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# SYNTHESIS OF THE DIAZATRICYCLIC CORE OF MADANGAMINES *VIA* CYCLIC *N,O*-ACETALIZATION–BRIDGEHEAD REDUCTION

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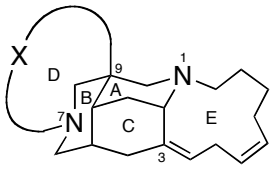
**Abstract** – A new approach to synthesize the diazatricyclic core of the madangamine alkaloids is described. The synthesis involves intramolecular *N,O*-acetalization of the keto-aminophenol which enables rapid construction of the 2-azabicyclo[3.3.1]nonane skeleton. Reductive C–O bond cleavage of the *N,O*-acetal has been accomplished by using $AlH_3$ as the source of nucleophilic hydrogen as well as the Lewis acid character. This strategy also demonstrates the utility of such approach in the stereoselective construction of the central 2,6-diazatricyclo[6.2.2.0$^{4,9}$]dodecane core with a quaternary carbon center at C-4 found in the madangamine alkaloids.

## INTRODUCTION

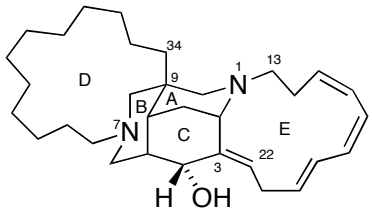
Madangamine A (**1**) is a novel pentacyclic alkaloid that was isolated from the marine sponge *Xestospongia ingens* in 1994.[1] Soon after, structural variations in the D-ring of this alkaloid class, madangamines B–E (**2**–**5**), were isolated.[2] More recently, madangamine F (**6**) that was the first example of the E-ring variant, was added to this class.[3] In addition to the novel pentacyclic structure, the diazatricyclic core, i.e., 2,6-diazatricyclo[6.2.2.0$^{4,9}$]dodecane (**7**), which commonly composes these alkaloids, is of a considerable interest to utilize as a molecular scaffold in drug discovery as well as a conventional synthetic target.[4–7]

During the course of our investigations on the synthesis of nitrogenous natural products, we have demonstrated the use of cyclic *N,O*-acetals for the elaboration of bridgehead alkylation of 2-azabicyclo[3.3.1]nonane employing a combination of Lewis acids (LA) and nucleophilic alkylmetal reagents (M–R), or alkylaluminum compounds ($AlR_3$) as Lewis acids with nucleophilic alkyl groups as

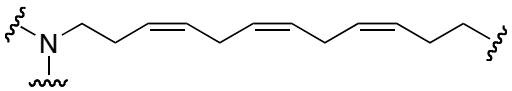
depicted in Scheme 1 (**9**→**10**→**11**).[8,9] In this context, we intended to examine the use of alane ($AlR_3$, R = H) for the synthesis of 2-azabicyclo[3.3.1]nonane **12**, the AC-ring of madangamines, by reductive cleavage of cyclic *N,O*-acetal **9** *via* bridgehead iminium ion **10**.

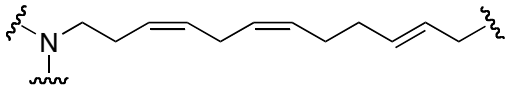


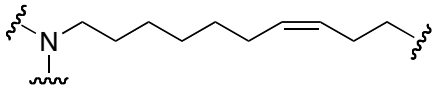
madangamines A–E (**1**–**5**)

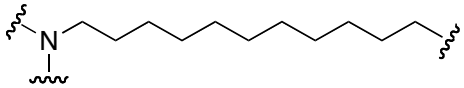


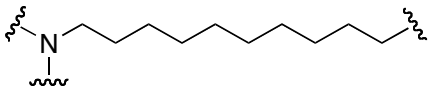
madangamine F (**6**)

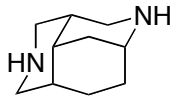
A (**1**): NX = 

B (**2**): NX = 

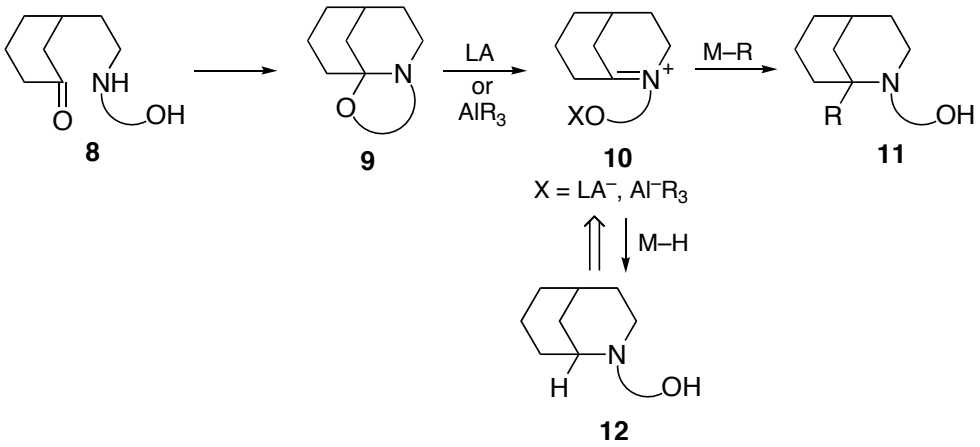
C (**3**): NX = 

D (**4**): NX = 

E (**5**): NX = 



**7**



**8** **9** **10** **11** **12**

**Scheme 1**

## RESULTS AND DISCUSSION

Synthesis of 2-azabicyclo[3.3.1]nonane.

The cyclic *N,O*-acetal (**16**) was prepared by the following two-step process which we had previously reported.[8] Reductive amination of the (formylmethyl)cyclohexane **13**[10] and 2-(aminomethyl)phenol (**14**) was carried out in the presence of sodium borohydride in methanol to yield the secondary amine **15** in a good yield (Scheme 2). Cleavage of the cyclic acetal **15** and intramolecular *N,O*-acetalization were carried out consecutively under acidic conditions (3.0 M hydrochloric acid–methanol, then *p*-toluenesulfonic acid, benzene at reflux) to give **16** as crystals suitable for X-ray crystallography.[11] The X-ray crystal structure of **16** revealed the 2-azabicyclononane ring and *trans*-fused quinolizidine system

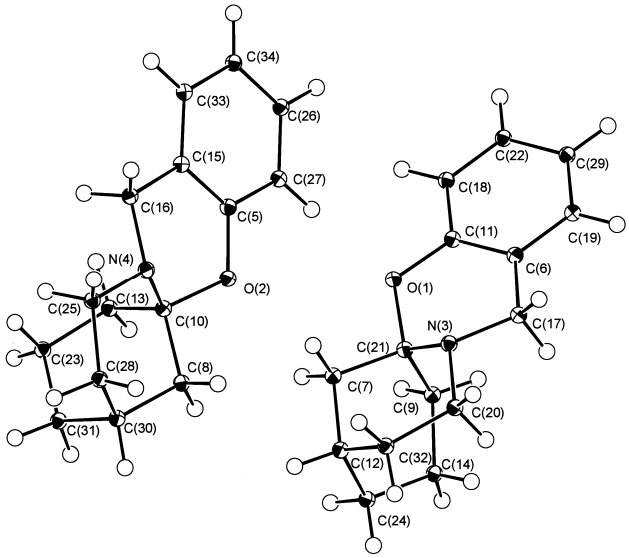
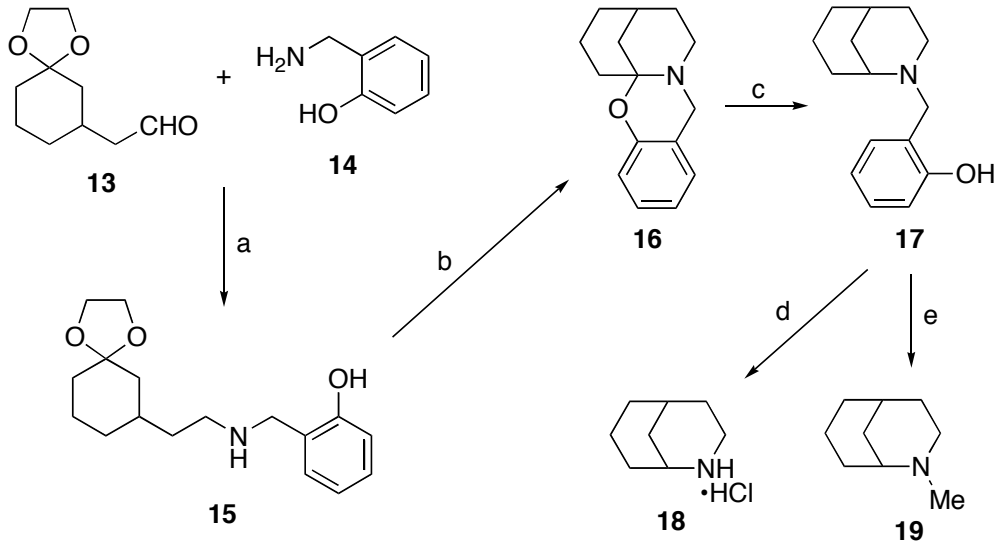


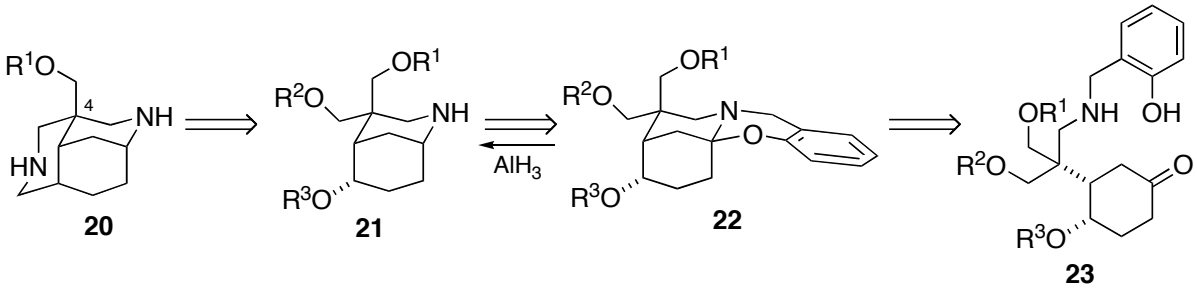

**Figure 1.** X-Ray crystallographic structure of **16**.




**Scheme 2.** Reagents and conditions: (a) $NaBH_4$, MeOH, 77%; (b) 3.0 M HCl, MeOH, then *p*-TsOH, reflux, 80%; (c) $AlH_3$,$Et_2O$, 0 °C, 85%; (d) $HCO_2H$, 10% Pd–C, then HCl, 48%; (e) 35% HCHO, $H_2$, 10% Pd–C, 86%.

to be in the chair–chair conformation as well as convincing evidence for the skeletal structure **16** (Figure 1). Treatment of **16** with $AlH_3$ as a Lewis acid with nucleophilic hydrogens provided the hydrogenated product **17** *via* the bridgehead iminium ion through the sequence (**9→10→12**) depicted in Scheme 1. The resulting hydrogenated product **17** was treated with formic acid in the presence of 10% palladium on carbon to give 2-azabicyclo[3.3.1]nonane (**18**), isolated as the hydrochloride salt in 48% yield. In the case of catalytic hydrogenation using 10% palladium on carbon in the presence of formaldehyde, 2-methyl-2-azabicyclo[3.3.1]nonane (**19**) was obtained in 86% yield.

The results obtained above prompted our efforts to develop a synthetic route to the 2,6-diazatricyclo[6.2.2.$0^{4,9}$]dodecane derivative **20**, which includes quaternary carbon center at C–4, *via* bridgehead reduction. Our strategy for **20** involves cyclization of 2-azabicyclononane derivative **21**, which is prepared through *N,O*-acetalization of **23** and Lewis acid mediated reduction of the resulting tetracyclic *N,O*-acetal **22** (Scheme 3).



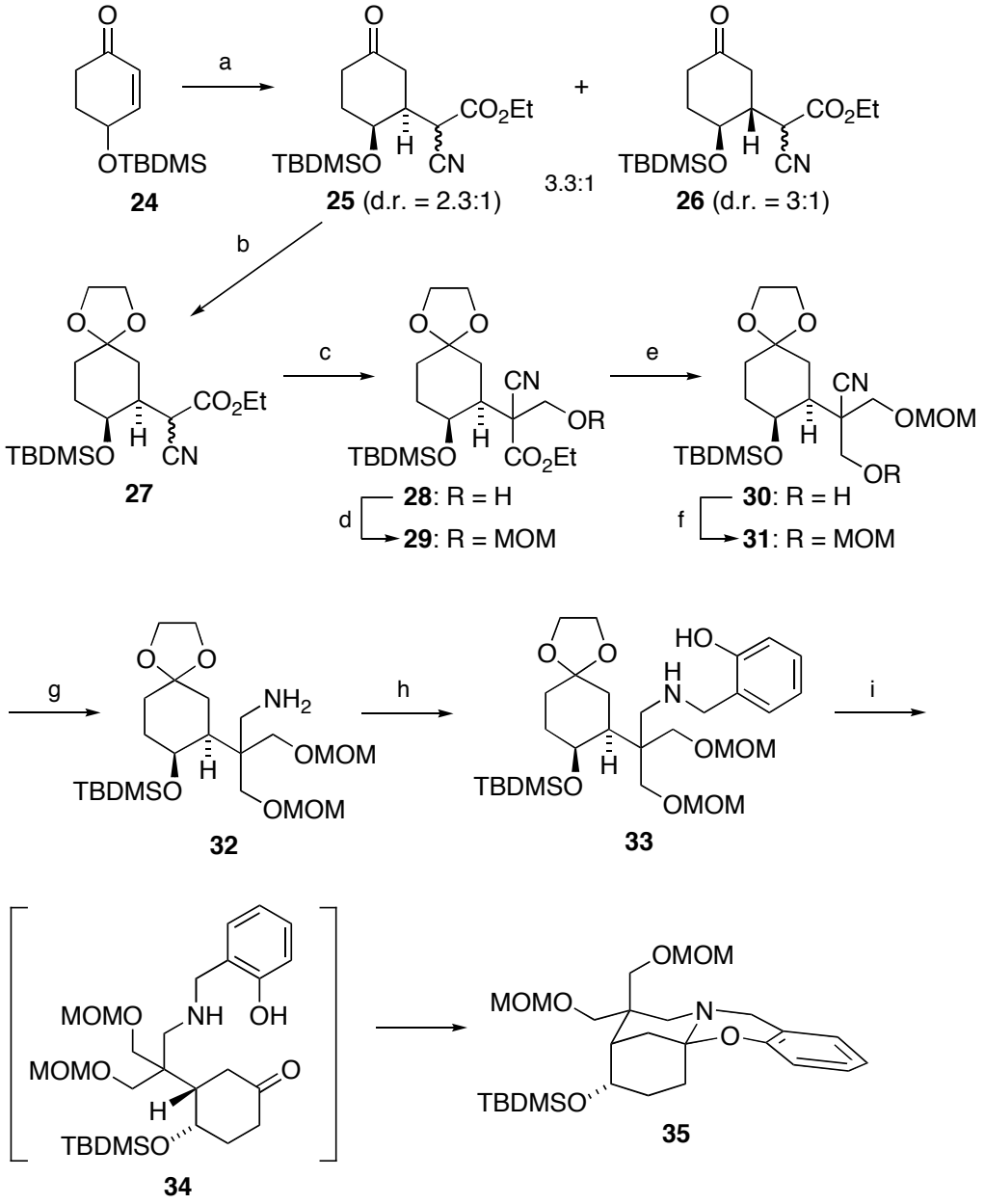

**Scheme 3**

Synthesis of 2,6-Diazatricyclo[6.2.2.$0^{4,9}$]dodecane.

The cyclohexenone **24**, which was prepared from cyclohexenone according to the protocol of Danishefsky,[12] was treated with cyanoethylacetate at 0 °C for 2 h to give a 9:4 diastereomeric mixture of the *cis*-Michael adduct **25** in 73% yield as a more polar component with accompanying a 3:1 diastereomeric mixture of the *trans*-adduct **26** in 22% yield as a less polar component.[13] These adducts were easily separated by column chromatography on silica gel. The *cis*-adduct **25** was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid to give the cyclic acetal **27** maintaining the same diastereoisomeric ratio. The acetal **27** was exposed to 35% aqueous formaldehyde in the presence of catalytic amount of potassium bicarbonate to yield the carbinol **28**, which was protected as a MOM ether in the usual manner to give **29**. The cyanoester **29** thus obtained as a 9:4 diastereomeric mixture was treated with $LiBH_4$ to give **30**, of which primary alcohol was protected as a MOM ether to give the biscarbinol derivative **31** as a single diastereomer. Reduction of nitrile moiety by DIBAL-H reduction yielded the primary amine **32**, which underwent reductive amination using salicylaldehyde and $NaBH_4$ to

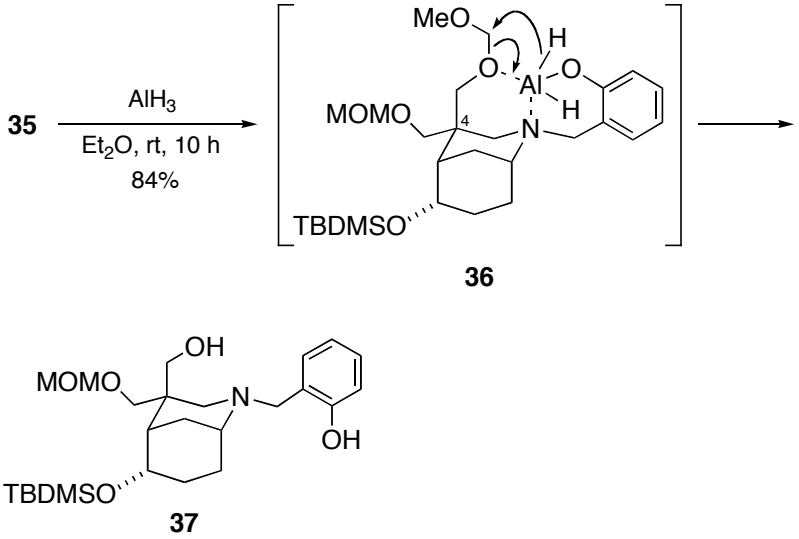
give the amino phenol **33**. Upon treatment of **33** with pyridinium *p*-toluenesulfonate in acetone–$H_2O$ at reflux, the transiently formed keto-aminophenol **34** was dehydrated to give the tetracyclic *N,O*-acetal **35** including the 2-azabicyclo[3.3.1]nonane skeleton.

With the tetracyclic *N,O*-acetal in hand, we next examined the bridgehead reduction established above. Treatment of **35** with $AlH_3$ in $Et_2O$ at rt led to reductive C–O bond cleavage of the *N,O*-acetal and selective deprotection of one of the two MOM ethers in one step, providing the amino alcohol **37** in good



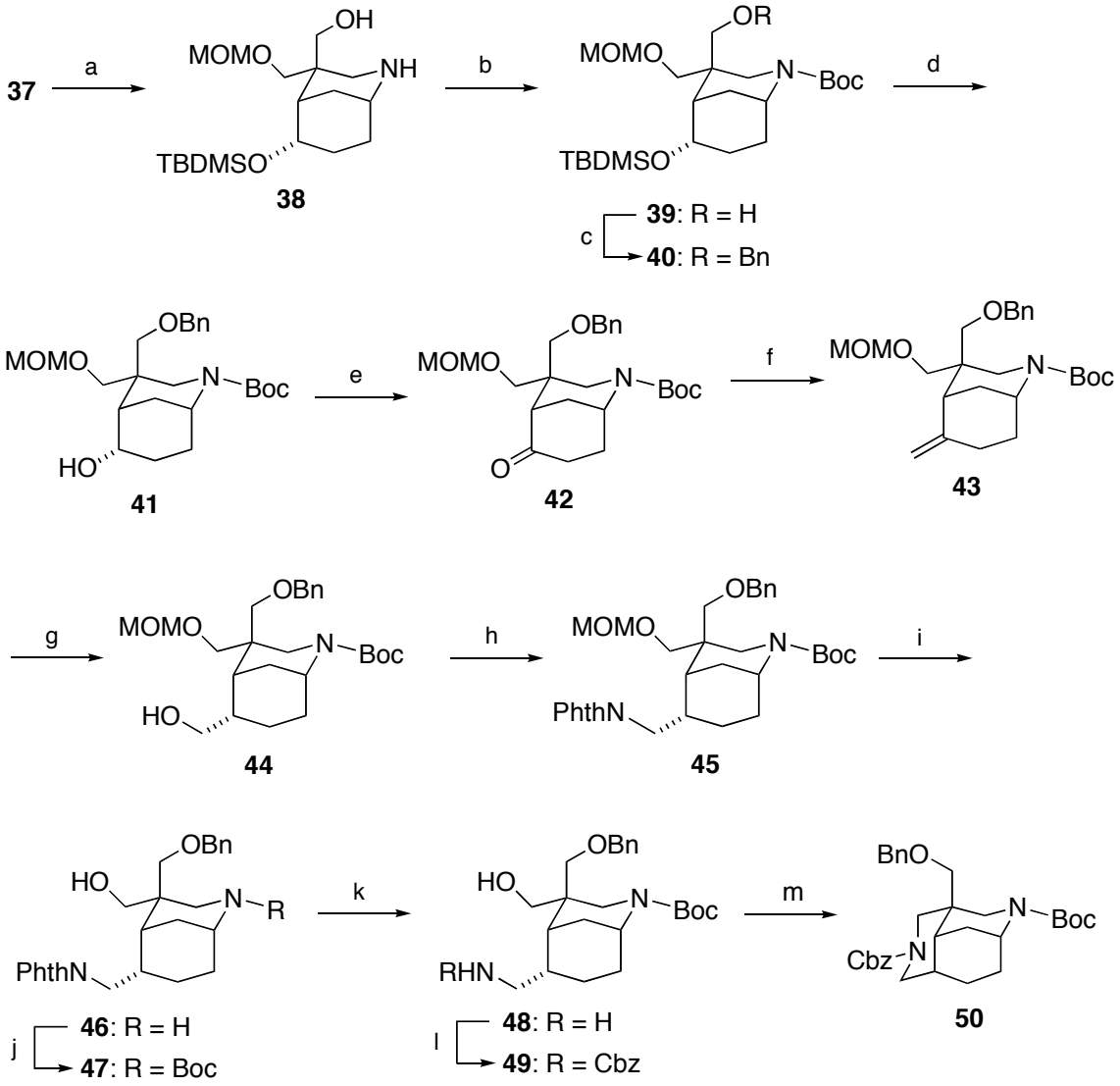

**Scheme 4.** Reagents and conditions: (a) $CH_2(CN)CO_2Et$, *t*-BuOK, toluene, 0 °C, 95% total yield: (b) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 99%; (c) 35% HCHO, $KHCO_3$, rt, 90%; (d) MOMCl, *i*-$Pr_2EtN$, $CH_2Cl_2$, rt, 90%; (e) $LiBH_4$ in THF, EtOH/$Et_2O$, reflux, 83%; (f) MOMCl, *i*-$Pr_2EtN$, $CH_2Cl_2$, rt, 90%; (g) DIBAL-H in hexane, $CH_2Cl_2$, 0 °C, 83%; (h) salicylaldehyde, EtOH, rt, then $NaBH_4$, 0 °C → rt, 98%; (i) PPTS, acetone/$H_2O$, reflux, 48 h, 75% for **35**.

yield (Scheme 5). The latter process involves selective deprotection of the MOM ether in which the chemically equivalent MOM ethers were efficiently differentiated, being suitable to perform the subsequent cyclization for the construction of the diazatricyclic core skeleton. This process presumably occurred *via* a chelated phenoxyaluminum hydride intermediate such as **36** where the hydride delivery preferentially occurred at the methoxymethyl group connected to the axially oriented C–4 methoxymethylene group.




**Scheme 5**

Removal of a (2-hydroxyphenyl)methyl group from **37** was performed by catalytic hydrogenation using palladium on charcoal in MeOH to give the amino alcohol **38**. Compound **38** was converted to the secondary alcohol **41** by sequential protection as the Boc carbamate and the benzyl ether followed by deprotection of the TBDMS ether with $Bu_4NF$ (Scheme 6). The secondary alcohol **41** was oxidized with PCC and the resulting ketone **42** was converted to the *exo*-methylene product **43** by using the Tebbe reagent. Hydroboration of **43** with 9-BBN from the less congested convex β-face followed by an oxidative workup with basic peroxide led to the primary alcohol **44** as a single diastereomer. Mitsunobu reaction with phthalimide afforded **45**, which on acidic treatment underwent deprotection of the MOM and Boc groups to yield **46**. After Boc-protection of the secondary amine as **47**, the phthaloyl unit was removed with hydrazine to give the amino alcohol **48**. The primary amino group was protected as Cbz-group to give the alcohol **49**. The primary alcohol **49** was mesylated and the resulting mesylate was exposed to *t*-BuOK in THF at rt to produce the expecting diazatricyclic compound **50**.




**Scheme 6.** Reagents and conditions: (a) $H_2$, Pd–C, MeOH, 86%; (b) $(Boc)_2O$, 0.5 M NaOH, dioxane, rt, 99%; (c) BnBr, NaH, $Bu_4NI$, DMF, rt, 87%; (d) TBAF, THF, rt, 99%; (e) PCC, $CH_2Cl_2$, rt, 99%; (f) Tebbe reagent, THF, rt, 8 h, 73%; (g) (i) 9-BBN, THF, rt; (ii) NaOH, $H_2O_2$, rt, 91% over 2 steps; (h) PhthNH, DEAD, $Ph_3P$, THF, rt, 72%; (i) HCl, MeOH, 60 °C, 83%; (j) $(Boc)_2O$, 0.5 M NaOH, dioxane, rt, 76%; (k) $H_2NNH_2{\cdot}H_2O$, EtOH, reflux, 96%; (l) CbzCl, $Na_2CO_3$, dioxane/$H_2O$, rt, 70%; (m) (i) MsCl, $Et_3N$, $CH_2Cl_2$, rt; (ii) *t*-BuOK, THF, rt, 72% from **49**.

## Conclusion

In summary, an efficient synthesis of the diazatricyclic core of the madangamine alkaloids has been accomplished. Our studies have shown that *N,O*-acetalization of the keto-aminophenol **15** enables the rapid construction of the 2-azabicyclo[3.3.1]nonane skeleton **16**. Reductive C–O bond cleavage of the *N,O*-acetal has been accomplished by reduction using $AlH_3$ as the source of nucleophilic hydrogen as well as the Lewis acid character to give **17**. This strategy applied to the synthesis of the 2-azabicyclo[3.3.1]nonane skeleton **37** with a quaternary carbon center at C–4 demonstrates the utility of

such approach in the stereoselective construction of the central diazatricyclic core found in the madangamine alkaloids. The strategy developed for stereocontrolled synthesis of **50** is amenable to the efficient synthesis of madangamines by using the keto-aminophenol with an appropriate functionality.

## EXPERIMENTAL

Melting points (uncorrected) were determined by using a Yanagimoto micro melting point apparatus. $^1$H NMR spectra were recorded at 400 MHz or 300 MHz using residual $CHCl_3$ (7.26 ppm) as reference. $^{13}$C NMR spectra were recorded at 100.6 MHz with $CDCl_3$ (77.05 ppm) as reference. IR spectra were taken with an FTIR instrument. Mass spectra were measured at an ionizing voltage of 70 eV or performed on a spectrometer equipped with a positive electrospray ionization mode (ESI). Organic solvents used were dried by standard methods. Silica gel 60 (230–400 mesh, Merck) was used for column chromatography, and precoated silica gel $60F_{254}$ plates (0.25 mm, Merck) were used for TLC.

**2-({[2-(1,4-Dioxaspiro[4.5]dec-7-yl)ethyl]amino}methyl)phenol (15).** To a stirred ice-cold solution of **13** (2.30 g, 12.5 mmol) in MeOH (100 mL) was added 2-(aminomethyl)phenol (**14**) (2.00 g, 16.2 mmol), and the reaction mixture was allowed to warm to rt, stirred for 1h, and then cooled to 0 °C. Sodium borohydride (0.85 g, 22.5 mmol) was added and the mixture was stirred at rt for 30 min. Water (50 mL) was added and the mixture was extracted with $Et_2O$ (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 400:9:1) to give **15** (2.82 g, 77%) as a colorless oil: IR (neat) 3290, 2932, 2349, 1614 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.87 (1H, qd, *J* = 12.1, 4.0 Hz), 1.18 (1H, t, *J* = 12.1 Hz), 1.35–1.58 (4H, m), 1.59–1.78 (5H, m), 2.69 (2H, t, *J* = 7.9 Hz), 3.87–3.96 (4H, m), 3.98 (2H, m), 6.76 (1H, td, *J* = 8.0, 1.0 Hz), 6.82 (1H, dd, *J* = 8.0, 1.0 Hz), 6.97 (1H, dd, *J* = 8.0, 1.0 Hz), 7.16 (1H, td, *J* = 8.1, 1.6 Hz); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 23.2 ($CH_2$), 31.8 ($CH_2$), 33.5 (CH), 34.9 ($CH_2$), 36.8 ($CH_2$), 41.8 ($CH_2$), 46.4 ($CH_2$), 52.9 ($CH_2$), 64.3 ($CH_2$), 64.4 ($CH_2$), 109.1 (C), 116.5 (CH), 119.0 (CH), 122.6 (C), 128.3 (CH), 128.7 (CH), 158.4 (C); EIMS *m*/*z* (relative intensity) 291 ($M^+$, 8), 246 (30), 136 (75), 107 (100); HRMS (ESI) calcd for $C_{17}H_{26}NO_3$ $[M+H]^+$ 292.1913, found 292.1930. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.75; H, 8.51; N, 4.71.

**2-Oxa-10-azatetracyclo[11.3.1.0$^{1,10}$.0$^{3,8}$]heptadeca-3(8),4,6-triene (16).** To a solution of **15** (2.30 g, 7.90 mmol) in MeOH (25 mL) was added 3.0 M HCl (25 mL) at once and the mixture was refluxed for 3 h, The mixture was neutralized with a saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3 x 80 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was redissolved in benzene (150 mL) including *p*-toluenesulfonic acid (115 mg) and the resulting solution was refluxed for 4

h with continuous azeotropic water removal using a Dean-Stark apparatus. Evaporation of the solvent and purification of the residue by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 1000:9:1) gave **16** (1.45 g, 80%) as white crystals. A part of the resulting crystals was recrystallized form EtOAc–hexane to afford colorless needles for analytical measurements: mp 92–93 °C; IR (KBr) 2921 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.51 (1H, td, *J* = 13.4, 6.4 Hz), 1.59–1.97 (7H, m), 2.15 (tdd, *J* = 13.4, 7.8, 4.8 Hz), 2.36 (1H, br s), 2.42 (1H, d quint, *J* = 13.9, 2.7 Hz), 3.05 (1H, td, *J* = 12.6, 5.5 Hz), 3.19 (1H, dd, *J* = 11.7, 7.8 Hz), 3.79 (1H, A part of ABq, *J* = 15.3 Hz), 3.80 (1H, B part of ABq, *J* = 15.3 Hz), 6.79 (1H, d, *J* = 7.6 Hz), 6.83 (1H, t, *J* = 7.6 Hz), 6.99 (1H, d, *J* = 7.6 Hz), 7.09 (1H, t, *J* = 7.6 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 22.1 ($CH_2$), 29.5 ($CH_2$), 29.9 ($CH_2$), 30.3 (CH), 30.4 ($CH_2$), 40.9 ($CH_2$), 49.7 ($CH_2$), 51.8 ($CH_2$), 86.1 (C), 116.9 (CH), 119.9 (CH), 120.3 (C), 126.5 (CH), 127.7 (CH), 151.8 (C); EIMS *m/z* (relative intensity) 229 ($M^+$, 15), 200 (10), 186 (100); HRMS (ESI) calcd for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1545, found 230.1549. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.41; H, 8.25; N, 5.96.

**[(2-Azabicyclo[3.3.1]nonan-2-yl)methyl]phenol (17).** Aluminum chloride (814 mg, 6.11 mmol) was added to a stirred ice-cold suspension of lithium aluminum hydride (695 mg, 18.3 mmol) in $Et_2O$ (20 mL) under argon atmosphere. After stirring at rt for 5 min, a solution of **16** (1.40 g, 6.11 mmol) in $Et_2O$ (10 mL) was added and stirring was continued at rt for 2 h. The reaction mixture was quenched by addition of 10% aqueous NaOH solution (10 mL) and filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 1000:9:1) to give **17** (1.20 g, 85 %) as a colorless oil: IR (neat) 2920, 2350 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.38–1.50 (1H, m), 1.62–1.88 (7H, m), 1.96–2.20 (3H, m), 2.88–2.95 (3H, m), 3.82 (1H, A part of ABq, *J* = 14.1 Hz), 3.93 (1H, B part of ABq, *J* = 14.1 Hz), 6.75–6.79 (2H, m), 6.97 (1H, dd, *J* = 7.4, 1.3 Hz), 7.12–7.17 (1H, td, *J* = 7.4, 1.1 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 21.9 ($CH_2$), 24.5 ($CH_2$), 25.4 (CH), 30.3 ($CH_2$), 30.6 ($CH_2$), 34.6 ($CH_2$), 48.6 ($CH_2$), 50.9 (C), 59.3 ($CH_2$), 115.8 (CH), 118.7 (CH), 121.7 (C), 128.3 (CH), 128.4 (CH), 158.6 (C); EIMS *m/z* (relative intensity) 231 ($M^+$, 51), 188 (100); HRMS (ESI) calcd for $C_{15}H_{22}NO$ $[M+H]^+$ 232.1701, found 232.1684. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.19; H, 9.24; N, 5.80.

**2-Azabicyclo[3.3.1]nonane (18).** To a stirred solution of **17** (750 mg, 3.07 mmol) in MeOH (44 mL) were added 10% Pd–C (750 mg) and formic acid (4.4 mL) under argon atmosphere at rt for 14 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. To the residue was added potassium carbonate and water (50 mL) and the mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and 1.0 M HCl in MeOH (2 mL) was added. After

concentration in vacuo, the residue was recrystallized from EtOH–acetone to give **18**·HCl (238 mg, 48%) as colorless needles: mp 287–289 °C (lit.[14] 288 °C); IR (neat) 2945, 2754 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.64 (1H, dd, *J* = 13.9, 2.4 Hz), 1.71–1.92 (6H, m), 2.06 (1H, s), 2.16–2.25 (2H, m), 2.35–2.38 (1H, m), 3.29 (1H, dd, *J* = 13.2, 6.9 Hz), 3.45 (1H, td, *J* = 13.2, 5.6 Hz), 3.65 (1H, br s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 20.4 ($CH_2$), 24.0 (CH), 26.8 ($CH_2$), 27.3 ($CH_2$), 29.5 ($CH_2$), 30.3 ($CH_2$), 40.0 ($CH_2$), 47.1 (CH); EIMS *m*/*z* (relative intensity) 125 ($M^+$–HCl, 18), 82 (100). Anal. Calcd for $C_8H_{16}ClN$: C, 59.43; H, 9.98; N, 8.66. Found: C, 59.63; H, 9.71; N, 8.26.

**2-Methyl-2-azabicyclo[3.3.1]nonane (19).** A mixture of **17** (1.00 g, 4.33 mmol), 10% Pd–C (1.00 g), and 35% formalin (0.5 mL) was stirred under a balloon pressure of hydrogen for 14 h, filtered, and concentrated in vacuo. To the residue was added 3.0 M HCl (20 mL) and the resulting mixture was washed with $Et_2O$ (2 x 20 mL) and concentrated in vacuo. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified column chromatography ($CHCl_3$–MeOH–concentrated $NH_4OH$, 100:9:1) to give **19** (519 mg, 86%) as a pale yellow oil: $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.36–1.39 (1H, m), 1.54–1.71 (6H, m), 1.83–1.89 (2H, m), 2.00–2.17 (2H, m), 2.42 (3H, s), 2.78–2.82 (2H, m), 2.88 (1H, td, *J* = 12.4, 5.1 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 22.2 ($CH_2$), 24.6 ($CH_2$), 25.2 (CH), 30.5 ($CH_2$), 30.7 ($CH_2$), 34.7 ($CH_2$), 43.3 ($CH_3$), 51.5 ($CH_2$), 53.3 (CH); EIMS *m*/*z* (relative intensity) 139 ($M^+$, 32), 96 (100).

**Ethyl (2*R**)- and (2*S**)-((1*S**,2*S**)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-oxocyclohexyl)(cyano)acetate (25) and Ethyl (2*R**)- and (2*S**)-((1*R**,2*S**)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-oxocyclohexyl)-(cyano)acetate (26).** To a stirred ice-cold suspension of *t*-BuOK (118 mg, 1.05 mmol) in toluene (7 mL) was added $CH_2(CN)CO_2Et$ (119 mg, 1.05 mmol). After 15 min, a solution of **24** (226 mg, 1.00 mmol) in toluene (3 mL) was added to the mixture and the stirring was continued for 2 h. After addition of water (10 mL), the mixture was extracted with $Et_2O$ (3 x 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to give as the first fraction **26** (74.7 mg, 22%) as colorless needles ($CHCl_3$–hexane): mp 85.3–86.8 °C; $^1H$ NMR (300MHz, $CDCl_3$) δ 0.13 and 0.15 (total 3H in 1:3 ratio, s each), 0.14 and 0.19 (total 3H in 1:3 ratio, s each), 0.89 and 0.91 (total 9H in 1:3 ratio, s each), 1.33 (3H, td, *J* = 7.1, 0.8 Hz), 1.68–1.91 (1H, m), 2.16–2.30 (1H, m), 2.31–2.70 (5H, m), 3.71 (0.25H, d, *J* = 4.0 Hz), 3.96 (0.75H, ddd, *J* = 10.0, 10.0, 4.5 Hz), 4.13 (0.75H, d, *J* = 2.5 Hz), 4.16–4.35 (2.25H, m, including 2H at δ 4.28, q, *J* = 7.1 Hz). The second fraction gave 25 (248 mg, 73%) as colorless oil: IR (neat) 2248, 1747, 1718 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.10 and 0.17

(total 3H in 4:9 ratio, s, each), 0.12 and 0.22 (total 3H in 4:9 ratio, s, each), 0.93 and 0.94 (total 9H in 4:9 ratio, s, each), 1.32 and 1.33 (total 3H in 4:9 ratio, t, $J$ = 7.1 Hz, each), 1.82 and 1.86 (total 1H in 4:9 ratio, tdd, $J$ = 14.2, 4.8, 1.9 Hz, and tdd, $J$ = 14.4, 4.7, 1.8 Hz, respectively), 2.09–2.70 (6H, m), 3.45 and 3.64 (total 1H in 4:9 ratio, dt, $J$ = 10.2, 5.5 Hz and d, $J$ = 8.6 Hz, respectively), 4.12 and 4.39 (total 1H in 4:9 ratio, br s each), 4.22–4.33 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –5.2 and –5.0 ($CH_3$, total 1 carbon in 4:9 ratio), –4.3 ($CH_3$), 14.0 ($CH_3$), 18.1 (C), 25.8 ($CH_3$, 3 carbons), 31.7 and 31.9 ($CH_2$, total 1 carbon in 4:9 ratio), 34.8 and 35.0 ($CH_2$, total 1 carbon in 4:9 ratio), 39.5 and 40.7 (CH, total 1 carbon in 4:9 ratio), 39.8 and 39.9 ($CH_2$, total 1 carbon in 4:9 ratio), 42.7 and 44.0 (CH, total 1 carbon in 4:9 ratio), 63.2 ($CH_2$), 65.8 and 66.0 (CH, total 1 carbon in 4:9 ratio), 115.0 and 115.4 (C, total 1 carbon in 4:9 ratio), 164.8 and 165.0 (C, total 1 carbon in 4:9 ratio), 207.7 (C); EIMS $m/z$ (relative intensity) 340 ($M^+$ + 1, 22), 282 (43), 169 (60), 142 (36), 99 (18), 73 (100). Anal. Calcd for $C_{17}H_{29}NO_4Si$: C, 60.14; H, 8.61; N, 4.13. Found: C, 60.22; H, 8.56; N, 4.11.

**Ethyl (2*R**)- and (2*S**)-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-(cyano)acetate (27).** A solution of **25** (diastereomeric mixture of β-cyano/α-cyano = 9:4, 19.0 g, 56.0 mmol), *p*-toluenesulfonic acid (533 mg, 2.80 mmol), and ethylene glycol (5.21 g, 84.0 mmol) in benzene (190 mL) was stirred for 1 h at reflux with continuous azeotropic water removal using a Dean–Stark apparatus. Evaporation of the solvent and purification by column chromatography on silica gel (hexane–EtOAc, 10:1) gave **27** (diastereomeric mixture of **27β**/**27α** = 9:4, 21.3 g, 99%) as a colorless oil: IR (neat) 2248, 1746 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.02 and 0.10 (total 3H in 4:9 ratio, s each), 0.05–0.14 (total 3H in 4:9 ratio, s each), 0.88 and 0.89 (total 9H in 4:9 ratio, s each), 1.30 (3H, t, $J$ = 7.1 Hz), 1.38–1.95 (6H, m), 2.31–2.43 (1H, m), 3.36 and 3.56 (total 1H in 9:4 ratio, d, $J$ = 11.2 Hz and d, $J$ = 10.0 Hz, respectively), 3.85–4.01 (4H, m), 4.16–4.32 (3H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –5.3 and –5.1 ($CH_3$, total 1 carbon in 4:9 ratio), –4.3 ($CH_3$), 14.0 ($CH_3$), 18.1 (C), 25.8 ($CH_3$, 3 carbons), 28.4 and 28.7 ($CH_2$, total 1 carbon in 9:4 ratio), 30.3 ($CH_2$), 33.2 and 33.3 ($CH_2$, total 1 carbon in 9:4 ratio), 39.4 and 39.5 (CH, total 1 carbon in 9:4 ratio), 40.5 and 40.8 (CH, total 1 carbon in 9:4 ratio), 41.9 and 43.4 (CH, total 1 carbon in 9:4 ratio), 62.6 and 62.7 ($CH_2$, total 1 carbon in 9:4 ratio), 64.3 ($CH_2$), 64.4 ($CH_2$), 66.1 and 66.2 (CH, total 1 carbon in 4:9 ratio), 108.1 and 108.2 (C, total 1 carbon in 9:4 ratio), 115.9 and 116.0 (C, total 1 carbon in 4:9 ratio), 165.5 (C); EIMS $m/z$ (relative intensity) 384 ($M^+$+1, 16), 326 (100), 282 (24), 142 (42), 99 (56), 75 (56), 57 (44). Anal. Calcd for $C_{19}H_{33}NO_5Si$: C, 59.50; H, 8.67; N, 3.65. Found: C, 59.63; H, 8.67; N, 3.62.

**Ethyl (2*R**)- and (2*S**)-2-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-2-cyano-3-hydroxypropanoate (28).** A mixture of **27** (diastereomeric mixture of **27β**/**27α** = 9:4, 200 mg,

0.52 mmol), 35% formalin (0.15 mL, 1.95 mmol), and $KHCO_3$ (16 mg, 0.16 mmol) were stirred vigorously at rt for 4 h. After addition of water (15 mL), the mixture was extracted with $Et_2O$ (3 x 20 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **28** (diastereomeric mixture of **28β**/**28α** = 9:4, 193 mg, 90%) as a colorless oil: IR (neat) 3456, 2247, 1744 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.08 and 0.11 (total 3H in 4:9 ratio, s each), 0.09 and 0.14 (total 3H in 4:9 ratio, s each), 0.92 (9H, s), 1.32 and 1.33 (total 3H in 9:4 ratio, t, *J* = 7.2 Hz, each), 1.50–1.95 (5H, m), 2.09 and 2.18 (total 1H in 4:9 ratio, t, *J* = 12.7 Hz, each), 2.28 and 2.36 (total 1H in 4:9 ratio, d, *J* = 12.8 Hz, each), 2.65–2.80 (1H, m), 3.86–4.10 (7H, m), 4.20–4.37 (2H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.6 and –4.1 ($CH_3$, total 1 carbon in 4:9 ratio), –4.3 and –3.9 ($CH_3$, total 1 carbon in 4:9 ratio), 14.0 ($CH_3$), 18.2 (C), 26.0 ($CH_3$, 3 carbons), 28.6 and 28.8 ($CH_2$, total 1 carbon in 9:4 ratio), 31.0 ($CH_2$), 31.4 and 32.3 ($CH_2$, total 1 carbon in 9:4 ratio), 43.3 and 43.5 (CH, total 1 carbon in 9:4 ratio), 54.1 and 54.4 (C, total 1 carbon in 4:9 ratio), 62.9 and 63.0 ($CH_2$, total 1 carbon in 9:4 ratio), 63.8 and 65.5 ($CH_2$, total 1 carbon in 9:4 ratio), 64.3 ($CH_2$, 2 carbons), 65.9 and 67.2 (CH, total 1 carbon in 4:9 ratio), 108.3 and 108.4 (C, total 1 carbon in 4:9 ratio), 117.5 and 117.6 (C, total 1 carbon in 4:9 ratio), 168.0 and 168.5 (C, total 1 carbon in 4:9 ratio); EIMS *m*/*z* (relative intensity) 414 ($M^+$+1, 15), 356 (80), 326 (100), 284 (32), 214 (24), 139 (44). Anal. Calcd for $C_{20}H_{35}NO_6Si$: C, 58.08; H, 8.53; N, 3.39. Found: C, 58.14; H, 8.52; N, 3.38.

**Ethyl (2*R**)- and (2*S**)-2-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-2-cyano-3-(methoxymethoxy)propanoate (29).** To a stirred solution of **28** (diastereomeric mixture of **28β**/**28α** = 9:4, 11.8 g, 28.5 mmol) in $CH_2Cl_2$ (100 mL) were added diisopropylethylamine (9.20 g, 71.3 mmol) and chloromethyl methyl ether (4.59 g, 57.0 mmol) under argon atmosphere. After 24 h, water (100 mL) was added to the mixture, then the the mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined extracts were washed with brine (150 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to give **29** (diastereomeric mixture of **29β**/**29α** = 9:4, 11.8 g, 90%) as a colorless oil: IR (neat) 2245, 1745 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.07 and 0.14 (total 3H in 4:9 ratio, s each), 0.09 and 0.15 (total 3H in 4:9 ratio, s each), 0.92 (9H, s), 1.31 and 1.32 (total 3H in 9:4 ratio, t, *J* = 7.0 Hz, each), 1.47–2.36 (7H, m), 3.35 (3H, s), 3.80–3.98 (6H, m), 4.03 and 4.10 (total 1H in 4:9 ratio, br s each), 4.21–4.36 (2H, m), 4.77 (2H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.6 and –4.1 ($CH_3$, total 1 carbon in 4:9 ratio), –4.4 and –3.9 ($CH_3$, total 1 carbon in 4:9 ratio), 14.0 and 14.1 ($CH_3$, total 1 carbon in 4:9 ratio), 18.2 (C), 26.0 ($CH_3$, 3 carbons), 28.7 and 28.8 ($CH_2$, total 1 carbon in 9:4 ratio), 31.0 and 31.1 ($CH_2$, total 1 carbon in 9:4 ratio), 31.5 and 32.4 ($CH_2$, total 1 carbon in 9:4 ratio), 43.9 and 44.0 (CH, total 1 carbon in 9:4 ratio), 52.7 and

52.8 (C, total 1 carbon in 9:4 ratio), 55.7 ($CH_3$), 62.7 and 62.8 ($CH_2$, total 1 carbon in 9:4 ratio), 64.2 ($CH_2$), 64.3 ($CH_2$), 65.7 and 67.2 (CH, total 1 carbon in 9:4 ratio), 68.2 and 69.8 ($CH_2$, total 1 carbon in 4:9 ratio), 96.4 and 96.5 ($CH_2$, total 1 carbon in 9:4 ratio), 108.3 and 108.4 (C, total 1 carbon in 4:9 ratio), 117.4 and 117.6 (C, total 1 carbon in 4:9 ratio), 167.4 and 167.5 (C, total 1 carbon in 9:4 ratio); EIMS *m*/*z* (relative intensity) 426 ($M^+$+1, 4), 400 (20), 370 (16), 356 (8), 296 (8), 258 (8), 57, (44), 45 (100). Anal. Calcd for $C_{22}H_{39}NO_7Si$: C, 57.74; H, 8.59; N, 3.06. Found: C, 57.69; H, 8.50; N, 2.91.

**(2*R**)- and (2*S**)-2-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-3-hydroxy-2-[(methoxymethoxy)methyl]propanenitrile (30).** To a stirred ice-cold solution of **29** (diastereomeric mixture of **29β**/**29α** = 9:4, 18.5 g, 40.4 mmol) in $Et_2O$ (100 mL) were added EtOH (6.80 mL, 121 mmol) and $LiBH_4$ (2.0 M solution in THF, 60.6 mL, 121 mmol). After being stirred at reflux for 1.5 h, the reaction was quenched by addition of 1 M NaOH (10 mL). The mixture was filtered through Celite. The filtrate was added water (100 mL), and the mixture was extracted with $Et_2O$ (3 x 150 mL). The combined extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **30** (diastereomeric mixture of **30β**/**30α** = 9:4, 14.0 g, 83%) as white crystals: IR (neat) 2245, 1745 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.16 (3H, s), 0.92 (9H, s), 1.50–1.71 (3H, m), 1.78–2.22 (4H, m), 2.66 and 2.73 (total 1H in 4:9 ratio, t, *J* = 6.0 Hz, each), 3.38 (3H, s), 3.65–3.98 (8H, m), 4.21 and 4.27 (total 1H in 9:4 ratio, br s each), 4.65 (2H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.4 ($CH_3$), –3.9 ($CH_3$), 18.2 (C), 26.0 ($CH_3$, 3 carbons), 28.8 ($CH_2$), 31.0 ($CH_2$), 31.4 ($CH_2$), 40.8 and 40.9 (CH, total 1 carbon in 9:4 ratio), 46.3 and 46.4 (C, total 1 carbon in 9:4 ratio), 55.8 ($CH_3$), 63.0 and 63.1 ($CH_2$ total 1 carbon in 4:9 ratio), 64.3 ($CH_2$), 64.4 ($CH_2$), 66.8 and 66.9 (CH, total 1 carbon in 4:9 ratio), 67.3 and 67.6 ($CH_2$, total 1 carbon in 9:4 ratio), 96.7 ($CH_2$), 108.6 (C), 120.4 (C); EIMS *m*/*z* (relative intensity) 416 ($M^+$+1, 16), 384 (10), 358 (44), 326 (20), 252 (20), 168 (24), 57 (60), 45 (100). Anal. Calcd for $C_{20}H_{37}NO_6Si$: C, 57.80; H, 8.97; N, 3.37. Found: C, 57.80; H, 8.75; N, 3.31.

**2-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-3-(methoxymethoxy)-2-[(methoxymethoxy)methyl]propanenitrile (31).** In the same manner describe above for the preparation of **29**, **30** (diastereomeric mixture of **30β**/**30α** = 9:4, 11.8 g, 28.4 mmol) was methoxymethylated. Workup and column chromatography on silica gel (hexane–EtOAc, 10:1) gave **31** (11.7 g, 90%) as white crystals: mp 59.5–61.0 °C; IR (KBr) 2238 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.16 (3H, s), 0.93 (9H, s), 1.50–1.56 (1H, m), 1.58–1.70 (2H, m), 1.82 (1H, dq, *J* = 14.2, 3.0 Hz), 1.93 (1H, td, *J* = 13.5, 4.2 Hz), 2.05 (1H, t, *J* = 12.8 Hz), 2.23 (1H, dt, *J* = 12.9, 2.2 Hz), 3.38 (6H, s), 3.63 (1H, A part of ABq, *J* = 9.7 Hz), 3.74 (1H, A' part of ABq, *J* = 9.6 Hz), 3.83 (1H, B' part of ABq, *J*

= 9.6 Hz), 3.88–3.98 (5H, m, including 1H at δ 3.90, B part of ABq, *J* = 9.7 Hz), 4.61–4.67 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –4.5 ($CH_3$), –3.9 ($CH_3$), 18.2 (C), 26.0 ($CH_3$, 3 carbons), 28.9 ($CH_2$), 31.1 ($CH_2$), 31.2 ($CH_2$), 40.7 (CH), 45.2 (C), 55.6 ($CH_2$, 2 carbons), 64.3 ($CH_2$), 64.4 ($CH_2$), 65.9 ($CH_2$), 66.4 ($CH_2$), 66.8 (CH), 96.6 ($CH_2$, 2 carbons), 108.7 (C), 120.5 (C); EIMS *m*/*z* (relative intensity) 460 ($M^+$+1, 2), 459 ($M^+$, 1), 402 (100), 372 (24), 340 (20), 260 (32), 89 (36), 45 (16). Anal. Calcd for $C_{22}H_{41}NO_7Si$: C, 57.49; H, 8.99; N, 3.05. Found: C, 57.54; H, 9.13; N, 3.07.

**2-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-3-(methoxymethoxy)-2-[(methoxymethoxy)methyl]-1-propanamine (32).** To a stirred ice-cold solution of **31** (5.90 g, 12.8 mmol) in $CH_2Cl_2$ (90 mL) under argon atmosphere was added diisobutylaluminum hydride (0.95 M solution in hexane, 40.4 mL, 38.4 mmol). After being stirred for 1 h, the reaction was quenched by addition of water (0.7 mL). The mixture was filtered through celite. The filtrate was rinsed with THF (400 mL). The combined filtrates were concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 300:9:1) to give **32** (4.92 g, 83%) as a colorless oil: IR (neat) 3397 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.09 (3H, s), 1.38 (2H, br s), 1.48–1.53 (1H, m), 1.55–1.67 (2H, m), 1.76 (1H, dq, *J* = 13.8, 2.8 Hz), 1.89 (2H, t, *J* = 12.8 Hz), 2.00 (1H, d, *J* = 13.4 Hz), 2.83 (1H, A part of ABq, *J* = 13.6 Hz), 2.96 (1H, B part of ABq, *J* = 13.6 Hz), 3.33 (6H, s), 3.58 (1H, A' part of ABq, *J* = 9.6 Hz), 3.60 (1H, A'' part of ABq, *J* = 9.3 Hz), 3.68 (1H, B' part of ABq, *J* = 9.6 Hz), 3.69 (1H, B'' part of ABq, *J* = 9.3 Hz), 3.88–3.98 (4H, m), 4.22 (1H, br s), 4.56 (2H, s), 4.57 (2H, s); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –4.4 ($CH_3$), –3.6 ($CH_3$), 18.2 (C), 26.1 ($CH_3$, 3 carbons), 29.1 ($CH_2$), 30.7 ($CH_2$), 32.0 ($CH_2$), 41.5 (CH), 43.5 (C), 46.2 ($CH_2$), 55.3 ($CH_3$), 55.4 ($CH_3$), 64.2 ($CH_2$), 64.3 ($CH_2$), 67.0 (CH), 69.6 ($CH_2$), 70.5 ($CH_2$), 96.9 ($CH_2$), 97.0 ($CH_2$), 109.6 (C); EIMS *m*/*z* (relative intensity) 460 ($M^+$+1, 48), 418 (73), 330 (24), 315 (32), 201 (40), 193 (62), 132 (96), 99 (90), 73 (93), 45 (100); HRMS Calcd for $C_{22}H_{45}NO_7Si$ [$M^+$] 463.2965, found 463.2954. Anal. Calcd for $C_{22}H_{45}NO_7Si$: C, 56.99; H, 9.78; N, 3.02. Found: C, 56.73; H, 9.61; N, 3.01.

**2-[({2-((7*S**,8*S**)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,4-dioxaspiro[4.5]dec-7-yl)-3-(methoxymethoxy)-2-[(methoxymethoxy)methyl]propyl}amino)methyl]phenol (33).** To a stirred ice-cold solution of **32** (1.90 g, 4.10 mmol) in EtOH (20 mL) was added salicylaldehyde (550 mg, 4.51 mmol), and the reaction mixture was allowed to warm to rt. After being stirred at rt for 30 min, the mixture was cooled to 0 °C and sodium borohydride (310 mg, 4.51 mmol) was added. The mixture was stirred at rt for 30 min, added water (20 mL), and extracted with $Et_2O$ (3 x 50 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 1000:9:1) to give **33** (2.29 g, 98%)

as a colorless oil: IR (neat) 3317 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.48–1.83 (4H, m), 1.89 (2H, t, *J* = 12.9 Hz), 2.12 (1H, d, *J* = 12.9 Hz), 2.82 (1H, A part of ABq, *J* = 11.7 Hz), 2.94 (1H, B part of ABq, *J* = 11.7 Hz), 3.31 (3H, s), 3.33 (3H, s), 3.57 (1H, A' part of ABq, *J* = 9.7 Hz), 3.65 (1H, A'' part of ABq, *J* = 9.7 Hz), 3.74 (1H, B'' part of ABq, *J* = 9.7 Hz), 3.75 (1H, B' part of ABq, *J* = 9.7 Hz), 3.86–4.00 (6H, m), 4.23 (1H, br s), 4.54–4.60 (4H, m), 6.75 (1H, td, *J* = 7.4, 1.1 Hz), 6.81 (1H, dd, *J* = 8.0, 1.0 Hz), 6.97 (1H, dd, *J* = 7.4, 1.2 Hz), 7.14 (1H, td, *J* = 7.7, 1.6 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.4 ($CH_3$), –3.7 ($CH_3$), 18.2 (C), 26.1 ($CH_3$, 3 carbons), 29.1 ($CH_2$), 30.7 ($CH_2$), 31.8 ($CH_2$), 41.4 (CH), 42.8 (C), 53.5 ($CH_2$), 55.4 ($CH_3$, 2 carbons), 64.3 ($CH_2$, 2 carbons), 66.9 (CH), 69.7 ($CH_2$), 70.6 ($CH_2$), 96.9 ($CH_2$, 2 carbons), 109.4 (C), 116.3 (CH), 118.8 (CH), 123.2 (C), 128.2 (CH), 128.6 (CH), 158.4 (C); EIMS *m*/*z* (relative intensity) 570 ($M^+$+1, 24), 524 (5), 464 (2), 418 (2), 299 (24), 238 (84), 136 (100), 107 (58), 45 (12); HRMS calcd for $C_{29}H_{51}NO_8Si$ [$M^+$] 569.3384, found 569.3389. Anal. Calcd for $C_{29}H_{51}NO_8Si$: C, 61.13; H, 9.02; N, 2.46. Found: C, 60.82; H, 8.87; N, 2.36.

**(1*S**,13*R**,14*S**)-14-{[*tert*-Butyl(dimethyl)silyl]oxy}-12,12-bis[(methoxymethoxy)methyl]-2-oxa-10-azatetracyclo[11.3.1.0$^{1,10}$.0$^{3,8}$]heptadeca-3,5,7-triene (35).** To a solution of **33** (1.00 g, 1.76 mmol) in acetone–water (5:1, 24 mL) was added pyridinium *p*-toluenesulfonate (4.42 g, 17.6 mmol), and the mixture was heated under reflux for 48 h. After cooling to rt, water (30 mL) was added. The mixture was extracted with $CHCl_3$ (3 x 30 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **35** (670 mg, 75%) as colorless needles: mp 92.5–93.0 °C; IR (KBr) 3427, 2936, 2884 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.56 (1H, td, *J* = 14.0, 6.8 Hz), 1.75–1.83 (2H, m), 1.91 (1H, qd, *J* = 13.5, 5.9 Hz), 2.25 (1H, dt, *J* = 13.0, 3.5 Hz), 2.42 (1H, dt, *J* = 14.0, 3.7 Hz), 2.50 (1H, br d, *J* = 2.9 Hz), 2.98 (1H, A part of ABq, *J* = 12.8 Hz), 3.03 (1H, B part of ABq, *J* = 12.8 Hz), 3.34 (3H, s), 3.35 (3H, s), 3.72 (1H, A' part of ABq, *J* = 10.2 Hz), 3.76 (2H, s), 3.78 (1H, A'' part of ABq, *J* = 9.8 Hz), 3.98 (1H, B'' part of ABq, *J* = 9.8 Hz), 4.06 (1H, B' part of ABq, *J* = 10.2 Hz), 4.08–4.14 (1H, m), 4.58 (2H, s), 4.63 (2H, s), 6.76 (1H, d, *J* = 8.1 Hz), 6.84 (1H, t, *J* = 7.4 Hz), 6.99 (1H, d, *J* = 7.4 Hz), 7.09 (1H, t, *J* = 7.6 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.9 ($CH_3$), –4.7 ($CH_3$), 18.0 (C), 25.9 ($CH_3$, 3 carbons), 27.8 ($CH_2$), 31.3 ($CH_2$), 36.3 ($CH_2$), 38.4 (CH), 42.4 (C), 49.5 ($CH_2$), 55.0 ($CH_3$), 55.2 ($CH_3$), 58.6 ($CH_2$), 68.5 ($CH_2$), 71.0 ($CH_2$), 74.9 ($CH_2$), 86.0 (C), 96.8 ($CH_2$), 96.9 ($CH_2$), 116.7 (CH), 119.9 (C), 120.0 (CH), 126.6 (CH), 127.7 (CH), 151.8 (C); EIMS *m*/*z* (relative intensity) 507 ($M^+$, 8), 462 (16), 432 (4), 364 (8), 335 (16), 334 (100), 330 (4), 258 (6). Anal. Calcd for $C_{27}H_{45}NO_6Si$: C, 63.87; H, 8.93; N, 2.76. Found: C, 63.67; H, 8.87; N, 2.74.

**2-({(4*S**,5*R**,6*S**)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-(hydroxymethyl)-4-[(methoxymethoxy)-methyl]-2-azabicyclo[3.3.1]non-2-yl}methyl)phenol (37).** Aluminum chloride (493 mg, 3.70 mmol) was added to a stirred ice-cold suspension of lithium aluminum hydride (421 mg, 11.1 mmol) in $Et_2O$ (30 mL) under argon atmosphere. After being stirred at rt for 5 min, a solution of **35** (1.88 g, 3.70 mmol) in $Et_2O$ (7.0 mL) was added to the mixture and the stirring was continued at rt for 10 h. The reaction mixture was quenched by addition of 10% aqueous NaOH (0.8 mL). The mixture was filtered through celite and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 1000:9:1) to give **37** (1.44 g, 84%) as a colorless oil: IR (neat) 3476 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.35 (1H, qd, *J* = 11.0, 4.2 Hz), 1.47 (1H, dt, *J* = 13.6, 2.6 Hz), 1.79–1.88 (2H, m), 2.06 (1H, br d, *J* = 2.9 Hz), 2.20 (2H, br d, *J* = 13.9 Hz), 2.79 (1H, A part of ABq, *J* = 12.8 Hz), 2.84 (1H, br s), 2.88 (1H, B part of ABq, *J* = 12.8 Hz), 3.32 (3H, s), 3.78–3.93 (6H, m), 3.96 (1H, td, *J* = 9.0, 3.9 Hz), 4.54 (2H, s), 6.76 (1H, td, *J* = 7.4, 1.1 Hz), 6.80 (1H, dd, *J* = 8.0, 0.8 Hz), 6.97 (1H, dd, *J* = 7.4, 1.1 Hz), 7.15 (1H, td, *J* = 7.7, 1.5 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.8 ($CH_3$), –4.7 ($CH_3$), 18.0 (C), 22.8 ($CH_2$), 25.9 ($CH_3$, 3 carbons), 31.1 ($CH_2$), 32.5 ($CH_2$), 35.5 (CH), 42.6 (C), 49.6 (CH), 54.1 ($CH_2$), 55.4 ($CH_3$), 58.7 ($CH_2$), 66.2 ($CH_2$), 73.6 ($CH_2$), 75.1 (CH), 96.9 ($CH_2$), 115,9 (CH), 119.0 (CH), 121.3 (C), 128.4 (CH), 128.7 (CH), 158.3 (C); EIMS *m*/*z* (relative intensity) 465 ($M^+$, 64), 408 (16), 376 (8), 331 (8), 292 (100), 200 (4), 107 (22), 57 (16); HRMS calcd for $C_{25}H_{43}NO_5Si$ [$M^+$] 465.2911, found 465.2926.

**{(1*R**,4*S**,5*R**,6*S**)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(methoxymethoxy)methyl]-2-azabicyclo-[3.3.1]non-4-yl}methanol (38).** A solution of *N*-(2-hydroxyphenyl)methyl compound **37** (3.85 g, 8.27 mmol) in MeOH (80 mL) was hydrogenated ($H_2$, 1 atm) over Pd–C (10%, 3.85 g) for 48 h. The mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 50:9:1) to give **38** (2.56 g, 86%) as white crystals: mp 98.0–99.0 °C; IR (KBr) 3289, 3124 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.88 (9H, s), 1.34 (1H, br d, *J* = 13.5 Hz), 1.69–2.09 (6H, m), 2.43 (2H, br s), 2.96 (1H, br s), 3.00 (1H, A part of ABq, *J* = 14.0 Hz), 3.23 (1H, B part of ABq, *J* = 14.0 Hz), 3.34 (3H, s), 3.74 (1H, A' part of ABq, *J* = 10.0 Hz), 3.80 (2H, s), 3.90 (1H, B' part of ABq, *J* = 10.0 Hz), 3.92–3.98 (1H, m), 4.55 (2H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.8 ($CH_3$), –4.7 ($CH_3$), 18.0 (C), 25.9 ($CH_3$, 3 carbons), 31.1 ($CH_2$), 31.8 ($CH_2$), 32.8 ($CH_2$), 37.1 (CH), 41.4 (C), 45.6 (CH), 46.8 ($CH_2$), 55.3 ($CH_3$), 67.3 ($CH_2$), 75.1 ($CH_2$), 75.7 (CH), 96.9 ($CH_2$); EIMS *m*/*z* (relative intensity) 360 ($M^+$+1, 92), 314 (16), 302 (20), 279 (80), 266 (100), 224 (12), 186 (36). Anal. Calcd for $C_{18}H_{37}NO_4Si$: C, 60.12; H, 10.37; N, 3.90. Found: C, 60.01; H, 10.35; N, 3.87.

***tert*-Butyl (1*R**,4*S**,5*R**,6*S**)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-(hydroxymethyl)-4-[(methoxymethoxy)methyl]-2-azabicyclo[3.3.1]nonane-2-carboxylate (39).** To a stirred ice-cold solution of **38** (920 mg, 2.56 mmol) in dioxane–0.5 M NaOH solution (1:1, 10.4 mL) was added di-*tert*-butyl dicarbonate (615 mg, 2.82 mmol). After 30 min, water (10 mL) was added and the mixture was extracted with $Et_2O$ (3 x 20 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silca gel (hexane–EtOAc, 5:1) to give **39** (1.17 g, 99%) as white crystals: mp 98.5–99.8 °C; IR (KBr) 3475, 1662 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 1.40 (1H, br t, *J* = 14.1 Hz), 1.44 (9H, s), 1.56–1.91 (6H, m), 2.59 and 2.66 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 3.26 (1H, t, *J* = 15.0 Hz), 3.35 and 3.36 (total 3H, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 3.56–3.75 (3H, m), 3.84–3.97 (3H, m), 4.04 and 4.21 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 4.56 (2H, br s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.8 ($CH_3$), –4.7 ($CH_3$), 18.1 (C), 25.9 ($CH_3$, 3 carbons), 28.5 ($CH_3$, 3 carbons), 29.2 ($CH_2$), 29.9 and 30.7 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 31.3 ($CH_2$), 35.0 and 35.6 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 41.6 and 41.7 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 44.4 and 45.4 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 46.2 and 46.5 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 55.4 ($CH_3$), 66.4 ($CH_2$), 73.1 and 73.3 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 75.1 (CH), 79.4 and 79.5 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 96.9 ($CH_2$), 155.6 (C); EIMS *m*/*z* (relative intensity) 460 ($M^+$+1, 7), 379 (6), 323 (8), 310 (100), 270 (14), 266 (34), 240 (8). Anal. Calcd for $C_{23}H_{45}NO_6Si$: C, 60.09; H, 9.87; N, 3.05. Found: C, 59.93; H, 9.80; N, 3.07.

***tert*-Butyl (1*R**,4*S**,5*R**,6*S**)-4-[(Benzyloxy)methyl]-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-[(methoxymethoxy)methyl]-2-azabicyclo[3.3.1]nonane-2-carboxylate (40).** To a stirred ice-cold solution of **39** (1.93 g, 4.20 mmol) in DMF (17 mL) were added NaH (672 mg, 16.8 mmol), tetrabutylammonium iodide (155 mg, 0.42 mmol), and benzyl bromide (1.08 g, 6.31 mmol). After being stirred at rt for 8 h, water (30 mL) was added carefully and the mixture was extracted with $Et_2O$ (3 x 30 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) to give **40** (2.01 g, 87%) as white crystals: mp 81.1–83.1 °C; IR (KBr) 1691 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.07 (3H, s), 0.90 (9H, s), 1.32 (1H, br t, *J* = 14.9 Hz), 1.44 (9H, s), 1.55–2.00 (5H, m), 2.32 (1H, br s), 3.29–4.02 (10H, m, including total 3H at δ 3.29 and 3.31, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 4.03 and 4.20 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s),

4.43–4.58 (4H, m), 7.30–7.40 (5H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –4.8 ($CH_3$), –4.7 ($CH_3$), 18.0 (C), 25.9 ($CH_3$, 3 carbons), 28.5 ($CH_3$, 3 carbons), 28.9 ($CH_2$), 30.1 and 30.8 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 31.4 ($CH_2$), 34.9 and 35.3 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 41.9 (C), 44.4 and 45.3 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 47.8 and 48.2 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 55.0 ($CH_3$), 70.2 ($CH_2$), 71.0 ($CH_2$), 73.1 ($CH_2$), 75.1 (CH), 79.3 and 79.4 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 96.7 ($CH_2$), 127.1 (CH, 2 carbons), 127.2 (CH), 128.2 (CH, 2 carbons), 139.0 (C), 155.7 (C); EIMS *m/z* (relative intensity) 550 ($M^+$+1, 32), 462 (10), 448 (12), 379 (100), 366 (40), 311 (20), 310 (92), 266 (40). Anal. Calcd for $C_{30}H_{51}NO_6Si$: C, 65.54; H, 9.35; N, 2.55. Found: C, 65.37; H, 9.28, N; 2.55.

***tert*-Butyl (1*R**,4*S**,5*R**,6*S**)-4-[(Benzyloxy)methyl]-6-hydroxy-4-[(methoxymethoxy)methyl]-2-aza-bicyclo[3.3.1]nonane-2-carboxylate (41).** Tetrabutylammonium fluoride (1.0 M solution in THF, 36.0 mL, 36.0 mmol) was added to a stirred solution of **40** (1.98 g, 3.60 mmol) in THF (36 mL) at rt and the stirring was continued at rt for 48 h. Water (50 mL) was added and the mixture was extracted with $Et_2O$ (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give **41** (1.55 g, 99%) as white crystals: mp 78.0–79.5 °C; IR (KBr) 3456, 1691 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.37 (1H, t, *J* = 13.3 Hz), 1.43 and 1.44 (total 9H, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 1.55–1.70 (1H, m), 1.82–1.99 (4H, m), 2.13 and 2.24 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 3.21–3.49 (6H, m, including 3H at δ 3.35, s), 3.65–3.97 (5H, m), 4.05 and 4.25 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 4.41–4.53 (2H, m), 4.63 (2H, s), 7.26–7.33 (5H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 28.5 ($CH_3$, 3 carbons), 29.6 ($CH_2$), 29.8 and 30.5 ($CH_2$, total 1 carbon, respectively, in ca 1:1 due to the carbamate rotamers), 30.4 ($CH_2$), 36.4 (CH), 41.0 and 41.1 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 43.9 (CH), 45.1 ($CH_2$), 45.2 (CH), 55.8 ($CH_3$), 70.3 and 71.3 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 72.0 ($CH_2$), 73.3 ($CH_2$), 74.1 (CH), 79.4 and 79.5 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 97.0 ($CH_2$), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH, 2 carbons), 138.4 (C), 155.6 and 155.7 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers); EIMS *m/z* (relative intensity) 436 ($M^+$+1, 20), 348 (10), 265 (20), 209 (20), 196 (64), 152 (30), 91 (78), 57 (100); HRMS calcd for $C_{24}H_{37}NO_6$ [$M^+$] 435.2621, found 435.2614. Anal. Calcd for $C_{24}H_{37}NO_6$: C, 66.18; H, 8.56; N, 3.22. Found: C, 65.91; H, 8.54, N; 2.96.

***tert*-Butyl (1*R**,4*S**,5*R**)-4-[(Benzyloxy)methyl]-4-[(methoxymethoxy)methyl]-6-oxo-2-azabicyclo-[3.3.1]nonane-2-carboxylate (42).** To a stirred solution of **41** (1.40 g, 3.21 mmol) in $CH_2Cl_2$ (30 mL) was added pyridinium chlorochromate (1.40 g, 6.42 mmol), and the stirring was continued at rt for 1.5 h. $MgSO_4$ (5.6 g) and $Et_2O$ (30 mL) were added and stirred for 10 min. The mixture was filtered through celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **42** (1.38 g, 99%) as white crystals: mp 71.6–73.5 °C; IR (KBr) 1692 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.64–1.75 (1H, br m), 1.96 (1H, br s), 2.05–2.17 (2H, m), 2.46–2.82 (3H, m), 3.24–3.39 (5H, m), 3.41–3.53 (3H, m), 3.83 (1H, d, *J* = 14.5 Hz), 4.30 and 4.40 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 4.41–4.55 (4H, m), 7.26–7.35 (5H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 28.5 ($CH_3$, 3 carbons), 30.2 ($CH_2$), 31.0 ($CH_2$), 39.1 ($CH_2$), 40.2 (C), 43.6 and 44.9 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 44.0 and 44.2 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 46.9 and 47.4 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 55.4 ($CH_3$), 69.6 ($CH_2$), 70.5 and 70.7 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 73.4 ($CH_2$), 80.1 (C), 96.9 ($CH_2$), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128,4 (CH, 2 carbons), 138.1 (C), 155.5 (C), 211.5 (C); EIMS *m*/*z* (relative intensity) 434 ($M^+$, 15), 376 (10), 332 (25), 263 (100), 207 (50), 194 (78), 150 (23), 91 (18), 57 (18). Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.14; N, 3.23. Found: C, 66.34; H, 8.13; N, 3.29.

***tert*-Butyl (1*R**,4*S**,5*S**)-4-[(Benzyloxy)methyl]-4-[(methoxymethoxy)methyl]-6-methylene-2-aza-bicyclo[3.3.1]nonane-2-carboxylate (43).** To a stirred ice-cold solution of **42** (1.10 g, 2.54 mmol) in THF (8 mL) was added Tebbe reagent (0.5 M in toluene, 7.62 mL, 3.81 mmol) as dropwise under argon atmosphere. The mixture was allowed to warm to rt and stirred at the same temperature for 1 h. The reaction mixture was diluted with $Et_2O$ (30 mL), and 0.1 M NaOH solution was added until gas evolution ceased. $MgSO_4$ (5.0 g) was added and the mixture was filtered through celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to give **43** (800 mg, 73%) as white crystals: mp 108.5–109.7 °C; IR (KBr) 1690, 1645 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.48 (1H, br s), 1.57–1.72 (1H, m), 1.84–2.06 (2H, m), 2.28–2.39 (1H, m), 2.40–2.53 (1H, m), 2.65 (1H, br d, *J* = 12.4 Hz), 3.07 (1H, A part of ABq, *J* = 14.5 Hz), 3.22–3.45 (4H, m, including total 3H at δ 3.29 and 3.31, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 3.40–3.51 (2H, m), 3.52–3.63 (1H, m), 3.74 (1H, B part of ABq, *J* = 14.5 Hz), 4.18 and 4.37 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 4.46–4.60 (4H, m), 4.76 (2H, m), 7.26–7.37 (5H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 28.5 ($CH_3$, 3 carbons), 29.9 ($CH_2$), 30.7 ($CH_2$), 31.4 and 32.2 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate

rotamers), 38.1 and 38.7 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 39.4 and 39.7 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 44.7 and 45.9 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 46.3 and 46.4 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 55.1 ($CH_3$), 69.5 ($CH_2$), 70.2 and 70.7 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 73.2 and 73.3 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 79.5 (C), 96.8 ($CH_2$), 111.3 ($CH_2$), 127.3 (CH), 127.5 (CH, 2 carbons), 128.3 (CH, 2 carbons), 138.7 (C), 147.5 (C), 155.8 (C); EIMS *m*/*z* (relative intensity) 432 ($M^+$+1, 2.3), 344 (1.6), 261 (2), 192 (13), 148 (6), 91 (44), 57 (100); HRMS calcd for $C_{25}H_{37}NO_5$ [$M^+$] 431.2672, found 431.2664. Anal. Calcd for $C_{25}H_{37}NO_5$: C, 69.58; H, 8.64; N, 3.25. Found: C, 69.26; H, 8.45, N; 3.22.

***tert*-Butyl (1*R**,4*S**,5*S**,6*S**)-4-[(Benzyloxy)methyl]-6-(hydroxymethyl)-4-[(methoxymethoxy)-methyl]-2-azabicyclo[3.3.1]nonane-2-carboxylate (44).** To a stirred ice-cold solution of **43** (200 mg, 0.46 mmol) in THF (3 mL) was added 9-BBN (0.5 M solution in THF, 1.39 mL, 0.70 mmol), and the stirring was continued at rt for 3 h. The mixture was cooled to ice-cold temperature, then the reaction was quenched by addition of EtOH (1 mL). To the mixture were added 3.0 M NaOH (0.30 mL, 0.90 mmol) and 30% $H_2O_2$ (0.3 mL) at rt. After 1 h, water (10 mL) was added, and the mixture was extracted with $Et_2O$ (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 1:1) to give **44** (190 mg, 91%) as a colorless oil: IR 3454, 1682 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.42 and 1.45 (total 9H, respectively, in ca. 3:2 due to the carbamate rotamers, each s), 1.50–2.13 (8H, m), 2.90 (1H, d, *J* = 14.0 Hz), 3.18 and 3.28 (total 1H, respectively, in ca. 2:3 due to the carbamate rotamers, each br s), 3.31–3.38 (4H, m, including total 3H at δ 3.35 and 3.36, respectively, in ca. 2:3 due to the carbamate rotamers, each s), 3.48–3.60 (3H, m), 3.61–3.72 (2H, m), 3.78–3.88 (1H, m), 4.15 and 4.36 (total 1H, respectively, in ca. 2:3 due to the carbamate rotamers, each s), 4.43–4.54 (2H, m), 4.56–4.64 (2H, m), 7.26–7.36 (5H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 24.3 and 24.4 ($CH_2$, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 28.5 ($CH_3$, 3 carbons), 28.8 (CH), 30.5 and 31.3 ($CH_2$, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 32.0 ($CH_2$), 42.0 and 42.2 (C, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 44.7 ($CH_2$), 45.2 and 46.4 (CH, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 46.7 (CH), 55.8 ($CH_3$), 67.0 ($CH_2$), 69.5 and 69.9 ($CH_2$, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 71.3 and 71.6 ($CH_2$, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 73.2 and 73.3 ($CH_2$, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 79.3 and 79.4 (C, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 97.3 ($CH_2$), 127.3 (CH), 127.4 (CH),

127.5 (CH), 128.3 (CH, 2 carbons), 138.4 and 138.5 (C, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 155.5 (C); EIMS *m*/*z* (relative intensity) 450 ($M^+$+1, 22), 350 (14), 279 (29), 210 (100), 166 (42), 91 (19), 57 (11); HRMS calcd for $C_{25}H_{39}NO_6$ [$M^+$] 449.2777, found 449.2771. Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.85; H, 8.66, N; 2.96.

***tert*-Butyl (1*R**,4*S**,5*S**,6*S**)-4-[(Benzyloxy)methyl]-6-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-methyl]-4-[(methoxymethoxy)methyl]-2-azabicyclo[3.3.1]nonane-2-carboxylate (45).** To a stirred ice-cold solution of **44** (92.0 mg, 0.20 mmol) in THF (2 mL) were added triphenylphosphine (68.2 mg, 0.26 mmol), phthalimide (38.3 mg, 0.26 mmol), and diethyl azodicarboxylate (40% in toluene, 0.10 mL, 0.26 mmol) under argon atmosphere. After being stirred at rt for 30 min, saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with $Et_2O$ (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (hexane–EtOAc, 7:1) to give **45** (85 mg, 72%) as a white amorphous solid: IR (neat) 2930, 1771, 1713, 1686 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.35–1.68 (12H, m, including 9H at δ 1.43, s), 1.70–2.04 (3H, m), 2.05–2.18 (1H, m), 2.23 and 2.31 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 3.15 and 3.18 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br d, *J* = 9.5 Hz), 3.34 (3H, s), 3.42 and 3.44 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 3.52–3.90 (6H, m), 4.09 and 4.25 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 4.44–4.57 (2H, m), 4.58–4.66 (2H, m), 7.26–7.36 (5H, m), 7.67–7.72 (2H, m), 7.81–7.86 (2H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 25.7 ($CH_2$), 28.5 ($CH_3$, 3 carbons), 30.8 and 31.4 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 32.4 ($CH_2$), 32.7 and 33.1 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 42.2 (C), 43.6 ($CH_2$), 44.2 (CH), 44.9 and 46.0 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 45.9 ($CH_2$), 55.5 ($CH_3$), 69.5 and 70.1 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 71.2 and 71.3 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 73.3 ($CH_2$), 79.3 and 79.4 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 96.9 ($CH_2$), 123.2 (CH, 2 carbons), 127.3 (CH, 2 carbons), 127.5 (CH), 128.3 (CH, 2 carbons), 132.1 (C, 2 carbons), 133.9 (CH, 2 carbons), 138.6 (C), 155.6 (C), 168.5 (C, 2 carbons); EIMS *m*/*z* (relative intensity) 579 ($M^+$+1, 2.4), 491 (8), 479 (13), 339 (78), 295 (100), 91 (58), 57 (38); HRMS calcd for $C_{33}H_{42}N_2O_7$ [$M^+$] 578.2992, found 578.2994. Anal. Calcd for $C_{33}H_{42}N_2O_7$: C, 68.49; H, 7.32; N, 4.84. Found: C, 68.26; H, 7.12; N, 4.68.

**2-{[(1*R**,4*R**,5*S**,6*S**)-4-[(Benzyloxy)methyl]-4-(hydroxymethyl)-2-azabicyclo[3.3.1]non-6-yl]-methyl}-1*H*-isoindol-1,3(2*H*)-dione (46).** To a stirred ice-cold solution of **45** (320 mg, 0.55 mmol) in

MeOH (5.5 mL) was added concentrated HCl (0.18 mL, 2.21 mmol). After being stirred at 60 °C for 8 h, the mixture was cooled to 0 °C and saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 150:9:1) to give **46** (198 mg, 83%) as white crystals: mp 161.7–162.7 °C; IR (KBr) 3462, 3060, 2911, 1769, 1710 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.42 (1H, dt, *J* = 13.3, 2.5 Hz), 1.56–1.71 (2H, m), 1.81–2.03 (3H, m), 2.11–2.23 (1H, m), 2.45 (1H, br s), 2.52 (1H, A part of ABq, *J* = 13.6 Hz), 2.98 (1H, br s), 3.10 (1H, B part of ABq, *J* = 13.6 Hz), 3.52 (1H, A' part of ABq, *J* = 9.1 Hz), 3.63 (1H, A'' part of ABq, *J* = 11.3 Hz), 3.70 (1H, B'' part of ABq, *J* = 11.3 Hz), 3.90–4.03 (3H, m, including 1H at δ 3.95, B' part of ABq, *J* = 9.1 Hz), 4.53–4.60 (2H, m), 7.27–7.39 (5H, m), 7.66–7.72 (2H, m), 7.78–7.85 (2H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 27.3 ($CH_2$), 32.0 (CH), 33.1 ($CH_2$), 33.8 ($CH_2$), 42.0 (C), 43.9 ($CH_2$), 44.3 (CH), 46.6 (CH), 46.7 ($CH_2$), 69.1 ($CH_2$), 73.7 ($CH_2$), 76.7 ($CH_2$), 123.2 (CH, 2 carbons), 127.7 (CH, 2 carbons), 127.9 (CH), 128.6 (CH, 2 carbons), 132.1 (C, 2 carbons), 133.8 (CH, 2 carbons),137.8 (C), 168.6 (C, 2 carbons); EIMS *m*/*z* (relative intensity) 345 ($M^+$+1, 5), 343 (18), 308 (14), 295 (32), 232 (28), 168 (20), 160 (52), 91 (100); HRMS calcd for $C_{26}H_{30}N_2O_4$ [$M^+$] 434.2206, found 434.2206. Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.70; H, 7.07; N, 6.30.

***tert*-Butyl (1*R**,4*R**,5*S**,6*S**)-4-[(Benzyloxy)methyl]-6-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2yl)-methyl]-4-(hydroxymethyl)-2-azabicyclo[3.3.1]nonane-2-carboxylate (47).** To a stirred ice-cold solution of **46** (198 mg, 0.46 mmol) in dioxane–0.5 M NaOH (1:1, 4.6 mL) was added di-*tert*-butyl dicarbonate (131 mg, 0.60 mmol) and the stirring was continued at rt for 20 min. Water (4.6 mL) was added and the mixture was extracted with $Et_2O$ (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **47** (186 mg, 76%) as a colorless oil: IR (neat) 3466, 2929, 1770, 1712, 1685, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.63–1.93 (5H, m), 2.15 (1H, br s), 2.44 and 2.55 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each s), 2.85 and 2.95 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 3.02 and 3.10 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each d, *J* = 14.4 Hz), 3.43–3.52 (2H, m), 3.71–3.75 (3H, m), 3.95 and 4.26 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 3.96–4.09 (2H, m), 4.48 (1H, A part of ABq, *J* = 12.1 Hz), 4.58 (1H, B part of ABq, *J* = 12.1 Hz), 7.31–7.35 (5H, m), 7.68–7.72 (2H, m), 7.81–7.84 (2H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 25.8 ($CH_2$), 28.4 ($CH_3$, 3 carbons), 30.7 and 31.3 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 30.8 (CH), 31.5 (CH), 32.0 ($CH_2$), 41.8 and 42.1 (C, total 1 carbon, respectively, in ca.1:1 due

to the carbamate rotamers), 43.5 ($CH_2$), 43.7 (CH), 45.0 and 46.2 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 45.5 and 46.0 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 68.0 and 68.8 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 73.6 and 73.7 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 75.9 ($CH_2$), 79.5 and 79.6 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 123.2 (CH, 2 carbons), 127.6 (CH), 127.9 (CH), 128.5 (CH, 2 carbons), 133.9 (CH, 2 carbons), 132.0 (C, 2 carbons), 137.52 and 137.56 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 155.4 and 155.5 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 168.6 (C, 2 carbons); HRMS (ESI) calcd for $C_{31}H_{39}N_2O_6$ $[M+H]^+$ 535.2808, found 5235.2784.

***tert*-Butyl (1*R**,4*R**,5*S**,6*S**)-6-(Aminomethyl)-4-[(benzyloxy)methyl]-4-(hydroxymethyl)-2-azabicyclo[3.3.1]nonane-2-carboxylate (48).** To a stirred solution of **47** (220 mg, 0.41 mmol) in EtOH (4.1 mL) was added hydrazine monohydrate (80.1 μL, 0.82 mmol). After being stirred at 70 °C for 2.5 h, the mixture was cooled to rt and $Et_2O$ (10 mL) was added. The resulting precipitates were filtered off, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH–concentrated $NH_4OH$, 150:9:1) to give **48** (159 mg, 96%) as a colorless oil: IR (neat) 3360, 3293, 3192 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.41–1.59 (10H, m, including 9H at δ 1.43, s), 1.59–1.66 (3H, m), 1.90–2.10 (4H, m), 2.72–2.84 (3H, m), 3.13 (2H, br s), 3.49 (2H, m), 3.57 and 3.66 (total 2H, respectively, in ca. 2:3 ratio due to the carbamate rotamers, each d, $J$ = 11.8 Hz), 3.79 and 3.90 (total 1H, respectively, in ca. 2:3 ratio due to the carbamate rotamers, each d, $J$ = 13.9 Hz), 4.35 and 4.47 (total 1H, respectively, in ca. 2:3 ratio due to the carbamate rotamers, each br s), 4.49 (1H, A part of ABq, $J$ = 12.2 Hz), 4.56 (1H, B part of ABq, $J$ = 12.2 Hz), 7.22–7.31 (5H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 26.4 and 26.8 ($CH_2$, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 27.8 and 28.0 (CH, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 28.5 ($CH_3$, 3 carbons), 30.9 ($CH_2$), 31.7 ($CH_2$), 42.9 and 43.3 (C, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 44.7 ($CH_2$), 45.1 (CH), 46.3 (CH), 46.8 ($CH_2$), 64.8 and 65.9 ($CH_2$, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 72.1 ($CH_2$), 73.4 ($CH_2$), 79.4 (C), 127.1 (CH), 127.25 (CH), 127.33 (CH), 128.2 (CH, 2 carbons), 138.8 and 138.9 (C, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 155.7 (C); EIMS *m*/*z* (relative intensity) 405 ($M^+$+1, 76), 349 (23), 278 (31), 265 (48), 209 (70), 148 (54), 91 (98), 57 (100); HRMS (ESI) calcd for $C_{23}H_{37}N_2O_4$ $[M+H]^+$ 405.2753, found 405.2744.

***tert*-Butyl (1*R**,4*R**,5*S**,6*S**)-6-({[(Benzyloxy)carbonyl]amino}methyl)-4-[(benzyloxy)methyl]-4-(hydroxymethyl)-2-azabicyclo[3.3.1]nonane-2-carboxylate (49).** To a stirred ice-cold mixture of **48**

(12.0 mg, 29.7 μmol) in dioxane–water (1:1, 0.3 mL) were added $Na_2CO_3$ (3.46 mg, 32.7 μmol) and benzyloxycarbonyl chloride (5.65 mg, 33.1 μmol). After being stirred at rt for 30 min, water (5 mL) was added and the mixture was extracted with $Et_2O$ (3 x 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **49** (11.2 mg, 70%) as a colorless oil: IR (neat) 3413, 2928, 1777, 1686 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.53–1.67 (3H, m), 1.89 (2H, m), 2.11 (1H, m), 2.29 and 2.39 (total 1H, respectively, in ca. 2:3 due to the carbamate rotamers, each br s), 2.87–3.01 (2H, m), 3.00 and 3.18 (total 1H, respectively, in ca. 2:3 due to the carbamate rotamers, each br s), 3.40 (2H, m), 3.55 (1H, t, *J* = 14.5 Hz), 3.58 (1H, dd, *J* = 2.4, 14.5 Hz), 3.65 (2H, m), 4.14 and 4.32 (total 1H, respectively, in ca. 3:2 due to the carbamate rotamers, each s), 4.45–4.57 (2H, m), 5.05 (1H, A part of ABq, *J* = 12.7 Hz), 5.13 (1H, B part of ABq, *J* = 12.7 Hz), 6.16 and 6.29 (total 1H, respectively, in ca. 2:3 due to the carbamate rotamaers, each d, *J* = 5.0 Hz), 7.27–7.39 (10H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 26.0 ($CH_2$), 26.6 and 27.5 (CH, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 28.5 ($CH_3$, 3 carbons), 30.7 ($CH_2$), 31.4 ($CH_2$), 41.9 and 42.3 (C, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 43.4 and 43.7 (CH, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 45.4 ($CH_2$), 45.8 and 46.0 ($CH_2$, total 1 carbon, respectively, in ca. 2:3 due to the carbamate rotamers), 46.6 (CH), 66.4 ($CH_2$), 68.4 ($CH_2$), 69.5 ($CH_2$), 73.6 and 73.7 ($CH_2$, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 79.7 (C), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH, 3 carbons), 128.6 (CH, 3 carbons), 136.9 (C), 137.3 and 137.4 (C, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 155.3 and 155.7 (C, total 1 carbon, respectively, in ca. 3:2 due to the carbamate rotamers), 156.6 (C); HRMS (ESI) calcd for $C_{31}H_{42}N_2O_6Na$ $[M+H]^+$ 561.2941, found 561.2931.

**6-Benzyl-2-*tert*-butyl (1*R**,4*S**,8*S**,9*S**)-4-[(Benzyloxy)methyl]-2,6-diazabicyclo[6.2.2.0$^{4,9}$]dodecane-2,6-dicarboxylate (50).** To a stirred ice-cold solution of **49** (10.0 mg, 18.6 μmol) in $CH_2Cl_2$ were added $Et_3N$ (2.26 mg, 22.3 μmol) and methanesulfonyl chloride (2.35 mg, 20.5 μmol) at rt under argon atmosphere. After being stirred at rt for 30 min, water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in THF (0.4 mL), *t*-BuOK (5.20 mg, 46.5 μmol) was added at 0 °C, and stirring was continued at rt for 1 h. Water (5 mL) was added and the mixture was extracted with $Et_2O$ (3 x 10 mL). The combined extracts were concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 5:1) to give **50** (7.0 mg, 72%) as a pale yellow oil: IR (neat) 3030, 2926, 2869, 1687 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.36 (1H, br t *J* = 12.2 Hz), 1.44 (9H, s), 1.49–1.79 (3H, m), 1.80-2.08 (4H, m), 2.79–3.03 (2H, m), 3.08–3.70 (4H, m),

3.77–4.14 (2H, m), 4.09 and 4.29 (total 1H, respectively, in ca. 1:1 due to the carbamate rotamers, each br s), 4.40–4.53 (2H, m), 5.14 (2H, br s), 7.24–7.40 (10H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 24.2 ($CH_2$), 28.6 ($CH_3$, 3 carbons), 28.9 (CH), 29,8 ($CH_2$), 30.5 ($CH_2$), 31.0 and 31.7 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 34.3 (CH), 36.8 and 37.2 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 44.8 (CH), 46.0 ($CH_2$), 49.4 and 50.0 ($CH_2$, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 67.2 ($CH_2$), 73.3 ($CH_2$), 79.6 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH). 128.4 (CH), 128.5 (CH, 3 carbons), 136.9 (C), 138.3 (C), 155.8 (C), 156.4 (C); EIMS *m/z* (relative intensity) 521 ($M^+$+1, 11), 419 (68), 321 (75), 265 (100), 221 (51), 91 (68), 57 (24); HRMS (ESI) calcd for $C_{31}H_{41}N_2O_5$ $[M+H]^+$ 521.3015, found 521.2988.

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