Tetrahedron Vol. 47, No. 4/5, pp. 541-548, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

A TWO-STEP SYNTHESIS OF 2-*EXO*-SUBSTITUTED 2-*ENDO*-AMINONORBORNENES FROM 2-ACETAMIDONORBORNENE-2-CARBOXYLIC ACIDS

Hiroyoshi Yamazaki, Hiroshi Horikawa, Takashi Nishitani, and Tameo Iwasaki*

Department of Synthetic Chemistry, Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa, Osaka 532, Japan.

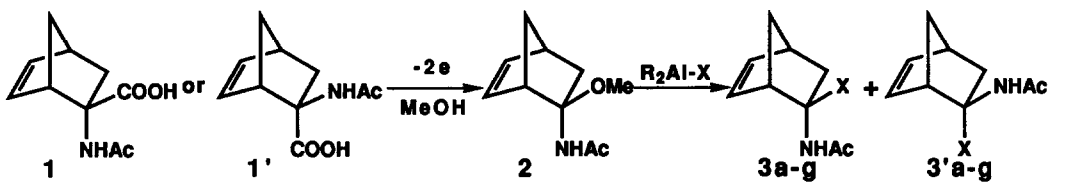
Kimio Okamura, and Tadamasa Date

Department of Analysis, Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Kawagishi, Toda-shi, Saitama 335, Japan.

(*Received in USA* 15 *August* 1990)

Summary: 2-*exo*-Substituted 2-*endo*-acetamidonorbornenes (**3**) were synthesized in a two-step procedure from 2-acetamidonorbornene-2-carboxylic acids (**1**, **1'**) with exceedingly high *exo*-selectivities based on a new approach involving anodic decarboxylation followed by organoaluminum-promoted nucleophilic substitution on 2-*endo*-acetamido-2-*exo*-methoxynorbornene (**2**).

2-*exo*-Substituted 2-*endo*-aminonorbornanes have attracted considerable attention since the discovery of their exciting biological activities.[1] The presence of the 2-*endo*-amino group is crucial for exhibiting the biological activities.[2] In connection with our synthetic studies in search of new compounds having intriguing biological activities, we now report a two-step synthesis of 2-*exo*-substituted 2-*endo*-acetamidonorbornenes (**3**) with exceedingly high *exo*-selectivities from 2-acetamidonorbornene-2-carboxylic acids (**1**, **1'**) based on a new approach involving anodic decarboxylation followed by organoaluminum-promoted nucleophilic substitution on 2-*endo*-acetamido-2-*exo*-methoxynorbornene (**2**) (Scheme 1). A synthesis of 2-*exo*-substituted 2-*endo*-aminonorbornane derivative (**6a**) will also be discussed.



a: X=SCH_2Ph **b:** X=SPh **c:** X=SEt **d:** X=SCH_2CO_2Me

e: X=NHPh **f:** X=C≡C-Ph **g:** X=C≡C-OTHP

Scheme 1

Anodic Oxidation

It is well-known that anodic oxidation is quite effective for preparation of *N*-acyl-α-methoxyalkylamines from *N*-acyl-α-amino acids.[3] Our study began with experiments to test the *exo*-selectivity in the anodic oxidation of **1** and **1'**. The requisite carboxylic acids (**1**, **1'**) were prepared by saponification of the corresponding

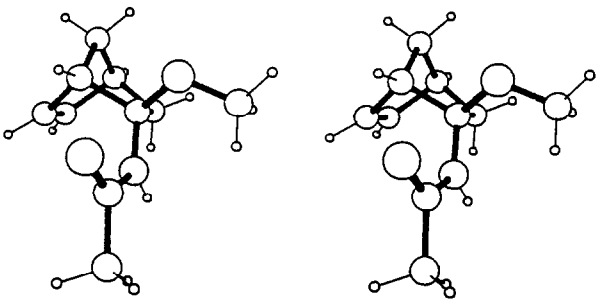
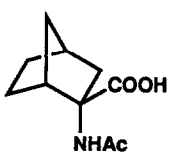
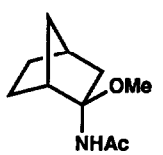


Fig. 1. Stereoscopic view of **2**

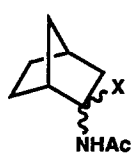
carboxylic acid esters which were readily obtained by the Diels-Alder reaction of ethyl α,β-dehydroalaninate with cyclopentadiene.[4] Anodic oxidation of **1** was carried out at a constant current of 15 mA/cm^2 in methanol containing a catalytic amount of NaOMe using graphite anode-graphite cathode in a non-divided cell.[3] The reaction proceeded with quantitative current efficiency to give **2** in 95 % yield without any formation of 2-*endo*-methoxy-2-*exo*-acetamidonorbornene. The result indicates that methanol attacks the rather stable *N*-acylimine generated in the anodic decarboxylation overwhemingly from the less hindered *exo*-side.[5] The structure of **2** was unambiguously determined by X-ray crystallographic analysis (Fig. 1). 2-*endo*-Acetamidonorbornane-2-carboxylic acid (**4**) was also treated under the same conditions as described above to furnish only the *exo*-methoxylated compound (**5**) in 96 % yield. On the other hand, when anodic oxidation of 2-*exo*-acetamidonorbornene-2-carboxylic acid (**1'**) was carried out under the same conditions as described above, the reaction did not proceed at all, the starting material being recovered. By increasing current density up to 60 mA/cm^2, the reaction was initiated[6] to afford **2** in 94 % yield,[7] in which no 2-*endo*-methoxylated product was formed.



4



5



6 (endo-NHAc)
6' (exo-NHAc)

Organoaluminum-Promoted Nucleophilic Substitution[8]

The nucleophilic substitutions on *N*-acyl-α-methoxyalkylamines under the influence of an acidic catalyst are well-recognized[9] to proceed through the highly reactive *N*-acyliminium ions in a process closely resembling an SN1 reaction. Thus, the nucleophilic substitution on **2** using an ordinary acidic catalyst can not be expected to proceed stereospecifically.[10] In fact, $SnCl_4$-catalyzed reaction of **2** with $PhCH_2SH$ proceeded smoothly but gave a mixture of **3a** and **3'a** in a ratio of 61:39 (run 1, Table 1). Similar results were also obtained in the reactions catalyzed by BF_3OEt_2, Me_3SiOTf, HCl, $ZnCl_2$, and methylaluminum bis(2,4,6-tri-*tert*-butylphenoxide) (MAT)[11] (runs 2-6, Table 1). On the other hand, Nozaki and Oshima noted that in the reaction of allylic phosphates with organoaluminum reagents in a polar solvent, the nucleophilic substitutions presumably take place *via* an intimate

ion-pair in a solvent cage, implying the intervention of an SN*i* mechanism.[12] With such information in hand, we examined the reaction of **2** with R_2Al-X (**7a-g**) type organoaluminum reagents .

Table 1. Lewis acid-catalyzed nucleophilic substitution

2 $\xrightarrow[\text{Lewis Acid}]{PhCH_2SH}$ **3a** + **3'a**

run	Lewis acid	Yield[a] (%)	3a : 3'a[b]
1	$SnCl_4$	71	61 : 39
2	BF_3OEt_2	95	67 : 33
3	Me_3SiOTf	91	65 : 35
4	HCl	99	64 : 36
5	$ZnCl_2$	92	50 : 50
6	MAT	63	45 : 55
7	$AlMe_3$	83	68 : 32

a) Yield of a mixture of **3a** and **3'a** isolated by silica gel column chromatography.
b) The ratio was determined by HPLC analysis of the reaction mixture.

Treatment of **2** with Me_2Al-SCH_2Ph (**7a**)[12] in CH_2Cl_2 for 1 hr at room temperature gave a mixture of **3a** and **3'a** in a ratio of 99 : 1 (run 1, Table 2). A similar *exo*-selectivity was also observed in the reaction using THF as solvent. It is noteworthy that the use of hexane lowered the *exo*-selectivity,[12] the **3a/3'a** ratio being 81 : 19. In marked contrast with the above results, the addition of $AlMe_3$ to a mixture of **2** and $PhCH_2SH$ in CH_2Cl_2 resulted in **3a/3'a** ratio of 68 : 32 (run 7, Table 1). The above results suggest that R_2Al-X type organoaluminum reagents would make the nucleophilic substitution proceed apparently *via* an SN*i* mechanism.

The generality of the present nucleophilic substitution is indicated in Table 2. Organoaluminum reagents having other sulfur (runs 2-4, Table 2) and nitrogen (run 5) functionalities as nucleophilic parts also worked

Table 2. Organoaluminum-promoted nucleophilic substitution

2 (or 5) $\xrightarrow{R_2Al\text{-}X\ (7)}$ **3 (or 6)** + **3' (or 6')**

	R_2Al-X (7)				
run	R	X	product	yield[a] (%)	3 (or 6) : 3' (or 6')[b]
1	Me	SCH_2Ph	3a	81	99 : 1
2	Me	SPh	3b	84	99 : 1
3	Me	SEt	3c	81	97 : 3
4	Me	SCH_2CO_2Me	3d	59	98 : 2
5	Me	NHPh	3e	33	≥99 : 1[c]
6	Me	SCH_2Ph	6a	73	99 : 1

a) Yield of a mixture of **3** (or **6**) and **3'** (or **6'**) isolated by silica gel column chromatography.
b) The ratio was determined by HPLC analysis of the reaction mixture.
c) **3'e** was not detected by HPLC analysis of the reaction mixture.

effectively. The nucleophilic substitution on 2-*endo*-acetamido-2-*exo*-methoxynorbornane (**5**) also resulted in high *exo*-selectivity (run 6, Table 2). The structures of all compounds described above were unambiguously determined by ^{1}H-NMR spectroscopy.[13]

Furthermore, it should be noted that the carbon-carbon bond forming reactions using **7f** and **7g** were realized by this operation to afford **3f** and **3g** in 70 % and 72 % yields, respectively with extremely high *exo*-selectivities.[14] The structure of **3f** was determined by X-ray crystallographic analysis.[15] The structure of **3g** was determined by comparing the ^{1}H-NMR spectrum with that of **3f**.[13]

This method should find application in the synthesis of 2-*exo*-substituted 2-*endo*-aminonorbornanes having interesting biological activities.[16]

Experimental Section

All melting points were uncorrected. IR spectra were recorded on a Shimadzu IR-420 Infrared Spectrophotometer. ^{1}H-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 Hitachi M-60 instrument. The electrolysis were carried out by the use of a Hokuto Potentio-Galvanostat (10 A-100 V) attached to a Hokuto HA-108A coulomb meter. The HPLC analyses were carried out by the use of Shimadzu LC-5A liquid chromatograph using a reversal-phase column (nucleosil $_5C_{18}$, 5 μm, 4.6 mm i.d. X 150 mm long) with CH_3CN/H_2O (1/1) as solvent (flow rate =1.0 ml/min).

2-*endo*-Acetamidonorbornene-2-*exo*-carboxylic acid (1)

To a solution of 2-*endo*-acetamidonorbornene-2-*exo*-carboxylic acid methyl ester (2.09 g, 10 mmol) in MeOH (10 ml) was added potassium hydroxide (1.34 g, 24 mmol) dissolved in 80 % aqueous MeOH (10 ml) under ice cooling. The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure. The residue was dissolved in water and the solution was washed with EtOAc. The aqueous layer was separated and acidified with concentrated hydrochloric acid under ice cooling. The resulting precipitates were collected by filtration to afford **1** (1.48 g, 78 %) as colorless needles. mp 232 °C (dp). IR (Nujol) 3350, 1700, 1620, cm^{-1}; ^{1}H-NMR (DMSO-d6) δ: 1.60-1.70 (3H, m), 1.73 (3H, s), 2.20-2.45 (1H, m), 2.51 (1H, br), 2.80 (1H, m), 3.23 (1H, m), 6.04 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 6.27 (1H, dd, *J*=3.0 Hz,6.0 Hz), 7.87 (1H, s); MS (*m/e*) 196 (M^++H); *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.61; H, 6.86; N, 6.93.

2-*exo*-Acetamidonorbornene-2-*endo*-carboxylic acid (1')

2-*Exo*-acetamidonorbornene-2-*endo*-carboxylic acid methyl ester (2.09 g, 10 mmol) was saponified in 80 % aqueous MeOH (30 ml) containing potassium hydroxide (1.81 g, 50 mmol) at 60 °C for 4 h. The reaction mixture was worked up by the same method as described above to give compound **1'** (1.49 g, 75 %) as colorless needles. mp 238 °C (dp). IR (Nujol) 3320, 1740, 1620 cm^{-1} ; ^{1}H-NMR (DMSO-d6) δ: 1.30-2.15 (3H, m), 1.82 (3H, s), 2.52 (1H, br), 2.83 (1H, m), 2.99 (1H, m), 5.83 (1H, dd, *J*=3.0 Hz,6.0 Hz), 6.24 (1H, dd, *J*=3.0 Hz,6.0 Hz), 8.35 (1H, br); MS (*m/e*) 177 (M^+-H_2O); Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18 Found: C, 61.40; H, 6.75; N, 6.89.

2-*endo*-Acetamido-2-*exo*-methoxynorbornene (2)

Compound **1** (3.9 g, 20 mmol) was dissolved in MeOH (40 ml) containing NaOMe (1 mmol). The solution was electrolyzed at 5-10 °C using graphite anode-graphite cathode (6.7 cm^2)in a non-divided cell. An electrolysis current was maintained at 100 mA (current density :15 mA/cm^2) during the electrolysis. After the theoretical amount of electricity was passed, the electrolyzed solution was evaporated to dryness *in vacuo*. The residue was dissolved in EtOAc. The solution was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford **2** (3.5 g, 95 %). Recrystallization from diisopropylether gave colorless prisms. mp 123 °C; IR (Nujol) 3300, 1655 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ: 1.30-1.90 (3H, m), 1.86 (3H, s), 2.50 (1H, m), 2.75 (1H, m), 3.06 (3H, s), 3.35 (1H, m), 5.87 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 6.18 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 8.00 (1H,br); MS (*m/e*) 181 (M^+); *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.49; H, 8.51; N,7.96.

Compound **1'** (3.9 g, 20 mmol) was also electrolyzed at a constant current of 400 mA (current density : 60 mA/cm^2) to give **2** in 88 % yield.

X-ray determination of 2

Crystal data: $C_{10}H_{15}NO_2$, Mw=181.24, a = 9.536(2), b = 13.771(2), c = 7.991(1)Å, α = 98.56(1), β = 90.20(1), γ = 108.78(1)° ,U = 981.0(3)Å^3, Triclinic, Space group $P\bar{1}$, Z = 4, Dx = 1.227 g/cm, F(000) = 392, μ(Cu Kα) = 7.323 cm^{-1}, T = 223°K.

The title compound shows sublimation at room temperature. The diffraction experiment was carried out at 223 °K using a colorless transparent prism (0.8x0.4x0.2 mm^3), which was obtained from isopropanol solution. The four-circle diffractometer (AFC/5, RIGAKU) was used with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular setting of 20 reflections (2 θ values in the range of 30 °- 60 °).

Three dimensional intensity data were measured by ω-2θ scan technique ($2\theta \leq 120°$). 2888 unique reflections were mesured, of which 2518 with $|Fo| \geq 2.67\,\sigma$ (F) were considered as observed. No absorption corrections were applied.

The structure was solved by the direct methods using SIR85[17] and difference Fourier method. The refinement of atomic parameters were carried out using block-diagonal matrix least-square's methods with anisotropic temperature factors for the non-hydrogen atoms. Of 30 hydrogen atoms, 25 atoms were located on the difference Fourier maps and refined with isotropic temperature factors. The positions of other hydrogen atoms were assumed geometrically and fixed throughout the refinement. The function $\Sigma w(|Fo|-|Fc|)^2$ was minimized in the refinement calculations. During the final refinement stage, the weighting scheme of $\sqrt{w} = \exp\{ 0.00014*|Fo|^2 + 1.75879*(\sin\theta/\lambda)^2 + 0.09063*|Fo|*(\sin\theta/\lambda) + (-0.03251)*|Fo| + 0.51709*(\sin\theta/\lambda) + 0.04646 \}$ was used. The final R value was 0.097(Rw = 0.100).

The atomic scattering factors were taken from " International Tables for X-ray Crystallography".[18]

2-*endo*-Acetamidonorbornane-2-*exo*-carboxylic acid (4)

Compound **1** (5.0 g, 25.61 mmol) was reduced in MeOH (70 ml) over 10 % palladium on charcoal (0.4 g) at 2 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 diisopropylether gave **4** (5.0 g, 99 %). mp 251 °C (dp); IR (Nujol) 3350, 1710, 1620 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ: 1.05-1.85 (7H, m), 1.82 (3H, s), 1.90-2.25 (2H, m), 2.52 (1H, m), 2.67 (1H, m), 8.06 (1H, br); MS (*m/e*) 179 (M^+-H_2O); *Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.55; H, 7.86; N, 6.77.

2-*endo*-Acetamido-2-*exo*-methoxynorbornane (5)

Compound **4** was electrolyzed at a current density of 15 mA/cm^2 under the same conditions as above to afford **5** in 84 % yield. mp 119-120 °C; IR (Nujol) 3300, 1660 cm^{-1}; ^{1}H-NMR (DMSO-d6) δ: 1.00-1.80 (8H, m), 1.83 (3H, s), 2.15 (1H, m), 2.86 (1H, m), 2.96 (3H, s), 8.05 (1H, brs); MS (*m/e*) 183 (M^+); *Anal.* Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.30; H,9.69; N, 7.53.

Typical procedure for the Lewis-acid catalyzed nucleophilic substitution on 2
Reaction of 2 using $SnCl_4$

To a mixture of **2** (1.81 g, 10 mmol) and $PhCH_2SH$ (1.49 g, 12 mmol) in CH_2Cl_2 (10 ml) was added $SnCl_4$(1.17 ml, 10 mmol) at 5 °C. The reaction mixture was stirred at 5 °C for 1 h, and then warmed to room temperature. The mixture was diluted with $CHCl_3$. The solution was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The resulting syrup was purified by column chromatography on silica gel ($CHCl_3$: acetone = 10 : 1) to afford compounds **3a** (1.18 g, 43.2 %) and **3'a** (0.760 g, 27.8 %).

2-*endo*-Acetamido-2-*exo*-benzylthionorbornene (3a): mp 132-133 °C; IR (Nujol) 3250, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.80 (2H, m), 1.78 (3H, s), 1.90-2.40 (2H, m), 2.86 (1H, m), 3.70 (1H, m), 3.97 (2H, s), 5.63 (1H, m), 5.95 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 6.20 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 7.10-7.40 (5H, m); MS (*m/e*) 273 (M^+); *Anal.* Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.01; N, 5.12; S, 11.73. Found: C, 69.94; H, 7.02; N, 5.03; S, 11.91.

2-*exo*-Acetamido-2-*endo*-benzylthionorbornene (3'a): mp 133-134 °C; IR (Nujol) 3250, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.95 (3H, m), 1.76 (3H, s), 2.25-2.50 (1H, m), 2.90 (1H, m), 3.19 (1H, m), 3.81 (2H, s), 5.81 (1H, m), 6.00 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 6.23 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 7.00-7.45 (5H, m); MS (*m/e*) 273 (M^+); *Anal.* Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.01; N, 5.12; S, 11.73. Found: C, 70.02; H, 7.04; N, 5.03; S, 11.79.

Reaction of 2 using $AlMe_3$

To a mixture of **2** (181 mg, 1 mmol) and $PhCH_2SH$ (149 mg, 1.2 mmol) in CH_2Cl_2 (1 ml) was added a 15 % hexane solution of $AlMe_3$ (0.48 ml, 1 mmol) at 5 °C. The mixture was worked up by the same procedure as described above to afford the mixture of compounds **3a** and **3'a** (yield 83 %). The isomeric ratio was determined by HPLC analysis.

Typical procedures for organoaluminum-promoted nucleophilic substitution

To a solution of $PhCH_2SH$ (248 mg, 2 mmol) in CH_2Cl_2 (1 ml) was added 15 % hexane solution of $AlMe_3$ (0.96 ml, 2 mmol) at 5 °C. The mixture was stirred at -5~0 °C for 20 min. To this was added a solution of **2** (181 mg, 1 mmol) in CH_2Cl_2. The mixture was warmed to 0~5 °C and stirred for 1 h. The solvent was removed under reduced pressure, and the residue was suspended in ether. To the suspension was added $NaHSO_4 \cdot 10H_2O$ (1 g) and the mixture was stirred at room temperature for 1 h. 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 ($CHCl_3$: acetone = 10: 1) to afford the mixture of compounds **3a** and **3'a** in 81 % yield. The **3a/3'a** ratio was determined by HPLC analysis (**3a/3'a** = 99 : 1).

2-*endo*-Acetamido-2-*exo*-phenylthionorbornene (3b): mp 184-185 °C; IR (Nujol) 3260, 1650 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.61-1.68 (2H, m), 1.83 (3H, s), 1.90-2.35 (2H, m), 2.91 (1H, m), 3.32 (1H, m), 5.44 (1H, br), 5.91 (1H, dd, *J*=3.0 Hz, 5.7 Hz), 6.27 (1H, dd, *J*=3.0 Hz, 5.7 Hz), 7.16-7.52 (5H, m); MS (*m/e*) 259 (M^+); *Anal.* calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40; S, 12.36. Found: C, 69.33; H, 6.71; N, 5.29; S, 12.49.

2-*exo*-Acetamido-2-*endo*-phenylthionorbornene (3'b): syrup; IR (Nujol) 3260, 1650 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.59-1.69 (2H, m), 1.93 (3H, s), 2.02-2.53 (2H, m), 2.70 (1H, m), 3.17 (1H, m), 5.89 (1H, br), 5.91 (1H, dd, *J*=3.0 Hz, 5.8 Hz), 6.27 (1H, dd, *J*=3.0 Hz, 5.8 Hz), 7.10-7.50 (5H, m); MS (*m/e*) 259 (M^+); *Anal.* calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40; S, 12.36. Found: C, 69.40; H, 6.69; N, 5.25; S, 12.52.

2-*endo*-Acetamido-2-*exo*-ethylthionorbornene (3c): mp 139-140 °C; IR (Nujol) 3280, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.23 (3H, t, *J*=7.6 Hz), 1.47-1.70 (2H, m), 1.89 (3H, s), 1.98-2.21 (2H, m), 2.72 (2H,q, *J*=7.6 Hz), 2.87 (1H, m), 3.67 (1H, m), 5.67 (1H, br), 6.01 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 6.22 (1H, dd, *J*=3.0 Hz, 6.0 Hz); MS (*m/e*) 211 (M^+); *Anal.* calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63; S, 15.17. Found: C, 61.89; H, 8.14; N, 6.52; S, 14.91.

2-*exo*-Acetamido-2-*endo*-ethylthionorbornene (3'c): mp 122-123 °C; IR (Nujol) 3270, 1655 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.21 (3H, t, *J*=7.5 Hz), 1.50-1.74 (3H, m), 2.01 (3H, s), 2.34-2.81 (3H, m), 2.93 (1H, m), 3.33 (1H, m), 5.98 (1H, br), 6.10 (1H, dd, *J*=3.2 Hz, 5.6 Hz), 6.27 (1H, dd, *J*=3.2 Hz, 5.6 Hz); MS (*m/e*) 211 (M^+); *Anal.* calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63; S, 15.17. Found: C, 61.95; H, 8.40; N, 6.61; S, 15.27.

2-*endo*-Acetamido-2-*exo*-methoxycarbonylmethylthionorbornene (3d): mp 101-102 °C; IR (Nujol) 3260, 1735, 1655 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.56-1.65 (2H, m), 1.90 (3H, s), 1.96-2.00 (1H, m), 2.12-2.20 (1H, m), 2.90 (1H, m), 3.47(1H, d, *J*=15.1 Hz), 3.59 (1H, d, *J*=15.1Hz), 3.68 (1H, m), 3.73 (3H, s), 5.91 (1H, br), 6.02 (1H, dd, *J*=3.0 Hz, 6.0 Hz), 6.25 (1H, dd, *J*=3.0 Hz, 6.0 Hz); MS (*m/e*) 255 (M^+); *Anal.* calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49; S, 12.56. Found: C, 56.06; H,6.68; N, 5.51; S, 12.55.

2-*exo*-Acetamido-2-*endo*-methoxycarbonylmethylthionorbornene (3'd): mp 132-133 °C; IR (Nujol) 3280, 1730, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.49-1.68 (3H, m), 2.01 (3H, s), 2.43-2.52 (1H, m), 2.93 (1H, m), 3.30(2H, m), 3.68 (1H, m), 3.74 (3H, s), 6.07 (1H, dd, *J*=3.0 Hz, 5.6 Hz), 6.11 (1H, br), 6.28 (1H, dd, *J*=3.0 Hz, 5.6 Hz); MS (*m/e*) 255 (M^+); *Anal.* calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49; S, 12.56. Found: C, 56.62; H,6.75 ; N, 5.40; S, 12.49.

2-*endo*-Acetamido-2-*exo*-phenylaminonorbornene (3e): syrup; IR (Nujol) 3320, 1650 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 1.38 (1H, dd, *J*=3.0 Hz, 11.8 Hz), 1.58-1.64 (1H, m), 1.76 (3H, s), 1.95-2.08(1H, m), 2.43 (1H, dd, *J*=3.7 Hz, 11.8 Hz), 2.95 (1H, m), 3.61 (1H, m), 5.25 (1H, br), 5.86 (1H, br), 6.06 (1H, dd, *J*=3.2 Hz, 5.6 Hz), 6.33 (1H, dd, *J*=3.0 Hz, 5.6 Hz) 6.68-6.80 (3H, m), 7.10-7.31 (2H, m); MS (*m/e*) 242 (M^+); *Anal.* calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.41; H, 7.60; N, 11.48.

2-*endo*-Acetamido-2-*exo*-benzylthionorbornane (6a): mp 139-140 °C; IR (Nujol) 3290, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.14-1.65 (6H, m), 1.68 (3H, s), 2.06-2.28 (3H, m), 2.94 (1H, m), 3.84 (1H, d, *J*=13.6 Hz), 3.92 (1H, d, *J*=13.6 Hz), 5.55 (1H, br) 7.16-7.36 (5H, m); MS (*m/e*) 276 (M^++H^+); *Anal.* Calcd for $C_{16}H_{21}NOS$: C, 69.79; H, 7.69; N, 5.09; S, 11.63. Found: C, 69.54; H, 7.90; N, 5.03; S, 11.45.

2-*exo*-Acetamido-2-*endo*-benzylthionorbornane (6'a): mp 155-156 °C; IR (Nujol) 3280, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.17-1.53 (6H, m), 1.66 (3H, s), 1.97-2.27 (3H, m), 2.49 (1H, m), 3.76 (2H, s), 5.30 (1H, br) 7.17-7.38 (5H, m); MS (*m/e*) 276 (M^++H^+); *Anal.* Calcd for $C_{16}H_{21}NOS$: C, 69.79; H, 7.69; N, 5.09; S, 11.63. Found: C, 69.47; H, 7.80; N, 5.02; S, 11.33.

2-*endo*-Acetamido-2-*exo*-phenylpropargylnorbornene (3f)

To a solution of phenylacetylene (225 mg, 2.2 mmol) in toluene (2 ml) was added 1.6 M hexane solution of *n*-BuLi (1.38 ml, 2.2 mmol) at -78 °C, and the mixture was stirred at the same temperature for 15 min (The Li salt of phenylacetylene precipitated.). To the suspension was added 1.8 M solution of Et_2AlCl in toluene (1.22 ml, 2.2 mmol) , and the mixture was stirred at room temperature for 1h. To the mixture was added a solution of **1** in THF (181 mg, 1 mmol) at -40 °C. The mixture was warmed to room temperature and stirred for 1.5 h. The reaction mixture was carefully quenched at 5 °C by addition of 10 % HCl (5 ml). The mixture was extracted with AcOEt. The separated organic layer was washed with brine and dried ($MgSO_4$). The solution was concentrated to dryness *in vacuo* and the resulting syrup was subjected to silica gel chromatography ($CHCl_3$: acetone = 7: 3) to afford **3f** (175 mg, 70 %). mp 134-135 °C; IR (Nujol) 3320, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.44 (1H, dd, *J*=3.1 Hz, 12.3 Hz), 1.62-1.65 (1H, m), 1.93 (3H, s), 1.96-2.01(1H, m), 2.54 (1H, dd, *J*=3.7 Hz, 12.3 Hz), 2.96 (1H, m), 3.68 (1H, m), 5.54 (1H, br), 6.02 (1H, dd, *J*=2.9 Hz, 5.6 Hz), 6.33 (1H, dd, *J*=2.9Hz, 5.6 Hz) 7.24-7.28 (3H, m), 7.39-7.44 (2H, m); MS (*m/e*) 251 (M^+); *Anal.* calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.16; H, 6.75; N, 5.50.

X-ray determination of 3f

Crystal data: $C_{17}H_{17}NO$, Mw=251.33, *a* = 12.499(2), *b* = 11.994(3), *c* = 10.001(1)Å, β = 102.89(1)°, U = 1464.4(8)Å3, monoclinic,P21/c, Z = 4, Dx = 1.140 g/cm, F(000) = 536, μ(Cu Kα) = 5.607 cm^{-1}, T = 291°K.

The diffraction experiment was carried out using a colorless transparent prism (0.5x0.4x0.3 mm^3). The four-circle diffractometer (AFC/5, RIGAKU) was used with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular setting of 25 reflections (2 θ values in the range of 30 °- 60 °).

2170 unique reflections ($2\theta \leq 120°$)were measured, of which 1772 with $|Fo| \geq 2.67\ \sigma$ (Fo) were considered as observed. No absorption corrections were applied. The structure was solved by the direct methods using MULTAN 80[19] and difference Fourier method. The refinement of atomic parameters were carried out using block-diagonal matrix least-square's methods with anisotropic temperature factors. 15 hydrogen atoms were located on the difference -Fourier maps and refined with isotropic temperature factors. The positions of residual hydrogen atoms were assumed geometrically. Throughout the refinement, the function $\Sigma w(|Fo|-|Fc|)^2$ was minimized. The weighting scheme of $\sqrt{W} = 1/\sigma$ (Fo) was used during the final refinement stage. The final R value was 0.089(Rw = 0.110). The atomic scattering factors were taken from " International Tables for X-ray Crystallography".[18]

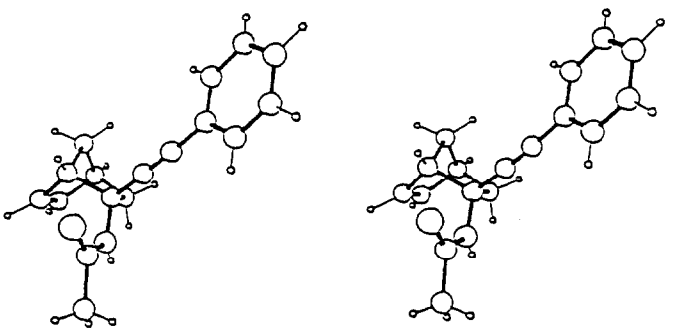
2-*endo*-Acetamido-2-*exo*-tetrahydropyranyloxymethylpropargylnorbornene (3g): syrup; IR (Nujol) 3300, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.22-1.83 (8H, m), 1.62-1.65 (1H, m), 1.89 (3H, s), 1.96-2.05(1H, m), 2.39-2.47 (1H, m), 2.91 (1H, m), 3.40-3.90 (3H, m), 4.26 (1H, d, *J*=13.4 Hz), 4.34 (1H, d, *J*=13.4 Hz), 4.82 (1H, m), 5.46 (1H, br), 5.97 (1H, dd, *J*=2.9 Hz, 5.3 Hz), 6.29 (1H, dd, *J*=2.9Hz, 5.3 Hz); MS (*m/e*) 251 (M^+); *Anal.* calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.55; H, 7.92; N, 4.91.

Acknowledgement: The authors thank Dr. Tetsuya Tosa, General Manager and Dr. Kazuo Matsumoto, Manager of our research laboratory for their encouragement and interest.

References and notes

1. Buchbauer, G.; Esterer, S ; Cermak, C. H. *Pharmazie* **1983**, *38*, 151, and references cited therein.
2. Tager, H. S.; Christensen, H. N. *Biochem. Biophys. Res. Commun.* **1971**, *44*, 185; Crooks, P. A. ; Burn, P.; Sewell, R. D. E.; Upton, N. *J. Pharm. Sci.* **1986**, *75*, 1010.
3. Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *Bull. Chem. Soc. Jpn* **1979**, *52*, 826; *idem. J. Org. Chem.* **1977**, *42*, 2419.

4. Horikawa, H.; Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. *Tetrahedron Lett.* **1980**, *21*, 4101.
5. A similar *exo*-selectivity was observed for the nucleophilic attack on the carbonyl group of norbornan-2-one. See, Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.
6. The result clearly indicates that the higher current density is required for initiation of the anodic oxidation of the sterically hindered carboxylic acid such as **1'**.
7. In these electrode reactions, no elimination and rearrangement reactions took place probably due to the intervention of the rather stable *N*-acylimines as a transient intermediate. On the other hand, anodic oxidation of norbornene-2-carboxylic acid in MeOH afforded 3-methoxynortricyclene *via* a non-classical cationic intermediate. See, Corey, E. J.; Bauld, N. L.; LaLonde, R. T.; Casanova Jr.,J.; Kaiser, E. T. *J. Am. Chem. Soc.* **1960**, *82*, 2645.
8. Preliminary communication: Yamazaki, H.; Horikawa, H.; Nishitani, T.; Iwasaki, T. *Tetrahedron Lett. in press.*
9. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367; Shono, T. *Tetrahedron* **1984**, *40*, 811.
10. Seebach *et al.* reported the Lewis acid catalyzed nucleophilic substitutions on *N*-acyl-α-methoxyalkylamines, but high diastereoselectivities were not observed. See, Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P. *Helv. Chim. Acta.* **1989**, *72*, 401, and references cited therein.
11. Maruoka, K.; Ito, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.
12. Itoh, A.; Ozawa, S.; Oshima, K.; Sasaki, S.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn* **1980**, *53*, 2357; Oshima, K.; Nozaki, H. *J. Synth. Org. Chem. Jpn* **1980**, *38*, 460.
13. The shielding effect of the 5,6-double bond of **3** shifts the NMR signals of the methyl protons of the acetamido group of **3** to a higher field than those of **3'**. See, ref. 4.
14. Attempts to prepare **3'f** and **3'g** as authentic samples failed. Accordingly, we did not estimate the accurate values of **3f/3'f** and **3g/3'g** ratio. The HPLC analyses of these reaction mixtures suggested that the **3f/3'f** and **3g/3'g** ratios are 98 : 2 and 97 : 3, respectively.
15. Stereoscopic view of **3f**



16. Some of these compounds reported herein showed moderate antiulcer activities. The details will be reported elsewhere in the near future.
17. SIR85: A computer program for atomic analysis of phase problem.; Giaccovazzo, C. ; Cascarano, G. L.; Polidori, G.; Spagna, R.; Viterbo, D. *Acta cryst.* **1982**, *A38*, 663 ; *Idem, ibid.* **1987**, *A43*, 22.
18. "International Tables for X-Ray Crystallography," Vol. IV, Birmingham Kynoch Press **1974**.
19. MULTAN 80: A computer program for atomic analysis of phase problem.; Main, P. ; German, G.; Woolfson, M.M. Univ. of York, England.