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SYNTHESIS OF N-PROTECTED *ERYTHRO*-PHENYLALANYLEPOXIDES

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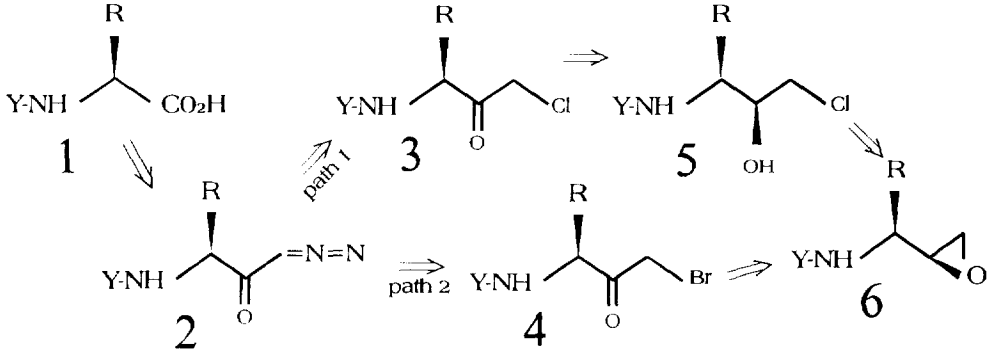
Abstract: The synthesis of *erythro*-isomers of N-α-t-Boc-, N-α-Fmoc- and N-α-Cbz-L-phenylalanylepoxides from the appropriate N-α-protected L-phenylalanines via bromomethylketone intermediates is described.

N-α-Protected amino epoxides of general formula (6) are potential building blocks for synthesis of hydroxyethylene dipeptide isomers [1,2,3]. These amino acid derivatives contain two stereogenic centers, which have been found to be important for their biological activity, but complicate chemical synthesis of these compounds. Stereoselective synthesis of *erythro*-isomers of several Cbz-N-α-protected α - amino epoxides has been described recently [4]. Supplementary to this study we describe here stereoselective synthesis of *erythro*-isomers of L-α-phenylalanylepoxides with N-α-Boc- and N-α-Fmoc protective groups, which are the most commonly used protective groups in solid phase peptide chemistry.



Y=t-Boc, Cbz, Fmoc R= $CH_2C_6H_5$

Two reaction paths, including chloromethyl- (**3**) or bromomethylketone (**4**) as intermediates, can be used for this synthesis. As both reduction and epoxide formation occur in a single step in the latter case, and the yields of this process were high enough, the N-α-protected phenylalanylepoxides were synthesized via the appropriate bromomethylketones following the reaction path 2.

Stereochemical direction of the latter reaction is governed by steric influence of the halogenoketone side group R, as shown by Cram [5] and other [6]. In the case of phenylalanine, the methylphenyl radical R was large enough to lead to complete *erythro*-isomer formation in the case of N-Boc- and N-Cbz-derivatives, as proved by analysis of ^{1}HNMR spectra, while some racemization (2:1) showed ^{1}HNMR spectra [4] was found in the case of N-Fmoc-derivative.

In summary, as stereoselectivity of the synthesis is governed by steric factor of R, the same synthetic scheme can be rather general for amino acids with bulky radicals R, or which side groups can modified with such groups. We have also demonstrated, that the method described by Albeck and Persky [4] is useful for preparation for both, Cbz- and Boc-N–α-protected *erythro* isomers of α-aminoepoxides while the synthesis of N-α-Fmoc-derivative by this mehod yields racemic mixture of *erythro*- and *threo*- isomers.

Experimental

Silufol - UV 254 nm plates were used for TLC analysis. Eluent hexane - EtOAc (3:2), spraying reagent starch/KI according to [7]. Purity of individual N-α-protected epoxides checked by analytical Nucleosil 120-3 C_{18} reverse phase HPLC Column (0.4x10cm) using LKB HPLC apparatus (SYSTEM PREP) at a flow rate 0.8 ml/min using a linear gradient from 0-50% (v/v) water/acetonitrile containing 0.1% TFA in 30 min. ^{13}C proton decoupled NMR spectra were recorded at 50.3 Mhz on a Bruker AC-200p (Spectrospin AG, Switzerland) spectrometer, using $CDCl_3$ as a solvent and TMS as a reference. Melting points were determined by capillary method.

N-protected phenylalanyldiazomethanes (2) were synthesized as described by B.Penke et al [8] from N-protected L-phenylalanines (**1**), isobutyl-chloroformate and diazomethane via formation of amino acid isobutylformate. N-α-Boc and N-α-Cbz-phenylalanyldiazomethanes were recrystallized from ether - petroleumether (1:1) mixture. N-α-Fmoc-phenylalanyldiazomethane was recrystallized from hexane -EtOAc (1:1) mixture.

N-α-Boc-phenylalanyldiazomethane: m.p. 69 - 70°C, yield 49%, R_f 0.60

N-α-Cbz-phenylalanyldiazomethane: m.p. 84- 85°C, yield 43%, R_f 0.50

N-α-Fmoc-phenylalanyldiazomethane: m.p. 135 -137°C, yield 18%, R_f 0.74

The yield depends upon stability of the N-α-protective groups, among which the N-Fmoc was the most unstable under acidic conditions.

N-protected phenylalanylbromomethylketones (3 and **4)** were obtained by treatment of diasomethyl-ketone by HBr as described in [9,10]. As reduction of the latter product yielded directly epoxide (path **2)**, while in the former case chlorohydrin should be separated and transfered into epoxide by treatment with NaOMe in MeOH (path **1**), the first possibility was used for preparative purposes.

N-α-Boc and N-α-Cbz bromomethylketones (**4**) were recrystallized from ethanol. N-α-Fmoc derivative was recrystallized from hexane - EtOAc (1:1) mixture.

N-α-Boc-phenylalanylbromomethylketone: m.p. 98 - 100°C, yield 74%, R_f 0.85

N-α-Cbz-phenylalanylbromomethylketone: m.p. 103 - 104°C, yield 82%, R_f 0.85

N-α-Fmoc-phenylalanylbromomethylketone: m.p. 139 - 141°C, yield 67%, R_f 0.90

N-protected phenylalanylepoxides (6) were obtained from the appropriate bromomethylketones **(4)** upon reduction of these intermediates by sodiumborhydride [9,11]

N-α-Boc and N-α-Cbz phenylalanylepoxides (**6**) were recrystallized from hexane. N-α-Fmoc was recrystallized from hexane - diClmethane (2:1) mixture.

N-α-Boc-phenylalanylepoxide: m.p. 111 - 112°C, yield 47%, R_f 0.79. Element.anal. calcd. for $C_{15}H_{21}NO_3$; C 68.4 ; H 7.98 ; N 5.3. Found ; C 68.24 ; H 7.76 ; N 5.06. Pure by HPLC. Data of ^{13}CNMR: 28.34 (CH_3), 37.80 (C_β), 46,66 (CH_2O), 52,98 (CHO), 53,35 (C_α), 79,71 ($OC(CH_2)_3$), 126,69, 128,57, 129,49, 136,96, (Ph), 155,39 (OCON). ^{1}HNMR 2.74 - 3.02 (m, 5H, CH_2O, CHO, CH_2), 3.65 - 3.71 (m, 1H,CH_α), 4.49 (d,1H, NH, J=7.4Hz), 7.20 - 7.34 (Ph)

N-α-Cbz-phenylalanylepoxide: m.p. 88 - 89°C, yield 45%, R_f 0.67. Element.anal. calcd. for $C_{18}H_{19}NO_3$; C 72.7 ; H 6.3 ; N 4.7. Found , C 72.2 ; H 6.75 ; N 4.51 Pure by HPLC. Data of ^{13}CNMR: 37.71 (C_β), 46,77 (CH_2O), 53,14 (CHO), 53,37 (C_α), 66,92 (OCH_2Ph), 126,89, 128,07, 128,19, 128,56, 128,71, 129,16, 136,52 (Ph), 155,88 (OCON). ^{1}HNMR 2.71 - 3.03 (m, 5H, CH_2, CHO, CH_2O), 3.73 - 3.80 (m, 1H, Ch_α), 4.65 - 4.75 (bm, 1H, NH), 5.04 (s, 2H, OCH_2Ph), 7.17 - 7.37 (10 H, Ph)

N-α-Fmoc-phenylalanylepoxide: m.p 109 - 111, yield 66%, R_f 0.64. (*erythro* : *threo* 2:1, according HPLC analysis and ^{1}HNMR (*erythro* 2.74 - 2.93 (3H, CH_2,O CHO) *threo* 2.46, 2.64 - 3.00 (3H,CH_2O, CHO))

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