Lipase-Catalyzed Enantioselective Synthesis of Optically Active Mephobarbital, Hexobarbital and Febarbamate

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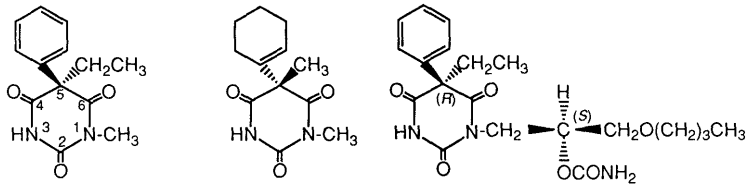
Chiral 5,5-disubstituted *N*-acyloxymethylbarbiturates have been obtained in 40—99% optical yields by lipase-catalyzed hydrolyses of 5,5-disubstituted *N,N'*-bisacyloxymethylbarbiturates in H_2O-saturated diisopropyl ether. These chiral barbiturates were readily converted into chiral drugs, mephobarbital, hexobarbital and febarbamate.

Keywords lipase; hydrolysis; organic solvent; asymmetric synthesis; *N*-acyloxymethyl group; chiral barbiturate; mephobarbital; hexobarbital; febarbamate

Enzymes are substrate-specific and highly enantioselective catalysts for asymmetric syntheses.[1] One group of enzymes, lipases, has been widely used for asymmetric hydrolysis and esterification. In particular, the use of lipases in organic solvents is a powerful and convenient procedure in organic synthesis. We have reported several asymmetric syntheses with lipase in organic medium.[2] In this paper we present the details of the first asymmetric synthesis of optically active barbiturates using lipase as a catalyst.[3]

Some barbiturates, such as mephobarbital, hexobarbital and febarbamate, have an asymmetric carbon atom at the C-5 position due to a dissymmetric *N*-methyl or *N*-[(2-aminocarbonyl)oxy]-3-butoxypropane substituent on their 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione skeleton[4] and their optical isomers have different pharmacodynamic and pharmacokinetic characteristics.[5] For example, (*R*)-(−)-5-ethyl-1-methyl-5-phenylbarbiturate (mephobarbital, **1**) is a sedative while its (*S*)-(+)-isomer may cause central nervous system excitation. On the other hand, (*S*)-(+)-5-(cyclohexen-1-yl)-1,5-dimethylbarbiturate(hexobarbital, **2**) is more anesthetically active than its (*R*)-(−)-antipode. Optically active barbiturates have been synthesized only by resolution of the racemates.[6] Therefore, the lack of efficient synthetic methods has made it necessary to use racemic mixtures of chiral barbiturates as drugs.

We designed acyloxymethyl groups as suitable functional groups for lipase-catalyzed hydrolysis. The lipase-catalyzed asymmetric synthesis was expected to be applicable to 5,5-disubstituted *N,N'*-bisacyloxymethylbarbiturates (**4**) (Chart 2). The alcohol (*N*-hydroxymethyl), which is the



(*R*)-mephobarbital ((*R*)-**1**) (*S*)-hexobarbital ((*S*)-**2**) (*R,S*)-febarbamate ((*R,S*)-**3**)

Chart 1

TABLE I. Lipase-Catalyzed Asymmetric Syntheses of Chiral Barbituric Acid Derivatives[a]

Entry	Substrate				Lipase	React. time (h)	Conversn.[b] (%)	Product			
	No.	R^1	R^2	R^3				No.	Isolated yield (%)[c]	% ee[d]	Confign.
1	**4a**	Ph	Et	*tert*-Bu	AY[e]	96	14	**5a**	11	75	*S*
2	**4b**	Ph	Me	Et	AY	1.5	100	**5b**	50	40	*R*
3	**4b**	Ph	Me	Et	CE	4	100	**5b**	49	99	*R*
4	**4c**	Ph	Et	Et	AY	2	100	**5c**	50	95	*S*
5	**4c**	Ph	Et	Et	CE	9	90	**5c**	52	99	*R*
6	**4d**	Ph	Pr	Et	AY	1.5	100	**5d**	62	43	*S*
7	**4d**	Ph	Pr	Et	CE	9	90	**5d**	34	93	*R*
8	**4e**		Me	Et	AY	2.5	100	**5e**	50	43	*S*
9	**4e**		Me	Et	CE	9	80	**5e**	48	95	*R*
10	**4f**		Et	Et	AY	1	100	**5f**	62	90	*S*
11	**4f**		Et	Et	CE	22	77	**5f**	33	81	*R*

a) All reactions were carried out with substrate (0.5 mmol), isopropyl ether saturated with H_2O and crude lipase (AY, 100 mg; CE, 500 mg) at 20°C unless otherwise noted. *b*) Conversion was determined based on the recovery of substrate. *c*) Only accompanied by a fully hydrolyzed barbiturate. *d*) Optical yields were determined by HPLC analyses using a column packed with Chiralcel OJ. *e*) Lipase (500 mg).

hydrolysis product, is readily decomposed to formaldehyde and an optically active monoacyloxymethyl derivative (**5**). Therefore, the reverse reaction does not occur and the hydrolysis goes to completion.

N,N'-Bisacyloxymethylbarbiturates (**4a—f**) were prepared by the reaction of sodium barbiturates with acyloxymethyl chloride. Table I shows the results of asymmetric hydrolysis of *N,N'*-bisacyloxymethylbarbitals (**4a—f**). Preliminary investigations revealed that lipase AY (from *Candida rugosa*) and lipase CE (from *Humicola lanuginosa*)[7] were effective for the hydrolysis of **4a—f**. The hydrolysis of *N,N'*-bispivaloyloxymethylphenobarbital (**4a**) was tested with lipase AY. The reaction was carried out by stirring a suspension of the substrate (0.5 mmol) and crude lipase AY (500 mg = 25000 U) in H_2O–saturated diisopropyl ether (20 ml) at room temperature. The hydrolysis proceeded to give (−)-*N*-pivaloyloxymethylphenobarbital (**5a**) in a 75% optical yield, but the reaction rate was very slow. The hydrolysis of *N,N'*-bispropionyloxymethylphenobarbital (**4c**) was examined with lipase AY (100 mg). This hydrolysis proceeded smoothly to give (+)-*N*-propionyloxymethylphenobarbital ((+)-**5c**) in a 95% optical yield. When lipase CE (500 mg = 2500 U) was used, the reaction rate was slower than that of lipase AY and the (−)-antipode ((−)-**5c**) was obtained in a 99% optical yield. The hydrolyses of the other barbiturates (**4b**, **d—f**) were conducted in order to investigate the applicability and stereoselectivity of lipase-catalyzed hydrolysis of these barbiturates. The lipase AY-catalyzed hydrolysis of the barbiturates except **4b** gave the *S*-products. On the other hand, the lipase CE-catalyzed hydrolysis gave the *R*-products in high optical yields in every case examined here. It is noteworthy that lipases show high stereoselectivity in spite of the distance separating the reaction site and the asymmetric carbon atom.

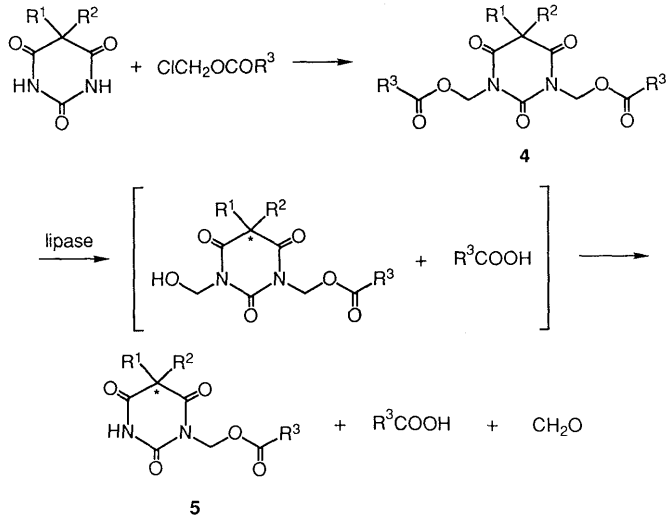


Chart 2

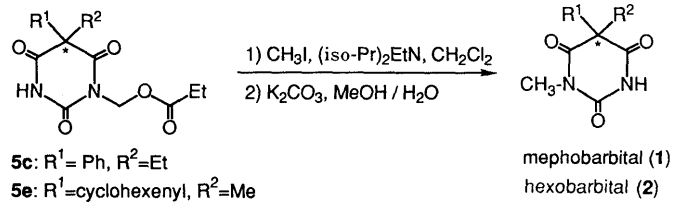


Chart 3

These optically active monopropionyloxymethylbarbiturates were applied to the synthesis of chiral drugs, *i.e.*, mephobarbital, hexobarbital and febarbamate.

Successive treatment of **5c** with methyl iodide in the presence of *N,N*-diisopropylethylamine followed by hydrolysis of potassium carbonate in H_2O–MeOH gave mephobarbital. A single recrystallization of the product from ethanol–H_2O gave optically pure mephobarbital. Optically pure hexobarbital was obtained from **5e** in a similar manner.

Similarly, optical isomers of febarbamate (**3**)[8] can be prepared from (*R*)- or (*S*)-**5c** and (*R*)- or (*S*)-2-(aminocarbonyl)oxy-3-butoxy-1-iodopropane (**13**). Further, (*R*)- and (*S*)-**13** were readily obtained from (*S*)- and (*R*)-2-*O*-benzyl-1-*O*-tosylglycerol (**6**),[9] respectively, which were prepared from (*S*)-1-*O*-acetyl-2-*O*-benzylglycerol.[10] After protection of (*R*)-**6** with dihydropyran, replacement reaction was carried out with sodium *n*-butoxide to give (*R*)-**8**. Deprotection of the tetrahydropyranyl (THP) group of (*R*)-**8** with pyridinium *p*-toluenesulfonate (PPTS) in ethanol followed by tosylation of (*R*)-**9** gave (*S*)-2-*O*-benzyl-1-*O*-butyl-3-*O*-tosylglycerol (**10**). Hydrogenolysis of (*S*)-**10** over 5% Pd–C in ethanol gave (*S*)-**11**. Iodination of the tosylate ((*S*)-**11**) was carried out with sodium iodide and the resulting compound ((*S*)-**12**) was allowed to react with sodium cyanate and trifluoroacetic acid to afford optically pure (*S*)-**13**. In the same manner, (*R*)-**13** was obtained from (*S*)-**6**.

Optically pure (*R*)- and (*S*)-**5c** were obtained by single recrystallization from petroleum ether. Then (*R*)- or (*S*)-**5c** was treated with sodium hydride in *N,N*-dimethylformamide to give the corresponding salt, which was reacted with (*R*)- or (*S*)-**13** to afford (*S,S*)-, (*R,R*)-, (*S,R*)- and (*R,S*)-**14** in about 80% yield. Finally (*R,S*)-, (*S,R*)-, (*R,R*)- and (*S,S*)-febarbamate (**3**) were obtained by hydrolysis of (*S,S*)-, (*R,R*)-, (*S,R*)- and (*R,S*)-**14**, with potassium carbonate, respectively.

The lipase-catalyzed asymmetric hydrolysis of *N,N'*-bisacyloxymethylbarbiturates now provides a new method for preparation of chiral barbiturates such as mephobarbi-

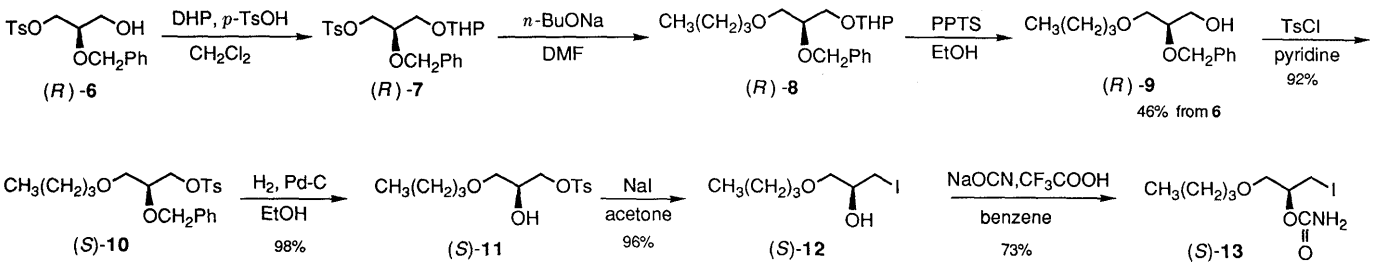
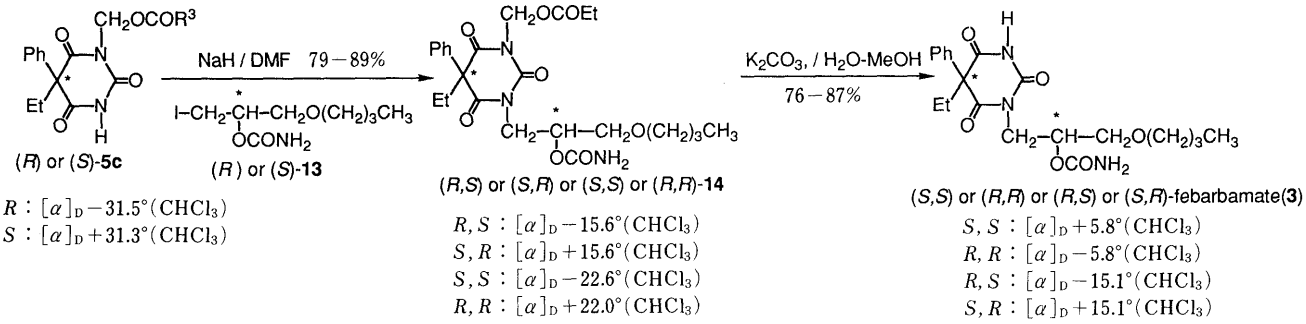


Chart 4



R : $[\alpha]_D$ −31.5°($CHCl_3$)
S : $[\alpha]_D$ +31.3°($CHCl_3$)

R,S : $[\alpha]_D$ −15.6°($CHCl_3$)
S,R : $[\alpha]_D$ +15.6°($CHCl_3$)
S,S : $[\alpha]_D$ −22.6°($CHCl_3$)
R,R : $[\alpha]_D$ +22.0°($CHCl_3$)

S,S : $[\alpha]_D$ +5.8°($CHCl_3$)
R,R : $[\alpha]_D$ −5.8°($CHCl_3$)
R,S : $[\alpha]_D$ −15.1°($CHCl_3$)
S,R : $[\alpha]_D$ +15.1°($CHCl_3$)

Chart 5

tal, hexobarbital and febarbamate, for use as chiral medicines.

Experimental

Melting points were determined on a micro melting point apparatus BY-1 (Yazawa) and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. IR spectra were taken on JASCO IR-810 IR spectrophotometers. ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 FT-NMR spectrometer using tetramethylsilane (in $CDCl_3$) as an internal standard. Abbreviations are as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HPLC was carried out with a JASCO Trirotar-V (ultraviolet detection) equipped with a column packed with Chiralcel OJ (ethanol). Column chromatography was carried out on a silica gel (Kiesel gel-60, 70—230 mesh, Merck). Thin-layer chromatography was used to monitor the reactions and to ascertain the purity of the reaction products. The following lipases were used; lipase AY and lipase CE (Amano Seiyaku Co., Ltd.).

5,5-Disubstituted *N,N'*-Bis(propionyloxymethyl)barbital (4) A 5,5-disubstituted barbital (6 mmol) was added to an ice-cooled and stirred suspension of oil-free sodium hydride (144 mg, 6 mmol) in dry *N,N*-dimethylformamide (DMF) (20 ml). Stirring was continued for 1 h, then chloromethyl propionate (735 mg, 12 mmol) was added and the mixture was stirred for an additional 1 h at room temperature. The reaction mixture was poured into ice-cold water and extracted with ether three times. The combined extracts were washed with brine and dried. The solvent was removed, and the residual oil was chromatographed on a short silica gel column with ethyl acetate and *n*-hexane to give a colorless solid. Recrystallization from petroleum ether gave **4** as a colorless powder.

1,3-Bis(propionyloxymethyl)-5-methyl-5-phenylbarbital (**4b**): Yield 1.05 g (45%), mp 81—82 °C. IR (KBr) cm^{-1}: 1750, 1710 (CO). ^{1}H-NMR: 1.12 (6H, t, J=7.3 Hz, 2×CH_3), 1.87 (3H, s, CH_3), 2.33 (4H, q, J=7.3 Hz, 2×CH_2), 5.93 (4H, ABq, J=9.9 Hz, 2×NCH_2O), 7.21—7.26 (2H, m, Ar-H), 7.33—7.38 (3H, m, Ar-H). *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.68; N, 7.18. Found: C, 58.38; H, 5.77; N, 7.14.

1,3-Bis(propionyloxymethyl)-5-ethyl-5-phenylbarbital (**4c**): Yield 1.31 g (54%), mp 91—92 °C. IR (KBr) cm^{-1}: 1760, 1700 (CO). ^{1}H-NMR: 0.98 (3H, t, J=7.3 Hz, CH_3), 1.12 (6H, t, J=7.7 Hz, 2×CH_3), 2.33 (4H, q, J=7.7 Hz, 2×CH_2), 2.47 (2H, q, J=7.3 Hz, CH_2), 5.96 (4H, ABq, J=9.5 Hz, 2×NCH_2O), 7.23—7.27 (2H, m, Ar-H), 7.32—7.36 (3H, m, Ar-H). *Anal.* Found for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.57; H, 5.95; N, 6.80.

1,3-Bis(propionyloxymethyl)-5-phenyl-5-propylbarbital (**4d**): Yield 853 mg (34%), mp 37—39 °C. IR (KBr) cm^{-1}: 1750, 1710 (CO). ^{1}H-NMR: 0.96 (3H, t, J=7.3 Hz, CH_3), 1.12 (6H, t, J=7.7 Hz, 2×CH_3), 1.26—1.39 (2H, m, CH_2), 2.32 (4H, q, J=7.7 Hz, 2×CH_2), 2.35—2.44 (2H, m, CH_2), 5.95 (4H, ABq, J=9.5 Hz, 2×NCH_2O), 7.24—7.29 (2H, m, Ar-H), 7.32—7.37 (3H, m, Ar-H). *Anal.* Calcd for $C_{21}H_{26}N_2O_7$: C, 60.28; H, 6.26; N, 6.69. Found: C, 60.20; H, 6.21; N, 6.68.

5-(1-Cyclohexenyl)-1,3-bis(propionyloxymethyl)-5-methylbarbital (**4e**): Yield 875 mg (37%), mp 72—73 °C. IR (KBr) cm^{-1}: 1750, 1700 (CO). ^{1}H-NMR: 1.14 (6H, t, J=7.3 Hz, 2×CH_3), 1.49—1.65 (4H, m, CH_2CH_2), 1.63 (3H, s, CH_3), 1.87—1.95 (2H, m, CH_2), 2.03—2.10 (2H, m, CH_2), 2.35 (4H, q, J=7.3 Hz, 2×CH_2), 5.64—5.69 (1H, m, CH=), 5.91 (4H, ABq, J=9.9 Hz, 2×NCH_2O). *Anal.* Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.88; H, 6.58; N, 7.10.

5-(1-Cyclohexenyl)-1,3-bis(propionyloxymethyl)-5-ethylbarbital (**4f**): Yield 588 mg (24%), mp 67—69 °C. IR (KBr) cm^{-1}: 1750, 1700 (CO). ^{1}H-NMR: 0.86 (3H, t, J=7.3 Hz, CH_3), 1.14 (6H, t, J=7.3 Hz, 2×CH_3), 1.49—1.64 (4H, m, CH_2CH_2), 1.87—1.95 (2H, m, CH_2), 2.03—2.10 (2H, m, CH_2), 2.23 (2H, t, J=7.3 Hz, CH_2), 2.35 (4H, q, J=7.3 Hz, 2×CH_2), 5.65—5.68 (1H, m, CH=), 5.91 (4H, ABq, J=9.9 Hz, 2×NCH_2O). *Anal.* Calcd for $C_{20}H_{28}N_2O_7$: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.79; H, 7.04; N, 6.66.

General Procedure for Lipase-Catalyzed Hydrolysis of 5,5-Disubstituted *N,N'*-Bis(propionyloxymethyl)barbital A mixture of **4** (0.5 mmol), lipase (100—500 mg), and diisopropyl ether saturated with water (20 ml) was stirred at room temperature. After removal of the lipase by filtration, the filtrate was cocentrated under reduced pressure. The residue was chromatographed on a short silica gel column (ethyl acetate–*n*-hexane = 1 : 1) to give mono(propionyloxymethyl)barbital (**5**). The optical purity of each product was determined by HPLC analysis. Yields and optically purities are listed in Table I.

5-Methyl-5-phenyl-1-(propionyloxymethyl)barbital (**5b**) (Obtained in Entry 3): mp 125—128 °C, $[\alpha]_D^{22}$ −42.4° (c=0.56, $CHCl_3$). ^{1}H-NMR: 1.12 (3H, t, J=7.3 Hz, CH_3), 1.88 (3H, s, CH_3), 2.33 (2H, q, J=7.3 Hz, CH_2), 5.90 (2H, ABq, J=9.9 Hz, NCH_2O), 7.25—7.33 (2H, m, Ar-H), 7.33—7.42 (3H, m, Ar-H), 8.18 (1H, s, NH). FAB-MS: m/z 304 $(M+H)^+$.

5-Ethyl-5-phenyl-1-(propionyloxymethyl)barbital (**5c**) (Obtained in Entry 5): mp 94—96 °C, $[\alpha]_D^{22}$ −31.5° (c=1.50, $CHCl_3$). ^{1}H-NMR: 0.97 (3H, t, J=7.3 Hz, CH_3), 1.12 (3H, t, J=7.7 Hz, CH_3), 2.32 (2H, q, J=7.7 Hz, CH_2), 2.48 (2H, q, J=7.3 Hz, CH_2), 5.93 (2H, ABq, J=9.5 Hz, NCH_2O), 7.29—7.37 (5H, m, Ar-H), 9.45 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.64; H, 5.82; N, 8.75.

5-Phenyl-5-propyl-1-(propionyloxymethyl)barbital (**5d**) (Obtained in Entry 7): Oil, $[\alpha]_D^{22}$ −25.2° (c=0.90, $CHCl_3$). ^{1}H-NMR: 0.96 (3H, t, J=7.5 Hz, CH_3), 1.11 (3H, t, J=7.5 Hz, CH_3), 1.26—1.39 (2H, m, CH_2), 2.31 (2H, q, J=7.5 Hz, CH_2), 2.35—2.43 (2H, m, CH_2), 5.92 (2H, ABq, J=9.5 Hz, NCH_2O), 7.24—7.39 (5H, m, Ar-H), 9.08 (1H, s, NH). FAB-MS: m/z: 332 $(M+H)^+$.

5-(1-Cyclohexenyl)-5-methyl-1-(propionyloxymethyl)barbital (**5e**) (Obtained in Entry 9): Oil, $[\alpha]_D^{22}$ −21.6° (c=1.50, $CHCl_3$). ^{1}H-NMR: 1.13 (3H, t, J=7.7 Hz, 2×CH_3), 1.50—1.67 (4H, m, CH_2CH_2), 1.62 (3H, s, CH_3), 1.90—1.98 (2H, m, CH_2), 2.03—2.12 (2H, m, CH_2), 2.35 (2H, q, J=7.7 Hz, CH_2), 5.74—5.78 (1H, m, CH=), 5.88 (2H, ABq, J=9.9 Hz, NCH_2O), 9.10 (1H, s, NH). FAB-MS m/z: 308 $(M+H)^+$.

5-(1-Cyclohexenyl)-5-ethyl-1-(propionyloxymethyl)barbital (**5f**) (Obtained in Entry 11): Oil, $[\alpha]_D^{22}$ −17.4° (c=1.10, $CHCl_3$). ^{1}H-NMR: 0.87 (3H, t, J=7.3 Hz, CH_3), 1.13 (3H, t, J=7.7 Hz, CH_3), 1.49—1.66 (4H, m, CH_2CH_2), 1.90—1.99 (2H, m, CH_2), 2.05—2.12 (2H, m, CH_2), 2.23 (2H, t, J=7.3 Hz, CH_2), 2.35 (2H, q, J=7.7 Hz, CH_2), 5.76–5.80 (1H, m, CH=), 5.92 (2H, ABq, J=9.9 Hz, NCH_2O), 8.86 (1H, s, NH).

Mephobarbital (1) and Hexobarbital (2) A solution of **5c** or **5e** (1 mmol), diisopropylethylamine (155 mg, 1.2 mmol), and methyl iodide (170 mg, 1.2 mmol) in dichloromethane (20 ml) was stirred at room temperature for 3 h. The reaction mixture was washed with water and brine, and dried. After removal of the solvent, a mixture of the residual oil and aqueous 10% K_2CO_3 in methanol was stirred at room temperature for 3 h. After removal of the solvent, the residue was dissolved in ether. This solution was wasl.ed with water and brine, dried, and concentrated. The residue was chromatographed on a short silica gel column to give mephobarbital (**1**) or hexobarbital (**2**). Single recrystallization from H_2O–EtOH gave optically pure products. The optical purity of **1** and **2** was determined by HPLC analysis.

(*R*)-Mephobarbital (**1**): Yield 221 mg (90%), mp 100—101 °C, $[\alpha]_D^{22}$ −8.5° (c=1.0, EtOH). IR (KBr) cm^{-1}: 3150 (NH), 1700 (CO). ^{1}H-NMR: 0.96 (3H, t, J=7.3 Hz, CH_3), 2.48 (2H, q, J=7.3 Hz, CH_2), 3.34 (3H, s, NCH_3), 7.27—7.39 (5H, m, Ar-H), 9.02 (1H, s, NH). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.41; H, 5.73; N, 11.38. Found: C, 63.24; H, 5.72; N, 11.30.

(*S*)-Hexobarbital (**2**): Yield 189 mg (80%), mp 153—154°C, $[\alpha]_D^{22}$ +11.5°C (c=1.0, EtOH). IR (KBr) cm^{-1}: 3250 (NH), 1700 (CO). ^{1}H-NMR: 1.50—1.67 (4H, m, CH_2CH_2), 1.62 (3H, s, CH_3), 1.90—1.97 (2H, m, CH_2), 2.05—2.13 (2H, m, CH_2), 3.30 (3H, s, NCH_3), 5.72—5.77 (1H, m, CH=), 8.76 (1H, s, NH). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.71; H, 6.62; N, 11.64.

(*R*)-2-*O*-Benzyl-1-*O*-butylglycerol (9) A solution of (*R*)-**6** (3.36 g, 10 mmol), dihydropyran (DHP) (1.0 g, 12 mmol), and *p*-toluenesulfonic acid (*p*-TsOH) monohydrate (190 mg, 1 mmol) in dichloromethane (20 ml) was stirred at 0 °C for 1 h. The reaction mixture was shaken with saturated $NaHCO_3$ aqueous solution, washed with brine, dried, and concentrated. The residual oil was chromatographed on a short silica gel column to give (*R*)-**7**.

Next, *n*-BuOH (10 mmol) was added to an ice-cooled and stirred suspension of oil-free sodium hydride in dry DMF (20 ml). This solution was stirred for 1 h, then (*R*)-**7** was added, and the mixture was heated at 60 °C for 3 h. The reaction mixture was cooled, poured into ice-cooled water, and extracted with ether three times. The combined extracts were washed with brine, dried, and concentrated. The residual oil and pyridinium *p*-toluenesulfonate (PPTS) (235 mg, 1 mmol) were dissolved in ethanol (10 ml) and heated at 55 °C for 3 h. After removal of the solvent, the residue was dissolved in ether. The solution was washed with water and brine, dried, and concentrated. The residual oil was chromatographed on a short silica gel column to give (*R*)-**9** (1.1 g, 46%). (*R*)-**9**: $[\alpha]_D^{22}$ +21.6° (c=1.02, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH). ^{1}H-NMR: 0.92 (3H, t, J=7.3 Hz, CH_3), 1.30—1.44 (2H, m, CH_2), 1.51—1.62 (2H, m, CH_2), 2.00 (1H, s, OH), 3.45 (2H, t, J=6.6 Hz, CH_2O), 3.50—3.80 (5H, m, CH_2CHCH_2), 4.67 (2H, ABq, J=11.7 Hz, $PhCH_2$), 7.33—7.36 (5H, m, Ar-H).

(*S*)-2-*O*-Benzyl-1-*O*-butyl-3-*O*-tosylglycerol (10) *p*-Toluenesulfonyl chloride (TsCl) (1.05 g, 5.5 mmol) was added to a solution of (*R*)-**9** (1.1 g, 4.6 mmol) in pyridine (20 ml) at 0 °C. The reaction mixture was stirred at room temperature for 12 h, then diluted with ether, washed with 10% hydrochloride solution three times, washed with brine, and dried. Removal of the solvent left an oil, which was purified by passing it through a short silica gel column to give (*S*)-**10** (11.66 g, 92%). (*S*)-**10**: $[\alpha]_D^{22}$ −4.40° (c=1.05, $CHCl_3$). IR (neat) cm^{-1}: 1370, 1180 (SO_2). ^{1}H-NMR: 0.89 (3H, t, J=7.3 Hz, CH_3), 1.23—1.36 (2H, m, CH_2), 1.42—1.52 (2H, m, CH_2), 2.43 (3H, s, Ar-CH_3), 3.56 (2H, t, J=6.6 Hz, CH_2O), 3.44—3.46 (2H, m, CH_2O), 3.71—3.80 (1H, m, CH), 4.05—4.24 (2H, m, CH_2O), 4.58 (2H, s, $PhCH_2$), 7.26—7.34 (7H, m, Ar-H), 7.77 (2H, d, J=5.6 Hz, Ar-H).

(*S*)-1-*O*-Butyl-3-*O*-tosylglycerol (11) (*S*)-**10** (1.66 g, 4.23 mmol) was hydrogenated over 5% Pd–C (150 mg) in ethanol at room temperature. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give (*S*)-**11** (1.25 g, 98%). (*S*)-**11**: $[\alpha]_D^{22}$ +5.10° (c=1.07, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1370, 1180 (SO_2). ^{1}H-NMR: 0.90 (3H, t, J=7.3 Hz, CH_3), 1.24—1.38 (2H, m, CH_2), 1.45—1.55 (2H, m, CH_2), 2.39 (1H, s, OH), 2.43 (3H, s, Ar-CH_3), 3.37—3.47 (4H, m, CH_2OCH_2), 3.93—4.02 (1H, m, CH), 4.04—4.12 (2H, m, CH_2O), 7.35 (2H, d, J=7.7 Hz, Ar-H), 7.80 (2H, d, J=5.6 Hz, Ar-H).

(*S*)-1-Butoxy-3-iodo-2-propanol (12) A solution of (*S*)-**11** (1.25 g, 4.15 mmol) and sodium iodide in acetone was heated at 60 °C for 12 h. The reaction mixture was diluted with ether, washed with 10% sodium thiosulfate and brine, and dried. After removal of the solvent, the residue was chromatographed on a short silica gel column to give (*S*)-**12** (1.03 g, 96%). (*S*)-**12**: $[\alpha]_D^{22}$ −1.7° (c=1.29, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1120 (CH_2I). ^{1}H-NMR: 0.92 (3H, t, J=7.3 Hz, CH_3), 1.30—1.44 (2H, m, CH_2), 1.52—1.62 (2H, m, CH_2), 2.75 (1H, s, OH), 3.23—3.37 (2H, m, CH_2I), 3.46—3.53 (4H, m, CH_2OCH_2), 3.72—3.80 (1H, m, CH).

(*S*)-2-(Aminocarbonyl)oxy-3-butoxy-1-iodopropane (13) Sodium cyanate (520 mg, 8 mmol) and trifluoroacetic acid (960 mg, 8.4 mmol) were added to a solution of (*S*)-**12** (1.03 g, 3.98 mmol) in benzene. The mixture was stirred at room temperature for 12 h, then washed with water, 5% sodium hydroxide solution and brine, and dried. Removal of the solvent and chromatography of the residue on a short silica gel column gave (*S*)-**13** (870 mg, 2.9 mmol). (*S*)-**13**: mp 39—41 °C, $[\alpha]_D^{22}$ +9.8° (c=1.00, $CHCl_3$). IR (neat) cm^{-1}: 3400 (NH), 1690 (CO), 1130 (CH_2I). ^{1}H-NMR: 0.92 (3H, t, J=7.3 Hz, CH_3), 1.30—1.44 (2H, m, CH_2), 1.51—1.61 (2H, m, CH_2), 3.32—3.70 (6H, m, CH_2OCH_2, ICH_2), 4.72—4.79 (1H, m, CH), 5.03 (2H, s, NH_2). *Anal.* Calcd for $C_8H_{16}INO_3$: C, 31.91; H, 5.36; N, 4.65. Found: C. 32.07; H, 5.32; N, 4.48.

The (*R*)-isomer was also obtained from (*S*)-**6** in a similar manner. (*R*)-**13**: mp 37—39 °C, $[\alpha]_D^{22}$ −9.8° (c=1.00, $CHCl_3$).

(*S*)-3-[2-(*R*)-[(Aminocarbonyl)oxy]-3-butoxypropyl]-5-ethyl-5-phenyl-1-propionyloxymethylbarbital (14) Optically pure (*S*)-**5c** (127 mmol, 0.4 mmol), obtained by recrystallization from petroleum ether, was added to an ice-cooled and stirred suspension of oil-free sodium hydride (10 mg, 0.4 mmol) in dry DMF. Stirring was continued for 1 h, then (*S*)-**13** (181 mg, 0.6 mmol) was added and the mixture was heated at 55 °C for 12 h. The reaction mixture was poured into ice-cooled water and extracted with ether three times. The combined extracts were washed with brine and dried. The solvent was removed and the residual oil was chromatographed on a short silica gel column with ethyl acetate and *n*-hexane to give (*S*,*R*)-**14** (160 mg, 81%). Similarly, (*R*,*S*)-, (*R*,*R*)- and (*S*,*S*)-**14** were obtained from (*R*)-**5b** with (*R*)-**13**, (*R*)-**5b** with (*S*)-**13** and (*S*)-**5b** with (*R*)-**13**, respectively.

(*S*,*R*)-**14**: mp 107—109°, $[\alpha]_D^{22}$ +15.6° (c=1.01, $CHCl_3$). (*R*,*S*)-**14**: mp 107—109°, $[\alpha]_D^{22}$ −15.6° (c=1.06, $CHCl_3$). IR (KBr) cm^{-1}: 1694, 1713, 1729 (CO). ^{1}H-NMR: 0.91 (3H, t, J=7.3 Hz, CH_3), 0.95 (3H, t, J=7.3 Hz, CH_3), 1.11 (3H, t, J=7.3 Hz, CH_3), 1.32—1.39 (2H, m, CH_2), 1.51—1.57 (2H, m, CH_2), 2.32 (2H, q, J=7.3 Hz, CH_2), 2.45 (2H, d, J=7.3 Hz, CH_2), 3.40—3.50 (2H, m, CH_2O), 3.58 (2H, d, J=4.8 Hz, CH_2O), 4.04 (H_A, dd, J=14.2, 2.8 Hz, NCH_2), 4.40 (H_B, dd, J=14.2, 8.7 Hz, NCH_2), 4.67 (2H, s, NH_2), 5.13—5.17 (1H, m, CH), 5.97 (2H, ABq, J=9.6 Hz, NCH_2O), 7.26—7.37 (5H, m, Ar-H). FAB-MS m/z: 492 $(M+H)^+$. *Anal.* Calcd for $C_{24}H_{33}N_3O_8$: C, 58.64; H, 6.77; N, 8.55. Found: C, 58.38; H, 6.73; N, 8.49.

(*R*,*R*)-**14**: $[\alpha]_D^{22}$ +22.0° (c=2.70, $CHCl_3$). (*S*,*S*)-**14**: $[\alpha]_D^{22}$ −22.6° (c=3.10, $CHCl_3$). IR (neat) cm^{-1}: 1694, 1713, 1729 (CO). ^{1}H-NMR: 0.91 (3H, t, J=7.3 Hz, CH_3), 0.97 (3H, t, J=7.3 Hz, CH_3), 1.16 (3H, t, J=7.3 Hz, CH_3), 1.26—1.42 (2H, m, CH_2), 1.48—1.58 (2H, m, CH_2), 2.33 (2H, q, J=7.3 Hz, CH_2), 2.39—2.59 (2H, m, CH_2), 3.37—3.51 (2H, m, CH_2O), 3.56 (2H, d, J=4.8 Hz, CH_2O), 3.98 (H_A, dd, J=13.9, 2.6 Hz, NCH_2), 4.46 (H_B, dd, J=13.9, 8.8 Hz, NCH_2), 4.70 (2H, s, NH_2), 5.14—5.22 (1H, m, CH), 5.97 (2H, ABq, J=9.5 Hz, NCH_2O), 7.29—7.33 (5H, m, Ar-H). FAB-MS m/z: 492 $(M+H)^+$. *Anal.* Calcd for $C_{24}H_{33}N_3O_8 \cdot H_2O$: C, 56.57; H, 6.92; N, 8.25. Found: C, 56.49; H, 6.92; N, 7.87.

(*R*,*R*)-Febarbamate (3) A mixture of (*S*,*R*)-**14** (123 mg, 0.25 mmol) and aqueous 10% K_2CO_3 in methanol (20 ml) was stirred at room temperature for 3 h and then evaporated under reduced pressure. The residual oil was partitioned between dichloromethane and water. The dichloromethane layer was washed with brine and dried. After removal of the solvent, the residue was chromatographed on a short silica gel column to give (*R*,*R*)-**3** (81 mg, 80%). Similarly, (*S*,*S*)-, (*S*,*R*)- and (*R*,*S*)-**3** were obtained from (*R*,*S*)- (*R*,*R*)- and (*S*,*S*)-**14**, respectively.

(*R*, *R*)-**3**: $[\alpha]_D^{22}$ −5.8° (c=1.76, $CHCl_3$). (*S*,*S*)-**3**: $[\alpha]_D^{22}$ +5.8° (c=1.20, $CHCl_3$). IR (neat) cm^{-1}: 1689, 1720 (CO). ^{1}H-NMR: 0.90 (3H, t, J=7.3 Hz, CH_3), 0.96 (3H, t, J=7.3 Hz, CH_3), 1.28—1.44 (2H, m, CH_2), 1.49—1.61 (2H, m, CH_2), 2.42—2.50 (2H, m, CH_2), 3.35—3.52 (2H, m, CH_2O), 3.58 (2H, d, J=4.8 Hz, CH_2O), 4.00 (H_A, dd, J=13.9, 2.6 Hz, NCH_2), 4.36 (H_B, dd, J=13.9, 8.8 Hz, NCH_2), 4.94 (2H, s, NH_2), 5.16—5.23 (1H, m, CH), 7.29—7.36 (5H, m, Ar-H), 10.12 (1H, m, NH). FAB-MS: m/z: 406 $(M+H)^+$.

(*S*, *R*)-**3**: $[\alpha]_D^{22}$ +15.1° (c=1.02, $CHCl_3$). (*R*, *S*)-**3**: $[\alpha]_D^{22}$ −15.1° (c=1.04, $CHCl_3$). IR (neat) cm^{-1}: 1689, 1720 (CO). ^{1}H-NMR: 0.92 (3H, t, J=7.3 Hz, CH_3), 0.98 (3H, t, J=7.3 Hz, CH_3), 1.31—1.44 (2H, m, CH_2), 1.52—1.63 (2H, m, CH_2), 2.32 —2.53 (2H, m, CH_2), 3.43—3.53 (2H, m, CH_2O), 3.56—3.68 (2H, m, CH_2O), 4.00 (H_A, dd, J=13.9, 1.1 Hz, NCH_2), 4.34 (H_B, dd, J=13.9, 9.2 Hz, NCH_2), 4.93 (2H, s, NH_2), 5.17—5.23 (1H, m, CH), 7.29—7.33 (5H, m, Ar-H), 10.12 (1H, m, NH). FAB-MS: m/z: 406 $(M+H)^+$.

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