SYNTHETIC COMMUNICATIONS, 30(24), 4443–4449 (2000)

EFFICIENT AND STEREOSPECIFIC SYNTHESIS OF (Z)–HEX-3-ENEDIOIC ACID, A KEY INTERMEDIATE FOR GLY-GLY *CIS* OLEFIN ISOSTERE

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Abstract. (z)-Hex-3-enedioic acid, a key intermediate in the synthesis of (z)-5-amino-3-pentenoic acid (a Gly-Gly *cis* olefin isostere), was synthesized by a short and efficient procedure of sequential oxidations. Thus, selective mono epoxidation of 1,4-cyclohexadiene was followed by periodate oxidation to the appropriate dialdehyde. Finally, Jones oxidation of the dialdehyde afforded the corresponding diacid product.

Peptide isosteres, containing a replacement of a specific amide bond in the peptide, have been extensively used as protease- and other enzyme inhibitors.[1] Of special interest among these are peptidyl olefin isosteres, used both as protease inhibitors[2] as well as intermediates for the synthesis of other peptidyl isosteres such as ethylene, diol, epoxide and hydroxyethelene.[2a,c,e,f,3] Most of the attention in this field has been focused on the *trans* isomer of the olefin isostere, mimicking the more common *trans* peptide bonds. Nevertheless, *cis* olefin isosteres were also

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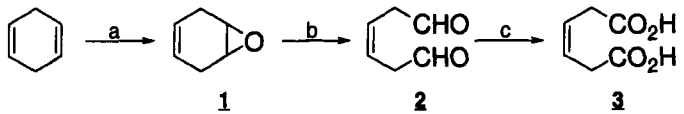
used.[2a,4] Likewise, most of the synthetic efforts were directed towards the synthesis of the *trans* olefin isostere,[2-5] while just a very few approaches to the *cis* isomer were introduced. Among the latter are the Wittig reaction between an α-amino aldehyde and a phosphonium ylide,[2a,6] catalytic ring closure metathesis,[7] and Schmidt rearrangement of the mono acyl azide of the dicarboxylic acid (*z*)-hex-3-enedioic acid, leading to (*z*)-5-amino-3-pentenoic acid (the Gly-Gly *cis* olefin isostere)[4]. (*E*)-hex-3-enedioic acid, the key intermediate in the preperation of Gly-Gly *trans* olefin isostere,[4] is commercially available. On the other hand, (*z*)-hex-3-enedioic acid (the corresponding intermediate for the Gly-Gly *cis* olefin isostere) has to be prepared. Alas, its synthesis (or that of the correspondig diester) is quite laborious and long, or proceeds in low yield or poor *Z:E* selectivity.[4,8] As part of our work on peptide isosteres[9] and protease inhibitors[10], we were interested in both the *trans*- and *cis* Gly-Gly olefin isostere.[11] Therefore, in the present work we describe a facile and short procedure for the preparation of (*z*)-hex-3-enedioic acid, as a key intermediate in the synthesis of (*z*)-5-amino-3-pentenoic acid, the Gly-Gly *cis* olefin isostere.

The synthesis of (*z*)-hex-3-enedioic acid is based on a set of three sequential oxidations, starting from the commercially available 1,4-cyclohexadiene (Scheme 1). Standard mCPBA epoxidation afforded the mono epoxide (**1**) in very good yield, alongside with traces of the di epoxide. The reaction conditions had to be optimized to maximize the yield of the former and minimize the amount of the latter. Therefore, excess oxidant was avoided. Other variations of this epoxidation protocol were previously used in the preparation of **1**.[12] The mono epoxide (**1**) could be purified by distillation under reduced pressure. However, the desired product, 1,4-cyclohexadiene monoxide (**1**), was much more reactive than the corresponding dioxide side product in the following oxidation reaction. Therefore,

it was unnecessary to remove traces of the latter prior to that reaction. Thus, periodate oxidation of the epoxide to the dialdehyde[13] proceeded in 80% yield.[14] The dialdehyde was immediately subjected to Jones oxidation, yielding the target diacid, (z)-hex-3-enedioic acid. It was conveniently purified by a set of extractions and could also be crystallized.



1 2 3

(a) mCPBA, CH_2Cl_2; (b) HIO_4, H_2O/CH_2Cl_2 ; (c) CrO_3, H_2SO_4, acetone

Scheme 1
Synthesis of (z)-hex-3-enedioic acid

The procedure described above afforded the desired (z)-hex-3-enedioic acid in about 40% overall yield. It was conducted on a 5-110 mmol scale, with only small variations in the yields and purity. Its simplicity and the well-defined single isomer obtained make it an attractive approach to the Gly-Gly *cis* olefin isostere. Formation of the mono acyl azide, followed by Schmidt rearrangement to this target compound indeed proceeded according to a published procedure.[4]

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$, unless otherwise specified. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or relative to solvent resonance in other solvents. Mass spectra were recorded in DCI mode with methane as the reagent gas. TLC was performed on E. Merck 0.2 mm precoated silica gel 60 F_{254} plates, and viewed by phosphomolybdic acid.

1,4-Cyclohexadiene monoxide (1): 1,4-cyclohexadiene (4 ml, 42 mmol), m-CPBA 70% (10.2 g, 41.3 mmol) and K_2HPO_4 (7.2 g, 41.4 mmol) were stirred in CH_2Cl_2 (300 ml) and water (2 ml) for 18 h. The solution was then successively washed with saturated $NaHCO_3$, 5% Na_2SO_3, saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was distilled off under atmospheric pressure, leaving the product monoepoxide (3.04 g, 77%) and traces of the byproduct diepoxide (0.36 g, 8%). The product monoepoxide could be purified by distillation under reduced pressure (22 mm Hg, 60°C).

^1H NMR: 2.44 (d, J=17.9 Hz, 2H); 2.57 (d, J=17.9 Hz, 2H); 3.24 (s, 2H); 5.44 (s, 2H). ^{13}C NMR: 24.78; 50.75; 121.32. HRMS for C_6H_9O (MH^+): calcd. 97.0653, found 97.0651.

(Z)-Hex-3-enedialdehyde (2): Epoxide (1) (2.44 g, 25.4 mmol) was stirred with periodic acid (5.72 g, 25.1 mmol) in water (50 ml) and CH_2Cl_2 (10 ml) at 4°C for 3.5 h. NaCl (solid) was added and the phases separated. The aqueous phase was extracted three times with EtOAc. The combined organic layers were treated with Na_2SO_3 (1 g), dried over $MgSO_4$ and filtered. Evaporation of the solvent afforded the product as an oil (2.29 g, 80%), which was transferred to the next reaction without further purification.

^1H NMR: 3.23 (symmetrical 2nd order signal, 4H); 5.91 (symmetrical 2nd order signal, 2H); 9.69 (t, J=1.65 Hz, 2H). ^{13}C NMR: 42.44; 123.46; 198.35. M.S.: 113 (MH^+, 33), 111 (100), 99 (41), 95 (56). HRMS for $C_6H_9O_2$ (MH^+): calcd. 113.0603, found 113.0597.

(Z)-Hex-3-enedioic acid (3): The dialdehyde (2) (0.849 g, 7.58 mmol) was subjected to standard Jones oxidation.[15] Water (50 ml) was added and the acetone evaporated. The aqueous solution was extracted three times with EtOAc, the organic phase was extracted back with basic water (pH 8.5, 100 ml) and the latter

aqueous phase was acidified with conc. HCl to pH 1. This solution was extracted first with CH_2Cl_2 (50 ml) and then with EtOAc (3x50 ml). The latter EtOAc solution was dried over $MgSO_4$, filtered and evaporated to dryness, yielding the diacid (0.626 g, 63%). The diacid could be crystallized from EtOAc : petroleum ether solution.[8e]

^{1}H NMR (acetone-d_6): 3.14 (symmetrical 2nd order signal, 4H); 5.74 (symmetrical 2nd order signal, 2H).[16] ^{13}C NMR (acetone-d_6): 32.58; 125.00; 172.17. M.S.: 145 (MH^+, 16), 127 (100), 99 (39). HRMS for $C_6H_9O_2$ (MH^+): calcd. 145.0501, found 145.0447.

Acknowledgment. This work was supported in part by the "Marcus Center for Pharmaceutical and Medicinal Chemistry" at Bar Ilan University.

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Received in the UK 25 January 2000