The Practical Synthesis of a Uterine Relaxant, Bis(2-{[(2*S*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)-phenyl]ethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide) Sulfate (KUR-1246)

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The synthetic route for a uterine relaxant, bis(2-{[(2*S*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)-phenyl]ethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide) sulfate (KUR-1246), was established by the coupling of optically active components, the bromohydrin 14 and the amine 24. We now describe the practical synthesis of these two optically active components. Bromohydrin 14 was obtained by the asymmetric borane reduction of the prochiral phenacyl bromide 13 using a catalyst prepared from aluminum triethoxide and a chiral amino alcohol. The other optically active component 24 was prepared from (*S*)-AMT.

Key words KUR-1246; β2-adrenoceptor agonist; uterine relaxant; asymmetric borane reduction

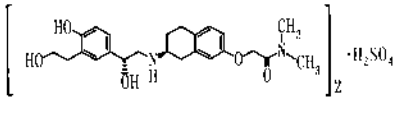
Preterm labor is the leading cause of neonatal morbidity and mortality in clinical practice. β-Adrenoceptor (AR) agonists such as ritodrine and terbutaline are the drugs of first choice for preventing this preterm labor. However, the usefulness of these drugs is limited by the occurrence of side effects such as maternal tachycardia and metabolic systems. To resolve this problem, we have developed a new selective β2-AR agonist, bis(2-{[(2*S*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide) sulfate (KUR-1246), as shown in Fig. 1. KUR-1246 at doses of 0.13 μg/kg/min intravenously suppressed 30% of the uterine contractions in late pregnant rats. The inhibitory potency with which KUR-1246 produced this effect was about 6 times that of terbutaline, and 400 times that of ritodrine. Moreover, it has been reported that KUR-1246 has an excellent selectivity for the myometrial β2-AR.[1] We now require a large amount of optically pure KUR-1246 for further evaluation of this compound as a uterine relaxant. In this paper, we describe the convenient and practical method for the synthesis of KUR-1246.

Our group reported the synthesis of KUR-1246, as shown in Chart 1.[2] The racemic mandelic acid derivative **2** was synthesized from the *O*-protected hydroxyethylphenol **1** through bromination, lithiation and reaction with diethyl oxalate under -95 °C, and hydrolysis with aqueous NaOH. The condensation of the acid **2** and (*S*)-2-amino-7-hydroxytetraline hydrobromide [(*S*)-AHT·HBr, **3**] gave a mixture of diastereomer, which was separated by column chromatography on silica gel to obtain the single isomer **4**. This synthetic method was unsuitable for large-scale synthesis, because of the ineffective diastereomer separation, the use of column chromatography, and the low reaction temperature.

We developed a synthetic strategy for KUR-1246, as shown in Chart 2, should be the condensation of the optically active halide **14** and the optically active amine **24** in order to avoid the above-mentioned difficulties. Furthermore, we planned the synthesis of the halide **14** by the asymmetric borane reduction of the phenacyl halide **13** that would be derived from 4′-hydroxyacetophenone (**7**). The amine **24** was prepared from (*S*)-2-amino-7-methoxytetraline [(*S*)-AMT].

The Synthesis of the Optically Pure (*R*)-Bromohydrin 14 The phenacyl bromide **13** was synthesized from the ketone **7** that was inexpensive and easily available in large quantity, as shown in Chart 3. The methyl ester **11** was obtained from **7** through chloromethylation,[3] cyanation with NaCN, hydrolysis with aqueous NaOH, and esterification with MeOH in the presence of H_2SO_4. The methyl ester **11** was reacted with benzyl chloride in the presence of KI and K_2CO_3 to give the ketone **12** in 78% yield. The bromination of **12** with Br_2 gave **13** in 72% yield.

Recently, we reported the efficient catalysts prepared from aluminum triethoxide [$Al(OEt)_3$] and chiral amino alcohols for asymmetric borane reduction.[4] We investigated our asymmetric reduction methodology to obtain this optically active bromohydrin **14** from **13** (Chart 4). These results are summarized in Table 1. The reaction of **13** with the borane dimethyl sulfide complex ($BH_3 \cdot Me_2S$) (120 mol%), $Al(OEt)_3$ (12 mol%) and (*R*)-α,α-diphenyl-2-pyrrolidinemethanol (**15**) (10 mol%) reduced both the ketone and the ester groups to give the crude **14** with 98.0% ee. After the recrystallization of the crude product, **14** was obtained in the good yield of 86% with the excellent optical purity of 99.9% ee (entry 1). The absolute configuration of the bromohydrin **14** was determined to be the *R*-configuration by X-ray crystallographic analysis using the anomalous dispersion effect of the bromine atoms, as shown in Fig. 2. Furthermore, we examined the possibility of decreasing the quantity of **15**. Using 5 mol% of **15** and 6 mol% of $Al(OEt)_3$ under these conditions



KUR-1246

Fig. 1

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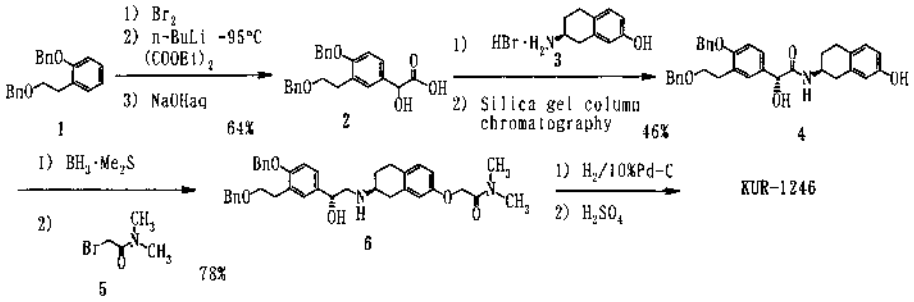

Chart 1

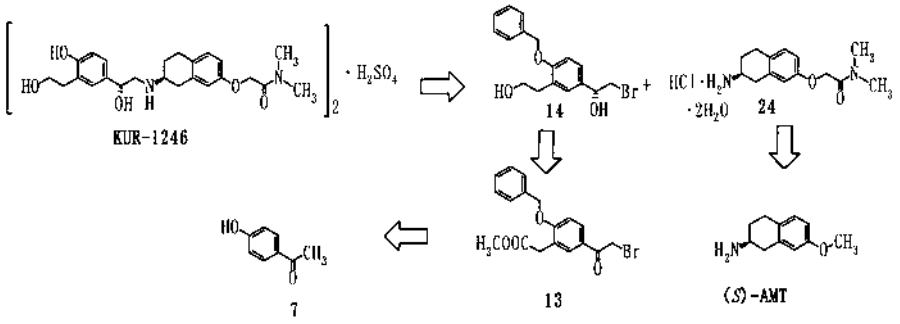

Chart 2

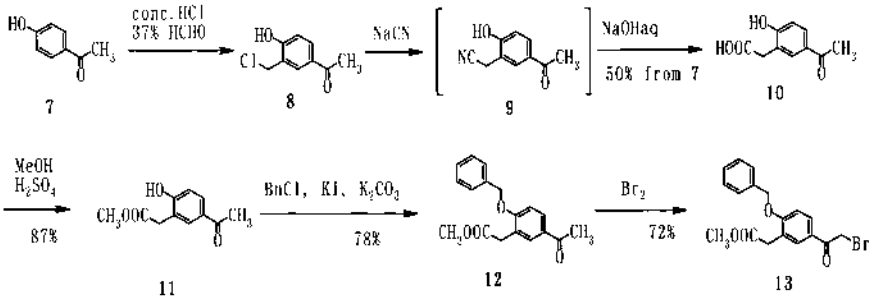

Chart 3

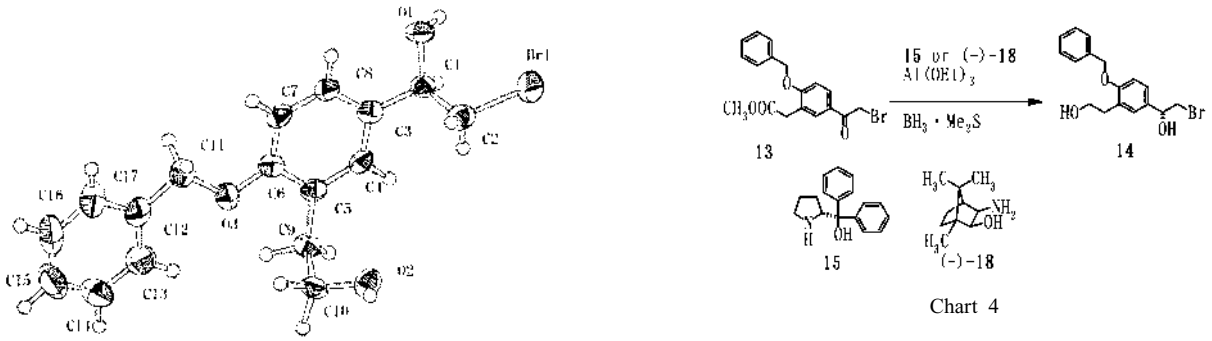

Chart 4

Fig. 2. ORTEP of **14**

led to a good result (90% yield, 99.5% ee, entry 2). However, the further reduction in the amount of **15** to 2 mol% gave **14** with the unsatisfactory optical purity of 95.4% ee in spite of recrystallization (entry 3). And furthermore, **15** had to be prepared from expensive D-proline.[5]

The asymmetric borane reduction of acetophenone using the amino alcohol (+)-**18** prepared from (−)-camphor gave (*R*)-1-phenylethanol with 88% ee.[6] The result was suggested that the reduction of **13** using of (−)-**18** prepared from inexpensive (+)-camphor produced **14**. (+)-Camphor was easily converted to (−)-**18**, which included *ca.* 11% of the *endo* form, and the intricate purification *via* the cyclic carbamate was reported.[7] We found that (−)-**18** was readily purified by recrystallization of its methanesulfonic acid salt (Chart 5). We then examined this asymmetric reduction using (−)-**18**. The optical purity of the crude product was 94.6% ee, and **14** was obtained in 85% yield with 98.3% ee after recrystallization (entry 4).

The Synthesis of the Optically Pure (*S*)-Amine 24 Some synthetic methods of the optically pure (*S*)-AMT have been reported[8] and we also published that (*S*)-AMT·HCl (**20**) was prepared from (*R*)-2-(3-methoxybenzyl)succinic acid.[9]

The amine **20** was demethylated in 48% hydrobromic acid under reflux to (*S*)-AHT·HBr (**3**) in 99% yield. The reaction of **3** with di-*tert*-butyl dicarbonate (Boc_2O) followed *O*-alkylation with 2-chloro-*N*,*N*-dimethylacetamide (**22**) gave the amide **23** in 76% yield. Compound **23** was treated with concentrated hydrochloric acid (conc. HCl) in iso-PrOH, and then the precipitate from the reaction solution was collected by filtration to give the amine **24** in 79% (Chart 6).

The Synthesis of KUR-1246 by Coupling of 14 and 24 These two optically active components, the bromohydrin **14** and the amine **24**, were coupled to produce KUR-1246, as shown in Chart 7. The bromide **25**, obtained from **14** with protection of the two hydroxyl groups using *tert*-butylchlorodimethylsilane (TBS-Cl), was reacted with **24** to give compound **26**. The TBS ethers of the crude **26** were cleaved by *p*-toluenesulfonic acid (TosOH) in aqueous tetrahydrofuran (THF), followed by crystallization with oxalic acid to produce the oxalate **27** in 69% yield from **14**. The benzyl group of the free amine of **27** underwent catalytic hydrogenolysis to give compound **28** in 89% yield. Finally, 0.5 M H_2SO_4 (50 mol%) was added to a solution of **28** in MeOH, and then the precipitate was collected by filtration to give KUR-1246 in 87% yield.

In conclusion, we established an efficient and practical route for the synthesis of the optically active uterine relaxant KUR-1246 by the coupling of the optically active bromohydrin **14** and the optically active amine **24** prepared from 4′-hydroxyacetophenone (**7**) and (*S*)-AMT·HCl (**20**), respectively. Furthermore, the optically active bromohydrin **14** was prepared by the asymmetric borane reduction of the phenacyl bromide **13** using $Al(OEt)_3$ and the chiral amino alcohol **15** or (−)-**18**.

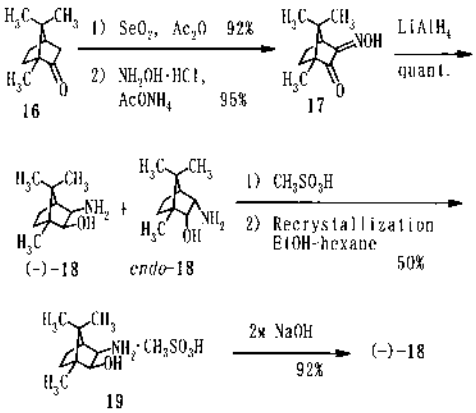

Chart 5

Table 1. Asymmetric Borane Reduction of **13**

Entry	Catalyst		**14**	
	Amino alcohol	mol%	Yield (%)	ee (%)[a] (Crude)
1	**15**	10	86	99.9 (98.0)
2	**15**	5	90	99.5 (94.5)
3	**15**	2	89	95.4 (92.9)
4	(−)-**18**	10	85	98.3 (94.6)

a) The optical purity was measured by HPLC analysis using a chiral column (Chiralpak AD).

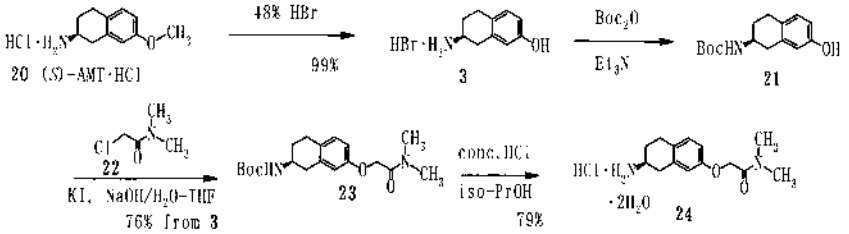

Chart 6

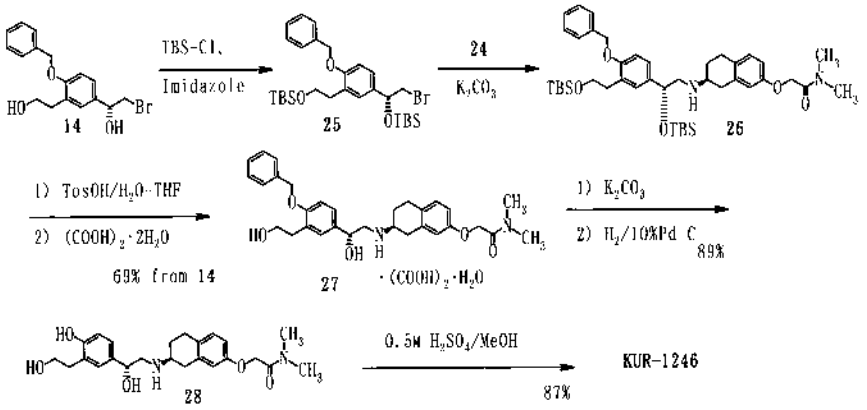

Chart 7

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-500 using tetramethylsilane or sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the internal standard. Mass spectra were measured using a JEOL JMS-SX102A mass spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter.

1-(3-Chloromethyl-4-hydroxyphenyl)ethanone (8) Formaldehyde (37% solution, 340 ml, 4.6 mol) was added to a suspension of 1-(4-hydroxyphenyl)ethanone (**7**) (136.0 g, 1.00 mol) in conc.HCl (1000 ml, 12.2 mol), and then the mixture was stirred for 4 h at 50 °C. The resulting red precipitate was collected by filtration and washed with water to give **8** (203.2 g, wet, 110%) as a red solid. The solid was used for the next reaction without further purification. An analytical sample was prepared by recrystallization from THF as a white solid. mp 172—175 °C. IR (KBr): 3154, 1656, 1586, 1289 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.50 (3H, s), 4.75 (2H, s), 6.97 (1H, d, J=8.4 Hz), 7.84 (1H, d, J=8.4 Hz), 7.99 (1H, s), 10.89 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 26.60, 41.93, 115.64, 124.22, 128.94, 131.31, 132.07, 160.54, 196.23. HR-MS (FAB) m/z: Calcd for $C_9H_{10}O_2Cl$ $(M+H)^+$: 185.0370. Found: 185.0380. *Anal.* Calcd for $C_9H_9O_2Cl$: C, 58.55; H, 4.91. Found: C, 58.54; H, 5.00.

(5-Acetyl-2-hydroxyphenyl)acetic Acid (10) A suspension of NaCN (98.0 g, 2.00 mol) in dimethylsulfoxide (0.5 l) was stirred for 30 min at 60 °C. Compound **8** (203.2 g, wet) in limited amounts was added to the mixture over 1 h and stirred for 1 h at the same temperature. A solution of NaOH (140.0 g, 3.50 mol) in water (0.5 l) was then added to the mixture and refluxed for 2 h. After cooling to room temperature, the mixture was diluted with water (2.5 l), washed with toluene (0.5 l), acidified with conc.HCl (0.4 l), and extracted with AcOEt (3×1 l). The organic layers were combined, washed with water (1.0 l), dried over $MgSO_4$, and concentrated under reduced pressure. Toluene (300 ml) was added dropwise to the suspension of the residue in AcOEt (100 ml) at 50 °C, and then cooled. The precipitate was collected by filtration to give **10** (97.6 g, 50% from **7**). An analytical sample was prepared by recrystallization from MeOH as a white solid. mp 204—206 °C. IR (KBr): 3345, 1712, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.47 (3H, s), 3.55 (2H, s), 6.89 (1H, d, J=8.4 Hz), 7.75 (1H, dd, J=2.0, 8.4 Hz), 7.78 (1H, d, J=2.0 Hz), 10.18—10.75 (1H, br), 11.81—12.49 (1H, br). ^{13}C-NMR (DMSO-d_6) δ: 26.57, 35.64, 114.80, 122.53, 128.73, 129.67, 132.29, 160.56, 172.78, 196.43. HR-MS (FAB) m/z: Calcd for $C_{10}H_{11}O_4$ $(M+H)^+$: 195.0657. Found: 195.0661. *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.72; H, 5.30.

Methyl (5-Acetyl-2-hydroxyphenyl)acetate (11) A mixture of **10** (97.6 g, 500 mmol) and H_2SO_4 (4.9 g, 48 mmol) in MeOH (200 ml) was refluxed for 1 h. A solution of K_2CO_3 (8.1 g, 96 mmol) in water (200 ml) was added to the mixture and cooled to room temperature. The precipitate was collected by filtration to give **11** (90.9 g, 87%). An analytical sample was prepared by recrystallization from MeOH as a white solid. mp 167—168 °C. IR (KBr): 3238, 1728, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.47 (3H, s), 3.60 (3H, s), 3.64 (2H, s), 6.90 (1H, d, J=8.4 Hz), 7.77 (1H, dd, J=2.2, 8.4 Hz), 7.80 (1H, d, J=2.2 Hz), 10.52 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 26.57, 35.33, 51.90, 114.86, 121.90, 128.80, 129.91, 132.29, 160.52, 171.75, 196.38. HR-MS (FAB) m/z: Calcd for $C_{11}H_{13}O_4$ $(M+H)^+$: 209.0814. Found: 209.0815. *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.22; H, 5.83.

Methyl (5-Acetyl-2-benzyloxyphenyl)acetate (12) A mixture of **11** (90.9 g, 440 mmol), benzylchloride (58.0 g, 460 mmol), KI (7.3 g, 44 mmol), and K_2CO_3 (63.4 g, 460 mmol) in *N*,*N*-dimethylformamide (DMF) (150 ml) was stirred for 1.5 h at 50 °C. Water (600 ml) was then added to the mixture and the precipitate was collected by filtration. The crude product was recrystallized from AcOEt–hexane to give **12** (101.4 g, 78%). mp 90 °C. IR (KBr): 1743, 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s), 3.63 (3H, s), 3.70 (2H, s), 5.14 (2H, s), 6.95 (1H, d, J=8.6 Hz), 7.30—7.40 (5H, m), 7.84 (1H, d, J=2.2 Hz), 7.88 (1H, dd, J=2.2, 8.6 Hz,). ^{13}C-NMR ($CDCl_3$) δ: 26.72, 36.50, 52.31, 70.64, 111.49, 124.04, 127.48, 128.51, 129.02, 130.39, 130.67, 132.01, 136.54, 160.93, 172.07, 197.07. HR-MS (FAB) m/z: Calcd for $C_{18}H_{19}O_4$ $(M+H)^+$: 299.1283. Found: 299.1293. *Anal.* Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.65; H, 6.13.

Methyl (2-Benzyloxy-5-bromoacetylphenyl)acetate (13) A solution of Br_2 (6.2 ml, 120 mmol) in hexane (15 ml) was added dropwise to a solution of **12** (32.8 g, 110 mmol) in AcOEt (160 ml) over 20 min. After 30 min, water was added to the mixture and the separated organic layer was washed with brine (50 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was recrystallized from AcOEt–hexane to give **13** (29.9 g, 72%) as a white solid. mp 95 °C. IR (KBr): 1731, 1689 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (3H, s), 3.71 (2H, s), 4.39 (2H, s), 5.17 (2H, s), 6.98 (1H, d, J=8.6 Hz), 7.30—7.42 (5H, m), 7.88 (1H, d, J=2.3 Hz), 7.92 (1H, dd, J=2.3, 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.14, 36.42, 52.37, 70.77, 111.76, 124.55, 127.29, 127.51, 128.62, 129.07, 131.18, 132.65, 136.31, 161.60, 171.88, 190.22. HR-MS (FAB) m/z: Calcd for $C_{18}H_{18}BrO_4$ $(M+H)^+$: 377.0388. Found: 377.0391. *Anal.* Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54. Found: C, 57.22; H, 4.52.

(1*R*,2*S*,3*R*,4*S*)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol Methansulfonate (19) A solution of (1*R*,4*S*)-3-hydroxyimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**17**)[6] (8.52 g, 47 mmol) in ether (120 ml) was added dropwise to a suspension of $LiAlH_4$ (5.32 g, 140 mmol) in ether (140 ml) over 45 min at room temperature, and then stirred overnight. 2 M NaOH (25 ml) was carefully added to the mixture and the mixture was dried over $MgSO_4$. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. A solution of methanesulfonic acid (4.50 g, 47 mmol) in ether (20 ml) was added to the solution of the obtained residue in ether (120 ml). The precipitate was collected by filtration to give the crude methansulfonic acid salt (10.4 g, 84%, (−)-**18**: *endo*-**18**=88.9 : 11.1). The crude salt (8.00 g) was recrystallized twice from EtOH–hexane to give the pure salt **19** (3.25 g, 41%, (−)-**18**: *endo*-**18**=99.6 : 0.4). mp 193—195 °C. IR (KBr): 3329, 2948, 1195, 1163, 1043 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.77 (3H, s), 0.85 (3H, s), 0.99—1.08 (5H, m), 1.38—1.43 (1H, m), 1.63—1.70 (1H, m), 1.82 (1H, d, J=4.6 Hz), 2.29 (3H, s), 3.09—3.14 (1H, m), 3.64 (1H, dd, J=5.7, 7.5 Hz), 6.04 (1H, d, J=5.9 Hz), 7.57 (3H, br s). ^{13}C-NMR (D_2O) δ: 10.70, 20.46, 20.92, 26.09, 32.37, 38.79, 46.74, 48.94, 49.25, 57.02, 77.69. $[\alpha]_D^{25}$ +1.4° (c=1.85, MeOH). *Anal.* Calcd for $C_{11}H_{23}NO_4S$: C, 49.79; H, 8.74; N, 5.28. Found: C, 49.57; H, 8.96; N, 5.62. The ratio of (−)-**18** to *endo*-**18** was measured by GC [column, CAM, 30 m×0.25 mm i.d.×0.25 μm, J&W Scientific; mobile phase, He 1.0 ml/min; sprit, 50/1; detection, FDI; column temperature, 160 °C; injection temperature, 220 °C; detection temperature, 230 °C].

(1*R*,2*S*,3*R*,4*S*)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol [(−)-18] 5 M NaOH (5 ml) was added to a solution of the pure salt **19** (3.24 g, 12 mmol) in water (5 ml), and extracted with ether (3×10 ml). The organic layers were combined, washed with brine (5 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give (−)-**18** (1.90, 92%) as a white solid. An analytical sample was prepared by sublimation at 100 °C/0.5 mmHg. mp 200—202 °C. IR (KBr): 2952, 1095, 1061 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, s), 0.95 (3H, s), 0.98—1.07 (5H, m), 1.40—1.45 (1H, m), 1.56 (1H, d, J=4.5 Hz), 1.67—1.74 (1H, m), 3.06 (1H, d, J=7.1 Hz), 2.10—1.80 (3H, br), 3.38 (1H, d, J=7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.80, 21.62, 22.35, 27.29, 33.54, 47.01, 49.11, 53.83, 57.76, 79.43. $[\alpha]_D^{25}$ −6.2° (c=1.0, MeOH). HR-MS (FAB) m/z: Calcd for $C_{10}H_{20}NO$ $(M+H)^+$: 170.1545. Found: 170.1542. *Anal.* Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.51; H, 11.14; N, 8.16.

(1*R*)-1-[4-Benzyloxy-3-(2-hydroxyethyl)phenyl]-2-bromoethan-1-ol (14) $Al(OEt)_3$ (59 mg, 0.36 mmol) was added to a solution of (*R*)-α,α-diphenyl-2-pyrolidinylmethanol (**15**) (76 mg, 0.30 mmol) in THF (3 ml), and the mixture was stirred at room temperature for 1 h under a N_2 atmosphere. After $BH_3\cdot Me_2S$ (10 M, 0.6 ml, 6 mmol) was added, a solution of **13** (1.132 g, 3 mmol) in THF (6 ml) was added dropwise *via* a syringe pump over 1 h at 25 °C. After 10 min, the mixture was stirred for 2 h at 50 °C, quenched with MeOH (1 ml), and concentrated under reduced pressure. AcOEt (10 ml) and 1 M HCl (3 ml) were added to the resulting residue, and then the separated aqueous layer was extracted with AcOEt (10 ml). The organic layers were combined, washed with water (5 ml) and brine (5 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was recrystallized from AcOEt–hexane to give **14** (0.910 g, 86%) as a white solid. The ee of **14** was determined to be 99.9% by HPLC using a chiral column [column, Chiralpak AD 4.6 mm i.d.×250 mm, Daicel Chemical Industries Co., Ltd.; mobile phase, hexane–iso-PrOH, 9 : 1; flow rate, 1.0 ml/min; detection, UV at 230 nm]. mp 86—87 °C. IR (KBr): 3249, 1568, 1448, 1253 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (1H, s), 2.89—2.95 (3H, m), 3.51 (1H, dd, J=8.9, 10.4 Hz), 3.57 (1H, dd, J=3.6, 10.4 Hz), 3.80—3.87 (2H, m), 4.79—4.84 (1H, m), 5.07 (2H, s), 6.90 (1H, d, J=8.1 Hz), 7.15—7.20 (2H, m), 7.29—7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.55, 40.53, 62.94, 70.55, 73.83, 112.19, 125.91, 127.65, 128.19, 128.44, 129.07, 129.16, 133.11, 137.22, 157.21. $[\alpha]_D^{29}$ −17.6° (c=1.0, MeOH). HR-MS (FAB) m/z: Calcd for $C_{17}H_{19}BrO_3$ M^+: 350.0518. Found: 350.0509. *Anal.* Calcd for $C_{17}H_{19}BrO_3$: C, 58.13; H, 5.45. Found: C, 57.97; H, 5.52.

Determination of the Absolute Configuration of 14 The absolute configuration of **14** was determined by a single crystal X-ray diffraction analysis. The recrystallization of **14** from AcOEt gave a colorless prism. Crystal

data were: $C_{17}H_{19}BrO_3$, monoclinic, $P2_1$ (No. 4), Z=2; a=4.985, b=11.139, c=14.445 Å; $\alpha=\gamma=90.000$, β=94.586°; V=799.55 Å^3; D_c=1.38 g·cm^{-3}; μ=17.98 cm^{-1}. Intensity data were collected at room temperature using graphite monochromated Mo-Kα radiation (λ=0.71069 Å) on a Rigaku RASA-7R diffractometer, 2θ(max)=55.0°. Of 4225 measured reflections, 2184 had $I>3\sigma$, and 1893, including Bijvoet pairs, were unique and used for the structure analysis. The structure was solved by the direct method (SIR-92) and refined through full-matrix least square method to R=0.042 and R_w=0.045 using the TEXSAN-TEXRAY Structure Analysis Package (Ver 1.9), Molecular Structure Corporation. Hydrogen atoms were incorporated at fixed position as with C–H=0.95 Å. The absolute configuration was confirmed by refining the inverted configuration which converged to a higher residual of $R/(R_w)$=0.0716/(0.0778) (heavy atoms only). The absolute configuration of **14** was confirmed to be *R* as shown in Fig. 2.

(7*S*)-7-Amino-5,6,7,8-tetrahydro-2-naphtol Hydrobromide (3) A mixture of **20** (10.0 g, 48 mmol) and NaOH (2.3 g, 58 mmol) in water (40 ml) was extracted with toluene (2×20 ml). The organic layers were combined, washed with water (10 ml), and concentrated under reduced pressure to give an oil. A mixture of the oil in 48% hydrobromic acid (27 ml) was refluxed for 4 h in a 140 °C oil bath. After concentration under reduced pressure, the resulting residue was recrystallized from iso-PrOH to give **3** (11.3 g, 99%) as a white solid. mp 154—156 °C. IR (KBr): 3372, 3027, 1504, 1267 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.65—1.75 (1H, m), 2.04—2.11 (1H, m), 2.67—2.78 (3H, m), 2.97 (1H, dd, J=4.7, 16.4 Hz), 3.38—3.45 (1H, m), 6.50 (1H, d, J=2.6 Hz), 6.57 (1H, dd, J=2.6, 8.4 Hz), 6.89 (1H, d, J=8.4 Hz), 8.01 (3H, br s), 9.13 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 26.30, 27.43, 33.43, 47.14, 114.25, 115.29, 125.22, 129.79, 133.87, 155.72. $[\alpha]_D^{28}$ −61.4° (c=1.0, MeOH). *Anal.* Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; N, 5.74. Found: C, 49.16; H, 6.17; N, 5.78.

(7*S*)-7-*tert*-Butoxycabonylamino-5,6,7,8-tetrahydro-2-naphthol (21) A solution of Boc_2O (11.1 g, 51 mmol) in DMF (30 ml) was added dropwise to a mixture of **3** (11.3 g, 46 mmol) and triethylamine (32 ml, 230 mmol) in DMF (70 ml) cooled in an ice bath over 10 min, and then the mixture was stirred overnight at room temperature. Water (200 ml) was added to the mixture and extracted with AcOEt (2×100 ml). The organic layers were combined, washed with water (100 ml), 4% citric acid (100 ml), water (100 ml), and brine (100 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give **21** (12.4 g, 102%) as a viscous oil. The oil was used for the next step without purification. An analytical sample was prepared by purification using silica gel chromatography (eluent; AcOEt : hexane=1 : 2) that produced a colorless oil. IR (neat): 3336, 1681, 1504, 1166 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.66—1.75 (1H, m), 1.98—2.06 (1H, m), 2.55 (1H, dd, J=8.2, 16.3 Hz), 2.77 (2H, t, J=6.5 Hz), 3.03 (1H, dd, J=3.8, 16.3 Hz), 3.86—4.00 (1H, br), 4.52—4.68 (1H, br), 5.13—5.28 (1H, br), 6.53 (1H, d, J=2.6 Hz), 6.62 (1H, dd, J=2.6, 8.4 Hz), 6.93 (1H, d, J=8.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 26.84, 28.87, 29.69, 36.67, 46.77, 80.20, 114.22, 116.00, 127.28, 130.12, 135.69, 154.64, 156.13. $[\alpha]_D^{26}$ −67.8° (c=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{15}H_{22}NO_3$ $(M+H)^+$: 264.1599. Found: 264.1643. *Anal.* Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04;N, 5.32. Found: C, 68.19; H, 8.05; N, 5.15.

2-{[(2*S*)-2-*tert*-Butyloxycabonylamino-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide (23) A solution of 2-chloro-*N*,*N*-dimethylacetamide (**22**) (6.2 g, 51 mmol) in THF (10 ml) was added dropwise to a mixture of **21** (12.4 g, 46 mmol), KI (8.5 g, 51 mmol), NaOH (3.9 g, 98 mmol), water (20 ml), and THF (50 ml) at room temperature. After stirring for 0.5 h, **22** (1.7 g, 14 mmol) was added dropwise to the mixture. After stirring for 1 h, AcOEt (200 ml) was added and the organic solution was washed with water (100 ml) and brine (50 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was recrystallized from AcOEt–hexane to give **23** (12.3 g, 76%) as a white solid. mp 88—89 °C. IR (KBr): 3330, 1704, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.68—1.75 (1H, m), 2.00—2.07 (1H, m), 2.59 (1H, dd, J=8.2, 16.3 Hz), 2.80 (2H, t, J=6.4 Hz), 2.97 (3H, s), 3.05—3.11 (4H, m), 3.89—4.01 (1H, br), 4.51—4.62 (1H, br), 4.64 (2H, s), 6.64 (1H, d, J=2.6 Hz), 6.75 (1H, dd, J=2.6, 8.3 Hz), 7.00 (1H, d, J=8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 26.75, 28.83, 29.52, 36.10, 36.68, 36.99, 46.53, 60.77, 67.99, 113.41, 115.26, 129.01, 130.18, 136.01, 155.72, 156.50, 168.36. $[\alpha]_D^{27}$ −60.8° (c=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{19}H_{29}N_2O_4$ $(M+H)^+$: 349.2127 Found: 349.2140. *Anal.* Calcd for $C_{19}H_{28}N_2O_4\cdot 0.4$AcOEt: C, 64.49; H, 8.20; N, 7.30. Found: C, 64.50; H, 8.39; N, 7.39.

2-{[(2*S*)-2-Amino-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide Hydrochloride Dihydrate (24) conc. HCl (17.5 ml) was added to a solution of **23** (12.29 g, 35 mmol) in iso-PrOH (50 ml) at room temperature, and then the mixture was stirred overnight. The precipitate was collected by filtration to give **24** (7.94 g, 79%) as a white solid. The ee of **24** was determined to be >99.9% by HPLC using a chiral column [column, SUMICHIRAL CBH 4.0 mm i.d.×100 mm, Sumika Chemical Analysis Service, Ltd.; mobile phase, 1% CH_3CN in 20 mM potassium phosphate buffer pH 6.5 +50 μM disodium ethylenediaminetetraacetate; flow rate, 1.0 ml/min; detection, UV at 230 nm]. mp 122—124 °C. IR (KBr): 3451, 1641 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70—1.81 (1H, m), 2.10—2.18 (1H, m), 2.68—2.87 (6H, m), 2.99 (3H, s), 3.06 (1H, dd, J=4.7, 16.1 Hz), 3.37—3.50 (5H, m), 4.74 (2H, s), 6.68 (1H, s), 6.71 (1H, d, J=8.4 Hz), 6.99 (1H, d, J=8.4 Hz), 8.47 (3H, br). ^{13}C-NMR (DMSO-d_6) δ: 26.45, 27.31, 33.51, 35.30, 35.99, 47.02, 66.15, 113.64, 114.52, 127.45, 129.73, 134.20, 156.59, 167.61. $[\alpha]_D^{29}$ −45.4° (c=1.0, MeOH). *Anal.* Calcd for $C_{14}H_{21}ClN_2O_2\cdot 2H_2O$: C, 52.41; H, 7.85; N, 8.73. Found: C, 52.44; H, 8.02; N, 8.75.

(1*R*)-1-[4-Benzyloxy-3-(2-*tert*-butyldimethylsilyloxyethyl)phenyl]-2-bromo-1-*tert*-butyldimethylsilyloxyethane (25) A solution of TBS-Cl (32.18 g, 214 mmol) in toluene (32 ml) was added to a solution of **14** (30.00 g, 85 mmol) and imidazole (29.07 g, 427 mmol) in DMF (100 ml) cooled in an ice bath, and then the mixture was stirred at room temperature for 6 h. A solution of TBS-Cl (2.57 g, 17 mmol) in toluene (2.5 ml) was added to the reaction mixture. After 2 h, water (100 ml) was added to the mixture and extracted with AcOEt (2×100 ml). The organic layers were combined, washed with water (2×100 ml) and brine (50 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give **25** (52.2 g, 118%) as a colorless oil. The oil was used for the next step without purification. An analytical sample was prepared by purification using silica gel column chromatography (eluent; hexane) that produced a colorless oil. IR (neat): 2955, 2929, 1501, 1251 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.09 (3H, s), −0.04 (6H, s), 0.10 (3H, s), 0.85 (9H, s), 0.89 (9H, s), 2.90 (2H, t, J=7.3 Hz), 3.35—3.46 (2H, m), 3.80 (2H, t, J=7.3 Hz), 4.78 (1H, dd, J=4.4, 7.9 Hz), 5.05 (2H, s), 6.86 (1H, d, J=8.3 Hz), 7.12—7.15 (2H, m), 7.32—7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: −4.95, −4.47, −4.24, 18.69, 18.75, 26.20, 26.37, 34.83, 40.34, 63.38, 70.38, 75.38, 111.53, 125.58, 127.72, 127.95, 128.25, 128.94, 129.33, 134.67, 137.58, 156.96. $[\alpha]_D^{31}$ −33.0° (c=1.0, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{29}H_{46}BrO_3Si_2$ $(M-H)^+$: 577.2169. Found: 577.2155. *Anal.* Calcd for $C_{29}H_{47}BrO_3Si_2$: C, 60.08; H, 8.17. Found: C, 59.97; H, 8.28.

2-{[(2*S*)-2-({(2*R*)-2-[4-Benzyloxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-phenyl]-2-*tert*-butyldimethylsilyloxyethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide (26) A mixture of **25** (58.2 g, 85 mmol), **24** (30.2 g, 94 mmol), and K_2CO_3 (18.9 g, 137 mmol) in *N*,*N*-dimethylacetamide (85 ml) was stirred for 6 h under an argon atmosphere in a 120 °C oil bath. After cooling to room temperature, water (200 ml) was added to the mixture and extracted with AcOEt (2×200 ml). The organic layers were combined, washed with water (2×100 ml) and brine (100 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give **26** (68.6 g, 108% from **14**) as a brown oil. The oil was used for the next step without purification. An analytical sample was prepared by purification using silica gel column chromatography (eluent; CH_2Cl_2 : MeOH=30 : 1) that produced a colorless oil. IR (neat): 2953, 2928, 1657, 1502, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.16 (3H, s), −0.04 (6H, s), 0.03 (3H, s), 0.85 (9H, s), 0.88 (9H, s), 1.49—1.59 (1H, m), 1,63—1.75 (2H, m), 1.99—2.02 (1H, s), 2.52—2.96 (9H, m), 2.97 (3H, s), 3.08 (3H, s), 3.81 (2H, t, J=7.4 Hz), 4.64 (2H, s), 4.75 (1H, dd, J=4.2, 8.2 Hz), 5.05 (2H, s), 6.66 (1H, d, J=2.6 Hz), 6.73 (1H, dd, J=2.6, 8.4 Hz), 6.85 (1H, d, J=8.3 Hz), 6.98 (1H, d, J=8.4 Hz), 7.12 (1H, dd, J=2.1, 8.3 Hz), 7.15 (1H, d, J=2.1 Hz), 7.32—7.44 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: −4.92, −4.53, −3.94, 18.57, 18.76, 26.27, 26.39, 27.71, 30.43, 34.90, 36.12, 37.06, 37.22, 53.53, 56.67, 63.48, 68.15, 70.37, 74.46, 111.46, 113.14, 115.15, 125.49, 127.66, 127.71, 128.19, 128.90, 129.32, 129.85, 130.04, 136.00, 137.01, 137.71, 156.39, 156.56, 168.50. $[\alpha]_D^{31}$ −56.9° (c=0.7, MeOH). HR-MS (FAB) *m/z*: Calcd for $C_{43}H_{67}N_2O_5Si_2$ $(M+H)^+$: 747.4588. Found: 747.4569. *Anal.* Calcd for $C_{43}H_{66}N_2O_5Si_2\cdot 0.5H_2O$: C, 68.30; H, 8.93; N, 3.70. Found: C, 68.17; H, 9.10; N, 3.84.

2-{[(2*S*)-2-({(2*R*)-2-[4-Benzyloxy-3-(2-hydroxyethyl)phenyl]-2-hydroxyethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide Oxalate Hydrate (27) A mixture of **26** (68.6 g, 85 mmol) and $TosOH\cdot H_2O$ (48.7 g, 256 mmol) in THF (480 ml) and water (24 ml) was stirred at room temperature overnight. After the addition of a solution of K_2CO_3 (39 g, 281 mmol) in water (300 ml), the mixture was extracted with AcOEt (300 ml) and 10% EtOH–AcOEt (300 ml). The organic layers were combined, washed with aqueous 0.4 M K_2CO_3 solution (200 ml) and brine (200 ml), then concentrated under reduced pressure. A solution of oxalic acid dihydrate (10.7 g, 85 mmol) in EtOH (80 ml) was added to the solution of the resulting residue in EtOH (120 ml) at 50 °C, and then toluene (430 ml) was added to the mixture and cooled to room temperature. The precipitate

was collected by filtration to give **27** (36.7 g, 69% from **14**) as a white solid. mp 169—173 °C. IR (KBr): 1635, 1506 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.71—1.87 (1H, m), 2.21—2.31 (1H, m), 2.61—3.25 (14H, m), 3.39—3.50 (1H, m), 3.61 (2H, t, J=7.3 Hz), 4.73 (2H, s), 4.92 (1H, d, J=9.1 Hz), 5.13 (2H, s), 6.66 (1H, s), 6.70 (1H, d, J=8.4 Hz), 6.99 (1H, d, J=8.5 Hz), 7.03 (1H, d, J=8.4 Hz), 7.22 (1H, d, J=8.5 Hz), 7.25 (1H, s), 7.34 (1H, t, J=7.2 Hz), 7.38—7.45 (4H, m). ^{13}C-NMR (DMSO-d_6) δ: 26.09, 26.93, 31.61, 34.32, 35.29, 35.94, 51.58, 54.02, 61.14, 66.11, 68.52, 69.57, 112.20, 113.57, 114.65, 125.24, 127.59, 127.69, 128.06, 128.66, 128.77, 128.82, 129.62, 134.17, 134.33, 137.75, 156.14, 156.62, 165.29, 167.55. $[\alpha]_D^{29}$ −67.8° (c=1.0, MeOH). *Anal.* Calcd for $C_{33}H_{40}N_2O_9 \cdot H_2O$: C, 63.25; H, 6.75; N, 4.47. Found: C, 63.07; H, 6.54; N, 4.43.

2-{[(2*S*)-2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]-ethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide (28) A mixture of **37** (36.7 g, 59 mmol) and K_2CO_3 (24.3 g, 176 mmol) in water (200 ml) and 10% EtOH–AcOEt (200 ml) was stirred for 1 h at 40 °C. The separated aqueous layer was extracted with 10% EtOH–AcOEt (2×100 ml), and then the organic layers were combined, washed with brine (50 ml), and concentrated under reduced pressure to give an oil. The solution of the oil in EtOH (150 ml) was hydrogenated over 10% Pd-C (50% wet, 3.7 g) for 8 h at 40 °C under atmospheric pressure. The Pd–C was filtered off, the filtrate was concentrated under reduced pressure, and the resulting residue was recrystallized from EtOH–hexane to give **28** (22.3 g, 89%) as a white solid. mp 136—137 °C. IR (KBr): 3310, 1654 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39—1.49 (1H, m), 1.52—1.75 (1H, br), 1.85—1.95 (1H, m), 2.43 (1H, dd, J=8.3, 16.0 Hz), 2.55—2.87 (10H, m), 2.90 (1H, dd, J=4.8, 16.0 Hz), 2.98 (3H, s), 3.55 (2H, t, J=7.4 Hz), 4.47 (1H, dd, J=3.9, 8.3 Hz), 4.69 (2H, s), 5.03 (1H, br s), 6.61 (1H, d, J=2.4 Hz), 6.64 (1H, dd, J=2.4, 8.1 Hz), 6.70 (1H, d, J=8.2 Hz), 6.93 (1H, d, J=8.1 Hz), 6.97 (1H, dd, J=2.0, 8.2 Hz), 7.03 (1H, d, J=2.0 Hz), 8.80—9.04 (1H, br). ^{13}C-NMR (DMSO-d_6) δ: 26.76, 29.68, 34.41, 35.28, 36.01, 36.83, 52.88, 55.38, 61.39, 66.23, 71.91, 112.69, 114.81, 114.87, 124.97, 125.11, 128.68, 128.79, 129.44, 135.12, 136.76, 154.57, 156.32, 167.67. $[\alpha]_D^{25}$ −59.6° (c=1.1, MeOH). HR-MS (FAB) m/z: Calcd for $C_{24}H_{33}N_2O_5$ $(M+H)^+$: 429.2389. Found: 429.2369. *Anal.* Calcd for $C_{24}H_{32}N_2O_5$: C, 66.27; H, 7.53; N, 6.54. Found: C, 66.92; H, 7.69; N, 6.52.

Bis(2-{[(2*S*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)-phenyl]ethyl}amino)-1,2,3,4-tetrahydronaphthalen-7-yl]oxy}-*N*,*N*-dimethylacetamide) Sulfate (KUR-1246) 2 M H_2SO_4 (26.0 ml, 26.0 mmol) was added to a solution of **28** (22.3 g, 52.0 mmol) in MeOH (130 ml) at 50 °C, and then the mixture was stirred overnight at room temperature. The precipitate was collected by filtration to give KUR-1246 (21.47 g, 87%) as a white solid. mp 211—215 °C (dec.). IR (KBr): 3418, 1636 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.57—1.68 (1H, m), 2.03—2.11 (1H, m), 2.60—3.22 (16H, m), 3.57 (2H, t, J=7.4 Hz), 4.66 (1H, dd, J=2.8, 9.4 Hz), 4.71 (2H, s), 6.63 (1H, d, J=2.6 Hz), 6.67 (1H, dd, J=2.6, 8.4 Hz), 6.74 (1H, d, J=8.2 Hz), 6.96 (1H, d, J=8.4 Hz), 7.03 (1H, dd, J=1.9, 8.2 Hz), 7.08 (1H, d, J=1.9 Hz), 9.24 (1H, br s). ^{13}C-NMR (DMSO-d_6) δ: 26.89, 27.00, 32.89, 34.37, 35.28, 35.96, 52.80, 53.70, 61.32, 66.15, 69.39, 113.29, 114.67, 115.01, 125.07, 125.37, 127.94, 128.64, 129.55, 133.29, 135.05, 155.05, 156.50, 167.58. $[\alpha]_D^{25}$ −70.8° (c=1.0, H_2O). *Anal.* Calcd for $C_{48}H_{66}N_4O_{14}S$: C, 60.36; H, 6.96; N, 5.87. Found: C, 60.18; H, 7.09; N, 5.82.

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References and Notes

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