Practical Chemoenzymatic Synthesis of Both Enantiomers of Propranolol

H. S. Bevinakatti* and A. A. Banerji

Alchemie Research Centre, ICI India Limited Site, Thane-Belapur Road, Thane-400 601, Maharashtra, India

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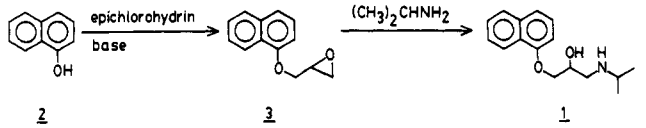
Synthesis of (*R*)- and (*S*)-propranolol in high optical and chemical yields was achieved starting from 1-naphthol and epichlorohydrin. Lipase-catalyzed kinetic resolution of key intermediates 1-chloro-3-(1-naphthyloxy)-2-propanol and its *O*-acetyl ester 1-chloro-2-acetoxy-3-(1-naphthyloxy)propane was studied using four different approaches.

Introduction

As stereochemistry in a drug molecule governs its biological activity,[1] chirality is emerging as a key issue in pharmaceutical research.[2] β-Blockers of the 3-(aryloxy)-1-(alkylamino)-2-propanol type, e.g., propranolol (1), are one such class of drugs where the activity resides mainly in the *S* isomers.[3-6] Moreover, (*R*)-1 is known to act as a contraceptive. One of the important ways of meeting the growing needs of the future chiral drug market is predicted to be through "environmentally friendly" biotransformations.[7,8] The ability of enzymes to work in organic solvents,[9] especially lipases,[10] due to their low cost and stability, now offers an attractive route for industrial exploitation.

In continuation of our work on lipase catalysis,[11] we report herein efficient syntheses of *S* and *R* isomers of propranolol via lipase-catalyzed kinetic resolution of key intermediates 1-chloro-3-(1-napthyloxy)-2-propanol (4) and its *O*-acetyl ester 1-chloro-2-acetoxy-3-(1-naphthyloxy)-propane (5).

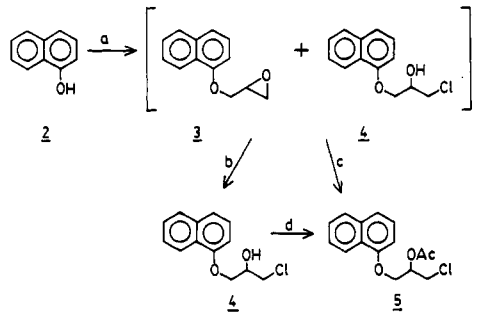
Scheme I[a]



2 3 1

[a] Industrial production of (±)-propranolol.

Scheme II[a]



2 3 4 5

[a] Key: (a) epichlorohydrin, pyridine, rt 24 h; (b) HCl, 0–5 °C, 94%; (c) CH_3COCl, 0–5 °C, rt, 3 h, 93%; (d) Ac_2O–Et_3N, 80–90 °C, 1 h, 92%.

Table I. Effect of Base Concentration and Temperature on the Product Distribution Ratio (3:4) in the Condensation of 1-Naphthol (2) with Epichlorohydrin[a]

base	mol %	temp (°C)	time (h)	product distribution 3:4
pyridine	1.25	100	10	45:55
	2.5	100	5	61:39
	10	rt	24	23:77
	25	60	2	65:35
	25	rt	16	37:63
aqueous K_2CO_3[b]	50	rt	24	22:78
	100	rt	24	57:43
	250	rt	24	100:00

[a] Reactions were carried out with 2:epichlorohydrin molar ratio = 1:5. [b] In presence of 5 mol % of TEBAC (with respect to 2).

Results and Discussion

While direct resolution of propranolol was reported to be unsuccessful,[12] successful preparation of (*S*)-propranolol via lipase-catalyzed hydrolysis/transesterification of glycerol derivatives[5b] and cyanohydrin intermediates[5a,c] was recently reported.[5] In spite of the excellent selectivity shown by lipase toward the intermediates used, these methods do not show any promise for industrial exploitation because of several disadvantages like multisteps

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(4) For recently reported preparations of (*S*)-propranolol and related compounds by nonenzymatic asymmetric synthesis, see: (a) Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5876. (b) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710 and references cited therein.

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Table II. Lipase-Catalyzed Kinetic Resolution of Acetate 5 and Chlorohydrin 4[a]

				-OH (4)			-OAc (5)			
sub.	lipase	reaction medium	time	convn (%)	$[\alpha]^{25}_D$ (1–5%, EtOH)	isomer	ee[b] (%)	$[\alpha]^{25}_D$ (1–5%, EtOH)	isomer	ee[b] (%)	E[c]
5	PPL[d]	BuOH–DIPE[e]	20 d	26	+3.3	S	37	−2.8	S	14	3
		BuOH	14 d	22	+3.2	S	35	−2.2	S	11	3
		H_2O	51 h	16	+4.2	S	47	−1.7	S	9	3
	CCL[f]	BuOH–DIPE	2 d	41	−5.0	R	56	+8.2	R	41	6
			3 d	58	−3.6	R	40	+11.8	R	59	4
		OctOH–DIPE[g]	5 d	58	−3.4	R	38	+10.8	R	54	4
	LPSA[h]	BuOH–DIPE	9 d	50	+9.0	S	>95	−19.9	S	>95	>100
		BuOH	5 d	47	+9.0	S	>95	−18.0	S	90	>100
		H_2O[i]	52 h	48	+8.7	S	>95	−17.5	S	88	>100
4	PPL	VA[j]	2 d	–							
	LPSA	VA	46 h	47	−8.1	R	90	+19.1	R	>95	>100
		VA[i]	13 d	50	−8.7	R	>95	+18.5	R	93	>100
		Ac_2O–DIPE[k]	41 h	51	−8.3	R	92	+17.5	R	88	53

[a] Reactions were carried out on 5–25-mmol scale of substrate 5 or 4 at ambient temperature. Unless otherwise mentioned, the ratio used for substrate–solvent (DIPE or BuOH or H_2O or VA)–lipase was 5 mmol:10 mL:500 mg. [b] See ref 21. [c] See ref 20. [d] Porcine pancreatic lipase. [e] 10 mmol of 1-BuOH in 10 mL of DIPE. [f] Lipase from *C. cylindracea*. [g] 10 mmol of 1-OctOH in 10 mL of DIPE. [h] Lipase PS "Amano" isolated from *P. cepacia*. [i] Substrate:lipase = 5 mmol:100 mg. [j] Vinyl acetate. [k] 10 mmol of Ac_2O in 10 mL of DIPE.

(more than six steps), low overall yields (less than 10%), use of hazardous and expensive reagents like sodium cyanide, lithium aluminium hydride, sodium borohydride, etc., and lastly, noncompatibility with the existing industrial process for racemic propranolol[13] (Scheme I).

To overcome these drawbacks, our obvious choices of the key intermediates for lipase-catalyzed studies were 4 and 5, which not only can be obtained in a single step from 1-naphthol (2) and epichlorohydrin but can also be converted easily to propranolol.

Condensation of 2 with epichlorohydrin, following known procedure,[14] in presence of 2.5 M % pyridine at 100 °C yielded a mixture of chlorohydrin 4 and glycidyl 1-naphthyl ether (3) in ca. 40:60 ratio. Treatment of this mixture with HCl at room temperature, however, yielded the required 4 contaminated with 2–3% of the unwanted regiomer 2-chloro-3-(1-naphthyloxy)-1-propanol, $C_{10}H_7O$-$CH_2CH(Cl)CH_2OH$; 4a (detected only by GC) obviously was generated after the ring opening of epoxide 3. This was confirmed by treatment of pure glycidyl 1-naphthyl ether[15] separately with HCl to give 5 and 2.5% of 4a at room temperature and <5 °C, respectively. As 4a, being primary alcohol, interfered in the lipase-catalyzed reactions, it was necessary to suppress/minimize its formation, which, in turn, was possible by suppressing the formation of epoxide 3 itself in the first step. With systematic optimization of temperature and amount of pyridine, it was possible to reduce the formation of epoxide from 60 to 23% (23:77 of 3:4). While aqueous K_2CO_3 in the presence of triethylbenzylammonium chloride (TEBAC) gave similar results, NaOH or KOH gave poorer results[16] (see Table I). The ease of workup, however, makes pyridine-catalyzed condensation a better choice for large-scale reactions.

The 77:23 mixture of 4 and 3 as obtained above, after treatment with HCl (either concd or gaseous) below 5 °C yielded the required chlorohydrin 4 in excellent overall yields (94% with <1% of the other isomer). While 4 could be smoothly converted to its *O*-acetate 5 using conventional methods (Ac_2O–Et_3N), interestingly the mixture of 4 and 3 (77:23) as obtained above, when stirred with acetyl chloride (<5 °C), directly gave 5 (93% yield with <1% other isomer[17]), thus avoiding an extra step of isolating 4 for the preparation of 5 (Scheme II).

Lipase-catalyzed deacylation of 5 was studied using our approach with 1-butanol[11b-e] as well as with water (conventional hydrolysis). Studies on acylation of 4 were carried out using cheap and readily available acylating agents such as vinyl acetate[18] and acetic anhydride.[19] Trihaloethyl butyrates, though found to be excellent acylating agents,[9a,12] were not tried because of cost and operability problems.

Transesterification/hydrolysis of acetate 5 with 1-butanol (or 1-octanol)/water using a lipase either from porcine pancreas (PPL) or *Candida cylindracea* (CCL) showed poor selectivity (E = 3–6).[20] A purified lipase from *Pseudomonas cepacia* (Lipase PS "Amano"; LPSA), however, was found to show excellent selectivity toward the *S* isomer. A 50% conversion using 1-butanol in diisopropyl ether (DIPE) resulted in (*S*)-4 and (*R*)-5 in >95% ee[21] (E = >100). Similar results were obtained with neat butanol or water (Table II). While hydrolysis worked faster than transesterification, the ease of workup and isolated yields were in favor of the latter.

In the acylation studies of 4, though PPL showed no reaction, LPSA once again showed excellent selectivity toward the *S* isomer. Whether the acylating agent used was vinyl acetate (used in excess as solvent also) or acetic

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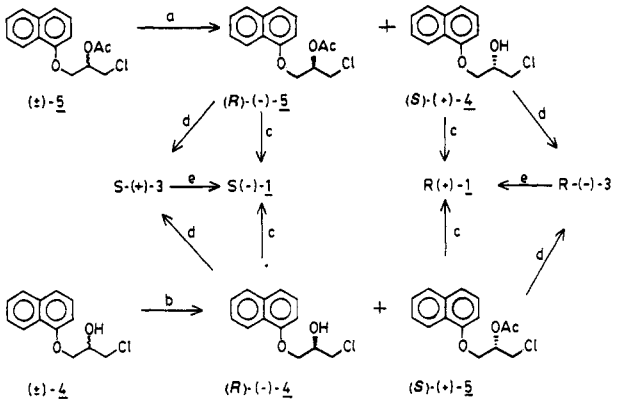
(14) Stephenson, O. *J. Chem. Soc.* **1954**, 1571.
(15) Prepared according to the known method;[13] now commercially available from Aldrich Chem. Co.
(16) (a) Lafon, V. (Orsymonde S.A.). Ger. Offen. 2,166,869, 1976; Chem. Abstr. **1976**, *85*, 62850. (b) Beasley, Y. M.; Petrow, V.; Stephenson, O. *J. Pharm. Pharmacol.* **1958**, *10*, 47.
(17) Treatment of pure glycidyl 1-naphthyl ether with acetyl chloride at room temperature gave 1-chloro-2-acetoxy-3-(1-naphthyloxy)propane (5) with 4–7% of other regiomer 1-acetoxy-2-chloro-3-(1-naphthyloxy)-propane.
(18) (a) Degueil-Casting, M.; DeJesco, B.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953. (b) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. (c) Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127.
(19) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531.
(20) Enantiomeric ratio, E, was calculated according to the method of: Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(21) Attempts to determine ee of chiral 4 and 5 or its other derivatives using chiral HPLC (Pirkle, DNBPG column) or NMR with $Eu(dcm)_3$ as chiral shift reagent were not successful. Hence, the ee (and absolute configurations) were determined by one of the following methods. (a) HPLC analysis of (−)-MTPA ester of 4 prepared according to: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *36*, 2543. (b) Conversion of chiral 4/5 to its chiral epoxide 3 or to chiral propranolol (1) and comparing the observed rotation with that of literature reported values.

Scheme III[a]



[a] Key: (a) Lipase PS, *n*-BuOH or H_2O, rt; (b) Lipase PS, vinyl acetate or Ac_2O–DIPE, rt; (c) $(CH_3)_2CHNH_2$, aqueous NaOH; (d) aqueous NaOH, *i*-PrOH; (e) $(CH_3)_2CHNH_2$.

anhydride (2 equiv in DIPE), both these acylations attained ca. 50% conversions in less than 48 h. These results show the excellent substrate selectivity exhibited by a lipase toward both forward (acylation) as well as backward (deacylation) reactions without getting affected by the medium used. Another notable factor about all the LPSA-catalyzed reactions, in favor of excellent selectivity, was that the initial rate of reaction drastically dropped down after 40% conversion, coming to a practical halt around 50% conversion (after consumption of all the *S* isomer).

Chiral **4** or **5** was then smoothly converted, in one step, to chiral propranolol by treating with aqueous isopropylamine in the presence of NaOH (>90% yield). The reaction works without using NaOH, albeit sluggish. As an alternative process, chiral **4** or **5** could also be converted to corresponding chiral epoxide **3** by simply stirring with NaOH in isopropyl alcohol. Comparison of the rotation of the isolated epoxides with that of known values also helped us in establishing the absolute stereochemistry and optical purity of the resolved products **4** and **5**.[21] Chiral epoxides, on treatment with isopropylamine, readily gave propranolol (Scheme III).

To summarize our results, we have shown that chiral propranolol with high optical purity (>95% ee) and chemical yields (>30% overall) can be obtained in essentially three steps by incorporating a single lipase-catalyzed kinetic resolution step into the existing two-step process for the preparation of propranolol. The "robust" selectivity of the enzyme was proved by carrying out kinetic resolution of the intermediates (**4** or **5**) using four different approaches. As other important β-blockers like practolol, oxprenolol, metaprolol, acebutolol, atenolol, moprolol, etc. are all closely related to propranolol and are made by the same basic route,[22] our present route should serve as a protocol for all these chiral drugs.

Experimental Section

^1H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard. GLC analyses were carried out by using an HP 101 capillary column (methyl silicone; 25 m × 0.2 mm thickness). Optical rotations were measured on a JASCO DIP-140 digital polarimeter. PPL (12 u/mg) and CCL (665 u/mg) were purchased from Sigma Chemical Co. LPSA from *P. cepacia* (30 u/mg) was a gift from Amano Pharmaceutical Co., Japan. All lipases were used straight from the bottle. Prior to use, 1-butanol and DIPE used in lipase reactions were dried overnight over 3A molecular sieves. Ambient temperature fluctuated between 25–35 °C.

1-Chloro-3-(1-naphthyloxy)-2-propanol (4). (a) Using Pyridine. Modification of Stephenson's method:[14] A solution of 1-naphthol (**2**; 28.8 g, 0.2 mol), epichlorohydrin (78 mL, 1 mol), and pyridine (1.6 mL, 0.02 mol) was stirred at ambient temperature until GC/TLC analysis showed completion (24 h). Removal of excess epichlorohydrin and pyridine under reduced pressure around 80–100 °C yielded 47.2 g of a crude mixture of **3** and **4** (ratio 23:77 by GC).

The crude mixture was stirred with $CHCl_3$ (100 mL) and concd HCl (50 mL) for 1 h below 5 °C. After ambient temperature was attained, water (100 mL) was added and layers were separated. Extraction of the aqueous layer again with $CHCl_3$ (100 mL) followed by washing of the combined organic layers with water (50 mL), drying, and removal of solvent yielded 49 g of crude **4**, filtration of which through a silica gel column ($CHCl_3$) to remove colored impurities gave 44.5 g (94%) of pure **4** as oil: IR (neat) ν (cm^{-1}) 3400 (OH); ^1H NMR ($CDCl_3$, 80 MHz) δ 2.6 (d, 1 H, J = 5.5 Hz, OH), 3.85 (d, 2 H, J = 4 Hz, CH_2Cl), 4.2–4.4 (m, 3 H, OCH_2CH), 6.7–8.2 (m, 7 H, aromatic).

(b) Using Aqueous K_2CO_3–TEBAC. A mixture of 1-naphthol (21.6 g, 0.15 mol), epichlorohydrin (57 mL, 0.75 mol), K_2CO_3 (10.35 g, 0.075 mol), triethylbenzylammonium chloride (1.68 g, 7.5 mmol), and water (15 mL) was stirred at ambient temperature for 24 h. After water (50 mL) and $CHCl_3$ (50 mL) were added, the reaction mixture was further stirred for 30 min. Separation of layers followed by removal of solvent afforded 36 g of crude mixture containing **3** and **4** (22:78). Treatment of this crude mixture with concd HCl following the procedure described previously gave 33 g (93%) of pure **4**.

1-Chloro-2-acetoxy-3-(1-naphthyloxy)propane (5). (a) From a Mixture of 3 and 4. A solution of 47.2 g of crude mixture of **3** and **4** (obtained by method a) in $CHCl_3$ (50 mL) and freshly distilled acetyl chloride (50 mL) was stirred for 1 h at <5 °C followed by 1–2 h at ambient temperature until TLC ($CHCl_3$) showed complete conversion to **5**. Removal of $CHCl_3$ and excess acetyl chloride under vacuum followed by filtration through silica gel column ($CHCl_3$) to get rid of colored impurities provided pure **5** as an oil (52 g, 93%): IR (neat) ν (cm^{-1}) 1740 (CO); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H, CH_3), 3.91 (d, 2 H, J = 5.0 Hz, CH_2Cl), 4.36 (d, 2 H, J = 5.0 Hz, OCH_2), 5.5 (pentet, 1 H, J = 5.1 Hz, CH), 6.8–8.3 (m, 7 H aromatic). Anal. Calcd for $C_{15}H_{15}ClO_3$: C, 64.64; H, 5.42; Cl, 12.72. Found: C, 64.60; H, 5.43; Cl, 12.61.

(b) From 4. A solution of **4** (4.73g, 20 mmol), Ac_2O (5 mL), and Et_3N (5 mL) was stirred at 80–90 °C for 1 h. Addition of cold water (25 mL) followed by $CHCl_3$ extraction (2 × 25 mL), water wash (20 mL), drying, removal of solvent, and purification on silica gel column gave 5.1 g (92%) of **5**.

General Procedure for Lipase-Catalyzed Transesterification of 5. A solution of **5** (1.4 g, 5 mmol) and 1-butanol (1 mL, 10 mmol) in DIPE (10 mL; or alternatively **5** in excess 1-butanol (10 mL) used both as a nucleophile and solvent) was stirred at ambient temperature with lipase (0.7 g). After a certain degree of conversion (GC) was attained (see Table II), the reaction was stopped by filtration. Removal of the solvent followed by separation on a column (CH_2Cl_2) yielded optically active **4** and **5** (90 ± 2% of theoretical expected yields).

Lipase-Catalyzed Hydrolysis of 5. A mixture of **5** (2.8 g, 10 mmol), LPSA (0.28g), water (20 mL), and phosphate buffer (pH 7, 10 mL) was magnetically stirred at ambient temperature while pH was maintained at 7 by slow addition of 0.5 M NaOH solution. After consumption of required amount of NaOH solution (10 mL) to hydrolyze 50% of **5** (52 h), the reaction mixture was extracted with $CHCl_3$ (2 × 50 mL). Drying and removal of solvent gave a mixture of **4** and **5** (47% conversion by GC), which, after separation on column (CH_2Cl_2), gave 1.28 g (86%) of (−)-**5** and 0.93 g (83%) of (+)-**4** (for $[\alpha]_D$, see Table II). IR and NMR spectra of (−)-**5** and (+)-**4** were identical with those of racemic **5** and **4** described previously.

General Procedure for Lipase-Catalyzed Acylation of 4. A mixture of **4** (1.18 g, 5 mmol), vinyl acetate (10 mL, or alternatively 10 mmol of Ac_2O and 10 mL of DIPE), and lipase PS "amano" (0.5 g or 0.1 g; see Table II) was magnetically stirred at ambient temperature until the desired conversion was achieved.

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Filtration and removal of solvents under vacuum followed by separation on column (CH_2Cl_2) gave (−)-4 and (+)-5 (oils; 90–95% yield).

A reaction using 25 mmol of 4 (5.9 g), vinyl acetate (50 mL), and lipase PS (0.5 g) gave, after 13 d, 2.78 g (94%) of (−)-4 and 3.16 g (91%) of (+)-5 (both oils; for $[\alpha]_D$ see Table II). IR and NMR spectra of (−)-4 and (+)-5 were identical with those of racemic 4 and 5.

General Procedure for Direct Conversion of Chiral 4 or 5 to Chiral Propranolol (1). A mixture of chiral 4 or 5 (1 mmol), excess isopropylamine (2.5 mL), and 10% aqueous NaOH (0.44 mL, 1.1 mmol) was stirred at ambient temperature for 16 h. After excess isopropylamine was removed, water (2 mL) was added and the mixture was extracted with ether (2 × 10 mL). After the ether layer was dried over Na_2SO_4, dry HCl was bubbled into the solution for ca. 15 min to give colorless chiral propranolol hydrochloride in quantitative yields.

For example, (−)-4 obtained from the vinyl acetate reaction as described earlier ($[\alpha]^{25}_D$ −8.7°; 0.95 g, 4 mmol) after reaction with isopropylamine (10 mL) and 10% aqueous NaOH (1.76 mL) gave 1.2 g (100%) of crude (*S*)-(−)-propranolol hydrochloride, $[\alpha]^{25}_D$ −22.9° (1.15, EtOH); mp 188–190 °C. A single crystallization in MeOH–Et_2O provided optically pure (*S*)-1 HCl, mp 194–196 °C; $[\alpha]^{25}_D$ −25.5° (1.05, EtOH) (lit.[4] $[\alpha]^{21}_D$ −25.9° (1.06, EtOH)).

General Procedure for Conversion of Chiral 4 or 5 to Chiral Glycidyl 1-Naphthyl Ether (3). To a solution of chiral 4 or 5 (1 mmol) in isopropyl alcohol (5 mL) was added 20% aqueous NaOH (0.24 mL, 1.2 mmol for 4 or 0.5 mL, 2.5 mmol for 5), and the mixture was stirred at ambient temperature until TLC (CH_2Cl_2) showed complete conversion to 3 (ca. 1–2 h). Removal of solvent followed by CH_2Cl_2 (10 mL) extraction, water (2 mL) wash, drying, and removal of solvent afforded chiral 3 (77–85% yield) as an oil.

(+)-4 ($[\alpha]^{25}_D$ +9.0° (1.9, EtOH), obtained from BuOH–DIPE reaction, see Table II) gave (−)-3, $[\alpha]^{25}_D$ −33.9° (1.55, MeOH) (lit.[23] for *S*-(+)-3, $[\alpha]^{21}_D$ +31.4° (1.5, MeOH)).

(−)-5 ($[\alpha]^{25}_D$ −19.9 (2.4, EtOH), obtained from BuOH–DIPE reaction, see Table II) gave (+)-3, $[\alpha]^{25}_D$ +32.9° (1, MeOH) (lit.[23] $[\alpha]^{21}_D$ + 31.4° (1.5, MeOH)).

^1H NMR ($CDCl_3$) data for 3: δ 2.8 (m, 2 H, epoxide CH_2), 3.1–4.6 (m, 3 H, $ArOCH_2CH$), 6.75–8.5 (m, 7 H, aromatic).

Chiral Propranolol (1) from Chiral 3. A solution of chiral 3 (1 mmol) in excess isopropylamine (2.5 mL) and two drops of water was stirred at ambient temperature until TLC (CH_2Cl_2–MeOH) showed completion (16–20 h). Removal of solvent yielded crude propranolol (free base), which could be either purified by recrystallization in hexane or, more conventiently, converted directly to its hydrochloride as described earlier (85–90%).

(−)-3 ($[\alpha]^{25}_D$ −33.9° (1.55, MeOH) as obtained previously) gave *R*-(+)-1, $[\alpha]^{25}D$ +9.82° (1.6, EtOH) (lit.[24] $[\alpha]^{21}_D$ +10.6° (1.02, EtOH), mp 70 °C (lit.[24] 73 °C).

(+)-3 ($[\alpha]^{25}_D$ +32.9 (1, MeOH) as obtained previously) gave *S*-(−)-1, $[\alpha]^{25}_D$ −9.7° (1.5, EtOH) (lit.[24] $[\alpha]^{21}_D$ −10.2° (1.02, EtOH), mp 71 °C (lit.[24] 73 °C).

Spectral data for 1: IR (KBr) ν (cm^{-1}) 3425 (OH), 3280 (NH); ^1H NMR ($CDCl_3$) δ 1.1 (6 H, *J* = 6.2 Hz), 1.9 (2 H, br s) 2.9 (3 H, m), 6.8–8.3 (7 H, m).

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Supplementary Material Available: ^1H NMR spectra of 1 and 3–5 (4 pages). Ordering information is given on any current masthead page.

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Enzymes in Organic Synthesis. 48.[1,2] Pig Liver Esterase and Porcine Pancreatic Lipase Catalyzed Hydrolyses of 3,4-(Isopropylidenedioxy)-2,5-tetrahydrofuranyl Diesters

Philip G. Hultin, Franz-Josef Mueseler, and J. Bryan Jones*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 1A1

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Pig liver esterase (PLE) and porcine pancreatic lipase (PPL) catalyzed hydrolyses of 2,5-bis(methoxycarbonyl) and 2,5-bis(acetoxymethyl) meso-diester derivatives of 3,4-(isopropylidenedioxy)tetrahydrofuran proceed with enantiotopic selectivity to give monoester products of up to 72% ee. Transesterification of the 2,5-bis(hydroxymethyl) derivative with trifluoroethyl laurate promoted by PPL in ether also proceeds stereoselectively but in the opposite stereochemical sense from the hydrolysis of the corresponding diacetate. The data provide further examples of heteroatom and ester moiety induced reversals of stereoselectivity for the two enzymes.

Introduction

The use of enzymes as catalysts for the production of a broad structural range of chiral synthons is well-documented.[3] Hydrolytic enzymes such as pig liver esterase (PLE, E.C. 3.1.1.1)[4,5] and porcine pancreatic lipase (PPL, E.C. 3.1.1.3)[6] have proven particularly valuable in this regard, particularly with respect to their abilities to dis-

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