Synthesis of Substituted 1-Norbornylamines with Antiviral Activity

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The reaction of (±)-camphor (**7**) with triflic anhydride (Tf_2O) yields the bridgehead triflate **8**. The Nametkin rearrangement of **8** to **3** was realized by treatment with triflic acid (TfOH). The solvolysis of the bridgehead triflates **3** and **8** in acetonitrile affords the *N*-acetyl-1-norbornylamines **4** and **9**. The Pd(0)-catalyzed hydrogenation of **4** and **9** gives the amides **5** and **10**. The corresponding 1-norbornylamines **2** and **13** and the *N*-ethyl derivatives **1**, **6**, **11**, and **12** were obtained by basic hydrolysis or reduction with $LiAlH_4$, respectively, of the amides **4**, **5**, **9**, and **10**. The antiviral activity of the hydrochlorides of some of the obtained 1-norbornylamines was evaluated against influenza A, herpes simplex 2, and African swine fever virus. Particularly noticeable is the activity of the hydrochlorides of **1** and **11** against influenza A virus (SI (selectivity index) = 1000).

Introduction

1-Adamantylamine (amantadine) and related compounds such as (α-methyl-1-adamantyl)methylamine (rimantadine) were shown to have prophylactic and therapeutic activity in infections of influenza A viruses.[1] A high activity is also present in 1-apocamphylamine derivatives.[2] However, progress in the promising field of the 1-norbornylamines is limited by their difficult synthesis.[2b,3] We report here on a facile synthesis of substituted 1-norbornylamines and on the antiviral activity of some of them.

Chemistry

The reaction of (±)-camphor (**7**) (Scheme 1) with triflic anhydride (Tf_2O), using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base, takes place under Wagner–Meerwein rearrangement, yielding 4-(triflyloxy)camphene (**8**).[4] Treatment of **8** with triflic acid (TfOH) in CH_2Cl_2 at 0 °C effects a Nametkin rearrangement to give 1-(triflyloxy)camphene (**3**).[5,6]

The solvolysis of the bridgehead triflates **3** and **8** in acetonitrile affords the *N*-acetylamines **4** and **9**. The highest yields were obtained in the presence of 2% (in volume) of water. It is noteworthy that this variation of the Ritter reaction[7] takes place through very unstable bridgehead carbocations.[8] As byproducts (ca. 10%), the corresponding 1-norbornanoles were formed by S–O cleavage.[9]

The amides **4** and **9** were hydrogenated in absolute ether over palladium on activated charcoal (5% Pd) to give a mixture of *endo*/*exo*-*N*-acetyl(2,2,3-trimethyl-1-norbornyl)amine and *endo*/*exo*-*N*-acetyl(2,3,3-trimethyl-1-norbornyl)amine (**5** and **10**), respectively, in which the *endo* isomer predominates (*endo*/*exo* = 74/26 for **5** and 76/24 for **10**) as analyzed by ^{1}H-NMR and capillary gas chromatography (GC).

Under the reaction conditions indicated in the literature[10] (60% KOH in 80% aqueous ethanol, 24 h, reflux) for the hydrolysis of *N*-acetyl-1-norbornylamine, there is no reaction in the cases of **4**, **5**, **9**, and **10**; however, the hydrolysis does take place in di(ethylene glycol) (DEG) containing 30% KOH at 180 °C (24 h), yielding the amines **2** and **13**.

The reduction of the amides **4**, **5**, **9**, and **10** was achieved by reaction with $LiAlH_4$ to give the *N*-ethylamines **1**, **6**, **11**, and **12**, respectively.

In Vitro Antiviral Activity

The hydrochlorides of the amines **1**, **2**, **6**, and **11**–**13** were tested for their activity against influenza A, herpes simplex virus type 2 (HSV-2), and African swine fever virus in Vero cells. The results are shown in Tables 1–3.

Most compounds have a rather low in vitro therapeutic index (SI) against HSV-2 and African swine fever virus. However, compounds **1** and **11** were found to be very interesting against influenza A virus, showing one of the highest SI values known (SI = 1000) for anti-influenza agents.[1,2] The anti-influenza activity seems to be favored by the presence of a *gem*-dimethyl group at the C-2 (or C-7)[2] position of the 1-norbornylamine framework. The *N*-ethyl derivatives are more active than the corresponding amino compounds (see **2** and **6**).

Further work on the antiviral activity of homochiral 1-norbornylamines is in progress.

Conclusions

We have succeeded in the synthesis of substituted 1-norbornylamines starting from the readily available (±)-camphor (**7**). Some of these compounds show a very high and promising activity against influenza A virus.

Experimental Section

The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 250 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded using electron

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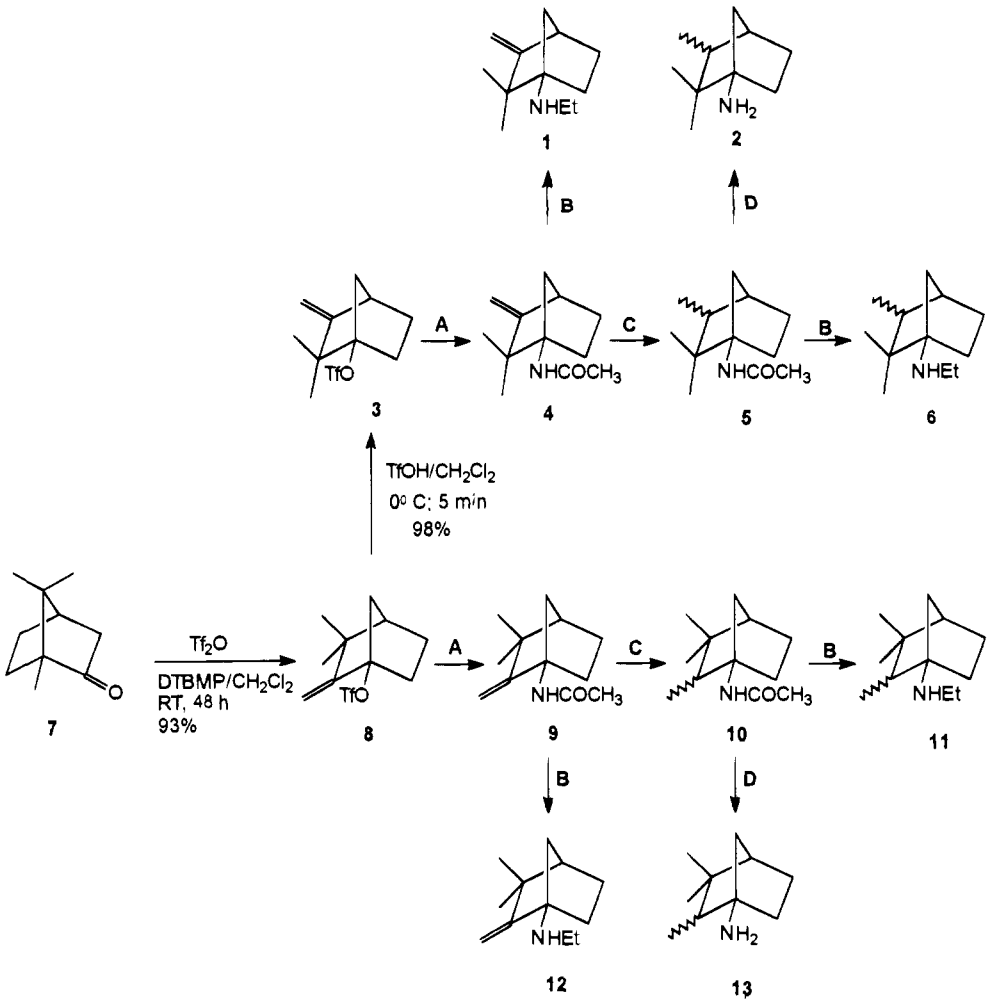
Scheme 1[a]



[a] (A) $CH_3CN/Et_3N/H_2O$, 180 °C, 48 h (72–76%); (B) $LiAlH_4/Et_2O$, 20 °C, 48 h (ca. 80%); (C) $H_2/Pd(C)/Et_2O$, room temperature, 3 atm, 48 h (98%); (D) 30% KOH/DEG, 180 °C, 24 h (ca. 95%).

Table 1. Biological Data against Influenza A[a]

compound	MIC_{50}[b] (μg/mL)	MTC_{50}[c] (μg/mL)	SI[d]
1	0.1	100	1000
2	5	50	10
6	<10	100	>10
11	0.1	100	1000
12	5	200	40
13	1	100	10
amantadine·HCl	0.5	300	600

[a] Test made with MDCK cells from dog kidney. [b] Minimum inhibitory concentration required to effect a 50% reduction in virus yield. [c] Minimum toxic concentration affecting 50% of the cells. [d] Selectivity index: Ratio of MTC_{50} to MIC_{50}.

Table 2. Biological Data against African Swine Fever Virus[a]

compound	MIC_{50}[b] (μg/mL)	MTC_{50}[c] (μg/mL)	SI[d]
1	30	400	13
2	25	200	8
6	25	300	12
11	30	300	10
12	100	300	3
13	30	300	10

[a] Test made with monkey kidney cells. [b] See footnotes to Table 1. [c] See footnotes to Table 1. [d] See footnotes to Table 1.

ionization (EI) on a Varian MAT-711 spectrometer. Infrared (IR) spectra were taken using a Perkin-Elmer 257 spectrometer.

(±)-Camphor was purchased from commercial suppliers and used without further purification. Reaction solvents were distilled from an appropriate drying agent before use.

Table 3. Biological Data against HSV-2[a]

compound	MIC_{50}[b] (μg/mL)	MTC_{50}[c] (μg/mL)	SI[d]
1	100	400	4
2	25	200	8
6[e]	25	300	12
11[e]	75	300	4
12	300	300	1
13	50	300	6

[a] Test made with monkey kidney cells. [b] See footnotes to Table 1. [c] See footnotes to Table 1. [d] See footnotes to Table 1. [e] Total inhibition of virus growth at 200 μg/mL.

1- and 4-(Trifluoxy)camphene (3 and 8). These compounds were prepared according to published methods[4-6] from (±)-camphor.

***N*-Acetyl-1- and *N*-Acetyl-4-camphenylamine (4 and 9). General Procedure.** A solution of the bridgehead triflate **3** or **8** (3.50 mmol) and triethylamine (1.80 g, 18 mmol) in CH_3CN/H_2O (98:2, v/v) (10 mL) was heated in a sealed tube at 180 °C for 48 h. The tube was then cooled and opened, and the solution was basified with saturated $NaHCO_3$ (100 mL). The mixture was extracted with dichloromethane (3 × 50 mL), washed with saturated NaCl (5 × 20 mL) and water (20 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was analyzed by GC (OV-101, 25 m, 120 °C), showing the presence of ca. 75% of **4** or **9** and ca. 10% of the corresponding bridgehead alcohol.[4] Pure **4** and **9** were isolated by elution chromatography (silica gel, first CH_2Cl_2 and then Et_2O).

***N*-Acetyl-1-camphenylamine (4):** yield 0.48 g (72%); mp 124–126 °C; IR 3300 (NH), 1650 (C=O), 1540 (NH), 1360 (CH_3-CO), 870 (=CH_2) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity)

193 (M⁺, 63), 178 (M⁺ − 15, 64), 150 (M⁺ − 43, 81), 136 (100), 108 (78), 43 (81); ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.55 (bs, 1H, NH), 4.76 (s, 1H, =CH), 4.56 (s, 1H, =CH), 2.59 (bs, 1H), 1.98 (s, 3H, CH_3CO), 1.95−1.80 (m, 4H), 1.35−1.25 (m, 2H), 1.18 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 169.84 (CO), 163.78 (C-3), 100.48 (=CH_2), 67.18 (C-1), 45.14 (C-2), 43.57 (C-4), 40.31 (C-7), 29.52 (C-5), 27.80 (C-6), 26.25 (CH_3), 24.22 (CH_3CO), 23.86 (CH_3). Anal. ($C_{12}H_{19}NO$) C, H, N.

***N*-Acetyl-4-camphenylamine (9):** yield 0.51 g (76%); mp 60−62 °C; IR 3300 (NH), 1665 (C=O), 1500 (NH), 1340 (CH_3-CO), 870 (=CH_2) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 193 (M^+, 49), 178 (M^+ − 15, 25), 150 (M^+ − 43, 97), 136 (60), 108 (100), 43 (60); ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.20 (bs, 1H, NH), 4.75 (s, 1H, =CH), 4.55 (s, 1H, =CH), 2.13−1.34 (m, 7H), 1.91 (s, 3H, CH_3CO), 1.00 (s, 6H, $2CH_3$); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 169.60 (CO), 163.63 (C-3), 97.79 (=CH_2), 66.70 (C-4), 45.19 (C-1), 42.22 (C-2), 40.60 (C-7), 32.71 (C-5), 29.43 (CH_3), 26.13 (CH_3), 24.25 (CH_3CO), 24.12 (C-6). Anal. ($C_{12}H_{19}NO$) C, H, N.

***endo*- and *exo*-*N*-Acetyl(2,2,3-trimethyl-1-norbornyl)amine (5) and *endo*- and *exo*-*N*-Acetyl(2,3,3-trimethyl-1-norbornyl)amine (10). General Procedure.** The substrate **4** or **9** (1.03 mmol) was hydrogenated with 0.04 g of palladium on activated charcoal (5% Pd) in absolute ether (50 mL) at 25 °C and 3 atm of pressure of hydrogen for 48 h in a glass bottle being shaken at about 120 strokes per minute. After filtration and elimination of the ether, the reaction mixture was analyzed by GC (OV-101, 25 m, 120 °C). The configuration of the products was elucidated by ^{1}H- and ^{13}C-NMR[11] from the mixture of *endo* and *exo* compounds.

***endo*/*exo*-*N*-Acetyl(2,2,3-trimethyl-1-norbornyl)amine (5):** yield 0.20 g (98%) as a mixture of *endo*/*exo* isomers (74/26); IR 3320 (NH), 1690 (C=O), 1500 (NH), 1360 (CH_3CO) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 195 (M^+, 3), 180 (M^+ − 15, 2), 166 (M^+ − 29, 3), 152 (M^+ − 43, 2), 124 (100), 82 (72); HRMS (EI, 100 eV) M^+ found 195.1623, calcd 195.1623. ***endo*-5:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.57 (bs, 1H, NH), 2.20−1.20 (m, 8H), 1.96 (s, 3H, CH_3CO), 0.91 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.84 (d, 3H, J = 6 Hz, *endo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 169.73 (CO), 67.97 (C-1), 45.32 (C-4), 40.74 (C-7), 40.16 (C-2, C-3), 29.10 (C-6), 28.89 (CH_3), 24.48 (CH_3CO), 21.35 (C-5), 19.31 (CH_3), 11.97 (*endo*-CH_3). ***exo*-5:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.57 (bs, 1H, NH), 2.20−1.20 (m, 8H), 1.96 (s, 3H, CH_3CO), 1.05 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.84 (d, 3H, J = 6 Hz, *exo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 169.88 (CO), 68.00 (C-1), 48.92 (C-4), 42.87 (C-3), 42.37 (C-2), 38.64 (C-7), 30.20 (C-6), 28.80 (C-5), 26.18 (CH_3), 24.44 (CH_3CO), 21.32 (CH_3), 16.66 (*exo*-CH_3).

***endo*/*exo*-*N*-Acetyl(2,3,3-trimethyl-1-norbornyl)amine (10):** yield 0.20 g (98%) as a mixture of *endo*/*exo* isomers (76/24); IR 3300 (NH), 1650 (C=O), 1550 (NH), 1350 (CH_3CO) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 195 (M^+, 2), 180 (M^+ − 15, 5), 166 (M^+ − 29, 3), 152 (M^+ − 43, 2), 138 (10), 124 (100), 82 (91), 43 (14); HRMS (EI, 100 eV) M^+ found 195.1623, calcd (195.1623). ***endo*-10:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.70 (bs, 1H, NH), 2.25−1.40 (m, 8H), 1.94 (s, 3H, CH_3CO), 0.99 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.78 (d, 3H, J = 7 Hz, *endo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 169.68 (CO), 65.67 (C-1), 46.24 (C-2), 45.93 (C-4), 39.92 (C-7), 37.08 (C-3), 31.87 (CH_3), 24.72 (C-6), 24.32 (C-5), 24.12 (CH_3CO), 21.62 (CH_3), 8.03 (*endo*-CH_3). ***exo*-10:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.10 (bs, 1H, NH), 2.25−1.40 (m, 8H), 1.95 (s, 3H, CH_3CO), 0.99 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.73 (d, 3H, J = 7 Hz, *exo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 169.88 (CO), 65.84 (C-1), 48.12 (C-4), 46.03 (C-2), 40.47 (C-3), 39.65 (C-7), 34.51 (C-6), 27.79 (CH_3), 25.16 (C-5), 24.93 (CH_3), 23.42 (CH_3CO), 12.37 (*exo*-CH_3).

***N*-Ethyl-1- and *N*-Ethyl-4-camphenylamine (1 and 12). *endo*/*exo*-*N*-Ethyl(2,2,3-trimethyl-1-norbornyl)amine (6) and *exo*/*endo*-*N*-Ethyl(2,3,3-trimethyl-1-norbornyl)amine (11). General Procedure.** The corresponding *N*-acetyl derivative (1.03 mmol) in absolute ether (5 mL) was added through a dropping funnel to lithium aluminum hydride (0.12 g, 3.10 mmol) in absolute ether (20 mL) at 25 °C. After stirring at room temperature for 48 h, the mixture was poured into 100 mL of ice−water and extracted with dichloromethane (3 × 30 mL). The amines were extracted with 10% aqueous HCl (3 × 30 mL). The aqueous solution was basified with 30% aqueous NaOH, and the mixture was extracted with dichloromethane (3 × 30 mL), washed with saturated NaCl (2 × 20 mL) and water (20 mL), and dried (KOH). After evaporation of the solvent, the *N*-ethylamines were purified by crystallization of their hydrochlorides from MeOH/Et_2O.

***N*-Ethyl-1-camphenylamine (1):** yield 0.14 g (76%); IR 3350 (NH), 1660 (C=C), 1150 (CN), 880 (=CH_2) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 179 (M^+, 62), 164 (M^+ − 15, 93), 150 (M^+ − 29, 100), 136 (M^+ − 43, 48), 122 (M^+ − 57, 25), 110 (65); HRMS (EI, 100 eV) M^+ found 179.1672, calcd 179.1674; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.50 (s, 1H), 4.35 (s, 1H), 2.62 (dq, J = 8 Hz, J = 3 Hz, 2H, CH_2N), 2.40 (m, 1H), 2.20−1.60 (m, 7H), 1.08 (t, J = 8 Hz, 3H, CH_2CH_3), 1.10 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 166.46 (C-3), 99.66 (=CH_2), 70.44 (C-1), 44.54 (C-4), 40.39 (C-7), 38.94 (CH_3CH_2), 37.68 (C-2), 30.06 (C-6), 26.73 (C-5), 26.65 (CH_3), 25.92 (CH_3), 16.48 (CH_2CH_3).

***N*-Ethyl-4-camphenylamine (12):** yield 0.14 g (76%); IR 3350 (NH), 1660 (C=C), 1140 (CN), 890 (=CH_2) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 179 (M^+, 50), 164 (M^+ − 15, 80), 150 (M^+ − 29, 100), 136 (M^+ − 43, 33), 122 (M^+ − 57, 23), 110 (60); HRMS (EI, 100 eV) M^+ found 179.1672, calcd 179.1674; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.72 (s, 1H, =CH), 4.65 (s, 1H, =CH), 2.65 (m, 2H, CH_2N), 1.83−1.20 (m, 8H), 1.14 (t, 3H, J = 6 Hz, CH_2CH_3), 1.10 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 164.82 (C-3), 97.66 (=CH_2), 70.76 (C-4), 44.98 (C-1), 42.11 (C-2), 39.88 (C-7), 38.45 (C-5), 33.54 (CH_2CH_3), 29.04 (CH), 26.04 (CH_3), 24.47 (C-6), 15.85 (CH_2CH_3).

***endo*/*exo*-*N*-Ethyl(2,2,3-trimethyl-1-norbornyl)amine (6):** yield 0.14 g (76%) as a mixture of *endo*/*exo* isomers (74/26); IR 3300 (NH), 1460, 1140 (CN) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 181 (M^+, 0.4), 166 (M^+ − 15, 2), 152 (M^+ − 29, 3), 138 (M^+ − 43, 11), 124 (M^+ − 57, 19), 110 (20), 82 (100); HRMS (EI, 100 eV) M^+ − 15 found 166.1593, calcd 166.1596. ***endo*-6:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.75 (m, 1H, CH_2N), 2.59 (m, 1H, CH_2N), 1.80 (bs, 1H), 1.70−1.38 (m, 8H), 1.09 (t, 3H, J = 6 Hz, CH_2CH_3), 0.90 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.82 (d, 3H, J = 7 Hz, *endo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 70.69 (C-1), 46.43 (C-4), 40.44 (C-7), 40.11 (C-3), 38.92 (CH_2CH_3), 38.91 (C-2), 28.29 (CH), 27.49 (C-6), 21.56 (C-5), 19.60 (CH_3), 16.51 (CH_2CH_3), 12.01 (*endo*-CH_3). ***exo*-6:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.75 (m, 1H, CH_2N), 2.59 (m, 1H, CH_2N), 1.80 (bs, 1H), 1.70−1.38 (m, 8H), 1.09 (t, 3H, J = 6 Hz, CH_2CH_3), 1.01 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.82 (d, 3H, J = 7 Hz, *exo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 70.40 (C-1), 50.15 (C-4), 42.27 (C-3), 41.69 (C-2), 39.27 (C-7), 38.48 (CH_2CH_3), 30.54 (C-6), 27.17 (C-5), 26.81 (CH_3), 20.58 (CH_3), 16.59 (*exo*-CH_3), 16.51 (CH_2CH_3).

***endo*/*exo*-*N*-Ethyl(2,3,3-trimethyl-1-norbornyl)amine (11):** yield 0.15 g (81%) as a mixture of *endo*/*exo* isomers (76/24); IR 3300 (NH), 1460, 1140 (CN) cm^{-1}; MS (EI, 100 eV) *m*/*z* (relative intensity) 181 (M^+, 1), 166 (M^+ − 15, 7), 152 (M^+ − 29, 4), 138 (M^+ − 43, 19), 124 (M^+ − 57, 7), 110 (51), 82 (100); HRMS (EI, 100 eV) M^+ − 15 found 166.1593, calcd 166.1596. ***endo*-11:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.62 (q, 2H, J = 6 Hz, CH_2N), 1.80−1.15 (m, 9H), 1.12 (t, 3H, J = 6 Hz, CH_2CH_3), 0.94 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.75 (d, 3H, J = 7 Hz, *endo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 69.17 (C-1), 46.05 (C-2), 45.99 (C-4), 39.63 (C-7), 37.99 (CH_2CH_3), 37.36 (C-3), 31.97 (CH_3), 25.32 (C-6), 24.29 (C-5), 21.68 (CH_3), 15.66 (CH_2CH_3), 7.68 (*endo*-CH_3). ***exo*-11:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.56 (q, 2H, J = 6 Hz, CH_2N), 1.80−1.15 (m, 9H), 1.09 (t, 3H, J = 6 Hz, CH_2CH_3), 0.97 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.78 (d, 3H, J = 7 Hz, *exo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 68.61 (C-1), 47.79 (C-2), 46.28 (C-4), 40.30 (C-3), 39.68 (C-7), 38.31 (CH_2CH_3), 33.23 (C-6), 27.99 (CH_3), 25.02 (CH_3), 24.83 (C-5), 15.46 (CH_2CH_3), 11.68 (*exo*-CH_3).

***endo*/*exo*-(2,2,3-Trimethyl-1-norbornyl)amine and *endo*/*exo*-(2,3,3-Trimethyl-1-norbornyl)amine (2 and 13). General Procedure.** A mixture of the corresponding *N*-acetylamine (**5** or **10**) (0.20 g, 1.03 mmol) and KOH (0.40 g, 8 mmol) in di(ethylene glycol) (2 mL) was heated for 24 h in a sealed

tube at 180 °C. After cooling, the tube was opened and the mixture poured into water (50 mL). The mixture was extracted with dichloromethane (3 × 30 mL) and washed with 10% aqueous HCl (3 × 30 mL). The aqueous solution was washed with dichloromethane (3 × 30 mL) and basified with 30% aqueous NaOH. The mixture was extracted with dichloromethane (3 × 30 mL), washed with saturated NaCl (2 × 10 mL) and water (20 mL), and dried (KOH). After evaporation of the solvent, the amines were purified by crystallization of their hydrochlorides from MeOH/Et_2O.

***endo/exo*-(2,2,3-Trimethyl-1-norbornyl)amine (2):** yield 0.15 g (95%) as a mixture of *endo/exo* isomers (74/26); IR 3250 (NH), 1475, 1600 (NH_2), 1060 (CN) cm^{-1}; MS (EI, 100 eV) *m/z* (relative intensity) 153 (M^+, 3), 138 ($M^+ - 15$, 18), 124 ($M^+ - 29$, 32), 110 ($M^+ - 43$, 18), 96 ($M^+ - 57$, 22), 81 (100), 40 (22); HRMS (EI, 100 eV) $M^+ - 15$ found 138.1280, calcd 138.1283. ***endo*-2:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.82–1.18 (m, 10H), 0.87 (s, 3H, CH_3), 0.84 (d, 3H, J = 7 Hz, *endo*-CH_3), 0.74 (s, 3H, CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 66.50 (C-1), 45.51 (C-4), 44.12 (C-7), 40.59 (C-3), 38.21 (C-2), 32.45 (C-6), 28.46 (CH_3), 21.97 (C-5), 18.00 (CH_3), 12.31 (*endo*-CH_3). ***exo*-2:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.82–1.18 (m, 10H), 0.92 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.83 (d, 3H, J = 7 Hz, *exo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 66.38 (C-1), 48.95 (C-4), 42.77 (C-3), 41.65 (C-7), 40.59 (C-2), 32.16 (C-6), 29.80 (C-5), 24.97 (CH_3), 20.83 (CH_3), 16.76 (*exo*-CH_3).

***endo/exo*-(2,3,3-Trimethyl-1-norbornyl)amine (13):** yield 0.15 g (95%) as a mixture of *endo/exo* isomers (76/24); IR 3350 (NH_2), 1470, 1620 (NH_2), 1060 (CN) cm^{-1}; MS (EI, 100 eV) *m/z* (relative intensity) 153 (M^+, 1), 138 ($M^+ - 15$, 13), 124 ($M^+ - 29$, 6), 110 ($M^+ - 43$, 3), 96 ($M^+ - 57$, 4), 81 (100), 40 (2); HRMS (EI, 100 eV) $M^+ - 15$ found 138.1280, calcd 138.1283. ***endo*-13:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.70–1.10 (m, 10H), 0.96 (s, 3H, CH_3), 0.80 (d, 3H, J = 7 Hz, *endo*-CH_3), 0.79 (s, 3H, CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 64.94 (C-1), 50.41 (C-2), 46.59 (C-4), 45.06 (C-7), 37.93 (C-3), 31.97 (CH_3), 27.01 (C-6), 25.82 (C-5), 21.68 (CH_3), 7.51 (*endo*-CH_3). ***exo*-13:** ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.70–1.10 (m, 10H), 0.97 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.83 (d, 3H, J = 7 Hz, *exo*-CH_3); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 64.45 (C-1), 50.62 (C-2), 47.09 (C-4), 42.34 (C-7), 40.46 (C-3), 37.71 (C-6), 27.88 (CH_3), 25.23 (C-5), 24.61 (CH_3), 11.84 (*exo*-CH_3).

Amine Hydrochlorides. General Procedure. A solution of the amine (1.00 mmol) in ether (50 mL) was saturated with HCl gas at 0–5 °C with stirring. The resulting precipitate was collected by filtration and recrystallized from MeOH/Et_2O.

The chromatographic (GLC) purity of the bridgehead amines, prepared by neutralization of the corresponding hydrochlorides, was ≥98%. In the case of dirty injection blocks, decomposition of the amines was observed.

Determination of the Antiviral Activity. Vero cells were infected with the virus at a multiplicity of infection of 0.1 PFU (plaque-forming units) per cell. After 1.30 h of adsorption, the cells were incubated to 37 °C in DMEM containing 2% newborn calf serum. The cells were harvested 72 h after infection (100% CPE (cytophatic effects) of virus control), and virus titor was measured by plaque assay. As reference standard was employed amantadine hydrochloride.

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