Synthesis and Platelet Aggregation Inhibitory Activities of 3-(2-Oxopropylidene)azetidin-2-one Derivatives. II[1,2]

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A series of 3-acylidene-4-methylazetidin-2-one derivatives bearing various substituents at the 1-position of the azetidin-2-one ring was synthesized. These compounds were evaluated for platelet aggregation inhibitory activities. Most of the compounds synthesized showed potent inhibitory activities against rabbit platelet aggregation induced by adenosine diphosphate or collagen *in vitro*. Structure–activity relationships are also discussed.

Keywords 3-(acylidene)azetidin-2-one; azetidin-2-one; platelet aggregation inhibition; adenosine diphosphate; collagen; structure–activity relationship

In the previous paper,[1] we showed that (*E* or *Z*)-3-(2-oxopropylidene)-4-methyl-1-phenylazetidin-2-ones inhibit rabbit platelet aggregation induced by adenosine diphosphate (ADP) or collagen *in vitro*, and the 3-acylideneazetidin-2-one skeleton is essential for the activity. In the next stage of the evaluation of this series of compounds, we have examined the synthesis of the azetidin-2-one derivatives bearing various acylidene moieties at the 3-position and various alkyl or substituted phenyl moieties at the 1-position of the azetidin-2-one ring. Synthesis of these compounds and the results of biological evaluations are described in this paper.

Chemistry The synthesis of 3-(acylidene)azetidin-2-ones (**10a**—**y**, **11a**—**p**) was accomplished by the methods shown in Chart 1.

Lithiation of 1,4-disubstituted-azetidin-2-ones (**1a**—**p**)[3] with lithium diisopropylamide (LDA) followed by condensation with the esters (**2**,[3] **3**[4] or **4**[5]) in tetrahydrofuran (THF) at −78 °C gave 3-acylazetidin-2-one derivatives (**5a**—**y**) as a single isomer in good yields. The stereochemistry of azetidin-2-one ring of (**5a**—**y**) was determined to be 3,4-*trans* based on the coupling constant (3—4 Hz) between C_3-H and C_4-H of (**5a**—**y**). Reduction of the ketone moiety of **5a**—**y** by $NaBH_4$ in MeOH at −78 °C proceeded in a stereoselective manner through a sodium cation chelated intermediate[1] to give corresponding α alcohols (**6a**—**y**) in excellent yields. The configuration of the hydroxy group of **6a**—**y** was determined by the stereochemistry of the product of elimination reaction described below. Compounds **6a**—**y** were treated with methanesulfonyl chloride (MsCl) in pyridine and triethylamine to give the corresponding mesylates (**7a**—**y**) in quantitative yields, which were treated with an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene under reflux to give a mixture of the *E* form olefins (**8**) and the *Z* form olefins (**9**). The geometry of the enone moiety of **8** was determined to be *E* and **9** was to be *Z* based on the characteristic olefinic proton signals observed in their ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum. The olefinic proton of **8** resonated at a lower field than that of **9** because of the deshielding effect of the carbonyl group of the azetidin-2-one ring. The ratio of the formation of the *E* isomer (**8**) and the *Z* isomer (**9**)

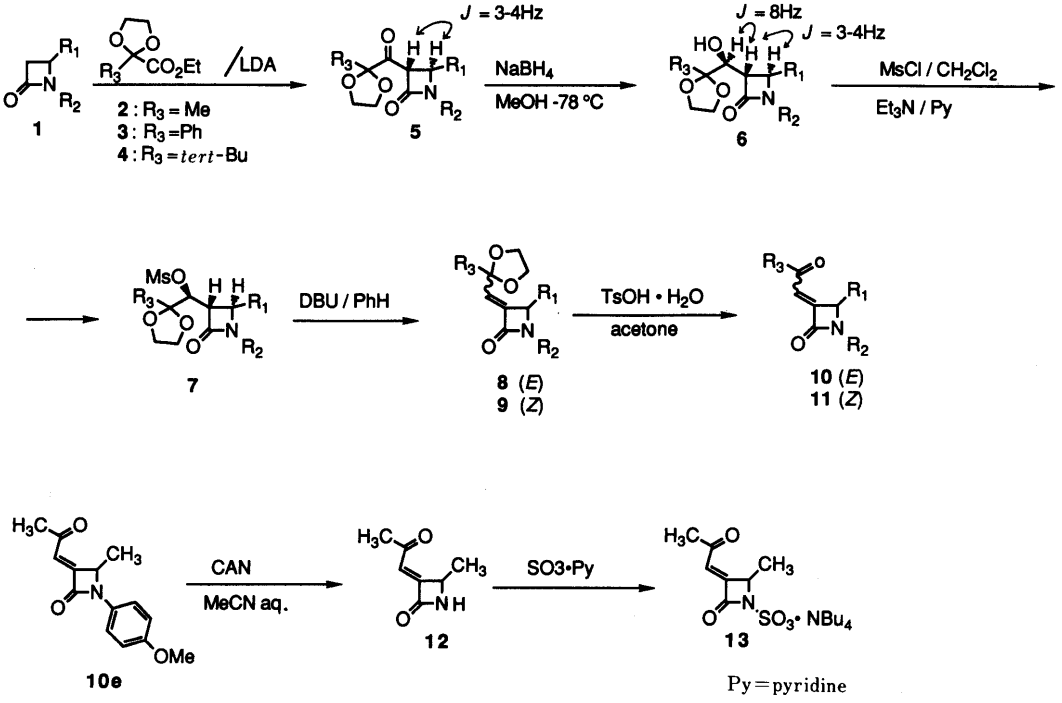


Chart 1

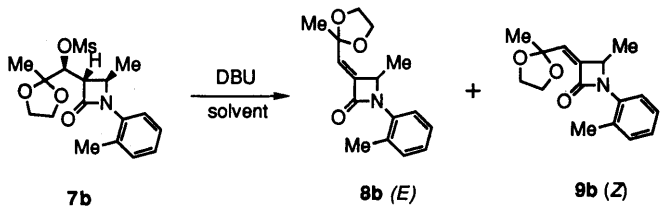
TABLE I. 3-Acylideneazetidin-2-one Derivatives and Their Inhibition of Platelet Aggregation

	R_1	R_2	R_3	Yield (%)	mp (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)			*In vitro*[a] IC_{50} (μM)	
							C	H	N	ADP	Collagen
10a	Me	Ph	Me	86	120—122 (EtOH)	$C_{13}H_{13}NO_2$	72.54 (72.33	6.09 5.96	6.51 6.43)	29.0	27.0[b]
10b	Me	2-Me-Ph	Me	65	74—76 (EtOH)	$C_{14}H_{15}NO_2$	73.34 (73.12	6.60 6.58	6.11 6.08)	18.4	8.6
10c	Me	3-Me-Ph	Me	47	59.5—61.5 (EtOH)	$C_{14}H_{15}NO_2$	73.34 (73.62	6.60 6.62	6.11 6.14)	25.0	17.0
10d	Me	2-MeO-Ph	Me	74	79.5—81 (Ether)	$C_{14}H_{15}NO_3$	68.56 (68.64	6.16 6.21	5.71 5.94)	33.0	24.0
10e	Me	4-MeO-Ph	Me	55	107.5—109 (EtOH)	$C_{14}H_{15}NO_3$	68.56 (68.44	6.16 6.13	5.71 5.76)	14.0	19.0
10f	Me	2-F-Ph	Me	56	73—75.5 (EtOH)	$C_{13}H_{12}FNO_2$	66.94 (66.82	5.18 5.27	6.01 5.96)	27.0	20.0
10g	Me	4-F-Ph	Me	87	123—124 (EtOH)	$C_{13}H_{12}FNO_2$	66.94 (66.97	5.18 5.35	6.01 5.99)	14.0	13.0
10h	Me	2-Cl-Ph	Me	90	Oil	$C_{13}H_{12}ClNO_2$		265.0557[c] (265.0527)		19.0	15.0
10i	Me	3-CF_3-Ph	Me	50	54—57 (EtOH)	$C_{14}H_{12}F_3NO_2$	59.37 (59.16	4.27 4.20	4.95 4.79)	29.0	18.0
10j	Me	3-Py	Me	56	105—107 (EtOH)	$C_{12}H_{12}N_2O_2$	66.65 (66.69	5.59 5.62	12.95 12.95)	15.2	10.5
10k	H	Ph	Me	60	154.5—156.5 (EtOH–hexane)	$C_{12}H_{11}NO_2$	71.63 (71.50	5.51 5.61	6.96 6.82)	35.0	26.0
11a	Me	Ph	Me	84	114—115.5 (Ether)	$C_{13}H_{13}NO_2$	72.54 (72.38	6.09 6.11	6.51 6.52)	52.0	19.0[b]
11b	Me	2-Me-Ph	Me	7	78—79.5 (Ether–hexane)	$C_{14}H_{15}NO_2$	73.34 (73.45	6.60 6.69	6.11 5.87)	15.7	6.1
11c	Me	3-Me-Ph	Me	19	95—96 (EtOH)	$C_{14}H_{15}NO_2$	73.34 (73.06	6.60 6.55	6.11 6.22)	9.9	8.2
11d	Me	2-MeO-Ph	Me	50	100—101 (Ether)	$C_{14}H_{15}NO_3$	68.56 (68.40	6.16 6.16	5.71 5.71)	24.0	24.0
11e	Me	4-MeO-Ph	Me	2	158.5—160.5 (EtOH)	$C_{14}H_{15}NO_3$	68.56 (68.25	6.16 6.09	5.71 5.51)	16.7	8.3
11g	Me	4-F-Ph	Me	56	113—114 (EtOH)	$C_{13}H_{12}FNO_2$	66.94 (67.08	5.18 5.45	6.01 6.04)	14.0	18.0
11j	Me	3-Py	Me	55	121.5—123.5 (EtOH)	$C_{12}H_{12}N_2O_2$	66.65 (66.78	5.59 5.63	12.95 13.13)	23.5	11.7
12	Me	H	Me	29	117.5—120.5 (Ether)	$C_7H_9NO_2$	60.41 (60.34	6.53 6.52	10.07 10.14)	43.7	38.6
10l	Me	Me	Me	20	Oil	$C_8H_{11}NO_2$		153.0790[c] (153.0820)		80.8	29.1
10m	Me	Pr	Me	37	Oil	$C_{10}H_{15}NO_2$		181.1103[c] (181.1079)		102.2	24.0
10n	Me	iso-Bu	Me	37	Oil	$C_{11}H_{17}NO_2$		195.1259[c] (195.1254)		65.0	21.0
10o	Me	cyclo-Hex	Me	55	Oil	$C_{13}H_{19}NO_2$		221.1416[c] (221.1386)		17.1	15.1
10p	Me	Bz	Me	6	Oil	$C_{14}H_{15}NO_2$		229.1103[c] (229.1122)		63.0	35.0
11l	Me	Me	Me	34	Oil	$C_8H_{11}NO_2$		153.0790[c] (153.0799)		218.1	75.3
11m	Me	Pr	Me	45	Oil	$C_{10}H_{15}NO_2$		181.1103[c] (181.1128)		215.6	47.7
11n	Me	iso-Bu	Me	18	Oil	$C_{11}H_{17}NO_2$		195.1259[c] (195.1278)		79.0	40.0
11o	Me	cyclo-Hex	Me	22	Oil	$C_{13}H_{19}NO_2$		221.1416[c] (221.1378)		24.4	13.6
11p	Me	Bz	Me	3	Oil	$C_{14}H_{15}NO_2$		229.1103[c] (229.1094)		44.0	36.0
10q	Me	Ph	Ph	31	134—135 (EtOH)	$C_{18}H_{15}NO_2$	77.96 (77.66	5.45 5.76	5.05 4.90)	9.4	9.6
10r	Me	2-Me-Ph	Ph	71	73.5—75.5 (EtOH)	$C_{19}H_{17}NO_2$	78.33 (78.35	5.88 5.92	4.81 4.76)	6.4	6.0
10s	Me	3-Me-Ph	Ph	31	121—121.5 (EtOH)	$C_{19}H_{17}NO_2$	78.33 (78.01	5.88 5.95	4.81 4.89)	9.9	12.0
10t	Me	4-MeO-Ph	Ph	66	185—186 (EtOH)	$C_{19}H_{17}NO_3$	74.25 (74.27	5.57 5.74	4.56 4.58)	7.8	6.2

TABLE I. (continued)

	R_1	R_2	R_3	Yield (%)	mp (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	*In vitro*[a] IC_{50} (μM) ADP	Collagen
10u	Me	2-F-Ph	Ph	54	114—115 (EtOH)	$C_{18}H_{14}FNO_2$	73.21 (72.97	4.78 4.71	4.74 4.95)	13.6	29.5
10v	Me	3-Py	Ph	44	151—153 (EtOH)	$C_{17}H_{14}N_2O_2$	73.37 (73.21	5.07 5.11	10.66 10.16)	2.1	4.0
10w	Me	iso-Pr	Ph	52	63—65 (EtOH)	$C_{15}H_{17}NO_2$	74.05 (74.31	7.04 7.21	5.76 5.65)	7.4	8.4
10x	Me	iso-Bu	Ph	24	71.5—73 (EtOH)	$C_{16}H_{19}NO_2$	74.68 (74.63	7.44 7.39	5.44 5.39)	6.8	6.4
10y	Me	2-Me-Ph	*tert*-Bu	50	71—72 (Ether)	$C_{17}H_{21}NO_2$	75.25 (75.19	7.80 7.58	5.16 5.19)	21.0	13.0
13	Me	SO_3NBu_4	Me		101.5—104.5 (EtOH)	$C_{23}H_{44}N_2O_5S$	59.95 (60.16	6.53 6.64	6.08 6.21)	>300	>300
Aspirine										>300	35.0
Ticlopidine										>300	>300

a) Micromolar condensation of test compound for 50% inhibition of rabbit platelet agregation induced by ADP (5 μM) or collagen (5 μg/ml). *b*) Ref. 1. *c*) High resolution MS (*m/z*).



7b **8b** (*E*) **9b** (*Z*)

solvent	condition	8b : 9b
benzene	reflux 2 h	4.7 : 1
$CHCl_3$	reflux 10 h	no reaction
CH_3CN	reflux 1 h	1 : 1.8
MeOH	reflux 2 h	1 : 1.8
DMSO	80 °C 2 h	1 : 5.6

Chart 2

in the elimination reactions was varied according to the substituents of R_3 and by the reaction solvent used. The ratio of *E* and *Z* isomer was about 5 : 1 in the case where R_3 was the methyl group, about 10 : 1 in the phenyl group, and 1 : 0 in the *tert*-butyl group, when the elimination reaction was carried out in benzene under reflux. Thus, it was obvious that the bulky substituent at R_3 tended to increase the formation of *E* form olefins (**8**). The next time, the effect of the solvents used in the elimination reaction was examined (Chart 2).

Although the formation of the *E* isomer was dominant in the less polar solvent such as benzene, the formation of the *Z* isomer has become dominant in polar solvents such as methanol or dimethyl sulfoxide (DMSO). The above result indicates that the *E* form olefins were formed from α form alcohols through *E*2 elimination in the less polar solvents. The mechanism of the formation of the *Z* form olefins is not clear but it seems to be formed through E_{CB}1-like elimination reactions. In the last stage of the synthesis, deprotection of the acetal moiety of **8** and **9** was accomplished by heating with a catalytic amount of *p*-toluenesulfonic acid in acetone to give the desired enone derivatives (**10**) and (**11**) in good yields (Chart 1). Compound (**10e**) was treated with ceric ammonium nitrate (CAN) to give **12**, which was further treated with sulfur trioxide to give sulfo derivative (**13**). In addition, the physiological and spectral data of **10a** and **11a** were identical with the data described in the previous paper.[1]

Pharmacological Results and Discussion

The platelet aggregation inhibitory activities of the compounds synthesized were tested on rabbit platelet-rich plasma (PRP) *in vitro* by the method shown in the previous paper.[1]

Almost all of the compounds tested showed potent platelet aggregation inhibitory activities *in vitro*, and the following structure activity relationships were investigated.

At first, the effect of the substituent at the acylidene moiety (R_3) was investigated. Although the substitution of the methyl group (**10b**) at the acylidene moiety with the *tert*-butyl group (**10y**) did not affect the activities, substitution with the phenyl group (**10r**) increased the activities 4-fold. Thus, the electron withdrawing group at the acylidene moiety seems to enhance the activities.

Next, the effect of the substituents at the 1 position of the azetidinone ring was investigated. Substitution of the phenyl group of (**10a**) with the cyclohexyl group (**10o**) did not affect the activities, but substitution with the hydrogen (**12**), methyl group (**101**), propyl group (**10m**), isobutyl group (**10n**) and sulfo group (**13**) decreased the activities. Substitution of the phenyl group of (**10a**) with the 3-pyridyl group (**10j**) increased the activities 2 to 4-fold, and the introduction of a substituent to the *ortho* position of the phenyl group tends to increase the activities. Those results indicate that the introduction of the relative bulky group at the 1 position of the azetidinone ring increases the activities 1.5 to 2-fold.

At last, the effect of the geometry at the acylidene moiety was investigaged, and there were no differences between the activities of the *E* isomers and the *Z* isomers.

Experimental

Melting points were determined by Mettler FP-60 melting point apparatus. Infrared (IR) spectra were taken on a Jasco X-1A spectrometer. ^{1}H-NMR spectra were recorded with a Varian XL-200 spectrometer (Me_4Si as an internal standard, δ ppm value), and the following abbreviations are used: singlet (s), broad singlet (br s), doublet (d), double

TABLE II. Spectral Data for the Compounds in Table I

	IR	MS (*m/z*)	NMR (δ, $CDCl_3$)
10b	1745 1660	229 (M^+)	1.46 (3H, d, J=6 Hz), 2.36 (3H, s), 2.38 (3H, s), 5.06 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.70 (1H, d, J=2 Hz), 7.2—7.35 (4H, m)
10c	1725 1650	229 (M^+)	1.63 (3H, d, J=6 Hz), 2.36 (6H, s), 4.97 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.67 (1H, d, J=2 Hz), 6.98 (1H, m), 7.15—7.4 (3H, m)
10d	1740 1650	245 (M^+)	1.47 (3H, d, J=6 Hz), 2.35 (3H, s), 3.86 (3H, s), 5.25 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.62 (1H, d, J=2 Hz), 6.93 (1H, m), 6.99 (1H, m), 7.16 (1H, m), 7.93 (1H, m)
10e	1725 1650	245 (M^+)	1.62 (3H, d, J=6 Hz), 2.35 (3H, s), 3.80 (3H, s), 4.95 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.64 (1H, d, J=2 Hz), 6.92 (2H, m), 7.41 (2H, m)
10f	1750 1660	233 (M^+)	1.58 (1H, dd, J=6, 1 Hz), 2.36 (3H, s), 5.17 (1H, m), 6.66 (1H, d, J=2 Hz), 7.05—7.2 (3H, m), 8.05 (1H, m)
10g	1740 1665	233 (M^+)	1.62 (3H, d, J=6 Hz), 2.38 (3H, s), 4.96 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.60 (1H, d, J=2 Hz), 7.08 (2H, m), 7.42 (2H, m)
10h	1750 1660	249 (M^+)	1.52 (3H, d, J=6 Hz), 2.38 (3H, s), 5.46 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.70 (1H, d, J=2 Hz), 7.20 (1H, m), 7.31 (1H, m), 7.43 (1H, m), 7.85 (1H, m)
10i	1750 1660	283 (M^+)	1.66 (3H, d, J=6 Hz), 2.39 (3H, s), 5.03 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.72 (1H, d, J=2 Hz), 7.4—7.7 (4H, m)
10j	1755 1655	216 (M^+)	1.68 (3H, d, J=6 Hz), 2.40 (3H, s), 5.05 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.71 (1H, d, J=2 Hz), 7.34 (1H, dd, J=8, 6 Hz), 7.94 (1H, dt, J_d=8 Hz, J_t=2 Hz), 8.43 (1H, dd, J=6, 2 Hz), 8.65 (1H, d, J=2 Hz)
10k	1740 1680	201 (M^+)	2.38 (3H, s), 4.49 (2H, d, J=2 Hz), 6.72 (1H, t, J=2 Hz), 7.18 (1H, m), 7.3—7.5 (4H, m)
11b	1720 1685	229 (M^+)	1.44 (3H, d, J=6 Hz), 2.38 (3H, s), 2.76 (3H, s), 4.76 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.99 (1H, d, J=1 Hz), 7.2—7.4 (4H, m)
11c	1730 1660	229 (M^+)	1.60 (3H, d, J=6 Hz), 2.38 (3H, s), 2.74 (3H, s), 4.67 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.97 (1H, d, J=1 Hz), 7.01 (1H, m), 7.2—7.4 (3H, m)
11d	1730 1665	245 (M^+)	1.44 (3H, d, J=6 Hz), 2.74 (3H, s), 3.87 (3H, s), 4.98 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.91 (1H, d, J=1 Hz), 6.96 (1H, m), 7.03 (1H, m), 7.21 (1H, m), 7.93 (1H, m)
11e	1730 1665	245 (M^+)	1.59 (3H, d, J=6 Hz), 2.75 (3H, s), 3.82 (3H, s), 4.64 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.95 (1H, d, J=1 Hz), 6.95 (2H, m), 7.43 (2H, m)
11g	1740 1665	233 (M^+)	1.60 (3H, d, J=6 Hz), 2.72 (3H, s), 4.65 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.98 (1H, d, J=1 Hz), 7.10 (2H, m), 7.45 (2H, m)
11j	1740 1665	216 (M^+)	1.65 (3H, d, J=6 Hz), 2.73 (3H, s), 4.76 (1H, dq, J_d=1 Hz, J_q=6 Hz), 6.02 (1H, d, J=1 Hz), 7.36 (1H, dd, J=6, 8 Hz), 8.00 (1H, dt, J_d=1 Hz, J_q=6 Hz), 8.45 (1H, dd, J=2, 6 Hz), 8.63 (1H, d, J=2 Hz)
11l	1750 1660	153 (M^+)	1.43 (3H, d, J=6 Hz), 2.32 (3H, s), 2.95 (3H, s), 4.39 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.52 (1H, d, J=2 Hz)
10m	1740 1660	181 (M^+)	0.96 (3H, t, J=8 Hz), 1.45 (3H, d, J=6 Hz), 1.65 (2H, m), 2.33 (3H, s), 3.15 (1H, dt, J_d=14 Hz, J_t=8 Hz), 3.46 (1H, dt, J_d=14 Hz, J_t=8 Hz), 4.46 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.53 (1H, d, J=2 Hz)
10n	1740 1655	195 (M^+)	0.96 (3H, d, J=6 Hz), 0.98 (3H, d, J=6 Hz), 1.45 (3H, d, J=6 Hz), 1.94 (1H, m), 2.32 (3H, s), 2.96 (1H, dd, J=14, 6 Hz), 3.32 (1H, dd, J=14, 8 Hz), 4.46 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.55 (1H, d, J=2 Hz)
10o	1745 1665	221 (M^+)	1.05—2.1 (10H, m), 1.47 (3H, d, J=6 Hz), 2.31 (3H, s), 4.50 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.51 (1H, d, J=2 Hz)
10p	1745 1660	229 (M^+)	1.35 (3H, d, J=6 Hz), 2.31 (3H, s), 4.24 (1H, d, J=14 Hz), 4.35 (1H, dq, J_d=2 Hz, J_q=6 Hz), 4.79 (1H, d, J=14 Hz), 6.56 (1H, d, J=2 Hz), 7.2—7.5 (5H, m)
11l	1750 1655	153 (M^+)	1.39 (3H, d, J=7 Hz), 2.68 (3H, s), 2.96 (3H, s), 4.13 (1H, dq, J_d=1 Hz, J_q=7 Hz), 5.81 (1H, d, J=1 Hz)
11m	1740 1670	181 (M^+)	0.98 (3H, t, J=8 Hz), 1.40 (3H, d, J=6 Hz), 1.66 (2H, m), 2.68 (3H, s), 3.20 (1H, dt, J_d=14 Hz, J_t=8 Hz), 3.46 (1H, dt, J_d=14 Hz, J_t=8 Hz), 4.18 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.81 (1H, d, J=1 Hz)
11n	1740 1670	195 (M^+)	0.97 (3H, d, J=6 Hz), 1.00 (3H, d, J=6 Hz), 1.40 (3H, d, J=6 Hz), 1.96 (1H, m), 2.69 (3H, s), 3.00 (1H, dd, J=14, 6 Hz), 3.30 (1H, dd, J=14, 8 Hz), 4.19 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.81 (1H, d, J=1 Hz)
11o	1740 1675	221 (M^+)	1.1—2.1 (10H, m), 1.43 (3H, d, J=6 Hz), 2.38 (3H, s), 3.62 (1H, m), 4.24 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.81 (1H, d, J=1 Hz)
11p	1740 1670	229 (M^+)	1.29 (3H, d, J=6 Hz), 2.71 (3H, s), 4.08 (1H, dq, J_d=1 Hz, J_q=6 Hz), 4.28 (1H, d, J=14 Hz), 4.78 (1H, d, J=14 Hz), 5.81 (1H, d, J=1 Hz), 7.3—7.5 (5H, m)
10q	1740 1635	277 (M^+)	1.71 (3H, d, J=6 Hz), 5.13 (1H, dq, J_d=2 Hz, J_q=6 Hz), 7.08 (1H, m), 7.4—7.7 (7H, m), 7.50 (1H, d, J=2 Hz), 8.05 (2H, m)
10r	1740 1630	291 (M^+)	1.51 (3H, d, J=6 Hz), 2.38 (3H, s), 5.19 (1H, dq, J_d=2 Hz, J_q=2 Hz), 7.2—7.4 (4H, m), 7.5—7.7 (3H, m), 7.51 (1H, d, J=2 Hz), 8.05 (2H, m)
10s	1730 1630	291 (M^+)	1.70 (3H, d, J=6 Hz), 2.39 (3H, s), 5.12 (1H, dq, J_d=2 Hz, J_q=6 Hz), 7.00 (1H, m), 7.2—7.4 (3H, m), 7.49 (1H, d, J=2 Hz), 7.5—7.7 (3H, m), 8.06 (1H, m)
10t	1722 1630	307 (M^+)	1.68 (3H, d, J=2 Hz), 3.81 (3H, s), 5.06 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.94 (2H, m), 7.45 (1H, d, J=2 Hz), 7.46 (2H, m), 7.60 (3H, m), 8.04 (2H, m)
10u	1745 1635	295 (M^+)	1.65 (3H, dd, J=1, 6 Hz), 5.34 (1H, m), 7.1—7.25 (3H, m), 7.49 (1H, d, J=2 Hz), 7.5—7.7 (3H, m), 8.0—8.15 (3H, m)
10v	1730 1635	278 (M^+)	1.73 (3H, d, J=6 Hz), 5.20 (1H, dq, J_d=2 Hz, J_q=6 Hz), 7.36 (1H, dd, J=6, 8 Hz), 7.5—7.7 (3H, m), 7.98 (1H, m), 8.05 (2H, m), 8.45 (1H, dd, J=6, 2 Hz), 8.69 (1H, d, J=2 Hz)
10w	1730 1635	243 (M^+)	1.32 (3H, d, J=6 Hz), 1.37 (3H, d, J=6 Hz), 1.54 (3H, d, J=6 Hz), 4.02 (1H, m), 4.66 (1H, dq, J_d=2 Hz, J_q=6 Hz), 7.31 (1H, d, J=2 Hz), 7.5—7.7 (3H, m), 8.0 (2H, m)
10x	1735 1635	257 (M^+)	0.96 (3H, d, J=6 Hz), 1.00 (3H, d, J=6 Hz), 1.49 (3H, d, J=6 Hz), 2.00 (1H, m), 3.00 (1H, dd, J=14, 6 Hz), 3.37 (1H, dd, J=14, 8 Hz), 4.61 (1H, dq, J_d=2 Hz, J_q=2 Hz), 7.35 (1H, d, J=2 Hz), 7.5—7.7 (3H, m), 8.01 (2H, m)
10y	1745 1655	271 (M^+)	1.23 (9H, s), 1.46 (3H, d, J=6 Hz), 2.37 (3H, s), 5.07 (1H, dq, J_d=2 Hz, J_q=6 Hz), 7.01 (1H, d, J=2 Hz), 7.2—7.4 (4H, m)

doublet (dd), double quartet (dq), double triple (dt), multiplet (m). Mass spectra (MS) were taken on a Hitachi M-80A spectrometer. Microanalytical data were obtained by using a Carlo Elba 1106R or a Perkin-Elmer 240C elemental analyzer. For column chromatography, Wakogel 200 (Wako Pure Chemical) was used, and thin layer chromatography (TLC) was performed on silica gel pre-coated plates (Merck, Kieselgel 60F-254).

3-(2,2-Ethylenedioxypropionyl)-4-methyl-1-phenylazetidin-2-one (5a) A solution of 4-methyl-1-phenylazetidin-2-one (**1a**) (7.65 g, 52 mmol) in THF (52 ml) was added to a solution of LDA which was prepared from diisopropylamine (7.4 ml, 52 mmol) and *n*-BuLi (32.5 ml of 1.6 M *n*-hexane solution, 52 mmol) in THF (80 ml) at −78 °C over 30 min and stirred at the same temperature for 5 min. And then, a solution of ethyl 2,2-ethylenedioxypropionate (**2**) (7.6 g, 48 mmol) in THF (40 ml) was added dropwise to the reaction mixture over 1 h and stirred for an additional 1 h. The reaction mixture was poured into 5% HCl (60 ml) and extracted with $CHCl_3$. The organic layer was washed with water, aqueous $NaHCO_3$ and brine, successively, dried ($MgSO_4$) and evaporated *in vacuo* to give **5a** (8.9 g, yield, 68%), which was recrystallized from EtOH to give colorless needles, mp 74.5—76.5 °C. IR (KBr) *v*: 1750, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.56 (3H, d, J=6 Hz), 3.9—4.2 (4H, m), 4.38 (1H, d, J=3 Hz), 4.50 (1H, m), 7.12 (1H, m), 7.38 (4H, m). MS *m/z*: 275 (M^+). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.43; H, 6.22; N, 5.06.

3-(2,2-Ethylenedioxy-1-hydroxypropyl)-4-methyl-1-phenylazetidin-2-one (6a) A solution of **5a** (16.4 g, 59.6 mmol) in MeOH (150 ml) was added dropwise to a solution of $NaBH_4$ (4.06 g, 107 mmol) in MeOH (300 ml) at −78 °C over 1 h, and stirred for 1 h. Then acetic acid (18 ml) was added dropwise to the reaction mixture which was poured into water (500 ml), and extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$ and brine successively, dried ($MgSO_4$), and evaporated *in vacuo* to give **6a** (13.0 g, yield, 79%), which was recrystallized from EtOH to give colorless needles, mp 94.5—96 °C. IR (KBr) *v*: 3400, 1735, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, s), 1.52 (3H, d, J=6 Hz), 2.85 (1H, d, J=4 Hz), 3.07 (1H, dd, J=8, 3 Hz), 3.91 (1H, dd, J=8, 4 Hz), 4.01 (4H, br s), 4.12 (1H, dq, J_d=3 Hz, J_q=6 Hz), 7.08 (1H, m), 7.38 (4H, m). MS *m/z*: 277 (M^+). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.93; H, 6.88; N, 4.98.

3-(2,2-Ethylenedioxy-1-methysulfonyloxypropyl)-4-methyl-1-phenylazetidin-2-one (7a) A solution of methanesulfonyl chloride (6.24 g, 56 mmol) in $CHCl_3$ (13 ml) was added dropwise to a mixture of **6a** (13.0 g, 46.9 mmol), triethylamine (11.4 g, 0.11 mol) and pyridine (130 ml) at 0 °C over 15 min and stirred for 1 h. Then the reaction mixture was poured into 10% HCl solution (700 ml) and extracted with $CHCl_3$. The organic layer was washed with water, aqueous $NaHCO_3$ solution and brine successively, dried over $MgSO_4$, and evaporated *in vacuo* to give **7a** (14.5 g, yield, 87%), which was recrystallized from EtOH to give a colorless amorphous solid, mp 135—139 °C. IR (KBr) *v*: 1745, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.59 (3H, d, J=6 Hz), 2.21 (3H, s), 2.27 (1H, dd, J=8, 3 Hz), 4.08 (4H, m), 4.20 (1H, dq, J_d=6 Hz, J_q=3 Hz), 4.87 (1H, d, J=8 Hz), 7.12 (1H, m), 7.38 (4H, m). MS *m/z*: 355 (M^+). *Anal.* Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94. Found: C, 54.11; H, 5.01; N, 4.21.

(*E*)-3-(2,2-Ethylenedioxypropylidene)-4-methyl-1-phenylazetidin-2-one (8a) and (*Z*)-3-(2,2-Ethylenedioxypropylidene)-4-methyl-1-phenylazetidin-2-one (9a) A solution of DBU (26.3 g, 170 mmol) in benzene (140 ml) was added dropwise to a solution of **7a** (20.4 g, 57.4 mmol) in benzene (280 ml) at 5 °C over 30 min, and the reaction mixture was heated under reflux for 1 h. Then the reaction mixture was evaporated *in vacuo* and extracted with $CHCl_3$. The organic layer was washed with 5% HCl, water and brine successively, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was separated on silica gel column chromatography (CH_2Cl_2) to give **8a** (10.7 g, yield, 71.8%) and **9a** (2.1 g, 14%). **8a**: colorless prisms from EtOH, mp 96—101 °C. IR (KBr) *v*: 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, s), 1.65 (3H, d, J=6 Hz), 3.85—4.05 (4H, m), 4.73 (1H, dq, J_q=2 Hz, J_q=6 Hz), 6.18 (1H, d, J=2 Hz), 7.10 (1H, m), 7.40 (4H, m). MS *m/z*: 259 (M^+). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.32; H, 6.62; N, 5.61. **9a**: a colorless viscous oil. IR (neat) *v*: 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, d, J=6 Hz), 1.62 (3H, s), 3.85—4.05 (4H, m), 4.48 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.75 (1H, d, J=1 Hz), 7.10 (1H, m), 7.40 (4H, m). MS *m/z*: 259 (M^+).

(*E*)-4-Methyl-3-(2-oxopropylidene)-1-phenylazetidin-2-one (10a) A mixture of **8a** (10.5 g, 40.5 mmol), *p*-TsOH·H_2O (1.09 g, 5.7 mmol) and acetone (500 ml) was heated under reflux for 3 h. Then the reaction mixture was evaporated *in vacuo*, and extracted with $CHCl_3$. The organic layer was washed with water, aqueous $NaHCO_3$ solution and brine successively, dried ($MgSO_4$), and evaporated *in vacuo* to give **10a** (8.5 g, yield, 97.9%), which was recrystallized from EtOH to give yellow prisms, mp 120—122 °C. *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.55; H, 6.09; N, 6.53. IR (KBr) *v*: 1745, 1650, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, J=6 Hz), 2.37 (3H, s), 4.98 (1H, dq, J_q=2 Hz, J_q=6 Hz), 6.67 (1H, d, J=2 Hz), 7.15 (1H, m), 7.42 (4H, m). MS *m/z*: 215 (M^+).

(*Z*)-4-Methyl-3-(2-oxopropylidene)-1-phenylazetidin-2-one (11a) Prepared from **9a** in the same manner as described above. Colorless needles from ether, mp 114—115.5 °C. *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.64; H, 5.98; N, 6.48. IR (KBr) *v*: 1740, 1660, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, d, J=6 Hz), 2.74 (3H, s), 4.68 (1H, dq, J_d=1 Hz, J_q=6 Hz), 5.98 (1H, d, J=1 Hz), 7.20 (1H, m), 7.45 (4H, m). MS *m/z*: 215 (M^+).

The spectral data of **10b**—**y** and **11b**—**p** were shown in Table II.

(*E*)-4-Methyl-3-(2-oxopropylidene)azetidin-2-one (12) A solution of CAN (15.4 g, 28.1 mmol) in 50% aqueous MeCN (80 ml) was added dropwise to a solution of **10e** (2.0 g, 8.16 mmol) in MeCN (40 ml) at 0 °C, and stirred for 2 h at the same temperature. Then the reaction mixture was extracted with AcOEt and the extract was washed with aqueous $NaHCO_3$ solution, saturated Na_2SO_3 solution and brine successively, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was purified on silica gel column chromatography to give **12** (0.24 g, yield, 29%), which was recrystallized from ether to give yellow plates, mp 117.5—120.5 °C. *Anal.* Calcd for $C_7H_9NO_2$: C, 60.41; H, 6.53; N, 10.07. Found: C, 60.34; H, 6.52; N, 10.14. IR (KBr) *v*: 3160, 1720, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, d, J=6 Hz), 2.34 (3H, s), 4.57 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.59 (1H, d, J=2 Hz), 6.72 (1H, br d). MS *m/z*: 139 (M^+).

(*E*)-Tetrabutylammonium 4-Methyl-3-(2-oxopropylidene)-1-sulfoazetidin-2-one (13) A mixture of **12** (101 mg, 0.73 mmol), pyridine–sulfur trioxide (247 mg, 1.55 mmol) and DMF (1 ml) was stirred at room temperature for 2 d. The reaction mixture was diluted with CH_2Cl_2 and extracted with 0.5 N KH_2PO_4 solution, then *n*-Bu_4NHSO_4 (247 mg, 0.73 mM) was added to the aqueous layer which was extracted twice with CH_2Cl_2, and the organic layer was dried ($MgSO_4$), evaporated *in vacuo* and the residue was purified on silica gel column chromatography (AcOEt : MeOH = 8 : 1) to give **13** (140 mg, yield, 47%), which was recrystallized from EtOH to give a colorless amorphous solid, mp 101.5—104.5 °C. *Anal.* Calcd for $C_{23}H_{44}N_2O_5S$: C, 59.95; H, 9.65; N, 6.08. Found: C, 60.28; H, 9.68; N, 5.98. IR (KBr) *v*: 1750, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (12H, t, J=7 Hz), 1.94 (8H, m), 1.65 (8H, m), 1.65 (3H, d, J=6 Hz), 2.30 (3H, s), 3.28 (8H, m), 4.81 (1H, dq, J_d=2 Hz, J_q=6 Hz), 6.55 (1H, d, J=2 Hz). MS (SIMS) *m/z*: 461 (M+H).

Preparation of PRP Blood was taken from the carotid artery of male New Zealand white rabbit into a plastic syringe containing a 10% volume of 3.2% sodium citrate dihydrate solution under ether anesthesia. The citrated blood was centrifuged at 150 g for 15 min at room temperature to obtain PRP. The sediment was further centrifuged at 1500 *g* for 10 min to obtain platelet-poor plasma (PPP). The platelet count was adjusted to approximately 5×10^5—6×10^5/μl by adding PPP.

Platelet Aggregation Test *in Vitro* Platelet aggregation was measured by a Aggrecoder PA-3210 (Kyoto Daiichi Kagaku) at 37 °C under stirring at 1000 rpm. The agents used were ADP (Sigma Chemical Co., final concentration; 5 μM), and collagen (Kyoto Daiichi Kagaku Co., Ltd., final concentration; 5 μg/ml). The compound to be tested was dissolved in DMSO and diluted by saline, which was added in the volume of 25 to 275 μl of PRP 3 min before the addition of the aggregating agents. Platelet aggregation was measured for 5 min and the IC_{50} value was calculated by the maximum decrease in absorbancy of PRP from comparison of the vehicle treated PRP.

References and Notes

1) Part I: Y. Kawashima, M. Sato, Y. Hatada, J. Goto, Y. Nakashima, K. Hatayama and S. Shibuya, *Chem. Pharm. Bull.*, **38**, 393 (1990).
2) A part of this work was presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1989.
3) S. Kano, S. Shibuya and T. Ebata, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 257; Y. Watanabe and T. Mukaiyama, *Chem. Lett.*, **1981**, 443; D. Reuschling, H. Pietsch and A. Linkies, *Tetrahedron Lett.*, **1978**, 615; H, Takahata, Y. Ohnishi, H. Takehara, K. Tsuritani and T. Yamazaki, *Chem. Pharm. Bull.*, **29**, 1063 (1981); M. Zrihen, R. Labia and M. Wakselman, *Eur. J. Med. Chem. Chim. Ther.*, **18**, 307 (1983).
4) A. Holland, J. M. Inglis and R. Slack, Brit. Patent 951115 (1964) [*Chem. Abstr.*, **60**, 15874*h* (1964)].
5) Prepard from ethyl phenylglyoxalate; a colorless viscous oil.