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Novel formation of a bridged bicyclic furan by rearrangement of a tetrahydroxydecalinone

Michael E. Jung* and Sun-Joon Min

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, USA

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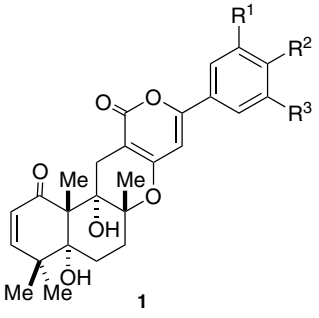
Abstract—In the course of a synthetic approach to the arisugacins, we prepared the tetrahydroxydecalinone **8a** (which exists as the hydroxytetrahydrofuran **8b**) by a straightforward route from hydroxy-β-ionone. On treatment with mesyl chloride and base, the desired mesylate **9** was not formed but rather **8ab** underwent a novel rearrangement to produce the bridged bicyclic furan **10** in excellent yield. A reasonable mechanism for the rearrangement is presented involving a retro-aldol reaction, a base-catalyzed β-elimination, and final furan formation from a β-hydroxymethyl enone.

One of the possible approaches for treating Alzheimer's disease (AD) and other forms of dementia is to inhibit the activity of acetylcholinesterase (AChE).[1] Tacrine, a known inhibitor of AChE,[2a] was first approved by the FDA for the treatment of AD type dementia. However, in a recent study, the compound was shown to have serious toxicity, caused by inhibition of butyrylcholinesterase (BuChE) present in the liver.[2b] Several tacrine analogues as well as other inhibitors of AChE have been screened for possible activity.[3] Arisugacins A and B, **1ab** (Fig. 1) were isolated from *Penicillium* sp. FO-4259 by Ōmura, et al. along with the structurally related territrem B **1d**, which was previously reported by Ling et al.[4] Among the members of the arisugacin family, arisugacins A and B show the most potent and selective inhibitory activity against AChE with IC_{50} values of 1 and 26 nM, respectively. In particular, arisugacin A exhibits significant selectivity against AChE over BuChE. The clinical importance of arisugacin A has prompted increased interest in its synthesis and has resulted in two recent reports of total synthesis.[5] We describe here a novel rearrangement observed during the transformation of the fully functionalized AB ring system of arisugacin A.

As outlined in Scheme 1, our synthetic plan involved the coupling of a substituted pyrone such as **2** with a fully functionalized decalin system **3** with a reactive mesylate or aldehyde group by a metal or transition metal promoted coupling and subsequent dehydration–cyclization. We envisioned that the olefinic triol **4** could be transformed into the required decalin system **3** with either the mesylate or aldehyde functionality.



1

a R^1=H, R^2=OMe, R^3=OMe Arisugacin A
b R^1=H, R^2=OMe, R^3=H Arisugacin B
c R^1,R^2=OCH_2O, R^3=OMe Territrem A
d R^1, R^2, R^3=OMe Territrem B
e R^1=OMe, R^2=OH, R^3=OMe Territrem C

Figure 1.

The synthesis of the fully functionalized decalin system **8** is shown in Scheme 2. Starting from hydroxy β-ionone, we have successfully synthesized the triol **4**, which was used as a key intermediate in Hsung's total synthesis,[5b] in several steps.[6] The primary alcohol of the triol **4** was selectively protected as the TBS ether **5**.

Keywords: Base-promoted rearrangement; Retro-aldol reaction; Furan formation.
* Corresponding author. Tel.: +1 3108257954; fax: +1 3102063722; e-mail: jung@chem.ucla.edu

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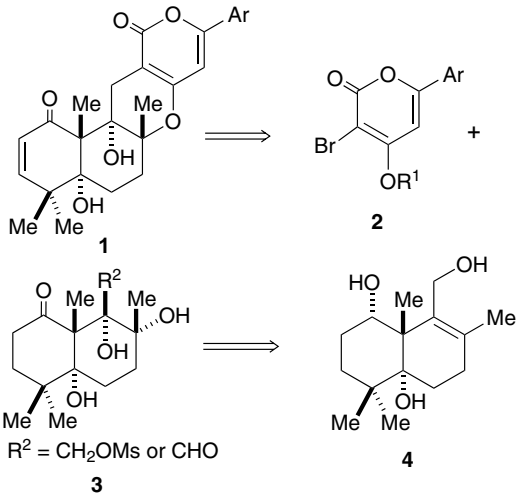
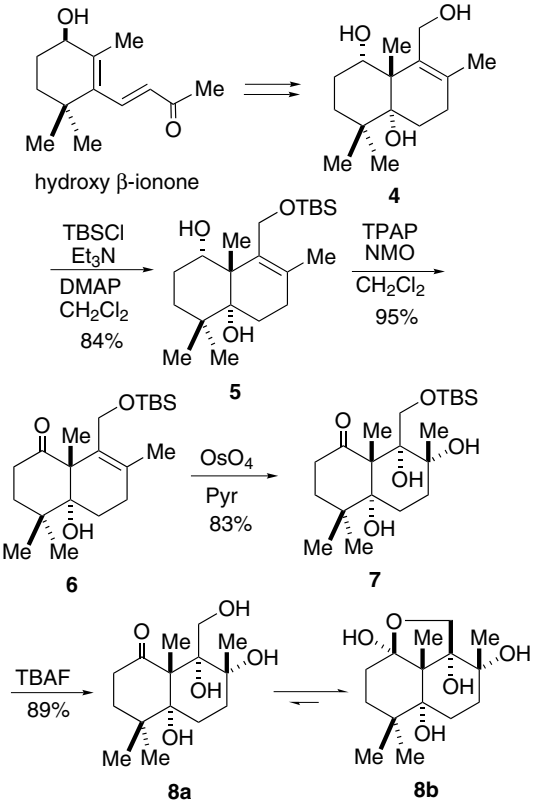
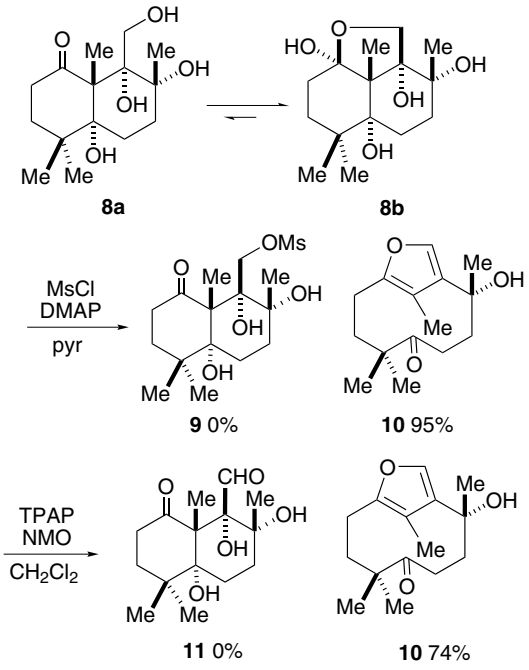


Scheme 1.



Scheme 2.

Unfortunately, the oxidation of **5** using PCC, Swern and Dess–Martin procedures was unsuccessful. However, the diol **5** was converted into the hydroxy ketone **6** in 95% yield using Ley's oxidation with TPAP/NMO. Treatment of **6** with osmium tetroxide in pyridine afforded the desired trihydroxy ketone **7** in 83% yield as a single diastereomer. The TBS protecting group of the triol **7** was easily removed by tetrabutylammonium fluoride to give the tetraol **8**. Spectroscopic analysis of

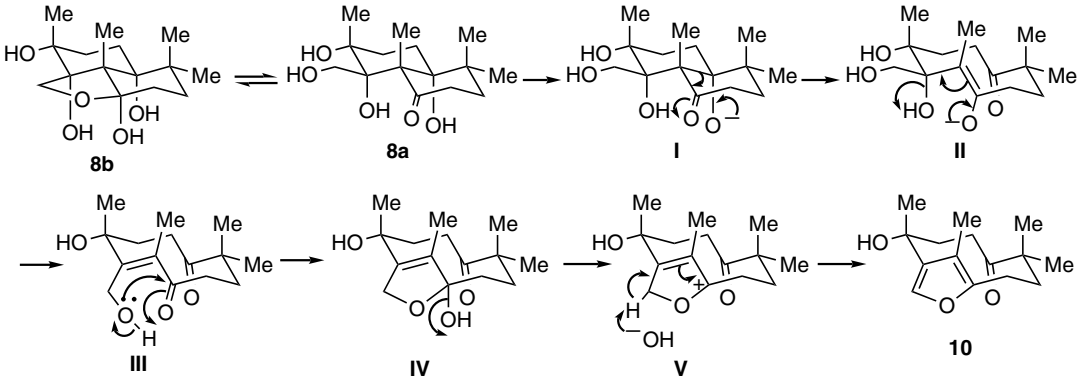


Scheme 3.

8 shows that it seems to exist as the hemiketal form **8b** instead of the corresponding hydroxy ketone **8a**.

Next, we tried to convert the primary alcohol of the hydroxy ketone form **8b** of the tetraol **8** to a more reactive functional group such as the mesylate or the aldehyde (Scheme 3). The tetraol **8** was first treated with methanesulfonyl chloride in the presence of pyridine and a catalytic amount of DMAP for 2.5 h at room temperature. Instead of the desired mesylate **9**, we obtained the unexpected bicyclic furan **10** as a single product in 95% yield. Oxidation of the tetraol **8** using TPAP and NMO was also attempted, but the reaction again provided the same product **10** in 74% yield with none of the desired keto aldehyde **11** being obtained. Remarkably, the tetraol **8** was rapidly converted to the furan **10** when deuteriochloroform was used as the NMR solvent. This is presumably due to a small amount of acid in the deuteriochloroform, which could have induced a very similar rearrangement on the acidic side to give compound **10** exclusively. The structure of **10** was confirmed on the basis of ^{1}H, ^{13}C NMR, IR and mass spectroscopic data.

The proposed mechanism for the transformation of the tetraol **8ab** to the unexpected bicyclic furan **10** is shown in Scheme 4. In the presence of base, the tetraol would furnish all the possible alkoxides, and alkoxide **I** could rapidly open the bicyclic ring by cleavage of the central C–C bond to afford the keto enolate **II** via a retro aldol reaction. It is conceivable that this retro aldol reaction is promoted by the steric hindrance afforded by the three axial methyl groups. This type of retro aldol reaction of a similar decalin system has been previously reported.[7] β-Elimination of the resulting β-hydroxy ketone enolate **II** would generate the β-hydroxymethyl enone **III**. Cyclization of the hydroxy group onto the nearby ketone would give the hydroxy dihydrofuran



Scheme 4.

IV, which would then lose water via **V** to form the highly strained bicyclic furan **10** with the final driving force being the formation of the aromatic ring. The production of **10** under acidic condition could be explained by the same mechanism but via protonated forms and enols rather than enolates. A small amount of acid in chloroform might also trigger the retro aldol reaction to provide the keto enol, which after subsequent β-elimination, cyclization and dehydration, would afford the furan **10**.[8]

In summary, we have demonstrated an unusual rearrangement of the tetraol **8** to the unexpected bicyclic furan **10** under mildly basic or acidic conditions during the preparation of AB ring intermediates for the synthesis of arisugacin A. Further work on the synthesis of arisugacin A is underway and will be reported in due course.

Acknowledgement

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8. Experimental procedure for the preparation of the furan: 2-hydroxy-2,6,6,12-tetramethyl-10-oxabicyclo[7.2.1]dodec-1(11)-en-5-one (**10**). 4-Dimethylaminopyridine (0.5 mg, 0.004 mmol) and methanesulfonyl chloride (5 μL, 0.06 mmol) were added to the solution of tetraol **8** (12 mg, 0.04 mmol) in pyridine (0.2 mL) at 0 °C. After the solution was stirred for 2.5 h, it was diluted with dichloromethane (0.5 mL) and poured into aqueous ammonium chloride (1 mL). The mixture was extracted with dichloromethane (5 mL×3) and ethyl acetate (5 mL). The combined organic layers were dried over magnesium sulfate and concentrated. Flash column chromatography (2:1, hexane/ethyl acetate) afforded the bicyclic furan **10** (10 mg, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.08 (s, 1H), 2.95 (m, 1H), 2.64 (ddd, J = 13.0, 13.0, 4.2, 1H), 2.53 (ddd, J = 13.2, 13.2, 4.1 Hz, 1H), 2.29 (s, 3H), 2.18 (t, J = 12.2 Hz, 1H), 1.62–1.57 (m, 3H), 1.59 (s, 3H), 1.43 (ddd, J = 13.1, 4.1, 1.8 Hz, 1H), 1.26 (s, 3H), 0.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 205.70, 153.81, 138.90, 127.48, 118.66, 73.47, 45.77, 45.44, 41.86, 31.99, 31.06, 28.91, 22.28, 21.59, 15.20. IR (neat): 3462, 2960, 2926, 1678, 1612, 1542, 1458, 1411, 1363, 1327, 1240, 1106, 1040, 893, 731 cm^{-1}. HRMS (EI) *m/z* found for M^+ 250.1560, calcd for $C_{15}H_{22}O_3$ 250.1569.