

## Synthesis and Utilisation of Chiral 3-Hydroxy Perhydropyrrolo [2,1-c] [1,4] oxazin-4-one as a Novel Precursor for the Enantioselective synthesis of $\alpha$ -Hydroxy Carboxylic Acids

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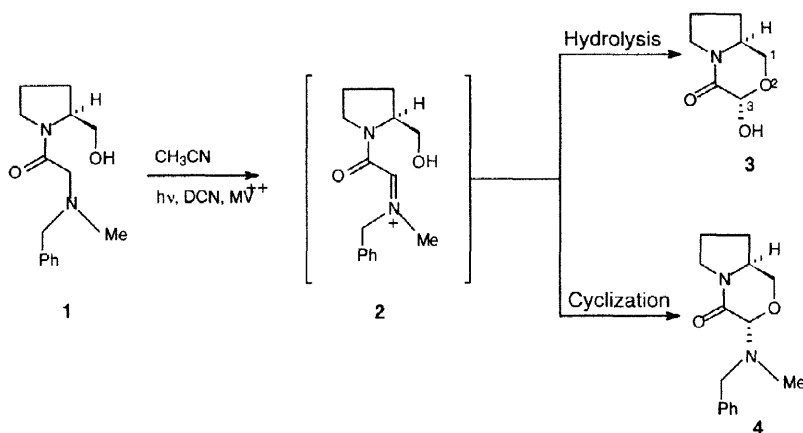
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**Abstract:** A novel strategy for the enantioselective synthesis of several  $\alpha$ -hydroxy carboxylic acids by the nucleophilic alkylation of chiral 3-hydroxy-(3*S*, 8*aS*)-perhydropyrrolo [2,1-*C*] [1,4] oxazin-4-one is reported. © 1998 Elsevier Science Ltd. All rights reserved.

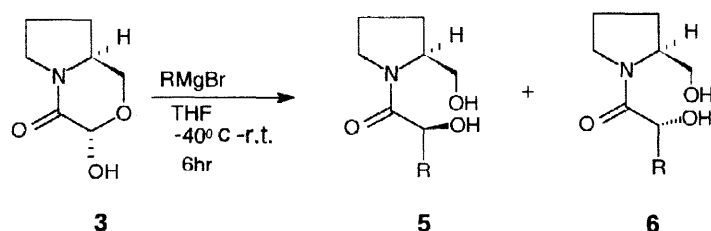
Recently, while designing **4** as a precursor<sup>1</sup> for the synthesis of optically pure  $\alpha$ -amino acids and their *N*-methyl derivatives by the Photoinduced Electron Transfer (PET) reaction<sup>2</sup> of **1**, we encountered the formation of **3** in small quantities, whenever the CH<sub>3</sub>CN used was moist. The formation of **3** was rationalized *via* hydrolysis of the iminium cation intermediate **2**, (**Scheme-I**) followed by the intramolecular acetalization reaction. PET reaction of **1** in aqueous CH<sub>3</sub>CN was, thus, obvious to provide **3** predominantly. The hemiacetal functionality of **3** led us to exploit this molecule for the synthesis of enantiomerically pure  $\alpha$ -hydroxy acids. We report our success in this communication.

### Scheme-I



The usual PET reaction<sup>1</sup> of **1** in aqueous CH<sub>3</sub>CN gave **3** in 90% yield (dr = 17:3). To transform **3** into a molecule from which the corresponding  $\alpha$ -hydroxy carboxylic acids could be obtained easily, nucleophilic alkylation was considered. Addition of various Grignard reagents<sup>3</sup> (4 equiv) to a stirred solution of **3** (1 equiv) in dry THF at -40°C followed by warming to rt over 6 h, gave easily separable mixtures of **5** and **6** together in 50 - 60% yield (**Scheme-II**). The absolute stereochemistry of the new chiral centre of **5** was established by comparing the rotation ( $\alpha_D$ ) values of the corresponding  $\alpha$ -hydroxy carboxylic acids, obtained after hydrolysis, with the known values of the commercially available authentic samples. As an alternative strategy, alkylation of **3** by adding allyltrimethylsilane in the presence of TiCl<sub>4</sub> in dry DCM was also carried out<sup>4</sup>. However, it gave a mixture of **7a** and **7b** in 4:1 ratio (**Scheme-III**), instead of the required ring opened structures of type **8** and **9**. This led us to protect the -OH group of **3** to -OMe as well as -OTBDMS, similar to the known strategies

## Scheme-II

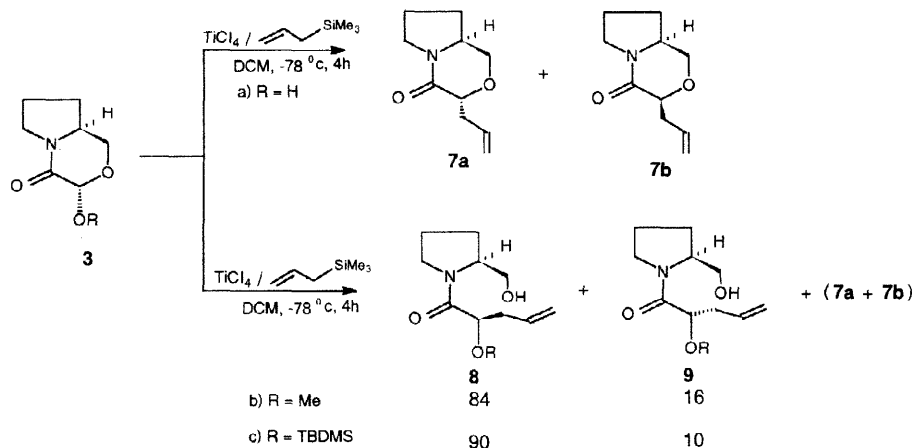


Entry	R	5/6 <sup>a</sup>	Yield <sup>b</sup> (%)	Acids <sup>c</sup>	Absolute <sup>d</sup> Configuration	obs[ $\alpha$ ] <sub>D</sub> <sup>25</sup>
a	Ph	80:20	50		(R)	-150.47 (c=1.6 H <sub>2</sub> O)
b	Me	85:15	60		(R)	+7.18 <sup>e</sup>
c	Allyl	82:18	60		(R)	+3.08 (c=2.26 H <sub>2</sub> O)

(a) Diastereomeric ratio measured from <sup>1</sup>H NMR spectra. (b) Isolated yields not optimised (c) obtained after the hydrolysis of 5 by heating with 1N H<sub>2</sub>SO<sub>4</sub> at 60<sup>o</sup>c for 0.5 h. followed by catalytic hydrogenation (d) Absolute configuration with respect to authentic sample. (e) Rotation value obtained after converting the acid to the corresponding methyl ester.

employed during the allylation of lactols<sup>5,6</sup>. Allylation of 3b-c, gave corresponding mixtures of 8 and 9 along with the minor amount of 7 (<8%).

## Scheme-III



The S-configuration of the new chiral center in 8b-c was also established by comparing the [ $\alpha$ ]<sub>D</sub> value of 2-hydroxy pentanoic acid, obtained after hydrolysis of 8b-c followed by the catalytic reduction, with the authentic material.

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