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Stereoselective Synthesis of Novel 4,5-Epoxy-1,2-oxazin-6-ones and α,β -Epoxy- γ -amino Acids from β -Lithiated Oxazolinyloxiranes and Nitrones

Vito Capriati, Leonardo Degennaro, Saverio Florio,* Renzo Luisi, and Pasqualina Punzi

Dipartimento Farmaco-Chimico, Università di Bari, C.N.R; Istituto di Chimica dei Composti OrganoMetallici "ICCOM", Sezione di Bari, Via E.Orabona 4, I-70125 Bari, Italy florio@farmchim.uniba.it

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ŃНВ R1 42-78 % $R^1 = cumvl, t-Bu$ dr > 98 : 2 > 99

A stereoselective synthesis of 9,10-epoxy-1,6-dioxa-4,7-diazaspiro[4,5]decanes has been developed on the basis of the addition of β -lithiated oxazolinyloxiranes to nitrones. Conversion of these spirocyclic derivatives into 4,5-epoxy-1,2-oxazin-6-ones and successively into $\alpha_{,\beta}$ -epoxy- γ -amino acids, α -hydroxy- γ -amino acids, and γ -butyrolactams is described.

Unnatural, structurally complex amino acids have recently been attracting a great deal of interest in medicinal chemistry due to the growing belief that structural modifications of amino acids in peptide strands may result in a greater control over related chemical and conformational properties.¹ Therefore, the development of synthetic procedures for the construction of conformationally constrained β - and γ -amino acids^{2,3} is challenging. A three-component synthesis of α,β cyclopropyl- γ -amino acids has been recently reported:⁴ due to the presence of the cyclopropane ring, these amino acids possess the structural rigidity which is paramount to the conformational mimicry of the peptide strand. In this context, we reasoned that a somewhat comparable rigidity could be introduced in a peptide strand by an oxirane ring of an α,β epoxy- γ -amino acid.

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Recent efforts in our group have focused on the use of lithiated oxazolinyloxiranes for the preparation of target molecules.^{5,6} Here, we wish to report the synthesis of 4,5epoxy-1,2-oxazin-6-ones and α,β -epoxy- γ -amino acids based on the reaction of β -lithiated oxazolinyloxiranes with ni-

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trones. Our interest for this kind of amino acids stems from the literature verification that they are rare and potentially useful for elaboration to other substances.⁷ (1*R**,2*S**)-1-Methyl-1-oxazolinyloxirane **2a** was prepared by the Darzens reaction of lithiated 2-(1-chloroethyl)-2-oxazoline with Ph-CHO, as reported.^{5a} When β -lithiated oxazolinyloxirane **3a**, generated from **2a** (*s*-BuLi/TMEDA, THF, -78 °C), was reacted with (*Z*)-*N*-*tert*-butylphenylnitrone **1a**, the perfectly stable 9,10-epoxy-1,6-dioxa-4,7-diazaspiro[4.5]decane **4a** formed in a good yield and diastereoselectively (dr > 98/ 2)⁸ (Scheme 1, Table 1). Similarly, **3a** reacted with nitrones



1b-**g** furnishing compounds **4b**-**g**, the spirocyclic structure of which was spectroscopically established (¹H and ¹³C NMR and FT-IR) and secured by an X-ray analysis in the case of **4b**.^{9,10} In CDCl₃ solution, as well as in THF- d_8 which is the reaction solvent, spirocyclic compounds **4a**-**g** equilibrate

Table 1. Reaction of β -Lithiated Oxazolinyloxirane **3a** with Nitrones **1a**-**m**: Preparation of Spirocyclic Compounds **4** and Isoxazinones **6**

nitrone 1	\mathbb{R}^1	R	$\begin{array}{c} {\bf 4} ({\rm yield}, \\ { \%})^{a,b} \end{array}$	$\substack{6 \text{ (yield,} \\ \%)^{a,b}}$
1a	<i>t</i> -Bu	C_6H_5	4a (71)	6a (80)
1b	"	$p-MeOC_6H_4$	4b (62)	6b (71)
1c	"	$p-\mathrm{CF}_3\mathrm{C}_6\mathrm{H}_4$	4c (55)	6c (71)
1d	"	p-ClC ₆ H ₄	4d (61)	6d (94)
1e	"	PhCH=CH	$4e(64)^{c}$	6e (71)
1f	"	C_6H_{11}	$4f(42)^d$	6f (64)
1g	"	C_7H_{15}	$4g(51)^{d}$	6g (40)
1 h	cumyl	C_6H_5	4h (78)	6h (71)
1i	,, °	$p-MeOC_6H_4$	4i (62)	6i (88)
1j	"	$p-ClC_6H_4$	4j (60)	6j (52)
1k	"	2-furyl	4k (72)	6k (87)
11	"	$5-(3-CF_3C_6H_4)-2-furyl$	41 (77)	61 (67)
1m	"	C_6H_{11}	$4m (52)^d$	6m (10) ^e

^{*a*} Isolated yields. ^{*b*} The diastereomeric ratio (dr > 98:2) was established from the analysis of the ¹H NMR spectra of the crude reaction mixture of **6** (see ref 8). ^{*c*} Partial hydrolysis takes place on silica gel to afford a small amount of 4,5-epoxy-1,2-oxazin-6-one **6e**. ^{*d*} These derivatives are mainly present as the hydroxylamino forms **5**. ^{*e*} In this case, compound **8** (Scheme 1) was isolated as the main product (see ref 21).

with the hydroxylamino forms $5\mathbf{a}-\mathbf{g}$ and *diast* $4\mathbf{a}-\mathbf{g}$,¹¹ the position of the equilibrium being dependent upon the nature of the nitrone: the hydroxylamino form **5** is favored with aliphatic nitrones, whereas the spirocyclic form **4** prevails with aromatic ones.^{12,13} For R = cyclohexyl, the hydroxylamine **5f** crystallizes from hexane, and its structure was confirmed by single-crystal X-ray analysis.¹⁴

Trifluoroacetic acid (TFA) catalyzed hydrolysis of compounds 4a-g, carried out in dioxane/H₂O, afforded in good yields and diastereoselectivity (dr > 98/2)⁸ 4,5-epoxy-1,2oxazin-6-ones 6a-g (Scheme 1) (see the Supporting Information). The intermediacy of the epoxyhydroxyamides 7 in the transformation of 4 to 6 was proved by quenching the reaction mixture at shorter reaction times (16 h).¹⁵ Compounds 7a,b,d,f were isolated and, upon hydrolysis, transformed quantitatively into the corresponding epoxy-1,2oxazinones 6a,b,d,f (see the Supporting Information). For 6d, the structure and relative configuration were confirmed by X-ray analysis.¹⁶

Reduction of *N-tert*-butylepoxy-1,2-oxazinones **6f**,**g** ($\mathbf{R} =$ alkyl) (H₂, 1 atm, Pd/C, 5 mol %, MeOH) gave the α , β -

^{(5) (}a) Capriati, V.; Degennaro L.; Favia, R.; Florio, S.; Luisi, R. *Org. Lett.* **2002**, *4*, 1551–1554. (b) Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Org. Lett.* **2003**, *5*, 2723–2726.

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⁽⁸⁾ The diastereomeric ratio of **4**, with reference to the newly created stereocenter at carbon 8, was ascertained by ¹H NMR analysis performed on the crude deblocked 1,2-oxazin-6-ones **6** (see text).

⁽⁹⁾ For a stereoselective synthesis of optically active 5-isoxazolidin-5ones and β -amino acids, see: (a) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2002**, 2961–2969. (b) Luisi, R.; Capriati, V.; Florio, S.; Vista, T. *J. Org. Chem.* **2003**, 68, 9861–9864.

⁽¹⁰⁾ CCDC 606445 contains the supplementary crystallographic data for compound **4b**. These data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

⁽¹¹⁾ Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9713–9718.

^{(12) &}lt;sup>13</sup>C NMR data give strong evidence of such an equilibration between 4 and 5 occurring in CDCl₃ as well as in THF- d_8 ; indeed, ¹³C resonances at 111–113 ppm and at ca. 164 ppm are diagnostic of two spirocyclic carbon atoms and of an oxazoline C=N group, respectively. On the other hand, in the solid state, only the spirocyclic skeleton of 4 was detected by means of an IR investigation (KBr); indeed, a diagnostic NH stretching band appeared at ca. 3360 cm⁻¹, whereas no oxazoline C=N bond stretching was observed at ca. 1668 cm⁻¹ which is the typical stretching frequency.

⁽¹³⁾ In the case of aromatic-substituted derivatives, spirocyclic compounds **4** are the main forms present in freshly prepared CDCl₃ solution, as checked by ¹H NMR; over time, the signals of the hydroxylamino forms **5** tend to increase. Under the same conditions, the alkyl-substituted derivatives are mainly present, from the beginning, as hydroxylamino forms.

⁽¹⁴⁾ CCDC 606447 contains the supplementary crystallographic data for compound **5f**. These data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

⁽¹⁵⁾ Such epoxyhydroxyamides are the main products when the reaction is performed with an excess of TFA.

epoxy-*γ*-amino acids **10a**,**b** with good yields, whereas *N*-tertbutylepoxy-1,2-oxazinones **6a**-**c** (R = aryl) under different conditions [H₂, 20 atm, Pd(OH)₂/C, 10 mol %, MeOH] furnished the α-hydroxy-*γ*-amino acids **11a**-**c** as the main products¹⁷ (Scheme 2). The structure of **11a** was confirmed



by an X-ray analysis.¹⁸

The *N*-tert-butyl substituent of **6** and **10** or **11** could not be removed. Therefore, we turned our attention to cumyl nitrones in view of the fact that the cumyl group can be easily removed under mild conditions.^{19,20} As expected, 4,5-epoxy-1,2-oxazinones **6h**-**m** could be prepared by hydrolysis of compounds **4h**-**m**, which in turn had been obtained by the addition of **3a** to *N*-cumylnitrones **1h**-**m** (Scheme 1 and Table 1).^{8,21} Reduction [H₂, 1 atm, Pd/C (5 mol %)] of *N*-cumylepoxy-1,2-oxazinones **6h**,**i**,**k** provided the α,β epoxy- γ -amino acid **12a**-**c** in good yields with the free amino group (Scheme 3). Moreover, treatment of **12a**-**c** with Me₃SiCHN₂ in dry MeOH gave α,β -epoxy- γ -butyrolactams **13a**-**c** quantitatively.²² *N*-Cumylepoxy-1,2-oxazinones **6h**-**j** too could be selectively *N*-deprotected under acidic conditions (TFA, CH₂Cl₂) giving epoxy-1,2-oxazinones **9a,b,d**

(17) It is worth noting that in the case of **6f**,g reduction even under 20 atm on Pd(OH)₂/C did not cause any oxirane ring-opening reaction leading, instead, to α,β -epoxy- γ -amino acids **10a,b** as the main products.

(18) CCDC 606448 contains the supplementary crystallographic for compound **11a**. These data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) For some examples concerning the easy deprotection of the cumyl group, see: (a) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, 2, 4229–4232. (b) Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. *Synlett* **2001**, 302–304.

(20) *N*-Benzyl nitrones are not useful because of the pronounced acidity of the benzylic hydrogens, which is able to protonate the starting lithiated oxirane.

(21) Hydrolysis of **4m** furnished the expected epoxy-1,2-oxazinone **6m** only in a low yield, the main product being the hydroxyamide **8** (Scheme 1). The formation of this compound, which is currently under investigation, could be explained with a concerted cumene hydroperoxide-type rearrangement involving a reactive delocalized phenonium ion as the intermediate further to an electrophilic aromatic substitution promoted by the π -electrons on the nitrogen atom linked to the cumyl group. See also: Hamann, H.-Y.; Liebscher, Y. J. Org. Chem. **2000**, 65, 1873–1876.



with very good yields. Reduction, instead, of epoxy-1,2oxazinones **9a,b,d** (Scheme 3) gave the α,β -epoxy- γ butyrolactams **13a,b**.²³

Next, we evaluated the possibility of performing an asymmetric synthesis of such epoxy-1,2-oxazinones, simply





^{*a*} Isolated yields. ^{*b*} The diastereomeric ratio (dr > 98:2) was established from the analysis of the ¹H NMR spectra of the crude reaction mixture of **6** (see ref 8). ^{*c*} The enantiomeric ratio was determined via HPLC (Diacel OD-H) or chiral gas chromatography on epoxy-1,2-oxazinones **6** in comparison with racemic samples.

(-)-40(51)

(-)-4p (65)

(-)-6 g (60)

(-)-**6h** (61)

 C_7H_{15}

 C_6H_5

cumyl

1g 1h

starting from optically active oxazolinyloxiranes. Lithiation of the optically active oxazolinyloxirane **2b** (er = 98/2),^{5a} followed by the coupling of the corresponding lithiated intermediate **3b** with *N*-tert-butylnitrones **1a**,**g** and *N*-cumylni-

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⁽¹⁶⁾ CCDC 606446 contains the supplementary crystallographic data for compound **6d**. These data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

trone **1h**, gave spirocyclic compounds **4n**-**p** (Table 2) with complete diastereo- and enantioselectivity.²⁴ Hydrolysis (TFA) of **4n**-**p** furnished highly enantioenriched *N*-tertbutylepoxy-1,2-oxazinones (*S*,*S*,*S*)-(-)-**6a**, (*S*,*S*,*S*)-(-)-**6g**, and *N*-cumylepoxy-1,2-oxazinones (*S*,*S*,*S*)-(-)-**6h**, respectively, which are amenable to the corresponding α , β -epoxy- γ -amino acids, as in the case of (-)-**12a** (Table 2).

In conclusion, we have reported a highly stereoselective synthesis of novel epoxy-1,2-oxazin-6-ones that can be easily transformed into α,β -epoxy- γ -amino acids and the corresponding α,β -epoxy- γ -butyrolactams. To date, these are rare examples of α,β -epoxy- γ -amino acids to be reported. The constraints of the oxirane ring in the backbone of these γ -amino acids could make this new derivatives very attractive

(24) In these cases, in contrast to that observed with spirocyclic compounds 4a-m, there was no equilibration with the corresponding hydroxylamino forms.

for study in the field of new peptides and peptidomimetics. An added value to these kinds of amino acids is given by the presence of the oxirane ring that could be manipulated for synthetic purposes.⁷ More work is underway in our laboratory to this end.

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Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²²⁾ α,β -Epoxy- γ -amino acids **12** convert spontaneously into α,β -epoxy- γ -butyrolactams **13** simply by keeping them in CDCl₃ for at least 24–36 h.

⁽²³⁾ Under reduction conditions, a dehalogenation of $9d (R = p-ClC_6H_4)$ occurred; see also: (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91–95. (b) Luisi, R.; Capriati, V.; Florio, S.; Vista, T. *J. Org. Chem.* **2003**, *68*, 9861–9864.