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SYNTHESIS OF CHIRAL EPOXY ALCOHOLS: SYNTHESIS OF (+)-DISPARLURE

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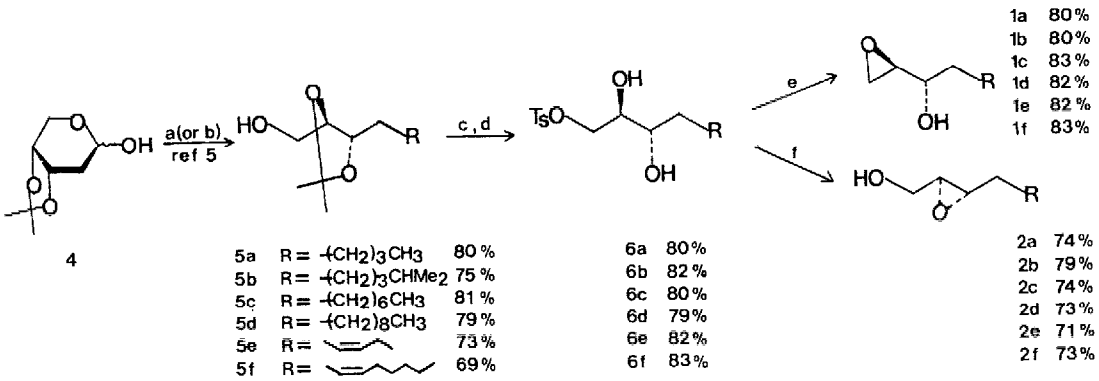
Summary: (2R,3S)-1,2-Epoxy alcohols **1**, (2S,3S)-2,3-epoxy alcohols **2**, and (2S,3S)-1,2-epoxy alcohols **3** were prepared from readily available (-)-2-deoxy-D-ribose. Using epoxy alcohol **3b** as a chiral synthon, (+)-disparlure,the pheromone of the gypsy moth, *Porthetria dispar*(L.), was synthesized.

Chiral epoxy alcohols such as 1,2-epoxy alcohols and 2,3-epoxy alcohols are important intermediates in organic synthesis because of their special reactivity under a wide range of reaction conditions. In the literature, optically active 2,3-epoxy-1,4-butanediol and 1,2-epoxy-1,4-butanediol derivatives have been prepared from D- or L-tartaric acid.[1] Recently, the synthesis of chiral 2,3-epoxy alcohols from allylic alcohols, known as Sharpless asymmetric epoxidation,[2] has become a useful synthetic tools.[3] By this Sharpless method, chiral 2,3-epoxy primary alcohols were prepared from suitable allylic alcohols with a high degree of enantioselectivety. Alternatively, chiral *threo* 1,2-epoxy secondary alcohols were obtained by the Sharpless kinetic resolution(SKR)[2b,4] from secondary allylic alcohols. To prepare chiral 1,2-epoxy alcohols by this kinetic resolution, the yield is limited to maximum 50% from racemic mixture like all resolutions. Our on-going synthesis of chiral insect pheromones from (-)-2-deoxy-D-ribose, chiral 1,2-epoxy alcohols with either *erythro* or *threo* stereochemistry are needed. Here we wish to report an enantiospecific synthesis of (2R,3S)-1,2-epoxy alcohols **1** and highly enantioselective synthesis of (2S,3S)-1,2-epoxy alcohols **3** and (2S,3S)-2,3-epoxy alcohols **2** from readily available (-)-2-deoxy-D-ribose.

The enantiospecific synthesis of (2R,3S)-1,2-epoxy alcohols **1** has been carried out, which is shown in Scheme 1. The (2R,3S)-2,3-Isopropylidenedioxy alcohols **5a-f** were prepared by our procedure.[5] The alcohol **5a** was converted to the (2R,3S)-2,3-diol-1-sulfonate ester **6a** by tosylation followed by deprotection of the acetonide with 70% acetic acid in 80% overall yield. Treatment of **6a** with 3 equiv of K_2CO_3 in methanol at room temperature for 30 min afforded (2R,3S)-1,2-epoxy-3-ol **1a** (TLC: SiO_2, hexanes/EtOAc 1:1,R_f=0.40), $[\alpha]_D^{22}$ +20.3°(c=3.1,$CHCl_3$), in 80% yield after column chromatographic separation. The (2R,3S)-1,2-epoxy-3-ols **1a-f**(Table 1) have characteristic nmr peak at δ 3.75ppm as a multiplet of C_3-proton. The reaction sequence was also applied to prepare (2R,3S)-1,2-epoxy alcohols **1b-f**, which is shown in Scheme 1. (2R,3S)-Epoxy alcohols **1a** and **1d** were used as chiral building blocks for the synthesis of LTA derivatives[6] and the mosquito oviposition pheromone,[7] respectively. When **6a** was treated with 3 equiv of K_2CO_3 in methanol for longer time(24h) at room temperature, the internal (2S,3S)-2,3-epoxy alcohol **2a**(TLC:SiO_2, hexanes/EtOAc 1:1,R_f=0.34), $[\alpha]_D^{22}$-29.4° (c=3.0,$CHCl_3$),was obtained by Payne's rearrangement,[8] without remained **1a**. The 2,3-epoxy alcohols **2a-f**(Table 1) have characteristic nmr peaks at δ 3.75 and δ 3.82 ppm as doublet(J=11 Hz) of the C_1-methylene protons. Alternatively, the epoxy alcohol **1a** isolated was treated again with 3 equiv of K_2CO_3 in methanol for 24h to afford **2a**. The epoxy alcohols **2b-f**, which can be also prepared by the Sharpless asymmetric epoxidation, were prepared by the same reaction

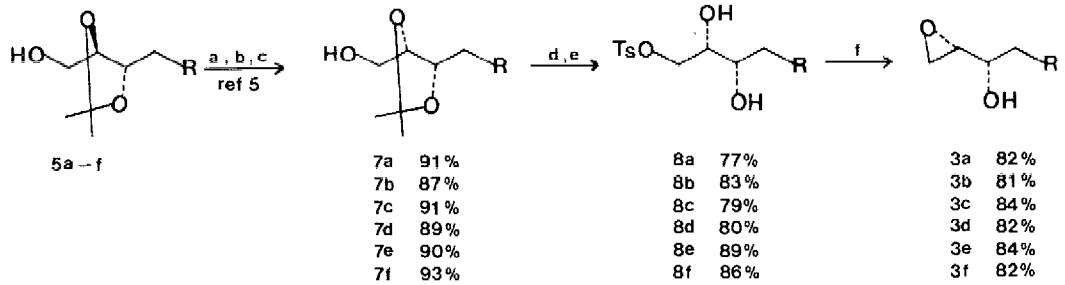
sequence (Scheme 1).



Reagents: a) $(C_6H_5)_3P{=}CHR^1$,THF,-50°C,12h; b) H_2, Pd/C,EtOAc/ MeOH(1:3), rt,atmospheric pressure,24h; c)p-TsCl,pyridine, CH_2Cl_2,0°C,8h; d)70% HOAc,MeOH,rt,7h;e)K_2CO_3,MeOH,rt,30 min; f)K_2CO_3,MeOH,rt,24h

Scheme 1

The (2S,3S)-1,2-epoxy alcohols **3a-f**(Table 1), which are not possible to prepare directly by the Sharpless kinetic resolution, were also synthesized from (-)-2-deoxy-D-ribose. The (2S,3S)-2,3-isopropylidenedioxy alcohols **7a-f**[10] were prepared from **4** by our procedure.[5] Tosylation of **7a** followed by deprotection with 70% acetic acid provided (2S,3S)-2,3-diol-1-sulfonate ester **8a**. On treatment of **8a** with 3 equiv of K_2CO_3 in methanol for 1h or more afforded only (2S,3S)-1,2-epoxy 3-ol **3a**(TLC:SiO_2, hexane/EtOAc 1:1, R_f=0.40),$[\alpha]_D^{22}$+4.90°(c=3.27,$CHCl_3$), without any Payne's rearrangement (Scheme 2). The (2S,3S)-1,2-epoxy 3-ols **3a-f**(Table 1) have characteristic nmr peak at δ 3.45 as multiplet of the C_3-proton. The reaction sequence was also applied to prepare (2S,3S)-1,2-epoxy alcohols **3h-f**(Scheme 2). The (2S,3S)-1,2-epoxy alcohol **3a** was used as a chiral building block for the synthesis of the grape borer pheromone[11] and used in the structure elucidation of laureoxolane.[12]



Reagents: a)DMSO,$(COCl)_2$,CH_2Cl_2,Et_3N,-70°C, 30min → rt,30min; b)K_2CO_3,MeOH,rt,5h; c)$NaBH_4$,95%EtOH,rt,10h;d)p-TsCl, pyridine, CH_2Cl_2,0°C,8h; e)70% HOAc,MeOH,rt,7h; f)K_2CO_3,MeOH,rt,12h.

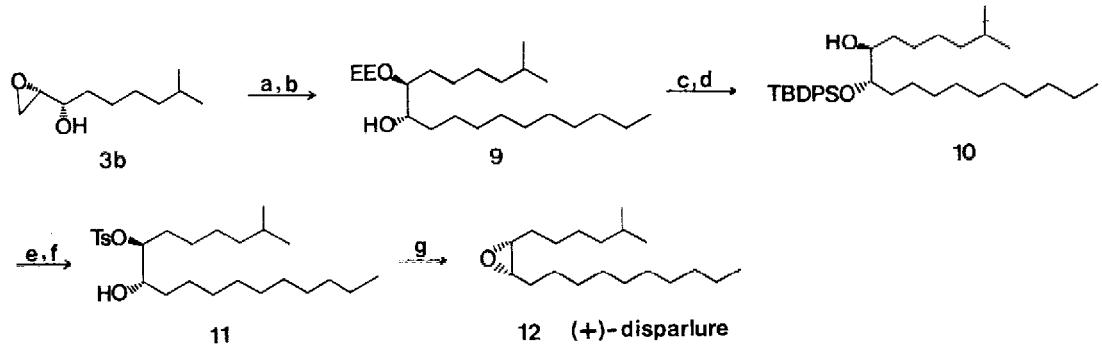
Scheme 2

Table 1 Specific rotations of epoxy alcohols **1-3** prepared

Epoxy Alcohol **1**[a] $[\alpha]_D$[b]	Epoxy Alcohol **2**[a] $[\alpha]_D$[b]	Epoxy Alcohol **3**[a] $[\alpha]_D$[b]
1a[13] $[\alpha]_D^{22}$+20.3°(c=3.1)[c]	**2a**[2b] $[\alpha]_D^{22}$-29.4°(c=3)[d]	**3a**[11,13] $[\alpha]_D^{22}$+4.9°(c=3.27)[e]
1b $[\alpha]_D^{25}$+6.3° (c=2.3)	**2b** $[\alpha]_D^{25}$-6.2° (c=2.25)	**3b** $[\alpha]_D^{22}$+12.3°(c=0.68)
1c $[\alpha]_D^{22}$+20.8°(c=1.83)	**2c**[14] $[\alpha]_D^{22}$-30.3°(c=6)[f]	**3c** $[\alpha]_D^{22}$+6.2° (c=6.6)
1d[7] $[\alpha]_D^{20}$+22.0°(c=5.4)[g]	**2d**[15] $[\alpha]_D^{20}$-24.0°(c=4.75)	**3d** $[\alpha]_D^{25}$+5.5°(c=0.9)
1e $[\alpha]_D^{23}$+10.3°(c=3)	**2e** $[\alpha]_D^{23}$-18.0° (c=3.5)	**3e** $[\alpha]_D^{22}$+7.71° (c=4.8)
1f $[\alpha]_D^{23}$+17.6°(c=2.1)	**2f** $[\alpha]_D^{23}$-5.3° (c=2.98)	**3f** $[\alpha]_D^{22}$ +7.10° (c=1.83)

[a] The %ee of the epoxy alcohols were > 99%, which was determined by HPLC analysis (μ-Porasil, n-hexane:CH_2Cl_2=2:1, 1 ml/min, 254 nm) of the corresponding (+)-MTPA esters. [b]$CHCl_3$ was used as solvent.[c]Lit.[13] -21.6°(c=1.43, $CHCl_3$) for the enantiomer. [d]Lit.[2b] -35.6° (c=2.35, $CHCl_3$). [e]Lit.[11] +4.40° (c=1.66, $CHCl_3$). [f]Lit.[14] -32.8°(c=1.0, $CHCl_3$). [g]Lit.[7] +15.7°(c=2.09, $CHCl_3$).

Using **3b** as a chiral synthon, (+)-disparlure,[15] the pheromone of the gypsy moth, *Porthetria dispar*(L.), was synthesized(Scheme 3). The (2S,3S)-epoxy alcohol **3b** was protected as ethoxyethyl group and then reacted with n-nonylmagnesium bromide to afford the condensed product **9**[16] (TLC:SiO_2 ,hexanes/EtOAc 8:1, R_f=0.64). The alcohol **9** was protected with t-butyldiphenylsilyl chloride followed by deprotection of ethoxyethyl group to give **10**. The alcohol **10** was treated with p-toluenesulfonyl chloride followed by deprotection to provide the penultimate compound **11**(TLC:SiO_2, hexanes/EtOAc 8:1,R_f=0.28), mp 37-39°C, which was converted[15a] to the(+)-disparlure,**12**,[17] (TLC:SiO_2, hexanes/EtOAc 8:1,R_f=0.68), $[\alpha]_D^{22}$+0.7° ±0.1°(c=1.7,CCl_4).



Reagents: a) EVE,$POCl_3$(cat.), PPTS, ether, 1h(95%); b) n-$C_9H_{19}MgBr$, CuBr,THF,-30°C rt,2h(88%);c)TBDPSCl,imidazole,DMF,rt, 12h (87%); d)0.5N HCl,0°C 30min→ rt 30min(84%);e)p-TsCl,pyridine,rt,6h(86%); f)$(t\text{-}Bu)_4NF$,THF,rt,2h(90%); g)ref.15a

Scheme 3

The use of these chiral epoxy alcohols in the synthesis of biologically active C-18 fatty acids is currently in progress.

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9. The compound **5e** isolated by column chromatography was assigned to be *cis*, which was confirmed by ^{1}H NMR(500 MHz) spectrum and GLC analysis(Column, HP-1, 0.53 mm X 5 m,160 °C,7.8 ml,N_2 ,RT=2.56 min). Physical and spectroscopic data of **5e**: TLC;SiO_2, hexanes/EtOAc 1:1,R_f =0.73. $[\alpha]_D^{22}$ +19.7°(c=3.4,$CHCl_3$). IR(neat) 3400cm^{-1}. ^{1}H NMR(500MHz,$CDCl_3$) δ 0.83(t,3H), 1.30(s,3H), 1.38(s,3H), 1.95(m,2H), 2.26(m,2H), 3.65(d,2H),3.83-4.18(m,2H), 5.30(m,1H), 5.48(m,1H).
10. By capillary GLC analysis, the ratio of **7**:**5** in the reduced alcohol **7** was ca 99.5:0.5.
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16. Spectroscopic data (^{1}H NMR,^{13}C NMR, IR) for **11**: ^{1}H NMR (80 MHz,$CDCl_3$) δ 0.84,0.90(d and t, J=5.8 Hz,9H), 1.10-1.80(m,34H), 3.31-3.78(m,4H), 4.77(m,1H); ^{13}C NMR(22.6 MHz, $CDCl_3$) δ 100.23, 80.06, 72.51, 60.94, 38.95, 33.54, 31.91, 3144, 29.71, 29.62, 29.32, 27.92, 27.68, 27.29, 25.83, 25.61, 25.53, 20.38, 15.25, 14.08, 2.63; IR(neat) 3450 cm^{-1}.
17. The spectral data (^{1}H NMR,IR) of (+)-disparlure,**12**, synthesized were identical with the data of the synthetic compound provided by Professor K. Mori (The University of Tokyo).

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