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A NEW SYNTHESIS OF α-AMINO ACIDS (E)-β,γ-ENOL ETHERS

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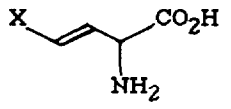
Summary: Various N-protected amino acids bearing an enol ether side chain were synthesized by a new method allowing a great versatility in the introduction of both the N-protective groups and the enol ether moieties. This method deals with a Wittig-Horner condensation to afford the α,β-dehydro homoserine ethers derivatives, followed by a regio and stereo selective isomerization into β,γ-enol ethers.

Dehydro-amino acids as well as dehydro peptides have received much attention in recent literature (1). As potent enzyme inhibitors or naturally occurring antimetabolites (2), they are targets of choice in the rational design of new drugs.

Among them, β,γ-unsaturated amino acids 1 or 2 have been shown to irreversibly inhibit PLP dependent enzymes (3) and a "suicide substrate" mechanism of action has been postulated (3ab, 4).



1 X= H, Alkyl

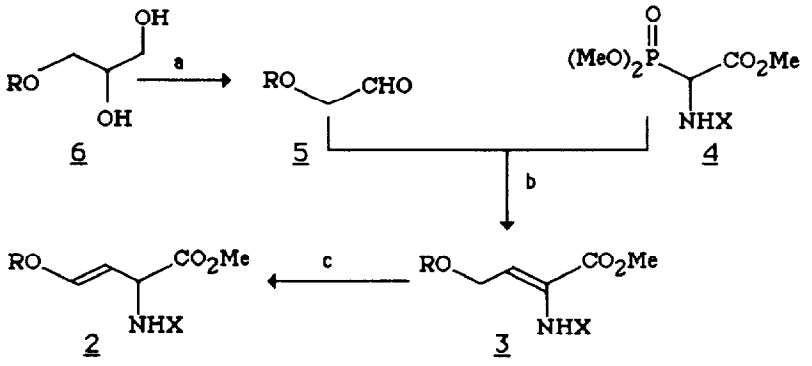
2 X= Alkoxy

In connection with our interest in enzyme inhibition, including either enzyme mechanism studies (3c, 4c) or the rational design of inhibitors (5), we needed a versatile synthetic route towards exotic amino acids bearing an enol ether side chain function (2, X= alkoxy).

Reported synthetic methods (7, 11) involve either elimination on aspartic β-semialdehyde derivatives (11b) or double bond migration on α,β-dehydro-homoserine derivatives (7, 11a). Both methods suffer from either lack of versatility or tedious access to the key intermediates.

This paper deals with a general and straightforward synthesis of these α,β-dehydro-homoserine derivatives based on a Wittig-Horner condensation to afford the ethylenic double bond (6), followed by a regio and stereoselective

isomerization into an enol ether (7) . The main steps of the sequence are outlined in scheme 1.



Scheme 1:

a-$NaIO_4$ / SiO_2 / CH_2Cl_2 / H_2O (9) b-tBuOK, CH_2Cl_2, -70°C, 30', then 25°C 3h (6) c-LDA, THF, -70°C, 30', NH_4Cl (5)

Glycerol 1-mono ether 6 and α-alkoxy acetadehydes 5 have been synthesized as previously described starting from chloro-3-propan-1,2-diol and the required alcohol in a classical Williamson reaction (8) followed by oxidative cleavage of diol 6 by metaperiodate adsorbed on wet silica gel (9).

Phosphonates 4 were obtained by a multistep procedure (6), starting from glyoxylic acid and benzyl carbamate. Different N-protected phosphonates 4 were obtained by hydrogenolysis of the N-Cbz protecting group and reacylation of the free amino function. Various attempts to extend the scope of the reported method (10) to simple amides (X= $CH_3C(O)$; $ClCH_2C(O)$; ...) were unsuccessful. The deprotection/reprotection procedure seems to be the most reliable method to obtain the N-protected phosphonates 4. Wittig-Horner condensation in dichloromethane at low temperature using potassium tert. butoxide as a base, afforded the desired α,β-dehydro-amino acid derivatives 3 (6) with a good stereoselectivity (Z/E > 5/1) and in fair yields (see table 1). Double bond migration was performed according to the procedure developped by Schöllkopf (7), which gave moderate yields of enol ethers but confirmed the rigorous stereoselectivity reported : only trans enol ether and starting material could be detected in the reaction mixture.

In a typical experiment, n-butyl lithium (2.5 M in hexane, 2 ml, 5 mmoles) was added to a solution of di-isopropyl amine (0.506 g, 5 mmoles) in dry THF (30 ml) at -70°C. A few minutes later, a solution of compound 3d (0.468 g, 2.5 mmoles) in dry THF (20 ml) was slowly added. The mixture was stirred for 15 min. at -70°C and quenched with 5% aqueous NH_4Cl (25 ml), without cooling. Classical workup followed by silica gel chromatography (eluent : trichloro- 1,1,1-ethane / ethanol 10:1) afforded the desired enol ether 2d (0.250 g, 51%).

Compound	R	X	Yield	Z / E	M (calc.)
3 a	iBu	CBz	72 %	6 / 1	321
3 b	iBu	CHO	56 %	7 / 1	215
3 c	iBu	Ac	72 %	9 / 1	229
3 d	Me	Ac	45 %	9 / 1	187
2 a	iBu	CBz	35 %	0 / 100	321
2 b	iBu	CHO	33 %	0 / 100	215
2 c	iBu	Ac	36 %	0 / 100	229
2 d	Me	Ac	50 %	0 / 100	187

Table 1

All compounds gave 250 MHz ^{1}H NMR spectra and mass spectra in agreement with the expected structure (12).
Yields of compounds 3 refer to glycerol 1-monoether 6.
* Physical data, including mp in agreement with ref. 11.

This short and straightforward synthetic pathway allows a great versatility in the introduction of both the N-protective group and the ether moiety of protected amino acids bearing an enol ether side chain function.

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12- ^1H NMR data, ppm vs TMS, $CDCl_3$: (The stereochemistry of compounds 3 was attributed according to Ref. 11, on the basis of the vinylic proton chemical shift.)

3a"Z" 7.36, s, 5H, Arom ; 6.75, s broad, 1H, NH ; 6.55, t, 1H, -CH=; 5.14, s, 2H, CH_2-Ph ; 4.14, d, 2H, 5.5 Hz, O-CH_2 ; 3.78, s, 3H, OMe ; 3.20, d, 2H, 6.6 Hz, O-CH_2 ; 1.85, m, 1H, CH_2-CH< ; 0.90, d, 6H, 6.6 Hz, CH_3. **3b"Z"** 8.23, s, 1H, CHO ; 7.49, s broad, 1H, NH ; 6.71, t, 1H, -CH=; 4.17, d, 2H, 5.45 Hz, O-CH_2 ; 3.80, s, 3H, OMe ; 3.21, d, 2H, 6.6 Hz, O-CH_2 ; 1.85, m, 1H, CH_2-CH< ; 0.89, d, 6H, 6.6 Hz, CH_3. **3c"Z"** 7.34, s broad, 1H, NH ; 6.62, t, 1H, -CH=; 4.08, d, 2H, 5.5 Hz, O-CH_2 ; 3.80, s, 3H, OMe ; 3.21, d, 2H, 6.6 Hz, O-CH_2 ; 2.12, s, 3H, C(O)-CH_3, 1.86, m, 1H, CH_2-CH< ; 0.91, d, 6H, 6.7 Hz, CH_3. **2a** 7.35, s, 5H, Arom ; 6.62, d , 1H, 10.5 Hz, O-CH= ; 5.40, m, 1H, NH; 5.10, s, 2H, CH_2-Ph ; 4.72, m, 2H, -CH<, =CH- ; 3.75, s, 3H, OMe ; 3.43, d, 2H, 6.7 Hz, O-CH_2 ; 1.92, m, 1H, CH_2-CH< ; 0.93, d, 6H, 6.5 Hz, CH_3. **2b** 8.19, s, 1H, CHO ; 6.64, d, 1H, 12.5 Hz, O-CH= ; 6.26, s broad, 1H, NH ; 5.03, m, 1H, -CH< ; 4.73, dd, 1H, 12.5 & 8.6 Hz, =CH- ; 3.77, s, 3H, OMe ; 3.45, d, 2H, 6.6 Hz, O-CH_2 ; 1.93, m, 1H, CH_2-CH< ; 0.93, d, 6H, 6.7 Hz, CH_3; **2c** 6.63, d broad, 9 Hz, 1 H, NH ; 6.50, d, 11.5 Hz, 1 H, O-CH= ; 4.77, m, 2H, -CH<, =CH- ; 3.65, s, 3 H, OMe ; 3.37, d, 6.5 Hz, 2 H, O-CH_2 ; 1.93, s, 3 H, C(O)-CH_3 ; 1.72, m, 1 H, CH_2-CH< ; 0.83, d, 7.0 Hz, 6 H, CH_3.

Mass Spectrometry data: (Chemical ionisation, NH_3)

3a 339 ($M+NH_4^+$) ; 322 ($M+H^+$) ; 248 ($M+H^+$-iBuOH). **3b** 233 ($M+NH_4^+$) ; 216 ($M+H^+$) ; 183 ($M+H^+$-iBuOH). **3c** 247 ($M+NH_4^+$) ; 230 ($M+H^+$) ; 156 ($M+H^+$-iBuOH). **2a** 339 ($M+NH_4^+$) ; 322 ($M+H^+$). **2b** 233 ($M+NH_4^+$) ; 216 ($M+H^+$). **2c** 247 ($M+NH_4^+$) ; 230 ($M+H^+$).

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