

Syntheses and Antiulcer Activities of 2-Aminonorbornene Derivatives

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2,2-Disubstituted norbornenes (1, 2), 2,2-Disubstituted norbornane (3), 2,2,3-trisubstituted norbornenes (4, 5), oxanorbornenes (6) and azanorbornenes (7) were synthesized by the Diels-Alder reaction using α,β -dehydroamino acids as a key step, and their antiulcer activities were examined. The oxazolidine derivative (1h) exhibited the most potent activities against several ulcer-models in rat.

Keywords 2-aminonorbornene; antiulcer; azanorbornene; oxanorbornene; Diels-Alder reaction

In the course of our synthetic studies in search of a new antiulcer agent, we found¹⁾ that a novel compound, 2-*endo*-dimethylamino-5-norbornene-2-*exo*-methanol (**1a**), exhibited antiulcer activity against several ulcer-models in rat without possessing anticholinergic activity. To develop an antiulcer agent having more potent activity, we have synthesized various derivatives having 2-aminonorbornene skeletons. We report here the syntheses and antiulcer activities of 2,2-disubstituted norbornenes (**1, 2**), 2,2-disubstituted norbornane (**3**), 2,2,3-trisubstituted norbornenes (**4, 5**), oxanorbornenes (**6**) and azanorbornenes (**7**).

Chemistry. 2,2-Disubstituted Norbornenes Compounds (**1a-f, h**) were synthesized starting from 2-*endo*-acetamido-5-norbornene-2-*exo*-carboxylic acid methyl ester (**8**)²⁾ (Chart 2). Compound (**8**) was treated with Meerwein's reagent to give the amino ester (**9**) in a 65% yield. Alkylation of **9** with HCHO-HCO₂H or the appropriate

alkyl halides in the presence of K₂CO₃ afforded the *N,N*-dimethylated derivatives (**10a**) or *N*-monoalkylated derivatives (**10b-f**), respectively, which were reduced with LiAlH₄ to furnish the corresponding amino alcohols (**1a-f**). Reaction of **1b** with formaldehyde in refluxing benzene resulted in the formation of the oxazolidine derivative (**1h**) in a 77% yield. The *N,N*-dimethylamino ether (**1g**) was also synthesized in a good overall yield starting from **8** by the procedures similar to those employed in the preparation of **1a**. On the other hand, **2a, b** were synthesized from 2-*exo*-acetamido-5-norbornene-2-*endo*-carboxylic acid methyl ester (**12**) by the same procedures as those employed in the preparation of **1a, b**. The norbornane derivative (**3b**) was obtained by the hydrogenation of **1b** over Pd/C.

2,2,3-Trisubstituted Norbornenes Compounds (**4, 5**) were synthesized starting from dimethyl acetamidofumarate

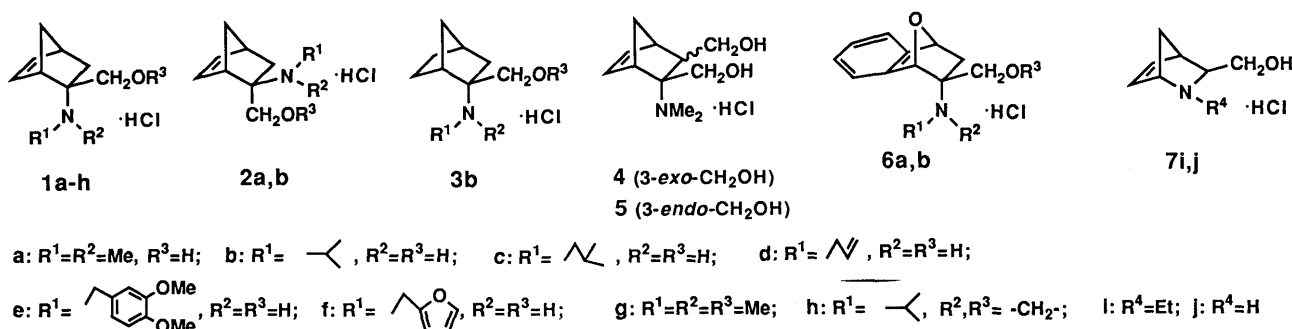
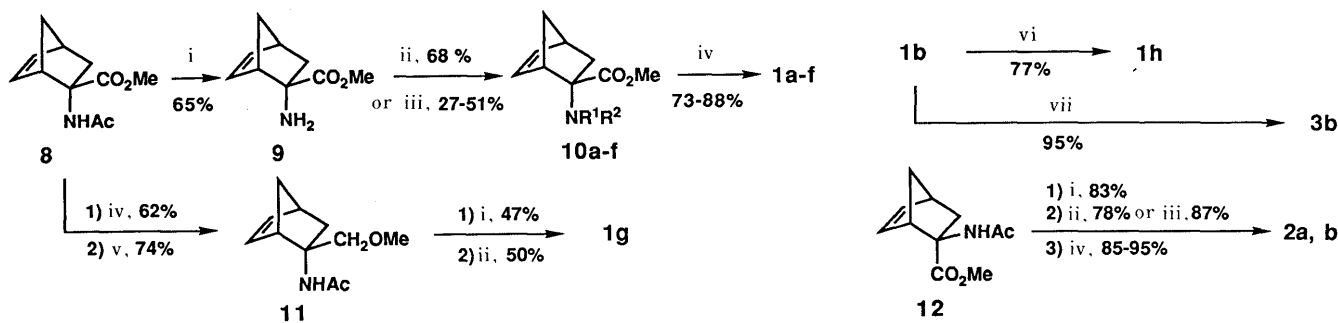


Chart 1



i) Et₃O⁺BF₄⁻/CH₂Cl₂, then NaHCO₃ ii) HCHO-HCO₂H iii) R¹X, K₂CO₃/HMPA iv) LiAlH₄/THF, then HCl/MeOH
v) MeI vi) HCHO vii) Pd-C/MeOH, H₂

Chart 2

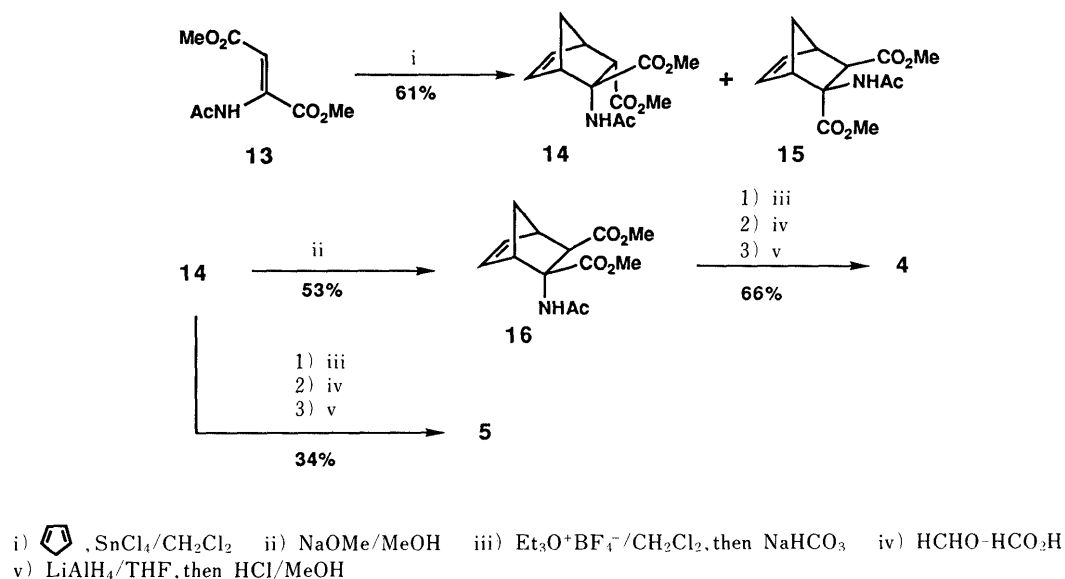


Chart 3

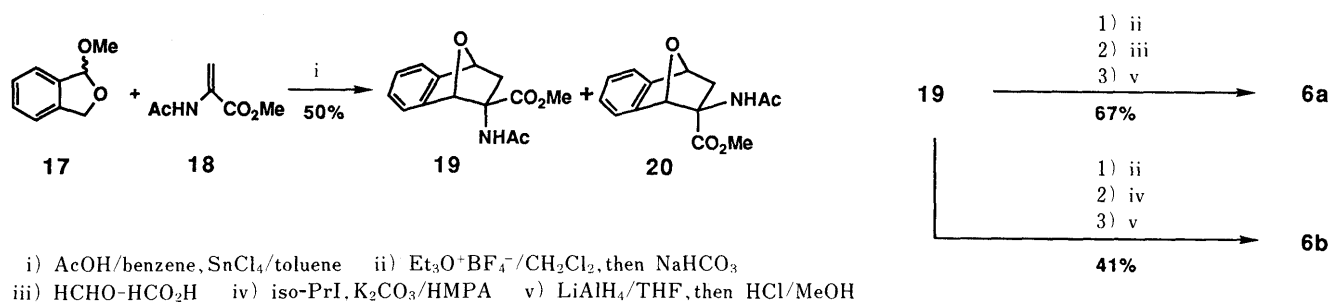


Chart 4

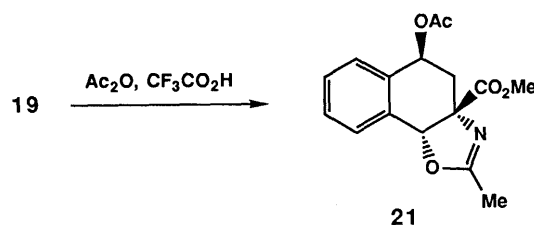


Chart 5

(**13**)³ derived from dimethyl *N*-acetylaspartate (Chart 3). Our study began with experiments to evaluate the reactivity of dimethyl acetamidofumarate as a dienophile toward cyclopentadiene. We first examined the reaction of **13** with cyclopentadiene in the absence of a catalyst under the reaction conditions employed in the Diels-Alder reaction of *N*-acetyl- α,β -dehydroalaninate with cyclopentadiene.²⁾ However, the desired Diels-Alder adducts were not formed. After an examination using a number of acidic catalysts, we found that the reaction proceeded smoothly in CH₂Cl₂ with the use of SnCl₄ as a catalyst to furnish a mixture of **14** and **15** in a 61% yield; thin-layer chromatography (TLC) (CHCl₃:Me₂CO=4:1) of a mixture of the products showed two spots of *R_f* values being 0.7 and 0.6. Each isomer was separated by column chromatography on silica gel, the ratio of the amount of the upper spot and the lower one being 3:1. To determine the structure of these products, we examined the epimerization at the 3-position of each product. On the other hand, it is well documented that an *endo*-methoxycarbonyl substituent on a norbornene skeleton is readily converted into the *exo*-position under base-catalyzed conditions,⁴⁾ while an *exo*-methoxycarbonyl substituent does not change at all.⁴⁾ Thus, treatment of the product (*R_f*=0.7) with NaOMe in MeOH gave rise to the epimerization at the 3-position in a good yield, while no epimerization was observed on treatment of the product (*R_f*=0.6) under the same reaction conditions as described above. These results

strongly indicate that the products of *R_f* values being 0.7 and 0.6 correspond to **14** and **15** respectively. Compound **16** was converted to **4** by using the same procedures as those employed in the preparation of **1a**. On the other hand, **5** was synthesized from **14** using the same procedures as those described for the synthesis of **1a**.

Oxanorbornenes Isobenzofurans generated *in situ* have been frequently used as reactive intermediates for the synthesis of 9-oxabenzonorbornenes.⁵⁾ We examined the reaction of 1-methoxyphthalane (**17**)⁶⁾ with methyl *N*-acetyl- α,β -dehydroalaninate (**18**),⁷⁾ and found that the reaction proceeded smoothly in refluxing benzene in the presence of a catalytic amount of AcOH to afford the adducts (**19** and **20**) in a good yield; the ratio of **19** to **20** was approximately 7:1 (Chart 4). The structure of each isomer was determined by proton nuclear magnetic resonance (¹H-NMR); the methyl protons of the acetyl group of **19** are shifted to higher field than those of **20**. To

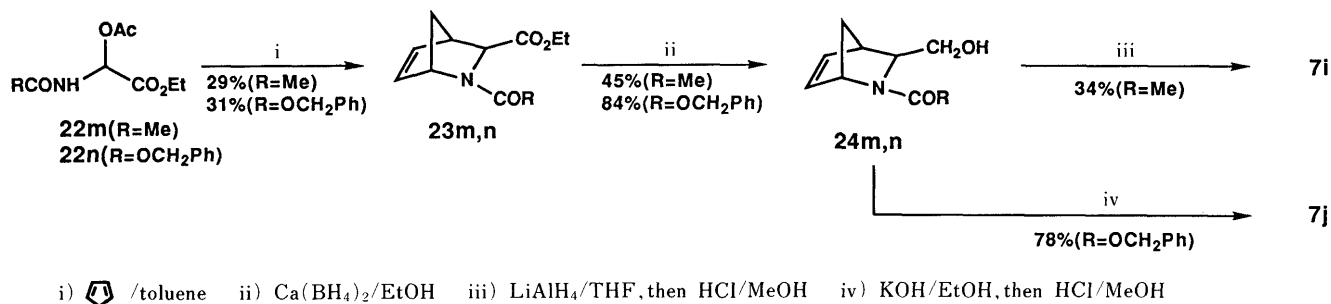


Chart 6

further confirm the structures of **19** and **20** by a chemical method, adduct (**19**) was treated with Ac_2O in the presence of $\text{CF}_3\text{CO}_2\text{H}$ to give the oxazoline (**21**) (Chart 5). On the other hand, no formation of the oxazoline (**21**) was observed on treatment of **20** under the same conditions as described above. From these results, it was confirmed that the structures of **19** and **20** are those having 2-*endo*-acetamido and 2-*exo*-acetamido groups, respectively. The adduct (**19**) was converted into **6a** and **6b** in good yields by the same procedures as employed in the preparation of **1a** and **1b**, respectively (Chart 4).

Azanorbornenes 2-Azanorbornene-3-carboxylic acid has already been synthesized by Jung *et al.*⁸⁾ and Gaitanopoulos *et al.*⁹⁾ utilizing the imino Diels–Alder reaction of the *N*-acylimine derived from glyoxylic acid ester with cyclopentadiene. However, these methods are not practical due to the difficulty in the generation of the *N*-acylimines. Thus, we have examined a practical method for the generation of the *N*-acylimine from α -acetoxy glycine derivatives¹⁰⁾ (**22m, n**). Treatment of **22m** and **22n** with cyclopentadiene in refluxing toluene afforded the adducts (**23m**⁸⁾ and **23n**⁸⁾) in 29 and 31% yield, respectively (Chart 6); in these reactions, the *exo*-isomer formed exclusively.^{8,9)} $\text{Ca}(\text{BH}_4)_2$ reduction of **23m** and **23n** gave **24m** and **24n** in 45 and 84% yield, respectively. Further reduction of the compound (**24m**) by LiAlH_4 gave **7i**. The compound (**24m**) was hydrolyzed by KOH to afford **7j**.

Pharmacological Results and Discussion

The norbornene derivatives synthesized above were evaluated initially for antiulcer activity against ethanol-induced gastric mucosal lesions in rat when they were administered orally at a dose of 100 mg/kg. The results are summarized in Table I.

The parent compound (**1a**) showed a significant antiulcer activity. On the other hand, the corresponding oxanorbornenes (**6a, b**) and azanorbornenes (**7i, j**) exhibited reduced activities. Furthermore, the norbornene derivative (**4**) having a hydroxymethyl group at the 3-position also reduced the potency. These results clearly indicate that the 2,2-disubstituted norbornene (**1a**) is favorable over the oxanorbornenes, azanorbornenes and 2,2,3-trisubstituted norbornene for exhibiting the antiulcer activities. Thus, we focused our attention on the synthesis of 2,2-disubstituted norbornene derivatives.

The substitution pattern on the amino group of 2-*endo*-amino-5-norbornene-2-*exo*-methanol profoundly influenced the activity. The replacement of the dimethylamino group of **1a** with the isopropylamino group (**1b**) preserved

TABLE I. Inhibition of EtOH-Induced Gastric Mucosal Lesions by the Norbornene Derivatives

Compounds	Antiulcer activity
1a	81
1b	88
1c	45
1d	30
1e	25
1f	6
1g	48
1h	85
2a	78
2b	62
3b	49
4	37
5	26
6a	34
6b	36
7i	50
7j	3

Test compounds were given orally at a dose of 100 mg/kg. ($N=5$) Each value represents the mean of % inhibition of ulcer formation induced by EtOH.

a good level of the activity. The introduction of isobutyl (**1c**), allyl (**1d**) and aryl (**1e, f**) groups onto the nitrogen atom resulted in the decrease of the activity. The activity of **1g**, in which the hydroxyl group of **1a** is substituted by a methoxy group, also decreased. These results clearly indicate that both the substituent on the amino group and the presence of the hydroxyl group at the 2-position are probably important factors contributing to the antiulcer activities. Thus, to improve the activity of **1b**, we synthesized the oxazolidine derivative (**1h**), which would be a prodrug form of **1b**.¹¹⁾ Although **1h** was stable under acidic conditions, it gradually decomposed into **1b** under neutral and basic conditions. As a result, the potency of **1h** was almost the same as that of **1b**.

In order to gain insight into both the effect of the stereochemistry of the β -amino alcohol moiety and the significance of the 5,6-double bond, we investigated the antiulcer activities of the stereoisomers (**2a, b**) of **1a** and **1b** and the norbornane derivative (**3b**). The compounds (**2a, b**) were found to retain the activity. However, a preliminary acute-toxicological experiment¹²⁾ revealed that both **2a** and **2b** are more toxic than **1a, b**. On the other hand, the antiulcer activity of **3b** was significantly reduced, indicating that the 5,6-double bond of **1b** is crucial for exhibiting the activity.

Among the compounds described above, we selected **1a**,

TABLE II. Effects of Compounds **1a**, **1b** and **1h** on Experimental Ulcers and Gastric Secretion in Rats

Compounds	Dose (mg/kg)	Antiulcer activity			GVJ	GAC	Acute toxicity ^{a)}
		EtOH	Stress	Aspirin			
1a	30	42		45			0/4
	100	81	43	86	43	-2	
1b	30	38		41			0/5
	100	88	41	79	30	9	
1h	30	70		61			0/3
	100	85	62		47	12	
Carbenoxolone	100	58	48	40	38	3	
Cetraxate	100	34	-2	20	56	70	

GVJ: gastric juice volume, GAC: gastric acid concentration. Each value represents the mean of % inhibition of ulcer formation and gastric secretion. (*N* = 5).
a) Mortality (number of mice died from toxicity/number of mice tested) in mice orally given 1000 mg/kg of each compound.

1b and **1h** for further evaluation. Preliminary experiments to evaluate the acute toxicity of these compounds showed that the toxicity levels of these compounds were very low (Table II). We next examined the antiulcer activities of **1a**, **1b** and **1h** against ethanol-induced gastric mucosal lesion, water immersion stress- and aspirin-induced gastric mucosal lesion in rat, when they are orally administered at 30 and 100 mg/kg. These activities were compared with those of carbenoxolone and cetraxate which enhance mucosal defensive factors.^{13,14)} The results are shown in Table II. These results clearly indicated that the oxazolidine derivative (**1h**) showed the most potent activities against the ulcer models in rat. Furthermore, we also examined antisecretory activities of **1a**, **1b** and **1h** in pylorus-ligated rats, when orally administered at 100 mg/kg. These compounds were found to slightly reduce the gastric juice volume, while the gastric acid concentrations were not significantly changed. The results suggest that the antiulcer activities of this class of compounds are probably not related to their antisecretory activities.

Experimental

All melting points were uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 IR spectrophotometer. ¹H-NMR spectra were taken at 200 MHz on a Bruker AC-200 spectrometer with tetramethylsilane as an internal reference. Mass spectra (MS) were given by a Hitachi M-60 instrument.

A Typical Procedure for the Deacetylation Using Meerwein's Reagent
To a solution of **8** (1.05 g, 5.0 mmol) in CH₂Cl₂ (20 ml) was added Meerwein's reagent (2.29 g, 5.0 mmol) in one portion at room temperature. The reaction mixture was stirred at room temperature for 2 h. To the mixture was added a cold aqueous NaHCO₃ solution (10 ml) and the reaction mixture was stirred for 18 h. The organic layer was separated, dried (MgSO₄) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃:EtOH = 30:1) to afford **9** (0.55 g, 65.4%) as a faintly yellow syrup.

2-endo-Amino-5-norbornene-2-exo-carboxylic Acid Methyl Ester (9): ¹H-NMR (CDCl₃) δ: 0.80–1.10 (m, 1H), 1.20–1.80 (m, 2H), 1.59 (s, 2H), 2.45–2.70 (m, 1H), 2.80–3.10 (m, 2H), 3.78 (s, 3H), 6.10–6.30, 6.40–6.55 (m, m, 2H). MS *m/z*: 167 (M⁺). Anal. Calcd for C₉H₁₃NO₂: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.91; H, 7.79; N, 8.11.

A Typical Procedure for the Dimethylation and Subsequent LiAlH₄-Reduction
A mixture of **9** (1.67 g, 10 mmol), 35% aqueous HCHO (2.0 g) and 98% HCO₂H (1.8 g) was refluxed for 1 h. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in H₂O and the solution was neutralized by the addition of aqueous K₂CO₃ solution. The separated oil was extracted with AcOEt. The organic layer was separated, dried (MgSO₄) and then evaporated to dryness *in vacuo* to afford **10a** as a syrup (1.5 g, 81%). To a suspension of LiAlH₄ (0.31 g, 8.2 mmol) in tetrahydrofuran (THF) (20 ml) was added a solution of the

above syrup in THF (10 ml) at -20°C. After the reaction mixture was stirred for 45 min under ice cooling, the reaction was quenched by the addition of 15% aqueous NaOH solution. The insoluble materials were filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting crystals were triturated with *n*-hexane to afford **1a** (1.45 g, 71% overall yield).

2-endo-Dimethylamino-5-norbornene-2-exo-methanol (1a): mp 81–82°C. IR (Nujol): 3180, 1330 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.50–2.00 (m, 4H), 1.41 (s, 6H), 2.60 (brs, 1H), 2.70–3.10 (m, 2H), 3.30–3.80 (m, 2H), 6.00–6.30 (m, 2H). MS *m/z*: 167 (M⁺). Anal. Calcd for C₁₀H₁₇NO: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.93; H, 10.18; N, 8.50.

A Typical Procedure for the Alkylation of 9 and Subsequent LiAlH₄-Reduction
To a solution of **9** (2.7 g, 16.1 mmol) in hexamethylphosphoramide (HMPA) (4 ml) was added isopropyl iodide (3.29 g, 19.3 mmol) and K₂CO₃ (2.45 g, 17.7 mmol). The reaction mixture was stirred at room temperature for 20 h and then at 40–50°C for 3 h. The reaction mixture was diluted with AcOEt. The solution was washed with H₂O. The organic layer was separated, dried (MgSO₄) and then evaporated to dryness *in vacuo*. The resulting syrup was purified by column chromatography on silica gel (CHCl₃:Me₂CO = 10:1) to afford **10b** as a syrup (1.47 g, 43.6%). To a suspension of LiAlH₄ (0.26 g, 6.9 mmol) in THF (20 ml) was added a solution of the above syrup in THF (10 ml) at -20°C. After the reaction mixture was stirred under ice cooling for 45 min, the reaction was quenched by the addition of 15% aqueous NaOH solution. The insoluble materials were filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting syrup was dissolved in 3 ml of 22% HCl in MeOH. The solvent was removed under reduced pressure. The resulting crystals were triturated with Me₂CO. Recrystallization from EtOH–AcOEt gave colorless needles (**1b**) (1.35 g, 38.4% overall yield).

2-endo-Isopropylamino-5-norbornene-2-exo-methanol Hydrochloride (1b): (38.7% overall yield) mp 192–194°C. IR (Nujol): 3230, 3080, 1585 cm⁻¹. ¹H-NMR (CDCl₃ + DMSO-*d*₆) δ: 1.00–2.00 (m, 1H), 2.94 (brs, 1H), 3.50–4.10 (m, 3H), 5.79 (brs, 1H), 6.10–6.30, 6.40–6.60 (m, m, 2H), 7.30–8.40 (br, 2H). MS *m/z*: 181 (free base M⁺). Anal. Calcd for C₁₁H₂₀ClNO: C, 60.68; H, 9.26; Cl, 16.28; N, 6.43. Found: C, 60.91; H, 9.44; Cl, 16.25; N, 6.56.

2-endo-(2-Methyl)propylamino-5-norbornene-2-exo-methanol Hydrochloride (1c): (42.8% overall yield) mp 163–165°C. IR (Nujol): 3200, 1570 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 0.96 (d, 6H), 1.30–2.20 (m, 5H), 2.60–3.30 (m, 4H), 3.60–4.10 (m, 2H), 3.70–6.00 (br, 1H), 6.05–6.20, 6.40–6.55 (m, m, 2H), 7.10–7.70 (br, 1H), 8.10–8.70 (br, 1H). MS *m/z*: 195 (free base M⁺). Anal. Calcd for C₁₂H₂₂ClNO: C, 62.19; H, 9.57; Cl, 15.30; N, 6.04. Found: C, 62.28; H, 9.66; Cl, 15.51; N, 6.29.

2-endo-Allylamino-5-norbornene-2-exo-methanol Hydrochloride (1d): (19.7% overall yield) mp 179°C (dec.). IR (Nujol): 3300, 1570 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 1.20–1.85 (m, 4H), 2.65–3.40 (m, 4H), 5.20–5.60 (m, 2H), 5.60–6.20 (br, 1H), 5.70–6.00 (m, 1H), 6.00–6.20, 6.35–6.50 (m, m, 2H), 7.80–9.00 (br, 2H). MS *m/z*: 179 (free base M⁺). Anal. Calcd for C₁₁H₁₈ClNO: C, 61.25; H, 8.41; Cl, 16.43; N, 6.49. Found: C, 61.51; H, 8.39; Cl, 16.52; N, 6.55.

2-endo-(3,4-Dimethoxybenzyl)amino-5-norbornene-2-exo-methanol Hydrochloride (1e): (41.5% overall yield) mp 220°C (dec.). IR (Nujol): 3300, 1610, 1595 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.40–2.00 (m, 4H), 2.95–3.00 (m, 1H), 3.20–3.30 (m, 1H), 3.84, 3.91 (s, s, 6H), 3.70–4.50 (m, 5H), 6.05–6.20, 6.40–6.55 (m, m, 2H), 6.80–7.50 (m, 3H), 7.80–8.30 (br, 1H), 8.60–9.10 (br, 1H). MS *m/z*: 289 (free base M⁺). Anal. Calcd for C₁₇H₂₄ClNO₃: C, 62.67; H, 7.42; Cl, 10.88; N, 4.30. Found: C, 62.58; H, 7.25; Cl, 10.79; N, 4.44.

2-endo-Furfurylamino-5-norbornene-2-exo-methanol Hydrochloride (1f): (34.0% overall yield) mp 167–168°C. IR (Nujol): 3210, 3060, 1555 cm⁻¹. ¹H-NMR (CDCl₃ + DMSO-*d*₆) δ: 1.20–2.00 (m, 4H), 2.91 (brs, 1H), 3.20 (br, 1H), 3.94, 4.14 (ABd, *J* = 13 Hz, 2H), 4.25, 4.52 (ABd, *J* = 15 Hz, 2H), 4.60, 5.90 (br, 1H), 6.00–6.20 (m, 1H), 6.35–6.60 (m, 2H), 6.75 (d, *J* = 3 Hz, 1H), 7.48 (d, *J* = 3 Hz, 1H), 8.10–9.30 (br, 2H). MS *m/z*: 219 (free base M⁺). Anal. Calcd for C₁₃H₁₈ClNO₂: C, 61.05; H, 7.09; Cl, 13.86; N, 5.48. Found: C, 61.34; H, 7.29; Cl, 13.58; N, 5.60.

2-endo-Acetamido-2-exo-methoxymethyl-5-norbornene (11)
To a suspension of LiAlH₄ (3.63 g, 95.6 mmol) in THF (200 ml) was added a solution of **8** (20.0 g, 95.6 mmol) in THF (150 ml) at -40°C. After the reaction mixture was stirred at -40–-10°C for 30 min, the reaction was quenched by the addition of 15% aqueous NaOH solution. The insoluble materials were filtered off and the filtrate was concentrated

to dryness *in vacuo*. The resulting syrup was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{MeOH}=20:1$) to afford 2-*endo*-acetamido-5-norbornene-2-*exo*-methanol (10.7 g, 62%). mp 136–137 °C. IR (Nujol): 3300–3200, 1600, 1553 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.00–2.20 (m, 4H), 1.91 (s, 3H), 2.70–3.00 (m, 1H), 3.30–3.60 (m, 1H), 3.85 (s, 2H), 5.10 (brs, 1H), 5.80–6.50 (m, 3H). MS m/z : 181 (M^+).

To a suspension of NaH (62.7% oil dispersion, 2.07 g, 58.9 mmol) in dimethylformamide (DMF) (50 ml) was added a solution of the alcohol obtained above (8.9 g, 49.1 mmol) in DMF (30 ml) at 5 °C. After the reaction mixture was stirred at room temperature for 2 h, the mixture was cooled to 5 °C. To the mixture was added MeI (4.6 ml, 73.7 mmol) and the whole was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt and the solution was washed with H_2O . The organic layer was separated, dried (MgSO_4) and then evaporated to dryness *in vacuo*. The resulting syrup was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{Me}_2\text{CO}=5:1$) to afford compound **11** (7.1 g, 74%). Recrystallization from *n*-hexane gave needles. mp 92–93 °C. IR (Nujol): 3250, 3050, 1630, 1550 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.80–1.60 (m, 4H), 1.86 (s, 3H), 1.80–2.20 (m, 1H), 2.80–3.00 (m, 1H), 3.38 (s, 3H), 3.68, 3.87 (ABq, $J=9$ Hz, 2H), 5.57 (brs, 1H), 6.00–6.15, 6.25–6.40 (m, m, 2H). MS m/z : 195 (M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.44; H, 8.57; N, 7.21.

2-*endo*-Dimethylamino-2-*exo*-methoxymethyl-5-norbornene Hydrochloride (1g) The Meerwein's reagent promoted deacetylation of **11** followed by dimethylation with $\text{HCHO-HCO}_2\text{H}$ gave the free base of **1g**. The resulting free base was dissolved in 22% HCl in MeOH. The solvent was removed under reduced pressure to afford hydrochloride (**1g**). Recrystallization from AcOEt gave faintly green prisms. (23.5% overall yield) mp 92–93 °C. IR (Nujol): 3230, 1570 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.90–2.20 (m, 4H), 2.35 (s, 6H), 2.70–3.20 (m, 2H), 3.34 (s, 3H), 3.53, 3.74 (ABq, $J=11$ Hz, 2H), 6.00–6.40 (m, 2H). MS m/z : 181 (free base M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{ClNO}$: C, 60.68; H, 9.26; Cl, 16.28; N, 6.43. Found: C, 60.69; H, 9.38; Cl, 16.62; N, 6.58.

Bicyclo[2.2.1]hept-2-ene-5-spiro-4'-(3'-isopropyl-1',3'-oxazolidine) Hydrochloride (1h) To a solution of free base of **1b** (2.2 g, 12.1 mmol) in benzene (30 ml) was added 35% aqueous HCHO solution (8 ml). The mixture was refluxed for 2 h under a Dean-Stark apparatus. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in AcOEt. The solution was washed with aqueous NaHCO_3 solution and H_2O . The organic layer was separated, dried (MgSO_4) and then evaporated to dryness *in vacuo*. The residue was dissolved in 3 ml of 22% HCl in MeOH. The solvent was removed under reduced pressure. The resulting crystals were triturated with acetone. Recrystallization from EtOH-AcOEt gave **1h** as needles (1.80 g, 77.0%). mp 134 °C (dec.). IR (Nujol): 2970, 1460 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.95, 1.03 (d, $J=6$ Hz each, 6H), 1.30–1.80 (m, 4H), 2.75–2.89 (m, 2H), 2.90–3.10 (m, 1H), 3.59 (s, 2H), 4.45, 4.55 (d, $J=6$ Hz each, 2H), 6.10–6.16, 6.27–6.31 (m, m, 2H). MS m/z : 193 (free base M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{ClNO}$: C, 62.73; H, 8.77; Cl, 15.43; N, 6.10. Found: C, 62.41; H, 8.54; Cl, 15.45; N, 6.06.

2-*endo*-Dimethylamino-5-norbornene-2-*endo*-methanol Hydrochloride (2a) This compound was prepared starting from **12** by the same procedures as those described for the synthesis of compound **1a**. (61.5% overall yield) mp 130 °C (dec.). IR (Nujol): 3250, 1350 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.60–2.05 (m, 4H), 1.45 (s, 6H), 2.55 (brs, 1H), 2.75–3.20 (m, 2H), 3.25–3.60 (m, 2H), 6.00–6.30 (m, 2H). MS m/z : 167 (free base M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{ClNO}$: C, 58.96; H, 8.91; Cl, 17.40; N, 6.88. Found: C, 58.73; H, 9.15; Cl, 17.42; N, 6.79.

2-*exo*-Isopropylamino-5-norbornene-2-*endo*-methanol Hydrochloride (2b) This compound was prepared starting from **12** by the same procedures as those described for the synthesis of compound **1b**. (61.4% overall yield) mp 189 °C (dec.). IR (Nujol): 3280, 1585 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6+\text{D}_2\text{O}$) δ : 1.00–2.10 (m, 4H), 1.31, 1.36 (d, d, 6H), 2.93 (brs, 1H), 3.17 (brs, 1H), 3.23, 3.56 (ABq, $J=12$ Hz, 2H), 3.50–3.90 (m, 1H), 6.05–6.35 (m, 2H). MS m/z : 181 (free base M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{ClNO}$: C, 60.68; H, 9.26; Cl, 16.28; N, 6.43. Found: C, 60.74; H, 9.19; Cl, 16.30; N, 6.58.

2-*exo*-Hydroxymethyl-2-*endo*-isopropylaminonorbornane Hydrochloride (3b) Compound **1b** (0.43 g, 1.97 mmol) was reduced in MeOH (30 ml) over 10% Pd/C (0.3 g) at 1.5 atm. After a theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. Crystallization of the residue from EtOH-AcOEt gave **3b** as needles (0.41 g, 95%). mp 212 °C (dec.). IR (Nujol): 3360, 3250, 1600, 1585 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.32,

1.37 (d, d, 6H), 1.10–1.90 (m, 8H), 2.19 (brs, 1H), 2.62 (brs, 1H), 3.30–3.90 (m, 3H), 5.60–5.85 (m, 1H), 8.10–8.80 (br, 2H). MS m/z : 183 (free base M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{22}\text{ClNO}$: C, 60.12; H, 10.09; Cl, 16.13; N, 6.37. Found: C, 60.05; H, 10.38; Cl, 16.27; N, 6.11.

2-*endo*-Acetamido-5-norbornene-2-*exo*-3-*endo*-dicarboxylic Acid Dimethyl Ester (14) and 2-*exo*-Acetamido-5-norbornene-2-*endo*-3-*exo*-dicarboxylic Acid Dimethyl Ester (15) To a solution of **13** (35.2 g, 175 mmol) and SnCl_4 (5.1 ml, 43.8 mmol) in CH_2Cl_2 (100 ml) was added cyclopentadiene (71 ml, 875 mmol) during 3 h at 5 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in AcOEt. The solution was washed with aqueous NaHCO_3 solution and H_2O . The organic layer was separated, dried (MgSO_4) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{Me}_2\text{CO}=10:1$) to afford **14** (20.9 g, 44.8%) and **15** (7.58 g, 16.2%).

14: Colorless needles (AcOEt-*n*-hexane), mp 97–99 °C. IR (Nujol): 3270, 3030, 1726, 1633, 1540 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.40–2.10 (m, 3H), 1.89 (s, 3H), 3.18 (brs, 1H), 3.44 (d, $J=3$ Hz, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 6.15–6.45 (m, 2H), 7.09 (brs, 1H). MS m/z : 267 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.65; H, 6.29; N, 5.18.

15: Colorless needles (AcOEt-*n*-hexane), mp 204–205 °C. IR (Nujol): 3270, 3070, 1728, 1640, 1552 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.55–1.80 (m, 1H), 1.97 (s, 3H), 2.91–2.45 (m, 1H), 2.95–3.15 (m, 2H), 3.30 (d, $J=2$ Hz, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 6.00–6.20, 6.30–6.50 (m, m, 2H), 6.74 (brs, 1H). MS m/z : 267 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.41; H, 6.33; N, 5.20.

2-*endo*-Acetamido-5-norbornene-2,3-*exo*-dimethanol (16) To a solution of **14** (0.53 g, 2.0 mmol) in MeOH (20 ml) was added 0.5 ml of 1N NaOMe in MeOH. The reaction mixture was stirred at room temperature overnight. The mixture was evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{Me}_2\text{CO}=5:1$) to afford **16** (0.28 g, 53.0%). Recrystallization from AcOEt gave needles. mp 170–171 °C. IR (Nujol): 3300, 3050, 1755, 1735, 1645, 1535 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.70–1.90 (m, 1H), 1.91 (s, 3H), 2.30–2.60 (m, 2H), 3.00 (brs, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.84 (brs, 1H), 6.10–6.25, 6.30–6.45 (m, m, 2H), 6.26 (brs, 1H). MS m/z : 267 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.36; H, 6.53; N, 5.11.

2-*endo*-Dimethylamino-5-norbornene-2,3-*exo*-dimethanol Hydrochloride (4) This compound was prepared starting from **16** by the same procedures as those described for the synthesis of compound **1a**. (66.0% overall yield) mp 221 °C (dec.). IR (Nujol): 3310, 3070, 2720 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.30–1.90 (m, 3H), 2.70 (brs, 1H), 2.83 (s, 3H), 2.89 (s, 3H), 2.47 (d, $J=7$ Hz, 2H), 3.44 (s, 1H), 3.71, 4.34 (ABq, $J=13$ Hz, 2H), 4.80–5.50 (br, 1H), 5.50–5.90 (br, 1H), 6.20–6.30, 6.50–6.65 (m, m, 2H), 8.20–8.70 (br, 1H). MS m/z : 197 (free base M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{ClNO}_2$: C, 56.53; H, 8.62; Cl, 15.17; N, 5.99. Found: C, 56.30; H, 8.85; Cl, 15.41; N, 6.14.

2-*endo*-Dimethylamino-5-norbornene-2-*exo*-3-*endo*-dimethanol Hydrochloride (5) This compound was prepared starting from **14** by the same procedures as those described for the synthesis of compound **1a**. (34.0% overall yield) mp 235 °C (dec.). IR (Nujol): 3310, 3070, 2730 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.41, 1.67 (ABq, $J=9$ Hz, 2H), 1.85–2.15 (m, 1H), 2.80–3.10 (m, 1H), 2.97 (s, 6H), 3.30–4.20 (m, 5H), 4.30–5.50 (br, 1H), 5.70–6.20 (br, 1H), 6.20–6.40, 6.40–6.60 (m, m, 2H), 8.10–8.60 (br, 1H). MS m/z : 197 (free base M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{ClNO}_2$: C, 56.53; H, 8.62; Cl, 15.17; N, 5.99. Found: C, 56.83; H, 8.69; Cl, 15.06; N, 5.82.

1,2,3,4-Tetrahydro-2-*endo*-acetamido-2-*exo*-methoxycarbonyl-1,4-epoxy-naphthalene (19) and 1,2,3,4-Tetrahydro-2-*exo*-acetamido-2-*endo*-methoxycarbonyl-1,4-epoxynaphthalene (20) To a solution of **17** (7.1 g, 47.2 mmol) and **18** (8.1 g, 56.6 mmol) in benzene (40 ml) was added acetic acid (2.83 g, 47.2 mmol). The reaction mixture was refluxed for 30 h. The mixture was evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{Me}_2\text{CO}=5:1$) to afford **19** (5.43 g, 44.0%) and **20** (0.73 g, 6.0%).

19: Colorless prisms (Me_2CO), mp 222–224 °C. IR (Nujol): 3270, 3040, 1755, 1650, 1550 cm^{-1} . $^1\text{H-NMR}$ ($\text{CDCl}_3+\text{DMSO}-d_6$) δ : 1.66 (s, 3H), 1.71 (d, $J=12$ Hz, 1H), 2.47–2.62 (dd, $J=8$ Hz, 1H), 3.74 (s, 3H), 5.33 (s, 1H), 6.01 (s, 1H), 7.10–7.40 (m, 5H). MS m/z : 261 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.32; H, 5.81; N, 5.44.

20: Colorless needles (AcOEt), mp 199–201 °C. IR (Nujol): 3290,

3050, 1745, 1725, 1650, 1550, 1530 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.99 (s, 3H), 2.11, 2.55 (dd, $J=5\text{ Hz}$, 1H), 2.69 (d, $J=16\text{ Hz}$, 1H), 3.41 (s, 3H), 5.24 (s, 1H), 5.52 (d, $J=5\text{ Hz}$, 1H), 6.92 (brs, 1H), 7.10–7.30 (m, 4H). MS m/z : 261 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.28; H, 5.77; N, 5.37.

2-Methyl-3a-trans-methoxycarbonyl-5-cis-acetoxy-(1a-cis, 3a, 4, 5-cis)-tetrahydronaphtho[2, 1-d]oxazoline (21) To a solution of **19** (9.7 g, 37.1 mmol) in Ac_2O (90 ml) was added $\text{CF}_3\text{CO}_2\text{H}$ (9 ml). The reaction mixture was allowed to stand at room temperature overnight. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in AcOEt . The solution was washed with water and aqueous NaHCO_3 solution. The organic layer was separated, dried (MgSO_4) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{Me}_2\text{CO}=10:1$) to afford **21** (8.5 g, 76%) as a faintly yellow syrup. $^1\text{H-NMR}$ (CDCl_3) δ : 2.02 (s, 3H), 2.08 (s, 3H), 2.33 (dd, $J=3.6$, 13.5 Hz, 1H), 2.63 (dd, $J=8.1$, 13.5 Hz, 1H), 3.83 (s, 3H), 5.93 (dd, $J=3.6$, 8.1 Hz, 1H), 6.05 (s, 1H), 7.2–7.6 (m, 4H). MS m/z : 303 (M^+).

1,2,3,4-Tetrahydro-2-endo-dimethylamino-2-exo-hydroxymethyl-1,4-epoxynaphthalene Hydrochloride (6a) This compound was prepared starting from **19** by the same procedures as those described for the synthesis of compound **1a**. (67.0% overall yield) mp 146–147°C. IR (Nujol): 3200 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (d, $J=12\text{ Hz}$, 1H), 2.06–2.21 (dd, $J=5\text{ Hz}$, 1H), 2.22 (s, 6H), 2.50–2.69 (br, 1H), 3.88, 4.01 (ABq, $J=11\text{ Hz}$, 2H), 5.24 (s, 1H), 5.29 (d, 1H), 7.10–7.50 (m, 4H). MS m/z : 219 (free base M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{ClNO}_2$: C, 61.05; H, 7.09; Cl, 13.86; N, 5.48. Found: C, 61.01; H, 7.23; Cl, 13.94; N, 5.35.

1,2,3,4-Tetrahydro-2-endo-isopropylamino-2-exo-hydroxymethyl-1,4-epoxynaphthalene Hydrochloride (6b) This compound was prepared starting from **19** by the same procedures as those described for the synthesis of compound **1b**. (41.0% overall yield) mp 89–90°C. IR (Nujol): 3150, 1460 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.74, 0.96 (d, d, 6H), 1.32 (d, $J=12\text{ Hz}$, 1H), 1.79, 1.92 (d, d, $J=5\text{ Hz}$, 1H), 1.40–2.20 (br, 2H), 2.50–2.85 (m, 1H), 3.72 (brs, 2H), 5.10 (s, 1H), 5.32 (d, 1H), 7.10–7.50 (m, 4H). MS m/z : 233 (free base M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{ClNO}_2$: C, 62.33; H, 7.47; Cl, 13.14; N, 5.19. Found: C, 62.57; H, 7.56; Cl, 13.38; N, 5.22.

2-Acetyl-2-azanorbornene-3-exo-carboxylic Acid Ethyl Ester (23m) To a solution of **22m** (20.2 g, 99.3 mmol) in toluene (60 ml) was added cyclopentadiene (45 ml, 555 mmol) during 20 h at 130°C. After cooling, the reaction mixture was evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{Me}_2\text{CO}=10:1$) to afford **23m** (6.1 g, 29%) as a syrup. $^1\text{H-NMR}$ (CDCl_3) δ : 1.30 (t, 3H), 1.50–1.70 (m, 1H), 2.00–2.30 (m, 1H), 2.11 (s, 3H), 3.25–3.40 (m, 1H), 3.70 (s, 1H), 4.24 (m, 2H), 4.60–4.70 (m, 1H), 6.40–6.50 (m, 2H). MS m/z : 209 (M^+). This compound was used in the next step without further purification.

2-Acetyl-2-azanorbornene-3-exo-methanol (24m) To a suspension of $\text{Ca}(\text{BH}_4)_2$, prepared from CaCl_2 (3.2 g, 29.1 mmol) and NaBH_4 (2.88 g, 75.7 mmol), in EtOH (170 ml) was added a solution of **23m** (6.1 g, 29.1 mmol) in EtOH (20 ml) at -15°C . After the reaction mixture was stirred at 5°C for 1 h, the reaction was quenched by AcOH. The insoluble materials were filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in CHCl_3 . The solution was washed with brine. The organic layer was separated, dried (MgSO_4) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3:\text{EtOH}=30:1$) to afford **24m** (2.2 g, 45%) as a syrup. $^1\text{H-NMR}$ (CDCl_3) δ : 1.50–1.90 (m, 2H), 2.11 (s, 3H), 2.95–3.10 (m, 1H), 3.20–3.40 (m, 1H), 3.55–3.90 (m, 2H), 4.50–4.65 (m, 1H), 4.80–5.40 (br, 1H), 6.30–6.60 (m, 2H). MS m/z : 168 ($\text{M}^+ + 1$). This compound was used in the next step without further purification.

2-Ethyl-2-azanorbornene-3-exo-methanol Hydrochloride (7i) To a suspension of LiAlH_4 (0.48 g, 12.5 mmol) in THF (15 ml) was added a solution of **24m** (2.1 g, 12.5 mmol) in THF (10 ml) at 10°C . After the reaction mixture was stirred at 15°C for 3 h, the reaction was quenched by the addition of 15% aqueous NaOH solution. The insoluble materials were filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 3 ml of 22% HCl in MeOH. The solvent was removed under reduced pressure. The resulting crystals were triturated with Me_2CO . Recrystallization from Me_2CO gave needles (**7i**) (0.8 g, 34.0%). mp 108°C (dec.). IR (Nujol): 3300, 3050, 2600, 1460 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (t, 3H), 1.80–2.05 (m, 1H), 2.35–2.60 (m, 1H), 2.60–2.95 (m, 2H), 3.05–3.45 (m, 2H), 4.04 (d, 2H), 4.67 (brs,

2H), 6.20–6.40, 6.80–7.00 (m, m, 2H), 1.10–11.70 (br, 1H). MS m/z : 153 (free base M^+). Anal. Calcd for $\text{C}_9\text{H}_{16}\text{ClNO}$: C, 56.99; H, 8.50; Cl, 18.69; N, 7.40. Found: C, 56.89; H, 8.68; Cl, 18.95; N, 7.26.

2-Benzoyloxycarbonyl-2-azanorbornene-3-exo-methanol (24n) This compound was prepared starting from **22n** by the same procedures as those described for the synthesis of **24m**. (26.0% overall yield) $^1\text{H-NMR}$ (CDCl_3) δ : 1.10–1.40 (m, 3H), 1.95–2.15 (m, 2H), 3.30–3.45 (m, 1H), 3.57 (s, 1H), 4.22 (br, 2H), 4.87 (brs, 1H), 5.14 (s, 2H), 6.30–6.60 (m, 2H), 7.34 (s, 5H). MS m/z : 259 (M^+). This compound was used in the next step without further purification.

2-Azanorbornene-3-exo-methanol Hydrochloride (7j) To a solution of **24n** (5.8 g, 22.4 mmol) in EtOH (20 ml) was added 2.7 N aqueous KOH solution. The reaction mixture was refluxed for 1 h. The mixture was passed through an ion-exchange resin (IR-120, H^+ form, 150 ml). The column was washed with H_2O . The product was eluted with 5% aqueous NH_4OH solution. The eluent was evaporated to dryness *in vacuo* to afford the free base of **7j** (2.2 g, 78%). The free base was dissolved in 3 ml of 22% HCl in MeOH. The solvent was removed under reduced pressure. The resulting crystals were triturated with Me_2CO . Recrystallization from AcOEt gave brown plates (**7j**). mp $83\text{--}85^\circ\text{C}$. IR (Nujol): 3250, 3060, 2710, 1560 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.20–1.70 (m, 2H), 2.30–2.60 (m, 1H), 2.75–2.85 (m, 1H), 3.27 (s, 2H), 3.50–3.70 (m, 2H), 3.97 (brs, 1H), 6.10–6.40 (m, 2H). MS m/z : 125 (free base M^+). Anal. Calcd for $\text{C}_7\text{H}_{12}\text{ClNO}$: C, 52.02; H, 7.48; Cl, 21.93; N, 8.67; Found: C, 51.95; H, 7.63; Cl, 22.20; N, 8.59.

Experimental Ulcers a) EtOH-Induced Gastric Mucosal Erosions: Male SD rats (Charles River Japan, 150–210 g) were fasted for 24 h. EtOH-induced lesions were produced according to the method of Rovert *et al.*¹⁵ Three hours after the oral administration of absolute EtOH (8 ml/kg), the stomach was removed and fixed by instilling 10 ml of 1% formalin solution. The stomach was opened along the greater curvature and examined for the lesions in the glandular portion. The sum of the length (mm) of each lesion was used as a lesion index. Test drugs were given orally 30 min before EtOH treatment.

b) H_2O Immersion Stress-Induced Gastric Erosions: Male SD rats (Charles River Japan, 160–240 g) were fasted for 24 h, and the stress erosion was induced according to the method of Takagi and Okabe.¹⁶ The animals were given the test drug orally 30 min before being placed in a stress cage and immersed vertically to the level of the xiphoid process in a water bath maintained at $23 \pm 0.5^\circ\text{C}$. Five hours later, the stomach was removed and fixed by instilling 10 ml of 1% formalin solution. The stomach was incised along the greater curvature and examined for mucosal lesions. The severity of each lesion was scored as 0.25 for weak hyperemia, 0.5 for severe hyperemia or weak hemorrhage, 1 for hemorrhage, and 2 for severe hemorrhage. Areas of mucosal damage were measured in mm^2 using a planimeter, multiplied by the corresponding score, and summed up to give an erosion index.

c) Aspirin-Induced Gastric Erosions: Male SD rats (Shizuoka Laboratory Animal Center, 245–295 g) were fasted for 24 h. Four hours after the oral administration of 200 mg/kg aspirin, the stomach was removed and fixed by instilling 10 ml of 1% formalin solution. The stomach was incised along the greater curvature and examined for lesions in the glandular portion. The sum of the length (mm) of each erosion was used as an erosion index. Test drugs were administered orally 30 min before the treatment with aspirin.

d) Gastric Secretion: Male SD rats (Charles River Japan, 150–190 g) were fasted for 24 h. The animals were anesthetized with ether, and the pylorus was ligated according to the method of Shay *et al.*¹⁷ Test drugs were administered immediately after the pylorus ligation. The stomach was removed 5 h after the subcutaneous administration. The gastric contents were centrifuged at 2500 rpm for 10 min, and then the volume of gastric juice (supernatant fluid) was measured. The acidity was titrated with 0.1 N NaOH to pH 7.0 using a titrator apparatus (TTT80, ABU80, Radiometer) and expressed as meq/l.

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References and Notes

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