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A Novel Synthesis of Piperidin-3-ones *via* an Intramolecular Amadori-type Reaction

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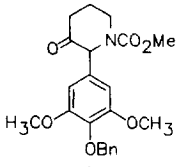
Abstract: 1-Methoxycarbonyl-2-(3,5-dimethoxy-4-benzyloxyphenyl)-piperidin-3-one **1** and *rac-5R, 8aS*-5-(3,5-dimethoxy-4-t-butyldimethylsiloxyphenyl)-oxazolo[3,4:1,6]-piperidin-3,6-dione **2** were synthesized *via* an intramolecular adaptation of the biochemically well-characterized Amadori reaction.

The emergence of DNA topoisomerase II (topo II) as a viable target for cancer chemotherapy[1,2] has prompted us to develop a research program aimed at the design and synthesis of novel topo II inhibitors.[3-5] As part of this project, the piperidin-3-one derivatives **1** and **2**, were desired as synthetic intermediates for a wide variety of potential topo II-directed agents. The limited availability of efficient syntheses of piperidin-3-ones suited to our needs precipitated the development of an alternative route to the construction of these intermediates.[6,7]



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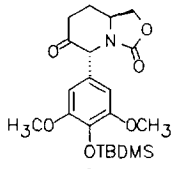

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We envisioned the key step in our syntheses **1** and **2**, to be an intramolecular Amadori-type reaction. The Amadori reaction is a biochemically well-characterized condensation/rearrangement between a reducing sugar and the amine of a protein or amino acid,[8] and commonly occurs during the heat processing and storage of food.[9,10] The initially formed glucosylamine spontaneously undergoes rearrangement to form a 1-amino-1-deoxy-2-ketose. The use of the Amadori reaction toward the synthesis of unnatural products has been limited,[11,12] yet we felt that the application of the basic transformation (eq. 1) would constitute a efficient pathway to the synthesis of the desired piperidin-3-one derivatives **1** and **2**.

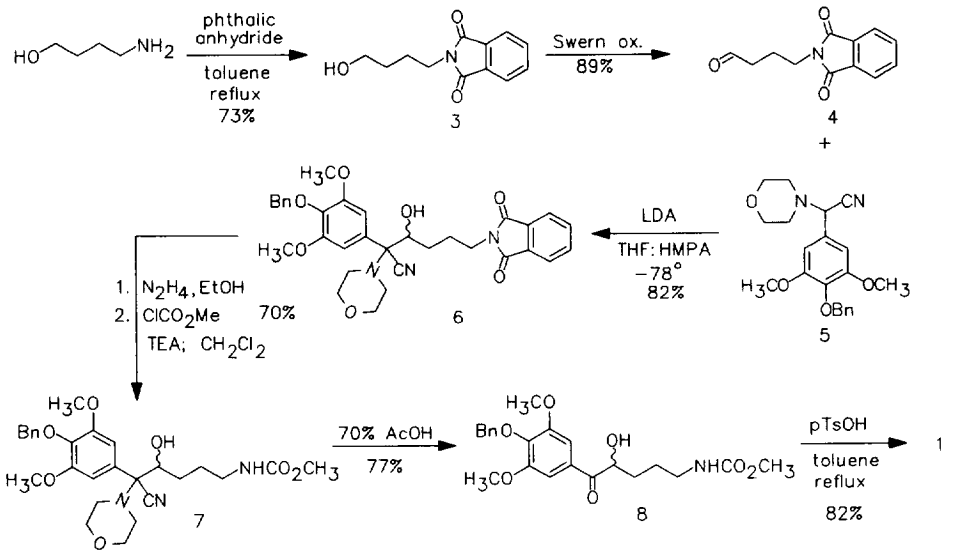
Amine + α-Hydroxycarbonyl → α-Hydroxyimine → β-Keto amine (eq. 1)

Our approach to the synthetically less demanding intermediate, **1**, is shown in scheme 1, beginning with phthalimide protection of 1-amino-3-propanol. Swern oxidation of the resulting alcohol, **3**, gave aldehyde

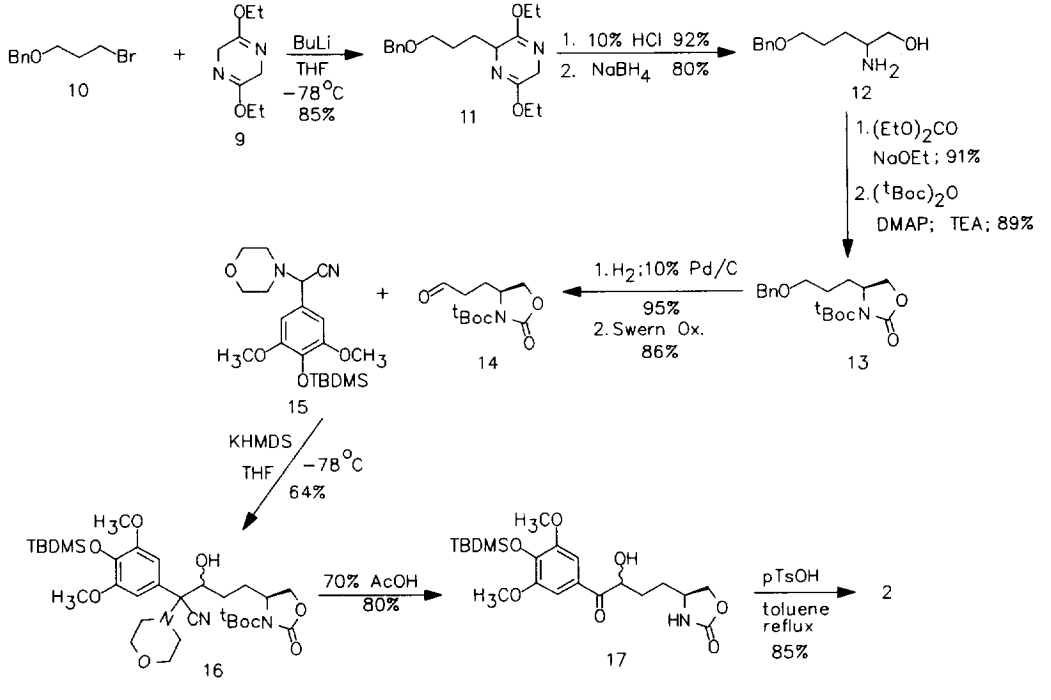
4 in 89% yield. Addition of the morpholinoacetonitrile acyl anion equivalent[13] of O-benzylsyringealdehyde **5** gave rise to **6**, the masked α-hydroxycarbonyl portion of the compound necessary for the intramolecular Amadori-type reaction. Removal of the phthalimide protecting group followed by carbamation of the free amine gave rise to the carbamate **7** in an overall 70% yield for the two steps. Treatment of **7** with 70% acetic acid at reflux released the α-hydroxyketone **8**, the precursor for the intramolecular Amadori-type reaction. The cyclization to the N-methoxycarbonylpiperidin-3-one **1** was catalyzed in 82% yield by p-toluenesulfonic acid upon heating the α-hydroxyketone **8** in toluene at reflux. The success of this reaction in the synthesis of a simple piperidin-3-one prompted us to attempt the synthesis of the more structurally complex compound **2**. This undertaking would effectively probe the usefulness of this methodology for the construction of strained fused ring systems.

Our approach to intermediate **2** is shown in scheme 2. Similarly to the synthesis of **1**, the synthetic route to compound **2** was seen to proceed through an α-hydroxyketone constructed by the addition of an appropriately functionalized acyl anion equivalent to the aldehyde containing the necessary amino functionality. In this case, the amino functionality is incorporated through the derivatization of the appropriately functionalized unnatural amino acid; the synthesis of which was accomplished by the method developed by Schollkŏpf.[14] The addition of the glycine equivalent **9** to the readily available 1-bromo-3-benzyloxypropane[15] **10** gave the masked unnatural amino acid **11** in 85% yield. Hydrolysis of the dihydropyrazine **11** to the amino ester with 10% HCl followed by reduction with sodium borohydride[16] gave rise to the amino alcohol **12**. Following oxazolidination and t-butoxycarbonyl protection, the resulting urethane **13** was transformed into the aldehyde **14** by sequential hydrogenation and Swern oxidation. The incorporation of the α-hydroxyketone functionality was accomplished in a similar fashion as described for the synthesis of **1**. Deprotonation of the morpholinoacetonitrile **15** with potassium hexamethyldisilazide followed by addition to the aldehyde **14** gave rise to doubly protected amino α-hydroxy ketone in 64% yield. Concurrent removal of the t-butoxycarbonyl and morpholinoacetonitrile protecting groups was accomplished in 80% yield by treatment with 70% acetic acid at reflux. As was the case in the simple N-methoxycarbonylpiperidin-3-one **1**, the cyclization of **17** occurred smoothly upon treatment with catalytic p-toluenesulfonic acid in toluene at reflux in 85% yield. The desired piperidin-3-one derivative **2** was formed as a single diastereomer with the aromatic ring in a *pseudo*-axial orientation as proven by a positive NOE between the 2'-hydrogens on the phenol ring and the 8a-hydrogen. This single product arises *via* the acid-catalyzed equilibration of the initially formed mixture of 5,8a-*cis* and 5,8a-*trans* products leading to the thermodynamically-favored product.[17] In this instance, the *pseudo*-axially substituted compound **2** predominates due to the minimization of the unfavorable interaction between the 2',6'-hydrogens on the aromatic ring and the urethane and C6-carbonyl oxygens present in the *pseudo*-equatorial orientation of the compound.

We have demonstrated the successful adaptation of the biochemically well-characterized Amadori reaction to the synthetic problem of constructing piperidin-3-ones and their derivatives mildly and in high



Scheme 1. Approach to the synthesis of 1-methoxypiperidin-3-one 1.



Scheme 2. Approach to the synthesis of piperidin-3-one derivative 2.

yield. A high level of substitution can be accommodated in this reaction allowing for the efficient synthesis of highly functionalized piperidin-3-ones. Additionally, as illustrated by the synthesis of **2**, there exists the potential for the stereospecific synthesis of simple piperidin-3-ones as well as more complex ring systems. This reaction should also prove effective for the construction of synthetic intermediates to various other heterocyclic compounds.

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REFERENCE AND NOTES:

1. Liu, L. F.; *Ann. Rev. Biochem.* **1989**, *58*, 351.
2. Saulnier,M. G.; LeBoulluec, K. L.; McGee, D. P. C.; Long, B. H.; *Biorg. Med. Chem. Lett.* **1993**, *3*, 1619.
3. Macdonald, T. L.; Lehnert, E. K.; Loper, J. T.; Chow, K. -C.; Ross, W. E.; In: DNA *Topoisomerases in Cancer Chemotherapy*, Potmesil, M.; and Ross, W. E. eds.. Oxford University Press, London, **1989**, 199.
4. Leteurtre, F.; Madalengoitia, J. S.; Orr, A.; Guzi, T. J.; Lehnert, E. K.; Macdonald, T. L.; Pommier, Y.; *Cancer Res.* **1992**, *52*, 4478.
5. Madalengoitia, J. S.; Macdonald, T. L.; *Tetrahedron Lett.* **1993**, *34*, 6237.
6. a) Lyle, R. E.; Adel, R. E.; Lyle, G. G.; *J. Org. Chem.* **1959**, *24*, 342. b) Sundberg, R. J.; Ligon, W. V.; Lin, L.-S.; *J. Org. Chem.* **1971**, *36*, 2471.
7. a) Kametani, T.; Seto, H.; Nemoto, H.; Fukumoto, K.; *J. Org. Chem.* **1977**, *42*, 3605. b) Katvalyan, H. T.; Shashkov, A. S.; Mistryukov, E. A.; *J. Het. Chem.* **1985**, *22*, 53. c) West, F. G.; Naidu, B. N.; *J. Am. Chem. Soc.* **1993**, *115*, 1177.
8. Hodge, J. E.; *Adv. Carb. Chem.* **1955**, *10*, 169.
9. Reynolds, J. E.; Anet, E. F. L. J.; *Aust. J. Chem.* **1957**, *10*, 182.
10. Bucala, R.; Model, P.; Cerami, A.; *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 105.
11. Albert, A.; Marbach, P.; Bauer, W.; Briner, U.; Fricker, G.; Bruns, C.; Pless, J.; *Life Sciences* **1993**, *53*, 517.
12. Sosnovsky, G.; Gnewuch, C. T.; Ryoo, E. S.; *J. Pharm. Sci.* **1993**, *82*, 649.
13. Albright, J. D.; McEvoy, F. J.; Moran, D. B.; *J. Het. Chem.* **1978**, *15*, 881.
14. Schollköpf, U.; Hartwig, W.; Groth, U.; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 863.
15. Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S.; *J. Am. Chem. Soc.* **1982**, *104*, 1054.
16. Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S.; *Chem. Pharm. Bull.* **1965**, *13*, 995.
17. Tomioka, K.; Kubota, Y.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 2953.

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