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2. Synthesis of Optically Active Oligoethers of (S)-1,2-Propanediol*

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SUMMARY

Optically active head-to-tail dimer and trimer of(S)-1,2-propanediol have been prepared by a step-wise synthetic procedure employing a strict chemical and stereochemical control, and by catalytic oligomerization of (R)-propylene oxide under anionic polymerization conditions.

INTRODUCTION

Since a few years our attention has been focused on the synthesis of structurally ordered segmented polyesters containing flexible oligoether segments (CHIELLINI et al.1980; GALLI et al.1982; SCHLEIER et al.1982).

Among these a particular interest is held by polyesters based on mesogenic hard segments flanked by flexible chiral segments such as those derived from propanediol and glycidol monoethers, capable of imparting to the polymers, other than a somewhat hydrophile character, a definite stereochemical assembling of hard segments in a cholesteric-type structural array.

Following a preliminary paper (MALANGA et al.1982), relevant to the description of the regioselective protection of hydroxyl group in (S)-1,2-propanediol,in the present work we are reporting on the synthesis of head-to-tail dimer and trimer of (S)-1,2-propanediol.

The synthesis of mesomorphic polyesters of the reported glycolethers will be described in a forthcoming paper (CHIELLINI et al.), submitted to this journal.

RESULTS AND DISCUSSION

Back in the early fifties it was reported (SEXTON et al.1953) that a racemic mixture of head-to-tail dimers of 1,2-propanediol could be obtained by reacting racemic

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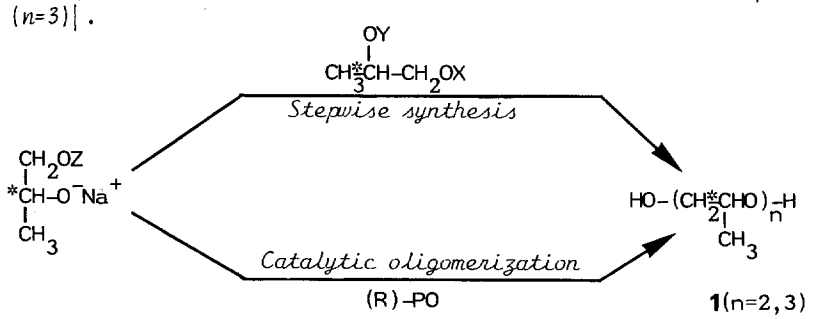
propylene oxide with racemic 1-methoxy-2-propanol, in the presence of sodium followed by demethylation of methoxy group under severe acid conditions. This procedure, that brought to a mixture of oligomers from which the dimer is separated with difficulty, cannot be used to prepare optically active compounds standing the reaction conditions adopted.

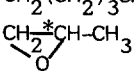
Since nothing was reported on the preparation of optically active head-to-tail oligomers of 1,2-propanediol it seemed worthwile to undertake a research project inherent into the synthesis of optically active oligoethers having the general structure $HO|CH_2^*CH(R)-O|_n^-H$ ($R=CH_3$, CH_2OR') .

They should be able not only to fulfill the perspectives adduced in the Introduction, but also to provide a breakthrough for interesting practical and speculative implications connected with the availability of chemical and stereochemical defined new oligoethers.

As represented in Scheme 1, two synthetic routes, based on a stepwise synthesis and a catalytic oligomerization respectively, have been applied for the preparation of optically active head-to-tail dimer and trimer of (S)-1,2-propanediol.

SCHEME 1 *Synthesis of (2S,5S)-2-methyl-3-oxahexan-1,5-diol | 1 (n=2) | and (2S,5S,8S)-2,5-dimethyl-3,6-dioxanonan-1,8-diol | 1 (n=3) |.*



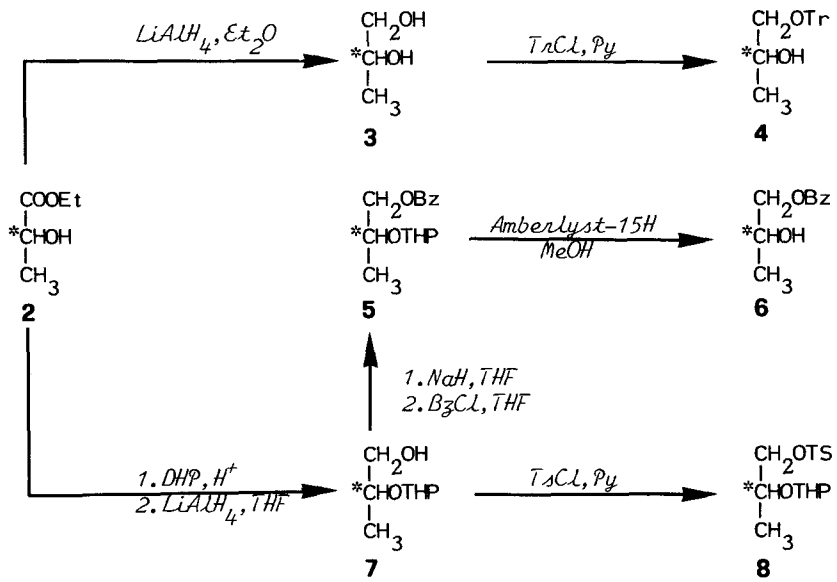
X= *p*-$CH_3C_6H_4SO_2$- (*Ts*); Y= $CH_2(CH_2)_3CH$- (*THP*); Z = $-CPh_3$ (*Tr*); $-CH_2Ph$ (*Bz*); (R)-PO= 

In both routes, commercially available optically active (S)-ethyl lactate **2** was used as starting material and, either as it is or after suitable protection of the hydroxyl group, was reduced to give free or partially

protected (S)-1,2-propanediol respectively.

The general procedures adopted for the preparation of the selectively protected precursors, to use in the oligomerization and stepwise procedure, are represented in Scheme 2.

SCHEME 2 *Synthesis of the selectively protected (S)-1,2-propanediol derivatives.*



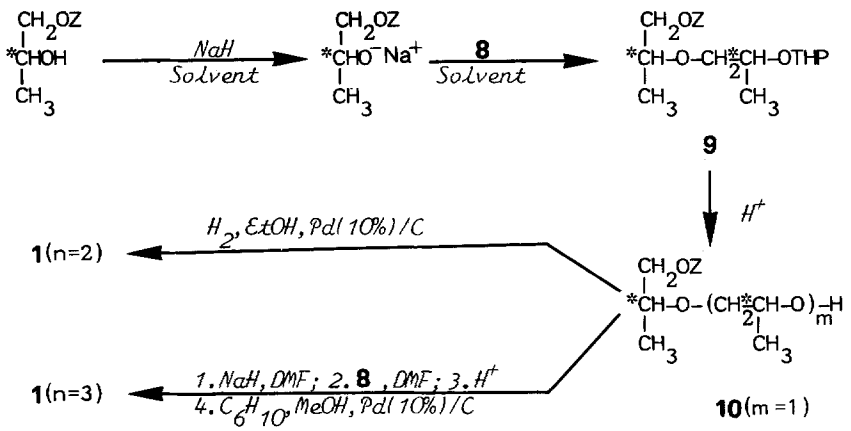
The basic idea to a stepwise synthesis, suitable to guarantee for head-to-tail placement of the structural units having the same optical purity of the precursors, implies among the other, the use of, easy-to-remove, protecting groups of the primary alcoholic function and experimental conditions capable of enhancing the nucleophilicity of the secondary alcoholic group anion.

Selectively mono- and diprotected (S)-1,2-propanediol derivatives **4**, **6** and **8** respectively, that can be prepared in good chemical yields under strictly controlled stereochemical pathways, appeared well in keeping with the mentioned general requirements.

The reaction of **4** or **6** with sodium hydride in tetrahydrofurane afforded the corresponding anion derivatives which by reacting with **8** gave the dimer **1** (n=2) in diffe-

rent yields depending on the experimental conditions (Scheme 3).

SCHEME 3 *Stepwise synthesis of head-to-tail dimer and trimer of (S)-1,2-propanediol.*



Z	*Solvent*	*T°C*	**10**(m=1)-*Yield(%)*
Tr	*THF*	*65*	*Traces*
Bz	*THF*	*65*	*15*
Bz	*DMF*	*50*	*95*

When the anion of **4** was treated in THF with compound **8**, no reaction occurs, whereas the anion of the derivative **6** is able to give rise to a displacement of the tosyl group of **8** . The reaction yield is strongly dependent on the nature of the solvent: in DMF an almost quantitative conversion is observed whereas a 15% yield was only obtained in THF even after a prolonged reaction time.

The failure of the reaction with the anion of **4** seems most probably due to the bulkiness of the blocking group which sterically hinders the approach of the anion.

A reasonable explanation of the solvent effect on the reactivity of the benzyl derivative **6** anion, can be afforded in terms of a possible interaction between the sodium cation and the oxygen of benzyloxy group resulting in a stabilized conformational and electronical array. The proposed structure is coherent with the ^{13}C-NMR data: an appreciable deshielding effect (larger than 5 ppm) is observed on the methylene carbon of the benzyl group when in going from the alcohol **6** , to its sodium

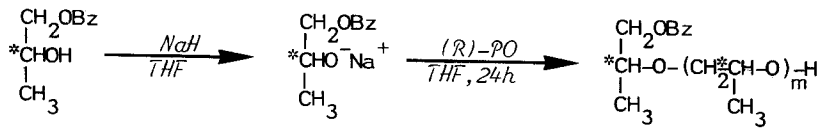
derivative, whereas the aromatic carbon atoms are only slightly perturbed (see Experimental).

The prepared dimer and trimer of (S)-1,2-propanediol were characterized by ^{1}H-, ^{13}C-NMR and optical rotation measurements. It has to be underlined that the ^{13}C-NMR spectra do not show any signal attributable to the presence of diastereoisomeric impurities.

Consequently an optical purity of 94% equal to that of the starting (S)-ethyl lactate, can be attributed to the dimer and the trimer.

The procedure based on the catalytic oligomerization was applied to the reaction of sodium alcoholate of (S)-**6** with a stoichiometric amount of 93% optically pure (R)-propylene oxide (Scheme 4).

SCHEME 4 *Oligomerization of optically active propylene oxide.*



6

10(m=1,2,3)

The optically active propylene oxide was obtained from the corresponding diol by using a procedure already described (LEVENE and WALTI 1926). A rather complex mixture of products having the following composition (as determined by GLC) was obtained : (S)-**6** 21%, 1-benzyloxyderivatives of (2S,5R)-**1** (n=2) 39%, of (2S,5R,8R)-**1** (n=3) 31%, of (2S,5R,8R,11R)-**1** (n=4) 3% and traces of the corresponding pentamer.

Chemically pure samples of (S)-**6** and 1-benzyloxyderivative of **1** (n=2,3) were recovered by preparative GLC. The structure of isolated compounds was established by ^{1}H-, ^{13}C-NMR, mass spectrometry and IR spectroscopy.

The comparison of their spectral profiles with those of the corresponding compounds obtained by step-by-step synthesis, clearly shows that the opening of the oxirane ring occurs regiochemically at the C_1 carbon atom only, as expected (CASE and RENT 1964).

EXPERIMENTAL PART

(S)-1-Benzyloxy-2-tetrahydropyranyloxypropane (*5*). To a suspension of 1.20g (0.05mol) of NaH in 25ml of THF, under N_2,

7.50g (0.05mol) of (S)-2-tetrahydropyranyloxy-1-hydroxypropane (**7**) (MALANGA et al.1982) are slowly added. The mixture is stirred at the reflux of the solvent for 3h and, after cooling at room temperature, a solution of 5.73g (0.05mol) of benzylchloride in THF (20ml) is added. The mixture is refluxed for 1h and then hydrolyzed with water and extracted with ether. Finally the organic phase is washed with water and dried ($CaCO_3$).Distillation gives 12.0g (yield 96%) of **5** (bp.130-135°C/4mm).
IR (film):ν 3050,3040,3000,2940,2860,2830,1500,1450,1130,1050, 990,930,750 and 700 cm^{-1}.
^{13}C-NMR ($CDCl_3$), δ (from TMS): 138.40(δ,C_1Ph),128.11(δ,$C_{2,6}$Ph), 127.33(δ,$C_{3,4,5}$Ph),97.29(2δ,C_2THP),75.04(2δ,C_1),72.97(δ,-OCH_2Ph), 71.03(2δ,C_6THP),62.24(2δ,C_2),30.84(δ,C_3THP),25.36(δ,C_5THP),19.51 (2δ,C_4THP) and 17.50(2δ,C_3) ppm; (δ: single signal).
(S)-1-Benzyloxy-2-hydroxypropane (*6*). A suspension of 7.50g (0.03mol) of **5** and 1.00g of Amberlyst-15H in 25ml of methanol is stirred for 3h then the catalyst is filtered off. Distillation gives 4.70g (yield 94%) of **6** | bp. 119°C/4mm, α^{25}_{589}+4.80°(neat, *ℓ*=1dm)| .
IR (film):ν 3380(broad),3050,3040,3000,2940,2900,2860, 2830,1450,1180,740 and 690 cm^{-1}.
^{1}H-NMR (CCl_4), δ (from TMS): 7.06(δ,5H),4.36(δ,2H),4.00-3.60(*m*,1H), 3.40-3.00(*m*,2H) and 1.10-0.90(*d*,3H) ppm.
^{13}C-NMR (THF,CD_3OD external reference),δ (from TMS): 138.37(δ , C_1Ph),128.46,127.78(2δ,$C_{2,3}$Ph),126.00(δ,C_4Ph),76.01(δ,-OCH_2Ph), 72.37(δ,C_1),65.38(δ,C_2) and 18.93(δ,C_3) ppm; (δ: single signal).
The sodium salt of (**6**) shows: ^{13}C-NMR (THF,CD_3OD external reference), δ (from TMS): 139.06(δ,C_1Ph),128.09,127.55(2δ,$C_{2,3}$Ph), 126.81(δ,C_4Ph),81.18(δ,-OCH_2Ph),72.71(δ,C_1),67.32(δ,C_2) and 25.48(δ,C_3) ppm; (δ:single signal).
(2S,5S)-1-Benzyloxy-2-methyl-5-hydroxy-3-oxahexane |*10* (*m*=*1*)|.To a suspension of 1.20g (0.05mol) of NaH in DMF (25ml), 30ml of a solution in the same solvent of 8.30g (0.05mol) of **6** are added. The mixture is vigorously stirred at 50°C for 3h then, after cooling at room temperature, a solution of 15.77g (0.05mol) of (S)-1-tosyloxy-2-tetrahydropyranyloxypropane **8** (GHIRARDELLI 1973) in DMF 30ml are added and the reaction mixture warmed at 50°C for 5h. After removal of the solvent, the crude dark brown oil **9** is dissolved in 50ml of methanol and treated with 5.00g of Amberlyst-15H. After stirring for 3h , the reaction mixture is worked up as already described to give 7.84g (yield 70%) of **10** (m=1) |bp.100°C/0.01mm, α^{25}_{589} +15.26°(neat,*ℓ*=1dm)| .
IR (film):ν3380(broad),3050,3040,3000,2940,2900,2860,2830,1450,

1180,740 and 690 cm^{-1}.
^{1}H-NMR (CCl_4), δ (from TMS): 7.00(*s*,5H),4.22(*s*,2H),3.80-2.80 (*m*,7H) and 1.20-0.80(2*d*,6H) ppm.
^{13}C- NMR ($CDCl_3$), δ (from TMS): 137.86(*s*,C_1Ph),128.55(*s*,$C_{2,6}$Ph), 127.53(*s*,$C_{3,4,5}$Ph),74.48(2*s*,C_1),73.79(*s*,C_5),73.12(*s*,-OCH_2Ph),65.79 (*s*,C_2),18.47(*s*,CH_3C_2) and 16.81(*s*,C_6) ppm; (*s*:single signal).
(2S,5S)-2-Methyl-1,5-dihydroxy-3-oxahexane |*1* (*n*=2)|. In a typical run 7.84g (0.035mol) of **10** (m=1) dissolved in 10ml of ethanol are reacted with H_2, (atmospheric pressure, room temperature) under continuous stirring, in the presence of 1.00g of Pd(10%)/C (Fluka A.G.Co.). When the theoretical volume of H_2 is absorbed (3 days), the catalyst is filtered off and solvent evaporated. Distillation gives 4.60g (yield 98%) of 97% chemically pure (SE 301) **1** (n=2){bp. 96°C/0.5mm, α^{25}_{589}+40.50°(neat,*ℓ*=*1*dm) ,|$\alpha|^{25}_{589}$+63.80(c=2.080,$CHCl_3$)}. Chemically pure **1** (n=2)(preparative GLC) shows: α^{25}_{589}+42.86° (neat,*ℓ*=*1 dm*).
IR (film):ν 3450,2970,2930,2870,1450,1375,1140,1085 and 1010 cm^{-1}.
^{1}H-NMR (CCl_4), δ (from TMS): 4.60(*s*,2H),4.30-3.40(*m*,2H),3.60-3.20 (2*d*,4H) and 1.40-1.00(2*d*,6H) ppm.
^{13}C-NMR ($CDCl_3/CD_3COCD_3$,1:1), δ (from TMS): 75.78(*s*,C_4),73.51(*s*, C_2),65.53(2*s*,$C_{1,5}$),18.32(*s*,C_6) and 15.40(*s*,CH_3C_2) ppm; (*s* : single signal).
(2S,5S,8S)-1-Benzyloxy-2,5-dimethyl-8-hydroxy-3,6-oxanonane |*10* (*m*=2)|. Starting from 7.84g (0.035mol) of **10** (m=1) 0.84g (0.035mol) of NaH, 30ml of DMF and 11.04g (0.035mol) of **8** and using the same reaction adopted for preparing **9**, 12.80g of 70% chemically pure tetrahydropyranyl derivative of **10**(m=2) is obtained as a dark brown oil (the main impurities are constituted by **8** and **10**(m=1). The crude product dissolved in methanol (100ml) is depyranylated in the presence of Amberlyst-15H (3g) to give 6.91g (yield 90%) of 90% chemically pure (CW 20M) **10** (m=2)(bp .135°C/0.4mm).
^{1}H-NMR (CCl_4), δ (from TMS): 7.35(*m*,5H),4.40(*s*,2H),4.20-3.00(*m*, 10H) and 1.40-0.90(3*d*,9H) ppm.
^{13}C-NMR ($CDCl_3$), δ (from TMS): 138.02(*s*,C_1Ph),128.04(*s*,C_2Ph),127.34 (*s*,C_3Ph),127.26(*s*,C_4Ph),74.95,74.71,74.36,73.78,73.07,72.97(6*s*,C_1, C_2,C_4,C_5,C_7,-OCH_2Ph),65.51(*s*,C_8),18.42(*s*,C_9) and 17.01,16.90(2*s*, CH_3C_2,CH_3C_5) ppm; (*s*: single signal).
(2S,5S,8S)-2,5-Dimethyl-1,8-dihydroxy-3,6-dioxanonane |*1* (*n*=3)|. A mixture of 6.91g of **10**(m=2), 3g of Pd(10%)/C (Fluka A. G.Co),and 70ml of cyclohexene in methanol (100ml) are stirred with refluxing under N_2 for 10h. The catalyst is filtered off and the mixture worked up as usual gives 4.08g of chemically pure (CW 20M) **1** (n=3) {bp.125°C/ 1mm, α^{25}_{589}+28.57°(neat,*ℓ*=*1*dm), |$\alpha|^{25}_{589}$+66.30(c=2.270,$CHCl_3$)}.

^{1}H-NMR (CCl_4), δ (from TMS): 3.90(*s*,2H),4.20-3.30(*m*,9H) and 1.40-1.00(3*d*,9H) ppm.
^{13}C-NMR ($CDCl_3$), δ (from TMS): 76.57(*s*,C_1),74.33,71.96(2*s*,C_4,C_5), 73.96(*s*,C_2),65.87,65.58(2*s*,C_7,C_8),18.41(*s*,C_9),16.38(*s*,CH_3C_5) and 15.52(*s*,CH_3C_2) ppm; (*s*: single signal).

(S)-1-Trityloxy-2-propanol (**4**). (S)-1,2-Propanediol (**3**) $|\alpha|^{25}_{589}$ +16.44°(neat,*l*=1dm)| (MALANGA et al.1982),16.00g (0.21mol) and 58.48g (0.21mol) of tritylchloride in anhydrous pyridine (100ml) are stirred at room temperature for 10h. The mixture is then filtered, hydrolyzed with water and extracted with ether. The crude yellow product is twice recristallized from pentane to give 53.42g (yield 80%) of **4** { mp.84°C,$|\alpha|^{25}_{589}$+13.57(c=1.990,$CHCl_3$)}.
^{13}C-NMR ($CDCl_3$), δ (from TMS): 143.76(*s*,C_1Ph),128.55(*s*,C_3Ph),127.75 (*s*,C_2Ph),126.97(*s*,C_4Ph),86.49(*s*,CPh_3),68.87(*s*,C_1),66.93(*s*,C_2) and 18.95(*s*,C_3) ppm; (*s*:single signal).

Oligomerization of (R)-propylene oxide. To a suspension of 2.40g (0.10mol) of NaH in THF (25ml) under N_2 , 16.60g (0.10mol) of **6** are added. After the alcoholate formation 5.40g (0.10mol) of (R)-propylene oxide,α^{25}_{589} +11.22°(neat, *l*=1dm), are added and the mixture stirred for 12h. The reaction mixture, recovered as usual, contains **6** and 1-benzyloxy derivatives of **1**(n=2,3,4,5) in the ratio 21:39:31:3:1 as established by GLC and mass spectrometry. Chemically pure samples of **6** ,(2S,5R)-1-benzyloxy-**1** (n=2) $|\alpha^{25}_{589}$ -2.17°(neat,*l*=1dm)| and (2S,5R,8R)-1-benzyloxy-**1** (n=3) $|\alpha^{25}_{589}$-10.01°(neat,*l*=1dm)| are recovered by preparative GLC(SE 301). Mass spectra (m/e,I%) of:**6** |166(M^+,26),90(100)|,1-benzyloxy derivatives of **1** (n=2) |264(M^+,12),58(100)|,of **1**(n=3) |282(M^+,0.5),58 (100)|, of **1** (n=4) |340(M^+,0.6),58(100)|, of **1** (n=5) |398(M^+,1),58 (100)|.

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