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Synthesis of (−)-TAN1251A using 4-hydroxy-L-proline as a chiral source

Shinji Nagumo,* Aoi Matoba, Yusuke Ishii, Syunji Yamaguchi, Noriaki Akutsu, Hideto Nishijima, Atsushi Nishida† and Norio Kawahara*

Hokkaido College of Pharmacy, Katuraoka 7-1, Otaru 047-0264, Japan

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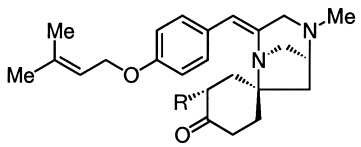
Abstract—A new synthetic route of (−)-TAN1251A possessing an antimuscarinic activity was developed on the basis of alkylation of a *trans*-4-hydroxy-L-proline derivative and the subsequent construction of an azaspiro ring as key steps. © 2002 Published by Elsevier Science Ltd.

TAN1251A and B are alkaloids isolated from a culture of *Penicillium thomii* RA-89 (Fig. 1).[1] These compounds exhibit cholinergic activity and cause acetylcholine-induced contraction of the guinea-pig ileum (ED_{50}: 8.0 and 10.0 nM, respectively). The affinity of TAN1251B to a muscarinic acetylcholine receptor is stronger than that of atropine. TAN1251A shows selective inhibition toward the M_1 subtype of the muscarinic receptor. Their structural features are very interesting for organic chemists because the central tricyclic skeleton that includes a 1-azaspiro[4.5]decane ring is unique. In 1998, we reported in a preliminary communication the first total synthesis of (±)-TAN1251A.[2,3] After the publication of our report, a few groups reported total syntheses of (−)-TAN1251A in which the construction of an enantiomeric 1-azaspiro[4.5]decane skeleton was regarded as a key step. Snider et al. constructed the skeleton by a 1,3-dipolar cycloaddition of nitron in the syntheses of optically active TAN1251A, B, C and D.[4] In Wardrop's



TAN1251A (R = H)
TAN1251B (R = OH)

Figure 1.

synthesis of (−)-TAN1251A, a spiro-cyclization of *N*-methoxy-*N*-acylnitrenium ion was used for the ring construction.[5] Honda et al. also achieved the formal synthesis of (−)-TAN1251A based on the construction of the ring system by spiro-cyclization using aromatic oxidation with a hypervalent iodine reagent.[6] In all of these methods, tyrosine was used as a chiral source. Another possible chiral source of an enantiomeric 1-azaspiro[4.5]decane skeleton is *trans*-4-hydroxy-L-proline. We report here the synthesis of (−)-TAN1251A based on the alkylation of 4-hydroxyproline and the subsequent construction of a spiro-ring system by an intramolecular aldol reaction.

Scheme 1 shows our retrosynthetic analysis of (−)-TAN1251A. We have already achieved a conversion of tricyclic amide (±)-**20** into racemic TAN1251A.[2,3] Wardrop's group has also applied this synthetic route to chiral synthesis.[5] Consequently, (+)-**20** is our target molecule and can also be prepared from (+)-**16** according to our racemic route. Compound (+)-**16** should be obtainable from **10** via installation of an azide group and *N*-alkylation. Excision of the cyclohexanone ring from **10** in a retrosynthetic sense leads to aldehyde **5**, which might be easily prepared by alkylation of **1** followed by a few steps of functional group interconversion.

Alkylation of **1** with 4-iodo-1-butene was carried out by using 2.5 equiv. of LDA to afford **2a** (67%) and **2b** (15%) (Scheme 2). The stereochemical finding (**2a**/**2b**=4.5:1) surprised us because the ratio of the products had been found to be ca. 2.7:1 in the case of using LDA (1.2 equiv.).[7] The selectivity should be important for carrying out a synthetic study of TAN1251B. However, both of the products **2a** and **2b** can be used in the synthetic study of TAN1251A. Next, DIBAH reduction of **2a** was carried out to give **3a**, which was converted into **4a** by TPAP oxidation.

Keywords: (−)-TAN1251A; anti-muscarinic activity; synthesis; 1-azaspiro[4.5]decane; *trans*-4-hydroxy-L-proline.

* Corresponding authors. Tel.: +81-134-62-1842; fax: +81-134-62-5161; e-mail: nagumo@hokuyakudai.ac.jp

† Present address: Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba-shi 263-8522, Japan.

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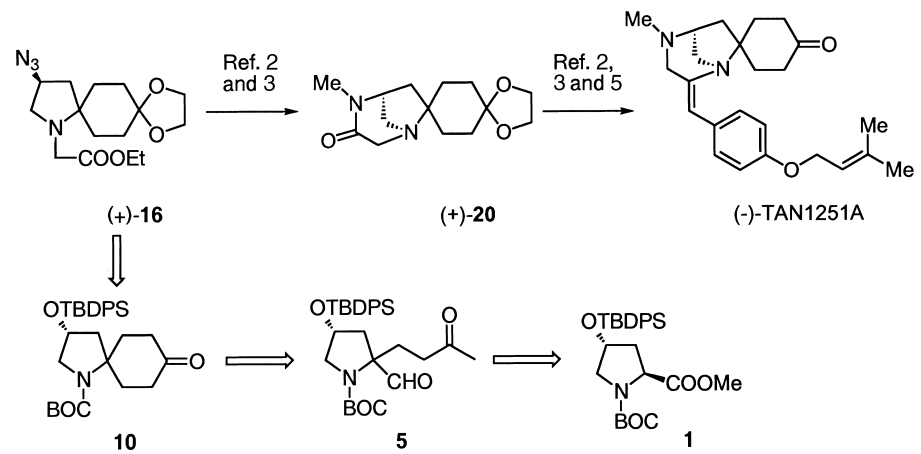
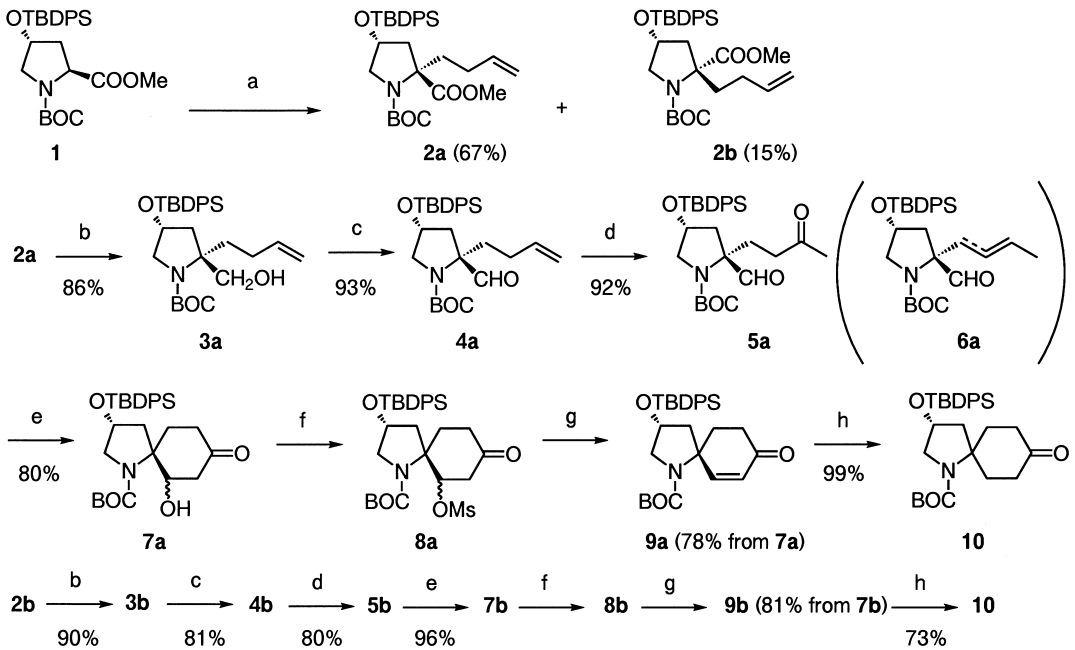


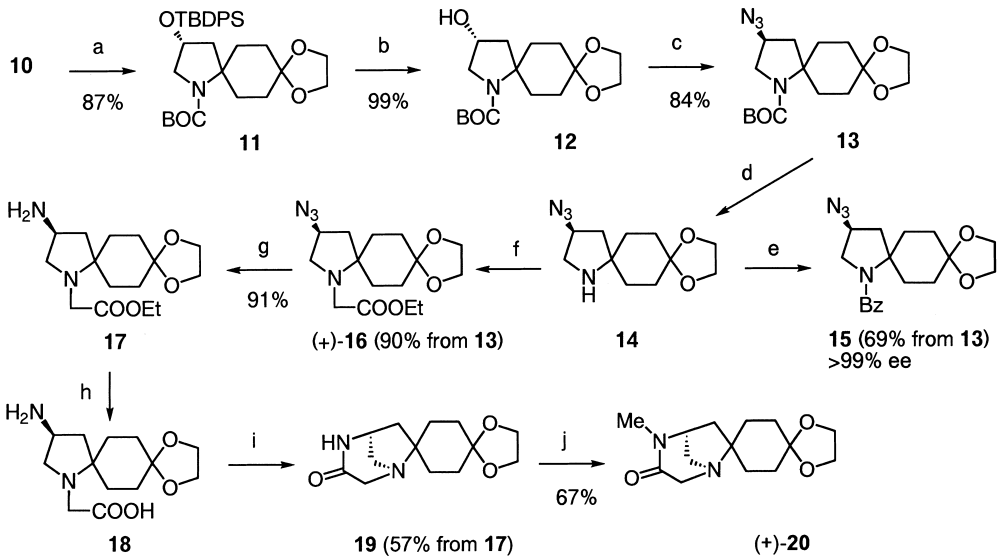
Scheme 1. Retrosynthetic route of (−)-TAN1251A.

Wacker oxidation of **4a** afforded ketone **5a** in high yield when sufficient oxygen was continuously supplied to the reaction mixture by a gas inlet tube. Otherwise, migration of a double bond occurred to give a mixture of olefinic isomers **6a**, and as a result **5a** was obtained in 62% yield. Exposure of **5a** to alkaline conditions produced aldol **7a**, which was converted to mesylate **8a**. When crude **8a** was subjected to column chromatography with silica gel, elimination occurred to give enone **9a** in 78% yield. Similarly, **2b** was successfully converted into **9b** in 45% overall yield. Catalytic hydrogenation of **9a** and **9b** was carried out by using 20% $Pd(OH)_2$–C in benzene to afford ketone **10**.

Acetalization of **10** with ethyleneglycol provided acetal **11**, which was subjected to desilylation by a conventional method to give alcohol **12** (Scheme 3). Mitsunobu-type reaction of **12** with DPPA[8] afforded azide **13** in 84% yield. In order to confirm the optical purity, **13** was subjected to removal of BOC group to give **14**, which was converted into **15** by benzoylation. The optical purity of **15** was found to be >99% ee by HPLC analysis with a chiral column. Alkylation of **14** with ethyl bromoacetate proceeded smoothly to provide ester (+)-**16** in high yield. Its ^1H and ^{13}C NMR spectroscopic data were identical with those of racemic **16**, which is a synthetic intermediate of racemic TAN1251A. Furthermore, (+)-**16** was converted into tricyclic amide (+)-**20** ($[\alpha]_D^{25}$=+18.1 ($CHCl_3$); reported:[9] $[\alpha]_D^{30}$=+15.3 ($CHCl_3$)) by the sequence of catalytic hydrogenation, hydrolysis of the ester group, lactam ring formation and methylation. Since Wardrop's group has already reported the conversion of (+)-**20** into (−)-TAN1251A using our racemic procedure, we developed a completely original route of (−)-TAN1251A.



Scheme 2. (a) LDA (2.5 equiv.), HMPA (10 equiv.), 4-iodo-1-butene, THF, −78°C; (b) DIBAH, toluene, −30°C; (c) TPAP, NMO, CH_2Cl_2; (d) $PdCl_2$, $CuCl_2$, O_2, H_2O, DMF; (e) KOH, EtOH, 0°C; (f) MsCl, Et_3N, CH_2Cl_2; (g) silica gel column chromatography; (h) 20% $Pd(OH)_2$–C, H_2, benzene.



Scheme 3. (a) $(CH_2OH)_2$, TsOH, benzene, reflux; (b) TBAF, THF; (c) DPPA, Ph_3P, DEAD, THF; (d) TFA; (e) PhCOCl, Et_3N, CH_2Cl_2; (f) $BrCH_2COOEt$, K_2CO_3, CH_3CN; (g) 5% Pd–C, H_2, MeOH; (h) LiOH, H_2O; (I) DPPA, Et_3N, DMF; (j) CH_3I, NaH, THF.

1. Experimental

1.1. General methods

The melting points were determined on Yanaco micro melting point apparatus and were uncorrected. Optical rotation was measured on JASCO DIP-370. IR spectra were recorded on JASCO FT/IR-7000 spectrometer. NMR spectra were recorded on a JEOL JNM-GX270 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. MS spectra were measured on a Hitachi M-2000 mass spectrometer. Column chromatography was carried out on Merck's Silica gel 60 (70–230 mesh ASTM).

1.1.1. *tert*-Butyl (2*S*,4*R*)-2-(but-3-enyl)-4-*tert*-butyldiphenylsilyloxy-2-hydroxymethyl-1-pyrrolidinecarboxylate (3a). To a solution of **2a** (2.06 g, 3.83 mmol) in toluene (10 ml) was added dropwise DIBAH (1 M in toluene, 9.6 ml, 9.6 mmol) at −78°C under an argon atmosphere. After being stirred for 2 h, the reaction was quenched with a small amount of H_2O and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (4:1) to give **3a** (1.67 g, 3.28 mmol, 86%) as a colorless oil. $[\alpha]_D^{23}$=+15.6 (c=1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ratio of conformers: ca. 4:1) δ: 7.70–7.60 (m, 4H), 7.48–7.34 (m, 6H), 5.96–5.78 (m, 1H), 5.17 (d, J=9.0 Hz, 1H), 5.06 (dd, J=17.3, 1.4 Hz, 1H), 4.95 (d, J=10.3 Hz, 1H), 4.40–4.30 and 4.30–4.20 (2m, 1H), 3.62–3.40 (m, 2H), 3.35 (d, J=4.4 Hz, 2H), 2.35–1.90 (m, 6H), 1.30 (s, 9H), 1.07 (s, 9H). The peak at 5.17 ppm was disappeared by addition of D_2O. ^{13}C NMR ($CDCl_3$) δ: 155.8 (s), 138.5 (d), 135.7 (d, 4C), 133.6 (s, 2C), 129.8 (d, 2C), 127.7 (d, 4C), 114.4 (t), 80.2 (s), 69.7 (d), 68.7 (t), 67.6 (s), 56.7 (t), 41.9 (t), 31.7 (t), 29.1 (t), 28.4 (q, 3C), 26.9 (q, 3C), 19.0 (s). IR (neat) cm^{-1}: 3396, 1671, 1660, 1591. EI-MS m/z: 478 (M^+-CH_2OH), 422, 378. HR-MS m/z: calcd for $C_{29}H_{40}NO_3Si$ (M^+-CH_2OH) 478.2775; found 478.2750.

1.1.2. *tert*-Butyl (2*R*,4*R*)-2-(but-3-enyl)-4-*tert*-butyldiphenylsilyloxy-2-hydroxymethyl-1-pyrrolidinecarboxylate (3b). $[\alpha]_D^{23}$=+13.6 (c=1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.66–7.63 (m, 4H), 7.48–7.26 (m, 6H), 5.70 (ddt, J=16.85, 10.26, 6.59 Hz, 1H), 5.29 (d, J=10.0 Hz, 1H), 4.98–4.83 (m, 2H), 4.20 (m, 1H), 3.97 (d, J=10.0 Hz, 1H), 3.68 (t, J=10.0 Hz, 1H), 3.40–3.23 (m, 2H), 2.07–1.66 (m, 6H), 1.43 (s, 9H), 1.17 (s, 9H). The peak at 5.29 ppm was disappeared by addition of D_2O. ^{13}C NMR ($CDCl_3$) δ: 155.8 (s), 138.3 (d), 135.7 (d, 4C), 133.2 (s, 2C), 130.0 (d, 2C), 127.8 (d, 4C), 114.4 (t), 80.2 (s), 69.45 (t), 69.35 (d), 67.3 (s), 56.4 (t), 43.5 (t), 32.4 (t), 28.4 (q, 3C), 27.5 (t), 26.8 (q, 3C), 19.0 (s). IR (neat) cm^{-1}: 3390, 1736, 1671, 1591. EI-MS m/z: 509 (M^+), 478, 422. HR-MS m/z: calcd for $C_{30}H_{43}NO_4Si$ 509.2959; found 509.2937.

1.1.3. *tert*-Butyl (2*S*,4*R*)-2-(but-3-enyl)-4-*tert*-butyldiphenylsilyloxy-2-formyl-1-pyrrolidinecarboxylate (4a). To a mixture of **3a** (1.40 g, 2.75 mmol), molecular sieves 4 Å (3 g) and CH_2Cl_2 (60 ml) was added *N*-methylmorpholine *N*-oxide (NMO, 487 mg, 4.13 mmol) and tetrapropylammonium perruthenate (TPAP, 96.7 mg, 0.28 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with ether and filtered through a florisil. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (4:1) to give **4a** (1.30 g, 2.56 mmol, 93%) as a colorless oil. $[\alpha]_D^{23}$=+2.1 (c=1.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ratio of conformers: ca. 2:1) δ: 9.42 and 9.26 (2s, 1H), 7.68–7.59 (m, 4H), 7.49–7.34 (m, 6H), 5.94–5.77 (m, 1H), 5.14–4.93 (m, 2H), 4.41–4.29 (m, 1H), 3.76 and 3.54 (2ddd, J=11.5, 6.4, 2.0 Hz, 1H), 3.46–3.36 and 3.34–3.22 (2m, 1H), 2.40–1.85 (m, 6H), 1.41 and 1.40 (2s, 9H), 1.07 and 1.06 (2s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 2:1) δ: 199.8 and 198.8 (2d), 153.9 and 153.1 (2s), 138.1 and 137.9 (2d), 135.6 (d, 4C), 133.2 and 133.1 (2s), 130.0 (d, 2C), 128.1 (d, 4C), 114.6 (t), 81.2

and 80.2 (2s), 70.4 and 69.4 (2d), 70.3 (d), 55.6 (t), 41.4 and 40.3 (2t), 32.2 and 31.6 (2t), 28.5 (t), 28.3 and 28.2 (2q, 3C), 26.8 (q, 3C), 19.0 (s). IR (neat) cm^{-1}: 1742, 1696. EI-MS *m/z*: 507 (M^+), 480, 424. HR-MS *m/z*: calcd for $C_{30}H_{41}NO_4Si$ 507.2803; found 507.2823.

1.1.4. *tert*-Butyl (2*R*,4*R*)-2-(but-3-enyl)-4-*tert*-butyldiphenylsilyloxy-2-formyl-1-pyrrolidinecarboxylate (4b). $[\alpha]_D^{23}=+2.1$ ($c=1.26$, $CHCl_3$). ^1H NMR ($CDCl_3$, ratio of conformers: ca. 2:1) δ: 9.85 and 9.81 (2s, 1H), 7.68–7.58 (m, 4H), 7.52–7.38 (m, 6H), 5.82–5.65 (m, 1H), 5.02–4.85 (m, 2H), 4.26 (br s, 1H), 3.78 and 3.56 (2d, $J=11.7$ Hz, 1H), 3.31 and 3.19 (2dd, $J=11.7$, 3.7 Hz, 1H), 2.33–1.69 (m, 6H), 1.47 and 1.46 (2s, 9H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 2:1) δ: 203.2 and 202.8 (2d), 154.3 and 153.6 (2s), 137.9 and 137.5 (2d), 135.6 (d, 4C), 133.03 and 132.98 (2s, 2C), 130.0 (d, 2C), 127.8 (d, 4C), 114.9 and 114.6 (2t), 81.0 and 80.2 (2s), 71.1 and 70.8 (2s), 70.4 and 69.8 (2d), 56.6 (t), 44.3 and 43.2 (2t), 31.7 and 30.8 (2t), 28.3 (q, 3C), 27.8 and 27.4 (t), 26.8 (q, 3C), 18.9 (s). IR (neat) cm^{-1}: 1734, 1694, 1642. EI-MS *m/z*: 478 (M^+-CHO), 433, 422, 394, 378. HR-MS *m/z*: calcd for $C_{29}H_{40}NO_3Si$ (M^+-CHO) 478.2775; found 478.2765.

1.1.5. *tert*-Butyl (2*S*,4*R*)-4-*tert*-butyldiphenylsilyloxy-2-formyl-2-(3-oxobutyl)-1-pyrrolidinecarboxylate (5a). A mixture of CuCl (203 mg, 2.05 mmol), $PdCl_2$ (100 mg, 0.56 mmol), H_2O (0.5 ml) and DMF (7 ml) was stirred for 1 h at room temperature under an oxygen atmosphere. To the mixture was added dropwise a solution of **4a** (1.00 g, 1.97 mmol) in DMF (6 ml) with continuous introduction of an oxygen by a gas inlet tube. After being further stirred for 5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous NH_4Cl and extracted with ether and hexane (1:1). The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (17:3) to give **5a** (952 mg, 1.82 mmol, 92%) as a colorless oil. $[\alpha]_D^{25}=-5.9$ ($c=1.20$, $CHCl_3$). ^1H NMR ($CDCl_3$, ratio of conformers: ca. 3:2) δ: 9.28 and 9.22 (2s, 1H), 7.70–7.60 (m, 4H), 7.52–7.38 (m, 6H), 4.46–4.36 (m, 1H), 3.74 and 3.57 (2dd, $J=11.7$, 6.1 Hz, 1H), 3.45 and 3.36 (2dd, $J=11.7$, 3.7 Hz, 1H), 2.88–2.26 (m, 4H), 2.16 and 2.14 (2s, 3H), 2.06–1.73 (m, 2H), 1.42 and 1.41 (2s, 9H), 1.08 and 1.07 (2s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 3:2) δ: 207.7 and 207.2 (2s), 198.3 and 197.9 (2d), 154.1 and 153.0 (2s), 135.5 (d, 4C), 133.0 and 132.7 (2s, 2C), 130.0 (d, 2C), 127.8 (d, 4C), 81.5 and 80.4 (2s), 70.8 and 69.6 (2d), 70.2 and 69.9 (2s), 55.9 and 55.8 (2t), 41.3 and 41.1 (2t), 38.9 and 38.7 (2t), 29.8 (q), 28.1 (q, 3C), 26.9 (t), 26.7 (q, 3C), 18.9 (s). IR (neat) cm^{-1}: 1735, 1715, 1696. EI-MS *m/z*: 524 (M^++1), 494, 468, 424. HR-MS *m/z*: calcd for $C_{30}H_{42}NO_5Si$ (M^++1) 524.2829; found 524.2805.

1.1.6. *tert*-Butyl (2*R*,4*R*)-4-*tert*-butyldiphenylsilyloxy-2-formyl-2-(3-oxobutyl)-1-pyrrolidinecarboxylate (5b). $[\alpha]_D^{22}=+11.5$ ($c=1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$, ratio of conformers: ca. 1:1) δ: 9.77 and 9.75 (2s, 1H), 7.65–7.56 (m, 4H), 7.48–7.34 (m, 6H), 4.32–4.20 (m, 1H), 3.77 and 3.56 (2d, $J=11.7$ Hz, 1H), 3.30 and 3.20 (2dd, $J=11.7$, 3.9 Hz, 1H), 2.55–1.76 (m, 6H), 2.09 (s, 3H), 1.48 (s, 9H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 1:1) δ: 208.4 and 207.5 (2s), 202.1 (d), 154.8 and 153.8 (2s), 135.9 (d, 4C), 133.23 and 133.17 (s, 2C), 130.3 (d, 2C), 128.2 (d, 4C), 81.7 and 80.8 (2s), 70.8 and 70.0 (2d), 70.8 (d), 56.7 and 56.4 (2t), 44.7 and 44.2 (2t), 38.9 and 38.2 (2t), 30.1 and 29.8 (2q), 28.5 (2q, 3C), 27.6 and 27.4 (2t), 27.1 (q, 3C), 19.2 (s). IR (neat) cm^{-1}: 1720, 1700, 1675. EI-MS *m/z*: 523 (M^+), 494, 438, 410. HR-MS *m/z*: calcd for $C_{30}H_{41}NO_5Si$ 523.2751; found 523.2734.

1.1.7. *tert*-Butyl (3*S*,5*R*)-3-*tert*-butyldiphenylsilyloxy-6-hydroxy-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (7a). To a solution of **5a** (1.00 g, 1.90 mmol) in EtOH (90 ml) was added KOH (64 mg, 0.96 mmol) at 0°C. After being stirred for 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. After removal of EtOH by evaporation, the mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (4:1) to give **7a** (798 mg, 1.52 mmol, 80%) as white crystals. Mp 131–132°C (AcOEt/hexane). $[\alpha]_D^{20}=-13.6$ ($c=1.02$, $CHCl_3$). Since **7a** is a mixture of two epimers at C6 position including two conformers, its ^1H and ^{13}C NMR spectroscopic data are complex. ^1H NMR ($CDCl_3$) δ: 7.68–7.59 (m, 4H), 7.49–7.35 (m, 6H), 4.86 (br s, 1H), 4.44–4.35 (m, 1H), 3.75–3.27 (m, 2H), 2.80–1.92 (m, 9H), 1.44 (s, 9H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 207.9 (s), 153.6 (s), 135.6 (d, 4C), 133.4 (s, 2C), 129.9 (d, 2C), 127.8 (d, 4C), 79.8 (s), 69.7 (d), 67.6 (d), 67.1 (s), 57.2 (t), 47.0 (t), 38.5 (t), 36.4 (t), 28.5 (q, 3C), 28.0 (t), 26.9 (q, 3C), 19.0 (s). IR ($CHCl_3$) cm^{-1}: 3425, 1710. EI-MS *m/z*: 523 (M^+), 437, 410. HR-MS *m/z*: calcd for $C_{30}H_{41}NO_5Si$ 523.2752; found 523.2764. Anal. Calcd for $C_{30}H_{41}NO_5Si$ C 68.81, H 7.89, N 2.68. Found: C 69.10, H 8.09, N 2.56.

1.1.8. *tert*-Butyl (3*R*,5*R*)-3-*tert*-butyldiphenylsilyloxy-6-hydroxy-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (7b). Mp 125–126°C (AcOEt/hexane). $[\alpha]_D^{20}=+11.6$ ($c=1.02$, $CHCl_3$). Since **7b** is a mixture of two epimers at C6 position including two conformers, its ^1H and ^{13}C NMR spectroscopic data are complex. ^1H NMR ($CDCl_3$) δ: 7.72–7.60 (m, 4H), 7.52–7.37 (m, 6H), 4.92 and 4.60 (2br s, 1H), 4.33–4.25 and 4.17–4.02 (2m, 1H), 3.76–3.33 (m, 3H), 2.86–1.76 (m, 8H), 1.44 (s, 9H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 207.6 (s), 153.3 (s), 135.6 (d, 4C), 132.6 (s, 2C), 130.2 (d, 2C), 127.9 (d, 4C), 80.0 (s), 69.5 (d), 68.5 (d), 67.2 (d), 55.8 (t), 48.0 (t), 38.11 (t), 38.06 (t), 29.7 (t), 28.4 (q, 3C), 26.7 (q, 3C), 18.9 (s). IR ($CHCl_3$) cm^{-1}: 3430, 1720, 1694. EI-MS *m/z*: 523 (M^+), 450, 440, 422. HR-MS *m/z*: calcd for $C_{30}H_{41}NO_5Si$ 523.2752; found 523.2780. Anal. Calcd for $C_{30}H_{41}NO_5Si$: C 68.81, H 7.89, N 2.68. Found: C 68.93, H 8.06, N 2.60.

1.1.9. *tert*-Butyl (3*S*,5*R*)-3-*tert*-butyldiphenylsilyloxy-8-oxo-1-azaspiro[4.5]dec-6-ene-1-carboxylate (9a). To a solution of **7a** (770 mg, 1.47 mmol) in CH_2Cl_2 (3 ml) was successively added methanesulfonyl chloride (0.15 ml, 1.8 mmol) and Et_3N (0.3 ml, 2.25 mmol) at 0°C under an argon atmosphere. After being stirred for 15 min at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and

concentrated under reduced pressure to give crude mesylate **8a**. The crude was purified by column chromatography on silica gel eluted with hexane/AcOEt (17:3) to give enone **9a** (578 mg, 1.14 mmol, 78%) as white crystals.

Mp 146–147°C (AcOEt/hexane). $[\alpha]_D^{23}=-5.0$ (c=1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, ratio of conformers: ca. 3:2) δ: 7.68–7.58 (m, 4H), 7.50–7.35 (m, 6H), 6.74 and 6.62 (2d, J=10.1 Hz, 1H), 5.89 and 5.82 (2d, J=10.1 Hz, 1H), 4.45–4.34 (br s, 1H), 3.70–3.30 (m, 2H), 3.02–2.14, 1.83–1.66 (m, 6H), 1.44 and 1.42 (2s, 9H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 3:2) δ: 198.5 and 198.3 (2s), 157.2 and 157.0 (2d), 153.4 (s), 135.6 (d, 4C), 133.2 and 132.9 (2s, 2C), 130.0 and 129.9 (2d, 2C), 127.9 (d, 4C), 126.9 and 126.5 (2d), 80.7 and 80.0 (2s), 70.9 and 70.1 (2d), 62.2 and 62.1 (2s), 56.2 (t), 42.8 and 42.1 (t), 35.5 and 35.2 (t), 31.5 and 30.3 (t), 28.4 (q, 3C), 26.8 (q, 3C), 18.9 (s). IR ($CHCl_3$) cm^{-1}: 1670. EI-MS m/z: 506 (M^++1), 450. HR-MS m/z: calcd for $C_{30}H_{40}NO_4Si$ (M^++1) 506.2724; found 506.2752. Anal. Calcd for $C_{30}H_{39}NO_4Si$: C 71.26, H 7.77, N 2.77. Found: C 71.73, H 7.96, N 2.72.

1.1.10. *tert*-Butyl (3*R*,5*R*)-3-*tert*-butyldiphenylsilyloxy-8-oxo-1-azaspiro[4.5]dec-6-ene-1-carboxylate (9b). Mp 146–147°C (AcOEt/hexane). $[\alpha]_D^{21}=-25.0$ (c=1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, ratio of conformers: ca. 1:1) δ: 7.68–7.54, 7.51–7.32 (m, 10H), 7.15 and 7.02 (2d, J=10.3 Hz, 1H), 5.92 and 5.85 (2d, J=10.3 Hz, 1H), 4.31 (quintet, J=4.9 Hz, 1H), 3.67–3.30 (m, 2H), 3.04–2.88 and 2.81–2.64 (m, 1H), 2.52–2.02 (m, 4H), 1.72–1.55 (m, 1H), 1.45 and 1.41 (2s, 9H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 1:1) δ: 198.5 (s), 158.9 (d), 154.0 (s), 136.1 (d, 4C), 133.7 (s, 2C), 130.4 (d, 2C), 128.3 (d, 4C), 126.9 and 126.4 (2d), 81.1 and 80.4 (2s), 70.5 and 69.8 (2d), 62.1 and 61.9 (2s), 55.5 and 55.2 (2t), 46.4 and 46.1 (2t), 36.0 and 35.7 (2t), 34.3 and 33.2 (2t), 28.8 (q, 3C), 27.2 (q, 3C), 19.4 (s). IR ($CHCl_3$) cm^{-1}: 1686. EI-MS m/z: 505 (M^+), 392. HR-MS m/z: calcd for $C_{30}H_{39}NO_4Si$ 505.2646; found 505.2673.

1.1.11. *tert*-Butyl (3*R*)-3-*tert*-butyldiphenylsilyloxy-8-oxo-1-azaspiro[4.5]decane-1-carboxylate (10). A mixture of **9a** (100 mg, 0.198 mmol), 20% $Pd(OH)_2$–C (5 mg) and benzene (25 ml) was stirred under H_2 atmosphere for 5 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (17:3) to give **10** (99.3 mg, 0.196 mmol, 99%) as white crystals. Mp 72–73°C (hexane). $[\alpha]_D^{20}=-5.8$ (c=1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, ratio of conformers: ca. 1:1) δ: 7.68–7.60 (m, 4H), 7.50–7.34 (m, 6H), 4.33–4.28 (m, 1H), 3.69–3.30 (m, 2H), 3.10–2.60 (m, 2H), 2.50–1.90 (m, 8H), 1.44 (s, 9H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 210.5 (s), 153.3 (s), 135.7 (d, 4C), 133.4 (s, 2C), 129.9 (d, 2C), 127.8 (d, 4C), 79.1 (s), 69.8 and 69.2 (2d), 62.1 and 61.8 (2s), 55.8 (t), 44.6 and 44.3 (2t), 38.6 (t, 2C), 33.3 (t), 31.9 (t), 28.5 (q, 3C), 26.8 (q, 3C), 19.0 (s). IR (neat) cm^{-1}: 1717, 1694. EI-MS m/z: 508 (M^++1), 452, 408. HR-MS m/z: calcd for $C_{30}H_{42}NO_4Si$ (M^++1) 508.2881; found 508.2883. Anal. Calcd for $C_{30}H_{41}NO_4Si$: C 70.98, H 8.14, N 2.76. Found: C 71.28, H 8.32, N 2.73.

1.1.12. (3*R*)-Dispiro[1-*tert*-butoxycarbonyl-3-*tert*-butyldiphenylsilyloxypyrrolidine-5,1′-cyclohexane-4′,2″-1,3-dioxolane] (11). A mixture of **10** (6.75 g, 13.3 mmol), ethylene glycol (1.5 ml, 26.6 mmol), $TsOH{\cdot}H_2O$ (230 mg, 1.33 mmol) and benzene (25 ml) was refluxed for 3 h fixed with Dean-stark apparatus. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (17:3) to give **11** (6.39 g, 11.6 mmol, 87%) as white crystals. Mp 92–93°C (AcOEt/hexane). $[\alpha]_D^{20}=-3.7$ (c=1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.66–7.61 (m, 4H), 7.44–7.32 (m, 6H), 4.21 (quintet, J=4.9 Hz, 1H), 3.92 (s, 4H), 3.59–3.30 (m, 2H), 3.00–2.52 (m, 2H), 2.08 (dd, J=13.2, 4.6 Hz, 1H), 1.89–1.47 (m, 7H), 1.46 (s, 9H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 1:1) δ: 154.3 and 153.1 (2s), 135.7 (d, 4C), 133.7 (s, 2C), 129.8 (d, 2C), 127.7 (d, 4C), 108.0 (s), 79.6 and 78.7 (2s), 69.9 and 69.2 (2d), 64.3 (t, 2C), 64.1 (t), 62.9 and 62.7 (2s), 55.6 (t), 44.5 and 43.7 (2t), 32.7 (t), 31.8 (t), 31.5 and 30.6 (2t), 28.6 (q, 3C), 26.8 (q, 3C), 19.0 (s). IR (neat) cm^{-1}: 1688. EI-MS m/z: 551 (M^+), 438. HR-MS m/z: calcd for $C_{32}H_{45}NO_5Si$ 551.3065; found 551.3054. Anal. Calcd for $C_{32}H_{45}NO_5Si$: C 69.67, H 8.22, N 2.54. Found: C 69.78, H 8.40, N 2.63.

1.1.13. (3*R*)-Dispiro[1-*tert*-butoxycarbonyl-3-hydroxypyrrolidine-5,1′-cyclohexane-4′,2″-1,3-dioxolane] (12). To a solution of **11** (8.52 g, 15.4 mmol) in THF was added a 1 M solution of TBAF (42 ml, 42.0 mmol) at 0°C under an argon atmosphere. The solution was further stirred for 5 h, then quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (1:2) to give **12** (4.80 g, 15.3 mmol, 99%) as white crystals. Mp 215–216°C (AcOEt/hexane). $[\alpha]_D^{25}=-12.7$ (c=1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 4.38–4.29 (m, 1H), 3.93 (s, 4H), 3.63 (dd, J=12.0, 4.6 Hz, 1H), 3.47 (br d, J=12.0, 1H), 3.00–2.55 (m, 2H), 2.30–1.90 (m, 3H), 1.70–1.22 (m, 6H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers ca. 1:1) δ: 154.4 (s), 107.9 (s), 79.9 and 79.6 (2s), 68.2 and 67.9 (2d), 64.3 (t), 62.9 (s), 55.6 (t), 44.4 (t), 43.9 (t), 32.7 (t), 32.6 (t), 32.2 (t), 31.2 (t), 28.8 (q, 3C). IR ($CHCl_3$) cm^{-1}: 3414, 1676. EI-MS m/z: 313 (M^+), 158. HR-MS m/z: calcd for $C_{16}H_{27}NO_5$ 313.1888; found 313.1913. Anal. Calcd for $C_{16}H_{27}NO_5$: C 61.32, H 8.68, N 4.47. Found: C 61.40, H 8.90, N 4.51.

1.1.14. (3*S*)-Dispiro[3-azido-1-*tert*-butoxycarbonylpyrrolidine-5,1′-cyclohexane-4′,2″-1,3-dioxolane] (13). To a solution of **12** (1.96 g, 6.25 mmol) in THF (60 ml) were successively added triphenylphosphine (3.36 g, 12.3 mmol), diethyl azodicarboxylate (2.1 ml, 12.3 mmol) and diphenylphosphoryl azide (2.79 ml, 12.3 mmol). The reaction mixture was stirred at room temperature for 15 min, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (9:1) to give **13** (1.77 g, 5.23 mmol, 84%) as white crystals. Mp 106–107°C (hexane). $[\alpha]_D^{20}=+8.9$ (c=0.99, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 4.40 (quintet, J=5.4 Hz, 1H), 3.93 (s, 4H), 3.76–3.60 (m, 1H), 3.60–3.35

(m, 1H), 3.00–2.60 (m, 2H), 2.20 (dd, J=13.0, 6.35 Hz, 1H), 2.15–2.00 (br s, 1H), 1.86–1.20 (m, 6H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, ratio of conformers ca. 1:1) δ: 154.0 (s), 107.7 (s), 80.1 and 79.4 (2s), 64.3 (t, 2C), 62.7 (s), 57.3 and 57.1 (2d), 52.2 (t), 41.4 and 40.5 (2t), 32.7 (t, 2C), 32.6 and 32.4 (2t), 31.4 and 30.9 (2t), 28.5 (q, 3C). IR ($CHCl_3$) cm^{-1}: 2108, 1763, 1692. EI-MS m/z: 338 (M^+), 239, 101. HR-MS m/z: calcd for $C_{16}H_{26}N_4O_4$ 338.1952; found 338.1932. Anal. Calcd for $C_{16}H_{26}N_4O_4$: C 56.79, H 7.74, N 16.56. Found: C 56.99, H 7.86, N 16.39.

1.1.15. (3*S*)-Dispiro[3-azido-1-benzoylpyrrolidine-5,1′-cyclohexane-4′,2″-1,3-dioxolane] (15). A solution of **13** (144 mg, 0.426 mmol) in trifluoroacetic acid (0.5 ml) was stirred at −10°C for 10 min, and then concentrated under reduced pressure to give crude amine **14**. To a solution of the crude **14** in CH_2Cl_2 (2 ml) were successively added triethylamine (0.2 ml, 1.43 mmol) and benzoyl chloride (0.06 ml, 0.353 mmol). The mixture was stirred for 1 h at room temperature, then quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (1:1) to give **15** (101 mg, 0.295 mmol, 69%) as a colorless oil. $[\alpha]_D^{20}$=+8.1 (c=1.09, $CHCl_3$). ^{1}H NMR ($CDCl_3$, ratio of conformers: ca. 2:1) δ: 7.38 (s, 5H), 4.20–3.90 (m, 5H), 3.69 and 3.62 (2dd, J=11.5, 6.0 Hz, 1H), 3.49 and 3.42 (2dd, J=11.0, 5.3 Hz, 1H), 3.38–3.14 (m, 2H), 2.70–1.97 (m, 2H), 1.90–1.56 (m, 5H), 1.49–1.37 (m, 1H). ^{13}C NMR ($CDCl_3$, ratio of conformers: ca. 2:1) δ: 169.5 (s), 138.6 (s), 129.8 and 129.4 (2d), 128.6 and 128.4 (2d, 2C), 126.3 and 126.2 (2d, 2C), 107.6 (s), 65.2 (s), 64.4 (t, 2C), 57.8 (d), 55.5 and 55.3 (2t), 40.7 (t), 32.6 (t), 32.5 (t), 30.8 (t), 30.5 (t). IR (neat) cm^{-1}: 2108, 1717. EI-MS m/z: 342 (M^+), 105. HR-MS m/z: calcd for $C_{18}H_{22}N_4O_3$ 342.1691; found 342.1662.

1.1.16. (3*S*)-Dispiro[3-azide-1-ethoxycarbonylmethylpyrrolidine-5,1′-cyclohexane-4′,2″-1,3-dioxolane] (16). Crude amine **14** was prepared from **13** (1.62 g, 4.79 mmol) according to the procedure previously described. To a solution of **14** in acetonitrile (25 ml) were successively added potassium carbonate (1.98 g, 14.3 mmol) and ethyl bromoacetate (0.79 ml, 7.1 mmol). The reaction mixture was stirred at room temperature for 18 h, then quenched with saturated aqueous NaCl and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane/AcOEt (1:4) to give **16** (1.40 g, 4.32 mmol, 90%) as a colorless oil. $[\alpha]_D^{22}$=+22.3 (c=1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 4.17 (q, J=7.2 Hz, 2H), 4.10–3.99 (m, 1H), 3.94 (s, 4H), 3.35 (s, 2H), 3.34 (dd, J=10.0, 6.8 Hz, 1H), 2.97 (dd, J=10.0, 4.4 Hz, 1H), 2.18 (dd, J=13.5, 8.4 Hz, 1H), 1.92 (dd, J=13.5, 4.1 Hz, 1H), 1.84–1.36 (m, 8H), 1.28 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.4 (s), 108.0 (s), 64.3 (t), 64.1 (t), 62.5 (s), 60.4 (t), 57.9 (d), 56.6 (t), 49.1 (t), 40.3 (t), 32.5 (t, 2C), 30.1 (t), 29.5 (t), 14.1 (q). IR (neat) cm^{-1}: 2108, 1748. EI-MS m/z: 325 (M^++1), 297. HR-MS m/z: calcd for $C_{15}H_{25}N_4O_4$ (M^++1) 325.1874; found 325.1861.

1.1.17. (3*S*)-Dispiro[3-amino-1-ethoxycarbonylmethylpyrrolidine-5,1′-cyclohexane-4′,2″-1,3-dioxolane] (17). A mixture of **16** (392 mg, 1.21 mmol), 5% Pd–C (trace amount) and MeOH (4 ml) was stirred under H_2 atmosphere for 3.5 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with chloroform/methanol (9:1), which was saturated by ammonia, to give **17** (327 mg, 1.10 mmol, 91%) as a colorless oil. $[\alpha]_D^{24}$=−5.8 (c=1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 4.16 (q, J=7.2 Hz, 2H), 3.93 (s, 4H), 3.59–3.48 (m, 1H), 3.41 (d, J=16.6 Hz, 1H), 3.22 (d, J=16.6 Hz, 1H), 3.07 (dd, J=9.3, 6.8 Hz, 1H), 2.79 (dd, J=9.3, 4.4 Hz, 1H), 2.26 (dd, J=12.9, 8.1 Hz, 1H), 1.80–1.36 (m, 11H), 1.27 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 172.0 (s), 108.3 (s), 64.3 (t), 64.1 (t), 62.8 (s), 60.7 (t), 60.5 (t), 49.5 (t), 48.9 (d), 44.4 (t), 32.6 (t), 32.4 (t), 31.8 (t), 28.7 (t), 14.2 (q). IR (neat) cm^{-1}: 3366, 1748. EI-MS m/z: 298 (M^+), 269. HR-MS m/z: calcd for $C_{15}H_{26}N_2O_4$ 298.1891; found 298.1890.

1.1.18. (3*S*)-Dispiro[1,4-diazabicyclo[3.2.1]octan-3-one-7,1′-cyclohexane-4′,2″-1,3-dioxolane] (19). To a solution of **17** (951 mg, 3.19 mmol) in H_2O (13 ml) was added lithium hydroxide (84.3 mg, 3.5 mmol). The reaction mixture was stirred at room temperature for 2 h, and then concentrated under reduced pressure to give crude amino acid **18**. To a solution of the crude **18** in DMF (40 ml) was added triethylamine (1.4 ml, 9.96 mmol). After being stirred for 10 min, diphenylphosphoryl azide (1.2 ml, 5.55 mmol) was added and the resulting reaction mixture was further stirred at room temperature for 2.5 h, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with chloroform/methanol (30:1), which was saturated by ammonia, to give **19** (460 mg, 1.83 mmol, 57%) as white crystals. Mp 230–231°C (AcOEt/hexane). $[\alpha]_D^{25}$=+17.9 (c=1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 6.44 (br, 1H), 3.95 (s, 4H), 3.85–3.78 (m, 1H), 3.62 (d, J=18.6 Hz, 1H), 3.53 (d, J=18.6 Hz, 1H), 3.18 (dd, J=12.2, 2.7 Hz, 1H), 3.06 (d, J=12.2 Hz, 1H), 2.01–1.50 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 170.5 (s), 107.9 (s), 64.31 (t), 64.28 (t), 64.2 (s), 56.2 (t), 55.0 (t), 53.3 (d), 47.8 (t), 36.5 (t), 32.8 (t), 32.6 (t), 31.9 (t). IR ($CHCl_3$) cm^{-1}: 1688. EI-MS m/z: 252 (M^+), 168. HR-MS m/z: calcd for $C_{13}H_{20}N_2O_3$ 252.1473; found 252.1481. Anal. Calcd for $C_{13}H_{20}N_2O_3$: C 61.88, H 7.99, N 11.10. Found: C 61.99, H 8.12, N 11.02.

1.1.19. (3*S*)-Dispiro[1,3-dioxolane-2,1′-cyclohexane-4′,7″-4-methyl-1,4-diazabicyclo[3.2.1]octan-3-one] (20). To a solution of 55% sodium hydride (12 mg, 0.275 mmol) in THF (1 ml) were successively added a solution of **19** (59.8 mg, 0.237 mmol) in THF (1 ml) and iodomethane (0.04 ml, 0.65 mmol) at 0°C. The reaction mixture was further stirred at room temperature for 1 h, then quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with chloroform/methanol (30:1), which was saturated by ammonia, to give **20** (42.1 mg, 0.158 mmol, 67%) as a colorless oil. $[\alpha]_D^{25}$=+18.1 (c=1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.94 (s, 4H), 3.63–3.59 (m, 1H), 3.59 (d, J=18.6 Hz, 1H), 3.48 (d, J=18.6 Hz, 1H), 3.24 (dd, J=12.2, 2.4 Hz, 1H), 3.05 (d, J=12.2 Hz, 1H), 2.90 (s, 3H), 1.94–1.48 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 168.2 (s), 107.9 (s),

64.28 (t), 64.24 (t), 64.1 (s), 60.0 (d), 56.3 (t), 55.1 (t), 45.1 (t), 36.4 (t), 33.3 (q), 32.7 (t), 32.5 (t), 31.9 (t). IR (neat) cm^{-1}: 1647. EI-MS *m/z*: 266 (M^+), 237, 113. HR-MS *m/z*: calcd for $C_{14}H_{22}N_2O_3$ 266.1629; found 266.1654.

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References

1. Shirafuji, H.; Tubotani, S.; Ishimaru, T.; Harada, S. PCT Int. Appl. WO 9,113,887, 1991; *Chem. Abstr.* **1992**, *116*, 39780t.
2. Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493.
3. For full report, see: Nagumo, S.; Nishida, A.; Yamazaki, C.; Matoba, A.; Murashige, K.; Kawahara, N. *Tetrahedron* **2002**, *58*, 4917.
4. Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643.
5. Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053.
6. Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411.
7. Nagumo, S.; Mizukami, M.; Akutsu, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209.
8. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.
9. See supporting information in Ref. 5.