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EFFICIENT SYNTHESES OF ENANTIOMERICALLY PURE L AND D-ALLOTHREONINES AND (S) AND (R) ISOSERINES

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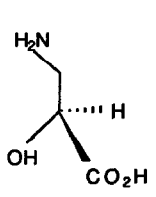
Abstract : Both enantiomers of (S) **1** and (R) **2** isoserine as well (D) **3** and (L) **4** allothreonine are prepared optically pure in three steps by asymmetric Sharpless epoxidation of crotyl and allylic alcohols into **7**- **10** followed by an improved $RuCl_3/NaIO_4$/water oxidation procedure to low molecular weight glycidic acids **11** -**14** and epoxide opening by ammonia with (20 - 33%) overall yields.

Aminohydroxy acids are of major importance as components of biologically active compounds.[1] (S) Isoserine ((S)-3-amino-2-hydroxypropanoic acid) not only inhibits several enzymes in mammals[2] but is a constituent of peptide antibiotics such as edeine[2] and tabutine.[3] Several syntheses of the optically active (S) **1** and (R) isoserines **2** have been reported quite recently.[4] Aminohydroxy acids also offer a potent chiral building block for epoxy ester synthesis[5]or β lactam frame work.[6] In this respect natural syn β–hydroxy α-aminoacid such as L - threonine is an inexpensive starting material and some asymmetric syntheses have been developed recently.[7] However optically active pure anti β-hydroxy α-aminoacids (e.g. D and L-allothreonine **3** and **4**) are very expensive and their syntheses are far fewer : Evans et al. have developed an aldol reaction of chiral oxazolidinone[8] and we have found an efficient electrophilic anti amination of chiral β- hydroxyester protected as their dioxanone form .[9]

Nucleophilic opening by heteronucleophiles[10] and carbonucleophiles of chiral epoxyalcohols or acids is a method of choice for controlling asymmetric centers.



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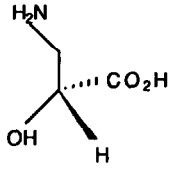

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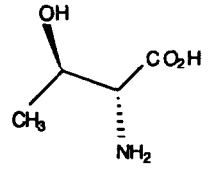

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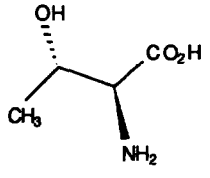

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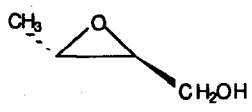
In this context, a heavy emphasis is being placed on the important and powerful Sharpless epoxidation[11] which provides 2,3 - epoxyalcohols with high enantiomeric purity and 2,3 - epoxyacids by subsequent oxidation of the allylic alcohol moiety.[12] To our knowledge, this technology has not been used for water-soluble glycidic acids.

We wish to present a practical protocol for the synthesis of a full set of water-soluble epoxyacids (table II) in optically active form and their nucleophilic amination into the corresponding α and β-hydroxy aminoacids such as (S) and (R) isoserines **1**, **2** and D and L-allothreonines **3** and **4**.[13] The synthesis of two epoxyalcohols **7** and **8** were prepared with enantiomeric purity (90 % ee) from crotyl alcohol using catalytic Sharpless epoxidation[11c] with molecular sieves (4A), titanium tetraisopropoxide, 2 eq. of t.butyl hydroperoxide and 0.5 eq. of (+)DIPT or (-) DIPT. Epoxidation of allylic alcohol requires cumene hydroperoxide [11c] for efficient epoxidation with DIPT as above after work-up and purification gave the two glycidols [14] **9** and **10** (entries 3 - 4 table II) with 45 % yield. The epoxyalcohols are first oxidized into epoxyacids on the basis of the preceding reports with ruthenium (III) chloride in the presence of a stoechiometric amount of $NaIO_4$ and a large amount of water (170 eq.)[12] with CCl_4/CH_3CN as solvents (entry 1, table I). Under these conditions the reaction is quite rapide but with these low molecular weight allylic alcohols the chemical yields were poor (20-31%) with substantial loss of selectivity (entries 1 - 2 table I). We recently reported a simple modification of $RuCl_3/NaIO_4$/water system which allows oxidation of primary alcohols into aldehydes .[15] The key feature of the catalytic modification is the use of 2.5 - 5 eq. of water in acetonitrile or methylene chloride.

Indeed, such a procedure applied with water soluble epoxy alcohols requires a longer reaction time (4 h) at room temperature but with good selectivity and chemical yields (81 %) (entry 3 table I). The simple modification presented here significantly expands the effectiveness and convenience **(no aqueous work-up)** of the reaction mixture. The (S) and (R) glycidols **9** -**10** were also successfully oxidized using the same procedure into the corresponding glycidic acids **13**-**14** (65-70%) (tableII).

Table I: Yield and selectivity dependence upon water content .[a]



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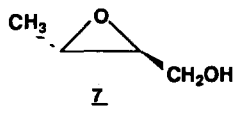
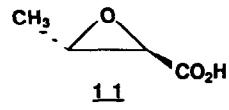
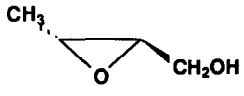
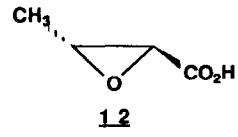
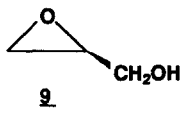
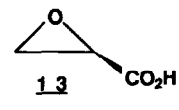
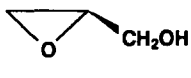
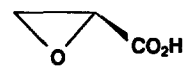
Entry	H_2O	Time (h)	$(\alpha)^\circ$	Yield (%)	e.e.
1	170 eq.[12]	0.2	-6.3	20	-
2	50 eq.[(b)]	0.2	-5	31	
3	5 eq.[(b)15]	4	- 52 [(c,d)]	80	90

a) All reactions were carried out at room temperature using 2.2 % $RuCl_3$, $3H_2O$; b) In pure acetonitrile; c) Crude product isolated by simple filtration over a pad of Celite; d) c = 1, C_6H_6; Lit.[16] $(\alpha)^\circ$=82 . e) There are significant differences with our values, the enantiomeric excesses were determined after nucleophilic opening with ammonia and HPLC analysis on the crude allothreonine on a chiralpak WH column (Daicel Chemical).

Nucleophilic opening with aqueous ammonia at room temperature (10 days) of trans optically active epoxy butyric acids **11** and **12** afforded[17] after recristallization pure D and L-allothreonine **4** and **3**[18] (40 % yield). Under the same conditions glycidic acids **13** and **14** gave after regioselective C-3 opening with aqueous ammonia the optically pure (R) **2**[19] and (S) **1** isoserines with 33 % overall yield.

Table II : Catalytic oxidation of water soluble epoxyalcohols.[a]

Entry	Epoxyalcohol	Yield(%)	(α)°	Epoxyacid	Yield(%)	(α)°
1	 **7**	86	-34	 **11**	86	-52
2	 **8**	85	+31	 **12**	81	+66
3	 **9**	45	-19	 **13**	70	+34
4	 **10**	45	+18	 **14**	65	-32

a) Reactions were performed on 1 mmole scale in CH_3CN at 25°C using 3 mol. eq. of $NaIO_4$, 2.5 mol. eq. of H_2O and 0,022 mol.eq. of $RuCl_3$. $(H_2O)_3$. The mixture began black then green and 2.5 more mol. eq. of H_2O were added and the mixture was vigourously stirred for 3 h. Simple addition of ether, filtration over a pad of Celite, concentration in vacuo and purification by flash chromatography on silica gel 60(70- 230 mesh ASTM) with ether as eluent gave the corresponding epoxyacids.

Low molecular weight epoxyacids are now conveniently available in large scale by asymmetric epoxidation of the corresponding allylic alcohols and subsequent oxidation of the alcohol moiety by this $RuCl_3/NaIO_4$ modified procedure. These highly desirable building blocks have been used in expeditive syntheses of enantiomerically pure α and β-hydroxy aminoacids[20] such as (S) and (R) isoserines and L and D-allothreonines. We are also investigating this methodology for other hydroxy aminoacids of biological interest and synthons in organic chemistry.

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18 $(\alpha) = +9°$ (c = 0.5, H_2O); Lit.: $(\alpha)^{26} = +9.6°$ $(\alpha) = 3.8$, H_2O) (D.F. ELLIOTT, J. Chem. Soc., 1950, 62). ^{1}H NMR 250 MHz (D_2O) δ ppm : 4.2 (m, 1 H); 3.6 (d, 1 H); 1.1 (d, J = 6.25 Hz, 3 H).

19 - After two recristallizations in water $(\alpha)^{23} = 31°$ (c= 1, H_2O); Lit.[4d] $(\alpha) = 31°$ 42. ^{1}H NMR (250 MHz) (D_2O) δppm : 4.05 (dd, J = 8.3 Hz, 4 Hz, 1 H); 3.15 (dd, J = 13 Hz, 4 Hz, 1 H); 2.95 (dd, J = 13 Hz, 8.3 Hz, 1 H).

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