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Total synthesis of (*R*)-(−)-actisonitrile via *O*-alkylation of optically active 4-hydroxymethyloxazolidin-2-one derivative

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ABSTRACT

The enantioselective synthesis of (*R*)-(−)-actisonitrile **1** has been achieved via *O*-alkylation of (4*R*,α*S*)-4-hydroxymethyl-3-(α-methylbenzyl)oxazolidin-2-one (α*S*)-**4** with 1-iodohexadecane in the presence of CsOH in DMF. Under these reaction conditions, the *O*-alkylation was much faster than the intramolecular acyl transfer of (α*S*)-**4**.

1. Introduction

Some natural products that possess a serinol moiety, for example didemniserinolipids A–C,[1,2] cyclodidemniserinol trisulfate,[3] shishididemniols,[4,5] inconspicamide,[6,7] and serinol-derived malyngamides[8] have been isolated from tunicates, ascidians, marine sponges, or a blue-green alga as biologically potent marine metabolites. Recently, (*R*)-(−)-actisonitrile **1** was isolated from an Actinocyclidae nudibranch, *Actinocyclus papillatus*[9] (Fig. 1). The structure has been established as a lipid based structure on a 1,3-propanediol ether skeleton by spectroscopic methods, while the absolute configuration of the stereogenic center was determined by comparing the optical properties of natural actisonitrile with those of (*R*)-(−)- and (*S*)-(+)-synthetic enantiomers, prepared from (*S*)-(−)- and (*R*)-(+)-glycidyl trityl ethers, respectively. The bioactivity of both (*R*)-(−)- and (*S*)-(+)-actisonitrile enantiomers has been tested in a fluorimetric culture cytotoxicity assay on tumor and nontumor mammalian cells. Both enantiomers exhibited a parallel concentration-dependent toxic profile, displaying IC_{50} values within the micromolar range. In particular, (*R*)-(−)-**1** and (*S*)-(+)-**1** showed moderate cytotoxicity against nontumor H9c2 rat cardiac myoblast cells (IC_{50} 23 ± 6 and 23 ± 6 μM, respectively).[9]

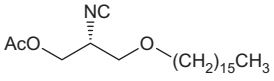
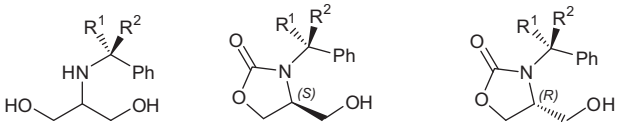


Figure 1. (*R*)-(−)-Actisonitrile **1**.

Due to the potent biological activity and the simple structure of (*R*)-(−)-actisonitrile **1**, a convenient synthetic method for the development of enantiomerically pure **1** would be of great interest to many chemists. Some serinolipids have been synthesized from the known *N*-Boc-serinol acetonide,[2,10–12] the etherification of which has been carried out using NaH as a base in DMF or THF at room temperature.

On the other hand, we have developed a synthetic method for 4-hydroxymethyloxazolidin-2-one (α*R*)-**3** from (*R*)-2-(α-methylbenzyl)aminopropane-1,3-diol (*R*)-**2** (Fig. 2) via the asymmetric desymmetrization process[13,14] and from (*R*)-α-methylbenzyl isocyanate and (*S*)-glycidol.[13] Oxazolidinone (α*S*)-**4** has also been also synthesized from an optically active aziridine.[15] Although these oxazolidinones can be easily synthesized in a few steps, they have not been used as synthetic intermediates except for the synthesis of the 3-(2-oxooxazolidin-4-yl)acrylate derivative from (α*S*)-**4**.[15] The benzyl and MOM ethers of 4-hydroxymethyloxazolidin-2-one derivatives have been synthesized using benzyl bromide[16] or benzyl 2,2,2-trichloroacetimidate[17] and methoxymethyl chloride,[18] respectively, in the presence of Et_3N and $^iPr_2EtN$; however, the synthesis of the alkyl ethers of the 4-hydroxymethyloxazolidin-2-ones has not been reported. Strong bases, such as ^{t}BuOK and NaH, convert (α*R*)-**3** to a diastereomeric mixture of (α*R*)-**3** and (α*R*)-**4** via an intramolecular acyl transfer.[13] In order to investigate the utility of these oxazolidinones as synthetic intermediates, we began to synthesize



(*R*)-**2**, R^1 = Me, R^2 = H
(*S*)-**2**, R^1 = H, R^2 = Me
(α*R*)-**3**, R^1 = Me, R^2 = H
(α*S*)-**3**, R^1 = H, R^2 = Me
(α*R*)-**4**, R^1 = Me, R^2 = H
(α*S*)-**4**, R^1 = H, R^2 = Me

Figure 2.

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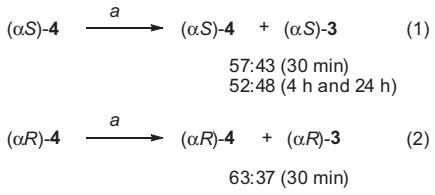
the serinol derivative **1** from (αS)-**4**. For this purpose we needed to develop *O*-alkylation conditions for (αS)-**4** without the intramolecular acyl transfer.

We also focused on the dehydration of a formamide to an isonitrile, which is the final stage of the synthesis of (*R*)-(−)-actisonitrile **1**. Mroczkiewicz and Ostaszewski have reported that the synthesis of enantiomerically pure (2*S*)-2-isocyano-4-methylpentyl acetate from (2*S*)-2-foramide-4-methylpentyl acetate was problematic.[19,20] After their examination of several synthetic methods, they found that reaction conditions using triphenylphosphine, carbon tetrachloride,[21] and triethylamine gave the product possessing the highest enantiomeric purity. Ichikawa et al. also used an identical reagent system using carbon tetrabromide[22] instead of carbon tetrachloride for the asymmetric synthesis of (+)-geranyllinaloisocyanide and determined its enantiomeric purity by comparison with two ^{1}H NMR spectra of urea derived from (+)- and (±)-geranyllinaloisocyanide and (*R*)-α-methylbenzylamine.[23]

2. Results and discussion

After the synthesis of oxazolidinone (αS)-**4** from serinol (*S*)-**2** according to the literature,[13] we investigated the epimerization of oxazolidinones (αS)-**4** and (αR)-**4** via intramolecular acyl transfer and their *O*-alkylation using CsOH in DMF.[24] Treatment of (αS)-**4** with CsOH·H_2O (1.1 equiv) in DMF (2.5 L/mol) at room temperature for 30 min gave a diastereomeric mixture of (αS)-**4** and (αS)-**3** (57:43, determined by ^{1}H NMR analysis) (Scheme 1, Eq. 1). The epimerization equilibrated within 4 h to give a mixture of (αS)-**4** and (αS)-**3** (52:48), and this ratio did not change after 24 h.



Scheme 1. Epimerization of 4-hydroxymethyloxazolidin-2-ones via intramolecular acyl transfer.[13] Reagents and conditions: (a) CsOH·H_2O (1.1 equiv), DMF (2.5 L/mol), rt.

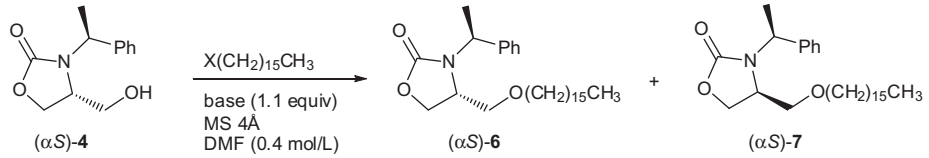
Oxazolidinone (αR)-**4**,[13,25] which was the (αR)-epimer of (αS)-**4**, was also treated with CsOH·H_2O (1.1 equiv) in DMF (2.5 L/mol) at room temperature for 30 min. In this case, the mixture of (αR)-**4** and (αR)-**3** (63:37) was obtained (Eq. 2). This rapid epimerization indicated that the *O*-alkylation of (αS)-**4** and (αR)-**4** should be faster than their epimerization to prevent the formation of a diastereomer.

Next, the *O*-alkylation of (αS)-**4** in DMF was studied, and the results are summarized in Table 1. *O*-Alkylation of (αS)-**4** in DMF with 1-iodohexadecane **5a** or hexadecanyl tosylate **5b**[26] in the presence of DBU, which is an ineffective base for the acyl transfer of (αR)-**3**,[13] did not proceed at 100 °C (entries 1 and 2). According to a reported procedure,[24] we attempted the *O*-alkylation using 1-bromohexadecane **5c** in the presence of tetrabutylammonium iodide (TBAI) as the catalyst and CsOH·H_2O or Cs_2CO_3 as the base.[24] The reaction using Cs_2CO_3 gave no product (entry 3). The reaction using CsOH·H_2O gave the desired ether (αS)-**6** in 19%; an undesired ether (αS)-**7** was also obtained (entry 4). The formation of (αS)-**7** was due to the rate of *O*-alkylation, which was not much faster than the rate of epimerization (Scheme 1, Eq. 1). In order to increase the *O*-alkylation rate, we next used 1-iodohexadecane **5a** instead of bromide **5c**. *O*-Alkylation using 1.0 and 6.0 equiv of **5a** gave ether (αS)-**6** in 48% and 59% yields, respectively (entries 5 and 6). Since no undesired ether (αS)-**7** was formed in these cases, the *O*-alkylation was much faster than the epimerization. *O*-Alkylation using tosylate **5b** was also examined; however, the low solubility of **5b** in DMF at room temperature decreased both the concentration of the reaction mixture and the yield (entry 7). The undesired ether (αS)-**7** was also obtained during the long reaction time (25 h).

The *O*-alkylation of (αR)-**4** using CsOH·H_2O in DMF at room temperature was also investigated using 1.0 and 6.0 equiv of 1-iodohexadecane **5a** and 6.0 equiv of tosylate **5b** (Table 2). The *O*-alkylation using 6.0 equiv of iodide **5a** gave ether (αR)-**6** in the best yield among the three examples and no epimeric ether (αR)-**7** (entry 2). The yield of (αR)-**6** was identical to the yield of the *O*-alkylation of (αS)-**4** (Table 1, entry 6).

We observed by ^{1}H NMR analysis that the crude mixture in entry 6 (Table 1) contained (αS)-**6** and 1-hexadecene. In this case, 1-hexadecene should be converted from 1-iodohexadecane by the elimination of hydrogen iodide. The molar ratio of (αS)-**6** and 1-hexadecene was 100:86 [59% and 51% based on (αS)-**4**]. Therefore, CsOH [1.1 equiv based on (αS)-**4**] was consumed completely within 30 min from the beginning of the reaction. The starting material (αS)-**4** was also observed in the crude reaction mixture in 16%

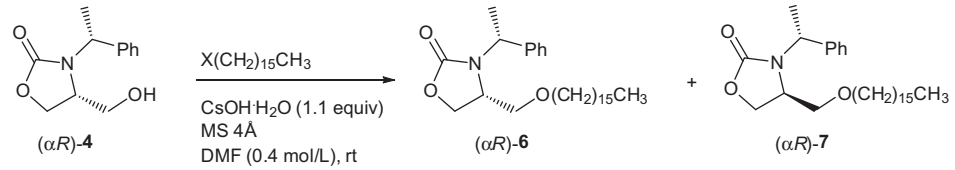
Table 1
O-alkylation of (αS)-**4**



Entry[a]	X(CH$_2$)$_{15}$CH$_3$			Base	Temp (°C)	Time (h)	Yield[b] (%)	
	No.	X	Equiv				(αS)-**6**	(αS)-**7**
1	**5a**	I	1.0	DBU	100	14	0	0
2	**5b**	TsO	1.0	DBU	100	14	0	0
3[c]	**5c**	Br	2.0	Cs_2CO_3	rt then 100	48 then 5	0	0
4[c]	**5c**	Br	2.0	CsOH·H_2O	rt then 50	14 then 2	19	2
5	**5a**	I	1.0	CsOH·H_2O	rt	0.5	48	0
6	**5a**	I	6.0	CsOH·H_2O	rt	0.5	59	0
7[d]	**5b**	OTs	6.0	CsOH·H_2O	rt	25	42	7

[a] The amount of (αS)-**4** was 10 mg except in entries 3, 4, 6 (100 mg), and 7 (50 mg), and 1.5 times the weight of powdered MS 4 Å was used.
[b] Isolated yield.
[c] TBAI (0.05 equiv) was also used.[22]
[d] The concentration of the mixture was 0.064 mol/L based on (αS)-**4**.

Table 2
O-alkylation of (αR)-**4**



Entry[a]	$X(CH_2)_{15}CH_3$			Time (h)	Yield (%)[b]	
	No.	X	Equiv		(αR)-**6**	(αR)-**7**
1	**5a**	I	1.0	0.5	19	0
2	**5a**	I	6.0	0.5	59	0
3[c]	**5b**	OTs	6.0	25	52	0

[a] The amount of (αR)-**4** was 10 mg in entries 1 and 2 and 20 mg in entry 3, and 1.5 times the weight of powdered MS 4 Å was used.
[b] Isolated yield.
[c] The concentration of the mixture was 0.064 mol/L based on (αR)-**4**.

recovery, and its epimer (αR)-**4** was not formed due to the consumption of CsOH within 30 min. In entry 2 (Table 2) using (αR)-**4**, the formation of 1-hexadecene was also observed, and (αS)-**4** was not observed in the crude mixture. Thus, the rates of the epimerizations of (αS)-**4** and (αR)-**4** were much slower than the rates of the *O*-alkylation of (αS)-**4** and (αR)-**4** and elimination of hydrogen iodide from 1-iodohexadecane.

We found a good method for the *O*-alkylation of (αS)-**4** and (αR)-**4** and continued the total synthesis of **1** using ether (αS)-**6**. Acidic debenzylation using methanesulfonic acid (MsOH)[27,28] and anisole in nitromethane, which is a good solvent for benzyl cationic reactions,[29] gave ether **8** in good yield. After hydrolysis of the oxazolidinone ring of **8**, N-formylation of aminoalcohol **9**† with ethyl formate[19,20] gave formamide **10**; the hydroxy group of **10** was acetylated with acetic anhydride in pyridine. Formamide **10** and acetate **11** have been synthesized[9] and the ^1H and ^{13}C NMR spectroscopic data were in good agreement with the reported values. Finally, the formamide group of **11** was converted to the isonitrile group using triphenylphosphine and carbon tetrabromide[21] to afford (*R*)-(−)-actisonitrile **1** in good yield. The ^1H and ^{13}C NMR spectroscopic properties of our synthetic material matched those of the reported data.[9] The specific rotation $[\alpha]_D$ values were $[\alpha]_D^{31} = -15.1$ (*c* 0.3, $CHCl_3$), with the same sign as the reported value $[\alpha]_D = -7.0$ (*c* 0.27, $CHCl_3$).[9]

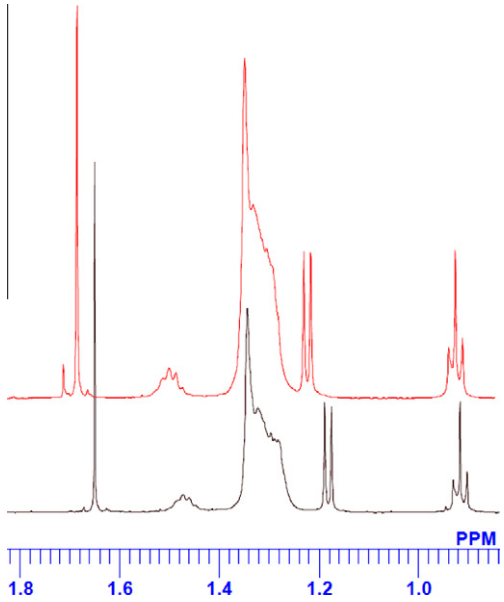


Figure 3. ^1H NMR spectra of the two diastereomers (αR)-**13** (red) and (αS)-**13** (black) in C_6D_6 (500 MHz).

The enantiomeric purity of **1** was determined after conversion of **1** to isocyanate **12** following the addition of (*R*)- and (*S*)-α-methylbenzyl amines to give two diastereomers of ureas (αR)-**13** and (αS)-**13**. ^1H NMR analyses of (αR)-**13** and (αS)-**13** in C_6D_6 displayed well-resolved resonances for the individual diastereomers (Fig. 3). Two different diagnostic methyl groups of the acetyl [singlet; δ 1.68 for (αR)-**13**, δ 1.65 for (αS)-**13**] and α-methylbenzyl groups [doublet; δ 1.21 for (αR)-**13**, δ 1.18 for (αS)-**13**] were observed. No diastereomer existed in each sample in the ^1H NMR spectra (Fig. 3). Thus, actisonitrile **1** was synthesized with excellent enantiomeric purity.

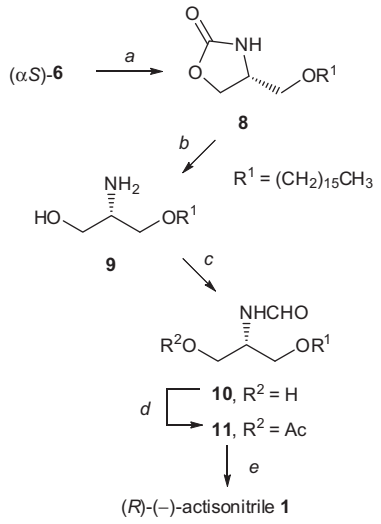
3. Conclusion

In conclusion, the *O*-alkylation of 4-hydroxymethyloxazolidin-2-one (αS)-**4** was performed efficiently using 1-iodohexadecane with $CsOH·H_2O$ in DMF at room temperature (Tables 1 and 2). Under these reaction conditions, *O*-alkylation from (αS)-**3** to (αS)-**7** (*path C*) should also proceed in the same way as the *O*-alkylation from (αR)-**4** to (αR)-**6** did; however, (αS)-**7** was not formed from (αS)-**4** because *path B* was much faster than *path A* (the intramolecular acyl transfer). Therefore, ether (αS)-**6** was obtained as the sole product (Scheme 4). The reaction of the formamide group of **11** to an isonitrile group using triphenylphosphine and carbon tetrabromide[21] was a good method to obtain enantiomerically pure actisonitrile **1** in good yield (Scheme 2). In addition, enantiomeric purity of **1** was easy to determine after the conversion of **1** to *N*-α-methylbenzyl urea derivatives (αR)-**13** and (αS)-**13** (Scheme 3 and Fig. 3).

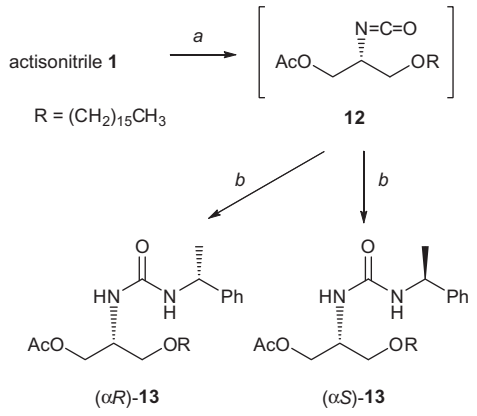
4. Experimental

Melting points were measured with Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. NMR spectra were obtained with a JEOL JNM-LA500 (^1H NMR: 500 MHz and ^{13}C NMR: 125 MHz) and a JEOL JNM-GSX400 (^1H NMR: 400 MHz and ^{13}C NMR: 100 MHz) spectrometers using tetramethylsilane as the internal standard. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. MS and high-resolution MS (HRMS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was per-

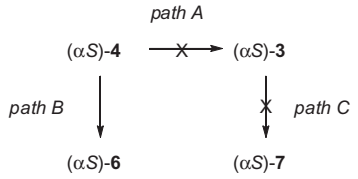
† Another monoalkyl serinol, (*S*)-2-amino-3-(dodecyloxy)propan-1-ol, has been also synthesized from L-Boc-Ser(Bn)-OH, and exhibited anti-inflammatory and analgesic activities.[30]



Scheme 2. Reagents and conditions: (a) MsOH, anisole, $MeNO_2$, 100 °C, 3 h, 88%. (b) LiOH, EtOH, H_2O, reflux, 1 h, 99%. (c) HCO_2Et, reflux, 2 h, 99%. (d) Ac_2O, Py, CH_2Cl_2, room temp, 2 h, 100%. (e) Ph_3P, CBr_4, CH_2Cl_2, −10 °C, 15 min, 90%.



Scheme 3. Synthesis of two diastereomers to determine the enantiomeric purity of synthetic **1** Reagents and conditions: (a) pyridine *N*-oxide, I_2, MS 4 Å, MeCN, room temp, 30 min. (b) (*R*)- or (*S*)-α-methylbenzylamine, 60 min [(α*R*)-**13**, 74% from **1**, (α*S*)-**13**, 71% from **1**].



Scheme 4. The desired *O*-alkylation from oxazolidinone (α*S*)-**4** to (α*S*)-**6** (*path B*). Reagents and conditions; see Table 1 and Section 4.

formed with Kanto Chemical Silica Gel 60 (spherical, 40–50 μm) otherwise noted. Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck).

4.1. Synthesis of (α*S*)-4

4.1.1. Diethyl (*S*)-(α-methylbenzyl)aminomalonate

According to our procedure,[13] we synthesized this compound from diethyl bromomalonate and (*S*)-(α-methylbenzyl)amine. $[\alpha]_D^{28} = -58.0$ (*c* 1.0, $CHCl_3$) {for the (*R*)-enantiomer, $[\alpha]_D^{22} = +61.6$ (*c* 1.1, $CHCl_3$)}.[13]

4.1.2. (*S*)-2-(α-Methylbenzyl)amino-1,3-propanediol (*S*)-2

According to our procedure,[13] we synthesized (*S*)-**2** from diethyl (*S*)-(α-methylbenzyl)aminomalonate $[\alpha]_D^{28} = -58.3$ (*c* 0.78, MeOH) {for the (*R*)-enantiomer, $[\alpha]_D^{21} = +57.1$ (*c* 1.0, MeOH)}.[13]

4.1.3. (4*R*,α*S*)-4-Hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone (α*S*)-4

According to our procedure,[13] we synthesized (α*S*)-**4** from (*S*)-**2**. In this case we used Et_3N and DMAP instead of pyridine. 2-Chloroethyl chloroformate (3.15 g, 22.0 mmol) was added to a mixture of serinol (*S*)-**2** (4.30 g, 22.0 mmol), Et_3N (2.23 g, 22.0 mmol), and DMAP (80 mg, 0.66 mmol) in CH_2Cl_2 (550 mL) at room temperature. After being stirred for 1 h at room temperature and then cooled with an ice bath, DBU (10.3 g, 66.1 mmol) was added dropwise to the mixture. The resulting mixture was stirred for 15 h with warming to room temperature. The reaction mixture was washed twice with 5% hydrochloric acid (52 mL, twice) and once with water (52 mL). The mixture was then dried over $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was chromatographed on silica gel (hexane/AcOEt, 1:2 to AcOEt) to afford a mixture of oxazolidinones (α*S*)-**4** and (α*R*)-**3** (2.42 g, 50% yield) as colorless crystals, which were recrystallized from *tert*-butyl methyl ether/THF (47 mL/5 mL) to give pure (α*S*)-**4** as colorless plates (1.55 g) and colorless crystalline material from the filtrate [0.87 g, (α*S*)-**4**/(α*S*)-**3**, 93.5:6.5 (0.815 g:0.057 g), ^{1}H NMR analysis[13]]. Therefore, the ratio of (α*S*)-**4**/(α*S*)-**3** was 97.5:2.5 (2.36 g:0.06 g) $[\alpha]_D^{27} = -99.1$ (*c* 1.0, $CHCl_3$) {for (α*R*)-**3**, $[\alpha]_D^{29} = +102.1$ (*c* 1.0, $CHCl_3$)}.[13]

4.2. *O*-alkylation of (α*S*)-4 and (α*R*)-4

4.2.1. Typical procedure (Table 1, entry 6)

At first, $CsOH{\cdot}H_2O$ (84 mg, 0.50 mmol) was added to a mixture of oxazolidinone (α*R*)-**4** (100 mg, 0.45 mmol), 1-iodohexadecane **5a** (853 μL, 2.71 mmol), and powdered molecular sieves 4 Å (150 mg) in DMF (1.1 mL),[24] and the resulting mixture was stirred for 30 min at room temperature. The reaction mixture was poured into H_2O and extracted three times with Et_2O. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 7:3) to afford (α*S*)-**6** (118 mg, 59%).

4.2.2. (4*R*,α*S*)-4-(Hexadecyloxymethyl)-3-(α-methylbenzyl) oxazolidin-2-one (α*S*)-6

R_f value, 0.34 (hexane/AcOEt, 7:3). Yellow solid, mp 44–46 °C. $[\alpha]_D^{25} = -49.2$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (2H, d, *J* = 7.3 Hz, Ar), 7.28–7.37 (3H, m, Ar), 5.15 (1H, q, *J* = 7.3 Hz, PhC*H*), 4.30 (1H, t, *J* = 8.8 Hz, OC*H*H), 4.12 (1H, dd, *J* = 8.8, 5.4 Hz, OCH*H*), 3.93–3.97 (1H, m, NCH), 3.08 (1H, dt, *J* = 9.3, 6.3 Hz, OC*H*HCH$_2$), 3.02 (1H, dt, *J* = 9.3, 6.3 Hz, OCH*H*CH$_2$), 2.96 (1H, dd, *J* = 9.7, 4.4 Hz, OC*H*HCHN), 2.91 (1H, dd, *J* = 9.8, 6.3 Hz, OCH*H*CHN), 1.70 (3H, d, *J* = 7.3 Hz, CH_3), 1.39 (2H, m, OCH$_2$C*H*$_2$), 1.25 (26H, m, $C_{13}H_{26}$), 0.88 (3H, t, *J* = 7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.4 (C=O), 141.3 (C), 128.4 (CH×2), 127.7 (C), 127.1 (CH×2), 71.4 (CH_2O), 70.4 (CH_2O), 65.6 (CO_2CH_2), 53.4 (CH), 51.6 (CH_2), 31.9 (CH_2), 29.70 (CH_2), 29.69 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.61 (CH_2), 29.57 (CH_2), 29.4 (CH_2), 29.42 (CH_2), 29.38 (CH_2), 29.37 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 16.4 (CH), 14.1 (CH_3). IR (KBr) cm^{-1}: 2916, 2858, 1733. HR-MS (positive FAB) *m*/*z*: 446.3642 $(M+1)^+$ (Calcd for $C_{28}H_{48}NO_3$: 446.3636). MS (positive FAB) *m*/*z*: 446 [$(M+1)^+$], 342, 190.

4.2.3. (4*S*,α*S*)-4-(Hexadecyloxymethyl)-3-(α-methylbenzyl)oxazolidin-2-one (α*S*)-7

This compound was obtained as the side product from the *O*-alkylation of (α*S*)-**4** (Table 1, entries 3 and 7). R_f value, 0.39

(hexane/AcOEt, 7:3). Yellow solid, mp 42–43 °C. $[\alpha]_D^{32} = +7.3$ (*c* 0.16, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37 (4H, d-like m, Ar), 7.28–7.32 (1H, m, Ar), 5.18 (1H, q, *J* = 7.3 Hz, PhC*H*), 4.18 (1H, d, *J* = 8.7 Hz, OC*H*H), 4.11 (1H, dd, *J* = 8.7, 3.7 Hz, OCH*H*), 3.51–3.56 (1H, m, NCH), 3.42 (1H, dd, *J* = 9.6, 5,5 Hz, OC*H*H), 3.31–3.38 (3H, m, OCH*H* and OCH_2), 1.64 (3H, d, *J* = 7.3 Hz, CH_3), 1.51 (2H, m, CH_2), 1.26 (26H, m, $CH_2\times13$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.4 (C=O), 139.2 (C, Ar), 128.7 (CH×2), 127.9 (C), 127.4 (CH×2), 71.8 (CH_2O), 71.3 (CH_2O), 65.6 (OCH_2), 53.8 (CH), 52.7 (CH), 31.9 (CH_2), 29.69 (CH_2), 29.67 (CH_2), 29.65 (CH_2), 29.60 (CH_2), 29.56 (CH_2), 29.46 (CH_2), 29.41 (CH_2), 29.35 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 18.3 (CH), 14.1 (CH_3). IR (KBr) cm^{-1}: 2912, 2848, 1733. HR-MS (positive FAB) *m*/*z*: 446.3637 $(M+1)^+$ (Calcd for $C_{28}H_{48}NO_3$: 446.3636). MS (positive FAB) *m*/*z*: 446 [$(M+1)^+$], 342, 190.

4.2.4. (4*R*,α*R*)-4-(Hexadecyloxymethyl)-3-(α-methylbenzyl)oxazolidin-2-one (α*R*)-6

This compound was obtained as the desired product from the *O*-alkylation of (α*R*)-**4** (Table 2). Yellowish solid, mp 43–45 °C. $[\alpha]_D^{28} = -10.3$ (*c* 0.43, MeOH). HR-MS (positive FAB) *m*/*z*: 446.3637 $(M+1)^+$ (Calcd for $C_{28}H_{48}NO_3$: 446.3636). MS (positive FAB) *m*/*z*: 446 [$(M+1)^+$], 342, 190. ^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) and IR (KBr) spectra were identical with those of (α*S*)-**7**.

4.3. Total synthesis of (*R*)-(−)-actisonitrile 1 from (α*S*)-6

4.3.1. (*R*)-4-(Hexadecyloxymethyl)-3-oxazolidin-2-one 8

Methanesulfonic acid (582 mg, 6.06 mmol) was added to a mixture of 2-oxazolidinone (α*S*)-**6** (270 mg 606 μmol) and anisole (328 mg, 3.03 mmol) in $MeNO_2$ (7.3 mL).[27,28] After being stirred for 3 h at 100 °C (bath temperature), the reaction mixture was cooled, diluted with AcOEt and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with AcOEt. The extracts were combined, washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt, 1:1) to give **8** (181 mg, 88%). Colorless solid, mp 62–65 °C. $[\alpha]_D^{30} = +24.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.53 (1H, br s, NH), 4.47 (1H, t, *J* = 8.8 Hz, OC*H*H), 4.12 (1H, dd, *J* = 8.8, 4.9 Hz, OCH*H*), 3.88–4.05 (1H, m, NCH), 3.88–4.05 (1H, m, NCH), 3.44 (4H, m, CH_2OCH_2), 1.55 (2H, m, CH_2), 1.26 (26H, m, $C_{13}H_{26}$), 0.88 (3H, t, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.3 (C=O), 72.5 (CH_2O), 71.9 (CH_2O), 67.1 (CO_2CH_2), 51.9 (CH_2), 31.9 (CH_2), 29.67 (CH_2), 29.64 (CH_2), 29.59 (CH_2), 29.56 (CH_2), 29.46 (CH_2), 29.42 (CH_2), 29.33 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3). IR (KBr) cm^{-1}: 3244, 2923, 2848, 1749, 1713. HR-MS (positive FAB) *m*/*z*: 342.3015 $(M+1)^+$ (Calcd for $C_{20}H_{40}NO_3$: 342.3010). MS (positive FAB) *m*/*z*: 342.3 [$(M+1)^+$]. Anal. Calcd for $C_{20}H_{39}NO_3$: C, 70.33; H, 11.51; N, 4.10. Found: C, 70.47; H, 11.65; N, 4.15.

4.3.2. (*S*)-2-Amino-3-(hexadecyloxy)propan-1-ol 9

A mixture of oxazolidinone **8** (165 mg, 483 μmol) and $LiOH\cdot H_2O$ (608 mg, 14.5 mmol) in EtOH (9.7 mL) was refluxed for 1 h. After cooling, the reaction mixture was diluted with H_2O and extracted three times with AcOEt. The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on neutral silica gel (Kanto Chemical Silica Gel 60 N, spherical, neutral, 40–50 μm) ($CHCl_3$/MeOH, 9:1) to afford **9** as a colorless solid (150 mg, 99%). Colorless solid, mp 63–66 °C. $[\alpha]_D^{29} = +3.2$ (*c* 1.00, MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ: 3.64 (1H, dd, *J* = 11.0, 6.4 Hz, OC*H*H), 3.52 (1H, dd, *J* = 11.0, 5.2 Hz, OCH*H*), 3.39–3.46 (4H, m, $OCH_2\times2$), 3.09 (1H, quint, *J* = 5.3 Hz, NCH), 1.56 (2H, quint, *J* = 6.9 Hz, CH_2), 1.26 (26 H, m, $CH_2\times13$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 73.7 (CH_2O), 71.7 (CH_2O), 64.9 (CH_2O), 52.1 (NCH), 31.9 (CH_2), 29.69 (CH_2), 29.65 (CH_2), 29.62 (CH_2), 29.59 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3). IR (KBr) cm^{-1}: 3343, 3122, 2928, 2853, 1472, 1052. HR-MS (positive FAB, glycerol)) *m*/*z*: 316.3218 $(M+1)^+$ (Calcd for $C_{19}H_{42}NO_2$: 316.3218). MS (positive FAB, glycerol) *m*/*z*: 316 [$(M+1)^+$].

4.3.3. (*S*)-*N*-(1-(Hexadecyloxy)-3-hydroxypropan-2-yl) formamide 10

A mixture of aminoalcohol **9** (60.0 mg, 190 μmol) in ethyl formate (1.9 mL) was refluxed for 2 h.[19,20] After the reaction mixture was concentrated in vacuo, the residue was chromatographed on silica gel (AcOEt) to give formamide **10** as a colorless powder (63.9 mg, 98%). Colorless solid, mp 65–67 °C. $[\alpha]_D^{29} = -13.4$ (*c* 0.62, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.23 (1H, s, NCHO), 6.27 (1H, br s, NH), 4.14 (1H, septet *J* = 4.0 Hz, NCH), 3.88 (1H, br d, *J* = 11.6 Hz, OC*H*H), 3.68–3.73 (1H, m, OCH*H*), 3.66 (1H, dd, *J* = 9.8, 4.0 Hz, OC*H*H), 3.61 (1H, dd, *J* = 9.8, 5.8 Hz, OCH*H*), 3.41–3.48 (2H, m, OCH_2), 2.86 (1H, d-like m, OH), 1.54–1.60 (2H, m, CH_2), 1.26 (26H, m, $CH_2\times13$), 0.88 (3H, t, *J* = *J* = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 161.2 (CHO), 72.0 (CH_2O), 71.6 (CH_2O), 64.1 (CH_2O), 49.5 (NCH), 31.9 (CH_2), 29.7 (CH_2), 29.65 (CH_2), 29.60 (CH_2), 29.56 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3). IR (KBr) cm^{-1}: 3339, 3267, 2919, 2853, 1649. HR-MS (positive FAB) *m*/*z*: 344.3160 $(M+1)^+$ (Calcd for $C_{20}H_{42}NO_3$: 344.3167). MS (positive FAB) *m*/*z*: 344 [$(M+1)^+$], 102.

4.3.4. (*R*)-2-Formamido-3-(hexadecyloxy)propyl acetate 11

Formamide **10** (49.3 g, 144 μmol) was dissolved in pyridine (0.28 ml) and treated with acetic anhydride (29 mg, 280 μmol). After being stirred for 2 h at room temperature, the reaction mixture was concentrated in vacuo to give pure **11** as a colorless solid (53.8 mg, 100%). Colorless solid, mp 61–62 °C. $[\alpha]_D^{30} = -4.1$ (*c* 0.65, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, s, CHO), 5.97 (1H, br d, *J* = 6.8 Hz, NH), 4.41 (1H, m, NCH), 4.24 (1H, dd, *J* = 11.2, 6.8 Hz, OC*H*H), 4.15 (1H, dd, *J* = 11.2, 5.9 Hz, OCH*H*), 3.55 (1H, dd, *J* = 9.5, 3.2 Hz, OC*H*H), 3.46 (1H, dd, *J* = 9.8, 4.9 Hz, OCH*H*), 3.42 (2H, t, *J* = 6.6 Hz, OCH_2), 2.07 (3H, s, Ac), 1.54 (2H, m, CH_2), 1.41–1.26 (26H, m, $C_{13}H_{26}$), 0.88 (3H, t, *J* = 6.8, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.9 (Ac), 160.8 (NHCHO), 71.7 (CH_2), 68.9 (CH_2), 63.3 (CH_2), 46.8 (CH), 31.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 20.8 (CH_3), 14.1 (CH_3). IR (KBr) cm^{-1}: 3280, 3066, 2919, 2848, 1732, 1662, 1527, 1463, 1384, 1266, 1115.HR-MS (positive FAB) *m*/*z*: 386.3267 $(M+1)^+$ (Calcd for $C_{22}H_{44}NO_4$: 386.3272). MS (positive FAB) *m*/*z*: 386 [$(M+1)^+$]. Anal. Calcd for $C_{22}H_{43}NO_4$: C, 68.53; H, 11.24; N, 3.63. Found: C, 68.50; H, 11.31; N, 3.57.

4.3.5. (*R*)-Actisonitrile 1[9]

A solution of formamide **10** (49.8 mg, 129 μmol), triphenylphosphine (102 mg, 0.48 mmol), and triethylamine (127 μL, 0.92 mmol) dissolved in CH_2Cl_2 (1.5 mL) was cooled to −10 °C. A solution of carbon tetrabromide (173 mg, 0.52 mmol) in CH_2Cl_2 (0.8 mL) was added to the mixture of **10**.[22,23] After the reaction mixture was stirred at −10 °C for 1 h, the reaction was quenched by the addition of water. The resulting mixture was extracted with Et_2O. The combined organic extracts were washed with 1.0 mol/L aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$. Concentration under reduced pressure afforded crude product which was purified by silica gel chromatography (hexane/AcOEt, 4:1) to provide **1** (42.5 mg, 90% yield). Yellow gel-like solid. $[\alpha]_D^{31} = -15.1$ (*c* 0.3, $CHCl_3$) {natural product, $[\alpha]_D = -7.0$ (*c* 0.27, $CHCl_3$)}.[9] ^1H NMR (500 MHz, $CDCl_3$) δ: 4.40 (1H, dd, *J* = 11.6, 4.3 Hz, OC*H*H), 4.20 (1H, dd, *J* = 11.3, 6.7 Hz, OCH*H*), 3.95 (1H, m, NCH), 3.62 (2H, m, OCH_2), 3.48 (2H, t, *J* = 6.7 Hz, OCH_2), 2.12 (3H, s, AcO), 1.56 (2H, m, CH_2), 1.34–1.23 (26H, m, $C_{13}H_{26}$), 0.88 (3H,

t, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.4 (AcO), 158.7 (NC), 72.0 (CH_2), 69.1 (CH_2), 62.7 (CH_2), 53.0 (CH), 31.9 (CH_2), 29.64 (CH_2), 29.55 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 20.6 ($COCH_2$), 14.1 (CH_3). IR (neat) cm^{-1}: 2930, 2853, 2138, 1749, 1463, 1368, 1229, 1118, 1047. HR-MS (EI) m/z: 367.3079 (M) (Calcd for $C_{22}H_{41}NO_3$: 367.3088). MS (EI) m/z: 367 (30%), 324 (60%), 294 (100%).

4.4. Synthesis of ureas (α*R*)-13 and (α*S*)-13

4.4.1. (*R*)-3-Hexadecyloxy-(3-(*R*)-α-methylbenzylureido)prop-2-yl acetate (α*R*)-13

Urea (α*R*)-**13** was synthesized from **1** according to the reported procedure.[23] Iodine (0.5 mg, 0.004 mmol) was added to a solution of actisonitrile (**1**) (15 mg, 0.041 mmol), pyridine *N*-oxide (11 mg, 0.12 mmol) and powdered molecular sieves 4Å (13 mg) in acetonitrile (0.7 ml). The reaction mixture was stirred at room temperature for 2 h, and (*R*)-α-methylbenzylamine (20 μl, 0.16 mmol) was added.[23] After stirring at room temperature for 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Concentration followed by silica gel chromatography (hexane/AcOEt, 1:1) furnished urea (α*R*)-**13** (15 mg, 74%). Yellow solid, mp 89–92 °C. $[\alpha]_D^{34} = -42.6$ (c 0.10, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6) δ: 4.94 (1H, quint, J = 6.9 Hz, PhC*H*), 4.28–4.42 (3H, m, NH and OCH_2), 4.12–4.15 (2H, m, NH and NCH), 3.30 (1H, dd, J = 9.5, 3.1 Hz, OC*H*H), 3.21 (1H, dd, J = 9.5, 4.6 Hz, OCH*H*), 3.13–3.18 (2H, m, OCH_2), 1.65 (3H, s, Ac), 1.46–1.51 (2H, m, CH_2), 1.28–1.34 (26H, m, $C_{13}H_{26}$), 1.18 (3H, d, J = 7.0 Hz, CH_3), 0.92 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.1 (C=O), 156.9 (C=O), 144.1 (C, Ar), 128.7 (CH×2, Ar), 127.3 (CH, Ar), 125.9 (CH×2, Ar), 71.6 (CH_2), 69.7 (CH_2), 63.9 (CH_2), 50.4 (CH_2), 49.0 (CH), 31.9 (CH_2), 29.64 (CH_2), 29.34 (CH_2,), 26.0 (CH_2), 23.3 (CH_3), 22.7 (CH_2), 20.8 (CH_3), 14.1 (CH_3). IR (KBr) cm^{-1}: 3378, 3327, 2919, 2857, 1749, 1638, 1555. HR-MS (positive FAB) m/z: 505.4007 $(M+1)^+$ (Calcd for $C_{30}H_{52}N_2O_4$: 505.4008). MS (positive FAB) m/z: 505 [$(M+1)^+$], 358.

4.4.2. (*R*)-3-Hexadecyloxy-(3-(*S*)-α-methylbenzylureido)prop-2-yl acetate (α*S*)-13

Urea (α*S*)-**13** was synthesized from **1** (28 mg, 0.076 mmol) according to the procedure described in the synthesis of (α*R*)-**13**. (*S*)-α-Methylbenzylamine was used instead of (*R*)-α-methylbenzylamine to afford (α*S*)-**13** (27.4 mg, 71%). Yellow solid, mp 77–80 °C. $[\alpha]_D^{33} = -5.1$ (c 0.06, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6) δ: 4.99 (1H, quint, J = 6.9 Hz, PhC*H*), 4.52 (1H, d, J = 7.9 Hz, N*H*), 4.29–4.37 (3H, m, NH and OCH_2), 4.14 (1H, m, NCH), 3.32 (1H, dd, J = 9.5, 3.6 Hz, OC*H*H), 3.15–3.26 (3H, m, OCH*H* and OCH_2), 1.68 (3H, s, Ac), 1.46–1.50 (2H, m, CH_2), 1.30–1.34 (26H, m, $C_{13}H_{26}$), 1.21 (3H, d, J = 6.7 Hz, CH_3), 0.92 (3H, t, J = 6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.9 (C=O), 156.8 (C=O), 144.0 (CH, Ar), 128.7 (CH×2, Ar), 127.3 (CH, Ar), 125.9 (CH×2), 71.6 (CH_2), 69.8, (CH_2), 63.8 (CH_2), 50.4 (CH_2), 49.0 (CH), 31.9 (CH_2), 29.64 (CH_2), 29.34 (CH_2), 26.1 (CH_2), 23.3 (CH_3), 22.7 (CH_2), 20.8 (CH_3), 14.1 (CH_3). IR (KBr) cm^{-1}: 3331, 2919, 2853, 1741, 1634, 1239. HR-MS (positive FAB) m/z: 505.4004 $(M+1)^+$ (Calcd for $C_{30}H_{52}N_2O_4$: 505.4008). MS (positive FAB) m/z: 505 [$(M+1)^+$], 358.

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