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The Mukaiyama-Michael Reaction of *N*-Acyl-2,3-dihydro-4-pyridones: Regio- and Stereoselective Synthesis of *cis*-2,6-Disubstituted 1,2,5,6-Tetrahydropyridines

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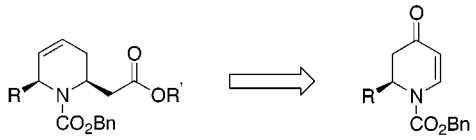
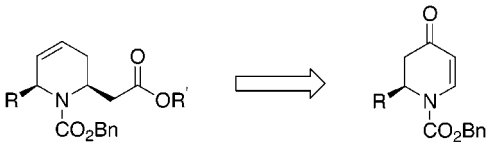
ABSTRACT



A convenient regio- and stereoselective preparation of 1,2,5,6-tetrahydropyridines of the type 1 has been developed, starting from readily available *N*-acyl-2,3-dihydro-4-pyridones 2.

The 1,2,5,6-tetrahydropyridine ring system is found in a variety of alkaloids and pharmacologically active agents.[1] Simple tetrahydropyridines are often readily prepared from a pyridinium salt or a 4-piperidone.[1a] The synthesis of 2,6-disubstituted derivatives with control of regio- and stereochemistry is a more difficult task. Although some routes are available,[2] most are not highly stereoselective or applicable to enantioselective synthesis of either antipode.

In support of a total synthesis project in our laboratories, we have investigated a novel route to enantiopure tetrahydropyridines **1** by starting from chiral dihydropyridones **2**, which are readily available as both enantiomers via asymmetric synthesis.[3]



The study began with racemic **3**, prepared by addition of isopropylmagnesium chloride to 1-((benzyloxy)carbonyl)-4-methoxypyridinium chloride[4] (Scheme 1). The Mukaiyama-Michael reaction[5] was chosen to introduce a methyl acetate unit at C-6 of **3**. Addition of BF_3 etherate to a mixture of **3**

(1) (a) Fowler, F. W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: London, 1984; Vol. 2, Part 2A, pp 365−394. (b) Coutts, R. T.; Scott, J. R. *Can. J. Pharm. Sci.* **1971**, *6*, 78. (c) Ferles, M.; Pliml, J. *Adv. Heterocycl. Chem.* **1970**, *12*, 43−101.

(2) For some recent work and leading references, see: (a) Angle, S. R.; Breitenbucher, J. G. In *Studies in Natural Products Chemistry: Stereoselective Synthesis*; Atta-ur Rahman, Ed.; Elsevier: New York, 1995; Vol. 16, Part J, pp 453−502. (b) Wang, C. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 583−621. (c) Waldmann, H. *Synthesis* **1994**, 535. (d) Schürer, S. C.; Blechert, S. *Tetrahedron Lett.* **1999**, *40*, 1877. (e) Aahman, J.; Somfai, P. *Tetrahedron Lett.* **1996**, *37*, 2495. (f) Castro, P.; Overman, L. E.; Zhang, X.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5243.

(3) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1994**, *35*, 7343. (c) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807. (d) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651.

(4) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.

(5) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163.

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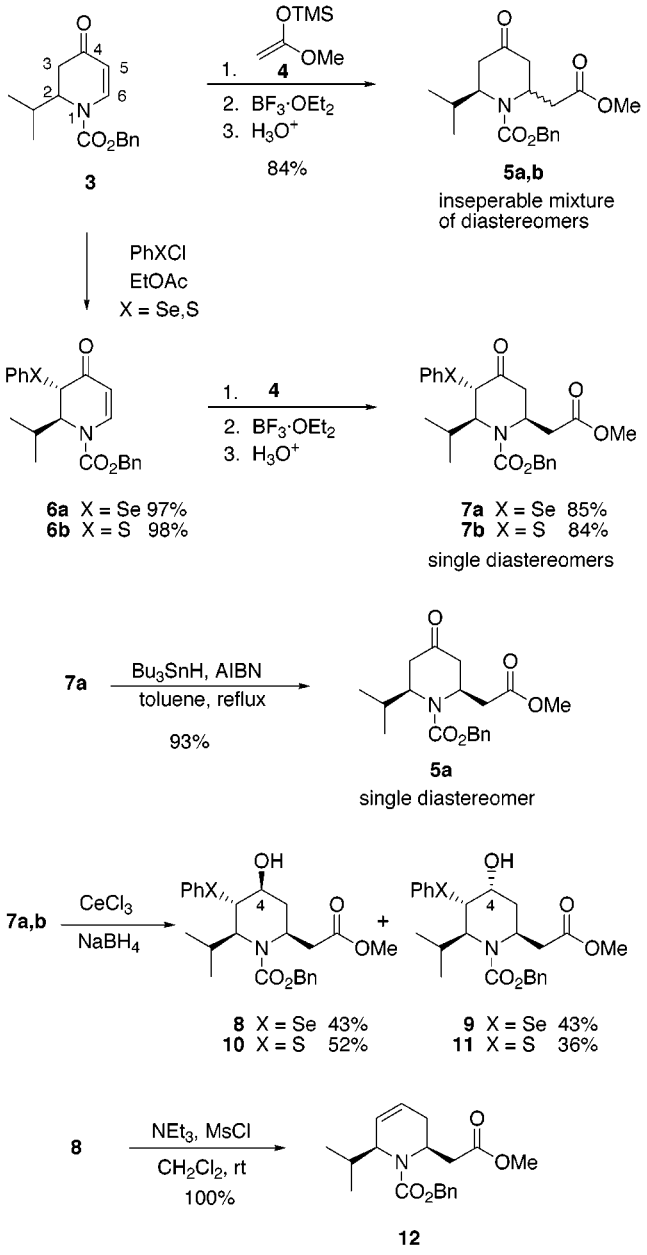
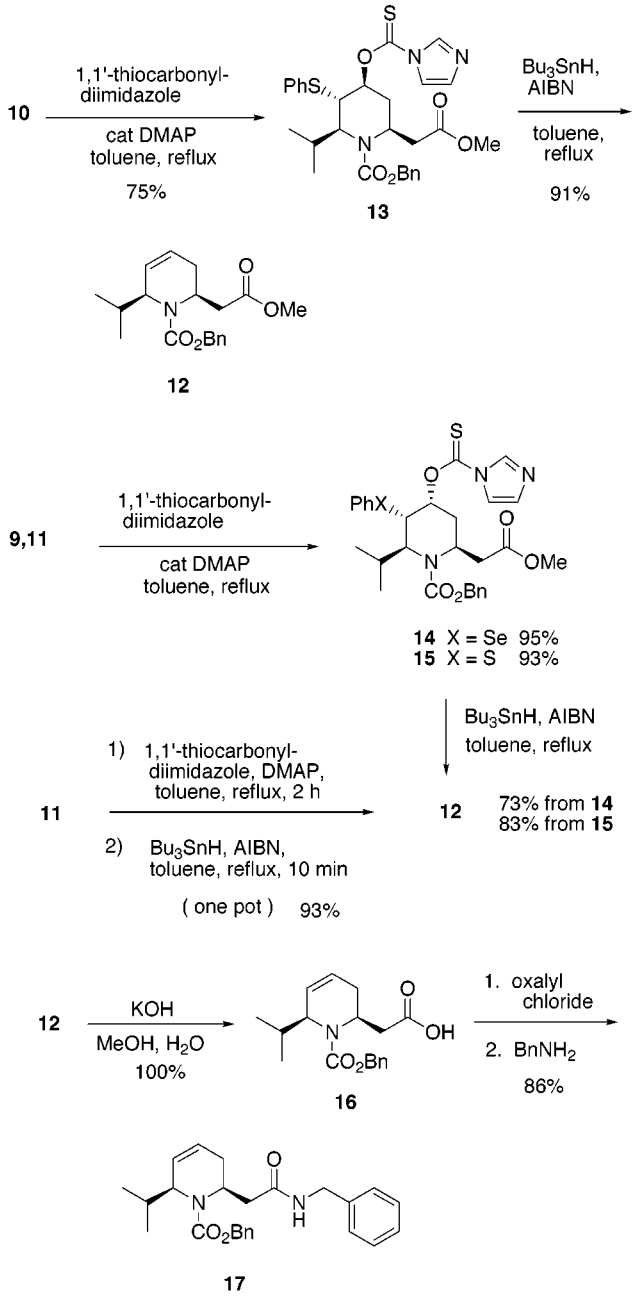
Scheme 1



Scheme 2



and *O*-silyl ketene acetal **4** (CH_2Cl_2, −78 °C, 30 min) followed by acidic workup provided an inseparable mixture (∼2/1) of diastereomers **5**.

Piperidone **5** was not an attractive tetrahydropyridine precursor, since its formation was not very stereoselective, and regioselective introduction of the desired C-3,4 olefin would likely be problematic. To circumvent these problems, a removable substituent was introduced at the C-3 position of **3**. Dihydropyridone **3** was treated with phenylselenenyl chloride in ethyl acetate to produce selenide **6a** in 97% yield. In a similar manner, phenyl sulfide **6b** was obtained (98%) from **3** and phenylsulfenyl chloride. The observed trans stereochemistry of products **6** (J_{H2-3} < 1.2 Hz) was anticipated on the basis of previous results from our laboratories.[6] The Mukaiyama−Michael reactions of **6a**,**b** afforded piperidones **7a**,**b** as the sole isolated products. The indicated stereochemistry was confirmed by free-radical reduction of **7a** to provide cis piperidone **5a** in high yield. The presence of the large C-3 axial substituent in dihydropyridone **6** rendered the Mukaiyama−Michael reaction completely facial selective.

With a stereospecific method for incorporation of the desired 2,6-substituents in hand, effort was directed toward regioselective alkene formation. Luche reduction of **7a** afforded an 86% yield of diastereomers **8** and **9**. The corresponding reduction of sulfide **7b** provided **10** and **11**

(6) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182 and references therein.

in similar yields. The C-4 stereochemistry of alcohols **8**−**11** was tentatively assigned by ^{1}H NMR and confirmed by the following results. Alcohol **8** on treatment with MsCl/TEA gave a quantitative yield of tetrahydropyridine **12**. The cis isomer **9** gave only the C-4 mesylate under the same conditions. It has been reported that trans stereochemistry is required for this type of olefin formation.[7]

To eliminate any stereochemical restriction during the olefin formation step, a free-radical process was investigated (Scheme 2). *trans*-*β*-Hydroxy sulfide **10** was treated with DMAP (5%) and 3 equiv of 1,1-thiocarbonyldiimidazole in refluxing toluene to yield the labile thiocarbamate **13**. In an analogous manner, *cis*-*β*-hydroxy selenide **9** and *cis*-*β*-hydroxy sulfide **11** were converted to thiocarbamates **14** and **15** in 95% and 93% yields, respectively. These three thiocarbamates, **13**−**15**, were individually converted to alkene **12** with Bu_3SnH/AIBN in refluxing toluene in 91%, 73%, and 83% yields, respectively.[8] The two-step reductive elimination can be carried out via a one-pot procedure. After formation of the thiocarbamate is complete by TLC, Bu_3SnH (1.1 equiv) and AIBN (cat.) are added to the reaction mixture, and reflux is continued for 10 min. Using this procedure, alkene **12** was prepared from *cis*-hydroxy sulfide **11** in 93% yield. An unpurified mixture of alcohols **8** and **9** was subjected to the one-pot procedure to give a 69% yield of **12**.

To explore the synthetic potential of tetrahydropyridines of the type **12**, hydrolysis of **12** was carried out to afford acid **16**. Conversion to the corresponding acid chloride and subsequent reaction with benzylamine provided the amide **17** in 86% overall yield from **12**.[9]

In summary, a convenient regio- and stereoselective preparation of tetrahydropyridines of the type **12** has been developed by starting from readily available *N*-acyl-2,3-dihydro-4-pyridones. Although this study used racemic starting material, the methodology can lead to enantiopure products by starting with readily available nonracemic dihydropyridones.[5] Application of this chemistry to the synthesis of natural products is underway in our laboratories and will be reported in due course.

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. NMR spectra and HRMS spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation.

Supporting Information Available: Characterization data for compounds **5a** and **6**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Reich, H. J.; Chow, F. *J. Chem. Soc., Chem. Commun.* **1975**, 790. (b) Rémion, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 1385.

(8) A similar radical 1,2-elimination reaction has been used with carbocyclic compounds; see: Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1977**, *18*, 4223.

(9) The structure assigned to each new compound is in accordance with its IR and ^{1}H NMR spectra and elemental analysis or high-resolution mass spectra.