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A New Process for Synthesis of the Astrocyte Activation Suppressor, ONO-2506

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Abstract:

Development of a new process for the synthesis of ONO-2506, an agent that suppresses astrocyte activation, is described. Previous processes that involved asymmetric synthesis with a chiral auxiliary were unsatisfactory from a cost perspective because the relatively expensive chiral auxiliaries were not recyclable. To develop a more cost-effective process, we designed a new process starting from chiral 1,2-epoxyoctane, which was readily prepared catalytically by Prof. Jacobsen's method. The new five-step process was developed with the establishment of a modified cyanation condition, in which lithium cyanide was prepared in situ by combining lithium hydroxide with acetone cyanohydrin. Then the mechanisms for racemization and the side reaction until the cyanation step were clarified, and these problems were solved. The main features of this process are crystallization of the amide intermediate, since its optical purity is readily improved by recrystallization up to 100% ee in addition to formation of the dibenzylamine salt with ONO-2506 that leads to improved chemical and optical purity of the final product. The shorter synthesis, including a one-pot reaction was ruled out because of the hazardous nature of the Katriztky hydrolysis conditions for the conversion of nitrile to amide in the presence of sodium cyanide.

Introduction

ONO-2506 **1** delays the expansion of cerebral infarction by modulating the activation of astrocytes through inhibition of *S*-100β synthesis. It has been developed as a novel therapeutic agent for stroke, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.[1] On asymmetric synthesis of the active pharmaceutical ingredient, purification by recrystallization was found to be necessary to remove the undesired stereoisomer prior to large-scale production. Since target agent **1** had a highly lipophilic component, however, it proved difficult to synthesize via crystalline intermediates. We recently described an asymmetric synthesis for this candidate using Oppolzer's camphorsultam[2] or [((1*S*)-1-phenylethyl)amino]phenol as the chiral auxilially.[3] Although these methods were accomplished successfully with good crystalline intermediates, the former chiral auxiliary was not economical to use (being relatively expensive and not recyclable) and the latter method resulted in moderate diastereoselectivity. Recently, another group reported a diastereoselective synthesis of **1** with moderate optical purity (89% ee) through photodeconjugation of α,β-unsaturated esters derived from diacetone-D-glucose.[4] To find a more cost-effective process for the synthesis of **1** with a high optical and chemical purity, we designed a different route of asymmetric synthesis using commercially available (*R*)-1,2-epoxyoctane as the starting material (Scheme 1).

This early stage synthesis had several areas for improvement, for example, inclusion of extra steps (benzoylation and debenzoylation), the use of undesirable lithium hydride at the cyanation step, the nonreproducible hydrolysis condition of nitrile **6**, and an optical purity outside the specifications required (not less than 99.0% ee) for the final target **1**. We report here an improved reproducible process that is amenable to scale-up.

Results and Discussion

Development of an Improved Process for 1. The early stage synthesis started from commercially available (*R*)-1,2-epoxyoctane, the optical purity of which (93.5% ee) was insufficient for our scheme. Prof. Jacobsen's hydrolytic kinetic resolution of racemic 1,2-epoxyoctane was highly suitable for this purpose.[5] By use of this procedure, (*R*)-1,2-epoxyoctane was obtained with a high enantiomeric purity (?99.0% ee). Furthermore, after purification by distillation, the residue could be used directly for one more cycle to give (*R*)-1,2-epoxyoctane with an excellent optical purity (98.5% ee). This result led to the omission of the extra steps (benzoylation and deacylation) necessary for improving the optical purity of alcohol **2**. In the next step, the tosylate **4** and mesylate **5**[6] (prepared from **2** purified by distillation) were investigated for selecting the better leaving group for nitrile substitution. The crude products **4** and **5** underwent displacement reactions separately with lithium cyanide

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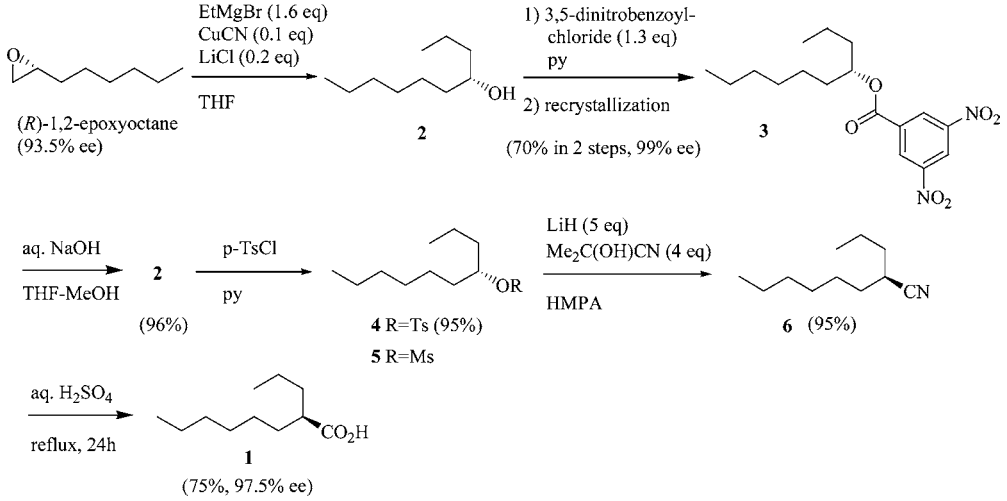
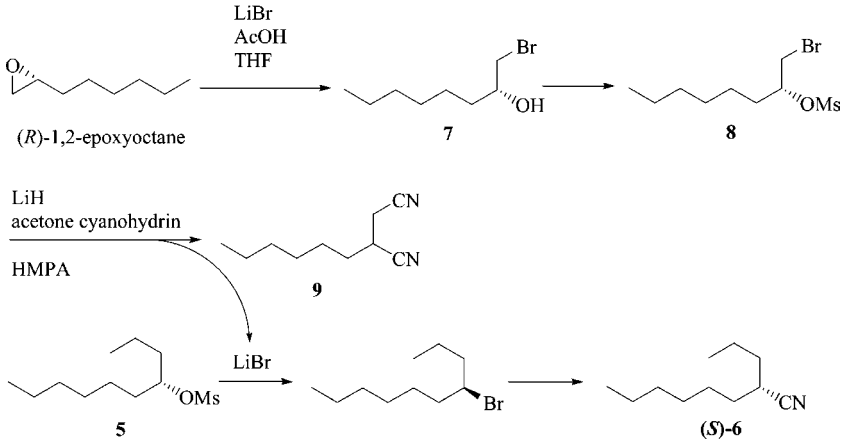
Scheme 1. **Early stage synthesis of 1**



Scheme 2. **Proposed racemization mechanism of 6**



(prepared from lithium hydride and acetone cyanohydrin) to obtain nitrile **6**, but a decrease in optical purity was recognized (85.4 and 82.7% ee, respectively).

Alcohol **2** (99.4% ee) purified by dinitrobenzoate crystallization in Scheme 1 was readily transformed to nitrile **6** without loss of optical purity (99.0% ee) through mesylation under the same conditions as those above. These results indicated that a certain impurity in alcohol **2** (purified by distillation) affected the epimerization. We assumed that the bromohydrin **7** was formed from (*R*)-1,2-epoxyoctane by magnesium bromide, which was generated by equilibrium between the cuprate preparation ($2Et_2CuMgBr \leftrightarrow MgBr_2 + (Et_2Cu)_2Mg$) (Scheme 2).[7]

After this, lithium bromide was generated under the course of the transformation between bromohydrin **7** to dinitrile **9** through mesylate **8**. This lithium bromide was reacted with the desired mesylate **5** and induced the antipode of nitrile **6**. To confirm this speculation, an addition test of bromohydrin mesylate **8** to pure **5** was performed and epimerization of nitrile **6** by cyanation was investigated (Figure 1).

The result suggested that the bromohydrin mesylate **8** reduced the optical purity of nitrile **6** in relation to the amount of **8** added. We also confirmed that bromohydrin mesylate

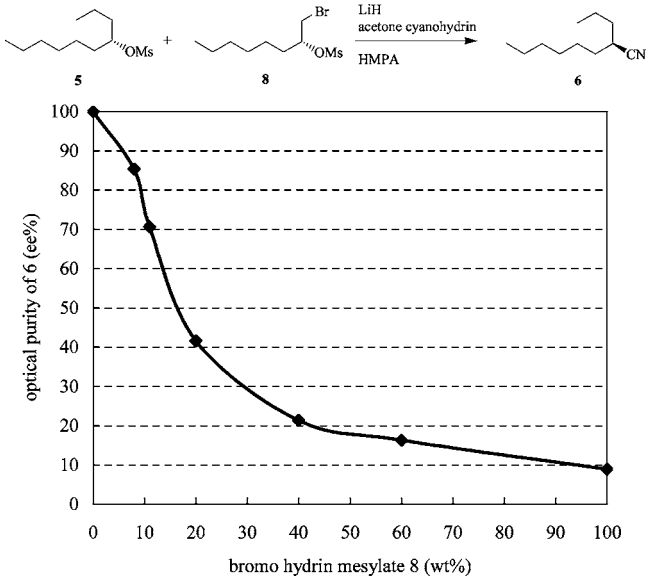


Figure 1. **Relation to optical purity of nitrile 6 with amount of 8.**

8 was readily transformed to dinitrile **9** in 87.5% yield under the cyanation condition, while the ethylation reaction of (*R*)-1,2-epoxyoctane produced bromohydrin **7** (0.4−1.1 area% by G. C. analysis), that could not be separated from alcohol **2** by distillation. To avoid such epimerization, a less

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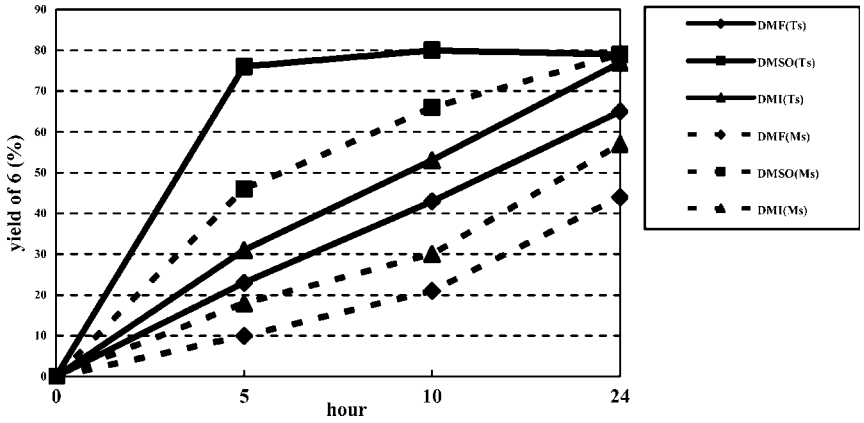
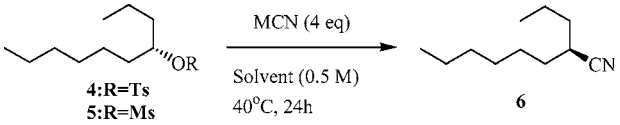


Figure 2. **Time course of cyanation with NaCN in several solvent systems.**

Table 1. **Screening of cyanation conditions**



entry	substrate[a]	MCN (4 equiv)	solvent	**6** yield[b] (%)	**6** ee (%)
1	4	KCN	DMSO	59	94.8
2	4	NaCN	DMSO	79	98.1
3	4	NaCN	DMF	65	95.4
4	4	NaCN	DMPU[c]	83	92.2
5	4	NaCN	DMI[d]	77	92.2
6	4	NaCN	DMA[e]	75	94.0
7	4	NaCN	NMP[f]	66	93.6
8	5	KCN	DMSO	47	98.5
9	5	NaCN	DMSO	79	99.2
10	5	NaCN	DMF	44	97.8
11	5	NaCN	DMPU	81	97.4
12	5	NaCN	DMI	57	98.2
13	5	NaCN	DMA	62	97.9
14	5	NaCN	NMP	50	98.0

[a] Purified starting materials (98.5% ee) were used. [b] The yield was determined by GC analysis using biphenyl as the internal standard. [c] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone. [d] 1,3-Dimethyl-2-imidazolidinone. [e] *N*,*N*-Dimethylacetamide. [f] 1-Methyl-2-pyrrolidinone.

nucleophilic chloride source would be effective for reducing the corresponding halohydrin formation during the ethylation step. The use of 1.4 equiv of ethylmagnesium chloride and 0.02 equiv of copper chloride worked well without the chlorohydrin formation (G. C. analysis) to provide crude alcohol **2** in quantitative yield. As a result, when this crude **2** was converted to nitrile **6** through tosylate **4** and mesylate **5**, no loss of optical purity was observed (99.2% ee for tosylate and 99.7% ee for mesylate). Lithium cyanide is well-known as a nonaqueous cyanation reagent for alkyl halides.[8] However, the present cyanation condition was not suitable for large-scale synthesis because lithium hydride needed to be crushed before use and also the large excess of reagents that were used.[9] We reinvestigated the various cyanation conditions, together with leaving group selection (tosylate or mesylate). The results are shown in Table 1. The reaction was performed using 4 equiv of cyanide at 40 °C for 24 h.

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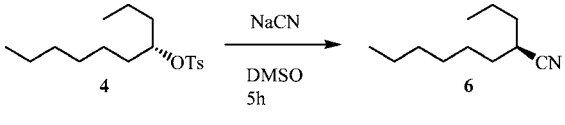
(9) Livinghouse, T. *Org. Synth. Coll. Vol*. VII **1990**, 517.

Table 2. **Optimization of cyanation**



entry	concn (M)	NaCN (equiv)	temp (°C)	**6** yield[a] (%)	**6** ee (%)
1	2	4	40	13	ND[b]
2	1	4	40	53	98.0
3	0.5	4	40	76	98.4
4	0.5	4	60	70	98.0
5	0.5	4	80	69	97.7
6	0.5	3	60	68	ND
7	0.5	2	60	69	ND
8	0.5	1	60	50	ND

[a] The yield was determined by GC analysis using biphenyl as the internal standard. [b] ND: not determined.

Table 3. **Stability test of 4 in several solvents**

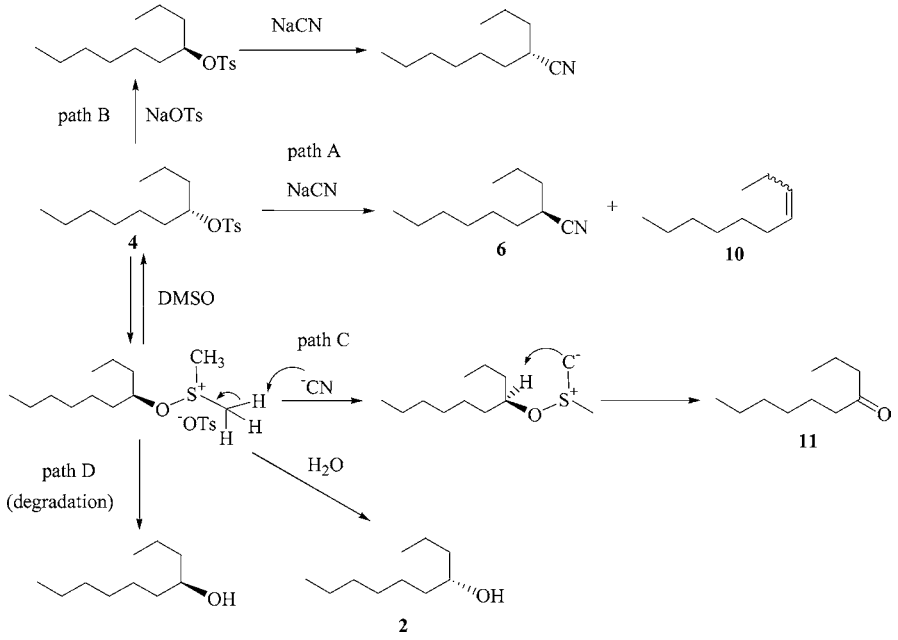
entry	solvent	residual **4** (%)
1	DMF	90.4
2	DMSO	51.5
3	DMPU	97.2
4	DMI	100.7
5	DMA	94.5
6	NMP	93.2

Sodium cyanide achieved a superior yield to potassium cyanide (entries 1, 2, 8, and 9). Use of DMPU or DMSO as the solvent provided higher yields than those of the other solvent systems (entries 2, 4, 9, and 11). The optical purity was dependent on the leaving group, and mesylate appeared to give less racemization than tosylate. The time course of the reactions using sodium cyanide indicated that the reaction rate of tosylate (closed line) was faster in every solvent system than that of mesylate (dotted line) although the leaving efficiency of mesylate was generally higher than that of tosylate (Figure 2).

Cyanation of tosylate **4** in DMSO was nearly complete after 5 h (entry 5). Based on this result, we selected the conditions in entry 5 and further optimized the reaction (Table 2).

The concentration of the reaction mixture had a critical influence on the yield: a higher concentration reduced the yield, because of the low solubility of sodium cyanide in

Scheme 3. **Possible mechanism of byproduct formation in cyanation**



the mixture (entries 1−3). A higher temperature induced a lower yield along with a slight decline in optical purity (entries 3−5). No influence on yield was observed by changing the amount of sodium cyanide over 2 equiv (entries 4 and 6−8). This cyanation process did not further improve the yield (up to 80%), because the alcohol formation proceeded as a side reaction. It was surprising that the alcohol formation was not restricted under any dry conditions examined, and so the stability of tosylate **4** in several solvents (0.3 M, at 40 °C, for 16 h) was investigated (Table 3).

Stability was assessed quantitatively by HPLC analysis using biphenyl as the internal standard. Tosylate **4** was found to be highly unstable in DMSO (entry 2) and was most stable in DMI (entry 4). After purification of the sample (entry 2), alcohol **2** was isolated in 42% yield with 75.3% ee and residual **4** was recovered in 50% yield. However, the absolute configuration of the isolated alcohol was the antipode of **2**, which indicated that alcohol formation during cyanation occurred via S_N2-substitution of the tosyl group by DMSO and degradation of the intermediate with retention of the chiral center. The impurity profiles of this reaction (entry 9, Table 1) were olefine **10** (6.0%), ketone **11** (1.4%), and alcohol **2** (7.0%). Based on these results, the possible mechanism of impurity formation under these cyanation conditions is presented in Scheme 3.

Path A is the normal reaction pathway to give the desired product **6** and unsaturated byproduct **10**. Minor racemization of nitrile **6** is generated by sodium tosylate formation in the course of the reaction through path B. The tosylate **4** reacts directly with DMSO to yield the intermediate which is deprotonated by a base in a process similar to Swern oxidation[10] to produce ketone **11** (path C) and to give the antipode of alcohol **2** through degradation (path D). Therefore, further improvement of the yield was difficult when DMSO was used as the solvent. Our attention turned to the use of other more soluble reagents or to improve the lithium cyanide preparation method (Table 4).

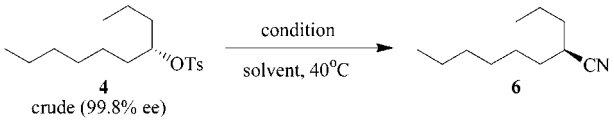
Tetra-*n*-butylammonium cyanide[11] prepared from $^nBu_4NHSO_4$, aqueous NaOH, and acetone cyanohydrin gave good results at very high concentration, but the complicated preparation procedure would not be applicable on a large scale (entries 1−3). The tetra-*n*-butylammonium salt prepared from sodium cyanide or acetone cyanohydrin with tetra-*n*-butylammonium hydroxide did not give good results (entries 4−6). The lithium *t*-butoxide system gave an excellent result, but this base was expensive (entry 7). As an alternative inexpensive lithium base, lithium hydroxide appeared to be relatively effective, and the monohydrate had no influence on the yield and optical purity (entries 8 and 9). In these cases, the minor racemization may be caused by deprotonation of the α-position of nitrile **6** with the base. We further optimized the solvent system of entry 8 and found that DMI/THF (7:3, 1 M) gave a higher yield with minor racemization (94%, 97.4% ee). Under this improved cyanation condition, nitrile **6** was obtained in 88% yield with 97.1% ee after distillation (82.8% purity by HPLC analysis) from crude tosylate **4** (82.5% purity). The impurity profile of this product showed olefine **10** (2.8%), ketone **11** (0%), and alcohol **2** (4.6%), which were reduced in comparison with those from entry 9 in Table 1 due to the higher nucleophilicity of the lithium salt compared with the sodium salt and the stability of tosylate **4** in the selected solvent system. Our new improved process is shown in Scheme 4.

After ethylation of (*R*)-1,2-epoxyoctane, tosylate **4** was directly prepared by internal quenching of the reaction with 1.1 equiv of tosyl chloride. Tosylate **4** was treated with 2 equiv of lithium hydroxide and acetone cyanohydrin in THF/DMI (7:3) for the transformation to nitrile **6** in 85.6% yield in two steps. Nitrile **6** was hydrolyzed to amide **12** by

(10) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(11) Victor, F.; Edward, A. L., III; Mark, J. S.; James, R. Z.; James, W. *Tetrahedron: Asymmetry* **1994**, *5*, 1131.

Table 4. **Various cyanation conditions for 4**



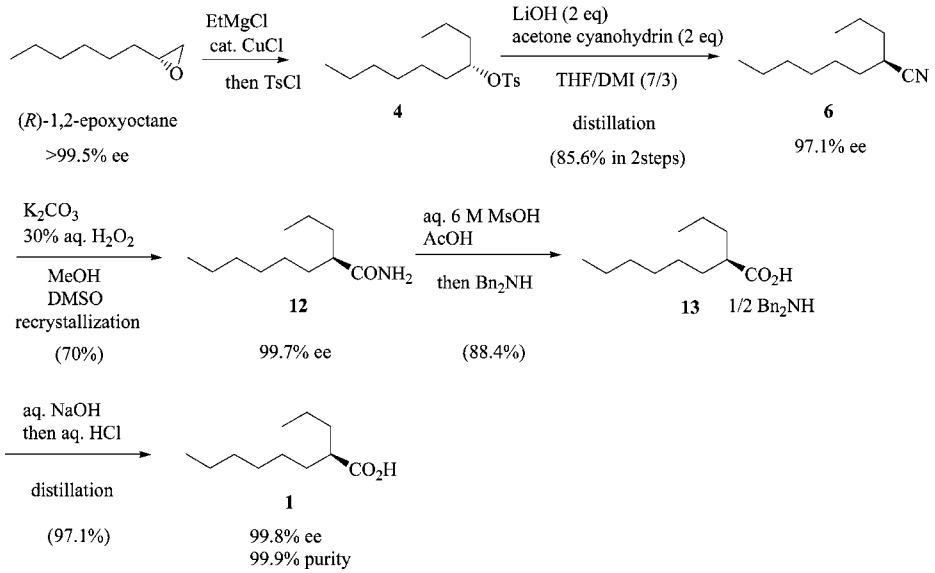
4
crude (99.8% ee)

6

entry	condition	solvent	concn (M)	time (h)	**6** yield[a] (%)	**6** ee (%)
1	$^{n}Bu_4NCN$[b]	DMSO	10	9	76	95.9
2		diglyme	5	6	78	94.7
3		DME	5	6	77	97.5
4	aq $^{n}Bu_4NOH$ (2 equiv), acetone cyanohydrin (1 equiv)	acetone	1	18	33	ND[c]
5		diglyme	1	18	39	30.9
6		DME	1	18	41	35.5
7	^{t}BuOLi (2 equiv), acetone cyanohydrin (2 equiv)	DMSO	1	14	97	97.0
8	anhydrous LiOH (2 equiv), acetone cyanohydrin (2 equiv)	DMSO	1	14	73	96.9
9	$LiOH-H_2O$ (2 equiv), acetone cyanohydrin (2 equiv)	DMSO	1	14	72	96.9

[a] The yield was determined by HPLC analysis using biphenyl as the internal standard. All reactions were conducted by heating mixtures of every reagent, and the reagent preparation in advance was not performed before cyanation. [b] Prepared from $^{n}Bu_4NHSO_4$ (1.2 equiv), aq NaOH (6 M, 2.4 equiv), and acetone-cyanohydrin (1.2 equiv). [c] ND: not determined.

Scheme 4. **New improved process for 1**



Katriztky's method.[12] The merit of this new process was that the optical purity was readily improved to 99.8−100% ee by recrystallization of amide **12** from aqueous acetonitrile. Therefore, restricted highly optical pure (*R*)-1,2-epoxyoctane was not necessary for this process. In the next step, screening of various acids for the hydrolysis of amide **12** (100% ee) was performed using acetic acid as the solvent at 105 °C for 10 h. The best conversion (87.4%) with minor racemization (99.5% ee) was achieved with aqueous methanesulfonic acid (6 M). Finally, numerous achiral amines were investigated for formation of crystalline salts with **1** in order to maintain the analytical criteria of the impurity profile. Interestingly, the half salt of dibenzylamine with **1** had very good crystalline properties, and it was able to improve both the chemical purity and the optical purity of the target compound. The salt **13** was readily freed by basic extraction to produce **1** with high chemical and optical quality (99.8% ee, 99.9% purity). This new process involved inexpensive materials, the overall yield was high (51.4%), and no special reactor was needed for the production. Therefore, the cost of ONO-2506 would be reduced compared with any of the previous processes.

Evaluation of Reaction Hazard in the One-Pot Preparation of Amide 12. Selecting sodium cyanide in DMSO as the cyanation condition may make it possible to realize a one-pot reaction, with the next hydrolysis to amide **12** providing for further cost reduction. We tried such a one-pot reaction, which proceeded as expected to afford enantiometrically pure amide **12** in 60% yield. However, a violent

(12) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949.

Table 5. **Hazard estimation of hydrolysis by DSC**

entry	NaCN (equiv)	H_2O_2 (equiv)	DMSO	nitrile **6**	onset temp (°C)	E_{exo}[a] (J/g)
1	0	add	none	none	ND[b]	ND
2	0	none	add	none	ND	ND
3	0	2.3	add	none	109	177
4	0	4.6	add	none	106	210
5	0	6.9	add	none	102	460
6	1	0	add	none	ND	ND
7	1	2.3	add	none	53	171
8	1	4.6	add	none	57	309
9	1	6.9	add	none	51	536
10	1	7.5	add	add	66	342

[a] Exothermal energy. [b] ND: Not detected.

exothermic response occurred in this reaction, with a time lag after addition of aqueous hydrogen peroxide. We estimated the hazardous nature of each material and blend by DSC (differential scanning calorimetry), especially focusing on sodium cyanide. The results are displayed in Table 5.

No exothermic response was observed for aqueous hydrogen peroxide or DMSO individually (entries 1 and 2). Blending of aqueous hydrogen peroxide with DMSO caused massive heat production (177 to 460 J/g), which increased in proportion with the amount of hydrogen peroxide (entries 3−5). It was shown that direct reaction of aqueous hydrogen peroxide with DMSO led to a violent exothermic response over 100 °C (onset temperature). However, a suspension of sodium cyanide in DMSO did not show exothermicity (entry 6). A mixture of sodium cyanide, aqueous hydrogen peroxide, and DMSO gave the same exothermal energy as that in the absence of sodium cyanide (entries 7−9). The important point about the presence of sodium cyanide was that the onset temperature shifted from ca. 100 °C to ca. 50 °C compared with those in entries 3−5. This indicated that sodium cyanide reduced the activation energy for oxidation of DMSO by hydrogen peroxide. Neither the presence nor absence of nitrile **6** had any influence on the exothermic response (entry 9 vs 10). The violent exothermic response seen during the one-pot reaction was due to oxidation of DMSO by H_2O_2 in the presence of sodium cyanide. This decreased onset temperature of the hazardous reaction was nearly equal to the hydrolysis reaction temperature. Based on this result, we judged that regulation of this explosive one-pot reaction would be impossible after scaling up. Although the separate hydrolytic conditions also created a fairly large amount of exothermal energy (entry 3), the heat production was related closely to the addition rate of hydrogen peroxide. Therefore, control of the exothermic response would be straightforward.

Conclusion

In summary, we have developed a new process for ONO-2506 synthesis from (*R*)-1,2-epoxyoctane as the starting material. The new process was constructed of five steps, including a modified cyanation condition of tosylate and a unique acidic hydrolysis of amide to carboxylic acid. The mechanisms for racemization until the cyanation step when copper bromide was treated at the ethylation step, and the side reaction at cyanation by use of NaCN in DMSO, were clarified and so allowed these problems to be solved. The optical purity of the final target was well controlled through two crystallized intermediates. This new process provides ONO-2506 economically with a high chemical and optical quality.

Experimental Section

General. Infrared (IR) spectra were recorded on a Jasco FT/IR-430 spectrometer. Fast atom bombardment mass spectra (FAB) and electron ionization (EI) were obtained on a JEOL JMS-DX303HF or a PerSeptive Voyager Elite spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a Hitachi M1200H spectrometer. ^{1}H NMR spectra were measured with a Varian Gemini-400 (400 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). Optical rotation was measured using a Jasco DIP-1000 polarimeter. Melting points (mp) were determined with a Yanaco micro melting point apparatus MP-500D. Elemental analyses for carbon, hydrogen, and nitrogen were carried out with a Perkin-Elmer PE2400 SeriesII CHNS/O analyzer. Column chromatography was performed with silica gel [Merck silica gel 60 (0.063−0.200 mm) or Wako Gel C200 or Fuji Silysia FL60D]. The reaction hazard was estimated using a DSC instrument (Mettler Toledo DSC-822).

Preparation of Authentic (4*S*)-Decan-4-ol 2. To a solution of LiCl (33 mg, 0.78 mmol) and CuCN (35 mg, 0.39 mmol) in THF was added (*R*)-1,2-epoxyoctane (600 μL, 3.9 mmol, 93.5% ee) at −10 °C. To this mixture was added dropwise a solution of ethylmagnesium bromide (0.89 mol/L, 5.7 mL, 5.07 mmol) in ether and stirred at 0 °C for 2 h. The mixture was cooled to −15 °C, and then the reaction was quenched with aqueous $KHSO_4$. The product was extracted twice with EtOAc/*n*-hexane. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **2** (617 mg, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (brs, 1H), 1.58−1.27 (m, 14H), 0.92 (t, 1H, J = 6.8 Hz), 0.88 (t, 3H, J = 3H); IR (Liquid film) 3347, 2957 cm^{-1}. Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 76.19; H, 14.07. $[\alpha]\ ^{20}_D = +1.9°$ (c = 2.00, EtOH).

Preparation of (1*S*)-1-Propylheptyl 3,5-Dinitrobenzoate 3. To a solution of **2** (8.30 g, 52.3 mmol) in pyridine (24 mL) was added 3,5-dinitrobenzoyl chloride (15.7 g, 68.1 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 14 h, after which it was diluted with EtOAc/*n*-hexane and washed with aqueous $KHSO_4$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **3** (6.0 g, 87%, 92.1% ee). The product (14.3 g) was recrystallized from 2-propanol (143 mL) to afford **3** (10.4 g, 72.7%, 99.2% ee) as white crystals. Further recrystallization of **3** (2.00 g) from 2-propanol gave enantiomerically pure **3** (1.53 g, 76.5%, 100% ee). HPLC; CHIRALPAK AD-H (DAICEL); *n*-hex-

ane/2-propanol = 97:3; flow rate, 0.3 mL/min; detection, 245 nm; retention time, 17.0 min (*R*) and 18.6 min (*S*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, 1H, J = 2 Hz), 9.15 (d, 2H, J = 2.4 Hz), 5.28−5.22 (m, 1H), 1.80−1.63 (m, 4H), 1.48−1.20 (m, 10H), 0.96 (t, 3H, J = 7.4 Hz), 0.87 (t, 3H, J = 6.8 Hz); IR (Liquid film) 2960, 2935, 1719, 1548, 1345 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 57.71; H, 6.64; N, 7.64; mp 66.5−67.6 °C; $[\alpha]^{20}_D$ = +30.4° (c = 0.10, EtOH).

Preparation of (4*S*)-Decan-4-ol 2 from 3. To a solution of **3** (1.30 g, 3.69 mmol) in THF/MeOH (4:1, 14 mL) was added aqueous NaOH (1 mol/L, 5.7 mL, 5.7 mmol) at 0 °C and stirred for 0.5 h. After the reaction mixture was concentrated until the volume was reduced to ca. 14 mL, sodium chloride was added. The resulting insoluble material was filtered off and washed with EtOAc/*n*-hexane (5:1, 50 mL). The filtrate was washed with water and brine, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to afford **2** (561 mg, 96.1%) as a colorless oil.

Preparation of (1*S*)-1-Propylheptyl 4-Methylbenzenesulfonate 4. To a stirred suspension of CuCl (4.6 g, 0.047 mol) in THF (642 mL) was added (*R*)-1,2-epoxyoctane (300 g, 2.34 mol) at −40 °C under an argon atmosphere. EtMgCl (2.1 mol/L in THF, 1309 g (1337 mL), 2.81 mol) was slowly added dropwise into the reaction mixture over 3 h, and the stirring continued for 30 min. After ethylation was complete, TsCl (491 g, 2.58 mol) was carefully added and the mixture was warmed to 0−20 °C and stirred for 4 h. Next, the mixture was treated with 10 v/v% H_2SO_4 (715 mL) and 5% NaCl (272 mL) and extracted with EtOAc (1.5 L). The organic layer was washed sequentially with 5% NaCl (636 mL), an aqueous solution of 10% K_2CO_3 (730 mL) and brine (200 mL), and brine alone (600 mL). The mixture was concentrated under reduced pressure to give **4** (758.7 g, 100% yield, 85.8% purity) as a brown oil. Purified **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 4.57 (m, 1H), 2.44 (s, 3H),1.64−1.49 (m, 4H), 1.35−1.10 (m, 10H), 0.87−0.82 (m, 6H); IR (Liquid film) 2958, 2872, 1361, 1306, 1176 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_3S$: C, 65.35; H, 9.03. Found: C, 65.21; H, 8.89. HPLC; CHIRALPAK AD-H (DAICEL); *n*-hexane/2-propanol = 99.5:0.5; flow rate, 1.0 mL/min; detection, 220 nm; retention time, 18.4 min (*R*) and 23.7 min (*S*); $[\alpha]^{20}_D$ = +2.7° (c = 2.00, EtOH).

Preparation of (1*S*)-1-Propylheptyl Methanesulfonate 5. To a solution of **2** (98.5% ee, 5.0 g, 32 mmol) in toluene (15 mL) were added Et_3N (8.8 mL, 63 mmol) and trimethylamine hydrochloride (302 mg, 3.16 mmol). The resulting suspension was cooled to 0 °C, and a solution of methanesulfonyl chloride (3.7 mL, 47 mmol) in toluene (30 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h after which the reaction was quenched with water. The product was extracted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **5** (6.0 g, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (m, 1H), 1.75−1.20 (m, 14H), 0.95 (t, 3H, J = 7.4 Hz), 0.89 (t, 3 H, J = 6.8 Hz); IR (Liquid film) 3027, 2933, 2872, 1354, 1175, 911 cm^{-1}. Anal. Calcd for $C_{11}H_{24}O_3S$: C, 55.89; H, 10.23. Found: C, 55.62; H, 10.23; $[\alpha]^{20}_D$ = −2.6° (c = 1.11, EtOH).

Preparation of (2*R*)-2-Propyloctanenitrile 6. To a stirred solution of **4** (85.8% purity, 758.7 g, 2.08 mol) in THF (1458 mL) and DMI (624 mL) were added acetone cyanohydrin (99.3% purity, 394 g, 4.60 mol) and LiOH (96.8 g, 4.05 mol) at 25 °C under an argon atmosphere. The reaction mixture was stirred for 14 h at 50 °C. After completion of the reaction, the mixture was cooled to room temperature and aqueous 15% NaCl (2.2 L) was added. The resulting mixture was extracted with *n*-hexane/EtOAc (2:1, 1660 mL), and the organic layer was washed with aqueous 15% NaCl (830 mL). Then the mixture was concentrated under reduced pressure, and the residue was purified by distillation to obtain **6** (335 g, 85.6% in two steps, 97.1% ee, 92.1 area%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ5.33 (dd, 1H), 4.35−4.20 (m, 1H), 3.75−3.40 (m, 4H), 2.60−2.43 (m, 1H), 2.15−1.77 (m, 3H), 1.77−1.15 (m, 15H), 1.00−0.80 (m, 6H). IR (Liquid film) 2959, 2931, 2236, 1467 cm^{-1}; Mass (FAB, Pos) 167(M + 1). Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 78.62; H, 12.67; N, 8.39. Bp 72−77 °C at 400 Pa; GC; β-DEX225 (0.25 mm i.d. × 28 m, 0.25 μm film, SUPELCO, 10403−02B); Column Temp, 90 °C; Carrier, He (22.3 cm/s); Injector Split (200 °C, Ratio 100/1); Injection Vol, 0.5 μL; Detector, FID (200 °C); Make up, He (40 mL/min); retention time, 91.0 min (*S*) and 92.6 min (*R*); $[\alpha]^{20}_D$ = −7.9° (c = 2.00, EtOH).

Preparation of (2*R*)-1-Bromooctan-2-ol 7. To a solution of (*R*)-1,2-epoxyoctane (5.0 g, 39 mmol) in AcOH (10 mL) and THF (50 mL) was added LiBr monohydrate (6.5 g, 62 mmol), and the mixture was stirred for 1 h. Water was added, and the product was extracted with MTBE. The organic layer was washed with water and then brine and was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **7** (6.09 g, 74.6%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (brs, 1H), 1.58−1.27 (m, 14H), 0.92 (t, 1H, J = 6.8 Hz), 0.88 (t, 3H, J = 3 Hz); IR (Liquid film) 3377, 2956, 2928, 2857 cm^{-1}; Mass (EI, Pos.) m/z 193 (M + 2 − H_2O), 191 (M − H_2O).

Preparation of (1*R*)-1-(Bromomethyl)heptyl Methanesulfonate 8. To a solution of **7** (1.00 g, 4.78 mmol) in toluene (8 mL) were added Et_3N (1.3 mL, 9.6 mmol) and trimethylamine hydrochloride (46 mg, 0.48 mmol). The resulting suspension was cooled to 0 °C, and a solution of methanesulfonyl chloride (0.56 mL, 7.2 mmol) in toluene (3 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h, and the reaction was quenched with water. The product was extracted with EtOAc and washed with aqueous HCl, water, and brine. Then the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **8** (913 mg, 66.6%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.8 (m, 1H), 3.57 (m, 2H), 3.10 (s, 3H), 1.82 (m, 2H), 1.39−1.30 (m, 8H), 0.9 (t, 3H, J = 5.6 Hz); IR (Liquid film) 2929, 2859, 1359, 1175, 908 cm^{-1}; Mass (EI, Pos) 288 (M

+ 2), 286 (M), 200, 190. Anal. Calcd for $C_9H_{19}BrO_3S$: C, 37.64; H, 6.67. Found: C, 37.69; H, 6.46. $[\alpha]^{20}_D = +13.0°$ (c = 1.99, EtOH).

Preparation of (2*S*)-2-(Cyanomethyl)octanenitrile 9. To crushed LiH (127 mg, 16.0 mmol) was added THF (4.5 mL), and the mixture cooled to 0 °C. To the resulting suspension was added acetone cyanohydrin (90 wt %, 1.3 mL, 13 mmol), and the system warmed to room temperature. Then the mixture was stirred for 2 h after which HMPA (2.5 mL) was added. The mixture was concentrated under reduced pressure, and a solution of **8** (913 mg, 3.20 mmol) in HMPA (1.5 mL) was added to the residue. The mixture was stirred for 20 h at room temperature and diluted with a mixture of *n*-hexane/EtOAc (9/1, 70 mL). This was washed twice with water (30 mL) and brine and was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford **9** (355 mg, 67.6%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (m, 1H), 2.75 (dd, 1H, J = 6.0, 19.0 Hz), 2.69 (dd, 1H, J = 7.6, 19.0 Hz), 1.77 (m, 2H), 1.65−1.32 (m, 8H), 0.9 (t, 3H, J = 7.2 Hz); IR (Liquid film) 2956, 2931, 2859, 2246, 1465 cm^{-1}; Mass (FAB, Pos) 165 (M + 1). Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; N, 17.06. Found: C, 72.87; H, 9.65; N, 16.80. $[\alpha]^{20}_D = -0.28°$ (c = 2.03, EtOH).

Preparation of (2*R*)-2-Propyloctanamide 12. To a stirred suspension of **6** (89.8 area%, 60 g, 322 mmol, 97.1% ee (*R*)) in MeOH (84 mL) and DMSO (95.6 g, 1.22 mol) was added K_2CO_3 (8.9 g, 64 mmol), and the mixture warmed to 50−60 °C. To this suspension was added 35% aqueous hydrogen peroxide (46.9 g (41.5 mL), 483 mmol) over 30 min at 50−70 °C, and the mixture was then stirred for 1 h at 50−70 °C. After completion of the reaction, aqueous Na_2SO_3 solution (Na_2SO_3 5 g and water 351 mL) was added to this mixture which then cooled to 5 °C. The slurry was stirred for 30 min at 5 °C. The resulting crystals were filtered off and were washed with cooled water/CH_3CN (2/1, 216 mL) and water alone (318 mL) to afford **6** (wet) (52 g, 97.1% ee (*R*), 88.9 area%) as a white powder. The wet **6** (20 g) was recrystallized from water/CH_3CN (1:1, 240 mL) to afford **12** (16 g, 70% yield, 99.7% ee (*R*), 98.7 area%) as a white powder. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84−0.94 (m, 6H), 1.26−1.64 (m, 14H), 2.04−2.15 (m, 1H), 5.42 (bs, 1H), 5.59 (bs, 1H); IR (KBr) 3372, 3182, 1656 cm^{-1}; Mass (APCI 20V Pos.) m/z 186 (M + 1). Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.37. Found: C, 71.14; H, 12.72; N, 7.56. Mp 116.8−117.9 °C; CHIRALPAK AD-RH(DAICEL); MeCN/H_2O = 40:60; flow rate, 0.5 mL/min; detection, 205 nm; retention time, 38.0 min (*S*) and 45.3 min (*R*); $[\alpha]^{20}_D = -5.0°$ (c = 2.00, EtOH).

Preparation of (2*R*)-2-Propyloctanoic Acid Dibenzylamine Salt 13. A stirred suspension of **12** (100 g, 540 mmol) and AcOH (230 mL) was dissolved at 40 °C, and aqueous methanesulfonic acid (MsOH 130 g/water 182 mL) was added to the mixture which was then heated at 105 °C (internal temperature) for about 13 h. After completion of the reaction, the mixture was cooled to 28 °C after which it was diluted with water (400 mL) and extracted with *n*-heptane/*i*-PrOAc (5:1, 500 mL). The organic layer was washed with water (400 mL, twice) and evaporated under reduced pressure to afford crude ONO-2506 as a pale yellow oil. To the residue (103 g) were added CH_3CN (1.5 L) and dibenzylamine (58.6 g, 297 mmol). This suspension was completely dissolved at 60 °C and stirred for 10 min. Then the clear solution was cooled to 10 °C and stirred for 30 min. The resulting white crystals were filtered off, washed with CH_3CN (200 mL) and dried under a vacuum at 40 °C to afford **13** (136 g, 88.4%, 99.8% ee (*R*)). The ee value was determined after conversion to ONO-2506.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 10H), 3.87 (s, 4H), 2.33 (dt, 2H, J = 5.2, 8.8 Hz), 1.60 (m, 4H), 1.35 (m, 24H), 0.91 (t, 6H, J = 7.2 Hz), 0.87(t, 6H, J = 6.8 Hz); IR (KBr) 2957, 2926, 2853, 1638 cm^{-1}. Anal. Calcd for $C_{36}H_{59}N$: C, 75.88; H, 10.44; N, 2.46. Found: C, 75.78; H, 10.25; N, 2.50. Mp: 79.5−79.8 °C; $[\alpha]^{20}_D = -3.6°$ (c = 2.00, EtOH).

Preparation of (2*R*)-2-Propyloctanoic Acid 1. Dibenzylamine salt **13** (100 g, 175 mmol) was dissolved in aqueous KOH (1 mol/L, 400 mL) at 20 °C, and the mixture was stirred for 10 min. The mixture was reverse-extracted with *i*-PrOAc (250 mL, twice). To the aqueous layer was added *n*-heptane/*i*-PrOAc (1/1, 500 mL) and concentrated HCl (40 mL) at 20 °C. The separated organic layer was washed with water (200 mL) and brine (200 mL) and was concentrated under reduced pressure to afford crude **1** (67.1 g) as a colorless oil. This was purified by distillation to afford **1** (63.5 g, 97.1%, 99.8% ee, 99.9% purity) as a colorless oil. ^{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, Pos) m/z 186 (M+), 169, 157, 144, 115, 102; IR (Liquid film) 2959, 2931, 1706, 1467 cm^{-1}; bp 120−121 °C at 133 Pa; $[\alpha]^{20}_D = -6.1°$ (c = 2.00, EtOH)

Determination of the optical purity of **1** was performed with the corresponding phenacylester as shown below. To a suspension of **1** (17.2 mg, 0.09 mmol) and K_2CO_3 (15.3 mg, 0.11 mmol) in acetone (1 mL) was added phenacylbromide (22 mg, 0.11 mmol). The mixture was stirred at room temperature for 1 h, and then it was filtered and the filtrate was concentrated under reduced pressure to afford the crude phenacylester. The residue was dissolved in 2-propanol (5 mL), and an aliquot (1 μL) was directly analyzed by HPLC. HPLC; CHIRALCEL OJ-R (DAICEL); MeCN/H_2O = 60:40; flow rate, 0.5 mL/min; detection, 244 nm; retention time, 21.1 min (*S*) and 22.8 min (*R*).

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