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Isomerization of *E*-α,β-epoxyamides to *Z*-α,β-epoxyamides and synthetic applications based on regio- and stereoselective oxirane ring openings

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This paper is dedicated to the memories of Professor López Herrera and J. M. Sánchez Porras, recently deceased, for their important contributions on this research

Abstract—The regioselective opening reaction of 2,3-epoxyamides with various nucleophiles offers a variety of β-hydroxyamides with diverse synthetic utility depending on the introduced nucleophile. Due to the exclusive stereoselectivity in the formation of *trans* epoxyamides in reactions of aldehydes with stabilized sulfur ylides, we studied the isomerization of *trans* epoxyamides into the *cis* isomers with the objective of obtaining the corresponding *syn* opening products, which together with the *anti* isomers represent a variety of enantiomerically pure building blocks.

The significant role of epoxides in organic chemistry is clearly proven by the intense and continuous flurry of synthetic activity in which the oxirane ring plays an essential role in synthesis,[1] constituting one of the most valuable classes of functional groups in organic synthesis.[2]

The stereoselective synthesis of epoxyamides by reaction of chiral aldehydes with stabilized sulfur ylides has occupied a central position in our research during the last years,[3] finding interesting synthetic applications in the field of carbohydrates.[4] In particular, the high stereofacial selectivity showed by 2,3-*O*-isopropylidene-D-glyceraldehyde **7** in its reactions with sulfur ylides represents an important synthetic feature with numerous applications in the synthesis of natural products.[5] Particularly, the regioselective opening with nucleophiles at C-2 offers an extensive range of synthetic possibilities via reactions with nitrogen nucleophiles,[6] halides,[7] sulfides,[8] selenides[9] and organometallics.[5a,10] In all cases, the *anti* relative stereochemistry of the resulting ring opened products is imposed by the *trans*-geometry of the starting epoxyamide. With the purpose of broadening the synthetic utility of epoxyamides, we decided to investigate a way of obtaining the corresponding *cis*-epoxyamides (compound **3**) from the *trans* isomer **1**, in order to access to the *syn*-ring opened products of type **4** (Scheme 1).

Our first approach directed towards the execution of this objective was based on the chemical properties of hydroxyl selenides type **2i**. Thus, oxidation of this selenide to the corresponding selenoxide (intermediate **A**) (Scheme 2), in the presence of a base,[11] resulted in the formation of the starting epoxyamide **1**, through the intermediate **B**, which evolves to **1** by the intramolecular attack of the emerging oxyanion with the concomitant formation of the epoxide. In a similar way, the phenylselenide **4i** should undergo, through the same synthetic pathway, to the *cis*-epoxyamide **3**. We initially tried the epimerization of **2i**, to obtain the *syn* hydroxyl selenide **4i**, through the silylether **5**, by treatment with base. However, after scanning a wide variety of basic conditions, that included reactions with LDA, sodium

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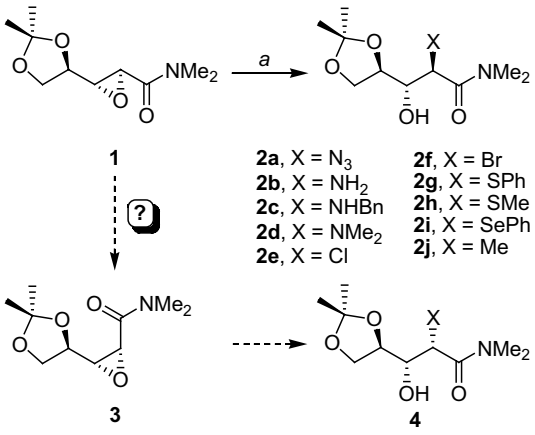
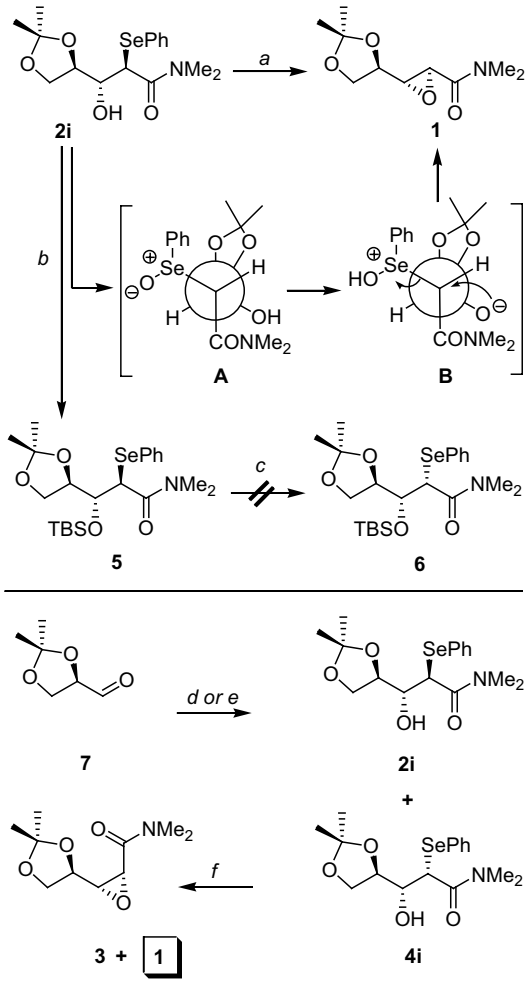


Scheme 1. Reagents and conditions: (a) (i) 12.0 equiv NaN_3, 5.0 equiv AcOH, DMF, 100 °C, 12 h, 70% for **2a**, (ii) 5.0 equiv NH_3, EtOH, 25 °C, 4 days, 97% for **2b**, (iii) 5.0 equiv H_2NBn, H_2O, reflux, 5 h, 90% for **2c**, (iv) 5.0 equiv $HNMe_2$, H_2O, 25 °C, 2 h, 96% for **2d**, (v) 2.0 equiv LiCl, 2.0 equiv AcOH, THF, reflux, 6 h, 70% for **2e**, (vi) 5.0 equiv NaBr, Amberlyst 15, acetone, −30 °C, 24 h, 87% for **2f**, (vii) 3.0 equiv NaSPh, 3.0 equiv AcOH, DMF, 25 °C, 24 h, 82% for **2g**, (viii) 3.0 equiv NaSMe, 3.0 equiv AcOH, DMF, 25 °C, 24 h, 75% for **2h**, (ix) 2.0 equiv Ph_2Se_2, 2.0 equiv $NaBH_4$, EtOH, 25 °C, 2 h, 75% for **2i**, (x) 2.0 equiv Me_2CuLi, Et_2O, 0 °C, 1 h, 90% for **2j**.

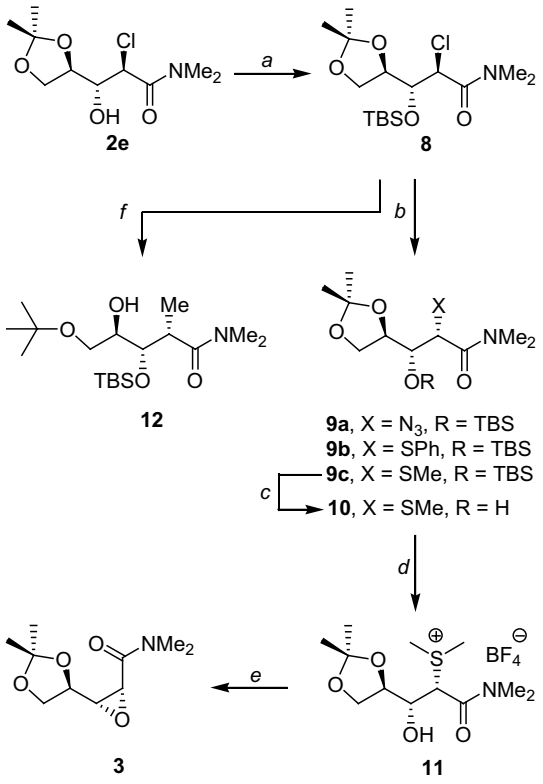
hydride, dicyclohexyliodoborane and sodium methoxide, the results were quite disappointing with the recovery of starting material. Alongside to this study, the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde **7** with the lithium enolate of *N*,*N*-dimethyl 2-phenylselenoacetamide[12] provided us a 2:1 mixture of stereoisomers **2i**–**4i**. Contrastingly, when this reaction was carried out with titanium tetrachloride and triethylamine as the enolization system, the proportion of the *syn* adduct was slightly increased, providing a 2:3 mixture of stereoisomers **2i**–**4i** in 80% yield. The inseparable mixture of stereoisomers was then subjected to the action of *m*-chloroperbenzoic acid, in the presence of potassium carbonate, to obtain the corresponding mixture of *E*–*Z* epoxyamides **1**–**3** in a 2:3 ratio in a poor yield of 45% (Scheme 2).



Scheme 2. Reagents and conditions: (a) 1.5 equiv *m*CPBA, 1.5 equiv K_2CO_3, MeOH, −15 °C, 15 min, 70%; (b) 1.5 equiv TBSOTf, 2.0 equiv 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 90%; (c) see text for conditions; (d) 1.2 equiv $PhSeCH_2CONMe_2$, 1.2 equiv LDA, THF, −78 °C → 0 °C, 40 min; then 1.0 equiv **7**, THF, −78 °C, 1 h, 85% of a 2:1 mixture of **2i**–**4i**; (e) 1.2 equiv $PhSeCH_2CONMe_2$, 1.2 equiv $TiCl_4$, 1.2 equiv Et_3N, CH_2Cl_2, −78 °C, 0.5 h; then 1.0 equiv **7**, CH_2Cl_2, −78 °C, 1 h, 80% of a 2:3 mixture of **2i**–**4i**; (f) 1.5 equiv *m*CPBA, 1.5 equiv K_2CO_3, MeOH, −15 °C, 15 min, 45% of a 2:3 mixture of **1**–**3**.

Our assessment of the interesting result obtained in the aldolic reaction and subsequent transformation of the hydroxyl selenides **2i** and **4i** to epoxides **1** and **3**, respectively, was that it was not satisfactory for synthetic purposes. Consequently, we decided to explore a second strategy based on a nucleophilic attack of the chloride **8**, obtained by silylation of chlorohydrine **2e**, that would lead to the desired *syn* isomers.[13] In fact, as it is depicted in Scheme 3, the *syn* products azide **9a**, phenylsulfide **9b** and methylsulfide **9c** were obtained without difficulty by treatment of **8** with the corresponding nucleophiles in DMF at reflux. Similarly, the displacement of chloride by a selenide was attempted and, unfortunately, in this case, the reactions did not yield the desired product. On the other hand, in a related strategy to the selenides, the sulfides could be activated and transformed into good leaving groups, amenable to an intramolecular displacement by the oxy anion, via formation of the corresponding sulfonium salt.[14] Thus, after silyl ether cleavage of **9** with TBAF to obtain alcohol **10**, the reaction of this compound with the Merwein's salt, yielded quantitatively the sulfonium salt **11**. Once again, the attempted cyclization of **11** by treatment with base resulted in a highly discouraging 30% yield of the targeted epoxyamide **3**. In contrast to the displacement reactions described before, the nucleophilic substitution of chloride by alkyl groups, by treatment with organometallics, required harsh conditions (e.g., Me_3Al, reflux). Under these conditions, in addition to the nucleophilic substitution, the reductive cleavage of the acetal occurred to afford *tert*-butylether **12** as the sole product in a 70% yield.

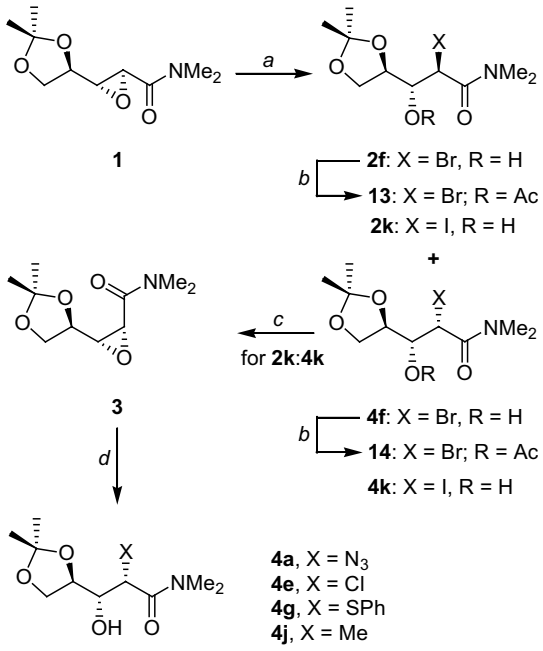
Our continuous efforts in our laboratories devoted to the epoxide opening reactions, led us to the fortuitous observation that the reaction of epoxide **1** with lithium bromide, under neutral conditions, afforded the formation of a 1:2 inseparable mixture of bromohydrines **2f**–**4f**, which were separated and identified as their acetates



Scheme 3. Reagents and conditions: (a) 1.5 equiv TBSOTf, 2.0 equiv 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 78%; (b) (i) 10.0 equiv NaN_3, DMF, reflux, 1 h, 95% for **9a**, (ii) 10.0 equiv NaSPh, DMF, reflux, 5 h, 75% for **9b**, (iii) 10.0 equiv NaSMe, DMF, reflux, 1 h, 73% for **9c**; (c) 1.2 equiv TBAF, THF, 25 °C, 1 h, 70%; (d) 1.5 equiv Me_3OBF_4, MeCN, 0 °C, 1 h, quantitative; (e) 1.1 equiv *t*BuOK, CH_2Cl_2, 0 °C, 0.5 h, less than 30%; (f) 3.0 equiv $AlMe_3$, toluene, reflux, 8 h, 70%.

13 and **14**, respectively. This unexpected and, in principle, promising result was ascribed to a thermodynamic equilibrium initiated with bromohydrine **2f** that suffered a S_N2 substitution by a new bromide anion with the consequent inversion of the configuration at C-2 position, with a resulting retention of configuration at this position.[15] In contrast to the chlorohydrine **2e**, the higher reactivity of the C–Br bond combined with the enhanced nucleophilicity of the bromide anion explain this observation. By the same reasoning, the iodohydrine **2k** should present even a larger tendency to this epimerization process with respect to the bromo derivative **2f**. Thus, treatment of epoxyamide **1** with lithium iodide, under the same conditions as before, led to a 1:9 mixture of iodohydrines **2k** and **4k**. Subsequent treatment of this inseparable mixture with sodium methoxide provided the epoxyamides **1** and **3**, which were separated by flash column chromatography, providing pure *cis*-epoxyamide **3** in a 70% overall yield from *trans*-epoxyamide **1**. Finally, a series of oxirane ring opening reactions of **3** were carried out to afford the corresponding *syn* opened products (**4a**, **4e**, **4g**, **4j**) in good yields as indicated in Scheme 4.

In conclusion, the synthetic availability of either *trans* or *cis* epoxyamides offers an extense battery of synthetic opportunities via regioselective opening of the epoxide



Scheme 4. Reagents and conditions: (a) (i) 2.0 equiv LiBr, 0.5 equiv AcOH, THF, reflux, 8 h, 80% of a 1:2 mixture of **2e**–**4e**, (ii) 2.0 equiv LiI, 0.5 equiv AcOH, THF, reflux, 8 h, 80% of a 1:9 mixture of **2e**–**4e**; (b) 5.0 equiv Ac_2O, pyridine, 25 °C, 12 h, 95%; (c) 0.2 equiv NaOMe, MeOH, 25 °C, 0.5 h, 98%; (d) (i) 12.0 equiv NaN_3, 5.0 equiv AcOH, DMF, 100 °C, 16 h, 61% for **4a**, (ii) 2.0 equiv LiCl, 2.0 equiv AcOH, THF, reflux, 96 h, 65% for **4e**, (iii) 3.0 equiv NaSPh, 3.0 equiv AcOH, DMF, 25 °C, 24 h, 55% for **4g**, (iv) 2.0 equiv Me_2CuLi, Et_2O, 0 °C, 8 h, 67% for **4j**.

by different nucleophiles, to obtain either *anti* or *syn* opening products. These products represent useful building blocks for the synthesis of diverse natural products. In this sense, we have described the synthesis of 2-amine-3-hydroxy, 2-sulfides-3-hydroxy, 2-halohydrines and 2-alkyl-3-hydroxy amides, which occur extensively as structural motifs in natural products.

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References and notes

1. (a) Gorzynski-Smith, J. *Synthesis* **1984**, 629–656; (b) Rao, A. S.; Paknikar, S. K.; Kirtane, J. K. *Tetrahedron* **1983**, *36*, 2323–2367; (c) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67–80; (d) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63; (e) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437; (f) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.

2. (a) Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1990; Vol. 6, pp 88–93; (b) Birkinshaw, T. N. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Roberts, S. M., Eds.; Pergamon: Oxford, 1990; Vol. 1, pp 204–220.
3. (a) López-Herrera, F. J.; Sarabia-García, F. R.; Pino-González, M. S. *Recent Res. Dev. Org. Chem.* **2000**, *4*, 465–490; (b) Valpuesta Fernández, M.; Durante Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1990**, *46*, 7911–7922; (c) Valpuesta Fernández, M.; Durante Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1993**, *49*, 9547–9560; (d) López Herrera, F. J.; Pino González, M. S.; Sarabia García, F.; Heras López, A.; Ortega Alcántara, J. J.; Pedraza Cebrián, M. G. *Tetrahedron: Asymmetry* **1996**, *7*, 2065–2071.
4. (a) López Herrera, F. J.; Heras López, A.; Pino González, M. S.; Sarabia García, F. *J. Org. Chem.* **1996**, *61*, 8839–8848; (b) López Herrera, F. J.; Sarabia García, F.; Heras López, A.; Pino González, M. S. *J. Org. Chem.* **1997**, *62*, 6056–6059; (c) Heras López, A.; Pino González, M. S.; Sarabia García, F.; López Herrera, F. J. *J. Org. Chem.* **1998**, *63*, 9630–9634; (d) Pino González, M. S.; Assiego, C.; López Herrera, F. J. *Tetrahedron Lett.* **2003**, *44*, 8353–8356; (e) Assiego, C.; Pino González, M. S.; López Herrera, F. J. *Tetrahedron Lett.* **2004**, *45*, 2611–2613.
5. (a) López Herrera, F. J.; Sarabia García, F.; Pedraza Cebrián, M. G.; Pino González, M. S. *Tetrahedron Lett.* **1999**, *40*, 1379–1380; (b) Sarabia, F.; Martín-Ortiz, L.; López-Herrera, F. J. *Org. Lett.* **2003**, *5*, 3927–3930.
6. (a) Valpuesta-Fernández, M.; Durante Lanes, P.; López Herrera, F. J. *Tetrahedron Lett.* **1995**, *36*, 4681–4684; (b) Azzena, F.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron* **1995**, *51*, 13409–13422; (c) Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. J. *Tetrahedron: Asymmetry* **2000**, *11*, 4509–4519.
7. (a) Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401–13408; (b) Righi, G.; Pescatore, G.; Bonadies, F.; Bonini, C. *Tetrahedron* **2001**, *57*, 5649–5656; (c) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4719–4722.
8. (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560; (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696–5704; (c) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560–1563; (d) Deng, B.-L.; Demillequand, M.; Laurent, M.; Touillaux, R.; Belmans, M.; Kemps, L.; Cérésiat, M.; Marchand-Brynaert, J. *Tetrahedron* **2000**, *56*, 3209–3217; (e) Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* **2001**, *66*, 5388–5394; (f) Cossy, J.; Bellosta, V.; Hamoir, C.; Desmurs, J.-R. *Tetrahedron Lett.* **2002**, *43*, 7083–7086; (g) Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9964–9965.
9. The oxirane opening of epoxyamide **1** was performed under similar conditions than reported by Gruttadauria, M.; Aprile, C.; D'Anna, F.; Lo Meo, P.; Riela, S.; Noto, R. *Tetrahedron* **2001**, *57*, 6815–6822.
10. (a) Sarabia García, F.; Pedraza Cebrián, G. M.; Heras López, A.; López Herrera, F. J. *Tetrahedron* **1998**, *54*, 6867–6896; (b) Schneider, C.; Brauner, J. *Tetrahedron Lett.* **2000**, *41*, 3043–3046; (c) Concellón, J. M.; Bardales, E. *Org. Lett.* **2003**, *5*, 4783–4785.
11. Demarcus, M.; Ganadu, M. L.; Mura, G. M.; Porcheddu, A.; Quaranta, L.; Reginato, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 697–706.
12. Nakamura, S.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Toru, T. *Tetrahedron* **2001**, *57*, 6703–6711.
13. (a) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557–3560; (b) Righi, G.; D'Achille, C.; Pescatore, G.; Bonini, C. *Tetrahedron Lett.* **2003**, *44*, 6999–7002.
14. Aggarwal, V.; Charmant, J.; Ciampi, C.; Hornby, J.; O'Brien, C.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159–3166.
15. Cardellach, J.; Font, J.; Ortuño, R. M. *Tetrahedron Lett.* **1985**, *26*, 2815–2816.