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RESOLUTION OF OXIRANES. APPLICATION TO THE SYNTHESIS OF THE PLATELET AGGREGATION FACTOR

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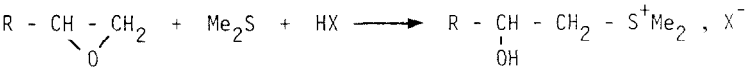
Abstract - Resolution of racemic oxiranes has been achieved through their conversion into hydroxy sulfonium salts of dibenzoyltartaric acid. Thus, resolution of n-octadecyl glycidyl ether followed by reaction with phosphorylcholine and acetylation led to C_{18}-P.A.F.

Whereas optically active ß-hydroxy oxiranes are now readily available through the Sharpless reaction [1], simple oxiranes are not so easily prepared in optically active form [2].

The reaction of oxiranes with thioethers and acids, which surprisingly was not known [3], occurred easily to give high yields of the ß-hydroxy sulfonium salts resulting from terminal attack on the 1,2-oxiranes. The onium ion provides a handle for resolution with optically active acids. In the event, (L)-dibenzoyltartaric acid (DBTA) proved efficient to bring about the resolution. The less soluble diastereoisomer was then converted by base into the optically active oxirane (Table 1).

Opening an oxirane with a secondary amine followed by resolution of the amino alcohol thus produced, followed by quaternization and treatment with base has been proposed [4] to achieve resolution. In the case of oxirane 1c, this technique has been compared with the sulfonium ion approach and found much less efficient.

The optically active acid can be used directly for the opening of the oxirane ring but little kinetic resolution was observed with DBTA. Recently, kinetic resolution has been observed in the reaction of oxiranes with thiols catalysed by zinc tartrate [5].

step 1 : 

1

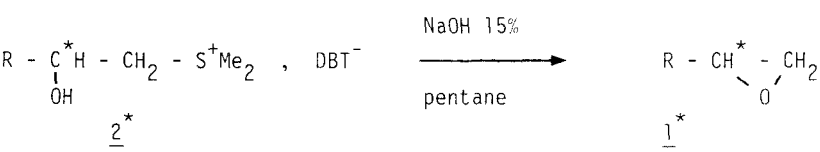
1a R = Et

1b R = n-Hex

1c R = $nC_{18}H_{37}$-OCH_2

1d trans 2,3-epoxybutane

step 2 : separation of (R)- R - CH(OH) - CH_2- S^+Me_2 , DBT^- and (S)- R - CH(OH) - CH_2 - S^+Me_2, DBT^-

step 3 : 

2*

1*

Table 1 : RESOLUTION OF OXIRANES

oxirane	acid	Step 1 [a] time h	Step 1 [a] Yield 2 %	Step 2 number of recrystallisations (solvent)	Step 2 Yield 2* %	Step 3 Yield 1* %	Step 3 ee 1* (major enantiomer)
1a	(L)-DBTA	24	99	7 (EtOH)	16	35 [b]	92.5 [c] (S)
1b	HBF_4 aq. 34%	0.5	95	6 (acetone) [d]	6	88 [b]	98.5 [c] (S)
1c	(D)-DBTA	24	76-90	8 (MeOH)	25	100	95 [f] (R)
1d	(L)-DBTA	0.5	60	4 (EtOH + acetone 3 : 1)	16	85 [b]	91.5 [c] (S, S)

a 1 eq. oxirane 1M in CH_2Cl_2 , 1 eq. acid, 5 eq. dimethyl sulfide, 20°C.

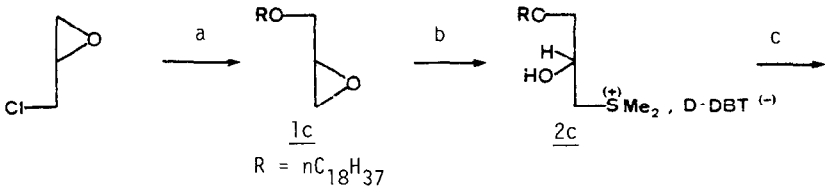
b Determined by GLC with an internal standard.

c The ee have been kindly determined by Prof. V. Schurig and Dr. U. Leyrer by GLC on a chiral column.

d After exchange of BF_4^- for DBT^-.

e Recrystallisation of the (D)-dibenzoyltartrate salt.

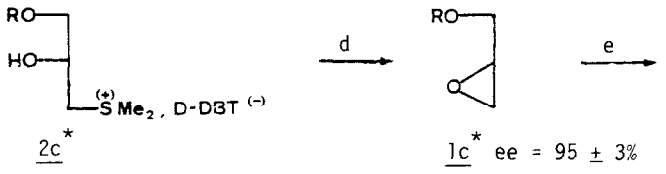
f Determined by ^1H NMR with $Eu(hfc)_3$ after opening the oxirane ring by sodium methoxide[6]



1c

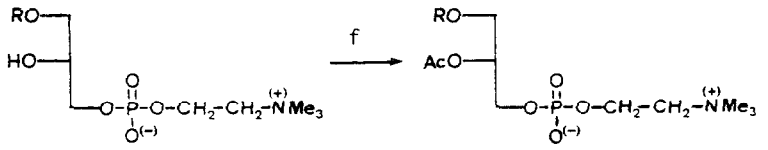
R = $nC_{18}H_{37}$

2c



2c*

1c* ee = 95 ± 3%



3

4

m.p. 214-215°C (dec)[g]

$[\alpha]_D^{24}$ = -1.65 ± 0.3° (c = 0.55, $CHCl_3$)[h]

a [9] NaOH 50%, Aliquat 336, cyclohexane , reflux ;
99% yield, m.p. 40-41°C (litt.[10] m.p. 38-39°C)

b,c,d See table 1 ; 1c* : m.p. 40-41°C (litt[11] m.p. 41-42°C)

e [13] Phosphorylcholine, AcOK cat., MeOH, reflux

f Ac_2O, DMAP, CH_2Cl_2 ;
36% yield from 1c* (after flash chromatography on silica gel 230-400 mesh)

g Litt. m.p. 260°C [11], 210°C (dec)[14], 212-215°C (dec)[16]

h $[\alpha]_D^{24}$ = -1.9° (c = 0.5, $CHCl_3$) for an authentic sample from BACHEM.

An obvious application was the production of glycidol derivatives [1] which are useful intermediates for the synthesis of drugs or phospholipids [7]. We selected as our target the Platelet Aggregating Factor 4, several syntheses of which have been published [8].

The optically active oxirane 1c* (ee = 95 ± 3%) was treated with phosphorylcholine and potassium acetate in methanol. After evaporation, washing with ether and drying, the crude lyso-PAF 3 was acetylated to give PAF 4 which was identical with an authentic sample as shown by ^1H NMR [14] and biological activity [15].

This route is being applied to the synthesis of other phospholipids.

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