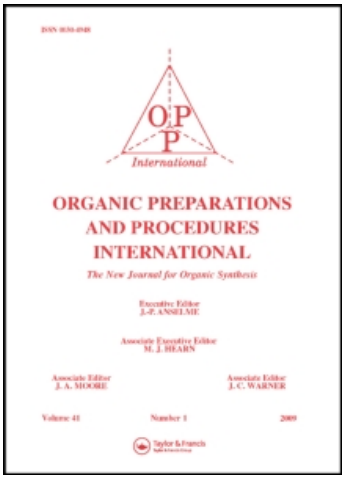

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REGIOSELECTIVE EPOXIDE RING-OPENING TO THE ENANTIOMERICALLY PURE α-HYDROXY ANALOGUE OF S-*tert*-BUTYL CYSTEINE

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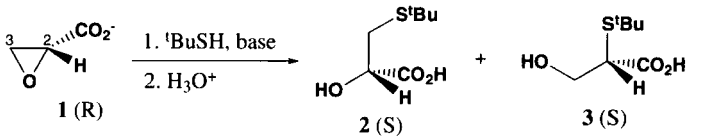
Our interest in α-hydroxy acids arose in connection with other work in which we required 2-hydroxy-3-mercapto propanoic acid in an optically active form. One usual method to prepare α-hydroxy acids is to convert α-amino acids by nitrous acid deamination.[1] However when initiated from cysteine, this reaction occurred with thiiran formation[2] and β-elimination, while with cystine, it yielded to many unwanted sulphur containing compounds,[3] resulting from oxidation side-reactions. Since it is known that thiolates open epoxides, we decided to investigate the reaction of potassium glycidate with *tert*-butyl thiol to lead to a S-protected hydroxy analogue of cysteine.



In a previous paper,[4] we showed that the ring-opening reaction of the epoxide (**1**) does in fact lead to two stereochemically pure alcohols: reaction at the β-carbon C-3 gives the desired α-hydroxy acid (**2**) whereas reaction at the α-carbon C-2 yields the β-hydroxy acid (**3**) with total inversion of configuration. Using *tert*-butyl mercaptan anion with potassium as counterion (*t*-BuSH/KOH, pH 10) gave two products (**2**) and (**3**) in a ratio of 85:15 respectively (Table, Entry 1). These two compounds have been isolated by preparative HPLC, allowing the targeted compound (**2**) to be fully characterized for the first time.[4] Unfortunately, this purification technique is rather expensive and not very convenient for the preparation of large quantities of compounds. The solution we proposed was to introduce the hydroxy analogue of cysteine into the targeted depsidipeptide as a mixture of (**2**) and (**3**) and to carry out the purification step afterwards, since a classical chromatography column of the crude coupling mixture proved to be efficient. Obviously, it would be preferable to suppress the formation of the unwanted compound (**3**) by increasing the regioselectivity of the ring-opening reaction.

In further investigations, we first attempted to improve this synthesis by the use of an acidic catalysis. Indeed, catalysis by Lewis acids provides different regioselectivity than attacks by thiolates.[5] While numerous examples can be found in recent literature concerning nitrogen nucleophiles,[6-10] few regard thiols.[11,12] Lanthanide's complexes have been reported to promote epoxide ring-opening,[9,11] but the stereoselectivity remains moderate. Accordingly, attempts using SmI_2 with tBuSH in dichloromethane or THF did not improve our results. Tetrabutylammoniumfluoride (TBAF) is also employed[12,13] because of its good solubility in most of the common organic solvents. With aliphatic thiols, high chemical yields are mentioned[12] but the selectivity seems to depend on the epoxide substituant and carboxylic epoxides have not been tested so far. In our hands, the reaction did not exhibit a better regioselectivity since both compounds **2** and **3** were obtained in proportion of 73:27, moreover in a very disappointing chemical yield of 49%.

We then considered again the basic epoxide ring-opening and we can now report that this approach is a viable and potentially useful route to stereo defined α-hydroxy analogues of cysteine as the S-protected version. Aiming to improve selectivity, we tested different mineral bases to find out the best counterion for the nucleophile. The nucleophilic attack of the racemic glycidate with MeSNa provided a mixture of (**2**) and (**3**) in racemic forms in a ratio of 64:36.[14] In a similar nucleophilic reaction on unsymmetrically substituted epoxide, the couple $C_6H_5CH_2SH$/NaOH has been shown to lead to two products in proportion of 80:20.[15] We observed the same percentage using *t*-BuSH/NaOH on our substrate (Table, Entry 2). Cesium has been claimed[16] to be a very good counter ion and thiols were reported to be deprotonated readily by Cs_2CO_3 or $CsHCO_3$. These conditions yielded the two compounds in an even less favorable ratio (Table, Entry 3). Lithium hydroxide was eventually used and proved to be far superior since a total selectivity (> 99%, determined by HPLC) was achieved, in a good chemical yield (82%) (Table, Entry 4). This total regioselectivity suppressed purification problems previously encountered.

TABLE. Nucleophilic ring-opening of glycidic acid with *tert*-butyl mercaptan

Entry	Base	Attack on C-3 **2**	Attack on C-2 **3**	Yield (%)
1	KOH	85	15	80
2	NaOH	80	20	84
3	$CsHCO_3$	70	30	78
4	LiOH	>99	<1	84

In summary, regioselective ring-opening at the β-carbon of glycidic acid to yield the targeted enantiomerically pure product (**2**) has been successfully achieved with *tert*-butyl mercaptan. While the use of Lewis acids (SmI_2 or TBAF) as catalyst does not improve the yield nor the regioselectivity, the nature of the base has been proved to be determinant. Indeed, with lithium hydroxide as base, regioselectivity has been improved until the point where the unwanted compound (**3**) cannot be detected by HPLC.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Brücker AC 250MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a JEOL DX 300 spectrometer. High-performance liquid chromatography (HPLC) was carried out with a Waters 600E system controller liquid chromatography equipped with a Waters 486 tunable absorbance detector and a Waters Baseline software.

Potassium Glycidate.- A solution of L-serine (21 g, 0.2 mol) and KBr (80 g, 0.7 mol) in 2M aqueous HBr (210 mL) was cooled to -15°. N_2 was bubbled through the solution and sodium nitrite (15.2 g, 0.22 mol, 1.1 equiv.) was added in small portions, waiting for the complete decoloration of the reaction mixture before each new addition. The solution was then allowed to warm to room temperature and stirred for 15 hours. Excess of nitrous oxide was removed by vigorous N_2 bubbling for 2 hours. The resulting pale green reaction mixture was extracted into ether (6 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford an oil (28.4 g, 85%) used in the next step without purification.

To a solution of this residue in anhydrous methanol (220 mL) cooled to -40° was added a solution of potassium hydroxide (19.6 g, 2 equiv.) in methanol (130 mL). After stirring for 1 hour at -40° then for another 15 hours at room temperature, half of the methanol was removed *in vacuo*. The potassium glycidate was then precipitated by addition of ether (700 mL), collected and dried. The salt was recrystallised from ethanol (10 mL per g of crude compound).

NMR 250 MHz (D_2O): δ 2.79 (dd, 1H, HCH, J_1 5.8Hz J_2 2.9Hz); 2.96 (dd, 1H, HCH, J_1 5.8Hz J_3 4.8Hz); 3.47 (dd, 1H, CH, J_2 2.9Hz J_3 4.8Hz). m.p. 150-152° ; α_D = +33 (c = 5, H_2O). α_D = +32 (c = 5, H_2O).[17]

Epoxide Ring-opening.- *tert*-Butyl mercaptan (24 mL, 211 mmol, 23.5 equiv.) and 2M LiOH (106 mL) were added to an aqueous solution of potassium glycidate (1.14 g, 9 mmol) and the reaction mixture was refluxed under stirring for 5 hours. The excess of thiol was removed by washing (3 times) the reaction mixture with ethyl acetate. The aqueous phase was acidified to pH 2 and the product was extracted into ethyl acetate (3 times). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford an oil, which solidified upon standing overnight in the cold. Yield 84%.

Expected compound **2**: NMR 250 MHz ($CDCl_3$) δ (ppm): 1.35 (s, 9H, $(CH_3)_3C$); 2.91 (dd, 1H, HCH, J_1 13.2Hz J_2 6.5Hz); 3.09 (dd, 1H, HCH, J_1 13.2Hz J_3 4.4Hz); 4.45 (dd, 1H, CHα, J_2 6.5Hz J_3 4.4Hz); 6.0 (br s, 1H, OH). HPLC: Column Nucleosil C18 5μ (250 x 10 mm) Flow: 5mL/min. RT. Conditions: 20% ACN/80% H_2O/0.1% TFA. Retention time: 11.43 mn.

m.p. 67-68° ; α_D +5.1 (c = 1, H_2O); Mass spectra (EI) m/z: $[M+2]^{+\cdot}$ 180 (15); $[M]^{+\cdot}$ 178 (20); $[(CH_3)_3C\text{-}S\text{-}CH_2]^+$ 103 (45); $[(CH_3)_3C]^+$ 57 (100).

Minor compound **3**: NMR 250 MHz ($CDCl_3$) δ (ppm): 1.40 (s, 9H, $(CH_3)_3C$); 3.48 (dd, 1H, CHα, J_1 6.0Hz J_2 8.5Hz); 3.79 (dd, 1H, HCH, J_1 6.0Hz J_3 11.5Hz); 3.90 (dd, 1H, HCH, J_2 8.5Hz J_3 11.5Hz); 6.0 (br s, 1H, OH). HPLC retention time: 6.00 mn.

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