

Stereospecific β -Lithiation of Oxazolinylloxiranes: Synthesis of α,β -Epoxy- γ -butyrolactones

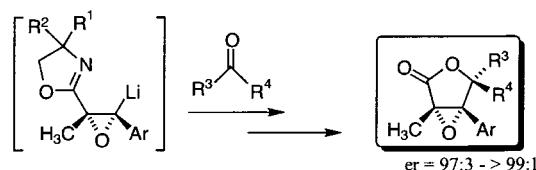
Vito Capriati, Leonardo Degennaro, Raffaele Favia, Saverio Florio,* and Renzo Luisi

Istituto di Chimica dei Composti OrganoMetallici-ICCOM, Dipartimento Farmaco-Chimico, Università di Bari, Via E.Orabona 4, I-70125 Bari, Italy

florio@farmchim.uniba.it

Received February 26, 2002

ABSTRACT



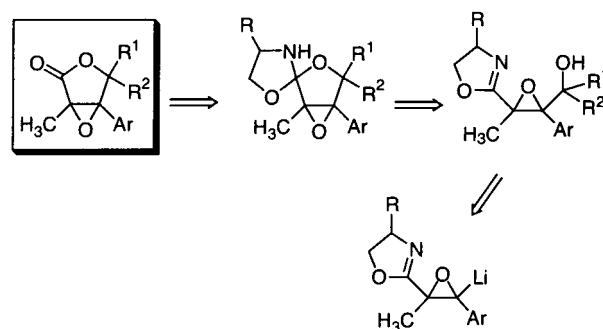
Stereospecific β -lithiation of β -aryl-substituted oxazolinylloxiranes is described. The trapping reaction of such reactive intermediates with carbonyl compounds gave α,β -epoxy- γ -butyrolactones after deblocking of the oxazoline moiety. This methodology has been also extended to the synthesis of optically active α,β -epoxy- γ -butyrolactones.

α,β -Epoxy lactones are versatile intermediates in synthetic organic chemistry. α,β -Epoxy- γ -butyrolactones, in particular, intervene in synthetic routes to precursors of natural products such as epolactaene, which has a potent neurite outgrowth activity in a human neuroblastoma cell line SH-SY55,¹ of (+)-cerulenine, a potent fungal inactivator of fatty acid synthetase,² and of α -methylenebis- γ -butyrolactones.³

Our continuing involvement in the chemistry of heterocyclic systems as well as of oxiranyl anions⁴ led us to consider the possibility that the chemistry of the oxazoline system combined with the oxiranyl anion based methodology might be exploited for the preparation of α,β -epoxy- γ -

butyrolactones according to the retrosynthetic approach shown in Scheme 1. In this Letter we report the results of a synthetic procedure based on such analysis.

Scheme 1



(1) Kuramochi, K.; Itaya, H.; Nagata, S.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 7367–7370.

(2) Mani, N. S.; Townsend, C. A. *J. Org. Chem.* **1997**, *62*, 636–640.

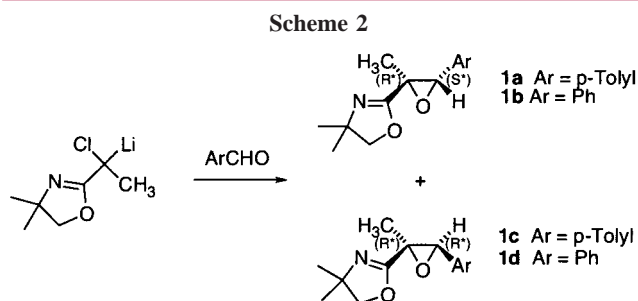
(3) Lertvorachon, J.; Thebtaranonth, Y.; Thongpanchang, T.; Thonyoo, P. *J. Org. Chem.* **2001**, *66*, 4692–4694.

(4) Abbotto, A.; Capriati, V.; Degennaro L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049–3058 and references therein.

(5) Relative configuration, distinguishing diastereoisomers, may be denoted by the configurational descriptors R^*,R^* and R^*,S^* meaning, respectively, that the two centres have identical or opposite configurations, as reported in: IUPAC. *Nomenclature of Organic Chemistry*, Sections A–F and H; Pergamon Press: Elmsford, NY, 1979; p 482, Rule E-4.10.

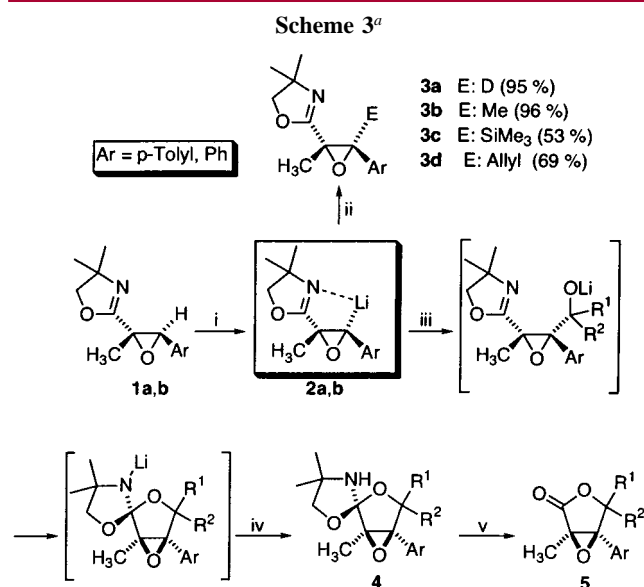
Our work started with the preparation of the needed precursors. $(1R^*,2R^*)$ - and $(1R^*,2S^*)$ -1-methyl-1-oxazolinylloxiranes **1a–d**⁵ were prepared by the Darzens reaction

of lithiated 2-(1-chloroethyl)-2-oxazoline, as reported (Scheme 2).⁶ Once separated by column chromatography, the relative



configuration to **1a,b** and **1c,d** could be assigned on the basis of the long-range $^3J_{\text{CH}}$ coupling constant between the methyl group and the oxirane β -hydrogen.^{4,7}

Lithiation of epoxides **1a,b** (*s*-BuLi/TMEDA, Et₂O, -98 °C) produced oxiranylithiums **2a,b**, which proved to be stable at low temperature for several hours. Trapping of **2a** (R = *p*-tolyl) with electrophiles (D₂O, MeI, Me₃SiCl, and allyl chloride) afforded tetrasubstituted epoxides **3a–d** in good to excellent yields upon warming to room temperature and conventional workup (Scheme 3).



^a (i) *s*-BuLi/TMEDA, Et₂O, -98 °C; (ii) E⁺; (iii) R¹R²CO; (iv) H⁺; (v) 2% w/w aq (COOH)₂.

The stabilizing assistance to oxiranylithiums **2a,b** is likely provided by both the oxazolinyl and the aryl groups. Indeed, Eisch and Galle's work on lithiated styreneoxides had amply

(6) Capriati, V.; Degennaro, L.; Florio S.; Luisi, R.; Tralli, C.; Troisi, L. *Synthesis* **2001**, 15, 2299–2306.

(7) Kingsbury, C. A.; Durham, D. L.; Hutton, R. *J. Org. Chem.* **1978**, 43, 4696–4700.

proved the stability of aryl-substituted lithiated oxiranes.⁸ Lithium cation is probably coordinated by the aza group of the oxazolinyl ring in lithiated species **2a,b**. β -Lithiation in substituted oxiranes has been recently reported.⁹ In all cases the reaction of lithiated oxiranes **2a,b** proceeded stereospecifically with complete retention of configuration, thus proving the configurational stability of such lithiated species.¹⁰ Interestingly, the reaction of lithiated oxiranes **2a,b** with symmetrical aliphatic and aromatic ketones afforded quite good yields of spirocyclic compounds **4a–f** (Table 1),

Table 1. Spirocyclic Compounds **4** and Epoxylactones **5**

Ar	R ¹	R ²	spirocyclic compound (% yield) ^a	epoxylactone (% yield) ^a
<i>p</i> -tolyl	Me	Me	4a (60)	5a (>95)
<i>p</i> -tolyl	Et	Et	4b (60)	5b (>95)
<i>p</i> -tolyl	–(CH ₂) ₄ –		4c (79)	5c (>95)
<i>p</i> -tolyl	–(CH ₂) ₅ –		4d (67)	5d (>95)
<i>p</i> -tolyl	Ph	Ph	4e (82)	5e (>95)
Ph	Ph	Ph	4f (60)	5f (>95)
<i>p</i> -tolyl	Me	H	4g (84) ^b	5g (>95)
<i>p</i> -tolyl	Ph	H	4h (94) ^c	5h (>95)
Ph	Ph	H	4i (95) ^d	5i (>95)

^a Isolated yield. ^b Diastereomeric ratio 51/49 by GC analysis. ^c Diastereomeric ratio 54/46 by GC analysis. ^d Diastereomeric ratio 67/33 by ¹H NMR analysis.

whose structure was established on the basis of spectroscopic evidence (IR, ¹H and ¹³C NMR). In all cases, in the FT-IR spectrum we could see no C–N double bond stretching of the oxazoline ring (typically at 1660 cm⁻¹) and in the ¹³C NMR a resonance at ca. 118 ppm, characteristic of an sp³ heterosubstituted carbon atom, was observed instead of the Csp² resonance of the C–N double bond of the oxazoline ring (ca. 162 ppm).

The formation of spirocyclic compounds **4a–f** could likely be explained with the nucleophilic addition of the intermediate alkoxide on the C–N double bond of the oxazoline ring. Such a cyclization took place diastereoselectively, furnishing just one diastereomer. In a NOESY phase-sensitive experiment carried out on the spirocyclic compound **4c**, a dipolar interaction between the NH group of the oxazolidine ring and the methyl group of the oxirane ring testified a spatial proximity relationship between the above groups. This seems to indicate that the intermediate alkoxide, originated by the stereospecific reaction of **2a,b** with the ketone, attacks just one of the diastereotopic faces (the *re* one) of the oxazoline moiety (Scheme 3).

It was nice to note that spirocyclic compounds **4a–f** could quantitatively be converted into epoxylactones **5a–f** upon treatment with 2% w/w oxalic acid (Table 1).

(8) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, 55, 4835–4840.

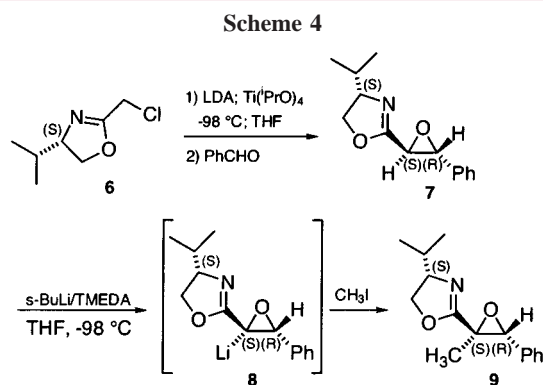
(9) Lertvorachon, J.; Thebtaranonth, Y.; Thongpanchang, T.; Thongyoo, P. *J. Org. Chem.* **2001**, 66, 4692–4694.

(10) Generation and stereospecific alkylation of an optically active α -trifluoromethyl oxiranyl anion has also been recently reported: Yamauchi, Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, 4, 173–176.

The reaction of **2a,b** with acetaldehyde and benzaldehyde furnished a mixture of two spirocyclic diastereomers **4g–i** (dr 51/49, 54/46, 67/33, respectively), which could be separated by flash chromatography and spectroscopically characterized. Probably, the coupling reaction of **2a,b** with aldehydes is not stereoselective with reference to the newly created stereogenic center, and as in the case of the addition of **2a,b** to ketones, the intermediate alkoxide attacks exclusively the *re* face of the oxazoline ring thus generating only two diastereomers. Deblocking of the masked carbonyl function of **4g–i** with oxalic acid yielded diastereomeric epoxy lactones **5g–i**.

The present oxazolinyloxiranyl anion based methodology to epoxy lactones has been successfully extended to the preparation of optically pure α,β -epoxy- γ -butyrolactones.

Optically pure (*S,S,R*)-oxazolinyloxirane **9** (dr > 99:1 by ^1H NMR) (Scheme 4) was prepared by the coupling



reaction of the titanium azaenolate of (4*S*)-4-isopropyl-2-chloromethyl-2-oxazoline¹¹ **6** with PhCHO, as similarly reported for other chiral nonracemic α -chloroalkyl-2-oxazolines.¹²

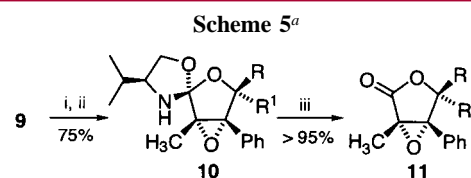
Compound **6** was first lithiated, transmetalated with Ti(*i*-PrO)₄, and then reacted with benzaldehyde to furnish (*S,S,R*)-epoxide **7** (dr *trans/cis* 90:10; er *trans* > 99:1), whose stereochemistry was assigned on the basis of ^1H and ^{13}C NMR data and unequivocally confirmed by crystallographic X-ray analysis.¹³ Treatment of **7** with *s*-BuLi/TMEDA in THF at $-98\text{ }^\circ\text{C}$ afforded oxiranyl lithium **8**, which proved to be configurationally stable and could be trapped with CH₃I to give, with complete retention of configuration, trisubstituted epoxide **9** (Scheme 4).

Lithiation of **9** and reaction with benzophenone gave spirocyclic compound **10a** in good yield (only one diaste-

(11) Florio, S.; Capriati, V.; Luisi, R. *Eur. J. Org. Chem.* **2001**, 2035–2038.

(12) Florio, S.; Capriati, V.; Luisi, R.; Abboto, A.; Pippel, D. J. *Tetrahedron* **2001**, *57*, 6775–6786.

(13) Crystallographic data for compound **7** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-179557). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: (int.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. ORTEP view and CIF file for compound **7** have been also reported as Supporting Information.



^a (i) *s*-BuLi/TMEDA, Et₂O, $-98\text{ }^\circ\text{C}$; (ii) RR¹CO; (iii) 2% w/w aq (COOH)₂.

reomer) that was quantitatively hydrolyzed with oxalic acid to the corresponding epoxy lactone **11a** with very good er value (Scheme 5, Table 2).

Table 2. Optically Active Spirocyclic Compounds **10a–c** and Epoxy lactones **11a–c**

R	R ¹	spirocyclic compound	epoxy lactone ^a	er
Ph	Ph	10a (70) ^a	11a (>95)	98:2 ^d
H	Ph	10b (50) ^b	11b (>95)	>99:1 ^e
Ph	H	10c (25) ^c	11c (>95)	>99:1 ^e

^a Isolated yields (%). ^b Major isomer; yield determined by ^1H NMR. ^c Minor isomer; yield determined by ^1H NMR. ^d Enantiomeric ratio by GC analysis on chiraldex B-DM capillary column. ^e Enantiomeric ratio by HPLC with OD-H column.

In the reaction of lithiated **9** with benzaldehyde, a diastereomeric mixture (67/33 ratio) of the two spirocyclic compounds **10b,c** was detected by ^1H NMR. Their purification by flash chromatography led straightforwardly to a mixture of the corresponding diastereomeric epoxy lactones **11b,c**. The latter could be quantitatively separated by preparative HPLC and showed excellent er values (Table 2).¹⁴

In conclusion, we have shown how useful α,β -epoxy- γ -butyrolactones can be conveniently prepared by combining the chemistry of lithiated oxazolinyloxiranes with that of the oxazoline system.

(14) The configuration at the new stereogenic center of **11b** and **11c** was determined by a careful inspection of the ^1H NMR chemical shifts. Taking into consideration that in the most stable conformation of styrene oxide derivatives a phenyl ring sets perpendicular to the plane of the oxirane ring even when steric factors are at their minimum (Lazzeretti, P.; Moretti, Z.; Taddei, F.; Torre, G. *Org. Magn. Reson.* **1973**, *5*, 385–389), the pronounced shielding effect observed for the two aromatic ortho ring protons ($\Delta\delta = \text{ca. } 0.4\text{ ppm}$ for both) of **11c**, should testify in favor of a *cis* relationship of the two aromatic rings so that the above-mentioned protons (probably those belonging to the γ -lactone phenyl ring) are forced to fall in the anisotropic shielding ring current of the oxirane phenyl ring. Moreover, the strong upfield shift observed ($\Delta\delta = \text{ca. } 0.2\text{ ppm}$) for the γ -lactone proton could be analogously explained taking into account the well-known anisotropic shielding effect exhibited by the oxirane ring on the protons lying above and below its plane, especially when the reference molecular system is rigid (Hassner, A. In *The Chemistry of Heterocyclic Compounds: Small Ring Heterocycles Part 3*; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons: 1985; pp 10–11). The latter consideration also could be applied for the stereochemistry assignment to the diastereomeric spirocyclic compounds **4g** (obtained from the reaction with CH₃-CHO) as well as of the corresponding epoxy lactones **4g**.

Acknowledgment. This work was carried out under the framework of the National Project “Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni” supported by the Ministero dell’Università e della Ricerca Scientifica e Tecnologica (MURST, Rome) and by the University of Bari and CNR (Rome). The authors are also indebted to Prof. Marcel Pierrot of the Centre Scientifique Saint-Jérôme, Marseille, France, for performing X-ray analysis of compound **7**.

Supporting Information Available: Full experimental details and characterization data (¹H and ¹³C NMR, physical data) for compounds **3a–d**, **4a–i**, **5a–i**, **7**, **9**, **10a**, **11a–c**; ORTEP view (Fig. S1) and CIF file for compound **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL025781I