Synthesis and β-Adrenergic Antagonist Activity of Stereoisomeric Practolol and Propranolol Derivatives

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A series of stereoisomeric practolol and propranolol derivatives has been synthesized in which the *N*-isopropyl group of the drug was replaced by an asymmetric heptanoic acid terminated by a substituted *p*-toluidide or *p*-(trifluoromethyl)anilide. The asymmetric epoxide, 3-(*p*-acetamidophenoxy)-1,2-epoxypropane, was allowed to react with a preformed enantiomeric 6-aminoheptanoic acid amide to yield the stereoisomeric practolol congener derivatives. An asymmetric drug precursor epoxide was prepared from *p*-acetamidophenol and enantiomeric 3-(tosyloxy)-1,2-epoxypropane (the Sharpless epoxide). For the propranolol congener derivatives, the preformed asymmetric 6-aminoheptanoic acid amides were allowed to react with one of the enantiomers of 3-(1-naphthyloxy)-1,2-epoxypropane. This drug precursor epoxide was prepared either by combining 1-naphthol with enantiomeric 3-(tosyloxy)-1,2-epoxypropane (the Sharpless epoxide) or by combining 1-naphthol with enantiomeric 3-(tosyloxy)-1,2-propanediol followed by epoxidation. Pharmacological studies carried out for the practolol derivatives demonstrated a significant dependence of enhanced potency and tissue/subreceptor specificity on both the configuration of the drug asymmetric carbon and the configuration of the spacer asymmetric carbon. The compounds containing the *S* configuration at the drug asymmetric center and the *R* configuration at the spacer asymmetric carbon exhibited an increase in potency over the other stereoisomeric congener derivatives and the progenitor drug. For the propranolol congener derivatives, a large decrease in potency was observed for all of the stereoisomers over the progenitor drug. The propranolol stereoisomers containing the *S* configuration at the drug asymmetric center were more active than those containing the *R* configuration at that center.

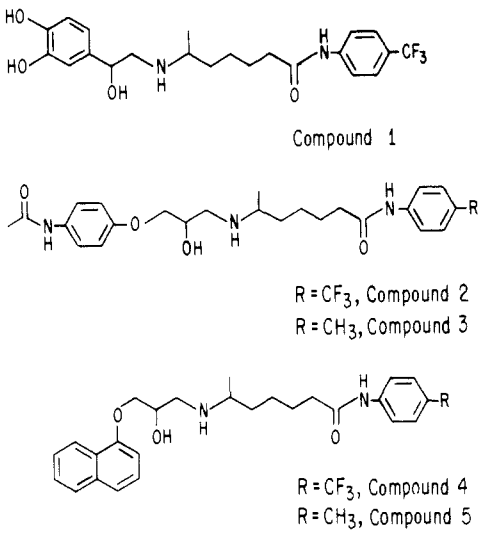
We have previously investigated the tissue specificity, selectivity, and receptor affinity of congener derivatives of β-adrenergic agonists, antagonists, and histamine.[1-12] These effects were observed with analogues of isoproterenol, practolol, propranolol, and histamine where the nitrogens are covalently attached to pharmacologically inert spacers composed of specifically designed alkyl groups terminated with amides, esters, etc.[1-3]

The purpose of investigating these derivatives was to develop a general method for improving drug delivery by attaching pharmacophores to carrier molecules such as globular proteins or antibodies. The spacer moiety was incorporated in order to sufficiently separate the carrier from the pharmacophore and prevent interference with the ligand–receptor interaction. However, when the carrier was reduced to a model system incorporating a functionalized aromatic ring, binding and efficacy over the progenitor drug could be substantially increased. We, therefore, prepared and tested a variety of derivatives with different spacer lengths and types of bonds (amides, esters, sulfonamides) between the spacer and the aromatic system.

Both the length of the alkyl spacer and the type of linkage between the spacer and the aromatic system were crucial for increased activity of these derivatives. For the β-adrenergic pharmacophore analogues, only a substituted heptanoic acid derivative yielded an increase in pharmacological potency. For the isoproterenol derivatives, a substantial increase in potency was observed for the stereoisomeric mixture of 6-[[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino]heptanoic acid *p*-(trifluoromethyl)-anilide over the progenitor drug. Other isoproterenol derivatives containing a four methylene spacer (as stereoisomeric mixtures) also showed increased activity. However, the *p*-(trifluoromethyl)anilide derivative was the most potent. After we established the dependence of biological activity on the structure of the spacer derivative, we next focused on the importance of chirality at the asymmetric center on the drug and the spacer group.

To investigate this, we extended the congener approach to drug design to include a study of the four separate stereoisomers of 6-[[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino]heptanoic acid *p*-(trifluoromethyl)anilide

Scheme I



(compound 1, Scheme I).[7,13] As expected, derivatives containing the *R* configuration at the asymmetric center

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of the drug showed binding behavior. However, chirality at the spacer asymmetric carbon also proved to be important for enhanced binding.

The *R,R* stereoisomer of the *p*-trifluoromethyl derivative of isoproterenol[13] (compound 1) demonstrated the strongest binding affinity of the stereoisomers tested in both S-49 mouse lymphoma cells (β_2) and turkey erythrocyte membranes (β_1). The *R,S* and *S,R* stereoisomers of compound 1 exhibited equal binding affinities and, as expected, the *S,S* stereoisomer showed the weakest binding.

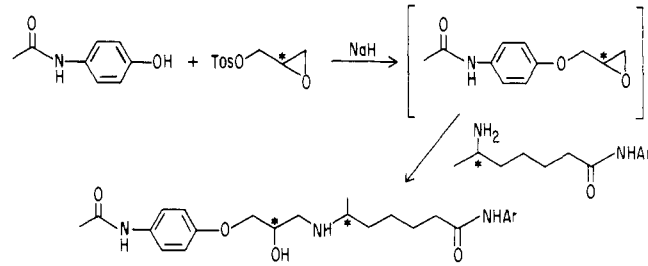
Investigation of the in vivo biological activity of the stereoisomers of compound 1 was also carried out. Intravenous administration of the *R,R* stereoisomer on anaesthetized, open-chested dogs demonstrated a doubling of myocardial contractile force when compared to results for racemic isoproterenol.[7] In addition, the same order of potencies for the stereoisomers was observed for increasing myocardial contractile force in isolated guinea pig left atria in agreement with the binding studies.[7]

We extended our studies to include β-adrenergic antagonist congener derivatives as stereoisomeric mixtures. The same spacer derivative responsible for altering agonist activity also alters blocking ability of selected antagonists. In addition, a four methylene spacer terminating in a toluidide derivative also alters blocking ability. A natural extension of this work led us to investigate the importance of chirality on the β-blocking activity of β-adrenergic antagonist congener derivatives.

The choice of β blockers for synthesis of the individual stereoisomers was based on potency and selectivity of the stereoisomeric mixtures of several β-adrenergic antagonist congener derivatives.[2] For the practolol congener derivatives, the individual stereoisomers of 6-[[3-(*p*-acetamidophenoxy)-2-hydroxypropyl]amino]heptanoic acid *p*-(trifluoromethyl)anilide (compound **2**) and 6-[3-(*p*-acetamidophenoxy)-2-hydroxypropyl]amino]heptanoic acid *p*-toluidide (compound **3**, Scheme I) were synthesized. Although practolol is known to be a β_1-specific blocker, these analogues (as stereoisomeric mixtures) were active in both β_1 and β_2 subreceptors as shown by in vitro experiments measuring the accumulation of c-AMP.[2] In binding studies, these congener derivatives showed enhanced tissue selectivity over practolol in rat heart.[2]

Derivatization of propranolol resulted in two analogues with altered subreceptor specificity. The two derivatives as stereoisomeric mixtures, 6-[[3-(1-naphthyloxy)-2-hydroxypropyl]amino]heptanoic acid *p*-(trifluoromethyl)anilide (compound **4**) and 6-[[3-(1-naphthyloxy)-2-hydroxypropyl]amino]heptanoic acid *p*-toluidide (compound **5**, Scheme I) were chosen for asymmetric synthesis because of their β_2 specificity although biological activity was considerably lower than that of the progenitor drug.[2] In addition, binding assays for the stereoisomeric mixtures of both compounds **4** and **5** demonstrated a slight preference for rat heart over rat lung when compared to the progenitor drug.[2] This suggests that derivatization of the β antagonists alters tissue selectivity. This paper covers our work on the synthesis and pharmacology of the stereoisomers of selected practolol and propranolol congener derivatives.

Scheme II



As depicted in Scheme I, these β-adrenergic congener derivatives are structurally very similar. The same modification leading to improved agonist potency generates antagonist derivatives with enhanced β_2 selectivity. In addition, the same drug modifier produces very different potencies, depending on the type of β blocker (either β_1 selective or nonselective).

Chemistry

The approach used for the synthesis of all the stereoisomers involved preparing the optically active 3-(aryloxy)-1,2-epoxypropane and 6-aminoheptanoic acid amides. These were coupled to form the target stereospecific drug congener derivative. The success of this synthesis resides in the preparation of the optically pure 3-(aryloxy)-1,2-epoxypropane and 6-aminoheptanoic acid anilides.

Several routes to the synthesis of asymmetric 3-(aryloxy)-1,2-epoxypropanes were considered. Recently, Sharpless and co-workers developed a practical method for the synthesis of asymmetric epoxides in high enantiomeric excess through incorporation of the titanium-catalyzed asymmetric epoxidation of allylic alcohols.[14-17] This method has been utilized in the synthesis of the individual enantiomers of 3-(tosyloxy)-1,2-epoxypropane (which we call the Sharpless epoxide) and resulting 3-(naphthyloxy)-1,2-epoxypropane.[18]

One approach to the preparation of stereospecific 3-(aryloxy)-1,2-epoxypropanes utilized in this paper involved synthesizing the asymmetric 3-(aryloxy)-1,2-epoxypropane in situ from enantiomeric 3-(tosyloxy)-1,2-epoxypropane (the Sharpless epoxide).[18] As shown in Scheme II, treatment of 4-acetamidophenol with enantiomeric 3-(tosyloxy)-1,2-epoxypropane afforded 3-(4-acetamidophenoxy)-1,2-epoxypropane. The appropriate amino amide was added in situ (as the free amine) and the desired product was obtained in >98% optical purity (as verified through high-resolution proton NMR).

A more complicated approach to the synthesis of enantiomeric 3-(aryloxy)-1,2-epoxypropanes was initiated in our laboratories prior to our use of the Sharpless epoxide. In 1939, Baer synthesized (*S*)-glycerol acetonide from

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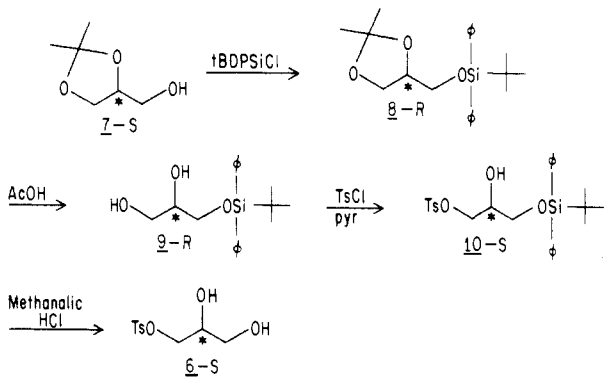
Scheme III[a]



[a] Where tBDPSiCl denotes *tert*-butyldiphenylsilyl chloride.

D-mannitol, a readily available chiral synthon.[19,20] Employing this synthesis, Danilewicz developed a route to (*R*)-3-(4-acetamidophenoxy)-1,2-epoxypropane from (*S*)-glycerol acetonide.[21] This was accomplished in reasonable yield and with high enantiomeric purity.

We employed a modification of the route of Danilewicz[21] and others[22] for the stereospecific synthesis of 3-(aryloxy)-1,2-epoxypropanes. Key to the synthesis was the utilization of (*R*)- and (*S*)-3-(tosyloxy)-1,2-propanediol (**6**-*R*, **6**-*S*). Stereospecific 3-(aryloxy)-1,2-epoxypropanes could be obtained from compounds **6**-*R* or **6**-*S* through displacement of the tosylate with the desired aryl alcohol followed by epoxidation.

The preparation of (*R*)-3-(tosyloxy)-1,2-propanediol (**6**-*R*) from D-mannitol through (*S*)-glycerol acetonide as an intermediate was carried out utilizing previously documented methods.[19,22]

Although methods for the preparation of **6**-*S* exist, we developed our own procedure. As shown in Scheme III, treatment of (*S*)-glycerol acetonide (**7**-*S*) with *tert*-butyldiphenylsilyl chloride (*t*-BDPSiCl) afforded (*R*)-3-*O*-*tert*-butyldiphenylsilyl)-1,2-glycerol acetonide (**8**-*R*). To obtain (*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-1,2-propanediol (**9**-*R*), compound **8**-*R* was treated with acetic acid. The primary alcohol of compound **9**-*R* was converted selectively to compound **10**-*S* with TsCl and pyridine. Finally, compound **6**-*S* was obtained by detachment of the silyl group using 5% methanolic HCl. The melting point and proton NMR of compound **6**-*S* were identical with those of compound **6**-*R*.

Treatment of either **6**-*R* or **6**-*S* with NaOH and the desired substituted phenol yielded the corresponding diol. The desired enantiomeric epoxide was obtained through conversion of the primary alcohol to the tosylate followed by ring closure to the epoxide using NaOH.[21] The desired 3-(aryloxy)-1,2-epoxide was allowed to react with the preformed enantiomeric amino amide (as the free amine) in DMSO. Column purification afforded the desired stereospecific product.

Synthesis of the stereospecific amino amide spacer derivatives was carried out in four steps. The compound, 6-oxoheptanoic acid, was prepared from α-methylcyclohexanol by previous methods.[23] As shown in Scheme IV, reaction of 6-oxoheptanoic acid with the appropriate

Table I. Biological Activity of Practolol Congener Derivatives on S-49 Mouse Lymphoma Cells (β_2)

compound	stereochemistry	K_i,[a] μM	RP[b]/drug
practolol		13.5 ± 0.3	1.0
2	*R,R*	2.17 ± 0.28	6.3
2	*R,S*	62 ± 7	0.22
2	*S,R*	0.146 ± 0.023	93.2
2	*S,S*	2.85 ± 0.15	4.77
2	mixture	0.39 ± 0.04	35.13
3	*R,R*	53.6 ± 4.6	0.25
3	*R,S*	9.24 ± 0.42	1.45
3	*S,R*	0.81 ± 0.05	16.7
3	*S,S*	15.6 ± 0.6	0.86
3	mixture	1.18 ± 0.05	11.35

[a] K_i was determined in vitro by accumulation of c-AMP as measured by the radioimmunoassay reported.[26] [b] Relative potency.

Table II. Biological Activity of Practolol Congener Derivatives on Rat Fat Cells (β_1)

compound	stereochemistry	K_i,[a] μM	RP[b]/drug
practolol		0.7 ± 0.2	1.0
2	*R,R*	0.24 ± 0.05	2.92
2	*R,S*	6.7 ± 0.3	0.104
2	*S,R*	0.031 ± 0.002	22.6
2	*S,S*	0.35 ± 0.01	2.0
2	mixture	0.13 ± 0.01	7.8
3	*R,R*	1.99 ± 0.06	0.351
3	*R,S*	2.62 ± 0.08	0.267
3	*S,R*	0.26 ± 0.01	2.71
3	*S,S*	1.58 ± 0.02	0.442
3	mixture	0.26 ± 0.01	2.71

[a] K_i was determined in vitro by accumulation of c-AMP as measured by the radioimmunoassay reported.[26] [b] Relative potency.

substituted aniline via a mixed anhydride intermediate yielded 6-oxoheptanoic acid *p*-toluidide (**11**). Compound **11** was refluxed with α-methylbenzylamine in toluene. Hydrogenation under pressure using Raney nickel[24] followed by recrystallization of the methanesulfonic acid salt yielded enantiomeric (α-methylbenzyl)amino amide **12**-*R,R* in high diastereomeric purity. Final hydrogenation using Pd/carbon afforded (*R*)-6-aminoheptanoic acid *p*-toluidide (**13**-*R*). Assignment of the absolute configuration of the spacer asymmetric carbon was based upon literature precedent for hydrogenation of imines formed with α-methylbenzylamine.[24,25]

Enantiomeric purity of the amino amide spacer derivatives was verified through proton NMR analysis of the Mosher amides.[26] In all cases, only one enantiomer was observed. The Mosher amides of the two enantiomers have different chemical shifts and were, therefore, easily discernible with proton NMR. As shown in Figure 1, the amide resonances in the amide/aromatic region of the *R,R* stereoisomer of 6-aminoheptanoic acid *p*-(trifluoromethyl)anilide are at δ 8.37 and 6.88. The *R,S* stereoisomer has the same amide protons resonating at δ 8.12 and 6.80. When the two stereoisomers are mixed together, the amide resonances of the individual stereoisomers are easily distinguishable from each other.

Diastereomeric purity of the stereoisomeric congener derivatives was also verified with proton NMR. Where a mixture of diastereomers gave a quartet for the asymmetric methyl group, a doublet was observed for the diastereomerically clean material.

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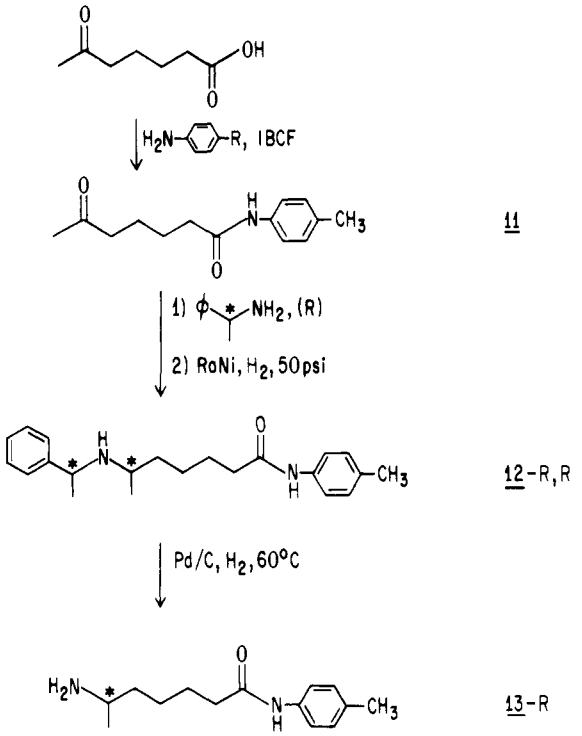
Scheme IV[a]



[a] Where IBCF denotes isobutyl chloroformate and RaNi denotes Raney nickel.

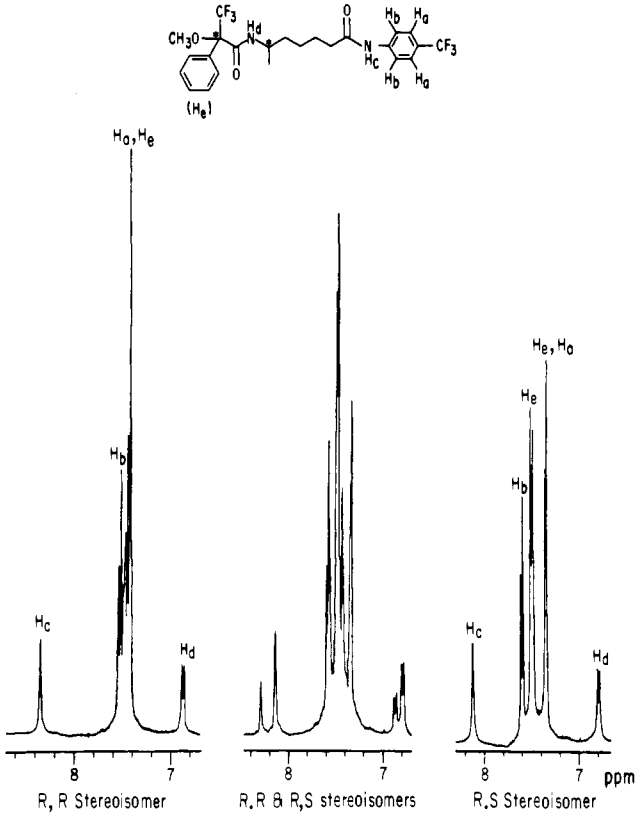


Figure 1. 360-MHz proton NMR of the Mosher amides of enantiomeric 6-aminoheptanoic acid *p*-(trifluoromethyl)anilide in $CDCl_3$.

Biological Results and Discussion

All biological assays were carried out in the laboratories of our collaborator, K. Melmon of Stanford University. The biological activity was determined by utilizing both S-49 mouse lymphoma cells (β_2) and rat fat cells (β_1) and was measured by the in vitro accumulation of c-AMP.[27] The cells were prepared exactly as outlined previously.[2] The K_i values of the antagonists were calculated by using the Cheng and Prusoff equation.[28] As shown in Tables I–III, the four individual stereoisomers of each selected congener derivative were tested for biological potency along with the corresponding stereoisomeric mixture and the progenitor drug.

Table III. Biological Activity of Propanolol Congener Derivatives on S-49 Mouse Lymphoma Cells (β_2)

compound	stereochemistry	K_i,[a] μM	RP[b]/drug
propanolol		0.78 ± 0.08	1.0
4	*R,R*	130 ± 9	0.006
4	*R,S*	179 ± 12	0.0043
4	*S,R*	45.9 ± 3.6	0.017
4	*S,S*	39 ± 4	0.02
4	mixture	78.0 ± 12.2	0.01
5	*R,R*	195 ± 3	0.004
5	*R,S*	195 ± 6	0.004
5	*S,R*	9.07 ± 0.73	0.086
5	*S,S*	41.0 ± 2.6	0.019
5	mixture	43.3 ± 0.3	0.018

[a] K_i was determined in vitro by accumulation of c-AMP as measured by the radioimmunoassay reported.[26] [b] Relative potency.

For the practolol *p*-(trifluoromethyl)anilide derivative **2**, Tables I and II show a correlation between increase in potency and the presence of the appropriate configuration at each chiral center. The *S,R* stereoisomer of this congener derivative shows substantially enhanced blockade over the stereoisomeric mixture and the progenitor drug at both S-49 and rat fat cell subreceptors. Both the *R,R* and *S,S* stereoisomers for this analogue show equal blocking activity and both are substantially less than that of the *S,R* stereoisomer. The *R,S* stereoisomer has the lowest activity and inappropriate configuration at both asymmetric centers.

As shown in Tables I and II, the β-blocking activity for practolol toluidide derivative **3** is highly dependent upon the configuration of the congener derivative. Of the stereoisomers tested, the most significant increase in potency is observed for the *S,R* stereoisomer.

In this series, the other stereoisomers show significantly less activity than the *S,R* stereoisomer. Unlike the isoproterenol (trifluoromethyl)anilide derivative 1, the practolol (trifluoromethyl)anilide stereoisomers containing only one appropriate configuration, i.e. the *R,R* and *S,S* stereoisomers, do not appear to demonstrate greater activity over the *R,S*, stereoisomer. This is true for both S-49 mouse lymphoma cells and rat fat cells.

For these practolol derivatives, the *R* configuration at the spacer asymmetric carbon crucial for generating enhanced binding for the isoproterenol derivative (compound 1), also improves β-adrenergic blockade. Most likely, this effect arises from improved binding to the receptor. This behavior is not subreceptor specific as demonstrated by the enhanced potency for the *S,R* stereoisomer of both practolol analogues in S-49 mouse lymphoma cells and rat fat cells.

The same drug modifiers that produce enhanced potency for practolol generate propranolol derivatives with greatly decreased potency over the progenitor drug (Table III). These derivatives show some activity for S-49 mouse lymphoma cells. However, the relative potency is sub-

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stantially less than propranolol. There is no activity for these derivatives in rat fat cells. For these analogues, the presence of the spacer derivative appears to hinder the drug from binding adequately to the receptor, resulting in weak blocking activity.

One of the most important aspects of the results with the practolol and isoproterenol derivatives is the ability of the *R* configuration at the asymmetric carbon of the drug modifier to improve both agonist binding and β-blocking activity. The structural element of the β-adrenergic receptor responsible for binding the drug modifier is configuration specific but is not agonist or antagonist specific.

In light of these results, we believe an auxiliary binding site may exist at the β-adrenergic receptor. This site appears to be stereospecific, as demonstrated by the enhanced potency for isoproterenol and practolol congener derivatives containing the *R* configuration at the spacer asymmetric carbon. Perhaps the drug modifier enhances binding to this auxiliary site for specific β_1 blockers over nonspecific blockers as demonstrated by the reduction in activity for propranolol congener derivatives over the progenitor drug. Further exploration will be necessary to determine the specific nature of this site and if derivatization of both β_1 selective and nonselective blockers in general leads to this trend.

In conclusion, we have demonstrated a further refinement of the congener approach to drug design by utilizing the individual stereoisomers of our β-antagonist congener derivatives. These findings have led to an increased understanding of the structural requirements of our drug modifiers necessary for improved receptor interaction.

Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using a 10-cm pathlength cell. High-pressure liquid chromatography was performed using two Waters Model 510 pumps, a Waters Model 680 automated gradient controller, a Perkin-Elmer LCI-100 laboratory computing integrator, and an Axxiom Sprectoflow 757 absorbance detector, which was set at 254 nm for all runs. High-resolution proton NMR spectra were obtained with a 360-MHz FT-NMR spectrometer built in-house from a continuous-wave Varian console equipped with an Oxford superconducting magnet and a Nicolet 1180E computer.

Reagent-grade solvents were utilized as received except for the following: THF was dried over KOH followed by distillation over lithium aluminum hydride. Acetone was dried by passing though potassium carbonate and drying over 4-Å molecular sieves. Dimethylformamide was dried over KOH, distilled from BaO, and stored over molecular sieves. *N*-Methylmorpholine was distilled and stored over molecular sieves. Methanol was dried by distillation and passed through a column of molecular sieves and finally stored over CaH_2. Dry ethanol was stored over molecular sieves. All chemicals were purchased from Aldrich Chemical Co. unless otherwise stated. Microchemical analysis was performed by Desert Analytics in Tuscon, Az.

Thin-layer chromatography was routinely carried out with aluminum-backed EM silica $60F_{254}$ plates (Merck). Products were visualized by UV and solutions of ninhydrin, fluorescamine, bromocresol green, and potassium permanganate. Column chromatography was carried out with Kieselgel 60 silica gel of either 70–270 mesh for normal column chromatography or 230–400 mesh for flash chromatography. Thin layer chromatography solvent systems typically used included chloroform/methanol/acetic acid (CMA), 85:10:5, 70:5:3, 95:5:3; chloroform/methanol/ammonium hydroxide (CMN), 85:10:5; butanol/acetic acid/water/pyridine (BAWP), 1:3:3:1; chloroform/methanol (CM), 9:1; and ethyl acetate/hexanes, in varying concentrations.

Synthesis of Drug Precursors. (*R*)- or (*S*)-3-(Tosyloxy)-1,2-epoxypropane. This reagent was initially developed in the laboratories of K. B. Sharpless. It was purchased from Aldrich Chemical Co. and was used without further purification.

(*R*)-3-(Naphthyloxy)-1,2-propanediol (15-*R*). To a solution of naphthol (3.5 g, 24.3 mmol) and compound 6-*R* (5 g, 20.3 mmol) in dioxane (60 mL), was added NaOH (1.35 g) in water (15 mL). The solution was stirred at 80 °C for 16 h. The solvent was removed under vacuum and the residue was brought up in CH_2Cl_2 and extracted with base. This removed the starting materials and left the product. The solvent was again removed under vacuum and the product was recrystallized with CH_2Cl_2 and acetone to yield 4 g (91%): $[\alpha]^{25}_D$ −8.5° (c 4.5, methanol); mp 106–106.5 °C; ^{1}H NMR (DMSO-d_6) δ 8.6–7 (m, 7, naphthyl H) 5.25 (d, 1, $-CH_2CH(OH)CH_2-$), 4.9 (t, 1 $CHCH_2OH$), 4.5–3.4 (m, 5, $-CH_2CHCH_2-$).

(*R*)-3-(Naphthyloxy)-1-(tosyloxy)-2-propanol (16-*R*). Compound 15-*R* (3.0 g, 13.74 mmol) was added to pyridine (30 mL). The solution temperature was reduced to −10 °C by using a KCl/dry ice bath. TsCl (2.2 g, 11.5 mmol) was added all at once and the mixture was stirred until the TsCl dissolved. The mixture was kept at 4 °C for 16 h. The reaction mixture was mixed with ethyl acetate (50 mL) and slowly added (with cooling) to sulfuric acid (15 mL) in water (100 mL). The layers were separated, and the aqueous layer was washed three times with ethyl acetate. The organic washes were combined and dried for 3 h using 4-Å molecular sieves. Ethyl acetate was removed under reduced pressure and the resulting oil was mixed with ether and put into a freezer for 16 h. A solid precipitated out and was filtered. A column was run with ethyl acetate as eluant and the product was collected and recrystallized from ethyl acetate/ether, yielding 3.0 g (59%): mp 118.5–120 °C; $[\alpha]^{25}_D$ +6.01° (c 5, methanol); ^{1}H NMR ($CDCl_3$) δ 8.1–6.5 (m, 11, naphthyl H, $bz_{2,3,5,6}H$), 4.3–4.0 (m, 5, $-OCH_2CHCH_2-$), 3.3 (d, 1, OH), 2.2 (s, 3, CH_3).

3-*O*-(*tert*-Butyldiphenylsilyl)-(*R*)-glycerol 1,2-Acetonide (8-*R*). Imidazole (21 g, 0.31 mol) was dissolved in dry DMF (35 mL). To this was added *tert*-butyldiphenylsilyl chloride (*t*-BDPSiCl, 40 g, 0.145 mol). After the solution stopped bubbling, compound 7-*S* (17.5 g, 0.132 mol) was added and the solution was stirred for 4 h. The workup involved adding cold water to the reaction mixture and extracting the product into ethyl ether. The ether layer was washed with 0.1 N HCl and water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure to give 50 g of an oil (93%): $[\alpha]^{20}_D$ +2.63 (c 2, methanol); ^{1}H NMR ($CDCl_3$) δ 8–7.3 (m, 10, $(bz)_2$) 4.4–3.7 (m, 5, $-CH_2CHCH_2-$), 1.43 (s, 3, CH_3), 1.49 (s, 3, CH_3), 1.15 (s, 9, $(CH_3)_3C$).

(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2,3-propanediol (9-*R*). Compound 8-*R* (5 g, 13.5 mmol) was mixed with 100 mL of 90% AcOH. After heating to reflux for 10 min, the solution was allowed to cool to room temperature slowly. The solvent was removed under vacuum and the resulting oil was subjected to column chromatography using 95:5:3 dichloromethane/methanol/acetic acid as the eluting solvent mixture. After the appropriate fractions were collected and concentrated, the resulting oil was placed under vacuum to yield starlike, off-white crystals. The product was recrystallized from ethyl acetate/hexanes, yielding 4.3 g (98%): $[\alpha]^{20}_D$ +6.5° (c 2, methanol); mp 54 °C; ^{1}H NMR ($CDCl_3$) δ 7.9–7.2 (m, 10, $(bz)_2$), 3.9–3.5 (m, 5, $-CH_2CHCH_2-$), 1.03 (s, 9, $(CH_3)_3C$).

(*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3-(tosyloxy)-2-propanol (10-*S*). To a solution of pyridine (40 mL) was added compound 9-*R* (5 g, 15.12 mmol). The solution was cooled to 0 °C and TsCl (2.70 g, 14.2 mmol) was added. The solution was stirred until all solids had dissolved. The solution remained at 4 °C for 16 h. Afterward, ethyl acetate was added and pyridine was removed by washing with 1.0 N HCl until the washes were acidic. The solvent was removed under reduced pressure and an oil (6.5 g, 94%) resulted: ^{1}H NMR ($CDCl_3$) δ 8.25–7.45 (m, 14, $(bz)_2$, tosylate $bz_{2,3,5,6}H$) 4.58–3.45 (m, 5, $-CH_2CHCH_2-$), 2.65 (s, 3, CH_3), 1.3 (s, 9, $(CH_3)_3C$).

(*S*)-1-(Tosyloxy)-2,3-propanediol (6-*S*). The oil from the above procedure was added to methanolic HCl (5 mL of acetyl chloride in 100 mL of MeOH, 50 mL) and the solution was stirred for 6 h. Afterward, the solution was concentrated under reduced pressure and a column was run with 70:10:5 chloroform/methanol/acetic acid as the eluting solvent mixture. The appropriate fractions were obtained and concentrated under reduced pressure. The resulting oil was left under vacuum in order for crystals to

form. The product was recrystallized from toluene. Both the NMR data and TLC showed the product to be identical with the *R* isomer: 1.5 g (77% yield); $[\alpha]^{20}_D$ +9.34° (c 5, methanol); mp 54–58 °C.

(*S*)-3-(Naphthyloxy)-1,2-propanediol (15-*S*). The procedure was identical with the protocol outlined for the *R* isomer, including amounts and yield: mp 105.5–106 °C; $[\alpha]^{20}_D$ +8.4° (c 4.5, methanol).

Synthesis of Chiral Spacer Derivatives. 6-Oxoheptanoic Acid *p*-Toluidide (11). A solution of compound 17 (9.5 g, 65.9 mmol) in THF (70 mL) was cooled to 0 °C. To this was added *N*-methylmorpholine (6.0 g, 59.3 mmol) and the solution was stirred at 0 °C for 10 min. Isobutyl chloroformate (8.95 g, 65.5 mmol) was added and the solution was stirred for an additional 10 min at 0 °C. A solution of *p*-toluidine (7.0 g, 65.3 mmol) in *N*-methylmorpholine (0.6 mL) and THF (15 mL) was added dropwise over 1 h. After the addition, the solution was allowed to come to room temperature and stirring was continued for 6–8 h (overnight). The solvent was removed under reduced pressure and the residue was suspended in 150 mL of EtOAc. After extraction with 0.1 N HCl, 0.1 N NaOH, and brine, the solution was dried with $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was suspended in toluene. The solution was heated to boiling and allowed to cool slowly. The product crystallized out as fluffy, white needles, yielding 12.0 g (87%): mp 110–110.5 °C; the product was shown to be homogeneous by thin-layer chromatography (CMA 85:10:5), R_f = 0.38; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2, $bz_{2,6}$H), 7.10 (d, 2, $bz_{3,5}$H), 2.50 (t, 2, $-CH_2CONH$), 2.38 (t, 2, CH_3COCH_2), 2.30 (s, 3, CH_3CO), 2.15 (s, 3, bz-CH_3), 1.66 (m, 4, $-CH_2CH_2-$). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

6-Oxoheptanoic Acid *p*-(Trifluoromethyl)anilide (18). Compound 18 was prepared from *p*-(trifluoromethyl)aniline (10.6 g, 64.6 mmol) in a manner similar to that of compound 11 to yield 16 g (86%): mp 139.5–140 °C (lit.[9] mp 139–140 °C); R_f = 0.68 (CMA 85:10:5); ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2, $bz_{2,6}$H), 7.55 (d, 2, $bz_{3,5}$H), 2.52 (t, 2, $-CH_2CONH-$), 2.40 (t, 2, CH_3COCH_2), 2.20 (s, 3, CH_3CO), 1.68 (m, 4, $-CH_2CH_2-$). Anal. ($C_{14}H_{16}NO_2F_3$) C, H, N.

(*R*)-[[(*R*)-α-Methylbenzyl]amino]heptanoic Acid *p*-Toluidide (12-*R*,*R*). To a 500-mL round-bottom flask was added toluene (400 mL) and compound 11 (6.0 g, 25.71 mmol), along with *R*-(+)-α-methylbenzylamine (3.26 g, 26.89 mmol) and toluenesulfonic acid (0.25 g, 1.45 mmol). A Dean–Stark trap was set up and the solution was refluxed for 4 h. Toluene was removed under reduced pressure and the resulting orange oil was brought up in 10 mL of anhydrous methanol. Raney nickel (10 mL) was prepared by washing with anhydrous ethanol (five times, 100 mL) and with anhydrous methanol (seven times, 100 mL). The catalyst was added to a Parr bottle along with the orange oil with anhydrous methanol as solvent. The total volume did not exceed 65 mL. The solution was hydrogenated for 24 h with a pressure of 50 psi. The solution was filtered and the solvent was removed under reduced pressure. To the residue was added dichloromethane (30 mL), ethyl ether (15 mL), and methanesulfonic acid (1.2 g). This solution was stirred and cooled to 0 °C. After 2 h, the resulting white precipitate was filtered and recrystallized from methanol, dichloromethane, and ethyl ether, yielding 3.39 g (30%): mp 135–135.5 °C; $[\alpha]^{20}_D$ +32.5° (c 1, methanol); R_f = 0.169 (CMA 85:10:5); ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1, CONH-bz), 7.57 (d, 2, $bz_{2,6}$H–CH(CH_3)–), 7.47 (m, 5, $bz_{3,4,5}$H–CH(CH_3), CONH-$bz_{2,6}$H), 7.10 (d, 2, CONH-$bz_{3,5}$H), 4.52 (br s, 1, –NH–), 2.9 (br s, bz-CH(CH_3)), 2.34 (s, 3, CH_3SO_3H), 2.30 (t, 2, $-CH_2CO-$), 2.25 (s, 3, CONH-bz-CH_3), 1.83 (br s, 1, $-NHCH(CH_3)CH_2-$), 1.6–1.3 (m, 6, $CH(CH_3)CH_2CH_2CH_2$) 1.55 (d, 3, bz-$CH(CH_3)$), 1.2 (d, 3, $-NHCH(CH_3)-$).

(*S*)-[[(*S*)-α-Methylbenzyl]amino]heptanoic Acid *p*-Toluidide (12-*S*,*S*). Compound 12-*S*,*S* was prepared from (*S*)-(–)-α-methylbenzylamine (3.26 g, 26.89 mmol), in a manner similar to that of compound 12-*R*,*R*, yielding 3.6 g (32%): mp 135 °C, $[\alpha]^{20}_D$ –32.4° (c 1, methanol); R_f = 0.169 (CMA 85:10:5).

(*R*)-[[(*R*)-α-Methylbenzyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide (19-*R*,*R*). Compound 19-*R*,*R* was prepared from compound 18 (7.38 g, 25.71 mmol), in a manner similar to that of compound 12-*R*,*R*, yielding 3.9 g (31%): mp 205 °C (lit.[7] mp 210–212 °C); $[\alpha]^{20}_D$ +32.7° (c 1, methanol) [lit.[7] $[\alpha]^{20}_D$ +32.7° (c 1.0, MeOH)]; R_f = 0.263 (CMA 85:10:5); ^{1}H NMR (DMSO-d_6) δ 9.5 (s, 1, CONH-bz), 7.84 (d, 2, CONH-$bz_{2,6}$H), 7.72 (d, 2, CONH-$bz_{3,5}$H), 7.55 (d, 2, $bz_{2,6}$H–CH(CH_3)), 7.48 (m, 3, $bz_{3,4,5}$H-CH(CH_3)), 4.55 (br s, 1, –NH–), 2.8 (br s, bz-CH(CH_3)), 2.4 (br s, 5, $-CH_2CO-$, CH_3SO_3H), 1.83 (br s, 1, $-NHCH(CH_3)CH_2-$), 1.6–1.3 (m, 6, $CH(CH_3)CH_2CH_2CH_2$), 1.56 (d, 3, bz-$CH(CH_3)$), 1.2 (d, 3, $-NHCH(CH_3)-$).

(*S*)-[[(*S*)-α-Methylbenzyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide (19-*S*,*S*). Compound 19-*S*,*S* was prepared from compound 18 (7.38 g, 25.71 mmol) and (*S*)-(–)-α-methylbenzylamine (3.26 g, 26.89 mmol) in a manner similar to that of compound 12-*R*,*R*, yielding 3.92 g (31%): mp 205.5 °C (lit.[7] mp 208–210 °C); $[\alpha]^{20}_D$ +32.7° (c 1, methanol) [lit.[7] $[\alpha]^{20}_D$ +33° (c 1, methanol)]; R_f = 0.263 (CMA 85:10:5).

(*R*)-Aminoheptanoic Acid *p*-Toluidide (13-*R*). To a Parr bottle that had been flushed with dry nitrogen was added compound 12-*R*,*R* (3.39 g, 7.79 mmol) along with 40 mL of absolute ethanol. To this was added 1.5 g of 5% Pd on carbon. The mixture was heated to 60 °C under a pressure of 45 psi for 24 h. Afterward, the solution was filtered and the solvent was removed under reduced pressure. The resulting clear, viscous oil crystallized as the methanesulfonic acid salt upon addition of anhydrous ethyl ether. The resulting white crystals were filtered and dried, yielding 2.5 g (100%): mp 139.5–140.5 °C; $[\alpha]^{20}_D$ +1.1° (c 1, methanol), R_f = 0.069 (CMA 85:10:5); ^{1}H NMR (DMSO-d_6) δ 7.8 (s, bz-NHCO), 7.52 (d, 2, $bz_{2,6}$H), 7.12 (d, 2, $bz_{3,5}$H), 3.17 (q, 1, $NH_2CH(CH_3)CH_2$, 2.41 (s, 3, CH_3SO_3H), 2.35 (t, 2, CH_2CH_2CONH-bz), 2.27 (s, 3, bz-CH_3), 1.64–1.33 (m, 6, $CH(CH_3)CH_2CH_2CH_2$), 1.19 (d, 3, $NHCH(CH_3)CH_2$). Anal. ($C_{15}H_{26}N_2O_4S$) C, H, N. Proton NMR of the Mosher amide [(+)-MTPACl,[26] pyridine, CCl_4] showed only one diastereomer.

(*S*)-Aminoheptanoic Acid *p*-Toluidide (13-*S*). Compound 13-*S* was prepared in a manner similar to that of compound 13-*R*, starting from compound 12-*S*,*S* (3.39 g, 7.79 mmol) to yield 2.5 g (100%): mp 140–141 °C; $[\alpha]^{20}_D$ –1.1° (c 1, methanol); R_f = 0.069 (CMA 85:10:5). Anal. ($C_{15}H_{26}N_2O_4S$) C, H, N. ^{1}H NMR of the Mosher amide [(+)-MTPACl,[26] pyridine, CCl_4] showed only one diastereomer.

(*R*)-Aminoheptanoic Acid *p*-(Trifluoromethyl)anilide (20-*R*). Compound 20-*R* was hydrogenated in a manner similar to that of compound 13-*R*, starting from compound 19-*R*,*R* (3.9 g, 7.97 mmol) to yield 3.06 g (100%): mp 164–165 °C (lit.[7] mp 162–164 °C); $[\alpha]^{20}_D$ +1.39° (c 1, methanol) [lit.[7] $[\alpha]^{20}_D$ +1.3° (c 1, methanol)]; R_f = 0.065 (CMA 85:10:5); ^{1}H NMR (DMSO-d_6) δ 7.82 (d, 2, $bz_{2,6}$H), 7.72 (s, bz-NHCO), 7.67 (d, 2, $bz_{3,5}$H), 4.41 (t, $NH_2CH(CH_3)$), 3.19 (m, 1, $NH_2CH(CH_3)CH_2$), 2.41 (s, 3, CH_3SO_3H), 2.41 (t, 2, CH_2CH_2CONH-bz), 1.64–1.33 (m, 6, $CH(CH_3CH_2CH_2CH_2)$, 1.19 (d, 3, $NHCH(CH_3)CH_2$. Anal. ($C_{15}H_{23}F_3N_2O_4S$) C, H, N. ^{1}H NMR of the Mosher amide [(+)-MTPACl,[26] pyridine, CCl_4] showed only one diastereomer.

(*S*)-Aminoheptanoic Acid *p*-(Trifluoromethyl)anilide (20-*S*). Compound 20-*R* was prepared by hydrogenating compound 19-*R*,*R* in a manner similar to that of compound 12-*R*,*R* (3.9 g, 7.97 mmol), yielding 3.06 g (100%): mp 164.5–165 °C, (lit.[7] mp 160–162 °C); $[\alpha]^{20}_D$ –1.3° (c 1, methanol) [lit.[7] $[\alpha]^{20}_D$ –1.1° (c 1.0, methanol)]; R_f = 0.065 (CMA 85:10:5). Anal. ($C_{15}H_{23}F_3N_2O_4S$) C, H, N. Proton NMR of the Mosher amide [(+)-MTPACl,[26] pyridine, CCl_4] showed only one diastereomer.

Synthesis of Stereoisomeric Congener Derivatives. (*S*)-Practolol. Sodium hydride (0.21 g, 5.0 mmol, 60% oil dispersion) was washed with dry CH_2Cl_2, dried under reduced pressure, and suspended in DMF (4.36 mL) at room temperature under N_2. A solution of 4-acetaminophenol (0.66 g, 4.9 mmol) in DMF (2.18 mL) was added to produce a purple sludge. After 20 min, a solution of (*S*)-3-(tosyloxy)-1,2-epoxypropane (1.0 g, 4.4 mmol) in DMF (2.18 mL) was added. A clear, brown-green solution resulted. This stirred for 3.5–4 h. Afterward, isopropylamine (3.7 mL) and water (0.37 mL) were added. This refluxed for 4 h at 90 °C. The workup involved diluting the solution with water and extracting it with ethyl ether. The ether layer was washed with 1 N NaOH and saturated NaCl and then dried using $MgSO_4$. After removal of the solvent under reduced pressure, the resulting oil was dissolved in CH_2Cl_2 and HCl was bubbled through. The product was recrystallized from methanol and ether, yielding 0.5 g (43%): mp 161–161.5 °C, (lit.[21] mp 130–131.5 °C as the free amine); R_f = 0.7 (CMN 25:10:5); $[\alpha]^{20}_D$

−22.87° (c 0.7, ethanol) [lit.[21] $[\alpha]^{20}_D$ for the *R* (+)-isomer +14° (c 1.9, H_2O)]; H NMR (DMSO-d_6), δ 9.99 (s, 1, −CONH−), 9.12 (br s, 1, $-CH_2NH(H)-$), 8.69 (br s, 1, $-CH_2NH(H)-$), 7.53 (d, 2 $bz_{2,6}H$, *J* = 9 Hz), 6.90 (d, 2, $bz_{3,5}H$, *J* = 9 Hz), 5.55 (br s, 1, OH), 4.23 (m, 1, $CH_2CH(OH)$), 3.95 (m, 2, $-OCH_2CH(OH)-$), 3.34 (m, 1, $CH(OH)CH(H)$), 3.11 (m, 1, $CH(OH)CH(H)$), 2.97 (m, 1, $NHCH(CH_3)$), 2.02 (s, 3, CH_3CONH), 1.27 (d, 6, $(CH_3)_2CH$, *J* = 7.2 Hz).

6(*S*)-[[3-(*p*-Acetimidophenoxy)-2(*R*)-hydroxypropyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (2-*S*,*R*). Sodium hydride (0.1 g, 2.5 mmol, 60% oil dispersion) was washed with dry THF, dried under reduced pressure, and suspended in DMF. Acetamidophenol (0.315 g, 2.0 mmol) was added as a DMF solution and the mixture was stirred for 20 min. During this time, the solution turned deep purple. Afterward, (*S*)-3-(tosyloxy)-1,2-epoxypropane (0.453 g, 1.98 mmol) dissolved in DMF was added and the solution stirred at room temperature for 4 h.

Compound **20**-*R* (0.50 g, 1.73 mmol) was added as the free base and the reaction mixture was heated to 90 °C for 16 h. The workup involved addition of water to the cooled solution and washing with CH_2Cl_2. The organic layer was washed with 1 N NaOH and saturated NaCl solution. The solution was dried with $MgSO_4$ and filtered and dry HCl gas was bubbled through. The solution was concentrated under reduced pressure and the remaining solid was recrystallized from ethanol and ether. A part of the recrystallized product was prepared for biological testing by lyophilizing it from water, yielding 0.196 g (21.3%): mp 189–189.5 °C; R_f = 0.07 (CMA 85:10:5), $[\alpha]^{20}_D$ −7.6° (c 3, methanol); ^{1}H NMR (MeOD) δ 7.78 (d, 2, CH_3CONH-$bz_{2,6}H$, *J* = 9 Hz), 7.58 (d, 2, CH_3CONH-$bz_{3,5}H$, *J* = 9 Hz), 7.45 (d, 2, CONH-$bz_{2,6}H$, *J* = 9 Hz), 6.92 (d, 2, CONH-$bz_{3,5}H$, *J* = 9 Hz), 4.25 (m, 1, $-CH_2CH(OH)CH_2-$), 4.02 (m, 2, $-OCH_2CH(OH)-$), 3.32 (m, 2, $-CH(OH)C(H)HNH-$, $NHCH(CH_3)$), 3.17 (m, 1, $-CH(OH)C(H)HNH-$), 2.48 (t, 2, CH_2CH_2CONH, *J* = 9 Hz), 2.10 (s, 3, CH_3CONH), 1.92–1.44 ($CH(CH_3)CH_2CH_2CH_2$), 1.35 (d, 3, $-NHCH(CH_3)-$, *J* = 7.2 Hz). Anal. ($C_{25}H_{33}F_3N_2O_4Cl$) C, H, N.

6(*S*)-[[3-(*p*-Acetamidophenoxy)-2(*S*)-hydroxypropyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (2-*S*,*S*). Compound **2**-*S*,*S* was prepared in a manner similar to that of compound **2**-*S*,*R*, starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **20**-*S* to yield 200 mg (22%): mp 186–187 °C; R_f = 0.10 (CMA 85:10:5): $[\alpha]^{20}_D$ −8.58° (c 3, methanol); ^{1}H NMR (MeOH) δ 7.79 (d, 2, CH_3CONH-$bz_{2,6}H$, *J* = 9 Hz), 7.58 (d, 2, CH_3CONH-$bz_{3,5}H$, *J* = 9 Hz), 7.45 (d, 2, CONH-$bz_{2,6}H$, *J* = 9 Hz), 6.93 (d, 2, CONH-$bz_{3,5}H$, *J* = 9Hz), 4.24 (m, 1, $-CH_2CH(OH)CH_2-$), 4.02 (m, 2, $-OCH_2CH(OH)-$), 3.31 (m, 2, $-CH(OH)C(H)HNH-$, $-NHCH(CH_3)-$), 3.15 (m, 1, $-CH(OH)C(H)HNH-$), 2.48 (t, 2, CH_2CH_2CONH, *J* = 9Hz), 2.10 (s, 3, CH_3CONH), 1.92–1.44 ($CH(CH_3)CH_2CH_2CH_2$), 1.37 (d, 3, $-NHCH(CH_3)-$, *J* = 7.2 Hz). Anal. ($C_{25}H_{33}F_3N_2O_4Cl$) C, H, N.

6(*R*)-[[3-(*p*-Acetamidophenoxy)-2(*R*)-hydroxypropyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (2-*R*,*R*). Compound **2**-*R*,*R* was prepared in a manner similar to that of compound **2**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **20**-*R* to yield 210 mg (23%): mp 186.5–187 °C; $[\alpha]^{20}_D$ +8.5° (c 3, methanol); R_f and NMR assignments were identical with those of compound **2**-*S*,*S*. Anal. ($C_{25}H_{33}F_3N_2O_4Cl$) C, H, N.

6(*R*)-[[3-(*p*-Acetamidophenoxy)-2-hydroxypropyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (2-*R*,*S*). Compound **2**-*R*,*S* was prepared in a manner similar to that of compound **2**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **20**-*S* to yield 190 mg (21%): mp 189–189.5 °C; $[\alpha]^{20}_D$ +7.61° (c 3, methanol); R_f and NMR assignments were identical with that of compound **2**-*S*,*R*. Anal. ($C_{25}H_{33}F_3N_2O_4Cl$) C, H, N.

6(*S*)-[[3-(*p*-Acetamidophenoxy)-2(*R*)-hydroxypropyl]amino]heptanoic Acid *p*-Toluidide Hydrochloride (3-*S*,*R*). Compound **3**-*S*,*R* was prepared in a manner similar to that of compound **2**-*S*,*R*, starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*R* (0.39 g, 1.66 mmol) to yield 230 mg (31%): mp 188.5–189 °C; R_f = 0.10 (CMA 85:10:5); $[\alpha]^{20}_D$ −5.5° (c 3, methanol); ^{1}H NMR (D_2O) δ 7.12 (t, 4, CH_3CONH-$bz_{2,3,5,6}H$, *J* = 8.28 Hz), 7.04 (d, 2, CONH-$bz_{2,6}H$, *J* = 8.64 Hz), 6.81 (d, 2, CONH-$bz_{3,5}H$, *J* = 8.64 Hz), 4.12 (m, 1, $-CH_2CH(OH)CH_2-$), 3.88 (m, 2, $-OCH_2CH(OH)-$), 3.14–3.0 (m, 3, $-CH(OH)CH_2NH-$, $-NHCH(CH_3)-$), 2.24 (t, 2, CH_2CH_2CONH, *J* = 7.2 Hz), 2.11 (s, 3, toluidide methyl), 1.96 (s, 3, CH_3CONH), 1.7–1.2 ($CH(CH_3)-CH_2CH_2CH_2$), 1.15 (d, 3, $-NHCH(CH_3)-$, *J* = 6.48 Hz). Anal. ($C_{25}H_{36}N_3O_4Cl$) C, H, N.

6(*S*)-[[3-(*p*-Acetamidophenoxy)-2(*S*)-hydroxypropyl]amino]heptanoic Acid *p*-Toluidide Hydrochloride (3-*S*,*S*). Compound **3**-*R*,*S* was prepared in a manner similar to that of compound **3**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*S* to yield 120 mg (16%): mp 188.5–189 °C; $[\alpha]^{20}_D$ +5.4° (c 3, methanol); R_f and NMR assignments were identical with those of compound **3**-*S*,*R*. Anal. ($C_{25}H_{36}N_3O_4Cl$) C, H, N.

(*S*)-Propranolol. Sodium hydride (0.21 g, 5 mmol, 60% oil dispersion) was washed with dry CH_2Cl_2, dried under reduced pressure, and suspended in DMF (4.36 mL) at room temperature under N_2. A solution of 1-naphthol (0.66 g, 4.9 mmol) in DMF (2.18 mL) was added to produce a green sludge. After 20 min, a solution of (*S*)-3-(tosyloxy)-1,2-epoxypropane (1.0 g, 4.4 mmol) in DMF (2.18 mL) was added. A clear, brown-green solution resulted. This was stirred for 3.5–4 h. Ether and water were added to the reaction mixture, and the product was extracted into the ether layer. After removal of the solvent under reduced pressure, the resulting oil was brought up in DMF (6 mL), isopropylamine (3.7 mL), and water (0.37 mL). This was refluxed for 4 hours at 90 °C. The workup involved dilution of the solution with water and extraction with ethyl ether. The ether layer was washed with 1 N NaOH and saturated NaCl and dried with $MgSO_4$. The drying agent was filtered off and dry HCl gas was bubbled into the solution. Product came out of solution as a white solid, which was filtered and recrystallized from methanol and ether, yielding 0.4 g (35%): mp 191.5–192.5 °C (lit.[8] mp, 192.5–193.5 °C); R_f = 0.307 (CMA 95:5:3); $[\alpha]^{20}_D$ −25.48° (c 2, ethanol) [lit.[18] $[\alpha]^{20}_D$ −25.7° (c 1.7, ethanol)]; ^{1}H NMR (MeOD) δ 8.3 (m, 1, naphthyl H), 7.8 (m, 1, naphthyl H), 7.55–7.32 (m, 4, naphthyl H), 6.95 (m, 1, naphthyl H), 4.47 (m, 1, $-CH_2CH(OH)CH_2N-$), 4.22 (m, 2, $-CH_2CH(OH)CH_2-$), 3.5 (m, 1, $-NHCH(CH_3)_2$), 3.42–3.22 (m, 2, $-CH(OH)CH_2NH-$), 1.19 (t, 6, $CH(CH_3)_2$, *J* = 7.2 Hz).

6(*S*)-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (4-*S*,*R*). Sodium hydride (0.21 g, 5.0 mmol, 60% oil dispersion) was washed with dry CH_2Cl_2, dried under reduced pressure, and suspended in DMF (4.36 mL) at room temperature under N_2. A solution of 1-naphthol (0.66 g, 4.9 mmol) in DMF (2.18 mL) was added to produce a green sludge. After 20 min, a solution of (*R*)-3-(tosyloxy)-1,2-epoxypropane (1.0 g, 4.4 mmol) in DMF (2.18 mL) was added. A clear, brown-green solution resulted. This was stirred for 3.5–4 h. Compound **20**-*R* (0.62 g, 2.2 mmol) was added as the free base and the reaction mixture was heated to 90 °C for 16 h. The workup involved addition of water to the cooled reaction mixture, washing of the mixture with ether three times, and then washing of the organic layer with 1 N NaOH and NaCl saturated water. The washed organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. A nonflash column was run with dichloromethane/methanol/acetic acid 70/5/3 to separate the product spot. The resulting oil was brought up in a small amount of ether. Hexanes were added, and the product was triturated to a powder. The solid was washed three times with hexanes. To obtain the HCl salt, the purified product was taken up in dichloromethane and HCl was bubbled through the solution. The solvent was removed under reduced pressure and the resulting oil was triturated to a powder by using ether as solvent. The solid was recrystallized with ethanol and ether. A portion of the product was prepared for biological testing by lyophilizing it from water and methanol to yield 170 mg (15%): mp 148.5–149 °C, $[\alpha]^{20}_D$ −8.2° (c 3, methanol); R_f and ^{1}H NMR were identical with that of compound **4**-*R*,*S*. Anal. ($C_{27}H_{32}F_3N_2O_3Cl$) C, H, N.

6(*S*)-[[3-(1-Naphthyloxy)-2(*S*)-hydroxypropyl]amino]heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (4-*S*,*S*). Compound **4**-*S*,*S* was prepared in a manner similar to that of compound **4**-*S*,*R* starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **20**-*S* to yield 180 mg (15.6%): mp 147–148 °C, $[\alpha]^{20}_D$ −8.8° (c 3, methanol); R_f values and ^{1}H NMR analysis were identical with that of compound **4**-*R*,*R*. Anal. ($C_{27}H_{32}F_3N_2O_3Cl$) C, H, N.

6(*S*)-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*S*,*R*). The protocol was the same as that for compound **5**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*R* (0.513 g, 2.2 mmol) to yield 150 mg (15%): mp 147–148 °C; R_f = 0.37 (CMA 70:5:3); $[\alpha]^{20}_D$ −6.3° (c 3, methanol); ^{1}H NMR (DMSO-d_6) δ 9.97 (s, 1, CON*H*-Ar), 8.98 (br s, 1, NH), 8.75 (br s, 1, NH), 8.55 (m, 1, naphthyl H), 7.86 (m, 1, naphthyl H), 7.6–7.4 (m, 5, naphthyl H, $bz_{2,6}$H), 7.1 (d, 2, $bz_{3,5}$H, J = 7.2 Hz), 7.00 (d, 1, naphthyl H, J = 9 Hz), 4.42 (m, 1, $CH_2CH(OH)CH_2$, 4.18 (m, 2, $-OCH_2CH(OH)-$), 3.28 (m, 2, $-CH(OH)CH_2(NH)-$), 3.14 (m, 1, $NHCH(CH_3)CH_2$), 2.34 (t, 2, CH_2CH_2CONH, J = 9 Hz), 2.24 (s, 3, bz-CH_3), 1.86 (m, 1, $CH(CH_3)CH_2$), 1.7–1.5 (m, 3, $CH(CH_3)CH_2$, CH_2CH_2CONH), 1.5–1.3 (m, 2, $CH(CH_3)CH_2CH_2$), 1.27 (d, 3, $-CH(CH_3)-$, J = 9 Hz). Anal. ($C_{27}H_{35}N_2O_3Cl$) C, H, N.

6(*S*)-[[3-(1-Naphthyloxy)-2(*S*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*S*,*S*). The protocol was the same as that for compound **5**-*S*,*R*, starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*S* to yield 170 mg (17%): mp 146–146.5 °C; R_f = 0.37 (CMA 70:5:3); $[\alpha]^{20}_D$ −9.3° (c 3, methanol); ^{1}H NMR (DMSO-d_6) δ 9.97 (s, 1, CON*H*-Ar), 9.16 (br s, 1, NH), 8.73 (br s, 1, NH), 8.30 (m, 1, naphthyl H), 7.90 (m, 1, naphthyl H), 7.63–7.4 (m, 5, naphthyl H, $bz_{2,6}$H), 7.08 (d, 2, $bz_{3,5}$H, J = 7.2 Hz), 7.00 (d, 1, naphthyl H, J = 9 Hz), 4.42 (m, 1, $CH_2CH(OH)CH_2$), 4.19 (m, 2, $-OCH_2CH(OH)-$), 3.30 (m, 2, $-CH(OH)CH_2(NH)-$), 3.15 (m, 1, $NHCH(CH_3)CH_2$), 2.35 (t, 2, CH_2CH_2CONH, J = 9 Hz), 2.22 (s, 3, bz-CH_3), 1.88 (m, 1, $CH(CH_3)CH_2$), 1.7–1.5 (m, 3, $CH(CH_3)CH_2$, CH_2CH_2CONH), 1.5–1.3 (m, 2, $CH(CH_3)CH_2CH_2$), 1.30 (d, 3, $-CH(CH_3)-$, J = 9 Hz). Anal. ($C_{27}H_{34}N_2O_3$) C, H, N.

6(*R*)-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*R*,*R*). The protocol was similar to that of compound **5**-*S*,*R*, starting from (*R*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*R* to yield 140 mg (14%): mp 146–147 °C, $[\alpha]^{20}_D$ +9.3° (c 3, methanol); the values for R_f and NMR were identical with that of compound **10**-*S*,*S*. Anal. ($C_{27}H_{35}N_2O_3Cl$) C, H, N.

6(*R*)-[[3-(1-Naphthyloxy)-2(*S*)-hydroxypropyl]amino]-heptanoic Acid *p*-Toluidide Hydrochloride (5-*R*,*S*). The protocol was similar to that of compound **5**-*S*,*R*, starting from (*S*)-3-(tosyloxy)-1,2-epoxypropane and compound **13**-*S* to yield 130 mg (13%): mp 147–148 °C, $[\alpha]^{20}_D$ +6.1° (c 3, methanol); the values for R_f and NMR were identical with that of compound **5**-*S*,*R*. Anal. ($C_{27}H_{35}N_2O_3Cl$) C, H, N.

6-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-(*S*)-heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (4-*R*,*S*). Compound **15**-*R* (1.28 g, 3.2 mmol) in DMSO (4 mL) was cooled to 0 °C and water (1 mL) containing NaOH (0.92 g) was added dropwise over a period of 15 min. The solution remained at 0 °C for 45 min and at room temperature for 10 min. Ice water was added to the solution and the product was extracted into ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure to give the crude epoxide as a brownish oil. This oil was used without further purification.

A mixture of compound **20**-*S* (1.1 g, 2.2 mmol) in 0.1 N NaOH (5 mL) was extracted with dichloromethane. The solvent was removed under reduced pressure and the residue was suspended in DMSO (20 mL). This was combined with the epoxide formed above and the solution was stirred at 90 °C for 22 h. The reaction was monitored by TLC (CMA 85:10:5) for the disappearance of starting amine. After 22 h, the product was cooled and water (10 mL) was added to the solution. The solution was extracted into dichloromethane, dried with $MgSO_4$, and filtered. The crude product was concentrated under vacuum. A flash column was run with 3:1 dichloromethane/2-propanol. the appropriate fractions were collected and concentrated under vacuum. The residue was brought up in CH_2Cl_2 and dry HCl gas was bubbled through. The solvent was removed under reduced pressure and the product was recrystallized from ethanol and ether. A portion of the recrystallized product was prepared for biological testing by lyophilizing it from methanol/water to yield 150 mg (13%): mp 147.5–148 °C; R_f = 0.38 (CMA 95:5:3); $[\alpha]^{20}_D$ +8.1° (c 3, methanol); ^{1}H NMR (MeOD) δ 8.3 (m, 1, naphthyl H), 7.85–7.7 (m, 3, naphthyl H, $bz_{3,5}$H), 7.6–7.5 (d, 2, $bz_{2,6}$H, J = 9 Hz), 7.5–7.3 (m, 4, naphthyl H), 6.9 (d, 1, naphthyl H, J = 7.2 Hz), 4.2 (m, 2, $-OCH_2CH(OH)-$), 3.8 (m, 1, $CH_2CH(OH)CH_2$), 3.3–3.0 (m, 3, $-CH(OH)CH_2NHCH(CH_3)-$), 2.42 (t, 2, $-CH_2CH_2CONH-$, J = 7.2 Hz) 1.8–1.4 (m, 6, $-CH(CH_3)CH_2CH_2CH_2-$), 1.24 (d, 3, $CH(CH_3)$, J = 5.4 Hz). Anal. ($C_{27}H_{32}F_3N_2O_3Cl$) C, H, N.

6-[[3-(1-Naphthyloxy)-2(*R*)-hydroxypropyl]amino]-(*R*)-heptanoic Acid *p*-(Trifluoromethyl)anilide Hydrochloride (4-*R*,*R*). The reaction conditions and amounts were identical with that for compound **4**-*R*,*S* except compound **20**-*R* was used, yielding 148 mg (13%): mp 147–148 °C; $[\alpha]^{20}_D$ +8.8° (c 3, methanol); R_f = 0.38 (CMA 95:5:3); ^{1}H NMR (MeOD) δ 8.3 (m, 1, naphthyl H), 7.85–7.7 (m, 3, naphthyl H, $bz_{3,5}$H), 7.6–7.5 (d, 2, $bz_{2,6}$H, J = 9 Hz), 7.5–7.3 (m, 4, naphthyl H), 6.9 (d, 1, naphthyl H, J = 7.2 Hz), 4.35 (m, 1, $CH_2CH(OH)CH_2$), 4.2 (m, 2, $-OCH_2CH(OH)-$), 3.4–3.0 (m, 3, $-CH(OH)CH_2NHCH(CH_3)-$), 2.42 (t, 2, $-CH_2CH_2CONH-$, J = 7.2 Hz), 1.85–1.4 (m, 6, $-CH(CH_3)CH_2CH_2CH_2-$), 1.27 (d, 3, $CH(CH_3)$, J = 5.4 Hz). Anal. ($C_{27}H_{32}F_3N_2O_3Cl$) C, H, N.

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Antihypertensive Dihydropyridines with 1,4,4-Trisubstitution

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Dihydropyridines with 1,4,4-trisubstitution were synthesized and tested for antihypertensive activity in a spontaneously hypertensive rat model. This substitution pattern on the dihydropyridine nucleus differs markedly from that found most active in the structure–activity relationship established for nifedipine-like compounds. However, some were found to significantly lower blood pressure at testing doses (30 mg/kg, ip and 100 mg/kg, po) for up to 24 h. Methyl 1,4-dihydro-4,4-dimethyl-1-pyridinepropanoate (**2**-1), for example, lowered blood pressure 71 mmHg at 30 mg/kg, ip and the effect endured for greater than 24 h. Unlike prototypical dihydropyridines such as nifedipine, these compounds did not seem to have any effect on calcium channels.

Dihydropyridines as a chemical class have been widely explored as cardiovascular agents in recent years. Nifedipine (1) has been approved for clinical use as an antianginal agent and represents the type of dihydropyridine structure found useful in both antianginal and antihypertensive therapy. A large body of evidence regarding the structural requirements for these activities has accrued[1]

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