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Synthesis of Bicyclic Ketals Related to Zaragozic Acid by a Novel Photoannulation

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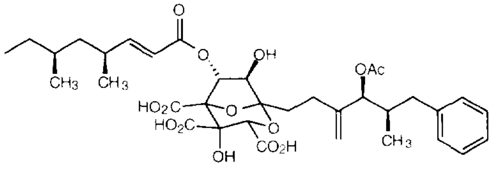
Abstract: The 2,8-dioxabicyclo[3.2.1]octane ring system of the zaragozic acids was synthesized by a Norrish Type II photochemical reaction. This reaction occured through an unusual 1,6-hydrogen abstraction to generate a 1,5-biradical. A solvent study found that using benzene provides the best yield of the desired cyclized product. Copyright © 1996 Elsevier Science Ltd

Recent disclosures describing the unique structures and biological activities of the zaragozic acids, or squalestatins, have generated much excitement in the chemical and pharmaceutical communities.[2] These compounds, particularly zaragozic acid A (**1**), were shown to be potent inhibitors of squalene synthase, the enzyme which catalyzes the first committed step in cholesterol biosynthesis.[2] Therefore, the zaragozic acids are promising lead compounds for the development of new cholesterol-lowering drugs. Additionally, members of this class of compounds were shown to inhibit ras farnesyl transferase, and thus have potential as antitumor agents.[3] These facts motivated our laboratory and others[4,5] to begin programs aimed at developing efficient routes to these compounds.

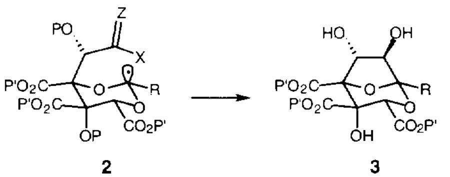


Zaragozic Acid A
(Squalestatin 1)
1

Scheme 1

Our proposed synthetic route to the zaragozic acids was influenced by our ongoing investigations of the reactivity and synthetic potential of oxygen-substituted radicals. The strategy relies on the cyclization of a carbon-based radical (**2**) bearing two oxygen substituents onto a radical acceptor to construct the unique 2,8-dioxabicyclo[3.2.1]octane ring system at a late stage in the sequence (Scheme 2). Such a strategy would allow the exploitation of symmetry elements within the molecule to the fullest extent.[4c,5f] Our initial efforts were directed toward the development of novel methods to generate the alkoxycarbinyl radical **2**, and the investigation of the feasibility of subsequent cyclizations to afford the zaragozic acid core structure (**3**).

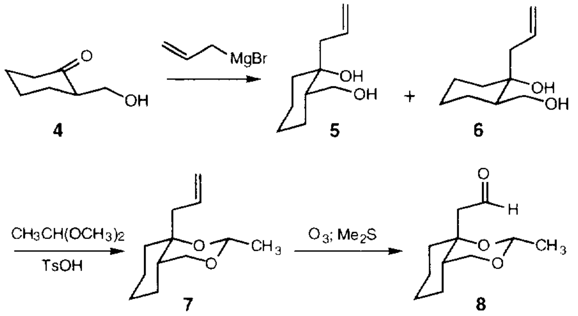
It was postulated that a method to access a radical such as **2** would involve abstraction of a hydrogen atom from an acetal carbon. Thus, a novel method to generate these acetal-derived radicals based on a Norrish



Scheme 2

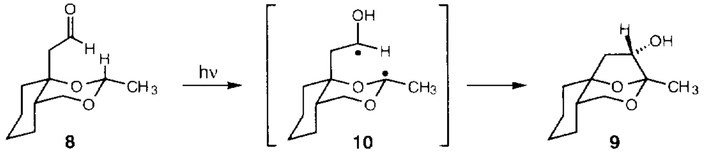
Type II photochemical reaction was devised.[6,7] The substrate that was chosen to investigate the Norrish reaction was aldehyde **8** (Scheme 3). Compound **8** contains a cyclic acetal appendaged to a cyclohexane template which provides rigidity and facilitates the cyclization of the intermediate diradical.

The synthesis of the photochemical precursor **8** commenced from compound **4**.[8] Reaction of **4** with 2.2 eq of allylmagnesium bromide (THF, 0 °C → rt) afforded the two diastereomeric products **5** and **6** in 65% yield as a separable 1:1 mixture. Since our objective was to investigate the cyclization reaction, no exhaustive attempt was made to improve this product ratio. Both **5** or **6** could be used for our study, and we arbitrarily chose **5**. The hydroxyl groups of **5** were engaged in a cyclic acetal ($CH_3CH(OCH_3)_2$, *p*-TsOH, 80 °C, 41%) to afford **7**,[9a] which was ozonized to give aldehyde **8**[9b] (i. O_3, $MeOH/CH_2Cl_2$, -78 °C; ii. Me_2S, 61%).



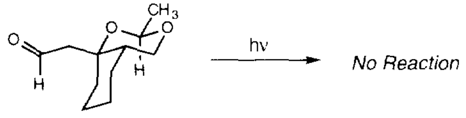
Scheme 3

Upon irradiation of aldehyde **8** in benzene for 32.5 h through a quartz filter, an intramolecular hydrogen abstraction by the excited aldehyde and subsequent cyclization occurred to generate in 59% yield the bicyclic ketal **9**,[10] via the intermediate diradical **10** (Scheme 4). A summary of the results from a detailed investigation of various conditions is shown in Table 1. In each instance, compound **9** is produced as the major or only detectable diastereomer at the carbinol carbon.[11] It was found that the reaction occurred most cleanly in benzene as solvent. There was essentially no effect when benzophenone was added as a sensitizer to the reactions performed in benzene (see entries 1, 2, 6, and 7). However, addition of banzophenone provided a modest increase in yield for the reactions in hexane (entries 3 and 8). Lower yields were obtained when the reactions were performed in acetone or acetonitrile, both of which are common solvents for



Scheme 4

photochemistry. No reaction occurred when solutions of **8** in various solvents were irradiated through a pyrex filter. That the hydrogen atom abstraction was occurring intramolecularly was demonstrated by the fact that irradiation of **11** (the acetal diastereomer of **8**) in either benzene or acetone led to no recognizable products and recovery of starting material (Scheme 5). An attempt to abstract the acetal hydrogen intermolecularly with excited acetone by irradiating a solution of compound **7** in acetone did not produce any products analogous to **9**.



11

Scheme 5

Table 1. Conditions for Norrish Reactions

Entry	*Solvent*	*Additive*	*Time*	*Yield of 9 (%)*[a]
1	benzene	–	32.5 h	59
2	benzene	–	18 h	42 (55 based on recovered **8**)[b]
3	hexane	–	30 h	34[c]
4	acetonitrile	–	30 h	20[d]
5	acetone	–	15.5 h	41
6	benzene	0.1 eq benzophenone	40 h	36
7	benzene	1 eq benzophenone	40 h	39
8	hexane	1 eq benzophenone	40 h	50

[a] If no diastereomeric ratio is reported, only one diastereomer was observed.

[b] 11:1 mixture of diastereomers.

[c] 21:1 mixture of diastereomers.

[d] 2:1 mixture of diastereomers.

The high yield and regioselectivity of this Norrish reaction is noteworthy. It has been determined that 1,5 hydrogen abstractions in Norrish Type II reactions are approximately 20 times faster than 1,6 abstractions.[12] Furthermore, the examples of cyclopentanol formation via 1,6 abstractions of δ C-H's that were previously reported occur only because an unreactive or nonexistent γ C-H bond precludes 1,5 abstraction.[6,7] However a 1,6 abstraction pathway predominates upon photolysis of **8**, even though 1,5 abstractions from several positions are possible. This unusual result can be rationalized by the relative weakness of the acetal C-H bond compared to an alkane-like C-H bond. As a point of reference, the theoretical difference in bond dissociation energy of a C-H bond that is anti to an oxygen lone pair in methanol is 5 kcal/mol lower than one which is gauche.[13] The latter is roughly comparable to a primary C-H bond.[13] Since the hydrogen atom being abstracted in **8** is anti to two oxygen lone pairs, it is expected that this bond will be even further weakened. Though no absolute value has been determined experimentally, it is not unreasonable to expect an additional decrease of approximately 1-2 kcal/mol. Additionally, the recombination of the diradical **10** to produce cyclopentanol **9** appears to be an unusually facile process. Diradical recombinations following γ C-H abstractions often compete with faster processes such as C-C bond cleavage to enols and fragmentation, thus resulting in low yields of cyclobutanols.[7] The detailed mechanistic factors responsible for the preference for 1,6 abstraction and the subsequent facile recombination of the resulting diradical in systems such as that reported here are worthy of further study.

In summary, a new method to synthesize the 2,8-dioxabicyclo[3.2.1]octane ring system of zaragozic acid was developed. Current efforts are directed toward the incorporation of this method into an efficient total synthesis of zaragozic acid. The scope of these Norrish reactions for the synthesis of other ring systems is currently under investigation. The results in these areas will be reported in the near future.

Acknowledgements

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9. (a) An inseparable 2:1 mixture of compound **7** and its diastereomer at the acetal carbon was produced. (b) The aldehyde that was derived from the minor diastereomer from the previous step was also isolated in 14% yield after the subsequent ozonolysis step.
10. The stereochemistry at the newly-formed carbinol carbon of **9** was definitively determined by NOE difference NMR spectroscopy. The presence of a crosspeak correlating the proton of the carbinol center with the ketal carbon in the HMBC spectrum further secured the structure of **9**.
11. Other products that appear to arise from abstraction of hydrogen atoms from either the ether methylene or from the ring fusion methine were also produced in minor (<10%) amounts.
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