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Synthesis of Different Chiral Amino γ-Butyrolactones and Amino γ-Butenolides

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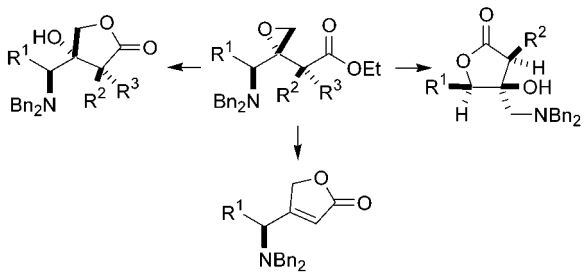
ABSTRACT

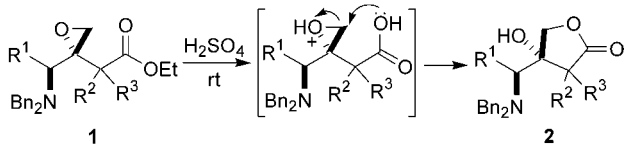


Different transformations of chiral epoxy esters 1 afford two different amino γ-butyrolactones 2 and 6, and amino γ-butenolides 8, by different nucleophilic opening–closing processes.

γ-Butyrolactones and butenolides form an important class of compounds which appear as substructures in many natural products, and they have been also employed as key intermediates for the synthesis of a wide range of bioactive compounds. In fact, many natural products have γ-butyrolactone[1] and butenolide[2] skeletons, and γ-butyrolactones have been used to prepare pharmacologically active compounds.[3]

Previously, we described the synthesis of chiral 3-(1′-aminoalkyl)-3,4-epoxy esters **1** (Scheme 1) by addition of

Scheme 1. Synthesis of β-Hydroxy-γ-butyrolactones **2**



ester enolates to chiral 1-aminoalkyl chloromethyl ketones.[4] The presence of different reactive functions in compounds **1**, such as an epoxide ring and an ester function, make epoxy esters **1** interesting as building blocks in organic synthesis. Thus, we report different transformations of chiral epoxy esters **1**, affording two different amino γ-butyrolactones **2** and **6**, and amino γ-butenolides **8**, by different nucleophilic opening−closing processes.

(1) (a) Grieco, P. A. *Synthesis* **1975**, 67−82. (b) Demir, A. S.; Gross, R. S.; Dunlap, N. K.; Bashir-Hashemi, A.; Watt, D. S. *Tetrahedron Lett.* **1986**, *27*, 5567−5570. (c) Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, *116*, 5473−5474. (d) Grieco, P. A.; Piñeiro-Núñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606−7615.

(2) Renard, M.; Ghosez, L. A. *Tetrahedron* **2001**, *57*, 2597−2608.

(3) (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1975; Vol. 1, pp 249−250. (b) Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aus. J. Chem.* **1981**, *34*, 383−395. (c) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771−2773. (d) Chamberlain, R.; Koch, C. *J. Org. Chem.* **1993**, *58*, 2725−2737 and references therein. (e) Lee, K.; Choi, Y.; Gullen, S.; Schlueter-Wirtz, S.; Schinazi, R. F.; Cheng, Y. C.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 1320−1328. (f) Rudler, H.; Parlier, A.; Certal, V.; Vaissermann, J. *Angew. Chem., Int. Ed.* **2000**, *19*, 3417−3419. (g) Han, X.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2543−2544. (h) García, C.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 1420−1428.

(4) Concellón, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1299.

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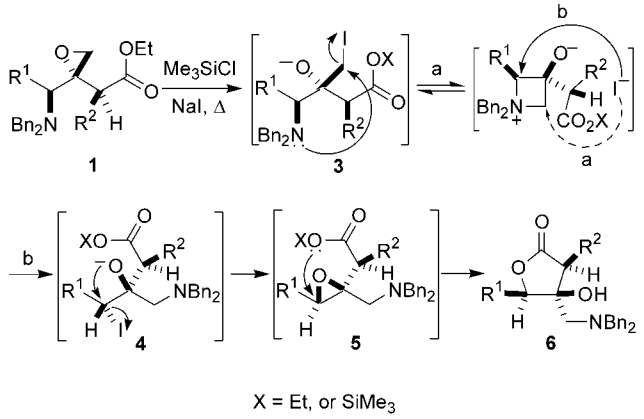
Starting with the hydrolysis of the ester function in epoxy esters **1**, we prepared two different β-hydroxy-γ-butyrolactones **2** (Scheme 1) and **6** (Scheme 2), depending on the

Scheme 2. Synthesis of β-Hydroxy-γ-butyrolactones **6**



hydrolysis conditions. Thus, the hydrolysis of **1** by sulfuric acid in dichloromethane at room temperature led to lactone **2** in high yields (Scheme 1 and Table 1, entries 1−4).[5] After

Table 1. Transformations of Epoxy Esters **1**

entry	product	R^1	R^2	R^3	yield (%)[a]
1	**2a**	methyl	H	H	85
2	**2b**	isobutyl	H	H	80
3	**2c**	benzyl	H	H	81
4	**2d**	isobutyl	methyl	methyl	85
5	**6a**	methyl	H		60
6	**6b**	isobutyl	H		60
7	**6c**	benzyl	H		62
8	**6d**[b]	methyl	benzyl		58
9	**8a**	methyl			82
10	**8b**	isobutyl			79
11	**8c**	benzyl			78

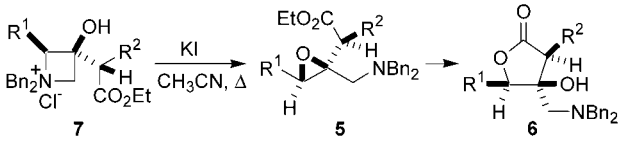
[a] Isolated yield based on the starting epoxy ester **1**. [b] This product was prepared from the corresponding azetidinium salt **7** (see text).

hydrolysis of the ester function to an acid, the epoxide suffers an intramolecular ring opening by carboxylic acid at the less substituted carbon, affording hydroxy lactones **2**. The presence of α-substituents at the carbonyl position does not affect to the lactonization process (Table 1, entry 4).

On the other hand, the hydrolysis of the ester function in **1** by in situ generated trimethylsilyl iodide (by reaction of trimethylsilyl chloride and sodium iodide) in acetonitrile at reflux temperature[6] afforded lactone **6** (Scheme 2).[7] The epoxide ring is opened by the iodide at the less substituted carbon, and this iodohydrin suffers a heterocyclization under the reaction conditions, yielding an azetidinium salt.[8] This azetidinium salt undergoes a new ring opening by iodide at the C-2 (Scheme 2, path b), despite being the disfavored attack.[9] Thus, the expected position of attack (carbon 4) leads to the initial iodohydrin **3**, which would be in an equilibrium with the azetidinium salt (Scheme 2, path a). But, once the attack takes place on C-2, the obtained compound **4** undergoes a new closure, yielding the internal epoxide **5**. Then, an intramolecular ring opening of the epoxide with the carboxylate group at the most favored position led to β-hydroxy-γ-butyrolactones **6** in good yields (Table 1, entries 5−8). In this lactonization process, no α,α-disubstituted lactones **6** could be prepared since no formation of azetidinium salts has been observed in these cases.[4]

According to this mechanism, lactones **6** could also be prepared from the azetidinium salts **7** (Scheme 3), which

Scheme 3. Ring Opening of Azetidinium Salts **7**



are easily available by reaction of 1-aminoalkyl chloromethyl ketones with ester enolates.[4] In fact, treatment of the azetidinium salts **7** with KI in acetonitrile at reflux temperature led to the corresponding γ-butyrolactones **6** (Scheme 3). Moreover, product **6b** was isolated together with a small amount of the corresponding epoxide **5b**. Therefore, this reaction could support the proposed mechanism for the formation of **6**.

Configurational assignments of lactone **6** were established by NOESY experiments with compounds **6a**,**c**,**d**. The NOE effects observed in these experiments are shown in Figure 1. In the case of lactones **6a**,**c**, the observation of NOE interactions between H-4 and α-hydrogens of the amino group and the absence of NOE between R^1 and CH_2NBn$_2$ in all cases show the *cis* relative configuration for R^1 and hydroxyl groups. When compound **6d** was analyzed, NOE was seen between H-2, H-4, and CH_2NBn$_2$. Moreover, the

(5) **Representative procedure for the synthesis of 2:** H_2SO_4 (6 drops) was added to a stirred solution of **1** (0.5 mmol) in CH_2Cl_2 (1 mL) at room temperature. After stirring at the same temperature overnight, the reaction was washed with water (2 × 1 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography (silica gel, hexane:ethyl acetate = 5:1) provided pure compound **2**.

(6) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247−1251.

(7) **Representative procedure for the synthesis of 6:** A solution of the corresponding epoxy ester **1** (0.5 mmol), NaI (0.22 g, 1.5 mmol), and Me_3-SiCl (0.19 mL, 1.5 mmol) in acetonitrile (1 mL) was stirred at reflux temperature for 48 h. Then, the reaction was hydrolyzed and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with water (2 × 5 mL) and $Na_2S_2O_3$ (2 × 5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography (silica gel, hexane: ethyl acetate = 5:1) provided pure compound **6**.

(8) Formation of azetidinium salts starting from halohydrins has been also observed in similar substrates: (a) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *J. Org. Chem.* **1997**, *62*, 8902−8906. (b) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1997**, *62*, 5974−5977. (c) Reference 4.

(9) A similar opening−closing process has been observed in aminoiodohydrins previously: Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *Tetrahedron Lett.* **2000**, *62*, 1231−1234.

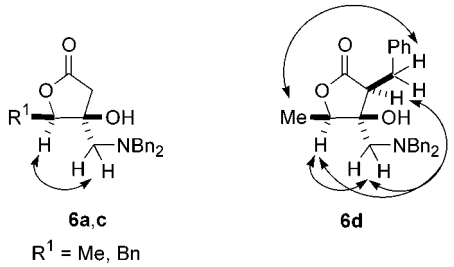


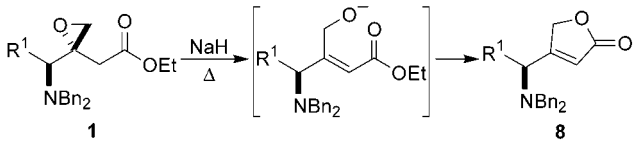
Figure 1. NOE effects observed in lactones **6**.

methyl group shows a cross-peak with CHCH_2Ph. Therefore, we can conclude that methyl, benzyl, and hydroxyl groups present a *cis* relationship. This relative stereochemistry is also in agreement with the proposed lactonization mechanism.

Finally, when epoxy esters **1** without α-substituents were treated with a base such as NaH, α,β-unsaturated lactones **8** were produced in high yields (Scheme 4 and Table 1, entries 9−11).[10] The base abstracts an α-hydrogen at the ester function and undergoes a spontaneous β-elimination and subsequent intramolecular transesterification, yielding compounds **8**. The intramolecular nucleophilic attack is too fast,

(10) **Representative procedure for the synthesis of 8:** To a stirred solution of the corresponding epoxy ester **1** (1 mmol) in THF (5 mL) was added NaH (0.07 g, 3.0 mmol) at room temperature. After stirring at reflux temperature for 30 min, the mixture was carefully quenched with water (5 mL) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography over silica gel (hexane:ethyl acetate = 15:1) provided pure compounds **8**.

Scheme 4. Synthesis of γ-Butenolides **8**



and the corresponding pure allylic alcohol intermediate could not be isolated, even at low temperature (−78 °C) and short reaction times (5 min).

In conclusion, we have described the synthesis of different chiral amino γ-butyrolactones and amino γ-butenolides from 3-(1′-aminoalkyl)-3,4-epoxy esters **1**, which are easily available, using simple methodologies.

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Supporting Information Available: Experimental procedure for the synthesis of compounds **6** from azetidinium salts, spectroscopic data for all new compounds **2**, **6**, and **8**, ^{13}C NMR spectra of **2**, **5b**, **6**, and **8**, and NOESY ^{1}H NMR spectra of **6a**,**c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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