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A Practical Synthesis of Optically Active (*R*)-2-Propyloctanoic Acid: Therapeutic Agent for Alzheimer's Disease

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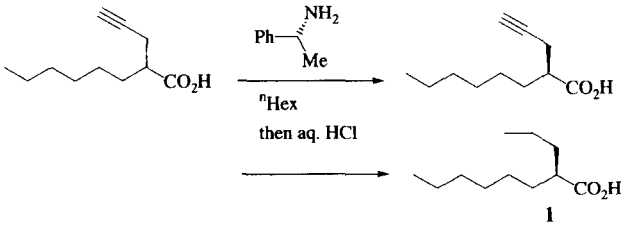
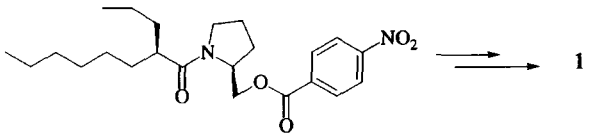
(*R*)-2-Propyloctanoic acid has been developed as a novel therapeutic agent for Alzheimer's disease. A large-scale synthesis of this candidate was achieved by using Oppolzer's camphorsultam as a chiral auxiliary under improved conditions. It was essential for the successful synthesis of this compound to utilize a new removal method for the chiral source with a combination of tetrabutylammonium hydroxide and hydrogen peroxide. The present process afforded the desired product in high yield with high optical purity.

Neurodegenerative diseases such as Alzheimer's disease are recognized as one of the most significant problems for human life in the coming aging society and the development of new therapeutic agents in this field is strongly demanded. Recent pharmacological research on neuronal death has suggested that the excessive response of reactive astrocytosis triggers neurodegenerative decidua.[1] Furthermore, a novel pathogenesis of these diseases has also been proposed by studying the induction of reactive astrocytosis.[2] Based on this hypothesis, a crucial agent possessing an activity to transform reactive astrocytes to normal would be the most effective for treating these diseases. By means of pharmacological screening systems, (*R*)-2-propyloctanoic acid **1** was found to improve the functional activities of such astrocytes; this agent was thus selected as a candidate for a clinical study.

A large-scale synthesis of this agent to produce an enantiomerically pure crystalline intermediate was troublesome because it included highly lipophilic portions consisting of only three different carbon chains. Although the first general synthesis was performed by the traditional optical resolution method of racemic 2-hexyl-4-pentynoic acid[3a] with (*R*)-(+)-α-methylbenzylamine, five recrystallization cycles were needed to obtain the (2*S*)-form with 90% ee (27% yield) (Eq. 1).[3b] The second general synthesis using (*L*)-prolinol as a chiral auxiliary[4] was more effective in enantioselectivity (96% ee, 20% overall yield) by simple recrystallization after protecting the hydroxy group as *p*-nitrobenzoate (Eq. 2).[5]



(1)



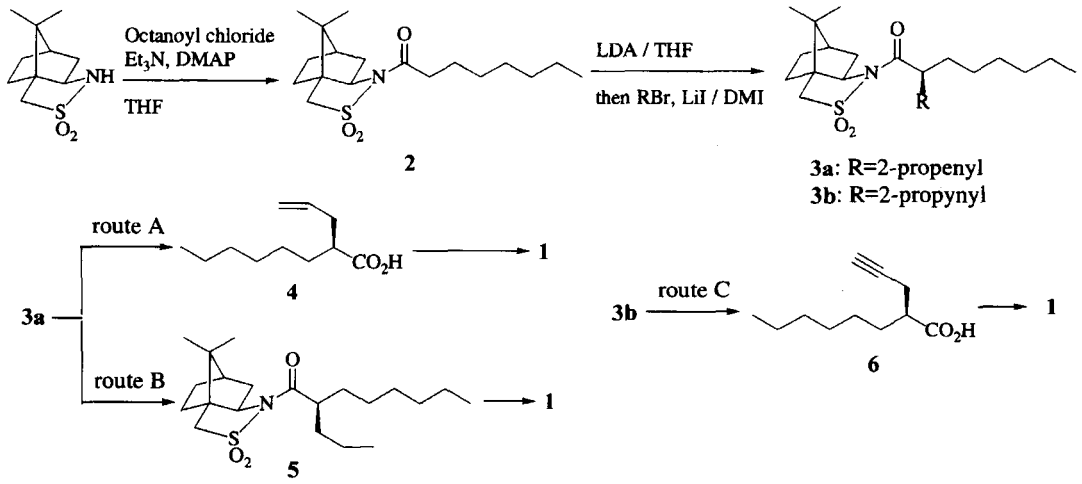
(2)

In other attempts by representative methods for asymmetric synthesis,[6] no crystalline products were obtained by use of oxazolidinones (4-isopropyl and benzyl),[7] and benzoxazinone derived from menthone for aldol reaction[8] was not effective for alkylation in this case. Furthermore, there was no opportunity to use pseudoephedrine[9] because of the narcotics control law in Japan, which inhibits its importation.

After further study, Oppolzer's camphorsultam has appeared to be a versatile chiral auxiliary for our synthesis with unexpected problems from the literature.[10] We wish to describe here in detail the third general synthesis of this attractive candidate toward the development of an industrial process. Three synthetic routes (A, B, and C) are shown in Scheme 1.

Acylation of (1*S*)-(−)-10,2-camphorsultam was achieved under mild basic conditions using Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) instead of the strong base (NaH) utilized in the general procedure,[11] and gave the pure **2** without purification in quantitative yield. Asymmetric alkylation of **2** was performed under conditions which were only slightly different from the previous method:[10a] in situ activation of the electrophile by transforming the bromide into the corresponding iodide with LiI, and replacement of the carcinogenic cosolvent, hexamethylphosphoramide, with 1,3-dimethyl-2-imidazolidinone (DMI). In the case of routes A and B, the common intermediate **2** was treated with allyl bromide to lead to **3a** in 71.7% yield with >99% de. after two recrystallizations from MeOH. The absolute configuration of the newly created stereocenter was determined by X-ray crystallographic analysis (Fig. 1).[12]

The compound **3a** was hydrolyzed to carboxylic acid **4**,



Scheme 1.

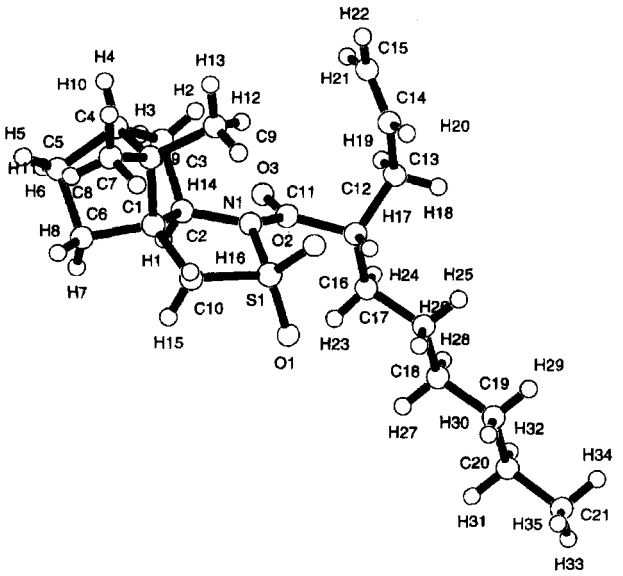
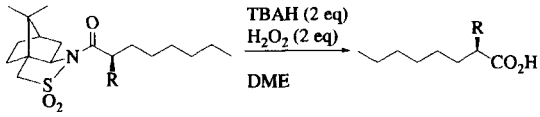


Fig. 1. The X-ray crystal structure of **3a**.

Table 1. Removal of Camphorsultam with TBAH and H_2O_2



Entry	Substrate	Temp/°C	Time/min	Yiled/%[a]
1	**5**	0	15	50
2	**5**	−20	50	59[b]
3	**3a**	0	60	75
4	**3a**	0	60	79[c]
5	**3a**	−10	120	82[c]
6	**3a**	r.t.	5 (h)	82[d]
7	**3a**	r.t.	5 (h)	79[c,d]
8	**3b**	−10	10	90[c]

a) Isolated yield. b) Dry-TBAH was used. c) In the presence of 2-methyl-2-butene (3 equiv). d) aq KOH was used as the base instead of aq TBAH.

followed by hydrogenation to produce the desired product **1** in route A, whereas hydrogenation and hydrolysis sequences (**3a**→**5**→**1**) were involved in route B. In the case of route C, 2-propynyl bromide was used as an electrophile at the alkylation step and **3b** was obtained in 83% yield with 97% de after chromatography. **3b** was hydrolyzed to carboxylic acid **6**, which was hydrogenated to afford **1**. In a preliminary communication, we reported on a new method for the removal of camphorsultam with a combination of tetrabutylammmonium hydroxide (TBAH) and H_2O_2, and the results for substrates (**3a**, **3b**, and **5**) are summarized in Table 1.[13]

The saturated substrate **5** was hydrolyzed to **1** in moderate yield (Entry 1). In this case, the starting material completely disappeared in 15 min, however, the competitive N–S bond cleavage was predominantly observed to afford the corresponding sulfonic acid. Because the dry-reagent[14] (high concentration in water) did not freeze even at −20 °C, the reaction would proceed more chemo-selectively at lower temperature than in Entry 1 to afford **1** in slightly good yield (Entry 2). The hydrolysis of allylated substrate **3a** gave the product **4** in 75% yield (Entry 3). In the same way as above, N–S bond cleavage was found to afford the sulfonic acid **7** as a main byproduct under the usual conditions (aq LiOH or KOH and H_2O_2). However, in our system, the intramolecular epoxidation of the intermediate, peroxycarboxylic acid, occurred as a major side reaction to yield the γ-lactone **8** (Fig. 2).[15]

It was difficult to completely suppress the troublesome reaction, though the addition of 2-methyl-2-butene was effective to some degree (Entries 4 and 5). Although potassium hydrogen peroxide was equally effective for the hydrolysis of compound **3a** (Entry 6), no improvement was observed in the same way as the present conditions (Entry 7). In addition, although the reason is not clear, the reaction was incomplete in a scaled-up synthesis by use of aq KOH as the base.

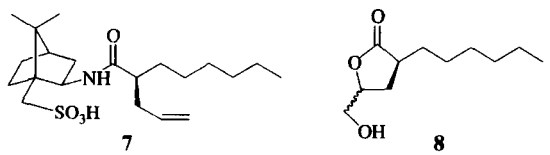
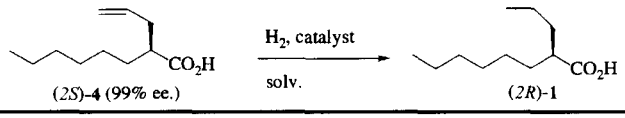


Fig. 2.

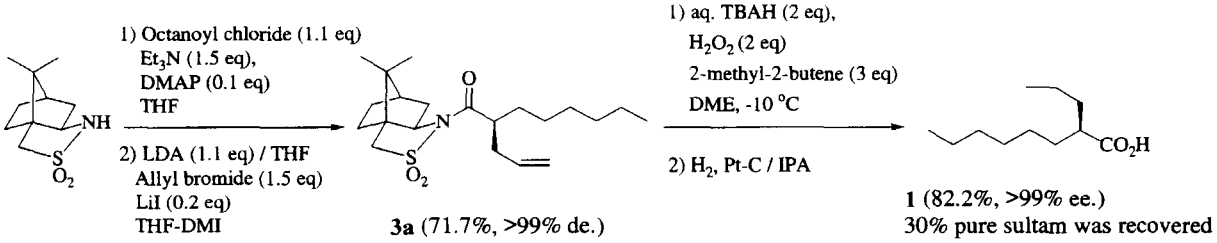
Table 2. Various Conditions for Hydrogenation of Carboxylic Acid **4**



(2S)-4 (99% ee.) (2R)-1

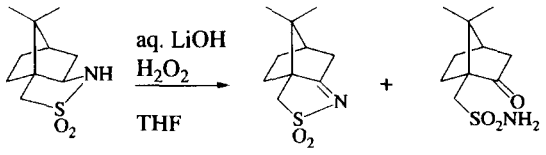
Entry	Pressure / atm	Catalyst	Solv.	Time/h	Yield/%[a]	ee./%[b]
1	1	10% Pd–C (10 wt%)	DME	1	100	93
2	1	10% Pd–C (10 wt%)	MeOH EtOAc	1	100	95
3	1	$RhCl(PPh_3)_3$ (3 mol%)	DME	54	78	98
4	1	5% Rh–C (10 wt%)	MeOH EtOAc	1.5	96	96
5	1	10% $Pd(OH)_2$ (3 wt%)	IPA[c]	2	73[d] (in 2 steps)	99
6	10	5% Pt–C (5 wt%)	IPA	1.5	99	99
7	5	5% Pt–C (5 wt%)	IPA	2	83[d] (in 2 steps)	99
8	10	5% Pt–C (5 wt%)	IPA	1.5	78[e] (in 2 steps)	97

a) Isolated yield. b) Determined by HPLC analysis after converting the product into the corresponding phenacyl ester (vide infra). c) 2-Propanol. d) Crude starting material was used; Hydrolysis was done with aq TBAH ad H_2O_2. e) Crude starting material was used; Hydrolysis was done with aq KOH and H_2O_2.



Scheme 2.

This may have been caused by an instability of the reactive species at room temperature; for success it is essential to use aq TBAH at low temperature. The propargyl derivative **3b** was found to be more reactive than **5** and **3a** (Entry 8). These tendencies would be explained by a steric hindrance at the α-position of the carbonyl group ("propyl > allyl > propargyl). Based on these results, route A was selected for the practical synthesis rather than routes B and C. Route B showed a lower yield of the hydrolysis step and route C could not afford the crystalline intermediate **3b** without chromatography, which was not suitable for a large-scale synthesis. Asymmetric syntheses of the optically active carboxylic acids using camphorsultam are widely utilized in organic synthesis and the chiral auxiliary is easily recycled. Disappointingly, all of our trials for recycling pure sultam resulted in low yield (<30%) under every condition used (aq LiOH, aq KOH or aq TBAH and H_2O_2). During the course of hydrolysis, one intermediate (not isolated) was observed by TLC analysis which was gradually changed into the desired camphorsultam and other products. This phenomenon was realized by treating camphorsultam with excess aq LiOH and H_2O_2 in THF at room temperature. The reaction provided imine **9** (11%) and sulfonamide **10** (12%) (Eq. 3).



9 **10** (3)

Accordingly, the formed intermediate (probably N-oxide) should be converted into imine **9** via dehydration and then hydrolyzed to sulfonamide **10**. We concluded that a high level of recycling of the chiral auxiliary was impossible under these hydrogen peroxide mediated hydrolyses. The hydrogenation process was investigated to avoid the racemization through olefin migration. These results are shown in Table 2.

Minor racemization was observed using palladium on carbon (Entries 1 and 2) and rhodium catalysts (Entries 3 and 4), whereas Pearlman's catalyst[16] and platinum on carbon showed successful results without any loss of the ee value, compared to the starting material (Entries 5, 6, and 7). The hydrogenation of the crude carboxylic acid **4**, after hydrolysis was accomplished with aq KOH as the base, led to a slight decrease in the optical purity (Entry 8). This probably occurred in the course of removal of the chiral auxiliary. The final conditions for the third general synthesis are summa-

rized in Scheme 2. The highly lipophilic carboxylic acid was obtained in high yield (59% overall) with an extremely high optical purity.

In conclusion, we have described here the development of the third general synthesis of a valuable therapeutic agent for Alzheimer's disease. The present process consists of simple sequences and easy purifications, and therefore it would be utilized for industrial applications. However, the unsatisfactory result was realized for recycling the chiral auxiliary, which directly affects the cost. Further studies on the development of a new chiral auxiliary for the asymmetric synthesis will be reported in due course.

Experimental

General. Analytical TLC was performed on E. Merck precoated (0.25 mm) silica-gel 60 F_{254} plates. Column chromatography was conducted using silica-gel 60 (E. Merck 9385, 230—400 mesh, 7734, 70—230 mesh) or silica gel 60 extra pure (E. Merck 107754, 70—230 mesh). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer or JASCO VALOR: III spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-DX303HF mass spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-300 (300 MHz) or Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane (δ=0). Microanalysis and X-ray crystallographic structure analysis were accomplished at Minase Research Institute, Ono Pharmaceutical Co., Ltd.

Preparation of *N*-Octanoyl-(1*S*)-(−)-10,2-camphorsultam 2. To a solution of (1*S*)-(−)-10,2-camphorsultam (15.0 g, 69.7 mmol) in THF (100 ml) was added Et_3N (14.6 ml, 105 mmol) and DMAP (0.85 g, 7.0 mmol), then the solution being cooled to 0 °C. To the mixture was added dropwise a solution of octanoyl chloride (12.5 g, 76.8 mmol) in THF (20 ml) and the mixture was stirred for 1 h. The reaction was quenched with H_2O (14 ml) and THF was removed under reduced pressure. The residue was diluted with EtOAc, washed sequentially with aq 2 M (1 M=1 mol dm^{-3}) HCl, H_2O, brine, aq 1 M NaOH, H_2O, and brine, dried over $MgSO_4$, and concentrated to afford **2** (24.0 g, 100%) as a pale yellow oil. The crude product was used in the next step without purification. Analytical sample was obtained after purification by silica-gel chromatography (EtOAc : Hex=1 : 9, 98.6% yield). ^{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); ^{13}C NMR (50 MHz, $CDCl_3$) δ=172.10, 65.23, 52.98, 48.36, 47.74, 44.66, 38.53, 35.51, 32.84, 31.63, 28.92 (2C), 26.45, 24.45, 22.55, 20.81, 19.88, 14.04; MS (FAB, Pos.) *m/z* 342 (M+1), 214, 127; IR (neat) 2957, 2930, 2857, 1698, 1458, 1414, 1375, 1331, 1271, 1237, 1217, 1165, 1134, 1109, 1065, 1040, 988 cm^{-1}. Found: C, 63.47; H, 9.21; N, 4.03; S, 9.31%. Calcd for $C_{18}H_{31}NO_3S$: C, 63.47; H, 9.21; N, 4.10; S, 9.39%.

Preparation of *N*-(2*S*)-(2-Hexyl-4-pentenoyl)-(1*S*)-(−)-10,2-camphorsultam 3a. To a solution of diisopropylamine (20.0 ml, 0.15 mol) in THF (40 ml) was added dropwise ^{n}BuLi (1.6 M in Hex, 94 ml, 0.15 mol) at 0 °C and the resulting LDA solution was stirred for 0.5 h. A solution of **2** (crude 52.2 g, 0.14 mol) in THF (80 ml) was cooled to −78 °C and the prepared LDA solution was added dropwise slowly. The resulting mixture was stirred for 0.5 h, and then a solution of allyl bromide (18 ml, 0.21 mol) and LiI (3.7 g, 28 mmol) in THF (15 ml)–DMI (23 ml) was added dropwise to the mixture. The mixture was stirred at −78 °C for 1 h, at −20 °C for 4 h, and at 0 °C for 1 h. After the reaction was quenched with H_2O, THF was removed under reduced pressure. The products were extracted with EtOAc and Hex (1 : 1), washed with aq 2 M-HCl, H_2O, aq sat.-$NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from MeOH to afford **3a** (37.4 g, 71.7% in 2 steps, >99% de.) as colorless crystals. ^{1}H NMR (200 MHz, $CDCl_3$) δ=5.80 (ddt, 1 H, J=15.6, 9.8, 7.2 Hz), 5.05 (ddt, 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ=175.10, 135.09, 117.09, 65.28, 53.23, 48.07, 47.65, 44.97, 44.61, 38.50, 38.02, 32.85, 31.60, 30.85, 29.32, 27.09, 26.41, 22.55, 20.81, 19.88, 14.02; MS (EI) *m/z* 381 (M$^+$), 310, 297; IR (KBr) 3075, 2994, 2857, 1682, 1640, 1471, 1445, 1418, 1401, 1327, 1291, 1273, 1252, 1238, 1217, 1167, 1136, 1117, 1069, 1042, 992, 947, 909 cm^{-1}. Found: C, 66.31; H, 9.25; N, 3.50; S, 8.56%. Calcd for $C_{21}H_{35}NO_3S$: C, 66.10; H, 9.25; N, 3.67; S, 8.40%. Mp=94—95 °C; HPLC: Chiralcel OJ-R; CH_3CN/H_2O=55/45; flow rate, 1 ml min^{-1}; detection, 210 nm; retention time, 10.7 min (*R*) and 12.4 min (*S*).

Preparation of *N*-(2*S*)-(2-Hexyl-4-pentynoyl)-(1*S*)-(−)-10,2-camphorsultam 3b. To a solution of diisopropylamine (6.7 ml, 51 mmol) in THF (13 ml) was added dropwise ^{n}BuLi (1.6 M in Hex, 32 ml, 51 mmol) at 0 °C and the mixture was stirred for 0.5 h. To a solution of **2** (crude 16.0 g, 46.4 mmol) in THF (27 ml) was added dropwise the prepared LDA solution at −78 °C over 0.5 h. The resulting mixture was stirred for 0.5 h and a solution of 2-propynyl bromide (5.2 ml, 69 mmol) and LiI (1.24 g, 9.26 mmol) in THF (5 ml)–DMI (7.6 ml) was added to the mixture dropwise over 10 min. The mixture was stirred at −78 °C for 1.5 h and at −30 °C for 2 h. After the reaction was quenched with H_2O (1 ml), THF was removed under reduced pressure. The products were extracted with EtOAc and Hex (1 : 1), washed sequentially with aq sat.-NH_4Cl, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel chromatography (EtOAc : Hex=5 : 95 to 1 : 9) to afford **3b** (15.0 g, 85.3%, 97% de.) as a slightly brown powder. The product was further purified by recystallization from IPA and H_2O (5 : 1) to afford **3b** (50%, 99% de.) as colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.93 (dd, 1 H, J=7.1, 5.4 Hz), 3.53 (d, 1 H, J=13.9 Hz), 3.45 (d, 1 H, J=13.9 Hz), 3.21 (m, 1 H), 2.55 (m, 2 H), 2.11 (m, 2H), 1.99 (t, 1 H, J=2.6 Hz), 1.87 (m, 4H), 1.57—1.23 (m, 11 H), 1.19 (s, 3 H), 0.98 (s, 3 H), 0.87 (t, 3 H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ=173.61, 80.61, 70.56, 65.23, 53.18, 48.30, 47.78, 44.59, 44.19, 38.44, 32.82, 31.58, 30.31, 29.20, 26.83, 26.49, 22.55, 22.43, 20.79, 19.90, 14.04; MS (FAB) *m/z* 380 (M+1), 182, 165, 154, 135; IR (KBr) 3318, 2970, 2945, 2850, 1690, 1470, 1458, 1433, 1418, 1397, 1323, 1280, 1270, 1238, 1220, 1165, 1134, 1110, 1061, 1040, 947 cm^{-1}. Found: C, 66.52; H, 8.75; N, 3.65; S, 8.61%. Calcd for $C_{21}H_{33}NO_3S$: C, 66.45; H, 8.76; N, 3.69; S, 8.45%. Mp=49—50 °C; HPLC: Chiralcel OJ-R; 0.5 M $NaClO_4/CH_3CN$=1/1; flow rate, 1 ml min^{-1}; detection, 210 nm; retention time, 12.8 min (*R*) and 15.0 min (*S*).

Preparation of (2*S*)-2-Hexyl-4-pentenoic Acid 4.[17] To a solution of **3a** (10.0 g, 26.2 mmol) in DME (100 ml) was added 2-methyl-2-butene (8.3 ml, 78 mmol) and aq H_2O_2 (30 wt%, 5.4 ml, 53 mmol) at −10 °C. To the resulting mixture was added dropwise aq TBAH (40 wt%, 34 ml, 52 mmol) over 8 min. After stirring for 2 h, the reaction was quenched with aq sat.-Na_2SO_3 (ca. 1.5 M, 35 ml), and then the mixture was warmed to room temperature and

stirred for 1 h. The mixture was cooled to 0 °C, acidified with aq 0.5 M-$(CO_2H)_2$ (180 ml), and extracted twice with EtOAc and $^iPr_2O$ (1 : 4). The combined organic layers were washed sequentially with aq 0.5 M-$(CO_2H)_2$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vaccuo. To the residue (9.2 g) was added $^iPr_2O$ and Hex (1 : 2, 30 ml) and the insoluble powder was filtered off. The filter cake (3.23 g) was recrystallized from EtOH (4 ml) and gave a recycled sultam (1.71 g, 30.4%) as a white powder. The filtrate was concentrated to afford crude **4** (5.72 g) as a colorless oil. The crude product was used in the next step without purification. Analytical sample was obtained after purification by silica-gel chromatography (60 extra pure, EtOAc : Hex=1 : 9, 82.2%). ^{1}H NMR (300 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=182.20, 135.23, 116.91, 45.23, 36.11, 31.63, 31.51, 29.16, 27.14, 22.57, 14.02; MS (EI) m/z 184 (M^+), 143, 113; IR (neat) 2930, 2859, 1709, 1644, 1460, 1420, 1289, 1250, 1210, 992, 916 cm^{-1}. Found: C, 71.56; H, 11.14%. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94%. $[\alpha]_D^{20}=-11.1°$ (c=1.00, EtOH); GC: cyclodex β; J & W; column temp, 140 °C; injector temp, 220 °C; retention time, 27.6 min (R) and 28.5 min (S).

(3*S*)-Hexyl-5-hydroxymethyl-4,5-dihydro-2(3*H*)-furanone 8. A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ=4.61 (m, 1 H), 3.89 (dd, 1 H, J=13.5, 4.5 Hz), 3.66 (dd, 1 H, J=13.5, 5.4 Hz), 2.72 (m, 1 H), 2.33 (ddd, 1 H, J=14.4, 9.0, 5.4 Hz), 2.02 (dt, 1 H, J=14.4, 9.0 Hz), 1.86 (m, 2 H), 1.53—1.23 (m, 8 H), 0.91 (t, 3H, J=6.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ=179.83, 78.57, 64.54, 39.59, 31.58, 31.23, 29.56, 28.96, 22.52, 14.00; MS (FAB, Pos.) m/z 201 (M^+), 137, 123, 109; IR (KBr) 3380, 2928, 2858, 1751, 1469, 1206, 1188, 1047 cm^{-1}. The stereochemistry of 5-position was not determined.

Preparation of (*R*)-2-Propyloctanoic Acid 1 from 4. To a flask containing Pt–C (250 mg) was added a solution of crude **4** (5.72 g) in ^{i}PrOH (50 ml). The vessel was purged three times with H_2 gas and the mixture was hydrogenated under 5 atm for 2 h. The catalyst was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by distillation to afford **1** (2.70 g, 55.3% in 2 steps) as a colorless oil. Using silica-gel chromatography (60 extra pure, EtOAc : Hex=5 : 95) for purification furnished **1** (82.5% in 2 steps). ^{1}H NMR (300 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=182.93, 45.34, 34.35, 32.18, 31.65, 29.21, 27.32, 22.59, 20.55, 14.02, 13.97; MS (EI) m/z 186 (M^+), 169, 157, 144, 115, 102; IR (neat) 2959, 2932, 1707, 1470, 1420, 1379, 1289, 1215, 943 cm^{-1}. Found: C, 70.90; H, 12.01%. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%. Bp 120—121 °C at 1 mmHg (1 mmHg=133.322 Pa); $[a]_D^{20}=-6.5°$ (c=2.00, EtOH) for 99% ee. The ee.value was determined by HPLC [Chiralcel OJ-R; CH_3CN/H_2O=3/2; flow rate, 1 ml min^{-1}; detection, 244 nm; retention time, 22.1 min (S) and 23.8 min (R).] after converted into the corresponding phenacyl ester (phenacyl chloride, Et_3N/CH_2Cl_2).

Preparation of *N*-(2*S*)-2-Propyloctanoyl-(1*S*)-(−)-10,2-camphorsultam 5. To a flask containing 10 wt% Pd–C (60.7 wet%, 500 mg) was added a solution of **3a** (99% de. 2.00 g, 5.24 mmol) in EtOAc (7 ml)–MeOH (7 ml). The reaction vessel was purged three times with H_2 gas and the mixture was hydrogenated for 1 h. The catalyst was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was azeotropically concentrated with EtOAc and toluene (1 : 3) and the crude product was purified by silica-gel chromatography (EtOAc : Hex=1 : 9) to afford **5** (2.01 g, 100%, 99% de.) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ=3.90 (t, 1 H, J=6.3 Hz), 3.51 (d, 1 H, J=13.2 Hz), 3.43 (d, 1 H, J=13.2 Hz) 3.01 (m, 1 H), 2.07 (m, 2 H), 1.88 (m, 3 H), 1.77—1.19 (m, 16 H), 1.16 (s, 3 H), 0.97 (s, 3 H), 0.89 (t, 3 H, J=6.8 Hz), 0.83 (t, 3H, J=6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ=176.60, 65.30, 53.27, 48.07, 47.68, 45.45, 44.65, 38.66, 35.89, 32.89, 31.63, 31.27, 29.41, 27.21, 26.43, 22.59, 20.73, 20.08, 19.90, 14.11, 14.06; MS (FAB, Pos.) m/z 384 (M+1), 214, 186, 169, 154, 135; IR (KBr) 2959, 2861, 1684, 1468, 1458, 1416, 1401, 1375, 1327, 1281, 1278, 1250, 1237, 1165, 1136, 1113, 1062, 1040 cm^{-1}. Found: C, 65.98; H, 10.01; N, 3.59; S, 8.58%. Calcd for $C_{21}H_{37}NO_3S$: C, 65.76; H, 9.72; N, 3.65; S, 8.36%. HPLC: Chiralcel OJ-R; 0.5 M $NaClO_4/CH_3CN$=1/1; flow rate, 1 ml min^{-1}; detection, 210 nm; retention time, 19.3 min (S) and 21.5 min (R).

Preparation of (*R*)-2-Propyloctanoic Acid 1 from 5. Preparation of Dry-TBAH: Commercially available aq TBAH (40 wt%, 1.4 ml, 2.1 mmol) was azeotropically concentrated three times with DME and toluene (1 : 1, 4 ml). The residue was used in hydrolysis without purification.

To a solution of **5** (99% de. 400 mg, 1.04 mmol) in THF (2 ml) was added aq H_2O_2 (30 wt%, 0.21 ml) at −20 °C. To the mixture was added dropwise a solution of prepared dry-TBAH in THF (2 ml) and the resulting solution was stirred for 50 min. After the reaction was quenched with aq sat.-Na_2SO_3 (ca. 1.5 M, 1.4 ml), the mixture was warmed to room temperature and stirred for 0.5 h. The mixture was concentrated, acidified with aq 1 M-HCl (4 ml), and extracted twice with EtOAc and $^iPr_2O$ (1 : 4). The combined organic layers were washed sequentially with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. To the residue was added $^iPr_2O$ and the insoluble powder was filtered off. The filtrate was concentrated and the residue was purified by silica-gel chromatography (60 extra pure, EtOAc : Hex=5 : 95) to afford **1** (115 mg, 59.3%, 99% ee.) as a colorless oil.

Preparation of (*S*)-2-Hexyl-4-pentynoic Acid 6. To a solution of **3b** (97% de. 400 mg, 1.05 mmol) in DME (4 ml) was added 2-methyl-2-butene (0.33 ml, 3.1 mmol) and aq H_2O_2 (30 wt%, 0.22 ml, 2.2 mmol) at −10 °C. To the resulting mixture was added dropwise aq TBAH (40 wt%, 1.4 ml, 2.1 mmol) over 3 min. After stirring for 10 min, the reaction was quenched with aq sat.-Na_2SO_3 (ca. 1.5 M, 2.3 ml); the mixture was then warmed to room temperature and stirred for 0.5 h. The mixture was concentrated, and then to the residue was added H_2O (4 ml), and the resulting aqueous phase was reverse extracted twice with EtOAc and $^iPr_2O$ (1 : 4). The aqueous layer was acidified with aq 2 M-HCl (2 ml) and the products were extracted twice with $^iPr_2O$. The combined organic layers were washed with H_2O and then brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica-gel chromatography (60 extra pure, EtOAc : Hex=1 : 9) to afford **6** (172 mg, 89.6%, 97% ee.) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.62 (m, 1 H), 2.54 (ddd, 1 H, J=16.6, 6.8, 2.6 Hz), 2.43 (ddd, 1 H, J=16.5, 6.7, 2.6 Hz), 2.03 (t, 1 H, J=2.6 Hz), 1.70 (m, 2H), 1.30 (m, 8 H), 0.90 (t, 3 H, J=6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ=181.00, 81.19, 69.94, 44.30, 31.56, 30.98, 29.05, 26.74, 22.55, 20.73, 14.00; MS (FAB, Pos.) m/z 365 (2M+1), 205 (M+Na), 183 (M+1), 165, 154; IR (neat) 3312, 2930, 1717, 1559, 1541, 1509, 1458, 1289, 938 cm^{-1}. Found: C, 72.16; H, 9.78%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%. $[a]_D^{20}=-18.2°$ (c=2.00, EtOH) for 99% ee; GC: cyclodex β; J & W; column temp, 140 °C; injector temp, 220 °C; retention time, 25.6 min (R) and 26.5 min (S).

The product contained a small amount of by-product (methyl ketone) which was easily formed by hydration of the terminal alkyne with moisture.

Preparation of (*R*)-2-Propyloctanoic Acid 1 from 6. To a flask containing Pt–C (10 mg) was added a solution of **6** (98% de. 200 mg, 1.10 mmol) in ^{i}PrOH (2 ml). The vessel was purged three times with H_2 gas and the mixture was hydrogenated under 5 atm for 2.5 h. The catalyst was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by silica-gel chromatography (60 extra pure, EtOAc : Hex=1 : 9) to afford **1** (193 mg, 94.6%, 98% ee.).

Degradation Experiment of (1*S*)-(−)-10,2-Camphorsultam. To a solution of (1*S*)-(−)-10,2-camphorsultam (100 mg, 0.46 mmol) in THF (6.5 ml) and H_2O (1.8 ml) was added aq H_2O_2 (30 wt%, 0.19 ml, 1.9 mmol), followed by aq 2 M-LiOH (0.46 ml, 0.92 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 d. After cooling to 0 °C, the reaction was quenched with aq Na_2SO_3 (ca. 1.5 M, 1.3 ml) and stirred for 20 min. The mixture was concentrated and the residue was diluted with H_2O (10 ml). The products were extracted with EtOAc and the extract was washed with H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel chromatography (the crude products were dissolved in THF-CH_2Cl_2 at charging, EtOAc : Hex=3 : 7 to 6 : 4) to afford **9** (11 mg, 11%) as a white powder and **10** (13 mg, 12%) as a white powder.

(7*S*)-(−)-10,10-Dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]dec-3-ene-5,5-dioxide 9. ^{1}H NMR (200 MHz, $CDCl_3$) δ=3.19 (d, 1H, J=13.4 Hz), 2.97 (d, 1H, J=13.4 Hz), 2.77 (ddd, 1H, J=19.4, 4.2, 1.8 Hz), 2.38 (d, 1H, J=19.4 Hz), 2.26, (t, 1H, J=4.2 Hz), 2.10—2.05 (m, 2H), 1.78 (t, 1H, J=9.2 Hz), 1.47 (t, 1H, J=9.2 Hz), 1.09 (s, 3H), 9.87 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=195.32, 64.44, 49.40, 47.92, 44.61, 35.87, 28.38, 26.59, 19.41, 18.95; MS (FAB, Pos.) *m/z* 214 (M+1), 154, 136; IR (KBr) 3006, 2968, 2894, 1645, 1418, 1324, 1217, 1173, 1135, 809 cm^{-1}.

(1*S*)-(+)-10-Camphorsulfonamide 10. ^{1}H NMR (200 MHz, $CDCl_3$) δ=5.43 (br s, 2H), 3.50 (d, 1H, J=15.2 Hz), 3.13 (d, 1H, J=15.2 Hz), 2.43 (ddd, 1H, J=18.4, 4.8, 2.6 Hz), 2.18—1.98 (m, 4H), 1.99 (d, 1H, J=18.4 Hz), 1.47 (m, 1H), 1.01 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=217.44, 59.37, 54.04, 49.10, 43.08, 42.83, 27.05, 26.81, 19.97, 19.37; MS (FAB, Pos.) *m/z* 232 (M+1), 215, 185; IR (KBr) 3305, 3229, 3126, 2965, 1732, 1338, 1155, 899 cm^{-1}.

Preparation of 2-[(2*S*)-2-Hexyl-4-pentenoylamino]-7,7-dimethylbicyclo[2.2.1]-heptylmethanesulfonic Acid 7. To a solution of **3a** (200 mg, 0.52 mmol) in DME (4.2 ml) was added aq TBAH (40 wt%, 0.7 ml, 1 mmol) and stirred for 40 min. To the mixture was added aq 1 M-HCl (2 ml) and concentrated. The product was extracted with EtOAc and the extract was washed sequentially with aq 1 M-HCl, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel chromatography (MeOH : $CHCl_3$=5 : 95 to 1 : 9) to afford **7** (55 mg, 26%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ=6.90 (br s, 1 H), 5.73 (m, 1 H), 5.08 (d, 1 H, J=13.5 Hz), 5.03 (d, 1 H, J=9.0 Hz), 4.60 (m, 1 H), 3.04 (d, 1 H, J=15.0 Hz), 2.80 (d, 1 H, J=15.0 Hz), 2.33 (m, 1 H), 2.20 (m, 1 H), 1.70 (m, 3 H), 1.43 (m, 3 H), 1.29 (s, 8 H), 0.93 (s, 3 H), 0.88 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=175.72, 135.56, 117.02, 53.85, 49.69, 49.58, 49.32, 48.32, 44.30, 39.51, 36.37, 31.84, 31.60, 31.11, 29.27, 27.19, 26.78, 22.72, 20.77, 20.55, 14.07; MS (EI) *m/z* 399 (M$^+$), 318, 235, 184, 152; IR (KBr) 3457, 2931, 1640, 1542, 1175, 1050 cm^{-1}; HRMS Found : *m/z* 399.2437. Calcd for $C_{21}H_{37}NO_4S$: (M$^+$), 399.2444.

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