Tetrahedron Vol. 48, No. 8, pp. 1531-1538, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Diols Obtained Via Chemo and Regioselective Ring Opening of Epoxy Alcohols: a Straightforward Synthesis of 2S,3S - Octandiol

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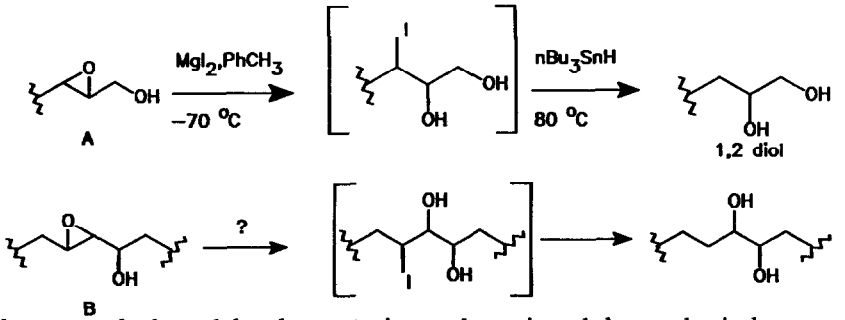
(*Received in UK* 28 *November* 1991)

Abstract: *epoxy alcohols are regio and chemoselectively opened to the corresponding iodohydrins and then reduced in situ to diols; the application of the described procedure leads to a short asymmetric synthesis of a well known pheromone. Also homoallylic (E and Z) epoxy alcohols and its benzylated derivatives shows high preference for regioselective opening affording the corresponding 1,3 diol.*

There is still a growing interest in the regio and chemoselective opening of the oxirane ring: in fact epoxides are often available in optically active form, as is the case of the epoxy alcohols[1] and also recently for unfunctionalized epoxides.[2]

Also recently the ring opening by halogens (metal halides[3] or molecular halides[4]) or hydride reagents[5] has been studied leading to the corresponding halohydrins or diols. In particular the reductive opening of 2,3 epoxy alcohols[5] (with the regioselective obtaining of 1,2 or 1,3 diols) has received much attention: nevertheless the use of the hydride reagents greatly limits the chemoselectivity of the methods adopted.

FIGURE 1



We have recently showed that the epoxy ring can be regio and chemoselectively opened by MgI_2 and other metal iodides to the corresponding iodohydrin that may be eventually reduced in situ by nBu_3SnH.[6]

The above methodology has been succesfully applied to 2,3 epoxy alcohols of type **A** (see figure 1), affording the corresponding iodohydrins and 1,2 diols in excellent regio and chemical yields.[7]

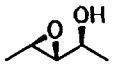
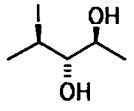
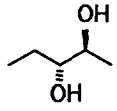
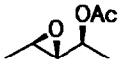
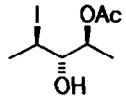
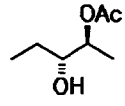
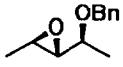
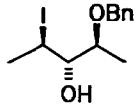
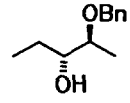
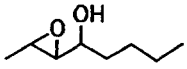
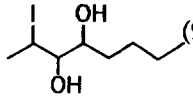
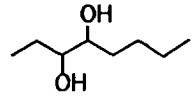
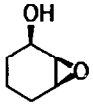
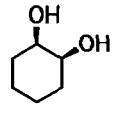
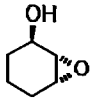
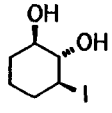
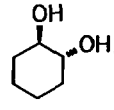
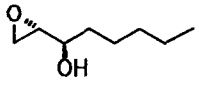
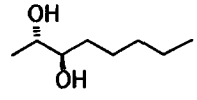
The most important features of this methodology are:

1. the possibility to obtain in the same sequence both the corresponding iodohydrins and/or directly the 1,2 diols.

2. the chemoselectivity of the reactions which is particularly attractive with respect to the use molecular iodine[4] and hydride reagents.[5]

Little is known of the reductive opening of α,β epoxy alcohols (erythro or threo) of type **B**. We were intrigued on the application of our procedure to these epoxy alcohols. Their reductive opening could lead (via a proposed metal chelate[4,7]) to the corresponding 3-iodo-1,2-diols or directly to the vicinal diols whose subunit is present in many natural products.[8]

TABLE I

Starting epoxide [a]	Main iodohydrin yield (%) [b]	Main diol yield (%)[b]	ratio[c]
1 	8  (95)	13  (80)	95:5
2 	9  (83)	14  (65)	99:1
3 	10  (95)	15  (81)	99:1
4 	11  (97)	16  (50)	84:16
5 		17  (67)	99:1
6 	12  (70)	18  (48)	99:1
7 		19  (90)	99:1

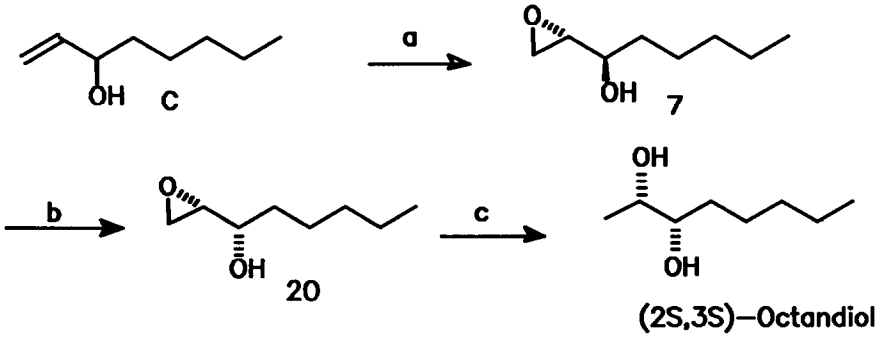
a. All the compounds were used in racemic form except 7 which was used in enantiomeric form (see experimental); compound 4 was used as a mixture of stereoisomers. b. Yields on isolated purified products. c. Ratios are referred to 1,2 diols/1,3 diols

As shown in Table I several epoxy alcohols were prepared by standard procedure[9](see experimental) and tested under the described conditions. A good to excellent level of regioselectivity was achieved in most of the cases expecially starting with pure erythro compounds (**1-3, 5** and **7**): in fact we obtained, with generally good chemical yields, the corresponding vicinal diols or, eventually, the intermediate iodohydrins (see compounds **1-4** and **6**). It is noteworthy that the regioselectivity still operates in the case of the alcohol derivatives (compound **2**[10] and **3**). The threo epoxy cyclohexanol **6** afforded the 1,2 cyclohexandiol in lower yield with respect to the erythro epoxy cyclohexanol **5** : on the other hand the same compound **6** gave completely unsatisfactory results, in the obtaining of the corresponding iodohydrin, by other procedure.[4]

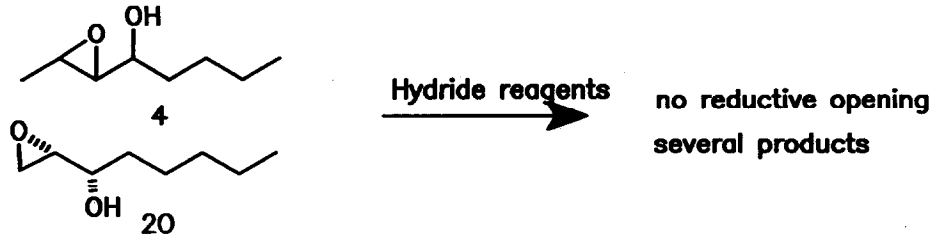
Starting with erythro epoxides (or enantiomerically pure compound such as **7**, easily prepared by the known AE/KR Sharpless procedure[11], see experimental section) our method provides the corresponding erythro diols. To our knowledge this is the first example of erythro diols directly obtained in optically pure form. In fact, apart from a method involving the isomerization of 2,3 epoxy alcohols [12], the other recent procedures employing an asymmetric osmium-catalyzed dihydroxylation [13], gave excellent enantiomeric excess only in the cases of trans (E) olefins, affording the corresponding threo diols.

A straightforward three-step synthesis of the optically active (2S,3S)-Octandiol (well known pheromone of the grape borer Xylotrechus pyrrhoderus [14]) clearly demonstrates the usefulness of this procedure (see figure 2). After the Sharpless AE/KR[11] performed on the commercially available allylic alcohol **C**[14b], the erythro epoxy alcohol **7** was epimerized in one pot[15] to the threo epoxyalcohol **20** and then directly opened to the target natural product with excellent yield .

FIGURE 2



a. D(+)-DIPT, $Ti(OiPr)_4$, TBHP in CH_2Cl_2at -20 °C, 12 h, 40%. b. DEAD, Ph_3P, HCOOH in THF at r.t., 12 h, then MeOH, Na (cat.), 52%. c. MgI_2 at -60 °C, toluene, then nBu_3SnH, AIBN at 70 °C, 1h, 91%.

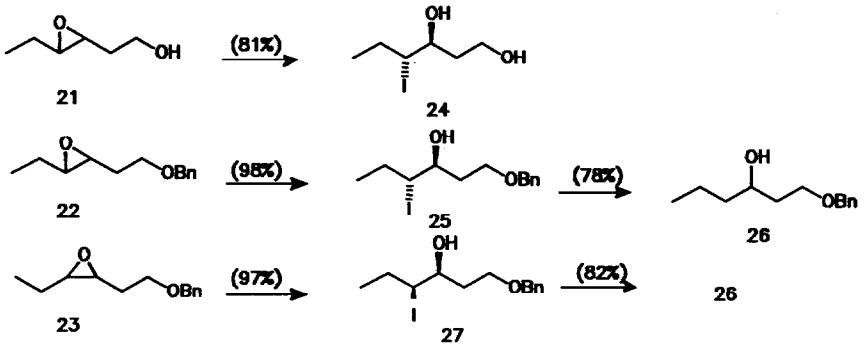


This sequence represents a substantial improvement over a similar synthesis by Mori[14b]; in fact the mildness of our procedure allows to perform the reductive opening of the oxirane ring without need of any protection of the hydroxyl group of compound **20**, as was for other cases.[14b,d]

Our attempts to utilize the other known reductive procedures (i.e. DIBAH or $AlLiH_4$) on compounds **4** and **20** completely failed, giving rise to several products.

Our methodology has been finally applied also to homoallylic epoxy alcohols: as shown in figure 3 the (E) epoxy alcohol **21** and the benzylated **22** nicely gave the C-4 opening of the ring affording the corresponding iodohydrins **24** and **25** or the 1,3 diol **26**. Quite nicely our procedure works also in the case of the (Z) benzylated epoxy alcohol **23**, with the obtaining of a single iodohydrin **27** and of the corresponding diol **26**. This result has never been obtained before by other procedures (see ref. 4 for a similar non regioselective opening of Z homoallylic alcohol), which makes our method useful also for such epoxy alcohols.

FIGURE 3



The above methodology will be applied to the synthesis of other natural products, and further elaborate to discover a complementary opening of epoxy alcohols leading to the corresponding skipped 1,3 diols, which are important subunits in many natural products.

EXPERIMENTAL SECTION

GENERAL: Flash chromatography was carried out on silica gel Merck (70-230 mesh). TLC analyses were carried out on Merck Kieselgel 60 F-254 plates. All the solvents used were distilled and dried. ^{1}H-NMR spectra were recorded on a Varian Gemini (200 MHz)instrument,with a $CDCl_3$ solution and $CHCl_3$ as internal standard. ^{13}C-NMR spectra were determined on the same instrument (50.3 MHz) in a $CDCl_3$ solution and $CHCl_3$ as internal standard. The regioisomer ratios of the iodohydrins and diols were determined from ^{1}H and ^{13}C-NMR spectra.

PREPARATION OF THE STARTING EPOXY ALCOHOLS AND DERIVATIVES

Epoxides **5**,6[16], **7**[14b] and 21[17] are known compounds.

Epoxy alcohols **1** and **4**: these epoxy alcohols were prepared, from the corresponding allylic alcohols, according to the procedure described in reference 9.

Epoxy alcohol **1**: oil. ^{1}H-NMR: 3.54 (m, 1H); 2.9 (m, 1H); 2.55-2.65 (bs, OH); 2.52 (m, 1H); 1.22 (d, J = 5 Hz, 3H); 1.19 ppm (t, J = 7 Hz, 3H). ^{13}C-NMR : 67.49; 63.62; 52.63; 19.41; 16.96 ppm. Anal. Calcd for $C_5H_{10}O_2$: C, 58.78; H, 9.80. Found: C, 58.64; H, 9.89.

Epoxide **2** (prepared by standard acetylation procedure from the epoxy alcohol **1**) : oil.^{1}H-NMR: 4.7 (quintet, J = 6.7 Hz, 1H); 2.85 (ddd, J = 6.7 and 2.2 Hz, 1H); 2.72 (dd, J = 6.7 and 2.2 Hz, 1H); 1.99 (s, 3H); 1.28 (d, J = 6.7 Hz, 3H); 1.22 ppm (d, J = 6.7 Hz, 3H). ^{13}C-NMR: 170.47; 70.37; 60.44; 52.02; 20.878; 17.01; 16.30 ppm.Anal. Calcd for $C_7H_{12}O_3$: C, 58.32: H, 8.39. Found: C, 58.25; H, 8.45.

Epoxide **3** (prepared from epoxy alcohol **1** by the benzylation procedure described in ref. 7): oil. ^{1}H-NMR: 7.2-7.4 (m, 5H); 4.73 (d, J = 10.9 Hz, 1H); 4.59 (d, J = 10.9 Hz, 1H); 3.3 (m, 1H); 2.55-2.95 (m, 2H); 1.31 (d, J = 5.5 Hz, 3H); 1.25 ppm (d, J = 7.3 Hz, 3H). ^{13}C-NMR: 138.74; 128.42; 127.78; 127.69; 127.57; 75.66; 71.08; 62.73; 50.47; 17.13; 17.11 ppm.Anal. Calcd. for $C_{12}H_{16}O_2$:C, 74.95; H, 8.39. Found: C, 75.01; H, 8.34.

Epoxy alcohol **4** (mixture of diastereoisomers): oil. ^{1}H-NMR: 3.7 (m, 1H); 3.35 (, 1H); 2.87-3.08 m, 1H); 2.6-2.7 (m, 1H); 1.2-1.6 (m, 6H); 1.27 (d, J = 6.1 Hz, 3H); 0.88 ppm (bt, 3H). ^{13}C-NMR: 71.29; 68.61; 62.75; 61.86; 52.74; 50.91; 33.85; 33.06; 27.24; 27.20; 22.51; 22.45; 16.99; 13.72 ppm.Anal. Calcd. for $C_8H_{16}O_2$: C, 66.61; H,11.19. Found: C, 66.39; H, H, 11.29.

Epoxide **22** (prepared from **21** by the benzylation procedure described in ref 7): oil. ^{1}H-NMR: 7.3 (s, 5H), 4.5 (s, 2H), 3.58 (t, J = 6.2 Hz, 2H), 2.82 (m, 1H), 2.68 (m, 1H), 1.45-1.98(m, 4H), 0.95ppm (t, J = 7.4 Hz, 3H). ^{13}C-NMR: 138.49, 128.53, 127.77, 73.08, 67.12, 59.86, 56.05, 32.51, 24.94, 9.64 ppm.Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.78; H, 8.8. Found: C, 75.71; H, 9.0.

Epoxide **23** (prepared from the corresponding known (Z) homoallylic alcohol[17], by the benzylation procedure described in ref.7) : oil. ^{1}H-NMR: 7.32 (s, 5H), 4.51 (s, 2H), 3.63 (t, J = 5.8 Hz, 2H), 3.06 (m, 1H), 2.88 (m, 1H), 1.43-1.98 (m, 4H), 1.01 ppm (t, J = 7.4 Hz, 3H). ^{13}C-NMR: 138.49, 128.53, 127.78, 73.12, 67.61, 58.11, 54.78, 28.33, 21.03, 10,30 ppm. Anal.Calcd.for $C_{13}H_{18}O_2$:C, 75.78; H, 8.8. Found: C, 75.69; H, 9.1.

PREPARATION OF THE IODOHYDRINS

General procedure for the preparation of iodohydrins **8-12** and **24-27**

A solution of epoxy alcohol (1.0 mmole) in dry toluene (25 mL), stirred and cooled at -60C under nitrogen atmosphere, was added of a solution of MgI_2 in ether(1.1 mmole). The reaction mixture was then vigorously stirred and the reaction was monitored by TLC (UV lamp and H_2SO_4 spraying). After 2-5 hours the reaction was completed and the temperature raised to r.t. The mixture was then quenched with saturated Na_2SO_4 (5 mL), diluted with ether and washed with brine. After drying with Na_2SO_4 the solvents were evaporated in vacuo affording the crude mixture of iodohydrins which was checked by ^{1}H and ^{13}C-NMR spectroscopy before purification. The mixture was then purified by silica gel chromatography (petroleum ether/ether as eluent) affording pure iodohydrins.

Iodohydrin **8**: yellow oil. ^{1}H-NMR: 4.25 (quintet, J = 5.3 Hz, 1H); 4.05 (m, 1H); 3.5 (bs, 2H, OH); 3.33 (m, 1H); 1.85 (d, J = 7.6 Hz, 3H); 1.16 ppm (d, J = 6.3 Hz, 3H). ^{13}C-NMR: 80.17; 67.57; 30.29; 22.76; 19.76 ppm.

Iodohydrin **9**: yellow oil. ^{1}H-NMR: 4.35 (m, 1H); 4.15 (quintet, J = 8.3 Hz, 1H); 3.6 (m, 1H); 2.31 (d, J = 6.6 Hz, OH); 2.06 (s, 3H); 1.92 (d, J = 6.7 Hz, 3H); 1.28 ppm (d, J = 6.6 Hz, 3H).^{13}C-NMR: 170.05; 78.69; 71.05; 28.11; 23.23; 20.24; 17.20 ppm.

Iodohydrin **10**: yellow oil. ^{1}H-NMR: 7.2-7.4 (m, 5H); 4.64 (d, J = 12 Hz, 1H); 4.47 (d, J = 12 HZ, 1H); 4.25 (quintet, J = 8.6 Hz, 1H); 4.08 (m, 1H); 3.48 (m, 1H); 2.43 (d, J = 8.6 Hz, OH); 1.96 (d, J = 6.9 Hz, 3H); 1.26 ppm (d, J = 6.6 Hz, 3H).^{13}C-NMR: 138.16; 128.77; 128.63; 128.12; 128.05; 80.15; 75.07; 71.26; 29.54; 24.10; 16.66 ppm.

Iodohydrin **11**: yellow oil. ^{1}H-NMR: 4.28 (quintet, J = 6.9 Hz, 1H); 3.92 (m, 1H); 3.55 (m, 1H); 2.85 (d, J = 7.0 Hz, OH); 2.48 (d, J = 4.6 Hz, OH); 1.91 (d, J = 7.0 Hz, 1H); 1.2-1.5 (m, 4H); 0.87 ppm (bt, J = 5.8 Hz, 3H).^{13}C-NMR: 78.46; 71.50; 33.80; 31.10; 27.45; 23.34; 22.41. 13.78 ppm.

Iodohydrin **12**: yellow oil.^{1}H-NMR:3.91 (m, 1H); 3.32-3.55(m, 2H); 3.31 (bs, 2H, OH); 2.28-2.45 (m, 1H); 2.11-1.88 (m, 2H); 1.6-1.2 ppm (m, 3H). ^{13}C-NMR: 81.37; 72.91; 38.08; 35.88; 31.84; 25.39 ppm.

Iodohydrin **24**: yellow oil. ^{1}H-NMR: 4.18 (m, 1H), 3.85 (m, 2H), 3.68 (m, 1H), 2.54 (bs, 2H, OH), 1.58-2.06 (m, 4H), 1.03 ppm (t, J = 7.2 Hz, 3H). ^{13}C-NMR: 74.51, 60.84, 49.72, 36.36, 28.32, 14.43.

Iodohydrin **25**: yellow oil. ^{1}H-NMR: 7.32 (s, 5H); 4.5 (s, 2H); 4.1 (m, 1H); 3.5-3.78 (m, 3H); 3.2 (bs, 1H, OH); 1.71-2.05 (m, 4H);1.01 ppm(t, J = 7.3 Hz,3H).^{13}-C-NMR: 137.84; 128.54; 128.45; 127.88; 127.77; 127.69; 73.84; 73.26; 68.08; 48.74; 34.66; 28.42; 14.27 ppm.

Iodohydrin **27**: yellow oil. ^{1}H-NMR: 7.3 (s, 5H); 4.5 (s, 2H); 4.05 (m, 1H);3.55-3.75 (m, 2H); 3.22-3.37 (m, 1H); 2.72 (d, J = 5.5 Hz, OH); 1.8-2.05 (m, 4H); 1.08 ppm (t, J = 4.8 Hz, 3H). ^{13}C-NMR: 138.00; 129.14; 128.57; 128.32; 127.89; 127.82; 73.27; 72.87; 67.84; 50.21; 36.87; 30.27; 14.40 ppm.

PREPARATION OF DIOLS

General Procedure for the Preparation of Diols **13-19** and **26**.

The previous procedure for the preparation of the iodohydrins from the epoxy alcohols was followed: after TLC monitoring (UV lamp) of the complete opening of the epoxide with MgI_2,the reaction mixture was raised at room temperature. Then AIBN (catalytic) and nBu_3SnH (1 mmole) were added and the temperature was raised to 70 C. The reaction was completed after 1-2 h (TLC monitoring, UV lamp and H_2SO_4 spraying), and most of the solvents were removed in vacuo. The residue was diluted with CH_3CN (30 mL), and washed with hexane (three portions) to eliminate the tin residues. The CH_3CN solution was then evaporate in vacuo and the residue chromatographed on silica gel (petroleum ether/ether as eluent) affording purified diols.

Diols **13**,**17** and **18** are commercially available products

Diol **14**: oil. ^{1}H-NMR: 3.80 (m, 1H); 3.45 (q, J = 6.9 Hz, 1H); 2.18 (s, 3H); 1.75-1.53 (m, 3H, OH); 1.18 (d, J = 7.0 Hz, 3H); 0.9 ppm (t, J = 7.2 Hz, 3H).Anal. Calcd. for $C_7H_{14}O_3$: C, 57.50; H, 9.66. Found: C, 57.42; H, 9.71.

Diol **15**: oil. ^{1}H-NMR: 4.65 (d, J = 12.3 Hz, 1H); 4.92 (d, J = 12.3 Hz, 1H); 3.46 (m, 2H); 2.64 (d, J = 3.3 Hz, 1H, OH); 1.71-1.22 (m, 2H); 1.17 (d, J = 6.2 Hz, 3H); 0.92 ppm (t, J = 7.8 Hz, 3H).Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.17; H, 9.34. Found: C, 73.99; H, 9.39.

Diol **16**: oil. ^{1}H-NMR: 3.64 (m, 2H); 1.87 (bs, 2H, OH); 1.22-1.65 (m, 8H); 0.97 (d, J = 7.7 Hz, 3H); 0.86 ppm (t, J = 8.6 Hz, 3H). ^{13}C-NMR: 76.20; 74.44; 30.76; 28.02; 24.02; 22.56; 13.83; 10.20 ppm.Anal. Calcd. for $C_8H_{18}O_2$: C, 65.69; H, 12.41. Found: C, 65.81; H, 12.37.

Diol **19**: oil. ^{1}H-NMR: 3.75 (m, 1H); 3.56 (m, 1H); 2.41 (m, 2H, OH); 1.68-1.12 (m, 8H); 1.1 (d, J = 6.5 Hz, 3H);0.9 ppm (t, J = 7.7 Hz, 3H). ^{13}C-NMR: 74.76; 70.26; 31.71; 31.56; 25.50; 22.41; 19.25; 13.36 ppm. Anal. Calcd. for $C_8H_{18}O_2$:C, 65.69;H, 12.41. Found: C, 65.61; H, 12.51.

Diol **26**: oil. ^{1}H-NMR: 7.3 (bs, 5H); 4.51 (s, 2H); 3.55-3.9 (m, 3H); 2.83 (d, J = 4 Hz, 1H, OH); 1.72 (q, J = 6.1 Hz, 2H);; 1.2-1.5 (m, 4H); 0.91 ppm (bt, J = 6.3 Hz, 3H). ^{13}C-NMR: 128.58; 127.86; 127.79; 73.29; 71.16; 69.27; 39.51; 36.27; 18.58; 13.91 ppm. Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.97; H, 9.65. Found: C, 74.92; H, 9.70.

SYNTHESIS OF 2S,3S-OCTANDIOL

Chiral epoxy alcohol **7** was prepared according to ref. 14b

Epoxy alcohol **20**: the procedure described in ref. 15 was followed. Compound **7** (270 mg, 1.8 mmol) was dissolved in dry THF (22 mL) under a nitrogen atmosphere with stirring. Then Ph_3P (980 mg, 3.7 mmol),and HCOOH (0.12 mL, 3.7 mmol) were added at room temp. To this a solution of diethyl azodicarboxylate (DEAD) (643 mg, 3.7 mmol in 4 mL of dry THF) was dropwise added.After 12 h the reaction was completed (TLC monitoring) and the solvent was evaporated in vacuo.The residue , dissolved in MeOH (20 mL), was added of catalytic Na under a nitrogen atmosphere and stirring. After 10 min the reaction was completed and the solvents were evaporated. The residue was then purified by silica gel chromatography (Petroleum ether: AcOEt 8/2 as eluent), affording pure **20** (140 mg, 52%). Oil. ^{1}H-NMR: 3.34 (m, 1H);2.87-2.97 (m, 1H); 2.776 (m, 1H); 2.65 (m, 1H); 2.46 (d,OH); 1.15-1.6 (m, 8H); 0.83 ppm (bt, J = 11.7 Hz, 3H).^{13}C-NMR: 71.71; 55.41; 45.01; 34.02; 31.56; 24.73; 22.28; 13.70 ppm.Anal. Calcd.for $C_8H_{16}O_2$:C, 66.61; H, 11.19. Found: C, 66.69; H, 11.15.

(2S,3S)-Octandiol: compound **20** (140 mg,0.97 mmol) was treated in the same reaction conditions as described in the general procedure for the preparation of the diols (see above). The synthetic octandiol (130 mg,91 %) shows the same spectroscopic data as described in ref. 14b.^{1}H-NMR:3.54 (quintet, J = 11.3 Hz, 1H), 3.28 (m, 1H), 1.6 (m, 8H), 1.15 (d, J = 11.3 Hz, 3H), 0.85 ppm (t, J = 9.43 Hz, 3H). ^{13}C-NMR: 76.21, 70.86, 33.17, 31.70, 25.07, 22.41, 19.31, 13.82 ppm. $[a]_D$ = -16.8 (c = 0.8 in $CHCl_3$).

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18. This work was partially supported by C.N.R. " Progetto Chimica Fine e Secondaria".