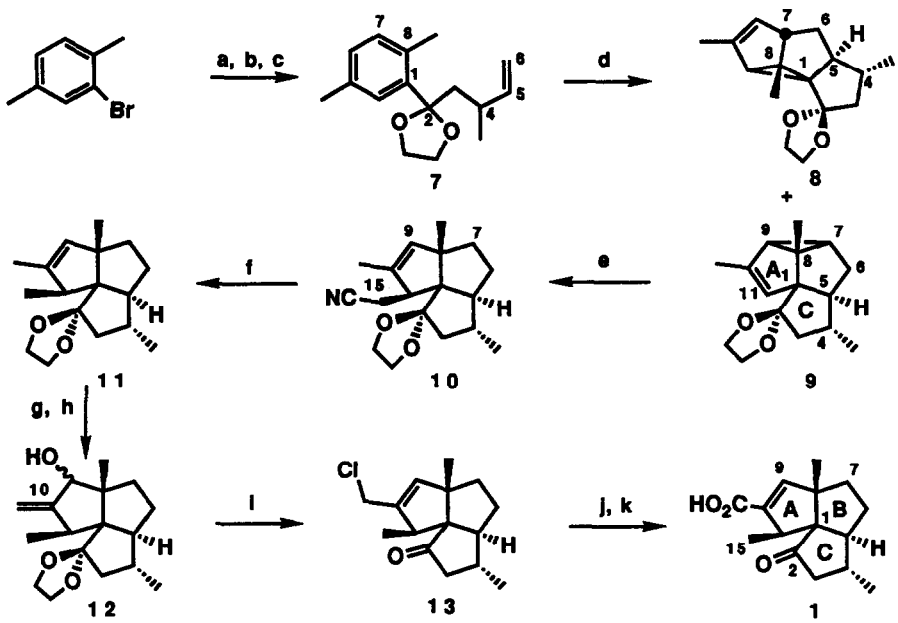
SCHEME I



At the fundamental level of connectivity analysis, the arene-alkene *meta*-photocycloaddition provides access to embedded five and seven-membered rings through [3+2] and [5+2] connections, respectively.[1d] As such, the B ring of subergorgic acid could be derived from either of two [3+2] cycloadditions (Scheme I: paths **a** and **b**) in which the starting tether and five arene atoms would emerge in the product as members of the flanking A and C rings. Path **a** was selected for study as it provided

an opportunity to evaluate the previously unexplored influence of a quaternary benzylic center (3: X=OCH_2CH_2O) in these cycloadditions. Previous studies[1c,1d] indicate that stereoinduction from less-substituted (tertiary) benzylic centers is uniformly high, raising concern about whether the replacement of a benzylic hydrogen with a sterically more demanding group would be tolerated.

SCHEME II



a: LI, Et_2O; 3-methyl-4-pentenal; b: PCC, CH_2Cl_2; c: $(CH_2OH)_2$, CSA, C_6H_6 reflux; d: hν, medium press. Hanovia, Vycor filter, cyclohexane; e: benzoyl peroxide, acetonitrile, reflux, 67%; f: K°, 18-Cr-6, toluene, 90%; g: *m*-CPBA, 80%; h: *N*-cyclohexyl,*N*-isopropyl amine, MeMgBr, 70%; i: $SOCl_2$ (excess), pyridine, 85%; j: 1) DMSO, $AgBF_4$; 2) Et_3N, 85%; k: $NaClO_2$

Construction of the desired cycloaddition precursor (7) was readily achieved from bromoxylene and 3-methyl-pent-4-enal.[3] While the racemic aldehyde allowed examination of the key issues in this study, the availability of enantiomerically pure aldehyde[4] provides the basis for an asymmetric synthesis. As might be expected for a labile ketal and for a process involving the development of three contiguous quaternary centers, the photolysis of 7 proved to be quite sensitive to reaction conditions. Trace amounts of ketone in the starting material resulting from incomplete ketalization or unscheduled hydrolysis resulted in complex photolysis product mixtures. However, careful purification of 7, freeze-thaw degassing of the solution before photolysis, and the use of an argon atmosphere served to suppress these problems. A complication involving the photolability of the cycloadducts was

also encountered but minimized by terminating the photolysis after partial conversion (ca. 66%). With these modifications, the photolysis of **7** provided cycloadducts **8** and **9** in a 1.8:1 ratio and in 42% yield (61% based on recovered starting material). C4 epimers of **8** or **9** were not detected by GC, suggesting a cycloaddition stereoselectivity of >98%. The relationship of **8** and **9** as vinyl cyclopropane isomers was demonstrated by their photo-interconversion. For preparative purposes, 2-3 grams of photocycloadducts can be formed in a single photolysis.

The photocycloaddition selectivities exhibited by the benzylic ketal **7** are consistent with expectations based on previous studies.[1c,1d] Thus, for weak donor-acceptor systems like **7**, a *meta*-mode of cycloaddition is expected and its regioselectivity is directed by the methyl (donor) substituent on the arene (C8 methyl in **7**). The *exo* selectivity of the cycloaddition is determined by the mechanical constraints imparted by the three atom tether (see **3**) which favors development of a cis-fused bicyclo[3.3.0]octane over the trans isomer that would arise from an endo approach. Finally, in the exciplex or product determining transition state, stereoinduction is regulated by the preference for the larger allylic group (see **3**: Me>H) to be located on the sterically less congested convex face of the developing diquinane subunit. In contrast to these selectivities, the vinyl cyclopropane selectivity is not determined kinetically as the two cycloadduct isomers can photo-interconvert under the cycloaddition conditions. The preference for formation of **8** over **9** is thus a reflection of the greater strain in the latter arising from the increased interaction (decreased distance) between two vicinal substituents on a sigma C1-C8 bond in **9** relative to the C1-C8 cyclopropane bond in **8**. For synthetic purposes, the near conventional behavior of **7** augurs well for the use of chiral benzylic ketals as control elements in asymmetric cycloaddition reactions.

Completion of the carbon framework of subergorgic acid from cycloadduct **9** requires introduction of the C15 methyl group at C11 and cleavage of the C7-C9 bond, processes which in related systems have been achieved in a single step by addition of a carbon free radical.[1c,1d] In the current effort, the free radical obtained from acetonitrile proved to be particularly effective, giving addition product **10** in 67% yield. Decyanation was then accomplished in 90% yield by the method of Oishi,[5] affording the complete carbon skeleton of subergorgic acid at a point (**11**) 6 steps removed from starting bromoxylene.

Introduction of the carboxylic acid functionality of subergorgic acid by allylic oxidation of **11** with selenium dioxide, *N*-bromosuccinimide, and palladium acetate proved ineffective. Consequently, a more conservative sequence was pursued. In

this route, **11** was first converted to the epoxide from which the allylic alcohol **12** was obtained. Conversion of the latter to the allylic chloride with concomitant ketal hydrolysis provided chloride **13**. Finally, **13** was oxidized[6] to the aldehyde[7] which upon further oxidation gave (±)-subergorgic acid (**1**), spectroscopically identical with the natural product. As a further confirmation of structure, the natural product was converted (LAH reduction[2a] followed by Jones oxidation) to subergorgic aldehyde which spectroscopically matched the aldehyde[7b] obtained in our synthetic route.

In summary, an 11 step synthesis of subergorgic acid based on bromoxylene is described. This study demonstrates that benzylic ketals can be utilized in intramolecular arene-alkene cycloadditions, thereby establishing the basis for the use of more complex precursor substitutions and for the control of absolute stereochemistry through chiral ketal auxiliaries. In addition, the use of acetonitrile as an equivalent of a methyl radical provides a potentially valuable procedure for the transformation of *meta*-cycloadducts and more generally for additions to unactivated double bonds. Further studies in this area are in progress.

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7. (a) All compounds gave satisfactory ^{1}H NMR, ^{13}C NMR, IR, and exact mass analysis. (b) The ^{1}H NMR and IR data reported (ref. 2b) for subergorgic aldehyde in $CDCl_3$ and $CHCl_3$, respectively, were actually recorded in CCl_4 (personal communication, Professor C. Iwata, Osaka University). A melting point difference between synthetic samples (ref. 2b: 170-172°C; this work: 72.2-72.5°C) has also been found, possibly resulting from different crystalline forms of the aldehydes, as both have been taken on to racemic subergorgic acid.

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