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Process Development of ONO-2506: A Therapeutic Agent for Stroke and Alzheimer's Disease

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Abstract:

A process for the synthesis of ONO-2506, an agent that suppresses astrocyte activation, has been developed. Significant improvement of the level of impurities in the final product has been achieved compared with the laboratory-scale procedure. Kilogram quantities of the compound have been supplied for preclinical studies by this improved process, with both a high quality (99.8%) and a high optical purity (99.6% ee). This was achieved by formation of a crystalline salt of an intermediate which could be recrystallized to give high purity. Toward the future launch of this product, residual problems such as byproduct formation during stereoselective allylation and removal of chiral auxiliary steps were also solved by further investigation.

Introduction

ONO-2506 (**1**) delays the expansion of cerebral infarcts by modulating the activation of astrocytes through inhibition of *S*-100β synthesis, and it has been developed as a novel therapeutic agent for stroke and Alzheimer's disease.[1] Laboratory-scale synthesis of this candidate was previously reported, which was achieved with a high optical purity by use of Oppolzer's camphorsultam.[2] The synthetic process involved the acylation of camphorsultam, diastereoselective allylation, removal of the chiral auxiliary by hydrogen peroxide-mediated hydrolysis in the presence of *n*-tetrabutylammonium hydroxide, and hydrogenation of the double bond (Scheme 1). To support continued development, kilogram quantities of **1** were required for various preclinical studies. Here we describe further improvements to the synthetic process before and after production on a pilot scale, especially with regard to removal of impurities and suppression of byproduct formation.

Results and Discussion

Improvements To Eliminate Impurities in the Final Product. The laboratory-scale procedure furnished **1** with a satisfactory result of enantiomeric purity and a high overall yield. However, the final product contained some impurities, the structures and profiles of which are shown in Figure 1 and Table 1.

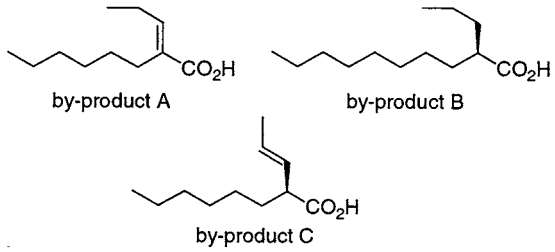

Figure 1.

Table 1. **Impurity profiles of 1**

	GC analysis (area%)			
entry	**1**	by-pro A	by-pro B	sultam
1[a]	98.7	0.03	0.24	0.73
2[b]	99.4	0.03	0.14	0.24
3[c]	99.6	ND[e]	0.21	ND
4[d]	99.9	ND	0.02	ND

[a] Distillation. [b] Distillation twice. [c] Purification via amine salt and distillation. [d] Use of pure *n*-octanoyl chloride and same as entry 3 [e] ND: not detected.

Byproduct A was formed during the hydrogenation step through palladium-mediated double bond migration, while byproduct B was derived from commercially available *n*-octanoyl chloride that containes a small amount of *n*-decanoyl chloride. Because the active pharmaceutical ingredient will be used as an injectable drug, the most critical problem for our project was contamination of **1** by highly crystalline camphorsultam, which could generate insoluble foreign matter. Analysis of **1** purified by distillation indicated a residual camphorsultam content of 0.73% (entry 1). Repeated distillation was effective in reducing the content (entry 2). Various attempts to prepare an amine salt of **1** all failed, but we found that crude **4** formed a good crystalline salt with cyclohexylamine (Scheme 2). The yield of **4** after hydrogen peroxide-mediated hydrolysis was estimated as 88% yield by HPLC analysis using 4-nonyloxybenzoic acid as the internal standard.[2b] Hence, 0.9 equiv of cyclohexylamine was employed with crude **4** to produce **5**. The amine salt was readily recrystallized from AcOEt to give **5** as colorless needles in 76% yield and was freed under usual acidic conditions to obtain pure **4** in small-scale synthesis. Subsequent hydrogenation and distillation in the same manner of entry 1 completely removed the troublesome impurity (entry 3). Although direct hydrogenation of **5** followed by acidic

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(1) Tateishi, N.; Ohno, H.; Kishimoto. K.; Ohuchida, S. JP 7-316092, 1995. Matsui, T.; Mori, T.; Tateishi, N.; Kagamiishi, Y.; Satoh, S.; Katsube, N.; Morikawa, E.; Morimoto, T.; Ikuta, F.; Asano, T. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 711; Tateishi, N.; Mori, T.; Kagamiishi, Y.; Satoh, S.; Katsube, N.; Morikawa, E.; Morimoto, T.; Matsui, T.; Asano, T. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 723.

(2) (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. Oppolzer, W.; Rosset, S.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 1539. (b) Hasegawa, T.; Yamamoto, H. *Synlett* **1998**, 882; Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423.

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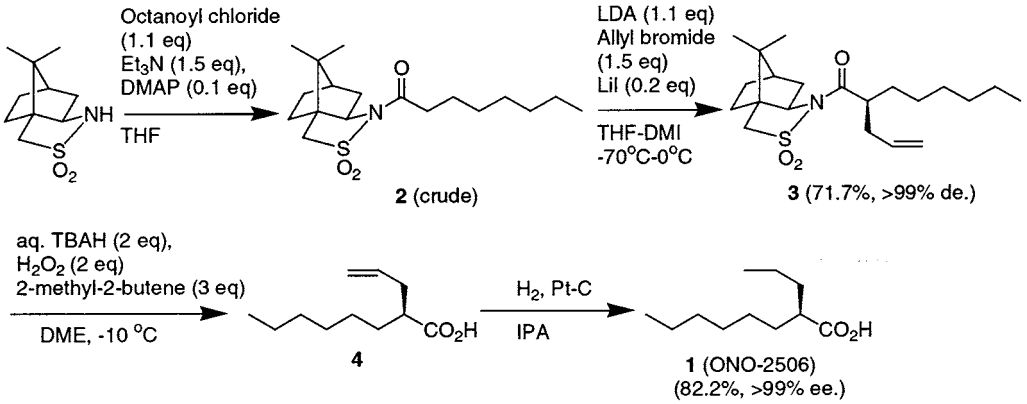
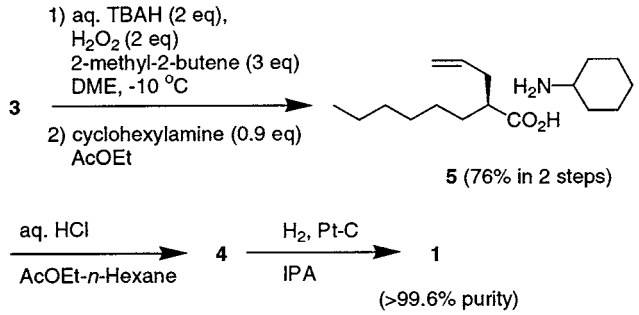
Scheme 1



Scheme 2



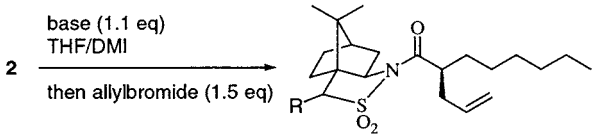
workup to achieve transformation into **1** seemed to be a more efficient alternative route, the process yielded crude **1** with a 5.5% content of byproduct C, which was difficult to remove by distillation. No change of byproduct C resulted from a longer hydrogenation time, so that the relatively basic substrate presumably induced deactivation of the catalyst. Finally, use of distilled pure *n*-octanoyl chloride provided the highest quality (entry 4). Pilot-scale synthesis was performed by the improved procedure described above with the optimized amounts of reagents.

To Suppress Byproduct Formation for Future Process Optimization. In the previous pilot-scale procedure, a cryogenic temperature was required during the allylation step due to an increase of byproduct **6** at higher temperatures through formation of dienolate **2** (Table 2, entries 1 and 2). The worst case was a 4.0% content of **6** when *n*-butyllithium was used as the base, even at −78 °C (entry 3). Because easy control of the reaction temperature is a crucial factor for development of a robust process, we examined the use of sterically hindered bases to prevent enolate formation at the α-position of sulfone by steric repulsion. Successful results were obtained by using LTMP or LIPC, which reduced the content of **6** to 0.5%, even at −20 °C, without any loss of diastereoselectivity (entries 4 and 5).[3] Raising the temperature to −5 to 5 °C led to an increase of **6** (entry 6). These results were useful for the next stage of process development.

Another problem was encountered during workup for removal of the chiral auxiliary. After quenching the reaction

(3) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318; Nudelman, N. S.; Pérez, D. *J. Org. Chem.* **1983**, *48*, 133; Nudelman, N. S.; Lewkowicz, E. S.; Pérez, D. G. *Synthesis* **1990**, 917; Nudelman, N. S.; Lewkowicz, E.; Furlong, J. J. P. *J. Org. Chem.* **1993**, *58*, 1847.

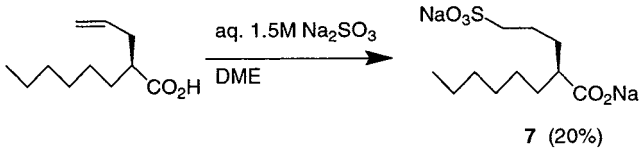
***Table 2.* Effect of bases to reduce byproduct for diastereoselective allylation**



entry	base	temp (°C)	HPLC (area %) 2	3	6	reaction (de %)	3 (de %)[a]	3 yield (%)[a]
1	LDA	−78	2.9	85.8	1.9	93.2	99.4	66
2	LDA	−40	2.9	71.4	5.4	91.7	97.2	53
3	*n*-BuLi	−78	10.0	77.5	4.0	92.7	–	–
4	LTMP[b]	−35 to −20	6.1	89.2	0.3	93.2	98.6	68
5	LIPC[c]	−35 to −20	3.5	89.0	0.5	91.8	99.4	69
6	LIPC	−5 to 5	8.3	75.1	3.2	86.3	98.7	36

[a] After purified by recrystallization twice. [b] LTMP: lithium 2,2,6,6-tetramethylpiperidide. [c] LIPC: lithium *n*-isopropylcyclohexylamide.

Scheme 3



with aqueous Na_2SO_3 solution, extension of the time for addition of aqueous HCl to the mixture was found to significantly decrease the yield of the desired product **4**. Several harsh tests of **4** reacted with aqueous Na_2SO_3 solution which indicated that hydrosulfonylation of the terminal olefin of **4** occurred at a neutral pH and produced compound **7** (Scheme 3).[4] Hence, inverse addition of aqueous HCl to maintain a low pH range of the reaction mixture seemed to be a critical point for further scaling up of production.

Conclusions

In summary, the laboratory synthesis procedure for ONO-2506 was improved to remove highly crystalline camphorsultam from the final product by addition of a purification step through amine salt **5**. This method provided high quality **1** and allowed easy access to development of the drug. Working toward full-scale production, we clarified the

(4) Sonnek, G.; Rabe, C.; Schmaucks, G. *J. Organomet. Chem.* **1991**, *405*, 179.

mechanism of byproduct formation and solved the problem by changing the reagent system and the workup procedure.

Experimental Section

General. Infrared (IR) spectra were recorded on a Jasco VALOR:III spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-DX303HF mass spectrometer. ^{1}H NMR spectra were measured with a Varian Gemini-300 (300 MHz) or a Varian Gemini-200 (200 MHz) spectrometer. The chemical shifts on ^{1}H NMR spectra were reported relative to that of tetramethylsilane (δ 0). Microanalysis and mass spectra (HRMS) were done at the Minase Research Institute, Ono Pharmaceutical Co., Ltd.

Preparation of *N*-Octanoyl-(1*S*)-(−)-10,2-camphorsultam 2. A 100-L stainless steel reactor was successively charged with (1*S*)-(−)-10,2-camphorsultam (6.00 kg, 27.9 mol), Et_3N (4.23 kg, 41.8 mol), 4-*N*,*N*-(dimethylamino)-pyridine (341 g, 2.79 mol), and THF (39 L). The resulting solution was cooled to −5 °C, and a solution of octanoyl chloride (4.99 kg, 30.7 mol) in THF (9.0 L) was added slowly at −5 to 0 °C. After stirring for 0.5 h, the reaction was quenched with water (5.6 L), and aqueous HCl (3.3 L, 38 mol of concentrated HCl in 5.6 L of water) was added. The batch was transferred to a 300-L stainless steel reactor and rinsed with AcOEt (80 L). Then the organic layer was separated and washed with brine (2.8 kg of NaCl in 16 L of water). Next, the organic layer was washed twice with aqueous NaOH (320 g, 8.0 mol of NaOH in 8 L of water) to remove excess octanoyl chloride and brine (1.6 kg of NaCl in 16 L of water and then 4.1 kg of NaCl in 12 L of water). Subsequently, the organic layer was transferred to a 100-L stainless steel reactor (rinsed with 6 L of AcOEt), and the solvent was removed under reduced pressure. The residue was diluted with THF (9 L) and concentrated to give **2** as a pale yellow oil. The crude product was used directly in the next step. A 100% yield was obtained by removing the solvent from the sample and calculating the weight of the oil to be 10.0 kg. GC 99.2 area %; water content 0.04 wt % by Karl Fischer titration. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.86 (t, 1 H, J = 6.3 Hz), 3.49 (d, 1 H, J = 13.2 Hz), 3.43 (d, 1 H, J = 13.2 Hz), 2.72 (dt, 2 H, J = 7.9, 2.6 Hz), 2.09 (m, 2 H), 1.88 (m, 3 H), 1.67 (m, 2 H), 1.31 (m, 10 H), 1.14 (s, 3 H), 0.96 (s, 3 H), 0.86 (t, 3 H, J = 6.8 Hz); IR (neat) 2931, 1698, 1332 cm^{-1}.

Preparation of *N*-(2*S*)-(2-Hexyl-4-pentenoyl)-(1*S*)-(−)-10,2-camphorsultam 3. Crude **2** (10 kg) in a 100-L stainless steel reactor was diluted with THF (15 L), transferred to a 150-L stainless steel reactor, and cooled to below −60 °C. Then a solution of LDA (2 mol/L in *n*-heptane/THF/ethylbenzene, 12.5 kg, 30.7 mol) was added and stirred for 0.5 h. Next a solution of allyl bromide (5.06 kg, 41.8 mol) in THF (450 mL) was added below −65 °C, and LiI (750 g, 5.6 mol) in THF (3.5 L)-DMI [5](4.77 kg) was added successively. The resulting mixture was warmed to −20 °C, after which it was stirred at −20 to −15 °C for 3 h and at −5 to 5 °C for 1 h. After the reaction was quenched with water (600 mL), aqueous HCl (3.3 L, 38 mol of concentrated HCl in 16.7 L of water) was added. The organic layer was separated, and was washed three times successively with water (20 L) and brine (3.0 kg of NaCl in 15 L of water). Subsequently, the organic layer was transferred to a 300-L glass-lined reactor (rinsed with 68.5 L of isopropyl alcohol), and 68.5 L of water was added. The mixture was heated to 70 °C, and the resulting solution was cooled to room temperature over 18 h. Then the slurry was cooled to 0 °C and stirred for 1 h, after which the mixture was filtered by a centrifuge to give the crude product (wet 7.75 kg). A 300-L glass-lined reactor was charged with the above crude cake, isopropyl alcohol (65.5 L), and water (23.8 L), and the recrystallization process was repeated. The resulting cake was washed with a mixture of water (8.1 L) and isopropyl alcohol (5.4 L), and dried at 60 °C under reduced pressure to afford **3** (6.31 kg, 59.3% in two steps) as colorless crystals. HPLC 99.8 area %, 99.7% de; Chiralcel OJ-R; CH_3CN/H_2O = 55/45; flow rate, 1 mL/min; detection, 210 nm; retention time, 10.7 min (*R*) and 12.4 min (*S*). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80 (ddt, 1 H, J = 15.6, 9.8, 7.2 Hz), 5.05 (dd, 1 H, J = 15.6, 2.2 Hz), 4.98 (dd, 1 H, J = 9.8, 2.2 Hz), 3.90 (t, 2 H, J = 6.3 Hz), 3.51 (d, 1 H, J = 13.9 Hz), 3.42 (d, 1 H, J = 13.9 Hz), 3.12 (m, 1 H), 2.36 (t, 2 H, J = 7.0 Hz), 2.03 (d, 2 H, J = 6.4 Hz), 1.88 (m, 2 H), 1.74 (m, 1 H), 1.26 (m, 10 H), 1.16 (s, 3 H), 0.96 (s, 3 H), 0.86 (t, 3 H, J = 6.4 Hz); IR (KBr) 2950, 1684, 1326 cm^{-1}, mp = 94−95 °C.

Preparation of *N*-(2*S*)-(2-Hexyl-4-pentenoyl)-(1*S*)-(−)-10,2-camphorsultam 3 Using LIPC. A solution of *n*-isopropylcyclohexylamine (2 mL, 12 mmol) in THF (5 mL) was cooled to −10 to −5 °C, and *n*-BuLi (1.6 M in hexane, 6.9 mL, 11 mmol) was added below 15 °C and stirred for 0.5 h. A solution of crude **2** (3.4 g, 10 mmol) in THF (7 mL) was cooled to −35 °C, and the prepared LIPC solution was added below −25 °C and stirred for 0.5 h. To this mixture was added allylbromide (1.3 mL, 15 mmol) and DMI (2 mL). The reaction mixture was stirred at about −20 °C for 2.5 h and then warmed to room temperature. To the mixture was added aqueous HCl (2 M, 15 mL) and the organic layer was separated. This layer was washed with water and brine, and concentrated in vacuo. Then the residue was crystallized from IPA (35 mL) and water (35 mL) to give the first crop (4.3 g, 97.0% de.), which was further recrystallized from IPA (4 mL) and water (6 mL) to afford **3** (2.6 g, 69%, 99.4% de) as colorless crystals.

Preparation of (2*S*)-2-Hexyl-4-pentenoic Acid Cyclohexylamine Salt 5. A 100-L glass-lined reactor was charged with **3** (3.50 kg, 9.17 mol), 2-methyl-2-butene (1.93 kg, 27.5 mol), aqueous hydrogen peroxide (30 wt %, 2.07 kg, 18.3 mol), and DME (37 L). A solution of aqueous *n*-Bu_4NOH (40 wt %, 11.8 kg, 18.2 mol) in DME (8.7 L) was added to the mixture at −10 to 0 °C and the oxygen level maintained at less than 5% by use of nitrogen gas purge. Then the reaction mixture was warmed to 0−5 °C and stirred for 3 h. The reaction was quenched with aqueous Na_2SO_3 (2.32 kg, 18.4 mol in 12 L of water) after which the mixture was warmed to 20−25 °C and stirred for 0.5 h. Next the mixture was transferred to a 300-L glass-lined reactor and cooled to 0 °C. To the mixture was added aqueous HCl (concentrated HCl, 17.5 L in 12.3 L of water), and the product was extracted with *tert*-butylmethyl ether (35 L). The organic layer was transferred to a 100-L glass-lined reactor and washed with aqueous oxalic acid dihydrate (1.76 kg, 14.9

(5) 1,3-Dimethyl-2-imidazolidinone.

mol in 17.5 L of water), water (17.5 L ×3), and brine (6.1 kg of NaCl in 17.5 L of water). Subsequently, the organic layer was concentrated under reduced pressure, and *n*-heptane (10.5 L) was added to the residue. The resulting slurry was filtered, and the cake was washed with *n*-heptane (7 L). The filtrate was concentrated under reduced pressure, and the residue was transferred to a 20-L stainless steel reactor (rinsed with 11.8 L of AcOEt). To the solution was added cyclohexylamine (820 g, 8.26 mol), and it was heated to 45−50 °C, after which the resulting solution was stirred at room temperature. The slurry was cooled to 5−10 °C, stirred for 1 h, and filtered by a centrifuge. Then the resulting cake was washed with AcOEt (6.9 L) and dried at 40 °C under reduced pressure to afford **5** (1.94 kg, 74.7%) as colorless needles. HPLC 97.1 area %, ^{1}H NMR(200 MHz, $CDCl_3$) δ 6.23 (4H, br), 5.81 (1H, m), 5.02 (1H, d, J = 15.4 Hz), 4.95 (1H, dd, J = 10.4, 2.0 Hz), 2.83 (1H, m), 2.20 (3H, m), 1.98 (2H, m), 1.75 (2H, m), 1.66−1.26 (16H, m), 0.87 (3H, t, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.5, 137.5, 115.3, 50.1, 48.3, 37.3, 32.6, 31.9, 29.6, 27.9, 25.0, 24.6, 22.7, 14.1; MS (EI, Pos): *m*/*z* 184 (M^+), 113, 100, 99, IR (KBr) 2928, 1640, 1540, 1400 cm^{-1}, mp = 104 °C.

Preparation of (2*S*)-2-Hexyl-4-pentenoic Acid 4. A 100-L stainless steel reactor was charged with **5** (1.70 kg, 6.00 mol), AcOEt (6.8 L), *n*-hexane (27 L), and aqueous HCl (concentrated HCl, 570 mL in 2.7 L of water). The resulting solution was stirred for 0.5 h, and the organic layer was separated. The organic layer was washed three times with water (8.4 L), and the product was reverse-extracted from the organic layer with aqueous NaOH (NaOH 950 g in 9.1 L of water). Then the aqueous layer was washed twice with a mixture of AcOEt (6.8 L) and *n*-hexane (27 L). To the aqueous layer was added aqueous HCl (concentrated HCl, 2.3 L in 10 L of water) at 10 °C, and the product was extracted with a mixture of AcOEt (6.8 L) and *n*-hexane (27 L). Subsequently, the organic layer was washed three times with water (9.1 L) and brine (1.5 kg of NaCl in 4.4 L of water), after which the solvent was removed under reduced pressure to afford crude **4** (1.11 kg, 100%) as a colorless oil. HPLC 97.5 area %, ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.78 (ddt, 1 H, J = 17.0, 10.1, 6.9 Hz), 5.10 (dd, 1 H, J = 17.0, 1.9 Hz), 5.05 (dd, 1 H, J = 10.1, 1.9 Hz), 2.44 (m, 2 H), 2.30 (m, 1 H), 1.64 (m, 1 H), 1.55 (m, 1 H), 1.30 (br s, 8 H), 0.90 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.2, 135.2, 116.9, 45.2, 36.1, 31.6, 31.5, 29.2, 27.1, 22.6, 14.0; MS (EI) *m*/*z* 184 (M^+), 143, 113; IR (neat) 2930, 1706, 1643, 917 cm^{-1}.

Preparation of (2*R*)-2-Propyloctanoic Acid 1. A 50-L glass-lined autoclave was flashed with N_2 gas. The reactor was charged with **4** (1105 g, 6.00 mol) and isopropyl alcohol (22 L), and then the mixture was stirred. The agitator was stopped, and the resulting solution was purged three times with N_2 gas at 0.5 MPa. To the mixture was added a suspension of 5% Pt/C (H_2O content: 44 wt %, 126 g) in isopropyl alcohol (5.4 L), after which the resulting suspension was purged four times with H_2 gas at 0.5 MPa and stirred at 30 °C for 3.5 h. The reaction mixture was filtered through a 30-L filter press (rinsed with 8.9 L of isopropyl alcohol); the filtrate was transferred to a 100-L stainless steel reactor and concentrated under reduced pressure. Then the residue was dissolved in a mixture of AcOEt (3.6 L) and *n*-hexane (17.9 L), and the product was reverse-extracted from the organic layer with aqueous NaOH (NaOH 481 g in 6 L of purified water). After the aqueous layer was separated, a mixture of AcOEt (3.6 L) and *n*-hexane (17.9 L) was added to the organic layer, and the the resulting mixture was acidified with concentrated HCl (1.1 L). The organic layer was washed three times with 5.4 L of purified water and brine (1.8 kg of NaCl in 5.4 L of water), dried over $MgSO_4$ (900 g), and filtered (rinsed with a mixture of AcOEt (630 mL) and *n*-hexane (3.2 L)). The filtrate was concentrated under reduced pressure, and the residue was purified by distillation to yield **1** (1045 g, 93.6%) as a colorless oil. GC 99.8 area %, 99.6% ee (The ee value was determined by HPLC [Chiralcel OJ-R; CH_3CN/H_2O = 3/2; flow rate, 1 mL/min; detection, 244 nm; retention time, 22.1 min (*S*) and 23.8 min (*R*).] After conversion into the corresponding phenacyl ester (phenacyl chloride, Et_3N/CH_2Cl_2).); $[\alpha]^{20}_D$ = −6.1° (*c* = 2.00, EtOH, 10 mL, 100 mm); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (m, 1 H), 1.55 (m, 2 H), 1.53−1.20 (m, 12 H), 0.94 (t, 3 H, J = 6.8 Hz), 0.90 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.9, 45.3, 34.4, 32.2, 31.7, 29.2, 27.3, 22.6, 20.6, 14.0 (2C); MS (EI) *m*/*z* 186 (M^+), 169, 157, 144, 115, 102; IR (neat) 2959, 2931, 1706, 1467 cm^{-1}; bp 120−121 °C at 133 Pa.

3-Allyl-[*N*-(2*S*)-(2-hexyl-4-pentenoyl)]-(1*S*)-(−)-10,2-camphorsultam 6. The regioisomer ratio was not determined. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.80 (m, 1 H), 5.40 (d, 1H, J = 15.8 Hz), 5.24 (d, 1H, J = 9.0 Hz), 5.08 (d, 1 H, J = 15.8 Hz), 5.00 (d, 1 H, J = 9.0 Hz), 4.08 (m, 1H), 3.75 (m, 1H), 3.42 (m, 1H), 3.24 (m, 1H), 2.78 (m, 1H), 2.38 (m, 2H), 2.03 (m, 2H), 1.88 (m, 2H), 1.20 (m, 1H), 1.26 (m, 10 H), 1.16 (s, 3 H), 0.96 (s, 3 H), 0.90 (t, 3 H, J = 7.2 Hz); MS (EI, Pos): *m*/*z* 421 (M^+), 350, 337, 174, 167; IR (KBr): 2959, 1700, 1327, 1217, 919 cm^{-1}. Anal. Calcd for $C_{24}H_{39}NO_3S$: C, 68.37; H, 9.32; N, 3.32; S, 7.60. Found: C, 68.39; H, 9.25; N, 3.33. S, 7.56.

Preparation of Disodium (2*S*)-2-(2-sulfonatoethyl)-octanoate 7. To a solution of (200 mg, 1.07 mmol) in DME (5.2 mL) was added aqueous Na_2SO_3 (1.5 mol/L, 1.4 mL, 2.1 mmol) and stirred for 22 h. The reaction mixture was concentrated under reduced pressure, and the residue was washed successively with DME and MeOH. The resulting powder was dissolved in MeOH, and insoluble materials were filtered, after which the filtrate was concentrated under reduced pressure to give **7** (61 mg, 20%) as a white powder. ^{1}H NMR (200 MHz, CD_3OD) δ 2.80 (t, 1H, J = 7.8 Hz), 2.19 (m, 1H), 1.80 (m, 2H), 1.53 (m, 2H), 1.28 (m, 10H), 0.88 (t, 3H, J = 6.4 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 185.4, 52.6, 34.4, 33.3, 32.7, 30.4, 28.7, 24.2, 23.5, 14.4 (methyne carbon was not detected); MS (FAB, Pos): *m*/*z* 333 (M + Na), 311 (M + 1); IR (KBr): 3511, 2925, 1572, 1415, 1225, 1182, 1053 cm^{-1}. HRMS (MALDI-TOF) *m*/*z* Found: 311.0914. Calcd for $C_{11}H_{20}Na_2O_5S$: (M+H) 311.0905.

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