Lipase Catalysis in Organic Solvents. Application to the Synthesis of (*R*)- and (*S*)-Atenolol†

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Synthesis of (*R*)- and (*S*)-atenolol (1) was achieved in five steps starting from *p*-hydroxyphenylacetic acid. Lipase from *Pseudomonas cepacia* showed excellent selectivity toward kinetic resolution of key intermediates 1-[*p*-[(butoxycarbonyl)methyl]phenoxy]-3-chloropropan-2-ol (**9**) and its *O*-acetyl ester, 1-[*p*-[(butoxycarbonyl)methyl]phenoxy]-2-acetoxy-3-chloropropane (**10**).

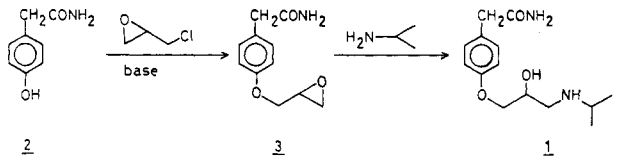
Since the biological activity in a racemic drug often resides in a single enantiomer, synthesizing such drugs in their optically pure form is becoming increasingly important.[1] One of the commercially attractive and environmentally compatible ways of making enantiomerically pure drugs is through biotransformations.[2] In continuation of our work on lipase catalysis,[3] we recently reported a convenient method for the synthesis of (*R*)- and (*S*)-propranolol.[4] We report here the extension of this protocol in the synthesis of both enantiomers of atenolol (**1**), one of the top five best-selling drugs in the world today.[5] While racemic atenolol is presently being marketed for the treatment of hypertension and angina and has shown promise in the treatment of post myocardial infarction, the *S* isomer has recently been found to avoid the occasional side effect of a lowered heart rate sometimes encountered with the racemate.[6] To our knowledge, this is the first report on the synthesis of chiral atenolol.[7]

To suit industrial requirements (see Scheme I, for the industrial route to atenolol[8]), an obvious choice of intermediates for subjecting to lipase-catalyzed kinetic resolution studies[4] was 1-[*p*-(carbamoylmethyl)phenoxy]-3-chloropropan-2-ol (**4**) and its *O*-acetyl ester 1-[*p*-(carbamoylmethyl)phenoxy]-2-acetoxy-3-chloropropane (**5**). Despite their easy preparation from *p*-hydroxyphenylacetamide (**2**) and epichlorohydrin following our previously reported methodology[4] (Scheme II), these intermediates could not be kinetically resolved using lipase due to their insolubility in any of the suitable organic solvents or water. To overcome this solubility problem, we decided to subject the relatively more soluble butyl esters, 1-[*p*-[(butoxycarbonyl)methyl]phenoxy]-3-chloropropan-2-ol (**9**) and 1-[*p*-[(butoxycarbonyl)methyl]phenoxy]-2-acetoxy-3-chloropropane (**10**) to lipase-catalyzed kinetic resolution studies.

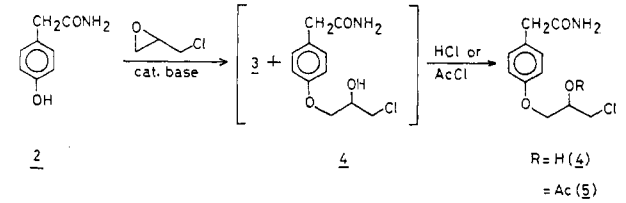
Esterification of *p*-hydroxyphenylacetic acid (**6**) with 1-butanol gave butyl *p*-hydroxyphenylacetate (**7**) in 95% yield. Condensation of **7** with epichlorohydrin using the best conditions previously established[4] using a catalytic amount of pyridine gave a mixture of 1-[*p*-[(butoxycarbonyl)methyl]phenoxy]-2,3-epoxypropane[9] (**8**) and **9** in a 30:70 ratio. Treating this mixture either with dry HCl or with acetyl chloride afforded **9** or **10** in ca. 90% overall yield (Scheme III).

Subjecting **9** to lipase-catalyzed acylation using lipase from *Pseudomonas cepacia* (Lipase Amano PS, LAPS) with acylating agents like vinyl acetate[10] (neat) or acetic anhydride[11] (in diisopropyl ether, DIPE) showed excellent selectivity toward the *S* isomer. Stopping the reaction at around 50% conversion gave (*R*)-**9** and (*S*)-**10** in high optical purities[12] (E = 100 and 48, respectively)[13] (Table I). The initial fast rate of the reaction considerably slowed

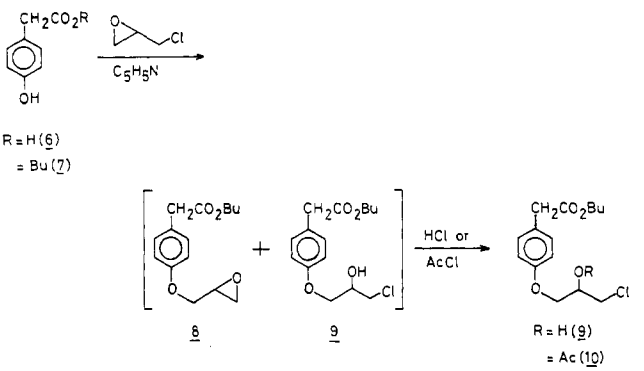
Scheme I



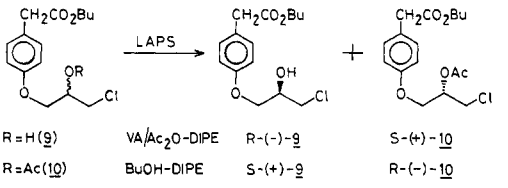
Scheme II



Scheme III



Scheme IV



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(2) For some recent reviews, see: (a) Margolin, A. L. *CHEMTECH* **1991**, *21*, 160. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (c) Wong, C.-H. *Science* **1989**, *244*, 1145. (d) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (e) Akiyama, A.; Bednarski, M.; Kim, M. J.; Simon, E. S.; Waldmann, H.; Whitesides, G. M. *CHEMTECH* **1988**, *18*, 640. (f) Yamada, H.; Shimizu, S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 622.

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Table I. Lipase-Catalyzed Acylation of 9 and Deacylation of 10

					OH (9)			OAc (10)				
sub	lipase	reaction medium	time, h	convn, %	$[\alpha]_D$[a]	isomer	ee,[b] %	$[\alpha]_D$[a]	isomer	ee,[c] %	reactive isomer	E[d]
9[e]	LAPS[f]	VA	43	50	−2.40	*R*	94	+22.1	*S*	>95	*S*	>100
	LAPS	Ac_2O–DIPE	30	53	−2.45	*R*	>95	+18.6	*S*	81	*S*	48
10[g]	CCL[h]	BuOH–DIPE	18	40	−1.69	*R*	66	+8.8	*S*	38	*R*	8
	LAPS	BuOH–DIPE	48	46	+2.45	*S*	>95	−18.7	*R*	81	*S*	>100
	LAPS[i]	BuOH–DIPE	27	51	+2.40	*S*	94	−22.1	*R*	>95	*S*	>100
	LAPS	BuOH[j]	168	45	+2.38	*S*	93	−17.5	*R*	76	*S*	63

[a] At 25 °C (C, 1–2% EtOH). [b] See ref 12a. [c] See ref 12b. [d] See ref 13. [e] Reactions carried out on 2-g scale (7.1 mmol) with 0.85 g of lipase and 15 mL of VA (or 14.2 mmol of Ac_2O in 15 mL of DIPE). [f] Lipase Amano PS from *P. cepacia*. [g] Reactions carried out on 5–15-mmol scale with ratio of 10:lipase:BuOH:DIPE = 5 mmol:0.6g:10 mmol:15 mL. [h] Lipase from *C. cylindracea*. [i] 10:lipase = 5 mmol:1.2 g. [j] 15 mL.

Table II. Conversion of Optically Pure 9/10 to 1 via 11

source[a]	substr (ee, %)	11; $[\alpha]_D$[b]	1; $[\alpha]^{25}_D$	isomer, ee (%)[c]
BuOH–DIPE	(*S*)-9 (94)	+2.20 (*R*)	+12.53 (0.9, EtOH)	*R*, >97
			+15.70 (0.6, 1 N HCl)	*R*, >97
	(*R*)-10 (>95)	−2.34 (*S*)	−13.10 (0.9, EtOH)	*S*, >99
			−16.10 (0.5, 1 N HCl)	*S*, >99
VA	(*R*)-9 (94)	−2.30 (*S*)	−12.46 (1, EtOH)	*S*, >95
	(*S*)-10 (>95)	+2.21 (*R*)	+12.53 (0.8, EtOH)	*R*, >97

[a] See Table I. [b] At 25 °C (1–2%, EtOH). [c] By comparison of observed rotation with literature values; for *S* isomer, −13.6 (1, 1 N HCl) (ref 7) and −16.0 (1, 1 N HCl) (Aldrich Catalog, 1990–91); *R* isomer, +16.0 (1, 1 N HCl) (Ibid.).

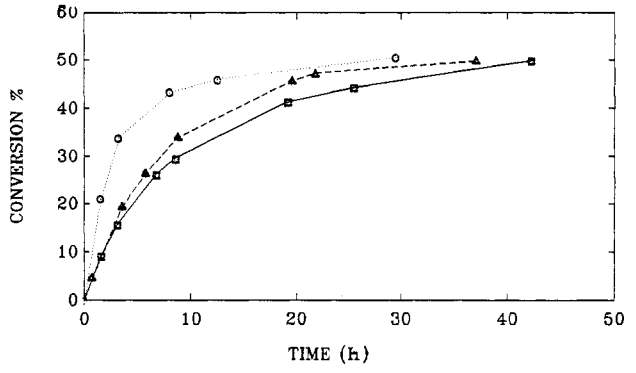
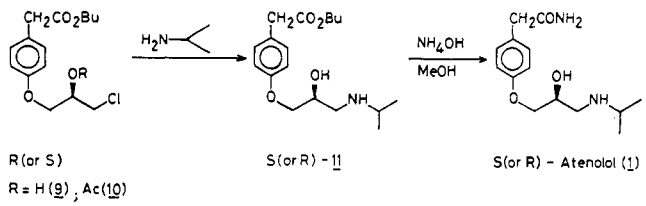


Figure 1. Acylation/deacylation of 9/10: (○) Ac_2O–DIPE; (△) BuOH–DIPE; (□) VA.

down after 40% conversion and almost stopped around 50% conversion as shown in Figure 1. In an alternative approach, **10** was subjected to deacylation using 1-butanol in DIPE.[3b] While LAPS once again showed excellent selectivity toward the *S* isomer, giving complimentary isomers (*S*)-**9** and (**R**)-**10** (E = 100), lipase from *Candida cylindracea*, on the other hand, showed opposite selectivity, albiet low (E = 8). LAPS-catalyzed deacylation in excess neat butanol instead of DIPE proceeded slower. An immobilized lipase from *Mucor miehei* (Lipozyme) showed no reaction at all (Scheme IV). While all the kinetic resolutions attempted in organic solvents worked well, attempts to resolve **10** in water were problematic. LAPS-catalyzed hydrolysis at pH 7 showed a satisfactory drop in pH but led to emulsions during solvent extraction.

Scheme V



Optically active **9** and **10** obtained from butanol–DIPE and vinyl acetate reactions with >94% ee were smoothly converted to (*R*)- or (*S*)-[*p*-(butoxycarbonyl)methyl]-phenoxy]-3-(isopropylamino)propan-2-ol (**11**) by treatment with aqueous isopropylamine followed by recrystallization from hexane (80–87%). While conversion of **9** required no additional base, **10** without NaOH did not go to completion. Conversion of **11** to pure atenolol (**1**) with >95% ee was finally achieved by treating **11** with ammonium hydroxide in methanol followed by a single recrystallization in ethyl acetate (Scheme V).

Experimental Section

^{1}H NMR (80 MHz) spectra were recorded in $CDCl_3$ using TMS as an internal standard. GLC analysis were carried out using a HP 101 capillary column (methyl silicone) (25 × 0.2 mm). HPLC analyses were performed on a μ-Porasil column (30 cm × 3.9 mm) using 9:5:86 EtOH/CH_3CN/hexane, flow rate 1.8 mL/min, with UV detection at 218 nm. Retention times, t_R, are expressed in minutes. Optical rotations were measured on a JASCO DIP-140

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(5) Barclays de Zoetc Wedd Research Report, Performance Chemicals, 1991, Vol. 6, No. 2, p 22.

(6) *Chem. Eng. News* **1991**, *69*(71), 16.

(7) An ICI patent claims synthesis of (*S*)-atenolol starting from D-mannitol: Tucker, H. (ICI Ltd.) Ger. Offen. 2453324, 1975; *Chem. Abstr.* **1975**, *83*, 96993.

(8) Sittig, M. *Pharmaceutical Manufacturing Encylopedia*, 2nd ed.; Noyes Publications: Park Ridge, NJ, 1988; Vol. 1, p 109.

(9) An authentic sample of **8** was prepared separately by using excess base: bp 158–60 °C/0.5 mm; IR (neat) (cm^{-1}) 1735; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, J = 6.4 Hz, CH_3), 1.1–1.9 (m, 4 H, $(CH_2)_2$), 2.6–3.0 (m, 2 H, epoxide CH_2), 3.15–3.5 (m, 1 H, CH), 3.5 (S, 2 H, $ArCH_2$), 3.8–4.4 (m, 4 H, $(OCH_2)_2$), 6.6–7.3 (AB q, 4 H, aromatic).

(10) (a) Degueil-Casting, M.; DeJesco, B.; Drouillard, S.; Mailard, 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.

(11) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531.

(12) (a) Enantiomeric excess (ee) of (*R*)-**9** obtained from vinyl acetate reaction ($[\alpha]^{25}_D$ = −2.40°; 94% ee) was determined by 300-MHz ^{1}H-NMR analysis of its (+)-MTPA ester prepared according to Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Optical purities of **9** obtained from other reactions were assigned on the basis of their relative rotations. (b) Enantiomeric excess of **10** was determined by comparision of the observed rotation with that of an authentic sample prepared from (*R*)-**9** (94% ee as determined above) using Et_3N–Ac_2O ($[\alpha]^{25}_D$ = −21.7°). Absolute configurations of both **9** and **10** were determined after their conversion to atenolol.

(13) Enantiomeric ratio, E, calculated according to Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

digital polarimeter. Lipases from *C. cylindracea* (CCL, 665 units/mg) and *P. cepacia* (LAPS, 30 units/mg) were purchased from Sigma and Amano Pharmaceutical Co., Japan, respectively. Room temperature fluctuated between 25 and 35 °C.

1-[*p*-(Carbamoylmethyl)phenoxy]-3-chloropropan-2-ol (4). A solution of *p*-hydroxyphenylacetamide (**2**, 2.5 g, 16.5 mmol), epichlorohydrin (13 mL, 165 mmol), water (5 mL), and NaOH (0.33 g, 8.2 mmol) was stirred at room temperature until TLC (CH_2Cl_2/MeOH, 3:1) showed completion of the reaction (ca. 48 h). Filtration and drying of the mixture afforded 3.5 g of solid containing 1-[*p*-(carbamoylmethyl)phenoxy]-2,3-epoxypropane[14] (**3**) and **4** (65:35 as determined by HPLC): **3** t_R 10.7; **4** t_R 21.3.

Dry HCl was passed through a cold solution of **3** and **4** (as obtained above) (1.5 g) in MeOH (25 mL) until TLC (CH_2Cl_2/MeOH, 95:5) showed complete conversion to **4** (1 h). Evaporation of MeOH followed by recrystallization of solid in $CHCl_3$ afforded 1.6 g (93% overall) of **4** as colorless crystals, mp 119–121 °C: HPLC t_R 21.3; IR (KBr) (cm^{-1}) 3360, 3180, 1660; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 3.4–3.8 (m, 4 H, $ArCH_2$, CH_2Cl), 4.1 (m, 3 H, OCH_2, CH), 6.6–7.3 (AB q, 4 H, aromatic).

1-[*p*-(Carbamoylmethyl)phenoxy]-2-acetoxy-3-chloropropane (5). A mixture of **3** and **4** (1.5 g) as obtained above was stirred with acetyl chloride (10 mL) at 25 °C. The initial suspension which became clear after ca. 30 min was further stirred until TLC (CH_2Cl_2/MeOH, 95:5) showed complete reaction (1 h). Removal of excess acetyl chloride under vacuum followed by recrystallization of the crude solid obtained from $CHCl_3$ gave 1.9 g (94% overall from **2**) of **5** as colorless crystals, mp 70–71 °C: HPLC t_R 17.0; IR (KBr) (cm^{-1}) 3360, 3180, 1745, 1660; ^1H NMR (CD_3OD) δ 2.1 (s, 3 H, CH_3), 3.5 (s, 2 H, $ArCH_2$), 3.9 (d, 2 H, *J* = 4.8 Hz, CH_2Cl), 4.2 (d, 2 H, *J* = 5.1 Hz, OCH_2), 5.3 (pentet, 1 H, *J* = 5 Hz, CH), 6.9–7.3 (Ab q, 4 H, aromatic).

Butyl *p*-Hydroxyphenylacetate (7). A solution of *p*-hydroxyphenylacetic acid (**6**) (30.4 g, 0.2 mol), 1-butanol (150 mL), and $NaHSO_4$ (1 g) was refluxed while water formed through azeotropic distillation was constantly being removed. After completion of the reaction as indicated by the amount of water collected (3.6 mL) and TLC (Et_2O), excess butanol was removed under reduced pressure. Continuation of the distillation under vacuum (132–136 °C/0.1 mm) yielded 39.5 g (95%) of **7**: GC t_R 3.08 (220 °C, isothermal); IR (neat) (cm^{-1}) 3400, 1740; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 6.3 Hz, CH_3), 1.1–1.8 (m, 4 H, $(CH_2)_2$), 3.5 (s, 2 H, $ArCH_2$), 4.1 (t, 2 H, *J* = 6.4 Hz, OCH_2), 6.7–7.2 (AB q, 4 H, aromatic). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.18; H, 7.76.

1-[*p*-[(Butoxycarbonyl)methyl]phenoxy]-3-chloropropan-2-ol (9). A solution of **7** (20.8 g, 0.1 mol), epichlorohydrin (39 mL, 0.5 mol), and pyridine (0.8 g, 10 mmol) was stirred at room temperature until TLC/GC showed completion of the reaction (ca. 48 h). Removal of excess epichlorohydrin and pyridine under reduced pressure yielded 31 g of an oily mixture of **8** and **9** (30:70, GC t_R 5.8 and 9.4, respectively, at 220 °C isothermal).

Dry HCl gas was passed through a solution of the above mixture (**8** and **9**, 15 g) in $CHCl_3$ (15 mL) at 0–5 °C for 1 h. Removal of the solvent under vacuum, followed by chromatography of the crude product on silica gel (CH_2Cl_2), afforded 13 g (89% overall from **7**) of pure **9** as an oil: GC t_R 9.4 (220 °C isothermal); IR (neat) (cm^{-1}) 3430, 1720; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 6.4 Hz, CH_3) 1.2–1.8 (m, 4 H, $(CH_2)_2$), 2.7 (d, 1 H, *J* = 5.1 Hz, OH), 3.6 (s, 2 H, $ArCH_2$), 3.7 (d, 2 H, *J* = 5.2 Hz, CH_2Cl), 4.0–4.2 (m, 5 H, OCH_2, CH), 6.8–7.3 (AB q, 4 H, aromatic). Anal. Calcd for $C_{15}H_{21}ClO_4$: C, 59.90; H, 7.04. Found: C, 59.81; H, 7.07.

1-[*p*-[(Butoxycarbonyl)methyl]phenoxy]-2-acetoxy-3-chloropropane (10). A mixture of **8** and **9** (7 g) as obtained above, $CHCl_3$ (10 mL), and acetyl chloride (10 mL) was stirred at 0–5 °C for 1 h followed by 2 h at room temperature. Removal of $CHCl_3$ and excess acetyl chloride under vacuum followed by purification of the crude product by chromatography on silica gel (CH_2Cl_2) afforded 31.4 g (92% from **7**) of **10** as an oil: GC t_R 12.2 (220 °C isothermal); IR (neat) (cm^{-1}) 1740; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 6.3 Hz, CH_3), 1.2–1.7 (m, 4 H, $(CH_2)_2$), 2.1 (s, 3 H, CH_3), 3.5 (s, 2 H, $ArCH_2$), 3.8 (d, 2 H, *J* = 5.2 Hz, CH_2Cl), 4.0–4.2 (m, 4 H, OCH_2), 5.3 (pentet, 1 H, *J* = 5.1 Hz, CH), 6.8–7.3 (AB q, 4 H, aromatic). Anal. Calcd for $C_{17}H_{23}ClO_5$: C, 59.56; H, 6.76. Found: C, 59.63; H, 6.77.

General Procedure for Lipase-Catalyzed Acylation of 9. A mixture of **9** (2 g, 7.1 mmol), vinyl acetate (15 mL) (or alternatively Ac_2O (1.44 mL, 14.2 mmol) in 15 mL of diisopropyl ether (DIPE)), and lipase from *P. cepacia* (LAPS) (0.85 g) was stirred at room temperature until the desired conversion was achieved (GC). Filtration and evaporation of solvents followed by separation of products by chromatography on silica of products by chromatography on silica gel (CH_2Cl_2) afforded (*R*)-**9** and (*S*)-**10** (as oils) in 90–95% of the theoretical yields.

General Procedure for Lipase-Catalyzed Deacylation of 10. A solution of **10** (1.71 g, 5 mmol), 1-butanol (0.9 mL, 10 mmol), and DIPE (15 mL) (or alternatively in excess 1-butanol (15 mL) without DIPE) was stirred at room temperature with lipase (LAPS) (0.6 g). After the desired conversion (followed by GC) was attained, the reaction was stopped by filtration. Evaporation of solvent, followed by separation of products by chromatography on silica gel (CH_2Cl_2), gave (*S*)-**9** and (**R**)-**10**, in the range of 90 ± 2% yield.

(*R*)- or (*S*)-1-[*p*-[(Butoxycarbonyl)methyl]phenoxy]-3-(isopropylamino)propan-2-ol (11): General Procedure. From 9. A mixture of optically pure **9** (1 mmol, 0.3 g), isopropylamine (3 mL), and water (1 mL) was stirred at room temperature until TLC ($CHCl_3$) showed completion of the reaction (ca. 24 h). Removal of excess isopropylamine, followed by $CHCl_3$ extraction, gave a semisolid, which after recrystallization from hexane gave colorless crystals of **11** (yields varied from 80–87%), mp 49–50 °C.

From 10. Essentially the same procedure as above was used except that NaOH (1.1 mmol) was also used (reaction time, 6–7 h): IR ($CHCl_3$) (cm^{-1}) 3400, 1730; ^1H NMR ($CDCl_3$) δ 1.0 (t, 3 H, *J* = 6.3 Hz, CH_3), 1.1 (d, 6 H, *J* = 6.2 Hz, $(CH_3)_2$), 1.2–1.6 (m, 4 H, $(CH_2)_2$), 2.4 (br, s, 2 H, NH, OH), 2.7–2.9 (m, 3 H, CH_2N, CHN), 3.5 (s, 2 H, $ArCH_2$), 3.9–4.2 (m, 5 H, $(OCH_2)_2$, OCH), 6.8–7.3 (AB q, 4 H, aromatic). Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.05. Found: C, 66.91; H, 8.98.

(*R*)- or (*S*)-Atenolol (1). A cold solution (0–5 °C) of optically pure **11** (0.32 g, 1 mmol), methanol (3 mL), and NH_4OH (1 mL) was stoppered and allowed to attain room temperature, where it was stirred until TLC (10% MeOH in $CHCl_3$ + 2–3 drops of NH_4OH) showed completion of the reaction (24–30 h). Removal of the solvents afforded crude **1** which was purified by boiling in MeOH and filtration to remove some insoluble impurities. Evaporation of MeOH followed by recrystallization from ethyl acetate gave pure **1** (60–70% yield), mp 147–151 °C, lit.[7] mp 151.5–153 °C, 148–152 °C (Aldrich): IR (KBr) (cm^{-1}) 3330, 3180, 1640; ^1H NMR (D_2O) δ 1.1 (d, 6 H, *J* = 6.4 Hz, $(CH_3)_2$), 2.7–3.3 (m, 3 H, CH_2N, CHN), 3.4 (s, 2 H, $ArCH_2$), 3.9–4.2 (m, 3 H, OCH_2, OCH), 6.8–7.2 (AB q, 4 H, aromatic).

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Supplementary Material Available: ^1H NMR spectra of **1**, **4**, **5**, **7**–**11**, and MTPA ester of (*R*)-**9** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) An authentic sample of **3** was prepared by a known method (ref 8).