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

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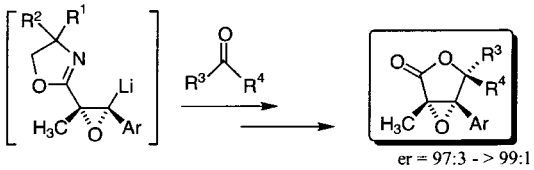
ABSTRACT

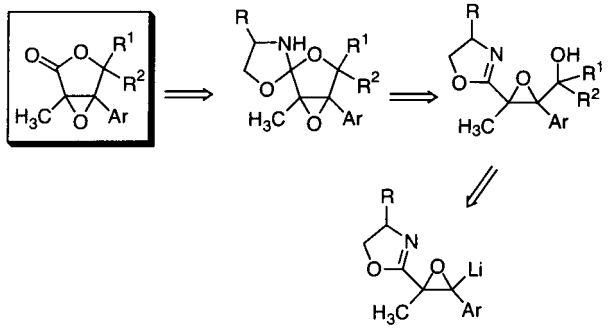


Stereospecific β-lithiation of β-aryl-substituted oxazolinyloxiranes is described. The trapping reaction of such reactive intermediates with carbonyl compounds gave α,β-epoxy-γ-butyrolactones after deblocking of the oxazoline moiety. This methodology has been also extended to the synthesis of optically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

α,β-Epoxylactones 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-SYS5,[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 anions[4] 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



Our work started with the preparation of the needed precursors. (1*R**,2*R**)- and (1*R**,2*S**)-1-methyl-1-oxazolinyloxiranes **1a**−**d**[5] were prepared by the Darzens reaction

(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.

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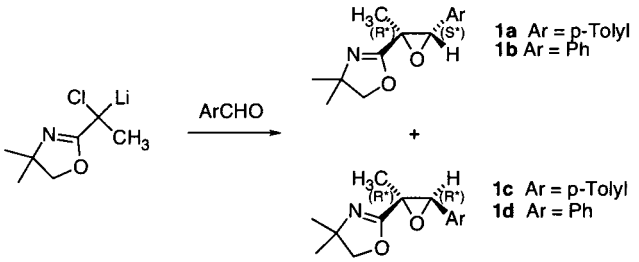
of lithiated 2-(1-chloroethyl)-2-oxazoline, as reported (Scheme 2).[6] Once separated by column chromatography, the relative

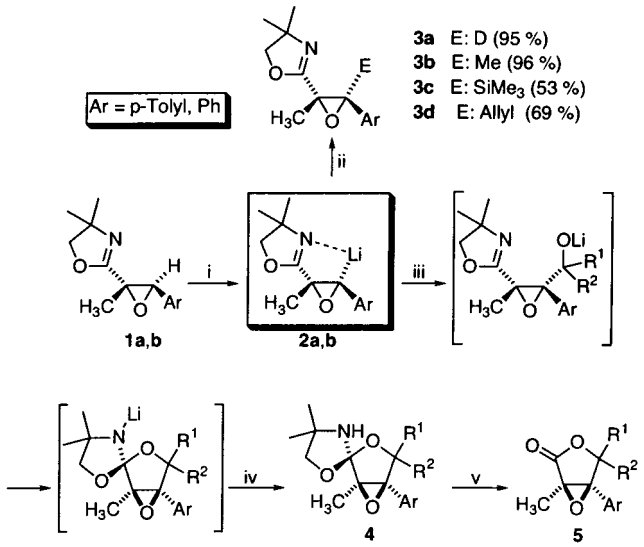
Scheme 2



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

Lithiation of epoxides **1a**,**b** (*s*-BuLi/TMEDA, Et_2O, −98 °C) produced oxiranyllithiums **2a**,**b**, which proved to be stable at low temperature for several hours. Trapping of **2a** (R = *p*-tolyl) with electrophiles (D_2O, MeI, Me_3SiCl, and allyl chloride) afforded tetrasubstituted epoxides **3a**−**d** in good to excellent yields upon warming to room temperature and conventional workup (Scheme 3).

Scheme 3[a]



[a] (i) *s*-BuLi/TMEDA, Et_2O, −98 °C; (ii) E^+; (iii) R^1R^2CO; (iv) H^+; (v) 2% w/w aq $(COOH)_2$.

The stabilizing assistance to oxiranyllithiums **2a**,**b** is likely provided by both the oxazolinyl and the aryl groups. Indeed, Eisch and Galle's work on lithiated styreneoxides had amply 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]
p-tolyl	Me	Me	**4a** (60)	**5a** (>95)
p-tolyl	Et	Et	**4b** (60)	**5b** (>95)
p-tolyl	$-(CH_2)_4-$		**4c** (79)	**5c** (>95)
p-tolyl	$-(CH_2)_5-$		**4d** (67)	**5d** (>95)
p-tolyl	Ph	Ph	**4e** (82)	**5e** (>95)
Ph	Ph	Ph	**4f** (60)	**5f** (>95)
p-tolyl	Me	H	**4g** (84)[b]	**5g** (>95)
p-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 ^{13}C 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 ^{13}C NMR a resonance at ca. 118 ppm, characteristic of an sp^3 heterosubstituted carbon atom, was observed instead of the Csp^2 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).

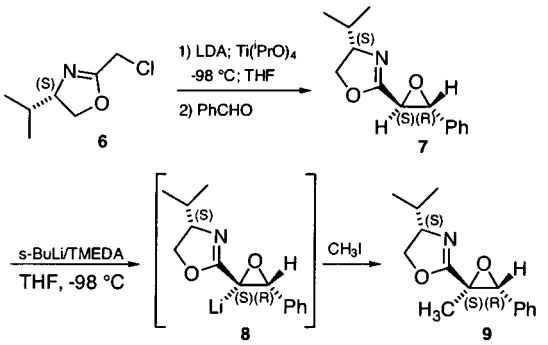
(6) Capriati, V.; Degennaro, L.; Florio S.; Luisi, R.; Tralli, C.; Troisi, L. *Synthesis* **2001**, *15*, 2299−2306.
(7) Kingsbury, C. A.; Durham, D. L.; Hutton, R. *J. Org. Chem.* **1978**, *43*, 4696−4700.
(8) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835−4840.
(9) Lertvorachon, J.; 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 epoxylactones **5g**−**i**.

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

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

Scheme 4

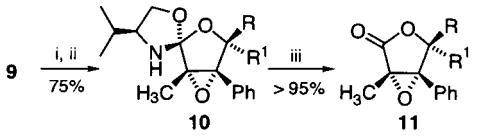


reaction of the titanium azaenolate of (4*S*)-4-isopropyl-2-chloromethyl-2-oxazoline[11] **6** with PhCHO, as similarly reported for other chiral nonracemic α-chloroalkyl-2-oxazolines.[12]

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 ^{1}H 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 °C afforded oxiranyllithium **8**, which proved to be configurationally stable and could be trapped with CH_3I 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 diastereomer) that was quantitatively hydrolyzed with oxalic acid to the corresponding epoxylactone **11a** with very good er value (Scheme 5, Table 2).

Scheme 5[a]



[a] (i) *s*-BuLi/TMEDA, Et_2O, −98 °C; (ii) RR^1CO; (iii) 2% w/w aq $(COOH)_2$.

Table 2. Optically Active Spirocyclic Compounds **10a**−**c** and Epoxylactones **11a**−**c**

R	R^1	spirocyclic compound	epoxylactone[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 ^{1}H NMR. [c] Minor isomer; yield determined by ^{1}H 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 ^{1}H NMR. Their purification by flash chromatography led straightforwardly to a mixture of the corresponding diastereomeric epoxylactones **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.

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

(12) Florio, S.; Capriati, V.; Luisi, R.; Abbotto, 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.

(14) The configuration at the new stereogenic center of **11b** and **11c** was determined by a careful inspection of the ^{1}H 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 ($\Delta\delta$ = ca. 0.4 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 ($\Delta\delta$ = ca. 0.2 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, expecially 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 CH_3-CHO) as well as of the corresponding epoxylactones **4g**.

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Supporting Information Available: Full experimental details and characterization data (^{1}H and ^{13}C 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.

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