Articles

Total Synthesis of (±)-Actinidine and of (±)-Isooxyskytanthine

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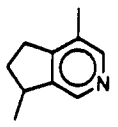
Short syntheses of (±)-actinidine and of-(±)-isooxyskytanthine have been realized by photoreductive cyclization of N,N-unsaturated dialkyl-2-oxocyclopentanecarboxamides.

Actinidine (1) and isooxyskytanthine (2) are two rare monoterpene alkaloids.[1] Actinidine is naturally occurring in *Actinidia polygama*[2] and in *Valeriana officinalis*.[3] This



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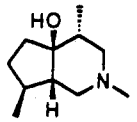

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compound has received special attention since it has been reported to be a constituent of the defensive secretion in certain ants[4] and has been described as a potent cat attractant.[2,5] Isooxyskytanthine, which is also called "alkaloid C", has been isolated from *Tecoma stans*,[6,7] and its structure has been established by single-crystal X-ray diffraction on the corresponding methiodide.[8]

These two products are composed of an 3-azabicyclo-[4.3.0]nonane skeleton which is substituted by methyl groups at C(5) and C(9). To produce this skeleton a metallo–ene reaction,[9] an acidic or basic hydrolysis of an unsaturated cyanodiester,[10] and an aldolization[11] process have previously been used. Other approaches involving thermal rearrangements[12] or the transformation of loganin into an azabicyclononane system have been reported.[4,13]

Recently, we have found that azabicyclo[4.3.0]nonane systems can be reached by a photoreductive cyclization of the corresponding 2-oxocycloalkanecarboxamides.[14] A retrosynthetic analysis of 1 and 2 indicated that both compounds should be attainable through a photoreductive cyclization of N,N-unsaturated dialkyl-2-oxocyclopentanecarboxamides of type A (Scheme I).

Results and Discussion

The preparation of ketoamides of type A was achieved in two steps from 4-methylcyclohexane-1,3-dione (3).[15] Treatment of 4-methylcyclohexane-1,3-dione (3) by tosyl azide in the presence of triethylamine led to the corresponding diazo compound 4.[16] A Wolff rearrangement[17] applied to the diazo diketone 4 in the presence of diallylamine gave a 1.6/1.0 mixture of two regioisomeric amides 5[18] and 6.[19] The major product 5 was isolated in 56% yield.[20] The irradiation of 4 in the presence of *N*-methylpropargylamine produced a 1.5/1.0 mixture of regioisomeric products 7[18] and 8[19] from which 7 was isolated in a 45% yield[20] (Scheme II).

The ^{1}H NMR spectra indicated that compounds 5 and 7 were consistent with the trans relative configuration of the cyclopentanone substituents on C(1) and C(5). The

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(18) The ^{1}H NMR and ^{13}C NMR spectra indicated that compounds 5 and 7 exist as two rotamers.
(19) The ^{1}H NMR and ^{13}C NMR spectra of 6 and 8 indicated that these two compounds are a mixture of two stereoisomers in a ratio of 2.5/1.0 for 6 and a ratio of 2.1/1.0 for 8. Each of the stereoisomers 6 and 8 is composed of two rotamers. Since 6 and 8 could not be separated, the interpretation of the ^{1}H NMR and ^{13}C NMR spectra was difficult.
(20) The regioselectivity of the Wolff rearrangement involves, as expected, the preferred migration of the secondary alkyl group rather than that of the primary alkyl group.

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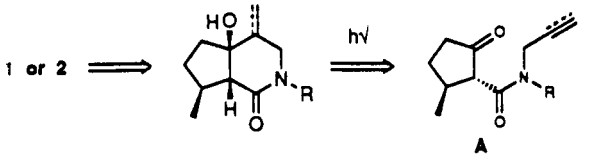
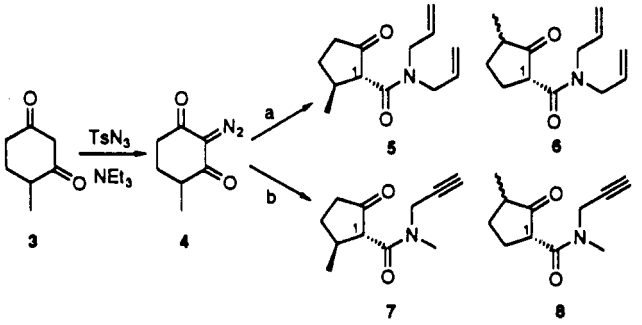
Scheme I

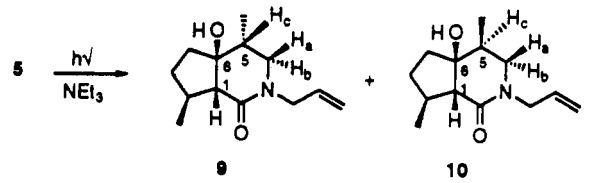


Scheme II[a]



[a] Key: (a) *hν*, diallylamine; (b) *hν*, *N*-methylpropargylamine.

Scheme III



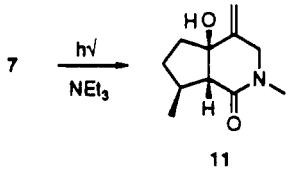
proton H-C(1) of **5** resonated as a doublet at δ_H = 2.97 ppm (J = 10.9 Hz), whereas that of **7** resonated as a doublet at δ_H = 3.09 ppm (J = 13.5 Hz). Steric repulsion between the methyl and the carboxamide groups is probably responsible for their trans relative configuration.

Irradiation (254 nm, quartz vessel) of a 5 × 10^{-2} molar acetonitrile (CH_3CN) solution of **5** in the presence of triethylamine (10 equiv) for 5 h led to a 1.7/1.0 mixture of **9** and **10** which could be separated by preparative TLC (Scheme III).

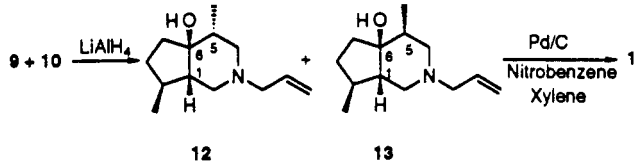
The trans relative configuration at the bridgehead centers C(1) and C(6) in **9** and **10** would be prohibitive, based on thermodynamic considerations.[21] The trans relative configuration of the methyl group at C(5) and the hydroxy group at C(6) of **9** may also correspond to the less sterically strained structure; also, the methyl group in this case occupies an endo position, whereas it is exo in **10**. Furthermore, the relative configuration of C(5) in compounds **9** and **10** could be deduced from the coupling constants of the protons H_a, H_b, and H_c.[22] The ^1H NMR spectra of **9** and **10**, with the help of double-irradiation experiments, confirmed the proposed structures.[23] In particular, the vicinal coupling constants between the H_a–H_c, H_b, and H_c protons of the six-membered ring were consistent only with structures **9** and **10**.

Irradiation of **7** under the same conditions as for **5** led to a single product **11** in 46% yield (Scheme IV). Its ^1H NMR spectrum showed for its methyl group at C(9) a doublet at δ_H = 1.29 ppm (J = 6.5 Hz). The two protons at C(4) resonated as a singlet at δ_H = 3.90 ppm whereas the two methylidene protons appeared as two doublets at δ_H = 5.07 ppm (J = 0.4 Hz) and 5.28 ppm (J = 0.4 Hz).

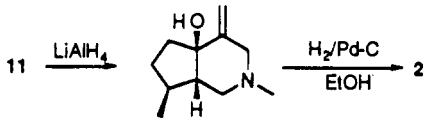
Scheme IV



Scheme V



Scheme VI



The transformation of the mixture of **9** and **10** into (±)-actinidine was achieved in two steps. The treatment of the mixture of **9** and **10** with lithium aluminium hydride ($LiAlH_4$), in (THF) at 20 °C, produced a 1.7/1.0 mixture of amine **12** and **13** (70%). Then, heating **12** and **13** in a 1/1 mixture of nitrobenzene and *p*-xylene in the presence of a catalytical amount of 10% palladium on charcoal[24] and 3-Å molecular sieves produced (±)-actinidine (**1**) (Scheme V).

The spectral data (IR, ^1H NMR, ^{13}C NMR, mass spectrum) of **1** obtained were identical with those reported for actinidine.[25]

Reduction of **11** with $LiAlH_4$ (20 °C) afforded **14** (43%). The methylidene group of **14** was hydrogenated stereospecifically with hydrogen in the presence of 10% Pd/C giving (±)-isooxyskytanthine (87%)[8,26] (Scheme VI).

This work demonstrates the efficiency of photoinduced reductive cyclization of N,N-unsaturated dialky-2-oxocyclopentanecarboxamides to generate the bicyclic alkaloid of monoterpenic alkaloid series. (±)-Actinidine and (±)-isooxyskytanthine were derived simply from the inexpensive cyclohexane-1,3-dione in 4% and 5% overall yield respectively.

Experimental Section

All experiments were run under an argon atmosphere. ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ employing Me_4Si as an internal standard. IR spectra were obtained as solutions in $CHCl_3$. Mass spectra were run at 70 eV. Preparative TLC was conducted on Merck Kieselgel 60, $PF_{254+266}$, and flash chromatography was accomplished with 230–400-mesh silica gel (Merck and Co).

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(22) The coupling constants between protons H_a–H_c (J = 5.0 Hz), H_a–H_b (J = 13.0 Hz), and H_b–H_c (J = 11.0 Hz) of **9** and between H_a–H_c (J = 8.0 Hz), H_a–H_b (J = 12.5 Hz), and H_b–H_c (J = 4.0 Hz) of **10** allowed one to attribute the trans relationship for the proton H_a and methyl groups in **9** and a cis relationship in the case of **10**.

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(26) When the reduction of the methylidene group of **11** preceeded the reduction of the lactam moiety a lower yield of (±)-isooxyskytanthine was obtained.

Preparative irradiations were conducted in a merry-go-round type system equipped with 12 low-pressure mercury Philips TUV 15 lamps (254 nm), using 10-mm o.d. quartz tubes. The solutions were degassed by bubbling argon through them for 30 min.

2-Diazo-4-methylcyclohexane-1,3-dione (4). Triethylamine (4.33 g, 42.8 mmol) was added to a stirred suspension of 4-methylcyclohexane-1,3-dione (**3**)[15] (42.8 mmol) in CH_2Cl_2 (30 mL). The temperature was decreased to 0 °C, and tosyl azide (8.43 g, 42.8 mmol) in CH_2Cl_2 (9 mL) was rapidly added. After 3 h at 0 °C, the solution was diluted with CH_2Cl_2 and washed successively with an aqueous KOH solution (2×10^{-2} M, 100 mL), with a second aqueous KOH solution (5×10^{-3} M, 100 mL), and then with water (100 mL). The organic layer was dried over $MgSO_4$ and evaporated. **4** was purified by flash chromatography with a mixture of petroleum ether (PE)/ethyl acetate (AcOEt) (70/30): yield 80%; IR 2150, 1640 (broad), 1460 cm^{-1}; ^1H NMR (80 MHz) δ 1.20 (d, 3 H, J = 7.0 Hz), 1.50–2.90 (m, 5 H); MS $C_7H_8N_2O_2$ m/z 152 (M^+, 100), 124 (46), 109 (55).

N,N-Dialkyl-5-methyl-2-oxocyclopentanecarboxamides. N,N-Dialkylamine (29.6 mmol, 3 equiv) was added to a degassed solution of the 2-diazo-4-methylcyclohexane-1,3-dione **4** (1.5 g, 9.87 mmol) in CH_3CN (200 mL, 5×10^{-2} M). The solution was irradiated for 2 h at 254 nm. After evaporation, the crude material was purified by flash chromatography with a mixture of petroleum ether (PE) and ethyl acetate (AcOEt).

***N,N*-Diallyl-5-methyl-2-oxocyclopentanecarboxamide (5).** **5** was purified by flash chromatography (PE/AcOEt = 80/20): yield 56%; mp 39–41 °C; IR 1740, 1650, 1635 cm^{-1}; ^1H NMR (300 MHz) δ 1.11 (d, 3 H, J = 6.2 Hz), 1.38–1.54 (m, 1 H), 2.15–2.47 (m, 3 H), 2.80–2.95 (m, 1 H), 2.97 (d, 1 H, J = 10.9 Hz), 3.56–3.85 (m, 2 H), 4.20–4.47 (m, 2 H), 5.07–5.27 (m, 4 H), 5.68–5.88 (m, 2 H); ^{13}C NMR (75 MHz) δ 19.5 (q), 60.9 (d), 132.7 (d), 133.4 (d), 168.4 (s), 214.2 (s); MS $C_{13}H_{19}NO_2$ m/z 221 (M^+, 3), 96 (100). Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.42; H, 8.72; N, 6.35.

***N,N*-Diallyl-3-methyl-2-oxocyclopentanecarboxamides (6).** **6** was purified by flash chromatography (PE/AcOEt = 80/20). Two stereoisomers were detected by NMR in a ratio of 2.5/1.0: yield 35%; IR 1735, 1650, 1630 cm^{-1}; ^1H NMR (300 MHz) major isomer δ 1.08 (d, 3 H, J = 6.0 Hz), 3.36 (dd, 1 H, J = 10.5, 8.0 Hz); minor isomer δ 1.10 (d, 3 H, J = 6.0 Hz), 3.48 (dd, 1 H, J = 9.0, 5.0 Hz); for the two isomers δ 1.28–1.45 (m, 1 H), 1.75–2.48 (m, 4 H), 3.60–3.85 (m, 2 H), 4.20–4.37 (m, 2 H), 5.03–5.20 (m, 4 H), 5.64–5.87 (m, 2 H); ^{13}C NMR (75 MHz) major isomer δ 13.8 (q), 44.6 (d), 51.9 (d), 132.86 (d), 133.4 (d), 169.3 (s), 215.8 (s); minor isomer δ 14.7 (q), 44.0 (d), 48.2 (t), 49.5 (t), 50.9 (d), 132.8 (d) 133.3 (d), 169.3 (s), 215.8 (s); MS $C_{13}H_{19}NO_2$ m/z 221 (M^+, 5), 96 (100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.72; H, 8.73; N, 6.46.

***N*-Methyl-*N*-propargyl-5-methyl-2-oxocyclopentanecarboxamide (7).** **7** was purified by flash chromatography (PE/AcOEt = 80/20). Two rotamers were detected by NMR in a ratio of 1.3/1.0: yield 45%; IR 3320, 1730, 1630, 1480 cm^{-1}; ^1H NMR (300 MHz) major rotamer δ 3.14 (s, 3 H); minor rotamer δ 3.02 (s, 3 H); for the two rotamers δ 1.12 (d, 3 H, J = 6.5 Hz), 1.39–1.55 (m, 1 H), 1.94–2.45 (m, 4 H), 2.70–2.91 (m, 1 H), 3.09 (d, 1 H, J = 13.5 Hz), 3.79–4.09 (m, 1 H), 4.39–4.53 (m, 1 H); ^{13}C NMR (75 MHz) major rotamer δ 19.3 (q), 34.6 (q), 35.69 (d), 60.4 (d), 71.8 (d), 78.4 (s), 167.8 (s), 213.7 (s); minor rotamer δ 19.2 (q), 33.8 (q), 35.6 (d), 60.5 (d), 72.7 (d), 78.4 (s), 167.5 (s), 213.2 (s); MS $C_{11}H_{15}NO_2$ m/z 194 (M^+, 2), 193 (M^+, 9), 68 (100). Anal. Calcd for $C_{11}H_{15}NO_2$: C 68.37, H 7.82, N 7.25. Found: C 68.14, H 7.91, N 7.39.

***N*-Methyl-*N*-propargyl-3-methyl-2-oxocyclopentanecarboxamide (8).** **8** was purified by flash chromatography (PE/AcOEt = 80/20). Two stereoisomers were detected by NMR in a ratio of 2.1/1.0. Each stereoisomer was constituted by two rotamers: yield 25%; IR 3320, 1745, 1650, 1405 cm^{-1}; ^1H NMR (300 MHz) major isomer δ 1.16 (d, 3 H, J = 5.5 Hz), 3.48 (dd, 1 H, J = 7.6, 15.7 Hz); major rotamer δ 3.22 (s, 3 H); minor rotamer 3.19 (s, 3 H); minor isomer δ 1.12 (d, 3 H, J = 5.5 Hz), 3.58 (dd, 1 H, J = 3.0, 9.0 Hz); major rotamer δ 3.04 (s, 3 H); minor rotamer δ 3.01 (s, 3 H); for the two isomers δ 1.37–1.70 (m, 1 H), 2.00–2.59 (m, 5 H), 3.81–4.12 (m, 1 H), 4.37–4.76 (m, 1 H); MS $C_{11}H_{15}NO_2$ m/z 194 (M + 1, 12); 193 (M^+, 9), 138 (54), 69 (100), 68 (100). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.21; H, 7.89; N, 7.31.

Formation of 2-Oxo-3-azabicyclo[4.3.0]nonan-6-ols. Triethylamine (2.45 g, 24.2 mmol, 10 equiv) was added to a degassed solution of **5** or **7** (2.42 mmol) in CH_3CN (48 mL, 5×10^{-2} M). The solution was irradiated for 5 h at 254 nm, and the solvent was evaporated under reduced pressure. The products were purified by flash chromatography ($CHCl_3/CH_3OH$ = 93/7).

3-Allyl-5,9-dimethyl-2-oxo-3-azabicyclo[4.3.0]nonan-6-ol (9) and (10). Two stereoisomers were detected by NMR in a ratio of 1.7:1.0: yield 50%; IR 3590, 3390 (broad), 1650 cm^{-1}; ^1H NMR (300 MHz) major isomer (**9**) δ 0.94 (d, 3 H, J = 6.8 Hz), 1.24 (d, 3 H, J = 6.3 Hz); minor isomer (**10**) δ 0.95 (d, 3 H, J = 6.8 Hz), 1.24 (d, 3 H, J = 6.3 Hz); for the two isomers δ 1.35–1.60 (m, 2 H, 1 H exchangeable), 1.60–1.90 (m, 3 H), 1.90–2.20 (m, 2 H), 2.85–3.10 (m, 3 H), 3.75–4.10 (m, 2 H), 5.05–5.15 (m, 2 H), 5.60–5.75 (m, 1 H); ^{13}C NMR (75 MHz) major isomer (**9**) δ 12.1 (q), 21.0 (q), 39.2 (d), 42.6 (d), 62.4 (d), 82.8 (s), 132.8 (d), 173.1 (s); minor isomer (**10**) δ 11.4 (q), 21.7 (q), 36.1 (d), 38.9 (d), 60.2 (d), 81.2 (s), 132.9 (d), 171.8 (s); HRMS calcd for $C_{13}H_{21}NO_2$ 223.1571, found 223.1559.

3,9-Dimethyl-5-methylene-2-oxo-3-azabicyclo[4.3.0]nonan-6-ol (11): yield 46%; IR 3240, 1660, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 1.29 (d, 3 H, J = 6.5 Hz), 1.49–2.28 (m, 6 H), 2.94 (s, 3 H), 3.90 (s, 2 H), 5.07 (d, 1 H, J = 0.4 Hz), 5.28, (d, 1 H, J = 0.4 Hz), 5.25–5.31 (m, 1 H); ^{13}C NMR (75 MHz) δ 21.2 (q), 34.1 (q), 40.2 (d), 62.0 (d), 81.0 (s), 144.1 (s), 171.8 (s); MS $C_{11}H_{17}NO_2$ m/z 195 (M + 1, 8), 195 (M^+, 39), 140 (32), 100 (100). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17. Found: C, 67.63; H, 8.75; N, 7.20.

Reduction of 9 and 10. A solution of $LiAlH_4$ (1 M in THF, 6.28 mL, 6.28 mmol, 2 equiv) was added dropwise to a stirred solution of **9** and **10** (3.14 mmol) in THF (20 mL) at rt. After 3 h, water was added dropwise. The solution was filtered through Celite, and the solvent was evaporated.. The crude material was purified by flash chromatography ($CHCl_3/CH_3OH$ = 92/8).

3-Allyl-5,9-dimethyl-3-azabicyclo[4.3.0]nonan-6-ol (12) and (13). Two isomers were detected by NMR in a ratio of 1.7/1.0: yield 70%; IR 3590, 3380 (broad), 1635 cm^{-1}; ^1H NMR (300 MHz) major isomer (**12**) δ 0.91 (d, 3 H, J = 6.9 Hz), 1.16 (d, 3 H, J = 7.0 Hz); minor isomer (**13**) δ 0.88 (d, 3 H, J = 6.7 Hz), 0.98 (d, 3 H, J = 6.6 Hz); for the two isomers δ 1.25–2.20 (m, 10 H, 1 H exchangeable), 2.48–2.90 (m, 2 H), 2.91–3.02 (m, 2 H), 5.08–5.22 (m, 2 H), 5.77–5.94 (m, 1 H); ^{13}C NMR (75 MHz) major isomer (**12**) δ 13.3 (q), 24.0 (q), 33.0 (d), 39.8 (d), 54.6 (d), 83.6 (s), 135.2 (d); minor isomer (**13**) δ 12.0 (q), 20.3 (q), 35.3 (d), 37.1 (d), 54.7 (d), 78.9 (s), 135.6 (d); MS $C_{13}H_{23}NO$ m/z 209 (M^+, 53), 208 (45), 70 (100).

Reduction of 3,9-Dimethyl-5-methylene-2-oxo-3-azabicyclo-[4.3.0]nonan-6-ol (11). The same procedure was used as for **9** and **10**.

3,9-Dimethyl-5-methylene-3-azabicyclo[4.3.0]nonan-6-ol (14): yield 43%; IR (CCl_4) 3340 (broad) cm^{-1}; ^1H NMR (300 MHz) δ 1.11 (d, 3 H, J = 6.0 Hz), 1.27 (s, 1 H), 1.45–2.08 (m, 7 H), 2.25 (s, 3 H), 2.68–2.83 (m, 2 H), 3.15–3.22 (m, 1 H), 4.98 (d, 1 H, J = 0.4 Hz), 5.25 (d, 1 H, J = 0.4 Hz); ^{13}C NMR (75 MHz) δ 22.5 (q), 36.28 (q), 45.57 (d), 55.34 (d), 80.52 (s), 109.97 (t), 148.05 (s); MS $C_{11}H_{19}NO$ m/z 182 (M + 1, 11), 181 (M^+, 33), 83 (100). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.85; H, 10.51; N, 7.76.

(±)-Actinidine (1). Molecular sieves (3 Å, 0.5 g) and 10% Pd/C (0.08 g) were added to a solution of **12** and **13** (0.35 g, 1.67 mmol) in a mixture of *p*-xylene (4.5 mL) and nitrobenzene (4.5 mL). The reaction mixture was stirred vigorously and refluxed for 5 h. After cooling, the solution was filtered, and the filtrate was treated with a solution of HCl (2 M, 3 × 30 mL). The acidic phase was washed with ether (20 mL), neutralized with solid K_2CO_3, and extracted with ether (4 × 30 mL). The organic layer was dried over $MgSO_4$ and evaporated. Actinidine was purified by preparative TLC ($CHCl_3/CH_3OH$ = 94/6): yield 35%; IR 1590, 1450, 1410 cm^{-1}; ^1H NMR (300 MHz) δ 1.28 (d, 3 H, J = 7.0 Hz), 1.53–1.66 (m, 1 H), 2.21 (s, 3 H), 2.27–2.38 (m, 1 H), 2.64–2.90 (m, 2 H), 3.25 (m, 1 H), 8.16 (s, 1 H), 8.23 (s, 1 H); ^{13}C NMR (75 MHz) δ 16.0 (q), 20.14 (q), 29.79 (t), 33.8 (t), 38.0 (d), 129.2 (s), 142.5 (d), 143.7 (s), 147.7 (d), 152.0 (s); MS $C_{10}H_{13}N$ m/z 147 (M^+, 49), 146 (29), 132 (100), 131 (18), 117 (37), 77 (13). The

spectroscopic constants of this product are identical to those described for (±)-actinidine.

Isooxyskytanthine (2). A solution of **14** (0.0173 g, 0.090 mmol) in ethanol (1 mL) in the presence of a catalytic amount of 10% Pd/C was hydrogenated for 5 h at room temperature. The solution was filtered through Celite, and the solvent was evaporated. Isooxyskytanthine was purified on preparative TLC ($CHCl_3/CH_3OH$ = 93/7): yield 87%; IR 3400 cm^{-1}; ^1H NMR (300 MHz) δ 0.92 (d, 3 H, J = 6.9 Hz), 1.14 (d, 3 H, J = 6.9 Hz), 1.27 (s, 1 H), 1.48–1.74 (m, 7 H), 1.90–2.07 (m, 2 H), 2.46 (s, 3 H), 2.75 (ddd, 2 H, J = 5.0, 11.0, 13.0 Hz); ^{13}C NMR (75 MHz) δ 13.1 (q), 23.9 (q), 30.4 (t), 33.9 (t), 36.9 (q), 39.6 (d), 45.6 (d), 54.3 (d), 60.6 (t), 61.5 (t), 83.0 (s); MS $C_{11}H_{21}NO$ m/z 183 (M^+, 48), 182 (56), 166 (22), 150 (36), 100 (42), 84 (46), 74 (51), 58 (72), 57 (100), 55 (82).

Supplementary Material Available: Proton NMR spectra for mixtures of compounds **9** and **10** and **12** and **13** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.