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Synthesis and Aldose Reductase Inhibitory Activity of *N*-Acylthiazolidinecarboxylic Acids

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Various mono- and dithiazolidinecarboxylic acids were synthesized by acylation of (4*R*)-4-thiazolidinecarboxylic acids and tested for aldose reductase inhibitory activity *in vitro*. (2*R*,4*R*)-3-(8-Carboxyoctanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid (**13**) and (2*R*,2'*R*,4*R*,4'*R*)-3,3'-azelaoylbis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid] (**24**) showed the most potent activity among them.

Keywords—dicarboxylic acid; thiazolidine; 4-thiazolidinecarboxylic acid; acylation; absolute configuration; aldose reductase inhibitor; (2*R*,4*R*)-3-(8-carboxyoctanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid; (2*R*,2'*R*,4*R*,4'*R*)-3,3'-azelaoylbis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]

In previous reports, we have described the syntheses and biological activities of various thiazolidinecarboxylic acid derivatives.¹⁻³⁾ In our most recent investigation, 2-arylthiazolidinecarboxylic acids (I) containing a disulfide bond were examined for aldose reductase (AR) inhibitory activity *in vitro*, and the symmetrical disulfides (II, III) and unsymmetrical disulfide (IV) were found to have potent activity (Fig. 1).³⁾ In the present paper, we report the synthesis and the AR inhibitory activity of *N*-acylthiazolidinecarboxylic acids in which the disulfide moiety of I is replaced by methylene, sulfide and oxide.

Chemistry

The monothiazolidinecarboxylic acids (**6—15**) and the symmetrical dithiazolidinecarboxylic acids (**16—28**) were obtained at the same time by acylation of 2-substituted (4*R*)-4-thiazolidinecarboxylic acids (**1—5**)⁴⁾ with acid chlorides, followed by separation by silica gel chromatography (Chart 1, Table I). The physicochemical properties of the compounds (**6—28**) are shown in Table II. In order to determine the configuration at the 2-position in the thiazolidine ring of these products, monothiazolidinecarboxylic acid **29** and its C₂-epimer **30** were synthesized by acylation of **1** with glutaric anhydride under two conditions (Chart 2). The acid **1** reacted with the anhydride in the presence of triethylamine in acetone to give **29** in 29% yield. The reaction in pyridine gave a mixture showing two spots on a thin-layer chromatogram (TLC).⁵⁾ Since this mixture could not be separated by silica gel chromatography, it was methylated with diazomethane and then separated by silica gel chromatography to give the methyl esters **31** and **32** in 32% and 14% yields based on **1**, respectively. Hydrolysis of **31** or **32** gave the corresponding acid **29** (64% yield) or **30** (88% yield).

Compound **29** was dextrorotatory (specific rotation, +163.2°) and its proton nuclear magnetic resonance (¹H-NMR) spectrum showed a large coupling constant ($J_{AX} + J_{BX} = 15.0$ Hz) in an ABX system consisting of C₄-H, C₅-H_A and C₅-H_B on the thiazolidine ring; the

Chart 2

TABLE I. Reaction of Thiazolidinecarboxylic Acids with Diacid Chlorides

Thiazolidine	X	Product (yield %) ^{a)}	
		Mono	Di
1	(CH ₂) ₄	6 (28)	16 (29)
1	(CH ₂) ₅	7 (17)	17 (17)
1	(CH ₂) ₆	8 (7)	18 (43)
1	(CH ₂) ₇	9 (6)	19 (20)
1	(CH ₂) ₈	10 (13)	20 (16)
1	(CH ₂) ₂ S(CH ₂) ₂	11 (11)	21 (11)
1	(CH ₂) ₂ O(CH ₂) ₂	12 (11)	22 (17)
2	(CH ₂) ₆		23 (30)
2	(CH ₂) ₇	13 (8)	24 (20)
2	(CH ₂) ₈		25 (41)
3	(CH ₂) ₇	14 (10)	26 (29)
4	(CH ₂) ₇		27 (54)
5	(CH ₂) ₇	15 (18)	28 (13)

a) Mono, monothiazolidinecarboxylic acid; di, dithiazolidinecarboxylic acid.

The above acids (6—28) were dextrorotatory (Table II) and showed a coupling constant ($J_{\text{AX}} + J_{\text{BX}}$) in the range of 12 to 16 Hz (Table IV), so it was concluded that 6—15 have (2*R*,4*R*)-configuration and 16—28 have (2*R*,2'*R*,4*R*,4'*R*)-configuration.

In order to study the contribution of the carboxyl group in the acyl moiety to the AR activity, the half-ester 33 and monocarboxylic acid 34 were synthesized by acylation of 2 in

TABLE II. Monothiazolidinecarboxylic Acids and Dithiazolidinecarboxylic Acids

Compd. No.	mp (°C) ^{a)} (Recrystn. solv.)	[α] _D deg. (c, MeOH, °C)	IR ν _{max} ^{Nujol} cm ⁻¹	
			CO ₂ H	CON
6	58—70 ^{b)}	+115.6 (1.0, 24)	1700	1622
7	158—159 (dec.) (AcOEt) ^{c)}	+128.6 (0.5, 25)	1710	1620
8	155—157 (dec.) (AcOEt) ^{d)}	+134.1 (0.5, 27)	1710	1620
9	153—154 (dec.) (AcOEt) ^{e)}	+70.9 (0.5, 26)	1705	1620
10	Oil	+100.3 (1.0, 24)	1710 ^{f)}	1620
11	159—160 (dec.) (AcOEt) ^{g)}	+136.4 (0.5, 27)	1710	1627
12	136—137 (AcOEt)	+147.6 (0.5, 25)	1710	1625
			1750	
13	Oil	+72.1 (0.4, 27)	1710 ^{f)}	1615
			(1525	1350) ^{h)}
14	Oil	+63.4 (0.5, 23)	1730 ^{f)}	1655
			1705	1610
15	50—73 ^{b)}	+108.3 (0.5, 23)	1720 ⁱ⁾	1660
			(1526	1345) ^{h)}
16	124—128 (MeOH) ^{j)}	+182.2 (1.0, 24) ^{k)}	1726	1620
17	Oil	+106.1 (0.5, 26)	1725 ^{f)}	1625
18	93—97 ^{b)}	+123.6 (0.5, 27)	1720	1620
19	110—125 ^{b)}	+142.7 (0.5, 26)	1720	1620
20	106—125 ^{b)}	+122.1 (1.0, 24)	1730	1628
21	110—125 ^{b)}	+129.3 (0.5, 27)	1720	1620
22	107—121 ^{b)}	+83.0 (0.5, 26)	1720	1625
23	78—100 ^{b)}	+97.5 (0.5, 21)	1730	1650
			(1520	1345) ^{h)}
24	84—99 ^{b)}	+96.2 (0.5, 27)	1725	1615
			(1520	1350) ^{h)}
25	75—120 ^{b)}	+102.2 (0.5, 25)	1735 ⁱ⁾	1620
			(1523	1345) ^{h)}
26	195—210 (dec.) (H ₂ O) ^{l)}	+103.9 (0.5, 25)	1590 ⁱ⁾	1620
27	82—93 ^{b)}	+94.8 (0.5, 21)	1735	1650
			(2250) ^{m)}	
28	121—150 ^{b)}	+167.9 (0.5, 23)	1725 ⁱ⁾	1640
			(1520	1342) ^{h)}

a) These compounds were purified by column chromatography on silica gel. b) Amorphous solid. c) *Anal.* Calcd for C₁₇H₂₁NO₆S (Found): C, 55.57; H, 5.76; N, 3.81 (C, 55.50; H, 5.87; N, 3.79). d) *Anal.* Calcd for C₁₈H₂₃NO₆S (Found): C, 56.68; H, 6.08; N, 3.67 (C, 56.58; H, 6.20; N, 3.64). e) *Anal.* Calcd for C₁₉H₂₅NO₆S (Found): C, 57.71; H, 6.37; N, 3.54 (C, 57.72; H, 6.42; N, 3.46). f) Measured by the film method. g) *Anal.* Calcd for C₁₆H₁₉NO₆S₂ (Found): C, 49.86; H, 4.97; N, 3.63 (C, 49.88; H, 4.89; N, 3.57). h) ν_{N=O}. i) Measured by the KBr disk method. j) *Anal.* Calcd for C₂₆H₂₈N₂O₈S₂·2H₂O (Found): C, 52.34; H, 5.41; N, 4.69 (C, 52.18; H, 5.01; N, 4.75). k) Measured in dimethylformamide. l) Isolated as the disodium salt. *Anal.* Calcd for C₂₉H₃₀F₂N₂Na₂O₆S₂·2.5H₂O (Found): C, 50.07; H, 5.07; N, 4.03 (C, 49.94; H, 5.24; N, 3.98). m) ν_{C≡N}.

good yield (Chart 3). The absolute configurations of **33** and **34** were also concluded to be (2*R*,4*R*), because they, like **29**, were dextrorotatory (**33**: +72.8°, **34**: +87.6°) and possessed a large coupling constant (**33** and **34**: $J_{AX} + J_{BX} = 13.0$ Hz). The half-amide **35** was obtained by aminolysis of **33** with methylamine in 62% yield.

We synthesized the following compounds so as to elucidate the effect of the acidic proton of the carboxyl group in the thiazolidine ring. The monocarboxylic acid **37** lacking the carboxyl group at the C-4 position was obtained by acylation of 2-(3-nitrophenyl)thiazolidine (**36**)⁷⁾ with azelaoyl chloride in 45% yield, accompanied by bithiazolidine **38** (Chart 4). The diester **39** with a masked carboxyl group at the C-4 position was obtained by treatment of the dicarboxylic acid **24** with diazomethane.

Chart 3

Chart 4

Biological Results and Discussion

The *N*-acylthiazolidine derivatives listed in Table III were examined for AR inhibitory activity *in vitro*. The assay was carried out by the method described in the previous paper.³⁾

Effect of Methylene Chain Length

First, we studied the effect of replacement of the disulfide bond of compounds II and IV by methylene on the inhibitory activity toward AR. When the methylene chain length was changed, monothiazolidinecarboxylic acids (8—10) and dithiazolidinecarboxylic acid (18—20) possessing hexylene to octylene moieties showed approximately equivalent activity to II

TABLE III. Inhibitory Activity against Aldose Reductase

Compd. No.	Activity ^{a)} IC ₅₀ (M)	Compd. No.	Activity ^{a)} IC ₅₀ (M)	Compd. No.	Activity ^{a)} IC ₅₀ (M)
6	6.8×10^{-6}	18	1.7×10^{-7}	30	0 ^{a/b)}
7	6.1×10^{-7}	19	3.8×10^{-7}	33	4.5×10^{-8}
8	5.4×10^{-8}	20	9.0×10^{-8}	34	2.1×10^{-8}
9	1.5×10^{-7}	21	8.4×10^{-7}	35	1.1×10^{-7}
10	3.2×10^{-7}	22	1.4×10^{-6}	37	2.9×10^{-6}
11	9.3×10^{-8}	23	4.1×10^{-8}	38	36 ^{a/b)}
12	1.8×10^{-6}	24	4.3×10^{-10}	39	6.4×10^{-6}
13	3.7×10^{-10}	25	7.0×10^{-9}	II	1.8×10^{-7}
14	7.6×10^{-7}	26	2.4×10^{-7}	III	5.8×10^{-9}
15	1.6×10^{-6}	27	1.1×10^{-7}	IV	1.4×10^{-8}
16	1.5×10^{-6}	28	1.0×10^{-6}	Quercitrin	$2.1 \times 10^{-7c)}$
17	3.6×10^{-7}	29	30 ^{a/b)}		

a) Molar concentration that causes 50% inhibition of purified rat lens aldose reductase using glyceraldehyde as a substrate. b) Inhibition (%) at 10^{-5} M. c) Mean of IC₅₀ (S.D.: $\pm 0.8 \times 10^{-7}$; $n=13$).

and IV: the distance between the two carbonyls of II and IV is nearly as long as that of **19** and **9** as determined from a molecular model. The activity of the sulfides **11** and **21**, in which methylene of **7** and **17** was replaced by sulfide, was substantially equal to that of the original compounds **7** and **17**, whereas the substitution of an oxide bond for methylene resulted in a slight decrease in the activity (**12** and **22**). Consequently, hexylene to octylene moieties were the most effective.

Effect of Configuration at C₂-Position in the Thiazolidine Ring

Compound **29** of 2*R*-configuration showed higher activity than **30** of 2*S*-configuration. This result is in agreement with that obtained with disulfides, described in the previous paper.³⁾

Substituent Effect in the Phenyl Nucleus

We attempted to substitute a 3-nitrophenyl group for the 2-hydroxyphenyl group of compounds (**9**, **18**—**20**) having hexylene to octylene moieties. (2*R*,4*R*)-3-(8-Carboxy-octanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid (**13**) and (2*R*,2'*R*,4*R*,4'*R*)-3,3'-azelaoylbis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid] (**24**) were about 10 times more active than III, which showed the most potent activity among the disulfides (I).³⁾

In order to find a more potent compound than **13** and **24**, compounds (**14**, **26** and **27**) having electron-withdrawing groups (fluoro, cyano) except for the nitro group were tested. The activity, however, was not enhanced by these substituents. Introduction of a chlorine atom into the phenyl nucleus in **13** and **24** resulted in a remarkable loss of potency (**15** and **28**).

Effect of Carboxyl Groups

The contribution of the carboxyl groups to the activity was investigated. Compound **13** having the carboxyl group in the acyl moiety was about 100 times more active than **33**—**35**. Compounds **37** and **39** lacking the carboxyl group on the thiazolidine ring were about 10000 times less active than **13** and **24**. Compound **38** without an acidic proton showed very little activity.

In summary, compounds in which a (2*R*,4*R*)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid moiety is linked to a carboxyl group or another thiazolidinecarboxylic acid moiety by a hexylene group showed the most potent inhibitory activity against AR (**13** and **24**).

Experimental

Melting points were determined on a Yamato MP-21 melting point apparatus and are uncorrected. Specific rotations were measured with a JASCO DIP-4 polarimeter. Infrared (IR) spectra were recorded on a JASCO IRA-302 spectrophotometer. NMR spectra were measured on a JEOL PMX-60 spectrometer using tetramethyl silane as an internal standard.

General Method for Monothiazolidinecarboxylic Acids (6–15) and Dithiazolidinecarboxylic Acids (16–28)—A Typical Example: Azelaoyl chloride (6.8 g, 0.03 mol) and a solution of (4*R*)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (**1**) (6.8 g, 0.03 mol) in 1 *N* NaOH (30 ml) were added dropwise to a stirred solution of K₂CO₃ (8.3 g, 0.06 mol) in water (60 ml) with cooling in an ice-salt bath. The resulting mixture was stirred in an ice bath for 1 h and at room temperature for 30 min, then acidified with 2 *N* HCl, and extracted with AcOEt. The organic layer was washed with water, dried over Na₂SO₄, and evaporated *in vacuo*. The residual oil was separated by silica gel column chromatography (benzene–AcOEt system) to give 0.7 g (6%) of **9** and 1.8 g (20%) of **19**.

(2*R*,4*R*)-3-(4-Carboxybutyryl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic Acid (29)—i) Glutaric anhydride (2.3 g, 0.02 mol) was added to a stirred solution of **1** (4.5 g, 0.02 mol) and triethylamine (5.6 ml, 0.04 mol) in acetone (100 ml). The resulting mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. After addition of 2 *N* HCl (30 ml) to the residue, the solution was extracted with AcOEt (100 ml). The organic layer was washed with water, dried over Na₂SO₄ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (benzene–AcOEt system) and recrystallized from AcOEt–EtOH to give 2.5 g (29%) of **29**, mp 160–161 °C (dec.), $[\alpha]_D^{23} + 163.2^\circ$ (*c* = 1.0, MeOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{−1}: 1707 (CO₂H), 1628 (CON). ¹H-NMR (DMSO-*d*₆) δ : 1.35–2.58 (6H, m, (CH₂)₃), 2.95 (1H, dd, *J* = 12.0 and 9.0 Hz, C₅-H_B), 3.38 (1H, dd, *J* = 12.0 and 6.0 Hz, C₅-H_A), 4.63 (dd, *J* = 9.0 and 6.0 Hz) and 4.87–5.22 (m) (1H, C₄-H), 6.30 (1H, s, C₂-H), 6.47–7.32 (3H, m, aromatic H), 7.57 (d, *J* = 7.0 Hz) and 7.86 (d, *J* = 7.0 Hz) (1H, aromatic H), 9.53 (br s) and 9.78 (br s) (1H, OH), 10.88–13.38 (2H, br, CO₂H × 2). *Anal.* Calcd for C₁₅H₁₇NO₆S: C, 53.09; H, 5.05; N, 4.13. Found: C, 53.13; H, 5.07; N, 4.16.

The *R_f* value of **29** on TLC was 0.66 (SiO₂; AcOEt–CHCl₃–AcOH = 10: 5: 3).

ii) The dimethyl ester **31** (0.37 g, 1.0 mmol) was added to 2 *N* NaOH (3 ml). The resulting solution was stirred for 2 h, acidified with 6 *N* HCl and extracted with AcOEt (15 ml × 3). The organic layer was dried over Na₂SO₄ and evaporated *in vacuo*. The residual crystals were recrystallized from EtOH–AcOEt to give 0.22 g (64%) of **29**. The melting point and other physicochemical properties of these crystals were identical with those of the product obtained by procedure (i).

Methyl (2*R*,4*R*)- and (2*S*,4*R*)-2-(2-Hydroxyphenyl)-3-[4-(methoxycarbonyl)butyryl]-4-thiazolidinecarboxylate (31) and (32)—Glutaric anhydride (4.1 g, 0.036 mol) was added to a stirred solution of **1** (6.8 g, 0.03 mol) in pyridine (40 ml). The resulting mixture was stirred at room temperature for 4 h, poured into ice-4 *N* H₂SO₄ (150 ml), and extracted with AcOEt (150 ml). The organic layer was washed with water, dried over Na₂SO₄ and evaporated *in vacuo*. The residue showed *R_f* values of 0.66 and 0.59 on TLC under the above conditions. Diazomethane in ether was added to a solution of the residue in AcOEt (150 ml) and then the solvent was removed *in vacuo*. The residual oil was separated by silica gel column chromatography (CHCl₃–MeOH system) to give 3.6 g (32%) of **31** and 1.6 g (14%) of **32**. **31**: mp 107–109 °C (CHCl₃–isopropyl ether), $[\alpha]_D^{25} + 145.1^\circ$ (*c* = 1.0, MeOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{−1}: 1747 and 1735 (CO₂), 1625 (CON). ¹H-NMR (CDCl₃) δ : 1.51–2.63 (6H, m, (CH₂)₃), 3.26 (2H, br d, *J* = 7.0 Hz, C₅-H₂), 3.58 (3H, s, CO₂CH₃), 3.78 (3H, s, CO₂CH₃), 4.91 (1H, t, *J* = 7.0 Hz, C₄-H), 6.34 (1H, br s, C₂-H), 6.63–8.13 (5H, m, aromatic H and OH). *Anal.* Calcd for C₁₇H₂₁NO₆S: C, 55.57; H, 5.76; N, 3.81. Found: C, 55.41; H, 5.76; N, 3.78. **32**: mp 123–125 °C (CHCl₃–isopropyl ether), $[\alpha]_D^{25} - 303.6^\circ$ (*c* = 0.5, MeOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{−1}: 1750 and 1723 (CO₂), 1637 (CON). ¹H-NMR (CDCl₃) δ : 1.54–2.69 (6H, m, (CH₂)₃), 3.16 (1H, dd, *J* = 12.5 and 1.3 Hz, C₅-H_B), 3.39 (1H, dd, *J* = 12.5 and 6.3 Hz, C₅-H_A), 3.56 (3H, s, CO₂CH₃), 3.77 (3H, s, CO₂CH₃), 5.26 (1H, dd, *J* = 6.3 and 1.3 Hz, C₄-H), 6.38 (s) and 6.51 (s) (1H, C₂-H), 6.60–7.20 (4H, m, aromatic H), 7.77 (br s) and 8.01 (br s) (1H, OH). *Anal.* Calcd for C₁₇H₂₁NO₆S: C, 55.57; H, 5.76; N, 3.81. Found: C, 55.49; H, 5.76; N, 3.78.

In TLC (SiO₂; CHCl₃–MeOH = 19: 1), **31** and **32** gave *R_f* values of 0.49 and 0.43, respectively.

(2*S*,4*R*)-3-(4-Carboxybutyryl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic Acid (30)—Dimethyl ester **32** (0.7 g, 1.9 mmol) was added to 2 *N* NaOH (5 ml). The resulting solution was stirred for 2 h, acidified with 6 *N* HCl and extracted with AcOEt (25 ml × 3). The organic layer was dried over Na₂SO₄ and evaporated *in vacuo*. The residual crystals were recrystallized from AcOEt–benzene to give 0.7 g (88%) of the benzenate of **30**, mp 126–128 °C, $[\alpha]_D^{26} - 267.7^\circ$ (*c* = 0.6, MeOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{−1}: 1717 (CO₂H), 1617 (CON). ¹H-NMR (acetone-*d*₆) δ : 1.55–2.73 (6H, m, (CH₂)₃), 3.20 (1H, dd, *J* = 12.5 and 1.5 Hz, C₅-H_B), 3.43 (1H, dd, *J* = 12.5 and 6.5 Hz, C₅-H_A), 5.28 (1H, dd, *J* = 6.5 and 1.5 Hz, C₄-H), 6.38 (s) and 6.48 (s) (1H, C₂-H), 6.62–7.15 (4H, m, aromatic H), 7.30 (6H, s, C₆H₆), 9.17–10.73 (3H, br, CO₂H × 2 and OH).

The *R_f* value of **30** on TLC under the same conditions as used for **29** was 0.59.

(2*R*,4*R*)-3-[8-(Ethoxycarbonyl)octanoyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic Acid (33)—8-Ethoxycarbonyloctanoyl chloride (11.7 g, 0.05 mol) was added dropwise to a stirred solution of 2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid (**2**) (12.7 g, 0.05 mol) and Na₂CO₃ (10.6 g, 0.1 mol) in water (100 ml) with cooling in an ice-salt bath. The reaction mixture was stirred for 1 h and at room temperature for 1 h, then acidified with 2 *N* HCl, and

TABLE IV. ^1H -NMR Spectral Data [δ (ppm), J =Hz in $\text{DMSO}-d_6$] for the Monothiazolidinecarboxylic Acids and Dithiazolidinecarboxylic Acids^{a)}

Compd. No.	C ₄ -H (1H)	C ₂ -H (1H)	Others
6	4.57 (dd, J =10.0, 6.0) and 4.83—5.25 (m)	6.25 (s)	1.00—1.75 (4H, m, CH_2CH_2), 1.77—2.40 (4H, m, $\text{COCH}_2 \times 2$), 2.98 (1H, dd, J =12.0, 10.0, $\text{C}_5\text{-H}_\text{B}$), 3.32 (1H, dd, J =12.0, 6.0, $\text{C}_5\text{-H}_\text{A}$), 6.43—7.28 (3H, m, aromatic H), 7.53 (br d, J =7.0) and 7.84 (d, J =7.0) (1H, aromatic H), 8.55—13.20 (3H, br, $\text{CO}_2\text{H} \times 2$, OH)
9	4.63 (dd, J =10.0, 6.0) and 4.87—5.25 (m)	6.31 (s)	0.37—1.75 (10H, m, $(\text{CH}_2)_5$), 1.80—2.40 (4H, m, $\text{COCH}_2 \times 2$), 3.03 (1H, dd, J =12.0, 10.0, $\text{C}_5\text{-H}_\text{B}$), 3.34 (1H, dd, J =12.0, 6.0, $\text{C}_5\text{-H}_\text{A}$), 6.52—7.28 (3H, m, aromatic H), 7.59 (br d, J =7.0) and 7.90 (d, J =7.0) (1H, aromatic H), 9.37—10.10 (1H, br, OH), 11.27—13.17 (2H, br, $\text{CO}_2\text{H} \times 2$)
11	4.67 (dd, J =9.0, 6.0) and 4.93—5.37 (m)	6.31 (s) and 6.40 (s)	1.70—2.93 (8H, m, $\text{CO}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{CO}$), 3.07 (1H, dd, J =12.0, 9.0, $\text{C}_5\text{-H}_\text{B}$), 3.42 (1H, dd, J =12.0, 6.0, $\text{C}_5\text{-H}_\text{A}$), 6.60—7.43 (3H, m, aromatic H), 7.58 (br d, J =7.0) and 7.93 (d, J =7.0) (1H, aromatic H), 8.67—14.33 (3H, br, $\text{CO}_2\text{H} \times 2$, OH)
12	4.65 (dd, J =9.0, 6.0) and 4.97—5.38 (m)	6.37 (s)	1.68—3.87 (10H, m, $\text{CO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CO}$, $\text{C}_5\text{-H}_2$), 6.52—7.32 (3H, m, aromatic H), 7.57 (br d, J =7.0) and 7.90 (d, J =7.0) (1H, aromatic H), 8.55—14.05 (3H, br, $\text{CO}_2\text{H} \times 2$, OH)
13	4.78 (dd, J =8.0, 7.0) and 5.08—5.43 (m)	6.33 (s) and 6.62 (s)	0.78—1.83 (10H, m, $(\text{CH}_2)_5$), 1.87—2.47 (4H, m, $\text{COCH}_2 \times 2$), 2.85—3.75 (2H, m, $\text{C}_5\text{-H}_2$), 7.00—12.00 (2H, br, $\text{CO}_2\text{H} \times 2$), 7.40—8.85 (4H, m, aromatic H)
14	4.70 (dd, J =8.0, 6.0) and 4.97—5.33 (m)	6.17 (s) and 6.38 (s)	0.73—1.80 (10H, m, $(\text{CH}_2)_5$), 1.87—2.47 (4H, m, $\text{COCH}_2 \times 2$), 3.10 (1H, dd, J =12.0, 8.0, $\text{C}_5\text{-H}_\text{B}$), 3.40 (1H, dd, J =12.0, 6.0, $\text{C}_5\text{-H}_\text{A}$), 6.67—7.93 (4H, m, aromatic H), 8.33—12.50 (2H, br, $\text{CO}_2\text{H} \times 2$)
15	4.72 (dd, J =9.0, 7.0) and 5.07—5.37 (m)	6.35 (s) and 6.50 (s)	0.77—1.77 (10H, m, $(\text{CH}_2)_5$), 1.83—2.43 (4H, m, $\text{COCH}_2 \times 2$), 2.83—3.80 (2H, m, $\text{C}_5\text{-H}_2$), 7.00—13.33 (2H, br, $\text{CO}_2\text{H} \times 2$), 7.68 (d, J =8.5) and 7.77 (d, J =8.5) (1H, $\text{C}_5\text{-H}$), 7.93—8.33 (1H, m, $\text{C}_4\text{-H}$), 8.93 (d, J =2.0) and 9.22 (d, J =2.0) (1H, $\text{C}_2\text{-H}$)
16	4.60 (dd, J =9.0, 7.0) and 4.83—5.13 (m)	6.22 (s)	0.90—1.63 (4H, m, CH_2CH_2), 1.67—2.40 (4H, m, $\text{COCH}_2 \times 2$), 3.00 (2H, dd, J =12.0, 9.0, $\text{C}_5\text{-H}_\text{B} \times 2$), 3.33 (2H, dd, J =12.0, 9.0, $\text{C}_5\text{-H}_\text{A} \times 2$), 4.20—10.70 (4H, br, $\text{CO}_2\text{H} \times 2$, OH $\times 2$), 6.47—7.30 (6H, m, aromatic H), 7.53 (d, J =7.0) and 7.85 (d, J =7.0) (2H, aromatic H)
19	4.60 (dd, J =9.5, 6.0) and 4.85—5.25 (m)	6.27 (s)	0.62—1.72 (10H, m, $(\text{CH}_2)_5$), 1.75—2.40 (4H, m, $\text{COCH}_2 \times 2$), 3.03 (2H, dd, J =12.0, 9.5, $\text{C}_5\text{-H}_\text{B} \times 2$), 3.34 (2H, dd, J =12.0, 6.0, $\text{C}_5\text{-H}_\text{A} \times 2$), 6.42—7.35 (6H, m, aromatic H), 7.57 (br d, J =7.0) and 7.87 (d, J =7.0) (2H, aromatic H), 8.35—14.00 (4H, br, $\text{CO}_2\text{H} \times 2$, OH $\times 2$)
21	4.59 (dd, J =8.0, 6.0) and 4.86—5.19 (m)	6.31 (s) and 6.34 (s)	1.97—2.74 (8H, m, $\text{COCH}_2\text{CH}_2 \times 2$), 2.96 (2H, dd, J =12.0, 8.0, $\text{C}_5\text{-H}_\text{B} \times 2$), 3.38 (2H, dd, J =12.0, 6.0, $\text{C}_5\text{-H}_\text{A} \times 2$), 6.45—7.31 (6H, m, aromatic H), 7.47 (br d, J =7.0) and 7.81 (d, J =7.0) (2H, aromatic H), 9.30—10.12 (2H, br, OH $\times 2$), 12.18—13.58 (2H, br, $\text{CO}_2\text{H} \times 2$)
22	4.65 (dd, J =9.0, 6.0) and 4.93—5.40 (m)	6.33 (s)	1.67—3.80 (12H, m, $\text{CO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CO}$, $\text{C}_5\text{-H}_2 \times 2$), 6.50—7.33 (6H, m, aromatic H), 7.55 (br d, J =7.0) and 7.92 (d, J =7.0) (2H, aromatic H), 8.63—14.13 (4H, br, $\text{CO}_2\text{H} \times 2$, OH $\times 2$)
24	4.75 (dd, J =9.0, 7.0) and 5.05—5.30 (m)	6.28 (s) and 6.58 (s)	0.58—1.75 (10H, m, $(\text{CH}_2)_5$), 1.78—2.45 (4H, m, $\text{COCH}_2 \times 2$), 2.82—3.78 (4H, m, $\text{C}_5\text{-H}_2 \times 2$), 5.45—10.28 (2H, br, $\text{CO}_2\text{H} \times 2$), 7.38—8.82 (8H, m, aromatic H)
26	4.48 (t, J =6.0)	6.22 (s)	0.67—1.77 (10H, m, $(\text{CH}_2)_5$), 2.00—2.42 (4H, m, $\text{COCH}_2 \times 2$), 3.27 (2H, dd, J =11.0, 6.0, $\text{C}_5\text{-H}_\text{B} \times 2$), 3.40 (5H, s, $2.5\text{H}_2\text{O}$), 3.47 (2H, dd, J =11.0, 6.0, $\text{C}_5\text{-H}_\text{A} \times 2$), 6.67—8.30 (8H, m, aromatic H)
27	4.77 (dd, J =8.0, 7.0) and 5.00—5.35 (m)	6.23 (s) and 6.47 (s)	0.60—1.80 (10H, m, $(\text{CH}_2)_5$), 1.83—2.67 (4H, m, $\text{COCH}_2 \times 2$), 2.80—3.77 (4H, m, $\text{C}_5\text{-H}_2 \times 2$), 7.17—8.43 (8H, m, aromatic H), 8.50—12.70 (2H, br, $\text{CO}_2\text{H} \times 2$)
28	4.72 (dd, J =9.0, 6.0) and 5.02—5.37 (m)	6.35 (s) and 6.47 (s)	0.57—1.73 (10H, m, $(\text{CH}_2)_5$), 1.80—2.43 (4H, m, $\text{COCH}_2 \times 2$), 2.80—3.82 (4H, m, $\text{C}_5\text{-H}_2 \times 2$), 5.53—9.87 (2H, br, $\text{CO}_2\text{H} \times 2$), 7.70 (d, J =9.0) and 7.77 (d, J =9.0) (2H, $\text{C}_5\text{-H} \times 2$), 7.95—8.33 (2H, m, $\text{C}_4\text{-H} \times 2$), 8.93 (d, J =2.0) and 9.23 (d, J =2.0) (2H, $\text{C}_2\text{-H} \times 2$)

a) Typical NMR data are listed in this table.

extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residual oil was purified by silica gel column chromatography (benzene–AcOEt system) to give 11.2 g (50%) of **33** as an oil; $[\alpha]_{\text{D}}^{23} + 72.8^\circ$ ($c = 1.0$, MeOH). IR $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$: 1735 (CO_2H and CO_2), 1663 (CON), 1533 and 1351 (NO_2). $^1\text{H-NMR}$ (CDCl_3) δ : 0.83–1.87 (13H, m, CH_3 and $(\text{CH}_2)_5$), 2.00–2.63 (4H, m, $\text{COCH}_2 \times 2$), 3.13–3.87 (2H, m, $\text{C}_5\text{-H}_2$), 4.10 (2H, q, $J = 7.0$ Hz, CO_2CH_2), 5.05 (1H, t, $J = 6.5$ Hz, $\text{C}_4\text{-H}$), 6.24 (s) and 6.37 (s) (1H, $\text{C}_2\text{-H}$). 7.38–8.68 (4H, m, aromatic H), 9.53 (1H, s, CO_2H).

(2R,4R)-2-(3-Nitrophenyl)-3-octanoyl-4-thiazolidinecarboxylic Acid (34)—Octanoyl chloride (3.6 g, 0.022 mol) was added dropwise to a stirred solution of **2** (5.1 g, 0.02 mol) and K_2CO_3 (5.5 g, 0.04 mol) in water (50 ml) and ether (20 ml) with cooling in an ice bath. The resulting mixture was stirred for 1 h then at room temperature for 1 h. After separation of the ether solution, the aqueous solution was acidified with conc. HCl and extracted with AcOEt (100 ml). The AcOEt layer was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residual oil was purified by silica gel column chromatography (benzene–AcOEt system) to give 7.6 g of **34** as an oil. After addition of 1 N NaOH (20 ml) to a solution of this oil in MeOH (20 ml), the MeOH was removed *in vacuo* and the resulting needles were filtered off to give 6.8 g (84%) of the sodium salt of **34**, mp $87\text{--}91^\circ\text{C}$ (H_2O), $[\alpha]_{\text{D}}^{24} + 87.6^\circ$ ($c = 0.7$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 1620 (CO_2 and CON), 1530 and 1350 (NO_2). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 0.48–1.82 (13H, m, $(\text{CH}_2)_5\text{CH}_3$), 2.40 (2H, br t, $J = 6.0$ Hz, COCH_2), 3.37 (2H, d, $J = 6.5$ Hz, $\text{C}_5\text{-H}_2$), 4.55 (1H, t, $J = 6.5$ Hz, $\text{C}_4\text{-H}$), 6.33 (s) and 6.45 (s) (1H, $\text{C}_2\text{-H}$), 7.47 (1H, t, $J = 8.0$ Hz, $\text{C}_5\text{-H}$), 8.02 (1H, br d, $J = 8.0$ Hz, $\text{C}_6\text{-H}$), 8.33 (1H, br d, $J = 8.0$ Hz, $\text{C}_4\text{-H}$), 8.62 (1H, br s, $\text{C}_2\text{-H}$). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{NaO}_5\text{S} \cdot 2\text{H}_2\text{O}$: C, 49.31; H, 6.21; N, 6.39. Found: C, 49.26; H, 7.00; N, 6.39.

(2R,4R)-3-[8-(Methylcarbamoyl)octanoyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic Acid (35)—A solution of **33** (2.0 g, 4.4 mmol) in tetrahydrofuran (THF, 3 ml) was treated with 40% aqueous methylamine (10 ml). The resulting mixture was stirred at room temperature for 10 h, acidified with 6 N HCl and extracted with AcOEt (40 ml). The organic layer was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residual oil was purified by silica gel column chromatography ($\text{CHCl}_3\text{--MeOH}$ system) to give 1.2 g (62%) of **35** as an oil, $[\alpha]_{\text{D}}^{25} + 65.6^\circ$ ($c = 1.0$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 1730 (CO_2H), 1640 (CON), 1531 and 1350 (NO_2). $^1\text{H-NMR}$ ($\text{CDCl}_3\text{--acetone-}d_6$) δ : 0.53–1.87 (10H, m, $(\text{CH}_2)_5$), 1.92–2.58 (4H, m, $\text{COCH}_2 \times 2$), 2.75 (3H, d, $J = 5.0$ Hz, NCH_3), 3.10–3.70 (2H, m, $\text{C}_5\text{-H}_2$), 5.00 (1H, t, $J = 6.0$ Hz, $\text{C}_4\text{-H}$), 6.33 (1H, s, $\text{C}_2\text{-H}$), 6.53–7.03 (1H, br, CONH), 7.52 (1H, m, $\text{C}_5\text{-H}$), 7.78–8.28 (2H, m, $\text{C}_4\text{-H}$ and $\text{C}_6\text{-H}$), 8.55 (1H, m, $\text{C}_2\text{-H}$), 8.72 (1H, br s, CO_2H).

3-(8-Carboxyoctanoyl)-2-(3-nitrophenyl)thiazolidine (37) and 3,3'-Azelaoylbis[2-(3-nitrophenyl)thiazolidine] (38)—A solution of 2-(3-nitrophenyl)thiazolidine hydrochloride (**36**) (4.6 g, 0.019 mol) and triethylamine (5.6 ml, 0.04 mol) in CH_2Cl_2 (100 ml) was added dropwise to a stirred solution of azelaoyl chloride (5.0 g, 0.022 mol) in CH_2Cl_2 (60 ml) at -10°C , followed by addition of 2 N NaOH (15 ml). The resulting mixture was stirred at -10°C for 30 min and at room temperature for 30 min. After addition of 1 N NaOH (50 ml), the organic layer was washed with water and 1 N HCl (50 ml $\times 2$), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in benzene (20 ml), and the solution was extracted with 0.2 N KOH (70 ml). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give 2.3 g (43%) of **38** as an oil. The aqueous layer was acidified with 6 N HCl and extracted with AcOEt. The AcOEt layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (benzene–AcOEt system) to give 3.2 g (45%) of **37** as an oil. **37**: IR $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$: 1727 and 1705 (CO_2H), 1645 and 1615 (CON), 1529 and 1346 (NO_2). $^1\text{H-NMR}$ (CDCl_3) δ : 0.70–1.95 (10H, m, $(\text{CH}_2)_5$), 1.98–2.68 (4H, m, $\text{COCH}_2 \times 2$), 3.17 (2H, br t, $J = 5.5$ Hz, $\text{C}_5\text{-H}_2$), 4.05 (2H, br t, $J = 5.5$ Hz, $\text{C}_4\text{-H}_2$), 6.18 (br s) and 6.43 (br s) (1H, $\text{C}_2\text{-H}$), 7.33–8.23 (4H, m, aromatic H), 8.35 (1H, br s, CO_2H). **38**: IR $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$: 1645 (CON), 1527 and 1349 (NO_2). $^1\text{H-NMR}$ (CDCl_3) δ : 0.93–1.90 (10H, m, $(\text{CH}_2)_5$), 2.08–2.63 (4H, m, $\text{COCH}_2 \times 2$), 3.12 (4H, t, $J = 5.5$ Hz, $\text{C}_5\text{-H}_2 \times 2$), 3.99 (4H, t, $J = 5.5$ Hz, $\text{C}_4\text{-H}_2 \times 2$), 6.20 (br s) and 6.41 (br s) (2H, $\text{C}_2\text{-H} \times 2$), 7.27–8.27 (8H, m, aromatic H).

Dimethyl (2R,2'R,4R,4'R)-3,3'-Azelaoylbis[2-(3-nitrophenyl)-4-thiazolidinecarboxylate] (39)—A solution of diazomethane in ether was added dropwise to a solution of **24** (3.3 g, 5.0 mmol) in AcOEt (50 ml). The resulting solution was stirred for 30 min and evaporated *in vacuo*. The residue was recrystallized from benzene to give 3.3 g (82%) of **39**, mp $61\text{--}63^\circ\text{C}$, $[\alpha]_{\text{D}}^{23} + 79.4^\circ$ ($c = 1.0$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 1740 (CO_2), 1652 (CON), 1527 and 1347 (NO_2). $^1\text{H-NMR}$ (CDCl_3) δ : 0.70–1.80 (10H, m, $(\text{CH}_2)_5$), 1.87–2.53 (4H, m, $\text{COCH}_2 \times 2$), 3.21 (2H, dd, $J = 10.0$ and 6.5 Hz, $\text{C}_5\text{-H}_B \times 2$), 3.37 (2H, dd, $J = 10.0$ and 6.5 Hz, $\text{C}_5\text{-H}_A \times 2$), 3.83 (6H, s, $\text{CO}_2\text{CH}_3 \times 2$), 4.94 (2H, t, $J = 6.5$ Hz, $\text{C}_4\text{-H} \times 2$), 6.14 (s) and 6.31 (s) (2H, $\text{C}_2\text{-H} \times 2$), 7.28 (9H, s, $\text{C}_6\text{H}_6 \times 1.5$), 7.43–8.63 (8H, m, aromatic H). Anal. Calcd for $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_{10}\text{S}_2 \cdot 1.5\text{C}_6\text{H}_6$: C, 59.61; H, 5.63; N, 6.95. Found: C, 59.56; H, 5.53; N, 7.08.

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