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Oxazolinyloxiranyllithium-Mediated Stereoselective Synthesis of α-Epoxy-β-amino Acids†

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

Dipartimento Farmaco-Chimico, Università di Bari, Via E. Orabona 4, I-70126 Bari, C.N.R., Istituto di Chimica dei Composti OrganoMetallici "ICCOM", Sezione di Bari, Italy

florio@farmchim.uniba.it

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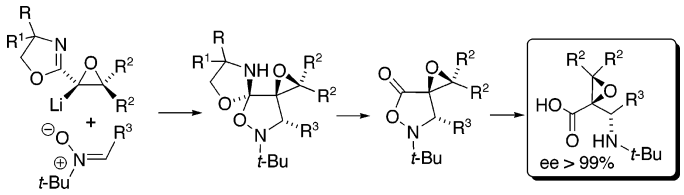
ABSTRACT

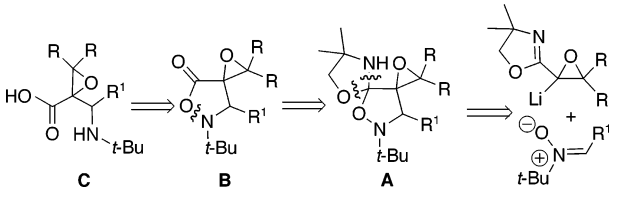


The stereoselective synthesis of novel α-epoxy-β-amino acids is described by a route that combines the chemistry of oxazolinyloxiranyllithiums with that of nitrones. The intermediate trioxadiazadispiro[2.0.4.3]undecanes 4 have been isolated and converted by hydrolysis into epoxy-5-isoxazolidinones 5 which can be transformed into the α-epoxy-β-amino acids 8 by N–O reduction.

Amino acids are fundamental constituents of a great variety of natural products and of other highly valuable substances. Specifically, β-amino acids,[1] after the Seebach's pioneering work on their use to create β-peptide foldamers,[2] are witnessing a great deal of interest because of their potential use as therapeutic agents[3] and their role as structure-forming elements in β-peptides.[4] Therefore, the development of stereoselective transformations for the synthesis of this kind of amino acids is a stimulating challenge for synthetic organic chemists.

As part of an ongoing program directed to investigate applications of the addition reaction of azaenolates of alkyloxazolines to nitrones,[5] we present herein the first synthesis of α-epoxy-β-amino acids that combines the chemistry of oxazolinyloxiranyllithiums we have recently developed in our laboratory[6] with that of nitrones. As shown in the retrosynthetic analysis of Scheme 1, the addition of

Scheme 1



the oxiranyllithium to the nitrone to give the dispirocyclic compound **A**, the hydrolysis of the oxazolidine moiety, and

† Dedicated to Prof. Paolo Edgardo Todesco of the University of Bologna on the occasion of his 70th birthday.

(1) For reviews on the synthesis of β-amino acids, see: (a) *Enantioselective Synthesis of β-amino acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983.

(2) (a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (b) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437.

(3) (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180.

(4) For biologically active β-peptides, see: (a) Werder, M.; Hausre, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774. (b) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.

(5) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2002**, 2961−2969.

(6) (a) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049−3058. (b) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445−2448.

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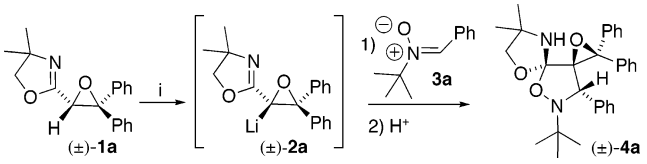
reduction of the N−O bond of the epoxy-5-isoxazolidinone **B** to give the target amino acid **C** are key steps. Because of the high ring strain, the formation of the dispirocyclic system **A**, in which three new contiguous stereogenic centers are created in a single step, is supposed to proceed highly stereoselectively. The importance of amino acids such as **C** resides also on the possible synthetic elaboration of the oxirane ring.

Our work commenced with the preparation of so far undescribed trioxadiazadispirocyclic compounds **A** from nitrones and oxazolinyloxiranyllithiums.

Lithiation of 3,3-diphenyl-2-oxazolinyloxirane **1a** was performed as previously reported.[6a] The resulting 2-lithiooxirane **2a** was reacted with the *Z*-*N*-*tert*-butyl-α-phenylnitrone[7] **3a** affording a good yield of the 7,7-dimethyl-2,2,11-triphenyl-10-*tert*-butyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]-undecane **4a** in a completely diastereoselective manner (Scheme 2).

Scheme 2[a]



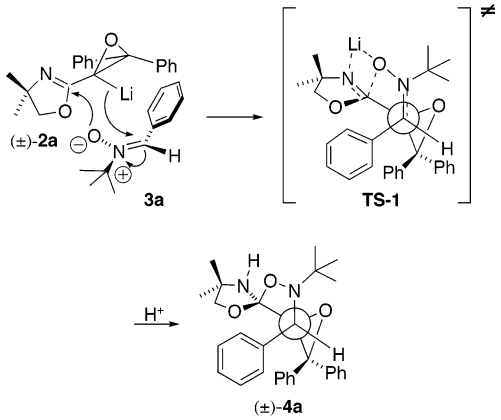
[a] Key: (i) *s*-BuLi/TMEDA, −98 °C, THF.

The spectroscopic analysis including ^{1}H and ^{13}C NMR measurements clearly showed that **4a** was just one diastereomer: its structure and relative configuration was ultimately confirmed by an X-ray analysis.[8] To explain the observed diastereoselectivity we propose a mechanism that involves a highly ordered transition state (**TS-1**), which originates from the addition of the oxiranyllithium to the nitrone (*re* face) ending up with the formation of **4a** after the acidic quenching, as outlined in Scheme 3.[9] Steric effects as well as lithium chelation must be playing a crucial role in the stereochemical control of such an addition.

According to what was previously reported,[10] addition of the nitrone (through the oxygen atom) to the C−N double bond of the oxazoline ring occurs on the *re* face of the latter.

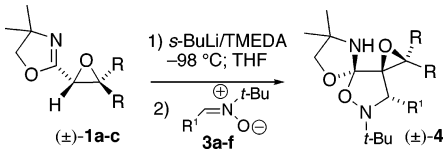
The reaction of **2a** leading to a dispirocyclic compound such as **4a** was not restricted to the nitrone **3a**: it worked

Scheme 3



well also with other nitrones such as **3b**−**d** affording dispirocyclic products **4b**−**h** (Table 1). All the reactions

Table 1. Preparation of Dispirocyclic Compounds **4**



epoxide **1**	R	R^1	nitrone **3**	compd **4** (% yield)[a]
1a	Ph	Ph	**3a**	**4a** (75)
	Ph	*p*-$MeOC_6H_4$	**3b**	**4b** (82)
	Ph	*p*-ClC_6H_4	**3c**	**4c** (75)
	Ph	Cy	**3d**	**4d** (45)
1b	Me	Ph	**3a**	**4e** (48)
	Me	*p*-$MeOC_6H_4$	**3b**	**4f** (67)
1c	Et	Ph	**3a**	**4g** (56)
1d	$-(CH_2)_5-$	Ph	**3a**	**4h** (68)

[a] Isolated yields after column chromatography.

occurred with the same excellent diastereoselectivity as with **3a**, the best chemical yields being obtained with aryl nitrones **3a**−**c**, while lower yields were observed with *N*-*tert*-butyl-α-cyclohexylnitrone **3d**.

Aliphatic as well as aromatic substituents are tolerated on the *β*-position of the starting epoxide. Indeed, lithiated oxazolinyloxiranes **2b**−**d**, smoothly obtainable by lithiation of oxiranes **1b**−**d**, reacted cleanly with nitrones yielding the corresponding dispirocyclic compounds **4e**−**h** (Table 1). In all cases the cyclization reaction took place with the same diastereoselectivity as established by the NMR evidence.

A careful examination of the structural features of compounds **4** encouraged us to evaluate the possibility of using them as intermediates for the synthesis of α-substituted *β*-amino acids[11] as shown in the retrosynthetic analysis of Scheme 1.

All attempts to isolate the expected 4-epoxy-5-isoxazolidinone (±)-**5** (Figure 1), which is the precursor of the

(7) Nitrones **3a**−**i** should have a *Z* configuration that is the typical stereochemistry of acyclic nitrones, as reported: (a) Gilbertson, S. R.; Lopez, O. D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1116−1119. (b) Dondoni, A.; Franco, S.; Junquear, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537−2550.

(8) CCDC-207742 and -207743 contain the supplementary crystallographic data for compounds (±)-**4a** and (+)-**4i**. These data can be obtained free of charge at www.ccdc.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: (internat.) +44−1223/336-033. E-mail: deposit@ccdc.cam.ac.uk.

(9) It is useful pointing out that the reaction of the same oxiranyllithium **2a** with aldehydes proceeds with very poor diastereoselectivity. See: Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A. *Eur. J. Org. Chem.* **1999**, 409−417.

(10) An example of stereoselective addition of the lithiated hydroxylamine to the C−N double bond of the oxazoline ring was already reported in ref 5.

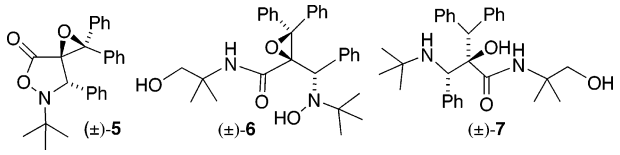
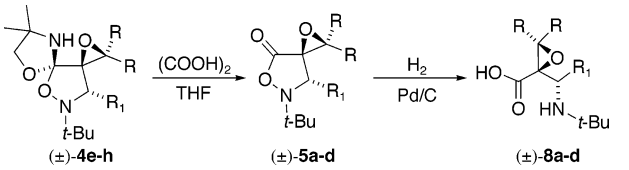


Figure 1.

expected amino acid, from **4a** failed and treatment with aq oxalic acid caused an almost quantitative transformation of **4a** into the β-hydroxylamino epoxycarboxamide (±)-**6**, while hydrogenation (H_2, Pd/C, EtOH) of **4a** furnished quantitatively the β-amino-α-hydroxycarboxamide (±)-**7** (Figure 1).

In contrast, hydrolysis of the dispirocyclic compound **4e** with aq oxalic acid furnished the 5-isoxazolidinone **5a** in good yield. Comparable results were obtained when dispirocyclic compounds **4f**−**h** were treated with aq oxalic acid to give the so far undescribed epoxy-5−isoxazolidinones **5b**−**d**. Interestingly, all the epoxy-5-isoxazolidinones **5a**−**d** could be easily and quantitatively reduced (H_2, Pd/C, MeOH, rt, 3 h) to the α-epoxy-β-amino acids **8a**−**d** (Table 2). It

Table 2. Preparation of 5-Isoxazolidinones **5** and β-Amino Acid **8**



4	R	R^1	**5** (% yield)[a]	**8** (% yield)[b]
4e	Me	Ph	**5a** (68)	**8a** (>98)
4f	Me	*p*-$MeOC_6H_4$	**5b** (85)	**8b** (>98)
4g	Et	Ph	**5c** (72)	**8c** (>98)
4h	$-(CH_2)_5-$	Ph	**5d** (61)	**8d** (>98)

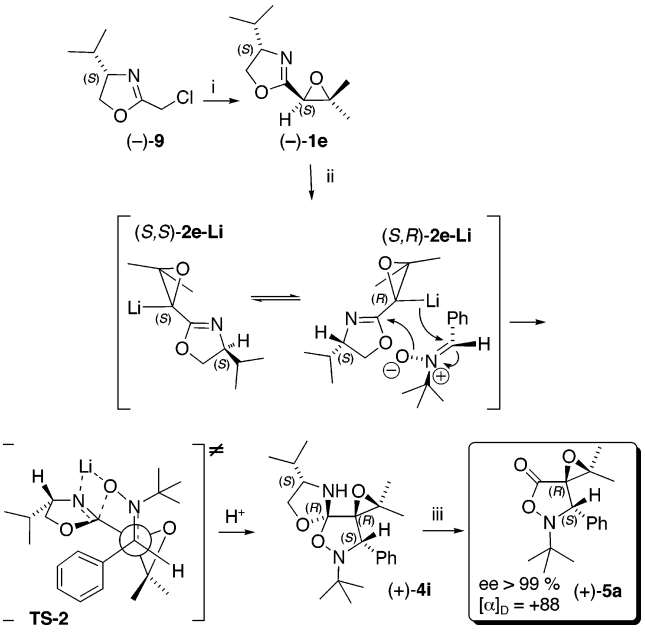
[a] Isolated yields after column chromatography. [b] Yield calculated by weighting the crude reaction product obtained after filtration of the catalyst and ^1H NMR analysis; no starting material or other byproducts could be observed.

seems that the hydrolysis of compounds **4** to the 5-isoxazolidinones **5** depends on the substituents which insist on the β-position of the oxirane ring: the transformation occurs when aliphatic substituents are present and it does not with aromatic groups.

The excellent diastereoselectivity of the reaction of 2-lithiooxiranes **2** with nitrones stimulated the pursuit of this work for the synthesis of optically active dispirocyclic compounds **4** and then optically active β-amino epoxyacids **8**. We reasoned it could be done using a chiral oxazolinyloxirane as the starting material. Enantiomeric oxazolinyl-

(11) (a) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575−1578. (b) Shindo, M.; Itoh, K.; Tsuchiya, C.; Shishido, K. *Org. Lett.* **2002**, *4*, 3119−3121.

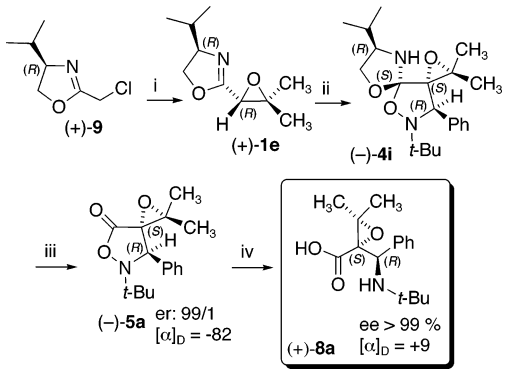
Scheme 4[a]



[a] Key: (i) (a) LDA, Ti(*i*-PrO)$_4$, (b) acetone, (c) NaOH/*i*-PrOH. (ii) (a) *s*-BuLi/TMEDA, −98 °C, THF, (b) **3a**. (iii) $H_2O/(COOH)_2$ 2% w/w.

oxiranes (+)- and (−)-**1e**[12] (Schemes 4 and 5) were prepared starting from the chiral 2-chloromethyl-2-oxazolines (+)- and (−)-**9** by lithiation followed by lithium−titanium transmetalation as similarly reported.[13] Then, the oxazolinyloxirane (*S*,*S*)-(−)-**1e** (dr 98/2, ee > 99%, $[\alpha]_D$ −79) was lithiated and reacted with **3a** to give the optically active (3*R*,4*R*,7*S*,-11*S*)-(+)-**4i** as a single diastereoisomer in a very good yield (75%) (Scheme 4). The structure and absolute configuration of (+)-**4i** was ascertained from 2D-NOESY correlations and finally confirmed by an X-ray crystal-structure analysis (see ORTEP in the Supporting Information).[8] Here again, the explanation for the observed diastereoselectivity resides in

Scheme 5[a]



[a] Key: (i) (a) LDA, Ti(*i*-PrO)$_4$, (b) acetone, (c) NaOH/*i*-PrOH. (ii) (a) *s*-BuLi/TMEDA, −98 °C, THF, (b) **3a**. (iii) $H_2O/(COOH)_2$ 2% w/w. (iv) H_2, Pd/C.

the way the lithiated oxazolinyloxirane **2e** and the nitrone **3a** interact with each other. It is worth pointing out that the configuration at the C-3 of (+)-**4i** was ascertained to be opposite (*R*) to that for the starting oxazolinyloxirane (*S*,*S*)-(−)-**1e**,[14] indicating that an inversion had occurred at this carbon.[15]

Configuration of the three newly created stereogenic centers is presumably established in the transition state **TS-2** (Scheme 4) that results from the nucleophilic addition of the lithiated oxirane **2e** on the *re* face of **3a**. To justify such a transition state we assume that the lithiated oxiranes (*S*,*S*)-**2e-Li** and (*S*,*R*)-**2e-Li**[14] interconvert; then, the diastereomeric lithiated oxirane (*S*,*R*)-**2e-Li** (having the isopropyl group on the C-4 of the oxazoline ring far away from the oxirane C−Li bond) preferentially reacts with the nitrone for experiencing a lower steric hindrance to produce (3*R*,4*R*,7*S*,11*S*)-(+)-**4i**.

Treatment of (+)-**4i** with aq oxalic acid afforded optically active 5-isoxazolidinone (+)-**5a** highly enantioenriched (ee > 99%) and in good yield (76%).

Similarly, lithiation of oxazolinyloxirane (*R*,*R*)-(+)-**1e** (dr 98/2, ee > 99%, $[\alpha]_D$ +79) (Scheme 5) followed by the addition of **3a** furnished, via (3*S*,4*S*,7*R*,11*R*)-(−)-**4i**, the enantiomeric 5-isoxazolidinone (−)-**5a** in high optical purity (ee > 99%, $[\alpha]_D$ −82) and good yield (60%). This could be quantitatively reduced to the corresponding epoxyamino acid (+)-**8a** (ee > 99%, $[\alpha]_D$ +9).

In conclusion, this paper describes how novel dispirocyclic compounds such as **4**, epoxy-isoxazolidinones **5**, and α-epoxy-β-amino acids **8**, all never reported before, can simply and highly stereoselectively be obtained just by combining the chemistry of lithiated oxazolinyloxiranes with that of nitrones.

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni" and the FIRB Project "Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi" supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome) and by the University of Bari and CNR (Rome). We are also grateful to Prof. Marcel Pierrot of the Centre Scientifique Saint-Jerome, Marseille, France, for performing X-ray analysis on compounds (±)-**4a** and **(+)-4i**.

Supporting Information Available: Spectroscopic and physical data for compounds (+)/(−)-**1e**, **4a**−**h**, **5a**−**d**, **6**, **7**, and **8a**−**d**, and crystallographic data for (±)-**4a** and (+)-**4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The (*S*,*S*) absolute configuration of the major diastereomer of oxazolinyloxirane (−)-**1e** (dr 98/2) was deduced by combining the results of a 2D-NOESY Phase-Sensitive experiment and calculations (see Supporting Information) and was in agreement with what reported for other optically active oxazolinyloxiranes prepared as just described for (−)-**1e** (see ref 13).

(13) Capriati, V.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2001**, 2035−2039.

(14) That an equilibrium between the two lithiated diastereomeric species (*S*,*S*)-**2e**-Li and (*S*,*R*)-**2e**-Li may occur, as shown in Scheme 5, was proved by the following experiment: when (*S*,*S*)-(−)-**1e** (dr 98: 2, ee > 99%) was lithiated with *s*-BuLi/TMEDA at −98 °C and the resulting mixture quenched after a few minutes with a D^+ source, an almost 1:1 mixture of (*S*,*S*)-**1e** and (*S*,*R*)-**1e** (both 95% D) was obtained.

(15) Concerning the configurational stability of oxiranyllithiums and their synthetic applications see: (a) Satoh, T. *Chem. Rev*. **1996**, *96*, 3303−3325. (b) Mori, Y. *Rev. Heteroatom Chem.* **1997**, *17*, 183−211. (c) Alickmann, D.; Frohlich, R.; Wurthwein, E.-U. *Org. Lett.* **2001**, *3*, 1527−1530. (d) Dechoux, L.; Agami, C.; Doris, E.; Mioskowski, C. *Eur. J. Org. Chem.* **2001**, 4107−4110. (e) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, *12*, 1625−1642. (f) Yamauchi, Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, *4*, 173−176. (g) Mori, Y.; Takase, T.; Noyori, R. *Tetrahedron Lett.* **2003**, *44*, 2605−2608.