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Enantiomerically Pure Pyruvate Derivatives by Epoxidation of Ylidenediketopiperazines

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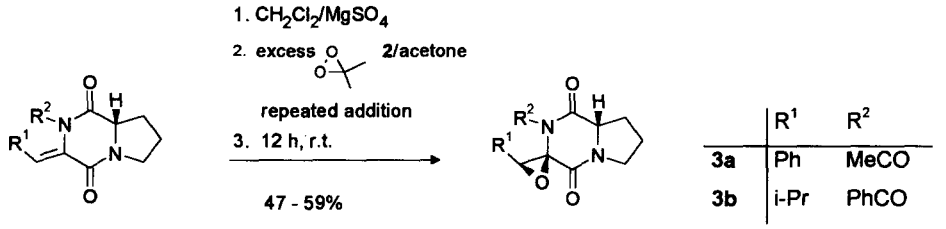
Abstract: Reaction of 3-ylidene-2,5-diketopiperazines **1** with 3,3-dimethyldioxirane (**2**) gives enantiomerically pure spiro-annelated epoxides **3**, which are chiral pyruvate derivatives.

Chiral pyruvates are of interest as building blocks, e. g. in the synthesis of natural products.[1] 3-Ylidene-2,5-diketopiperazines such as **1** are didehydroamino acid derivatives and can easily be obtained from oxazolones and α-amino acids, i. e. (S)-proline. [2] Addition reactions to the exocyclic C-C double bond of such piperazine derivatives create two stereogenic centers and are expected to be stereoselective. Thus ylidenediketopiperazines **1** were successfully used in the stereoselective cycloadditions of diazomethane affording diketopiperazines that are spiro-annelated to a pyrazoline ring .[3] We now report asymmetric epoxidation of ylidenediketopiperazines **1**. As also reported for the achiral 3,5-bisylidene-2,4-diketopiperazine series,[4] m-chloroperoxybenzoic acid and other conventional epoxidizing reagents left diketopiperazines **3** unaffected. Therefore 3,3-dimethyldioxirane (**2**) was applied, which proved a very potent epoxidizing reagent even for α,ß-unsaturated carbonyl species.[5] Treatment of ylidenediketopiperazines **1** in CH_2Cl_2 with excess 3,3-dimethyldioxirane (**2**) in acetone gives corresponding epoxides **3** in about 50% yield[6], and unreacted **1** can be recovered. Only one stereoisomer could be observed by ^{13}C-NMR spectroscopy. X-ray crystal structure analysis of **3a** (Fig. 1) [7] based on the known configuration at C9 proved the absolute configuration and indicated anti-attack (with respect to the annelated proline ring) of the dioxirane **2** at the ylidenediketopiperazine **1** .Since the ylidenediketopiperazine epoxides **3** are formally derived from an enamine structure, they represent novel derivatives of chiral 3-hydroxypyruvic acid. Furthermore, reduction of **3** provides a new access to derivatives of chiral serine homologues. These results and an alternative access to epoxides **3** via bromohydrins[8] will be reported soon.



1

	R^1	R^2
3a	Ph	MeCO
3b	i-Pr	PhCO

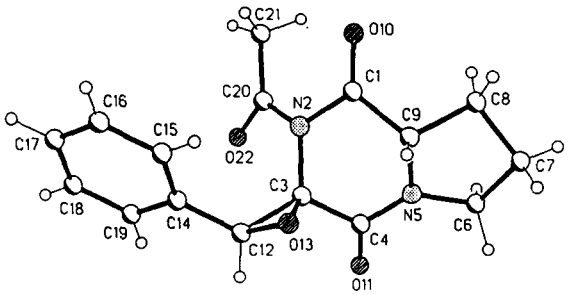


Fig. 1: X-ray crystal structure analysis of epoxide **3a**

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References and Notes

Dedicated to Prof. Dr. Helmut Vorbrüggen on the occasion of his 65th birthday

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6. **3a**: Yield: 47%; m.p. 137-139°C; $[\alpha]_D^{20}$ = -168.8 (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm; J / O, 7.25 (m, 5H) C_6H_5; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm 23.4; 26.3; 27.0; 44.8; 60.3; 62.7; 71.7; 126.6; 128.2; 128.9; 132.5; 161.3; 169.8; 171.5. **3b**: Yield 59%; m.p. 181 °C; $[\alpha]_D^{20}$ = + 131.7 (c = 2.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm: 0.85 (d, 3H, J = 6.4) CH_3; 0.99 (d, 2H, J = 6.5) CH_3; 1.90 (m, 1H) $C\underline{H}Me_2$; 2.15 - 2.23 (m, 4H) $2CH_2$; 3.50 (2H, m) CH_2-N; 3.62 (d, 1H, J = 5.9) CH-O; 4.55 (t, 1H, J = 7.7) CH-N; 7.50 - 7.70 (m, 5H) C_6H_5; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 18.5; 20.3; 23.4; 26.4; 27.9; 45.2; 59.0; 67.4; 73.0; 128.6; 130.4; 133.4; 134.2; 161.9, 170.3; 170.8

7. X-Ray structure determination of compound **3a**: *Crystal data*: monoclinic, space group $P2_1$,a = 938.6 (2). b = 795.4 (2), c = 959.5 (2) pm, ß = 92.09 (2)°, V = 0.7159 nm^3, Z = 2, T = 143 K. *Data collection*: Crystal 0.8 x 0.7 x 0.4 mm, Stoe STADI-4 diffractometer, 1759 unique data to 2θ (Mo Kα) 55 °. *Structure refinement:* On F^2 (program SHELXL- 93, G. M. Sheldrick, University of Göttingen), H atoms with riding model; *wR* (F^2) 0.080, *R* (F) 0.030, for 200 parameters. Full details can be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the full literature citation and the reference number CSD 401558.

8. A method was used that was previously reported by Marcuccio [4] for the barely stereoselective epoxidation of racemic ylidenediketopiperazine derived from phenylalanine.

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