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Preparation of the Zaragozic Acid Core through the Rearrangement of an Oxonium Ylide[1]

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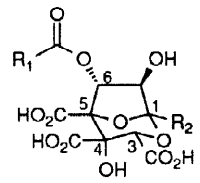
Abstract: The diastereoselective formation of a 2,8-dioxabicyclo[3.2.1]octane skeleton was accomplished through the generation and rearrangement of a bicyclic oxonium ylide. The skeleton which was formed is common to the zaragozic acid family and possesses appropriate functionality for further manipulation. The study also revealed the first example of an exocyclic 2,3-shift from a acetal-derived oxonium ylide.

The zaragozic acids (**1**), known also as the squalestatins, are a family of fungal metabolites which have attracted significant interest due to their intriguing molecular architecture and their potent competitive inhibition of squalene synthase.[2] Being intimately involved in cholesterol biosynthesis, squalene synthase represents an attractive target for the development of agents designed to control cholesterol levels.[3] Since members of the zaragozic acid family have been shown to be effective inhibitors of cholesterol biosynthesis both *in vitro* and *in vivo*,[4] these natural products have been recognized as attractive lead compounds for the design of cardiovascular agents.



1 Zaragozic Acid

Considerable effort has been directed toward the development of synthetic approaches to these natural products. The presence of multiple stereocenters on the two side chains and a diverse array of oxygen functionality on a 2,8-dioxabicyclo[3.2.1]octane skeleton has served to establish the zaragozic acids as challenging synthetic targets. Numerous approaches toward the preparation of the side chains and the 2,8-dioxabicyclo[3.2.1]octane core have been reported.[5] Four of these efforts have culminated in the total synthesis of a member of the zaragozic acid family.[6] Many of the synthetic approaches have relied upon a strategy in which complex functionality was assembled on an acyclic skeleton followed by intramolecular acetalization. An alternate synthetic strategy would be to assemble a highly functionalized bicyclic acetal core which would be followed by functional group and stereochemical manipulation. We report herein the rapid, efficient, and remarkably simple stereoselective synthesis of a highly functionalized 2,8-dioxabicyclo[3.2.1]octane ring system.

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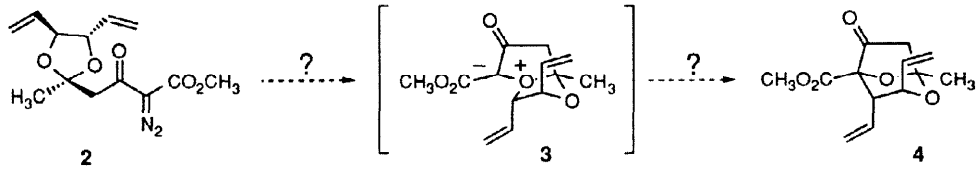
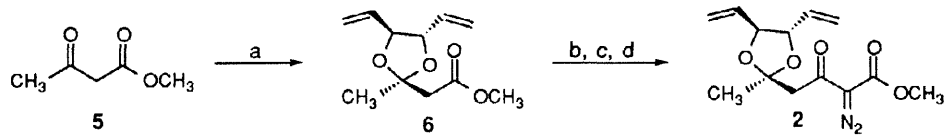
We recently reported that the rearrangement of bicyclic oxonium ylides generated by the intramolecular exposure of metallocarbenoids to acetals resulted in the efficient formation of a 2,9-dioxabicyclo[3.3.1]nonane skeleton.[7] Specifically, we observed that acetal substituents and ring size play major roles in determining the course of subsequent rearrangements. One variation on the starting material structure which had not been studied was the tether length between the acetal and the diazo ketone. If substrate **2**, in which the tether length has been shortened to a single methylene, was prepared and exposed to catalytic decomposition, a similar exocyclic 1,2-shift of an intermediate oxonium ylide would generate the 2,8-dioxabicyclo[3.2.1]octane skeleton **4** common to all members of the zaragozic acid family (Scheme 1). It merits mentioning that the influence of the shortened tether on the formation and rearrangement of oxonium ylide **3** was unknown. A similar [3.3.0]bicyclic oxonium ylide had been reported to rearrange to the isomeric 2,5-dioxabicyclo[4.2.0]octane skeleton,[8] although the vinyl groups on dioxolane **2** were expected to promote the exocyclic 1,2-shift of **3** and the formation of the 2,8-dioxabicyclo[3.2.1]octane skeleton **4**.



2 **3** **4**

Scheme 1

Methyl acetoacetate **5** was converted to stereoisomeric dioxolanes upon exposure to a mixture of the *meso*- and *d,l*-1,5-hexadien-3,4-diols. The *d,l*-isomer **6** was separated by chromatography and saponified with KOH in methanol. Following acidification, the carboxylic acid was converted to the β-ketoester through application of the procedure of Masamune.[9] Diazotization of the β-ketoester was performed with p-carboxybenzenesulfonazide[10] and provided the targeted substrate **2**.



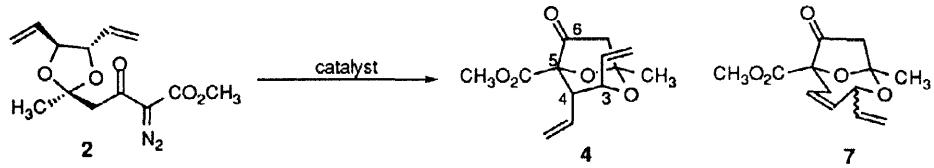
5 **6** **2**

(a) mix of *meso*- and *d,l*-1,5-hexadien-3,4-diol, p-TsOH; (b) KOH, CH_3OH; (c) i) carbonyl diimidazole, ii) $Mg^{2+}(^{-}O_2CCH_2CO_2CH_3)_2$; (d) p-carboxybenzenesulfonylazide, Et_3N;

Scheme 2

Exposure of **2** to catalytic Cu(hfacac)$_2$ at 80 °C resulted in its conversion to a mixture of two compounds. On the basis of ^{1}H- and ^{13}C-NMR spectra the structure of one compound was assigned as that of the targeted bridged bicyclic structure **4**.[11] The most specific evidence that the intermediate oxonium ylide **3** had undergone a 1,2-shift to generate the bridged bicyclic structure 4 was the ^{13}C-resonance at 104.5 ppm which indicated the continued presence of an acetal carbon. This data, along with the observed upfield shift of the C4 proton, was consistent with our previous studies in which an intermediate oxonium ylide rearranged via an exocyclic 1,2-shift to the allylic carbon.[7] The *trans*-diaxial stereochemistry of the two vinyl substituents was assigned on the basis of a ^{1}H-^{1}H coupling constant (5.5 Hz) consistent with the twist-boat conformations observed in the previous studies.[7,12]

The second compound isolated from the reaction of **2** with $Cu(hfacac)_2$ was acid-sensitive and could not be completely purified. However, extensive ^1H-decoupling studies on the crude reaction mixture indicated that **7** arose via an unprecedented exocyclic 2,3-shift of an intermediate oxonium ylide. The *cis*-stereochemistry of the internal olefin was assigned on the basis of a 7.5 Hz coupling constant, however, the stereochemistry of the C3 vinyl group could not be established.



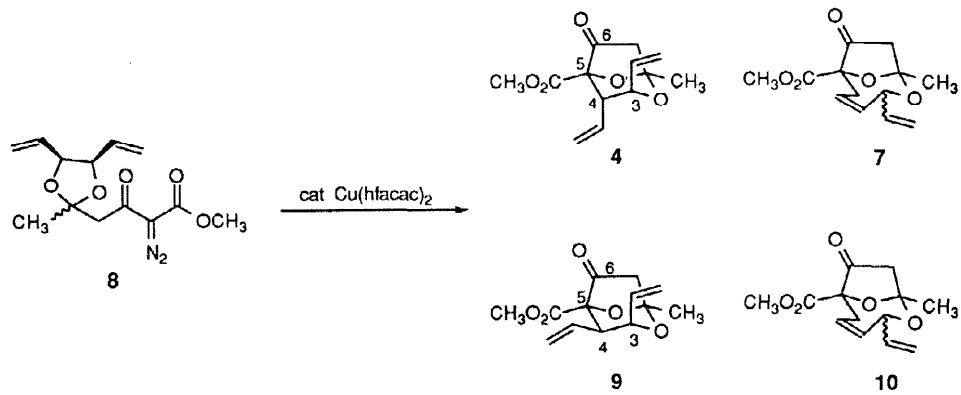
Conditions	4	7
cat. $Cu(hfacac)_2$, benzene, 80 °C;	42 %	20 %
cat. $Rh_2(OAc)_4$, benzene, 25 °C	64 %	-

Scheme 3

Previous studies of oxonium ylide formation and rearrangement indicated that electron deficient Cu(II) catalysts generally provide the best environment for efficient reactivity.[7a,13] It was unanticipated, therefore, that $Rh_2(OAc)_4$ would facilitate the most efficient preparation of the bridged bicyclic skeleton **4**. It has not been clarified whether the selectivity of the rhodium catalyst for the 1,2-rearrangement is due to the repression of the 2,3-shift pathway or to efficient discrimination of the diastereotopic oxygens. Nevertheless, the ability of $Rh_2(OAc)_4$ to promote selective formation of **4** through the rearrangement of the oxonium ylide further illustrates the influence of catalyst on ylide formation and rearrangement.

A mixture of two *meso* compounds **8** were prepared through the same sequence of reactions described earlier. Surprisingly, treatment of **8** with $Rh_2(OAc)_4$ generated no ylide derived products. However, exposure of this mixture of two *meso* compounds to $Cu(hfacac)_2$ resulted in the formation of a complex mixture of four ylide-derived compounds.

Two of the products, **4** and **7**, were the identical substances isolated from the reaction of *d,l*-diazoacetal **2**. The isolation of **4** from the *meso*-starting material was unanticipated, since this required the 1,2-shift take place with inversion of configuration. The two other *meso*-derived products were identified



Scheme 4

as a second 1,2-shift product **9** and a second 2,3-shift product **10**. The stereochemistry of **9** was established through the observation of NoE enhancement between a C7 methylene proton and the vinylic

protons and NoE enhancement between the C1 methyl group and the C3 methine. These data are consistent with the twist boat conformation of **9**. Neither the olefin stereochemistry nor the C3 stereochemistry of the acid-sensitive 2,3-shift product **10** has been clarified.

In summary, we have established that a highly functionalized 2,8-dioxabicyclo[3.2.1]octane skeleton can be generated from methyl acetoacetate in five steps. The similarities between **4** and the zaragozic acid core include the presence of the bridgehead carboxylate, two vinyl groups (masked carboxylates) at C3 and C4, and oxygen functionality at C6. The preparation of this highly functionalized ring system appears to provide an efficient entry into the zaragozic acid family of natural products.

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11 **Spectroscopic data for Compound 4:** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.99-5.83 (m, 1H), 5.84-5.73 (m, 1H), 5.31-5.18 (m, 4H), 4.35 (dd, 1H, *J* = 5.3, 5.5 Hz) 3.78 (s, 3H), 2.89 (dd, 1H, *J* = 5.5, 9.0 Hz), 2.67 (d, 1H, *J* = 17 Hz), 2.63 (d, 1H, *J* = 17 Hz), 1.79 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.8, 164.8, 136.0, 133.0, 120.2, 117.8, 104.5, 87.0, 75.1, 52.9, 52.0, 84.4, 23.8; IR (film) 3000-2800, 1750, 1700, cm-1; MS (CI, NH_3) 253, 235, 196, 154, 139, 95; HRMS (CI, NMH)MH$^+$ calcd for $C_{13}H_{17}O_5$ 253,1076, found 253.1068.

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