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A HIGHLY EFFICIENT SYNTHESIS OF OPTICALLY PURE γ-IODO ALLYLIC ALCOHOLS AND THEIR CONVERSION INTO VARIOUS OPTICALLY ACTIVE ALLYLIC ALCOHOLS

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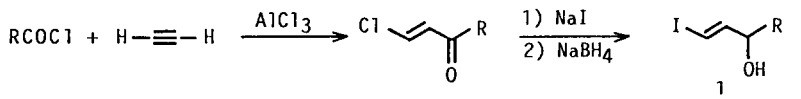
Summary: Kinetic resolution of γ-iodo allylic alcohols 1 by the Sharpless asymmetric epoxidation reaction proceeds with very large rate differences for the two enantiomers, thus providing a highly efficient method for preparation of optically pure 1. The alcohols 1 thus prepared can be readily converted into various secondary allylic alcohols through the coupling reaction with nucleophiles.

In a continuation of our studies on the kinetic resolution of the racemic secondary allylic alcohols possessing a heteroatom substituent at olefinic position by the Sharpless asymmetric epoxidation reaction as well as the application of the reaction products in organic synthesis,[2-6] we have now found that the kinetic resolution of γ-iodo allylic alcohols 1 proceeds highly efficiently. This reaction represents a major advance in the synthesis of optically pure 1, the synthesis of which has attracted much interest in recent years especially in relation to the synthesis of metabolites of arachidonic acid and their analogs.[7]

Racemic 1 can be readily obtained in large quantities according to the reported procedure shown in eq 1[8] and/or eq 2.[9]



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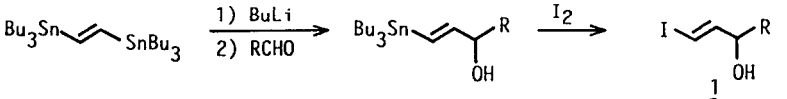
a, R = Am (79% yield based on the acid chloride)
b, R = Et (38%)
c, R =  (72%)
d, R =  (59%)

(1)

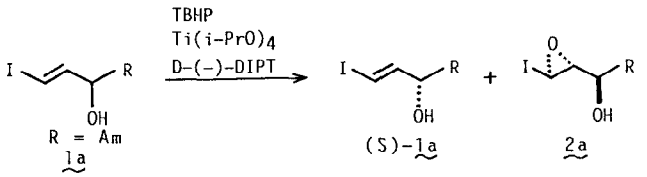


1

a, R = Am (83% yield based on the aldehyde)
e, R = Ph (72%)

(2)

Table 1 summarizes the enantiomerical purity of the epoxy alcohol produced and the unreacted allylic alcohol when the kinetic resolution of 1a was carried out using D-(-)-diisopropyl tartrate (D-(-)-DIPT) as a chiral source (eq 3).



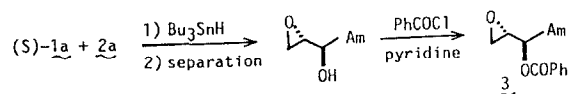
(3)

Entry 2 in Table 1 shows that the kinetic resolution carried out under the reaction conditions mentioned in Table 1 goes to completion in 42 hours to afford 2a with more than 99% ee and (S)-1a with more than 99% ee, simultaneously. This result indicates that the rate difference of the epoxidation reaction between two enantiomers of 1a, in contrast to the usual secondary allylic alcohols[10] but similarly to γ-trimethylsilyl allylic alcohol,[2] is very large. The resulting epoxy alcohol 2a and the remaining allylic alcohol (S)-1a were not separable by column chromatography, because the compounds coincide on TLC. However, fortunately, work-up with aqueous NaOH of the reaction mixture resulted

Table 1. The results of the kinetic resolution of 1a

Entry	Reaction condition[a] Ti/DIPT/1a	Temp(°C)	Time(h)	Optical purity (% ee) (S)-1a[b]	2a[c]
1	1.0/1.2/1.0	-20	36	96.2	>99
2	1.0/1.2/1.0	-20	42	>99[d]	>99[d]
3	0.2/0.24/1.0[e]	-20	28	>99[f]	96.9
4	0.2/0.24/1.0[e,g]	+20	18	98.0[h]	-

a)Except where noted, reaction was carried out using 1.5 equiv. of TBHP. b)Determined by ^{1}H NMR analysis of the derived MTPA ester. c)Determined by HPLC analysis using a chiral column (Daicel Chemical Ind. Ltd., Chiralpak OT(+)) of the benzoate derivative 3 of the epoxy alcohol obtained by reduction of 2a with Bu_3SnH.

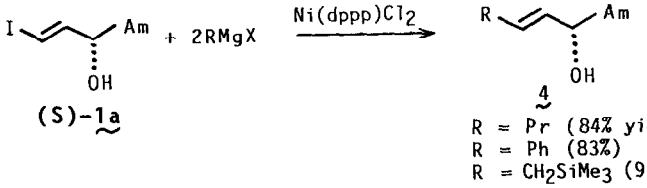


d)Yields of recovered (S)-1a and 2a are respectively more than 49%, checked by ^{1}H NMR analysis. e)Powdered 4A molecular sieves were present. f)>99.9% ee was recorded by HPLC analysis (SUMIPAX OA-4100) after converting into the corresponding carbamate prepared from the reaction of (S)-1a and 3,5-dinitrophenylisocyanate. Isolated yield and $[\alpha]_D$ value of (S)-1a were 45% and $[\alpha]_D^{25}$ +9.9° (c 2.16, MeOH)(lit. $[\alpha]_D^{24}$ +9.87° (c 1.57, MeOH)[11], $[\alpha]_D$ +10.2° (c 2.59, MeOH))[8b], respectively. g)0.6 equiv TBHP was used. h)(S)-1a was obtained in 45% isolated yield.

in the decomposition of 2a into the unidentified compound(s) which is very soluble in water, thus making 1a easily isolable. Kinetic resolution was also found to proceed effectively by using 20% catalyst in the presence of molecular sieves[12] (entry 3). Thus, synthesis of optically pure 1 can be carried out most practically by the epoxidation using 20% catalyst and work-up with aqueous NaOH followed by isolation by column chromatography on silica gel.[13] The yields and optical purity of various 1 prepared by this method are as follows[14] ; for 1b: 40% (based on the racemic 1b), >98% ee, 1c: 42%, >99% ee , 1d: 44%, >99% ee, and 1e: 43%, >98% ee. Needless to say, their enantiomer can be obtained by the kinetic resolution using L-(+)-DIPT as a chiral source instead of D-(-)-DIPT.

Previously we reported the preparation of optically pure γ-iodo allylic alcohols by using the similar kinetic resolution of γ-trimethylsilyl allylic alcohols[5] or γ-tributylstannyl allylic alcohols[4] as the key step. The present method offers a new and more direct approach to 1, and by using these three methods properly, it is now possible to prepare various kinds of 1 with high optical purity.

The practical method for preparation of 1 in hand, our next attention has been directed to apply 1 for the construction of chiral organic frameworks using the reactivity of the vinyl iodide moiety in 1. Herein, we report the preliminary results of the synthesis of various allylic alcohols through the coupling reaction of 1 with nucleophiles. Treatment of 1a with two equivalents of PrMgBr, PhMgBr or Me_3SiCH_2MgCl in the presence of a catalytic amount of $Ni(dppp)Cl_2$ (10 mol%) in tetrahydrofuran[16] provides the corresponding coupling product 4 in the yields shown in eq 4.[17]



(S)-1a

4

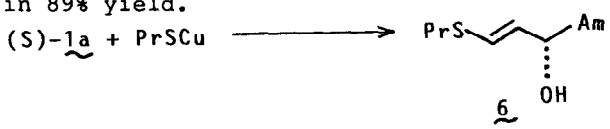
R = Pr (84% yield)
R = Ph (83%)
R = CH_2SiMe_3 (95%)

(4)

Coupling reaction of 1a with 1.1 equiv. of CuCN in N-methylpyrolidone (130°C, 3h)[18] proceeds readily to afford 5 in 83% yield.[17] Similarly reaction of 1a

5

with PrSCu, prepared in situ by the reaction of PrSLi and CuI,[18] furnished the coupling product 6 in 89% yield.[17]



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Further study on the conversion of optically active 1 into other allylic alcohols and also on the application of the compounds 4, 5, and 6 prepared here in organic synthesis is in progress.

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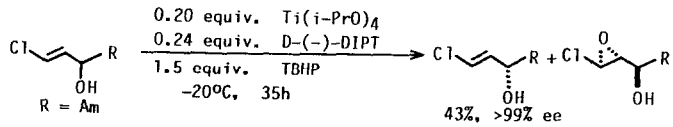
13. Kinetic resolution of γ-chloro allylic alcohol was also found to proceed effectively to afford the optically pure allylic alcohol in 43% yield.



14. Enantiomeric excesses (ee) were determined by ^{1}H NMR analysis of the derived MTPA esters. $[\alpha]_D^{25}$ values are as follows; 1b: +0.46° (c 1.50, MeOH), 1c: +16.2° (c 1.56, MeOH)(lit.[15] $[\alpha]_D^{25}$ +17.0° (c 1.34, MeOH)), 1d: +12.2° (c 1.50, MeOH)(lit.[15] $[\alpha]_D^{25}$ +12.7° (c 0.59, MeOH)), and 1e: +10.5° (c 1.02, MeOH).
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17. $[\alpha]_D^{25}$ values of 4, 5, and 6 are as follows; 4 (R = Pr): -5.0° (c 0.92, $CHCl_3$), 4 (R = Ph): +3.5° (c 1.03, $CHCl_3$), 4 (R = CH_2SiMe_3): -23.3° (c 0.92, $CHCl_3$) 5: +36.8° (c 0.99, $CHCl_3$), 6: +8.5° (c 0.96, $CHCl_3$). The optical purity of 4 (R = Pr) was confirmed to be more than >99% ee by converting into (S)-(-)-2-acetoxyheptanal via ozonolysis after acetylation. $[\alpha]_D^{20}$ -38.3° (c 0.58, $CHCl_3$) (lit.[11] $[\alpha]_D^{20}$ -37.8° (c 0.5, $CHCl_3$). $[\alpha]_D^{20}$ value of (S)-(-)-2-acetoxyheptanal obtained from 4 (R = Ph) was -38.0° (c 0.50, $CHCl_3$). The enantiomers were not detected by ^{1}H NMR analysis on the corresponding MTPA derivatives of 4 (R = CH_2SiMe_3) and 5. The enantiomer was not detected by ^{1}H NMR analysis on the corresponding acetate of 6 in the presence of (-)-Pr(DPPM)$_3$.
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