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

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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.

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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 Omura, 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 IC50 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.

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.
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 2.

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 methane-sulfonyl chloride in the presence of pyridine and a catalytic amount of DMAP for 2.5h 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 1H, 13C 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.
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.

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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References and notes

6. For a communication on the synthesis of the triol 4, see: Jung, M. E.; Min, S.-J., Abstract No. ORGN-190, 226th ACS National Meeting, New York, NY, Fall 2003.
8. Experimental procedure for the preparation of the furan: 2-hydroxy-6,6,12-tetramethyl-10-oxabicyclo[7.2.1]dodec-5-ene 1. 4-Dimethylaminopyridine (0.5 mg, 0.004 mmol) and methanesulfonyl chloride (5.0 L, 0.06 mmol) were added to the solution of tetraol 8 (12 mg, 0.064 mmol) in pyridine (0.1 mmol). The mixture was stirred for 2.5 h, it was diluted with dichloromethane (7.0 mL) and ethyl acetate (5 mL). The combined organic layers were dried over magnesium sulfate and concentrated.

Scheme 4.