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Oxidation of Functional Olefines : Synthesis of Protected Amino Acids Bearing a Terminal α-Hydroxyketo Group.

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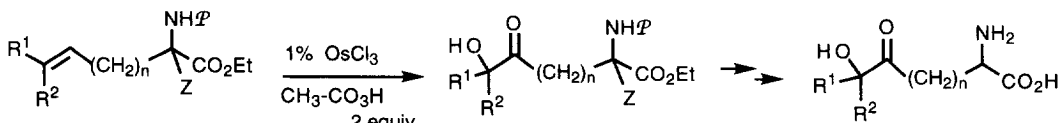
Abstract : The osmium trichloride-catalyzed oxidation with peracetic acid of olefinic compounds bearing a protected α-amino acid group leads to α-ketol amino acid precursors related to the 5-Hydroxy-4-Oxo-Norvaline antibiotic.

Among the numerous hydroxylated α-amino acids known for their biological interest[1] , (-)-(S)-5-Hydroxy-4-Oxo-Norvaline **I** (HON) has been the subject of some studies since its isolation[2] and the disclosure of its antitubercular[3] and antifungal[4] activities. Several synthesis of racemic HON have been described[5], while synthesis of (-)-HON appeared only in the last few years[6].

We report herein on a new access to HON and several homologous amino acid precursors displaying an α-ketol function via the oxidation of olefinic amino acid precursors according to the following scheme.



1-5 **a** $\mathcal{P}$ = Ac Z = H
b $\mathcal{P}$ = Ac Z = CO_2Et
(n = 1-3) **c** $\mathcal{P}$ = CO-OtBu Z = CO_2Et

6-10

I (n = 1, R^1= R^2= H)
II (n = 1, R^1= R^2= CH_3)

Indeed, several oxidation procedures of double-bonds to α-ketol were recently described by Murahashi's group through $RuCl_3$[7] and $OsCl_3$[8] catalyzed oxidations from which the later seemed more adapted to our project. Preliminary experiments were carried out with several allylic type compounds in order to delineate experimental conditions leading to chemical compatibility of the amino acid functionalities with the oxidative conditions[9] : allyl glycine and its ethyl ester, treated at room temperature with 2 equivalents of peracetic acid (30% solution in acetic acid) in a $CH_2Cl_2/CH_3CN/H_2O$: 1/1/1 solution in the presence of 1% molar $OsCl_3$ gave only mixture of oxidized products, while acetamidoester **2a** led to the expected α-ketol **7a**, thus demonstrating the necessity of using a protected amino acid function. Furthermore, we observed that this oxidation was optimized with a dropwise addition (about 5 mmol per hour) of the peracid solution, which led to 38% of **7a** (Table, run 2).

We then compared the oxidations of several amino acid precursors, namely acetamidoesters (**2-5**)**a**, acetamidomalonates (**2-5**)**b** and N-Boc-aminomalonates (**2-5**)**c**[10]. Table summarizes the oxidation of these precursors according to the previously defined conditions (run 2) which seemed the most advantageous[11]. Higher yields were obtained from N-protected aminomalonates (**2-5**)**b-c**, which suggests that acetamidoesters (**2-5**)**a** lead to over oxidation products because of the presence of the tertiary proton α to nitrogen atom (run 2, 7, 10). Oxidation of N-Boc-aminomalonates (**2-5**)**c** seemed also more efficient (compare runs 3, 5, 8, 11 with 4, 6, 9, 12 respectively). The reactions were totally regioselective whatever the olefinic precursor (**1-5**)**a-c** was, which is in good accordance with Murahashi's results[8].

Run	Olefinic precursor **1-5**		α-ketol **6-10**	yield *
1	H_2C=CH-CH_2-C(CO_2Et)$_2$-NHBoc	**1c**	**6c**	51%
2	(CH_3)$_2$C=CH-CH_2-CH(CO_2Et)-NHAc	**2a**	**7a**	38%
3	(CH_3)$_2$C=CH-CH_2-C(CO_2Et)$_2$-NHAc	**2b**	**7b**	52%
4	(CH_3)$_2$C=CH-CH_2-C(CO_2Et)$_2$-NHBoc	**2c**	**7c**	60%
5	(CH_3)HC=CH-CH_2-C(CO_2Et)$_2$-NHAc	**3b**	**8b**	32%
6	(CH_3)HC=CH-CH_2-C(CO_2Et)$_2$-NHBoc	**3c**	**8c**	68%
7	H_2C=CH-(CH_2)$_2$-CH(CO_2Et)-NHAc	**4a**	**9a**	6%
8	H_2C=CH-(CH_2)$_2$-C(CO_2Et)$_2$-NHAc	**4b**	**9b**	23%
9	H_2C=CH-(CH_2)$_2$-C(CO_2Et)$_2$-NHBoc	**4c**	**9c**	30%
10	H_2C=CH-(CH_2)$_3$-CH(CO_2Et)-NHAc	**5a**	**10a**	23%
11	H_2C=CH-(CH_2)$_3$-C(CO_2Et)$_2$-NHAc	**5b**	**10b**	30%
12	H_2C=CH-(CH_2)$_3$-C(CO_2Et)$_2$-NHBoc	**5c**	**10c**	30%

Table. * Isolated yields after flash chromatography.

In summary, this osmium trichloride-catalyzed oxidative transformation of olefinic protected amino acids to α-ketols allows the synthesis of derivatives and homologous compounds of 5-Hydroxy-4-Oxo-Norvaline. For example diethyl N-Boc-aminomalonates **1c** and **2c** were easily hydrolyzed to racemic HON **I** (85%) and dimethyl-HON **II** (73%) respectively.

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10. These protected aminomalonates (**1-5**)**b-c** were obtained through the alkylation of diethyl acetamidomalonate and N-Boc-aminomalonate; decarboxylation of acetamidomalonates (**2-5**)**b** led classically to acetamidoesters (**2-5**)**a**.
11. **Typical procedure** is as follows (run 4): Ethyl 2-(N-Boc-amino)-2-carboethoxy-5-methyl-5-hexenoate **7c**. Osmium trichloride (13 mg, 0.044 mmol) and N-Boc-aminomalonate **2c** (1.5 g, 4.4 mmol) were stirred at room temperature for 15 min in a mixture of acetonitrile (4 mL), CH_2Cl_2 (4 mL) and water (4 mL). A 32% solution of peracetic acid in acetic acid (1.8 mL, 8.8 mmol) was then added with a microsyringe within 20 portions (92 µL each) over a period of 105 min. After 4 h stirring at 20°C, the reaction mixture was poured in brine and extracted with CH_2Cl_2 (5 x 5 mL) ; the extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to a brown oil which was then purified via flash chromatography (5:5 petroleum ether : ethyl acetate ; Rf = 0.57) giving 990 mg (60% yield) of pure α-ketol **7c** as a clear oil. ^1H NMR ($CDCl_3$, 200 MHz) δ ppm : 1.25 (6H, t, J=7.1 Hz) ; 1.36 (6H, s) ; 1.40 (9H, s) ; 3.56 (OH, broad s) ; 3.78 (2H, s); 4.07-4.35 (4H, m) ; 6.15 (NH, broad s).

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