Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 5. Synthesis and Evaluation of Enantiomers of 8-[[(4-Chlorophenyl)sulfonyl]amino]-4-(3-pyridinylalkyl)octanoic Acid

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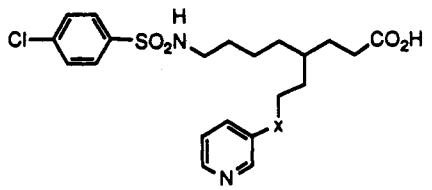
The enantiomers of 8-[[(4-chlorophenyl)sulfonyl]amino]-4-(3-pyridinylpropyl)octanoic acid (1) and its pyridinyl ether analog (2) were synthesized using the highly diastereoselective method of alkylation of acyloxazolidinone. These enantiomerically pure compounds were compared with the corresponding racemic compounds 1 and 2 for their in vitro activity. Compounds 1, 1*R*, and 1*S* and 2, 2*S*, and 2*R* were equipotent as thromboxane receptor antagonists (TxRAs) and thromboxane synthase inhibitors (TxSIs) (IC_{50} = 2–30 nM). Upon oral administration to guinea pigs, the enantiomers inhibited the ex vivo U 46619-induced platelet aggregation with potency similar to that of the corresponding racemic compound. This indicates that the enantiomers have pharmacologic profile and bioavailability similar to that of the corresponding racemic compound.

One facet of antithrombotics research focusing on the inhibition of the actions of thromboxane A_2 (TxA_2) is based on the understanding that TxA_2 plays an important role in the pathogenesis of circulatory disorders.[1,2] Therefore, thromboxane synthase inhibitors (TxSIs) and thromboxane receptor antagonists (TxRAs) have been developed.[3] We have undertaken a program to develop compounds which possess both TxRA and TxSI activities.[4-7] In a previous publication[7] we have described the structure–activity relationships (SAR) and in vitro/in vivo profile of 1 and 2 which behave as TxRA and TxSI. The presence of one chiral center in both 1 and 2 suggested the preparation and testing of their enantiomers. The failure to resolve 1 and 2 and some of their synthetic intermediates necessitated the synthesis of each of the enantiomers. In this paper we report the enantioselective syntheses of the enantiomers of 1 and 2 and their activity profile in comparison with the corresponding racemic compounds.



1 (x = CH_2)

2 (x = O)

Chemistry

The highly diastereoselective method of alkylation of enantiomerically pure 4-benzyl-*N*-acyloxazolidinone developed by Evans[8] was employed to introduce the only chiral center in the molecules. Thus, the pivaloyl mixed anhydride, prepared from 6-(benzyloxy)hexanoic acid, was treated with the lithium anion of (*S*)-(−)-4-benzyloxazolidinone (Scheme I). Treatment of this compound with lithium diisopropylamide (LDA) at −78 °C gave the enolate which upon alkylation with allyl bromide at −10 °C gave 3 which was 99.4% diastereomerically pure by GC.[9] Reduction of 3 with $LiBH_4$, followed by mesylation of the resulting alcohol, malonate alkylation, and decarboxylation gave 4. Hydroboration of 4 using 9-borabicyclononane (9-BBN) followed by coupling of the resulting borane[10] in the same reaction flask with 3-bromopyridine in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst gave 5. Debenzylation of 5 and conversion of the resulting alcohol to the *tert*-butoxycarbonyl (BOC)-protected 4-chlorobenzenesulfonamide in one step by treatment with *N*-(*tert*-butoxycarbonyl)-4-chlorobenzenesulfonamide[11] under Mitsunobu reaction conditions gave 6. Treatment of 6 with trifluoroacetic anhydride (TFA) followed by saponification gave the *R*-enantiomer 1*R*. It was presumed that there was very little, if any, epimerization in any of the reactions following the enantioselective introduction of the alkyl group. The *S*-enantiomer 1*S*, was prepared analogously starting from (*R*)-(+)-4-benzyloxazolidinone. The optical rotation, $[\alpha]^{25}_D$, of 1*R* and 1*S* was <0.5°. This is not surprising in view of the fact that the α- and β-atoms of the three side chains around the asymmetric center are identical.

The pyridinyloxy compound 2*S* was prepared from 4 as shown in Scheme II. Oxidation of the double bond of 4 using $NaIO_4$ followed by $NaBH_4$ reduction gave the primary alcohol 7. Esterification of 7 with 3-hydroxypyridine under Mitsunobu reaction conditions gave the pyridinyl ether 8. Compound 8 was converted to 2*S* using the same sequence of reactions as shown for the conversion of 5 to 1*R* in Scheme I. The *R*-enantiomer 2*R* was prepared analogously starting from the enantiomer of 4 which in turn was prepared from (*R*)-(+)-4-benzyloxazolidinone for the synthesis of 1*S*. The optical rotation, $[\alpha]^{25}_D$, of 2*S* and 2*R* was +2.3° and −2.9°, respectively, in MeOH.

Results and Discussion

The enantiomerically pure compounds 1*R*, 1*S*, 2*S*, and 2*R* were tested and compared with 1 and 2 for their ability to inhibit thromboxane synthase and antagonize the platelet and vascular receptors for TxA_2 according to the methods described previously.[7] The IC_{50} values for thromboxane synthase inhibition in a microsomal platelet preparation and inhibition of the TxA_2/PGH_2 mimetic (U 46619)-induced aggregation of washed human platelets and platelet-rich plasma are listed in Table I.

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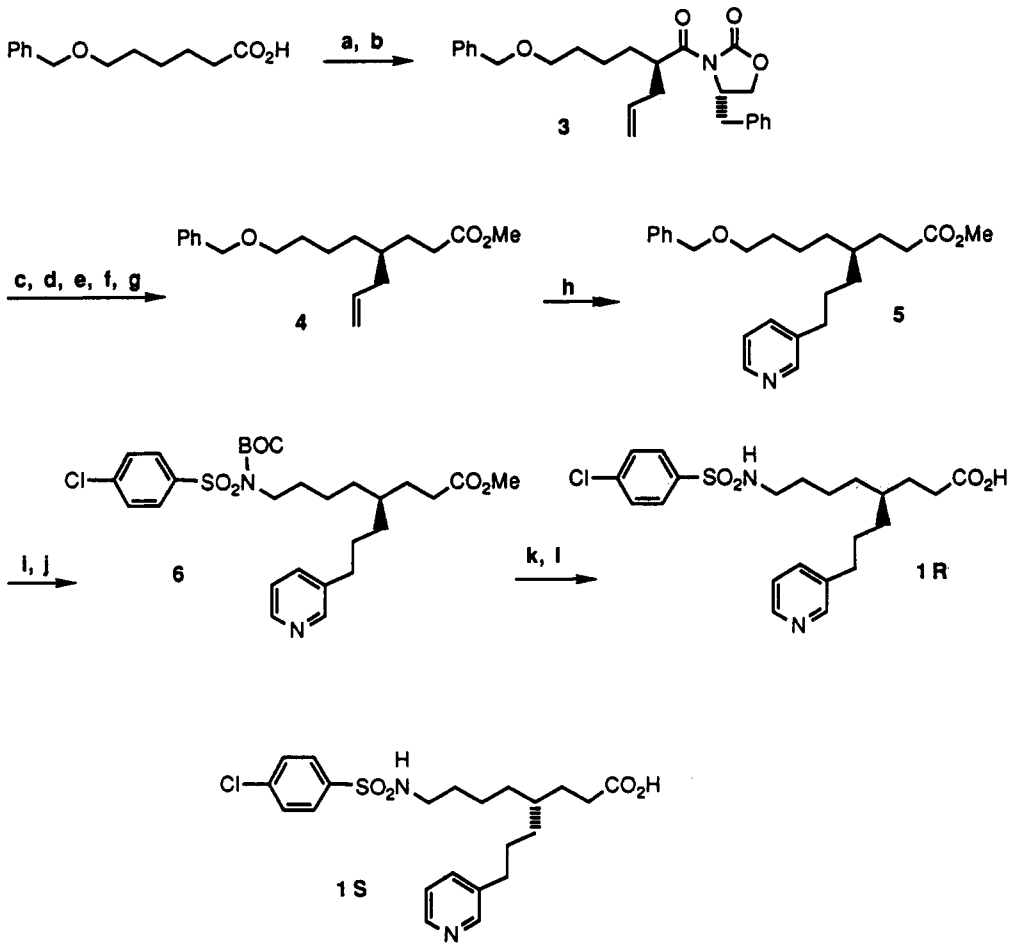
Scheme I [a]



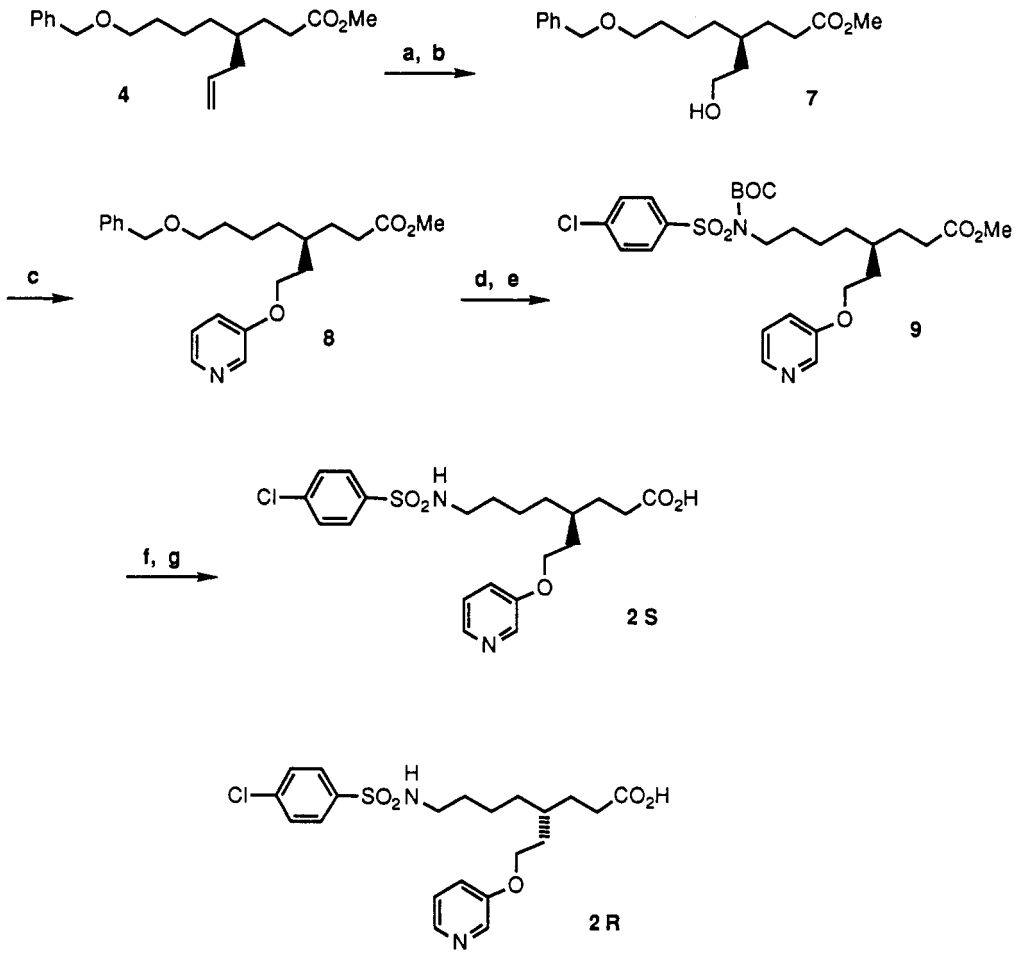
[a] (a) t-C_4H_9COCl, Et_3N; lithium anion of 4(S)-benzyloxazolidinone, THF, −78 °C; (b) LDA, −78 °C; allyl bromide, −10 °C; (c) $LiBH_4$, Et_2O; (d) CH_3SO_2Cl, Et_3N; (e) $CH_2(CO_2Et)_2$, NaH; (f) KOH, decarboxylation; (g) CH_2N_2; (h) 9-BBN, $(Ph_3P)_4Pd$ (cat.), K_3PO_4, 3-bromopyridine; (i) palladium hydroxide, cyclohexene; (j) 4-$ClC_6H_4SO_2NHBOC$, Ph_3P, DEAD; (k) CF_3CO_2H, CH_2Cl_2; (l) NaOH.

The TxSI activity of 1***R*** and 1***S*** were similar to that of their racemate 1. Although 2***R*** was slightly less active than 2 and 2***S*** as a TxSI, one is tempted to state that the two enantiomers of 2 were nearly equipotent as TxSIs in vitro. The U 46619-induced aggregation of human washed platelet was potently inhibited by the enantiomers of 1 and 2. The six compounds in Table I have the IC_{50} values in this assay between 9–26 nM. One may conclude that the difference in the TxRA and TxSI activities of the racemic compounds 1 and 2 and their enantiomers is not very significant. It is probable that both the enzyme and the receptor accommodate the enantiomers of 1 and 2 equally well. The flexible nature of the three side chains around the only chiral center of 1 and 2 could help understand this enantio-nonselectivity. In fact, if one examines the X-ray structure of the methyl ester of 1,[12] one gets some support for this postulate. From the model of the X-ray structure of the methyl ester of 1, two enantiomeric models were generated (excluding H atoms for simplicity). When these two models were overlapped on top of each other it was found that the overlap volume (volume occupied by the two models together) was very close to the volume of each model (see Figure 1). It is clear from Figure 1 that the three-dimensional shape and volume of the two enantiomers in the solid state are very similar and their polar and nonpolar groups are close to each other in the three-dimensional space. Since the three-dimensional shape and volume of molecules with their polar and nonpolar groups are important for their interaction with a receptor or enzyme, one may conclude that the receptor and the enzyme which normally distinguish the two enantiomers of a ligand may not do so in the case of 1 and 2. This could help explain the equipotent TxSI and TxRA activity of the enantiomers of 1 and 2. In fact, this could explain why the conventional resolution methods were not successful for 1 or its synthetic intermediates.

The TxRA activity of the enantiomers, as measured by their ability to inhibit the U 46619-induced aggregation of human platelet-rich plasma was also similar to that of the respective racemates. The IC_{50} values for the six compounds in this assay were in the range 0.28–0.55 μM. The weaker activity in platelet-rich plasma as compared to that in washed platelets is probably a reflection of the extent of plasma protein binding of these compounds. It appears that the extent of plasma protein binding of these compounds is similar. The enantiomers of 1 were also tested for their ability to antagonize the vascular receptor for TxA_2 which is proposed to be different from the platelet receptor.[13] Compounds 1, 1***R***, and 1***S*** were nearly equipotent (with pA_2 values of 8.9, 9.15, and 9.21, respectively) in inhibiting the U 46619-induced contraction of dog saphenous vein (data not shown).

The enantiomers were further compared for their bioavailability and duration of action by testing them in guinea pigs. The method, described previously,[7] involved oral administration of equal doses of the enantiomers to guinea pigs and assessment of the extent of inhibition of the U 46619-induced aggregation of the platelet samples

Scheme II [a]



[a] (a) OsO_4, $NaIO_4$; (b) $NaBH_4$; (c) 3-hydroxypyridine, Ph_3P, DIAD; (d) palladium hydroxide, cyclohexene; (e) 4-$ClC_6H_4SO_2NHBOC$, Ph_3P, DEAD; (f) CF_3CO_2H; (g) NaOH.

Table I. In Vitro TxRA/TxSI Activity[a]

compound	formula[b]	mp, °C	thromboxane synthase inhibition IC_{50},[c] nM	inhibition of U 46619-induced aggregation of human washed platelets IC_{50},[d] nM	inhibition of U 46619-induced aggregation of human platelet-rich plasma IC_{50},[d] mM
1*R*	$C_{22}H_{29}ClN_2O_4S$	113–114	5	11	0.38
1	$C_{22}H_{29}ClN_2O_4S$	114–115	2	19[e]	0.39[f]
1*S*	$C_{22}H_{29}ClN_2O_4S$	115–116	4.5	26	0.55
2*S*	$C_{21}H_{27}ClN_2O_5S$	89–90	3.5	10	0.32
2	$C_{21}H_{27}ClN_2O_5S$	87–87	2.6	13[g]	0.28[h]
2*R*	$C_{21}H_{27}ClN_2O_5S$	86–87	13	9	0.53

[a] See ref 7 for description of methods. [b] C, H, and N analyses were within ±0.4% of calculated values. All the compounds had ^1H NMR, IR, and mass spectra consistent with their structure. [c] Values represent average of two determinations. [d] Values represent single determination, except where indicated. [e] Ten determinations, SEM = ±3. [f] Seven determinations, SEM = ±0.02. [g] Three determinations, SEM = ±1. [h] Four determinations, SEM = ±0.1.

from the animals taken at 1-h postdosing. The values were expressed as concentration ratio which indicates the increase in concentration of U 46619 that is needed to cause platelet aggregation to the same extent as in control animals (see Table II). The concentration ratios for 1, **1*R***, and **1*S*** were in the range 27–54, indicating desirable activity in this assay. The enantiomers **1*R*** and **1*S***, which were nearly equipotent in vitro, displayed similar ex vivo activity in guinea pigs. These two compounds seem to possess similar bioavailability in this species. At an oral dose of 3 mg/kg, **2**, **2*S***, and **2*R*** displayed extremely potent ex vivo activity with the concentration ratio in the range 65–100. Again, the difference in the activity of the two enantiomers **2*S*** and **2*R*** in this assay is not very large indicating that they may have similar bioavailability in guinea pigs. Clearly **2**, **2*S***, and **2*R***, which were equipotent in vitro to 1, **1*R***, and **1*S***, were relatively more active in the exo vivo assay. This difference is likely to be due to relatively better bioavailability of this class of compounds in the guinea pig.

Conclusion

The enantiomers of 1 and **2** were synthesized using a highly enantioselective method. The in vitro profile of **1*R*** and **1*S*** were similar to that of 1 and of **2*S*** and **2*R*** to that of **2**. This lack of enantioselectivity implies that the enantiomers in this case are too flexible to be differentiated by the TxA_2 receptors and TxA_2 synthase. Examination of the X-ray structure of the methyl ester of 1 indicated that, in the solid state, the three-dimensional shape and volume of the two enantiomers are very similar and their polar and nonpolar groups are close to each other. The

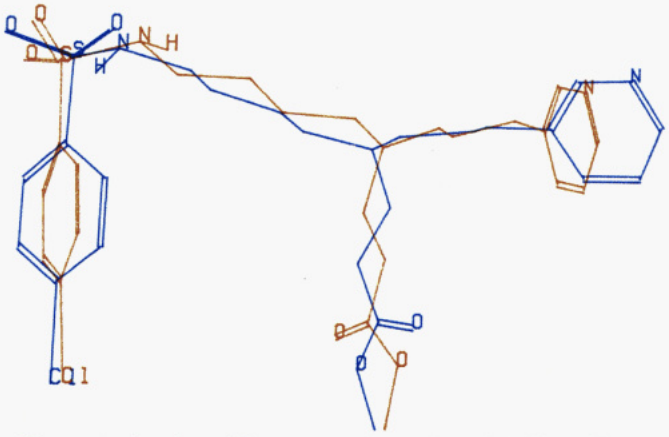


Figure 1. Overlap of the two enantiomeric models derived from the X-ray structure of the methyl ester of 1.

Table II. Ex Vivo Inhibition of U 46619-Induced Aggregation of Guinea Pig Platelets[a]

compound	dose, mg/kg, po	n	time,[b] h	concentration ratio[c] ± SEM
vehicle	–	22		1.0
1	10	5	1	27 ± 5
1*R*	10	6	1	43 ± 14
1*S*	10	4	1	54 ± 19
2	3	4	1	>100
2*S*	3	6	1	90 ± 10
2*R*	3	6	1	66 ± 16

[a] See ref 7 for methodology. [b] Time at which blood samples were taken out to measure platelet aggregability. [c] Concentration ratio = EC_{50} for drug/EC_{50} for control.

enantiomers of **1** and **2** were also found to be similar in their bioavailability in an ex vivo model in guinea pigs. These observations suggest that the racemic compounds **1** and **2** could produce a pharmacologic effect similar to that of their respective enantiomers in further studies.

Experimental Section

Infrared (IR) spectra were recorded on a Nicolet 5SXFT spectrometer. Proton NMR spectra were recorded on a Varian XL-300 or Varian XL-400 spectrometer. Chemical shifts are reported in ppm (δ) using tetramethylsilane, $CDCl_3$, or CD_3OD as internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Methylene chloride (CH_2Cl_2) was dried over 4-Å molecular sieves for 72 h before use. Organic solutions during workup were dried using anhydrous $MgSO_4$ or Na_2SO_4. Flash chromatography was performed using silica gel 60 (0.04–0.06 mm) (Merck).

(2′*R*,4*S*)-4-Benzyl-3-[2′-allyl-6′-(benzyloxy)hexanoyl]oxazolidin-2-one (3). To a solution of 6-(benzyloxy)hexanoic acid (7.9 g, 35.1 mmol) in Et_2O (53 mL) at 0 °C was added Et_3N (5.2 mL, 37 mmol) followed by pivaloyl chloride (4.4 mL, 35.7 mmol), and the resulting suspension was allowed to stir for 2 h at 0 °C. The reaction mixture was cooled to −78 °C, and the lithium anion prepared separately from (4*S*)-4-benzyloxazolidin-2-one (7.2 g, 41 mmol) in THF (53 mL) using *n*BuLi (15 mL, 2.5 M solution in hexane, 37.5 mmol) was added. The reaction mixture was allowed to warm up to room temperature over a period of 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extract was dried, filtered, and evaporated under vacuo to give 16.3 g of an oil which was purified by flash chromatography on silica gel using 1:4 EtOAc–hexane to yield 9.2 g (67%) of 4(*S*)-benzyl-3-[6-(benzyloxy)hexanoyl]oxazolidin-2-one as a colorless liquid: $[\alpha]^{25}_D$ = +70.45° (10.1 mg/mL in MeOH).

To a solution of lithium diisopropylamide prepared from diisopropylamine (4.0 mL, 29 mmol), THF (43 mL), and *n*BuLi (9.6 mL, 2.5 M solution in hexane, 24 mmol) at −78 °C was added a solution of 4(*S*)-benzyl-3-[6-(benzyloxy)hexanoyl]oxazolidin-2-one (9.2 g, 24 mmol) in THF (20 mL), and the resulting solution was allowed to stir for 30 min at −78 °C. An excess of allyl bromide (9.8 mL, 0.12 mol) was added and the reaction mixture was allowed to stir at −10 °C for 2 h. The reaction was quenched using saturated aqueous NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 50 mL), and the combined organic extract was dried, filtered, and evaporated in vacuo to give 10.3 g of an oil. Purification by flash chromatography using 15:85 EtOAc–hexane as eluent gave 8.2 g (80%) of **3** as a colorless oil: diasterioselectivity was determined using a RTX-5 column with helium as carrier gas (10 cc/min, flame ionization, 200–290 °C, 15 °C/min); $[\alpha]^{25}_D$ = +85.39° (10.1 mg/mL in MeOH); IR (CH_2Cl_2) 2938, 1779, 1698, 1387, 1209, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.4 (m, 10 H), 5.83 (m, 1 H), 5.0–5.13 (m, 2 H), 4.65 (m, 1 H), 4.49 (s, 2 H), 4.11 (d, J = 6 Hz, 2 H), 3.9 (m, 1 H), 3.45 (t, J = 7 Hz, 2 H), 3.3 (dd, J = 12.5, 4 Hz, 1 H), 2.65 (dd, J = 12.5, 10 Hz, 1 H), 2.46 (m, 1 H), 2.33 (m, 1 H), 1.3–1.85 (m, 6 H).

(4*S*)-Methyl 4-Allyl-8-(benzyloxy)octanoate (4). To a solution of **3** (8.4 g, 20 mmol) in Et_2O (420 mL) at 0 °C was added H_2O (0.4 mL, 22 mmol) followed by $LiBH_4$ (11.1 mL, 2 M solution in THF, 22.2 mmol). The cold bath was removed and the reaction mixture was allowed to stir 30 min. The reaction was quenched by adding 1 N NaOH and the layers were separated. The aqueous layer was saturated with NaCl and then extracted with ether (3 × 100 mL). The combined organic layer was dried, filtered, evaporated in vacuo, and purified by flash chromatography using 1:4 EtOAc–hexane as eluent to give 4.1 g (83%) of 2(*R*)-allyl-6-(benzyloxy)hexan-1-ol as a colorless oil: $[\alpha]^{25}_D$ = −3.06° (10.1 mg/mL in MeOH); IR (CH_2Cl_2) 3622, 2935, 2863, 1639, 1454, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.81 (m, 1 H), 5.05 (m, 2 H), 4.5 (s, 2 H), 3.54 (d, J = 7 Hz, 2 H), 3.47 (t, J = 7 Hz, 2 H), 2.22 (t, J = 7 Hz, 2 H), 1.25–1.7 (m, 8 H).

To a solution of 2(*R*)-allyl-6-(benzyloxy)hexan-1-ol (5.0 g, 20 mmol) in CH_2Cl_2 (85 mL) at 0 °C was added Et_3N (4.6 mL, 33 mmol) followed by methanesulfonyl chloride (2.0 mL, 26 mmol). The reaction was allowed to stir at 0 °C for 2 h and then washed with saturated aqueous $NaHCO_3$. The organic phase was dried, filtered, and evaporated in vacuo to give 6.8 g (100%) of the mesylate which was used as is for further elaboration: ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.72 (m, 1 H), 5.05 (m, 2 H), 4.5 (s, 2 H), 4.1 (d, J = 7 Hz, 2 H), 3.47 (t, J = 7 Hz, 2 H), 2.98 (s, 3 H), 2.13 (t, J = 7 Hz, 2 H), 1.8 (m, 1 H), 1.3–1.65 (m, 6 H).

To a suspension of NaH (3.3 g, 60% dispersion in oil, 82.5 mmol) in THF (40 mL) was added slowly diethyl malonate (12.6 mL, 83 mmol) at room temperature. The reaction mixture was allowed to stir for 30 min at room temperature, and a solution of the mesylate prepared above (6.8 g, 24 mmol) in THF (5 mL) was added and then refluxed for 18 h. The reaction mixture was cooled down to room temperature and poured into saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 (1 × 300, 2 × 50 mL). The combined organic extract was dried, filtered, evaporated in vacuo, and then purified by flash chromatography using 1:9 EtOAc–hexane to give 12.7 g of a 1:2 mixture of (4*S*)-ethyl-4-allyl-8-(benzyloxy)-2-carbethoxyoctanoate and diethyl malonate. This mixture was used as is for the next step: ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.7 (m, 1 H), 5.0 (m, 2 H), 4.49 (s, 2 H), 4.2 (m, OEt of compound + malonate), 3.44 (m, 3 H), 3.35 (s, CH_2 of malonate), 2.06 (t, J = 7 Hz, 2 H), 1.84 (t, J = 7 Hz, 2 H), 1.58 (m, 1 H), 1.2–1.45 (m, 6 H of compound + OEt of malonate).

To the impure malonate prepared above (12.7 g) in an ice bath was added a solution of KOH (10.4 g, 87% pure, 0.16 mol) in H_2O (56 mL). Dioxane (400 mL) was added to the resulting milky-white suspension to make it a clear solution. The reaction mixture was allowed to stir at room temperature for 18 h and then evaporated to remove most of the volatiles. The residue was taken up in H_2O (100 mL) and made acidic (pH = 4.0) using concentrated HCl with ice cooling. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extract was dried, filtered, and evaporated to give 5.9 g of a residue which was heated at 125 °C in an oil bath for 1 h. The temperature was increased to 140 °C and maintained at that temperature for 2 h. The residue was taken up in Et_2O (200 mL) and treated with excess diazomethane at 0 °C for 10 min. Excess diazomethane

was destroyed using HOAc. The mixture was washed with saturated $NaHCO_3$ solution and then dried, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using 1:9 EtOAc–hexane as eluent to give 4.7 g (77% from the primary alcohol) of 4 as a colorless oil: $[\alpha]^{25}_D = -1.94$ (7.75 mg/mL in MeOH); IR (CH_2Cl_2) 2937, 2863, 1732, 1458, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 5.74 (m, 1 H), 5.0 (m, 2 H), 4.5 (s, 2 H), 3.67 (s, 3 H), 3.46 (t, J = 7 Hz, 2 H), 2.29 (t, J = 7 Hz, 2 H), 2.02 (t, J = 7 Hz, 2 H), 1.2–1.65 (m, 9 H).

(4*R*)-Methyl 8-(Benzyloxy)-4-[3-(3-pyridinyl)propyl]octanoate (5). A solution of 9-BBN (23.6 mL, 0.5 M, 11.8 mmol) in THF was added to 4 (2.4 g, 7.9 mmol), and the mixture was allowed to stir at room temperature for 18 h. In a separate flask tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.11 mmol) was dissolved in THF (24 mL), and K_3PO_4 (5.4 g, 23.3 mmol) was added followed by the borane solution prepared above and 3-bromopyridine (1.2 mL, 12.5 mmol). The reaction mixture was refluxed for 47 h and then cooled down to 0 °C. A 15% solution of NaOH (8.9 mL) was added followed by 30% H_2O_2 (8.9 mL). The mixture was allowed to stir at room temperature for 1.5 h and then diluted with Et_2O (100 mL). The organic layer was washed with saturated Na_2SO_3 (30 mL) and brine (3 × 30 mL). The organic phase was dried, filtered, and evaporated to give 4.0 g of a dark oil. Purification by flash chromatography using 3:2 Et_2O–hexane as eluent gave 1.8 g (58%) of 5 as a light yellow oil: $[\alpha]^{25}_D$ = negligible (10.5 mg/mL in MeOH); IR (CH_2Cl_2) 2987, 2937, 2862, 1733, 1420, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (m, 2 H), 7.49 (m, 1 H), 7.15–7.35 (m, 6 H), 4.5 (s, 2 H), 3.66 (s, 3 H), 3.45 (t, J = 7 Hz, 2 H), 2.57 (t, J = 7 Hz, 2 H), 2.25 (t, J = 7 Hz, 2 H), 1.2–1.7 (m, 13).

(4*R*)-Methyl 8-[*N*-[(4-Chlorophenyl)sulfonyl]-*N*-(*tert*-butoxycarbonyl)amino]-4-[3-(3-pyridinyl)propyl]octanoate (6). To a solution of 5 (1.7 g, 4.2 mmol) in EtOH (30 mL) was added 20% palladium hydroxide on carbon followed by cyclohexane (15.6 mL). The reaction mixture was heated at reflux for 25 h. The catalyst was filtered off and washed with EtOH. The combined filtrate was evaporated in vacuo and then purified by flash chromatography using 9:1 EtOAc–hexane as eluent to give 1.1 g (92%) of (4*R*)-methyl-8-hydroxy-4-[3-(3-pyridinyl)-propyl]octanoate as a light yellow oil: IR (CH_2Cl_2) 3617, 2937, 2862, 1732, 1437, 1197, 1175, 1028 cm^{-1}.

To a solution of the alcohol prepared above (1.1 g, 3.9 mmol) in CH_2Cl_2 (18 mL) was added *N*-(*tert*-butoxycarbonyl)-4-chlorobenzenesulfonamide (1.6 g, 5.4 mmol) and triphenylphosphine (2.0 g, 7.6 mmol) followed 10 min later by diethyl azodicarboxylate (0.85 mL, 5.4 mmol). After 1 h, the reaction mixture was evaporated in vacuo and the residue purified by flash chromatography using 7:3 EtOAc–hexane as eluent to give 3.2 g (100%) of 6 contaminated with triphenylphosphine oxide: IR (CH_2Cl_2) 2938, 2863, 1731, 1479, 1356, 1154, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.42 (m, 2 H), 7.83 (d, J = 8 Hz, 2 H), 7.49 (m, 3 H), 7.22 (dd, J = 8, 4.5 Hz, 1 H), 3.79 (t, J = 7 Hz, 2 H), 3.67 (s, 3 H), 2.59 (t, J = 7 Hz, 2 H), 2.27 (t, J = 7 Hz, 2 H), 1.2–1.8 (m, 22 H).

(4*R*)-8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[3-(3-pyridinyl)propyl]octanoic Acid (1*R*). A solution of impure 6 (3.2 g, 3.9 mmol) in trifluoroacetic acid (30 mL) was allowed to stir at room temperature for 20 h. The solvent was evaporated in vacuo and the residue poured into saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extract was dried, filtered, and evaporated to give 3.0 g of a white solid. Purification of this solid by flash chromatography using 7:3 EtOAc–hexane as eluent gave 1.5 g (76% from 5) of (4*R*)-methyl-8-[[(4-chlorophenyl)sulfonyl]amino]-4-[3-(3-pyridinyl)propyl]octanoate as a white solid: mp 85–87 °C; $[\alpha]^{25}_D$ = negligible (11.5 mg/mL in MeOH); IR (CH_2Cl_2) 3376, 2938, 1732, 1478, 1337, 1155, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.42 (m, 2 H), 7.8 (d, J = 8 Hz, 2 H), 7.5 (m, 3 H), 7.22 (dd, J = 8, 4.5 Hz), 4.65 (t, J = 6 Hz, 1 H), 2.92 (q, J = 7 Hz, 2 H), 2.48 (t, J = 7 Hz, 2 H), 2.22 (t, J = 7 Hz, 2 H), 1.23–1.7 (m, 13 H).

The ester prepared above (1.5 g, 3.2 mmol) was dissolved in dioxane (15 mL) and 1 N NaOH (6.6 mL, 6.6 mmol) was added. The reaction mixture was allowed to stir for 20 h and the solvent was evaporated in vacuo. The residue was dissolved in H_2O and adjusted to pH = 5.0 with 2 N HCl. The precipitated product was filtered and washed with H_2O (4 × 5 mL) and Et_2O (4 × 5 mL). Upon drying, the filter cake gave 1.4 g (93%) of 1*R* as a white solid: mp 113–114 °C; $[\alpha]^{25}_D$ = not significant (11.5 mg/mL in MeOH); IR (KBr) 3275, 2942, 2864, 1707, 1476, 1424, 1333, 1162, 1091 cm^{-1}; ^1H NMR (CD_3OD) δ 8.37 (d, J = 1 Hz, 1 H), 8.33 (dd, J = 4.5, 1 Hz, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.7 (br d, J = 8 Hz, 1 H), 7.56 (d, J = 7 Hz, 2 H), 7.35 (dd, J = 8, 4.5 Hz, 1 H), 2.83 (t, J = 7 Hz, 2 H), 2.62 (t, J = 7 Hz, 2 H), 2.2 (t, 7 Hz, 2 H), 1.15–1.7 (m, 13 H). Anal. ($C_{22}H_{29}ClN_2O_4S$) C, H, N. Compound 1*S*: the *S*-enantiomer had mp 115–116 °C and $[\alpha]^{25}_D$ = negligible (10.5 mg/mL in MeOH); IR and ^1H NMR were identical to that of 1*R*.

(4*S*)-Methyl 8-(Benzyloxy)-4-(2-hydroxyethyl)octanoate (7). To a solution of 4 (2.4 g, 7.8 mmol) in THF (70 mL) was added H_2O (24 mL) followed by a solution of OsO_4 (9.4 mL, 10 mg/mL in toluene, 0.37 mmol). $NaIO_4$ (3.6 g, 16.7 mmol) was added in small portions over a period of 0.5 h. After 1 h the reaction mixture was poured into H_2O and extracted with ether (3 × 30 mL). The combined organic extract was dried, filtered, and evaporated to give 2.4 g (100%) of the corresponding aldehyde as an oil which was used as is for further elaboration: IR (CH_2Cl_2) 2939, 2863, 2727, 1725, 1437, 1100 cm^{-1}.

To a solution of the crude aldehyde (2.4 g, 7.8 mmol) prepared above in EtOH (22 mL) was added $NaBH_4$ (0.3 g, 8.1 mmol). After 0.25 h the reaction mixture was poured into water and the pH was adjusted to 8.0 by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extract was dried, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using 1:1 EtOAc–hexane as eluent which gave 1.6 g (67% from 4) of 7 as a light yellow oil: $[\alpha]^{25}_D = -1.22°$ (10.2 mg/mL in MeOH); IR (CH_2Cl_2) 3619, 2937, 2864, 1732, 1454, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8 (m, 5 H), 4.48 (s, 2 H), 3.63 (overlapping s and m, 4 H), 3.44 (t, J = 7 Hz, 1 H), 2.3 (t, J = 7 Hz, 2 H), 1.2–1.7 (m, 11 H).

(4*S*)-Methyl 8-(Benzyloxy)-4-[2-(3-pyridinyloxy)ethyl]octanoate (8). To a solution of 7 (1.6 g, 5.2 mmol) in CH_2Cl_2 (20 mL) was added 3-hydroxypyridine (0.5 g, 5.4 mmol) followed by triphenylphosphine (1.8 g, 7 mmol). The reaction mixture was allowed to stir for 10 min and diisopropyl azodicarboxylate (1.0 mL, 5.3 mmol) was added slowly. After 2 h at room temperature, the reaction mixture was evaporated in vacuo and the residue purified by flash chromatography using 1:1 EtOAc–hexane as eluent to give 1.1 g (53%) of 8 as a light yellow oil: $[\alpha]^{25}_D = +0.51°$ (10.4 mg/mL in MeOH); IR (CH_2Cl_2) 2939, 2864, 1733, 1576, 1473, 1280, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) 8.29 (br s, 1 H), 8.19 (m, 1 H), 7.12–7.35 (m, 7 H), 4.48 (s, 2 H), 4.0 (t, J = 7 Hz, 2 H), 3.63 (s, 3 H), 3.44 (t, J = 7 Hz, 2 H), 2.31 (t, J = 7 Hz, 2 H), 1.3–1.8 (m, 11 H).

Compound 8 was debenzylated, converted to the sulfonamide, and deprotected to give 2*S* using the procedure described above for the conversion of 5 to 1*R*.

(4*S*)-8-[[(4-Chlorophenyl)sulfonyl]amino]-4-[2-(3-pyridinyloxy)ethyl]octanoic acid (2*S*): mp 89–90 °C; $[\alpha]^{25}_D$ = +2.32° (10.1 mg/mL in MeOH); IR (KBr) 3276, 2943, 2865, 2200–3300 (br), 1712, 1577, 1425, 1332, 1275, 1162, 1093 cm^{-1}; ^1H NMR (CD_3OD) δ 8.2 (d, J = 1.5 Hz, 1 H), 8.1 (br d, J = 4.5 Hz, 1 H), 7.7 (d, J = 8 Hz, 2 H), 7.56 (d, J = 8 Hz, 2 H), 7.38 (m, 2 H), 4.09 (t, J = 7 Hz, 2 H), 2.87 (t, J = 7 Hz, 2 H), 2.3 (t, J = 7 Hz, 2 H), 1.3–1.8 (m, 11 H). Anal. ($C_{21}H_{27}ClN_2O_5S$) C, H, N.

Compound 2*R*, the *R*-enantiomer, had $[\alpha]^{25}_D = +2.92°$ (25.2 mg/mL in MeOH) and mp 86–87 °C; IR and ^1H NMR were identical to that of 2*S*.

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