The Practical Synthesis of a Uterine Relaxant, Bis(2-[(2S)-2-[(2R)-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-[(2S)-2-[(2R)-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. β2-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-[(2S)-2-[(2R)-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 Chart 1.2) The racemic mandelic acid derivative 3-(2-hydroxyethyl)phenyl]ethyl]amino)-1,2,3,4-tetrahydro-naphthalen-7-yl]oxy]-N,N-dimethylacetamide) sulfate (KUR-1246) was synthesized from the optically active diastereomer 15, which was separated by column chromatography on silica gel to obtain the single isomer, as shown in Chart 2. The racemic mandelic acid derivative 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

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 H2SO4. The methyl ester 11 was reacted with benzyl chloride in the presence of KI and K2CO3 to give the ketone 12 in 78% yield. The bromination of 12 with Br2 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 sulfoxide complex (BH3·Me2S) (120 mol%), Al(OEt)3 (12 mol%) and (R)-α,α-diphenyl-2-pyrridinidemethanol (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....

![Fig. 1](image-url)
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 \( \cdot \) 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 \( \cdot \) HBr (3) in 99% yield. The reaction of 3 with di-tert-butyl dicarbonate (Boc\(_2\)O) 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 \( \text{tert} \)-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\(_2\)SO\(_4\) (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 \( \cdot \) 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.

Table 1. Asymmetric Borane Reduction of 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino alcohol</th>
<th>Yield (%)</th>
<th>ee (%) (^a) (Crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>86</td>
<td>99.9 (98.0)</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>90</td>
<td>99.5 (94.5)</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>89</td>
<td>95.4 (92.9)</td>
</tr>
<tr>
<td>4</td>
<td>((-))-18</td>
<td>85</td>
<td>98.3 (94.6)</td>
</tr>
</tbody>
</table>

\(^a\) The optical purity was measured by HPLC analysis using a chiral column (Chiralpak AD).
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. H- and 13C-NMR spectra were recorded on a Bruker DRX-500 using tetramethylsilane or sodium 3-(trimethylsilyl)propionate-2,2,3,3-d4 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 (374 g, 4 mol) was added to a solution of 4-hydroxyacetophenone (7) (136.9 g, 1 mol) in MeOH (200 ml) and 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) as a red solid. This 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.

206 °C. IR (KBr): 3345, 1712, 1645 cm−1. 1H-NMR (DMSO-d6): δ: 2.60 (3H, s), 4.75 (2H, s), 6.97 (1H, J = 8.4 Hz), 7.84 (1H, J = 8.4 Hz), 7.99 (1H, J = 8.4 Hz), 10.89 (1H, J = 8.4 Hz). 13C-NMR (DMSO-d6): 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 C16H10O2Cl (M+H): 289.0576. Found: 289.0576. Anal. Caled for C16H10O2Cl: C, 59.49; H, 3.51.

Found: C, 58.54; H, 5.00.

(5-Acetyl-2-hydroxyphenyl)acetic Acid (10) A solution of NaCN (98.0 g, 2.0 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, 3.5 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), and then concentrated under reduced pressure. The precipitate (300 ml) was added dropwise to the solution of 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 203—206 °C. IR (KBr): 3345, 1712, 1645 cm−1. 1H-NMR (DMSO-d6): δ: 2.47 (3H, s), 6.69 (1H, J = 8.4 Hz), 7.78 (1H, J = 2.0 Hz), 10.18—10.75 (1H, J = 4.1 Hz, 1H, J = 8.4 Hz), 11.81—12.49 (1H, J = 8.4 Hz). 13C-NMR (DMSO-d6): δ: 26.65, 35.64, 118.40, 122.53, 124.73, 129.67, 132.29, 160.56, 172.78, 196.43. HR-MS (FAB) m/z: Calcd for C15H12O2 (M+H+): 247.0730. Found: 247.0728. Anal. Caled for C15H12O2: C, 73.15; H, 5.43. Found: C, 72.65; H, 5.13.

Methyl (2-Benzoxyl-5-bromoacetylphenyl)acetate (13) A solution of BrO3− (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 MgSO4, 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. 1H-NMR (CDCl3) δ: 3.64 (3H, J = 3.7 Hz, 3H, J = 4.3 Hz, 2H, J = 6.9 Hz, 1H, J = 8.6 Hz), 7.30—7.42 (5H, m), 7.88 (1H, J = 2.3 Hz, 7.92 (1H, J = 2.3, 8.6 Hz). 13C-NMR (CDCl3) 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 C33H25BrO3 (M+H): 577.3388. Found: C, 73.10; H, 5.45. Anal. Caled for C33H25BrO3: C, 73.15; H, 5.43. Found: C, 72.72; H, 5.42.

1R,2S,3R,4S-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol Methanesulfonate (11) A solution of (1R,3S)-3-hydroxymino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (7) (8.5 g, 47 mmol) in ether (120 ml) was added dropwise to a suspension of LiAlH4 (3.52 g, 140 mmol) in ether (140 ml) over 45 min at room temperature, and then stirred overnight. 2M NaOH (25 ml) was carefully added to the mixture and the organic layers were combined, washed with water (5 ml), dried over MgSO4, and 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, washed with ether (20 ml), and then dried to give the crude methanesulfonic acid salt (10.4 g, 84%). The ee of 11 (8.8 g, 100%) was recrystallized from EtOH–hexane to give the pure salt (8.8 g, 88.9:11.1). The ee of 11 (8.8 g, 100%) was recrystallized from EtOH–hexane to give the pure salt (8.8 g, 88.9:11.1). The ee of 11 (8.8 g, 100%) was recrystallized from EtOH–hexane to give the pure salt (8.8 g, 88.9:11.1).

1R,2S,3R,4S-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol [1R,2S,3R,4S-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (7)] (9.4 g, 47 mmol) was added to a solution of LiAlH4 (3.52 g, 140 mmol) in ether (140 ml) over 45 min at room temperature, and then stirred overnight. 2M NaOH (25 ml) was carefully added to the mixture and the organic layers were combined, washed with water (5 ml), dried over MgSO4, and 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 methanesulfonic acid salt (10.4 g, 84%). 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_{12}H_{13}BrO, monoclinic, P_{2} (No. 4), Z=2; a=4.985, b=11.139, c=14.445 Å; \alpha=\gamma=90.00, \beta=94.856^\circ; V=799.55 Å^{3}; D_{m}=1.38 g cm^{-3}; \mu=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=55.00. Of 4225 measured reflections, 2184 had I>3σ(I), and 1893, including Bijvoet pairs, were unique and used for structure solution. The structure was solved by the direct method (SIR-92) and refined through full-matrix least square method to R=0.042 and R_{wp}=0.045 using the TEXSAX-TEXRA Y Structure Analysis Package (Ver 1.9), Molecular Structure Corporation. Hydrogen atoms were incorporated at fixed position as with C–H 0.045 Å. The absolute configuration was confirmed by refining the inverted configuration which converged to a higher residual of R_{w} (R_{wp})=0.0716 (0.0778) (heavy atoms only). The absolute configuration of 14 was confirmed to be F as shown in Fig. 2.

A solution of 2-chloro-

Butoxycarbonylamino-5,6,7,8-tetrahydro-2-naphthol (21)

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% yield). Analysis of the sample was prepared by purification using silica gel column chromatography (eluent: hexane) that produced a colorless oil. IR (neat): 2955, 2928, 2868, 2929, 1501, 1251 cm^{-1}. \text{H-NMR (CDCl}_{3}: δ = 0.09 (3H, s), 0.03 (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). MS (FAB): m/z: 577.2169. Found: 577.2155. Anal. Calcd for C_{29}H_{46}BrO_{3}Si_{2} (M_{r}=577): C, 52.41; H, 7.85; N, 8.75. Found: C, 52.44; H, 8.02; N, 8.75.

2-(12S)-2-(4-Benzoyloxy-3-(2-hydroxyethyl)phenyl)-2-bromo-1,2-tert-butyldimethylsilyloxylethyl-phenyl)-2-tert-butyldimethylsiloxyethylamino-1,2,3,4-tetrahydro-2-naphthalen-7-yl-oxo)-N,N-dimethylacetamide Oxalate Hydrate (27) A mixture of 26 (68.6 g, 85 mmol) and TosOH·H_{2}O (48.7 g, 256 mmol) in THF (480 ml) and water (24 ml) was stirred at room temperature overnight. After the addition of K_{2}CO_{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 0.45 molar K_{2}CO_{3} solution (200 ml) and brine (200 ml), then concentrated under reduced pressure. A solution of acetic 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 to give a slurry. The mixture was filtered to give 27 (5.94 g, 79% as a white solid. The ee of 24 was determined to be >99.9% by HPLC using a chiral column [column, SUMICHLIR CBH 4.0 mm i.d.×100 mm, Sumika Chemical Analy- sis Service, Ltd.; mobile phase, 1% CH_{3}CN in 20 mM potassium phosphate buffer pH 6.5 + 50 mM disodium ethylenediaminetetraacetate; flow rate, 1.0 ml/min; detection, UV at 230 nm]. mp 122—124°C (IR (KBr): 3451, 2927, 2873 cm^{-1}. \text{H-NMR (DMSO-d}_{6}: δ = 1.01 (6H, s), 2.63—2.67 (8H, m), 2.99 (3H, s), 3.06 (1H, dd, J=4.7, 16.1 Hz), 3.37 3.50 (5H, m), 3.39 (2H, s), 4.31 (2H, m), 6.80 (1H, d, J=8.4 Hz), 6.99 (1H, d, J=8.4 Hz), 8.47 (3H, br). \text{C-NMR (DMSO-d}_{6}: δ = 26.45, 27.31, 33.51, 35.30, 35.99, 47.02, 66.15, 113.64, 114.52, 124.75, 129.73, 134.20, 156.59, 167.61. [\text{RF}_{D}^{25}: −45.4^°] (c=1.0, MeOH). Anal. Calcd for C_{29}H_{46}BrO_{3}Si_{2}: C, 52.07; H, 7.85; N, 8.75. Found: C, 52.10; H, 7.88; N, 8.73.

1. \text{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, 16.1 Hz), 3.38—3.45 (1H, m), 6.50 (1H, dd, J=2.6, 6.7 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). \text{C-NMR (DMSO-d}_{6}: δ = 26.30, 27.43, 33.43, 47.14, 114.25, 115.29, 123.29, 127.99, 133.87, 155.72. [\text{RF}_{D}^{25}: −61.4^°] (c=1.0, MeOH). Anal. Calcd for C_{20}H_{22}BrNO: C, 49.20; H, 5.78; N, 7.30. Found: C, 49.16; H, 6.17; N, 7.58.

3-Amino-1,2,3,4-tetrahydronaphthalen-7-yl-oxo)-N,N-dimethylacetamide Hydrochloride Dihydrate (24) conc. HCl (17.5 ml) was added to a solution of 23 (12.2 g, 35 mmol) in iso-PrOH (50 ml) at room temperature, and then the mixture was stirred overnight. The precipi-

7-yl{]oxy}
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. ¹H-NMR (DMF-d₇): 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), 6.60 (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). ¹³C-NMR (DMF-d₇): δ: 26.09, 26.93, 31.61, 34.32, 35.29, 35.94, 51.58, 54.02, 61.14, 64.11, 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. [α]D²⁷ —67.8° (c = 1.0, MeOH). Anal. Calcd for C₁₃H₁₆NO₂: C, 66.92; H, 7.69; N, 6.54. Found: C, 66.9; H, 7.7; N, 6.4.

Bis(2-[(2R)-2-hydroxy-2-[4-hydroxy-3-[(2-hydroxyethyl)phenoxy]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yl]oxy]-N,N-dimethylacetamide (28) A mixture of 37 (36.7 g, 59 mmol) and K₂CO₃ (36.7 g, 69% from 22) 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. ¹H-NMR (DMSO-d₆): 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, d, 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, d, J = 1.9 Hz), 7.08 (1H, d, J = 1.9 Hz), 9.24 (1H, br s). ¹³C-NMR (DMSO-d₆): δ: 26.89, 27.00, 32.89, 34.37, 35.28, 35.96, 52.80, 53.70, 53.70, 61.32, 66.15, 69.39, 113.29, 114.67, 115.01, 125.07, 125.37, 127.94, 129.55, 133.29, 135.05, 155.05, 156.50, 167.58. [α]D¹⁷ —7.08° (c = 1.0, H₂O). Anal. Calcd for C₃₃H₄₀N₂O₉·H₂O: C, 63.25; H, 6.6; N, 5.87. Found: C, 63.18; H, 7.09; N, 5.82.

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References and Notes