An Alternative Convenient Synthesis of Piperidazine-3-carboxylic Acid Derivatives

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The short-step synthesis of the unsubstituted, 5-hydroxy- and 5-chloropiperidazine-3-carboxylic acids using an aza Diels–Alder reaction between the 1,3-diene and azodicarboxylate was described. This synthetic methodology could be used for the preparation of the optically active piperazic acid in a 35% overall yield.

Key words aza Diels–Alder reaction; piperidazine-3-carboxylic acid; azodicarboxylate; piperazic acid

Hexahydropyridazine-3-carboxylic acid (piperazic acid, Piz) is a novel cyclic α-hydrazino acid, and a subunit often found in cyclic depsipeptides. Both of its enantiomeric forms have been encountered in many pharmacologically active molecules that include the azinothricin family of antitumor antibiotics,[1] verucopeptin,[2] the aurantimycins,[3] the C5a antagonist L-156,602,[4] the immunosuppressant IC101,[5] the oxytocin antagonist L-156,373,[6] and the matylastantin type-IV collagenase inhibitors.[7—9] There are several reports[10—13] about the synthesis of the racemic Piz. However, these reports have indicated some obstacles still to be overcome; the aza Diels–Alder (DA) reaction for the construction of the pyridazine framework has a low yield, and the *N*-deprotection was done under strict basic conditions. Recently, Hale and co-workers[14,15] described the enantioselective synthesis of the (3*R*)- and (3*S*)-piperazic acids by the electrophilic hydrazination of a chiral oxazorizinone derivative. More recently, Hamada and co-workers reported two synthetic methods for optically active piperazic acids by the use of a proline-catalyzed asymmetric α-hydrazination[16] and the titanium tetrachloride-mediated aza DA reaction.[17] Although (3*S*,5*S*)-5-HO-Piz was also prepared, the methodology for the preparation of these compounds requires multiple steps, which is not practical. In this report, we describe three new findings for the synthesis of the Piz derivatives; (1) the short-step convenient synthesis of Piz, (2) the practical preparation of the 5-hydroxy and 5-chloro Piz, and (3) the (*R*)- and (*S*)-Piz enantioselective synthesis.

Results and Discussion

Convenient Synthesis of Piperidazine-3-carboxylic Acids In order to prepare the pyridazine-3-carboxylic acid derivative, the DA reaction using the 1,3-diene and azodicarboxylate was carried out. The hetero DA reaction between the di-*tert*-butyl azodicarboxylate (**4**) and the 1,3-dienes (**1**, **2**), which have an electron withdrawing group, such as a methoxycarbonyl or cyano group, produced the 1,2-di-*tert*-butyl 1,2,3,6-tetrahydropyridazine-1,2-carboxylate adducts (**5**, **6**) in 47 and 40% yields, respectively. In contrast, a similar reaction of the azodicarboxylate (**4**) with methoxy-1,3-diene (**3**), which has an electron donating group, gave the 3-methoxypyridazine (**7**) in almost quantitative yield (Chart 1).[18] Therefore, we examined the transformation of the methoxy group in the 3-methoxypyridazine (**7**) into the cyano group for preparation of the subtitled compounds. We have described the smooth conversion of the methoxy group of the DA adducts into the dimethylphosphono group by treatment with trimethylphosphite in the presence of a Lewis acid.[18—20] The treatment of the methoxy DA adduct (**7**) with trimethylsilyl cyanide (TMSCN) in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid at $-40\,^{\circ}C$ in dry CH_2Cl_2 gave the 3-cyano-1,2,3,6-tetrahydropyridazine (**6**) in 94% yield *via* the acyliminium cation intermediate. When $TiCl_4$ was used in this cyanation reaction, the 3-cyanopyridazine (**6**) was also produced in almost a similar yield. In addition, the one-pot preparation of the 3-cyanopyridazine (**6**) was established. The reaction of 1-methoxy-1,3-butadiene (**3**) with di-*tert*-butyl azodicarboxylate (**4**) in dry CH_2Cl_2 at room temperature, followed by the addition of TMSCN and $BF_3 \cdot OEt_2$ at $-40\,^{\circ}C$ directly afforded the desired 3-cyanopyridazine (**6**) in 91% yield. The DA reaction using 1-trimethylsilyloxy-1,3-diene (**8**) and azodicarboxylate (**4**) under similar conditions produced the **6** in 80% yield (Chart 2).

The catalytic hydrogenation of the olefin moiety in **6** using Pd–C or PtO_2 in EtOH was examined. The results of the hydrogenation are summarized in Chart 3 and Table 1. The 10% Pd–C hydrogenation of **6** at the 1 or 3 atom of H_2 gave the desired 3-cyanohexahydropyridazine (**9**) and the aminomethyl derivative (**11**), which was isolated as the *N*-Boc derivative **12** by the treatment with Boc_2O (entries 1—3). In the case of using PtO_2, 3-cyano-1,2,5,6-tetrahydropyridazine (**10**) was produced as the major product (entry 5). Fortunately, the PtO_2 hydrogenation of **6** at the 1 atom of H_2 in EtOH with 2 drops of a 70% $HClO_4$ solution as an additive

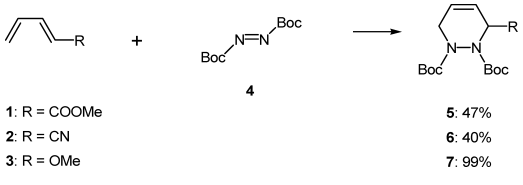

Chart 1

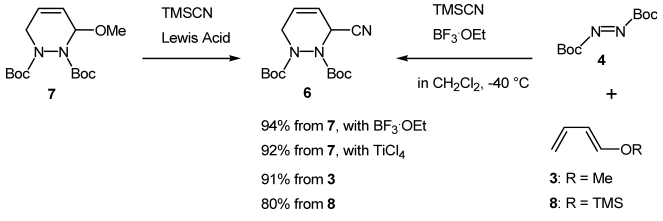

Chart 2

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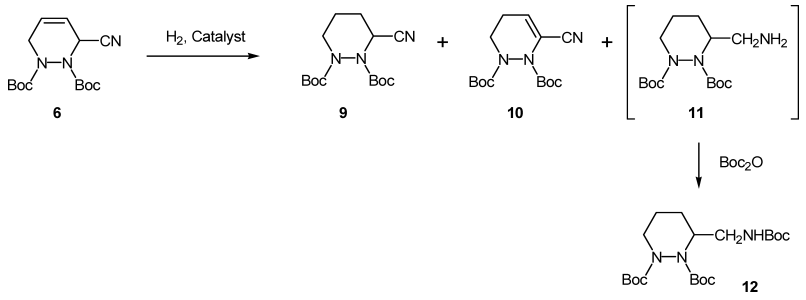

Chart 3

Table 1. Catalytic Hydrogenation of **6**

Entry	Reaction conditions				Product yield (%)		
	Catalyst	Additive	Pressure (atm)	Time (h)	**9**	**10**	**12**
1	10% Pd–C[a)]	—	3	2	54	—	27
2	10% Pd–C[a)]	—	1	10	64	—	22
3	10% Pd–C[b)]	—	1	3	54	—	37
4	10% Pd–C[b)]	$HClO_4$	1	1	59	—	17
5	PtO_2	—	1	5	17	77	—
6	PtO_2	$HClO_4$	1	1	95	—	—

a) 40 mg, *b*) 420 mg.

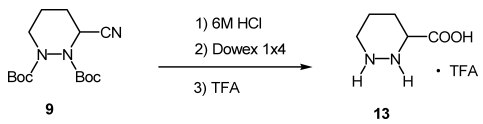

Chart 4

afforded the desired 3-cyanohexahydropyridazine (**9**) in 95% yield as the sole product (entry 6). **9** was obtained in 59% yield together with **12** in 17% yield using a 10% Pd–C catalyst under similar conditions (entry 4).

In order to convert into the desired Piz, the deprotection of the *N*-Boc group and hydrolysis of the 3-cyanohexahydropyridazine (**9**) were carried out (Chart 4). Refluxing **9** in 6 M HCl for 24 h, followed by the treatment with an ion-exchange resin (Dowex 1×4), and then the addition of trifluoroacetic acid (TFA) furnished the desired Piz **13** in 93% yield. The ^{1}H-NMR spectral data of **13** was in good agreement with that of the known optically active compound in the literature.[16)]

Synthesis of 5-Substituted Piperidazine-3-carboxylic Acids We next planned the synthesis of the 5-substituted piperidazine-3-carboxylic acids through the aza-DA reaction between the Danishefsky reagent (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) and azodicarboxylate. The aza-DA reaction of 3-trimethylsilyloxy-1,3-butadiene (**14**) with **4** in dry CH_2Cl_2, followed by the treatment with TMSCN in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid at −40 °C, and then $NaHCO_3$ hydrolysis, successfully gave the 3-cyano-5-oxohexahydropyridazine (**17**) in 94% yield in one-pot *via* the intermediates **15** and **16**. The $NaBH_4$ reduction of **17** in EtOH at −20 °C gave a mixture of the 5-hydroxy derivatives *cis*-**18** and *trans*-**19** in the ratio of 72 : 28 with a 95% yield, which could be easily separated by silica gel column chromatography. This $NaBH_4$ reduction quickly proceeded at room temperature giving **18** and **19**, however, the selectivity of the reduction decreased. The lithium tri-*tert*-butoxyaluminumhydride reduction of **17** in tetrahydrofuran (THF) at −20 °C produced **18** and **19** in almost a similar ratio and 96% yield. The hydride reduction seemed to occur by the apparent less hindered attack on the carbonyl group at the C-5 position of the most stable quasi-chair conformer of the 5-oxohexahydropyridazine ring **17A**, which is more favored than **17B** due to the steric hindrance of the two Boc groups as shown in Chart 6. Therefore, the stereochemistry of the cyano and hydroxy groups in the major isomer seems to be *cis*, although specific evidence for this isomer is not available. This stereochemistry was finally determined by conversion into the 5-hydroxy Piz from the major *cis*-isomer.

Both isomers **18** and **19** were heated in a refluxing mixed solution of 6 M HCl and AcOH for 24 h to afford the corresponding acids **20** and **21**, which were immediately converted into the *N*-dinitrophenyl (DNP) derivatives **22** and **23** by the reaction with 1-fluoro-2,4-dinitrobenzene in 92 and 72% yields, respectively. The ^{1}H-NMR spectral data of the *cis*-DNP derivatives **22** was in complete agreement with that of (3*S*,5*S*)-1-DNP-5-OH-Piz in the literature.[21)]

Both of the 5-hydroxy enantiomers **18** and **19** were chlorinated using the Mitsunobu[22)] reaction, which is well known as the stereospecific inversion of the hydroxy group into the chloro group. The *cis*-5-chlorohexahydropyridazine (**25**) was produced by the reaction of **19** with PPh_3 and CCl_4 in THF in 60% yield. Similarly, the *trans*-derivative **24** was obtained from the corresponding **18** in 70% yield, and then hydrolyzed with 6 M HCl to give the pyridazinecarboxylic acid (**26**), which was transformed into the DNP derivative **27** without isolation in 81% yield. The ^{1}H-NMR spectral data of the *trans*-DNP derivatives **27** was in accord with that reported for the optically active compound.

Optically Active Piperidazine-3-carboxylic Acids Finally, we achieved the asymmetric synthesis of both enan-

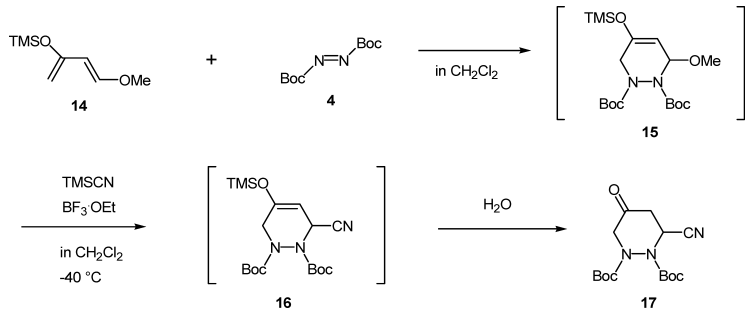

Chart 5

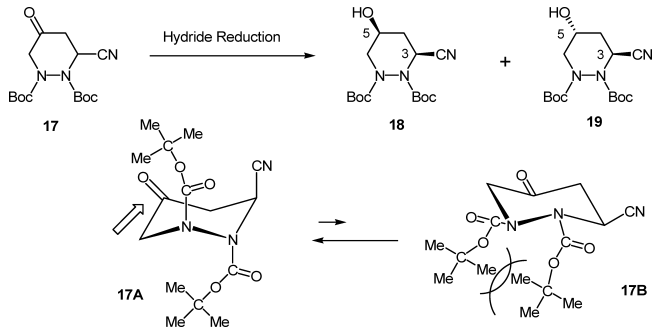

Chart 6

tiomers of the Piz from the 1,3-dienes and optically active azodicarboxylate as the starting material by the previously described method. While several reports[14—17,23,24] on the syntheses of the optically active Piz are known, these preparations remain much less explored regarding the synthetic steps and the yields for the preparation of both enantiomers. The treatment of 1-methoxy-1,3-diene (**3**) with di-(−)-menthyl azodicarboxylate (**28**) in dry CH_2Cl_2 at room temperature, followed by the addition of TMSCN in the presence of $BF_3 \cdot OEt_2$ or $TiCl_4$ at −40 °C gave the desired 3-cyano-1,2,3,6-tetrahydropyridazine (**29**) as a mixture of the two diastereomers in excellent yields, which were not able to be separated. The PtO_2 catalytic hydrogenation of the olefin moiety in **29** in the presence of 70% $HClO_4$ gave the (*R*)-form **30** and (*S*)-form **31** in 42 and 40% yields, respectively. The diastereomers **30** and **31** could be easily separated by silica gel column chromatography. Transformation from the (*S*)-form **31** into the (*R*)-form **30** under basic conditions was found. The catalytic hydrogenation of **29** gave a mixture of **30** and **31**, epimerization of which with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing EtOH for 2 h finally afforded the mixture of **30** and **31** in 50 and 11% isolated yields, respectively. The hydrolysis of the (*R*)-form **30** with 6 M HCl, followed by purification using an ion-exchange resin (Dowex 1×4), and then the addition of TFA gave the optically pure Piz **32** {mp 145—147 °C, $[\alpha]_D^{22}$ −11.6 (c=0.97, MeOH)} in 95% yield. The melting point and the optical rotation of the product were in good agreement with those already reported (3*R*)-Piz {lit.[14] mp 147—149 °C, $[\alpha]_D^{22}$ −12.0 (c=1, MeOH)}. Similarly, **33** {mp 145—147 °C, $[\alpha]_D^{22}$ +11.6 (c=0.97, MeOH)} was obtained from the (*S*)-form **31** in 95% yield. Thus, the absolute configuration of the levorotatory Piz **32** and its precursor Piz was assigned the (*S*)-configuration {lit.[16] mp 149—151 °C, $[\alpha]_D^{22}$ +11.1 (c=0.98, MeOH)}.

Conclusion

In this study, we established the short-step preparation of the racemic unsubstituted, 5-hydroxy and 5-chloro Piz, and succeeded in the preparation of both enantiomers of the optically active Piz in three steps with 35% overall yields through the DA reaction and cyanation.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Horiba FT-720 spectrometer. Mass spectra (MS) and HR-MS were recorded on a JEOL JMS-DX300 instrument. NMR spectra were determined with a JEOL EX-90A (90 MHz) or a JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$, DMSO-d_6 or D_2O using tetramethylsilane as internal standard and J values are given in Hz. Microanalyses were performed in the Microanalytical Laboratory in this Faculty.

Starting 2,4-Dienes and Azodicarboxylate Methy pentadienate (**1**),[25] penta-2,4-dienenitrile (**2**)[26] and di-*tert*-butyl azodicarboxylate (**4**)[27] were prepared by the reported methods.

General Procedure for the Diels–Alder Reaction of 1,3-Diene with Azocarboxylate 1,3-Butadiene (**1**—**3**, 10 mmol) was added to a solution of di-*tert*-butyl azodicarboxylate (**4**, 2.30 g, 10 mmol) in an appropriate solvent (10 ml). The mixture was refluxed or stirred for 2—72 h until disappearance of the starting material, and then evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography to give **5**—**7**.

Di-*tert*-butyl 3-Methyl 1,2,3,6-Tetrahydropyridazine-1,2,3-tricarboxylate (5) The reaction was carried out in refluxing benzene for 72 h. Colorless prisms, mp 100—103 °C (from hexane). MS m/z 342 (M^+). IR (KBr) cm^{-1}: 1759, 1697 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (18H, s, *t*-Bu×2), 3.74 (3H, s, 3-COOMe), 3.56—3.92 and 4.24—4.52 (each 1H, m, 6-H_2), 5.07—5.40 (1H, m, 3-H), 5.87—6.01 (2H, m, 4-, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 28.21 (q), 28.24 (q), 41.5 (t), 52.3 (q), 55.5 (d), 80.7 (s), 82.0 (s), 122.3 (d), 125.5 (d), 153.9 (s), 154.4 (s), 169.1 (s). *Anal.* Calcd for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.12; H, 7.48; N, 8.26.

Di-*tert*-butyl 3-Cyano-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (6) The reaction was carried out in refluxing benzene for 60 h. Colorless needles, mp 95—96 °C (from hexane). MS m/z 309 (M^+). IR (KBr) cm^{-1}: 2239 (CN), 1724, 1701 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 and 1.50 (total 9H, intensity ratio 3 : 4, each s, *t*-Bu), 1.51 (9H, s, *t*-Bu), 3.50—3.89 and 4.41—4.72 (2H, m, 6-H_2), 5.19—5.57 (1H, br, 3-H), 5.63—5.93 (1H, br, 4-H), 5.93—6.22 (1H, br, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 27.9 (q), 28.0 and 28.2 (each q), 42.1 (t), 43.0 (d), 81.6 and 82.3 (each s), 83.0 (s), 83.5 and 83.7 (each s), 115.3 (s), 119.3 and 119.6 (each d), 128.4 and 129.1 (each d), 152.9 (s), 153.6 and 154.2 (each s). *Anal.* Calcd for $C_{15}H_{23}N_3O_4$: C, 58.24; H, 7.49; N, 13.58. Found: C, 58.04; H, 7.35; N, 13.82.

Di-*tert*-butyl 3-Methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7) The reaction was carried out in CH_2Cl_2 at room temperature for 2 h. Colorless oil. MS m/z 314 (M^+). IR (neat) cm^{-1}: 1706 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.49 and 1.50 (each 9H, s, *t*-Bu×2), 3.49 and 3.53 (total 3H, intensity ratio 4 : 1, each s, OMe), 3.55—3.83, 4.31 and 4.49 (1H, m, total 1H, intensity ratio 1 : 4, d, J=18.7 Hz and dd, J=18.0, 2.9 Hz, 6-H_2), 5.25—5.66 (1H, br, 3-H), 5.77—6.15 (2H, m, 4-, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 28.26 (q), 28.34 (q), 41.7 and 43.6 (each t), 56.2 (q), 80.3 (d), 80.8 and 81.0 (each s), 81.6 (s), 123.8 and 124.3 (each d), 127.2 and 127.7 (each d), 154.5 (s), 154.9

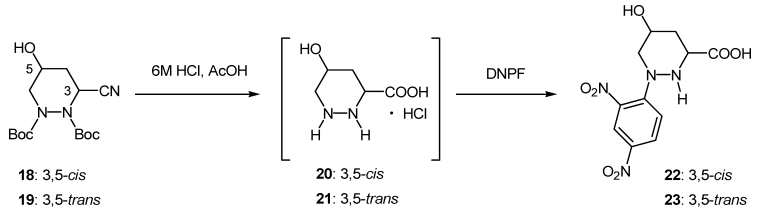

Chart 7

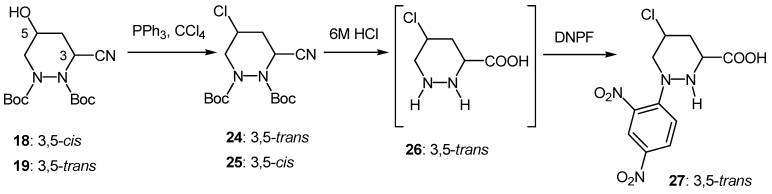

Chart 8

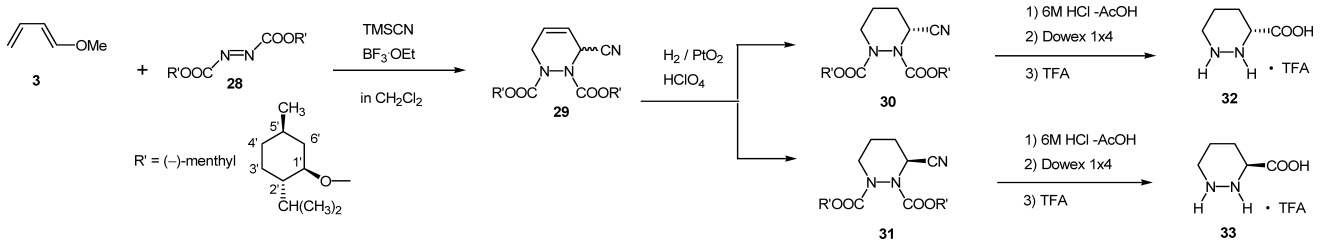

Chart 9

(s). HR-MS *m/z*: 314.1842 (Calcd for $C_{15}H_{26}N_2O_5$: 314.1842).

Cyanation of 3-Methoxy-1,2,3,6-tetrahydropyridazine (7) TMSCN (2.00 ml, 15 mmol) was added to a solution of **7** (3.14 g, 10 mmol) in CH_2Cl_2 (40 ml) at −40 °C under argon atmosphere. $BF_3 \cdot OEt$ or $TiCl_4$ (5 mmol) in CH_2Cl_2 (10 ml) was added to the reaction mixture. The mixture was stirred under the conditions for 5 h ($TiCl_4$: 1 h). 2% $NaHCO_3$ solution was added to the mixture, and the aqueous mixture was vigorously stirred at room temperature for 1 h. The mixture was extracted with $CHCl_3$ (100 ml×3). The organic layer was washed with water (200 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using AcOEt–hexane to give **6**.

$BF_3 \cdot OEt$: 2.90 g, 94%.

$TiCl_4$: 2.83 g, 92%.

One-Pot Synthesis of 3-Cyano-1,2,3,6-tetrahydropyridazine (6) To a solution of azodicarboxylate (**4**, 2.30 g, 10 mmol) in CH_2Cl_2 (10 ml) was added 1-methoxy-1,3-butadiene (**3**, 1.11 ml, 11 mmol) or 1-trimethoxysilyloxy-1,3-butadiene (**8**, 1.93 ml, 11 mmol) at room temperature. After stirring for 30 min, a solution of TMSCN (2.00 ml, 15 mmol) in CH_2Cl_2 (30 ml) and then a solution of $BF_3 \cdot OEt$ (0.63 ml, 5 mmol) in CH_2Cl_2 (10 ml) were added to the stirring mixture at −40 °C under argon atmosphere. The mixture was stirred under the conditions until disappearance of the starting material. 2% $NaHCO_3$ solution (100 ml) was added to the mixture, and the aqueous mixture was vigorously stirred at room temperature for 1 h. The mixture was extracted with $CHCl_3$ (100 ml×3). The organic layer was washed with water (200 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using AcOEt–hexane to give **6**.

91% yield from **3**.

80% yield from **8**.

Hydrogenation of 3-Cyano-1,2,3,6-tetrahydropyridazine (6) A mixture of **6** (0.93 g, 3 mmol) and 10% Pd–C (40 mg) or PtO_2 (90 mg) in EtOH (8 ml) was shaken in H_2 (1 atm pressure) at room temperature for 1—10 h (until disappearance of the starting material). After removal of the catalyst, the filtrate was evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using AcOEt–hexane to give **9**, **10** and **12**.

Hydrogenation of 3-Cyano-1,2,3,6-tetrahydropyridazine (6) with 70% $HClO_4$ A mixture of **6** (0.93 g, 3 mmol), 10% Pd–C (40 mg) or PtO_2 (90 mg) and 70% $HClO_4$ (2 drops) in EtOH (8 ml) was shaken in H_2 (1 atm pressure) at room temperature for 1 h. After removal of the catalyst, $NaHCO_3$ saturated aqueous solution (5 ml) was added to the mixture. The aqueous mixture was extracted with AcOEt (30 ml×3). The combined organic layer was washed with brine (20 ml×2), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using AcOEt–hexane to give **9** and **12**.

Di-*tert*-butyl 3-Cyanohexahydropyridazine-1,2-dicarboxylate (9) Coleorless prisms mp 104—105 °C (from hexane). MS *m/z* 311 (M^+). IR (KBr) cm^{-1}: 2241 CN), 1697 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 and 1.50 (each 9H, s, *t*-Bu), 1.67—1.73 and 1.86—2.05 (1H, m , 3H, m, 5-H_2, 4-H_2), [2.82 and 2.87—3.11 (total 1H, intensity ratio 2 : 1, t, J=11.8 Hz, m), 3.94, 4.10 and 4.28 (total 1H, intensity ratio 1 : 6 : 20, d, J=12.8 Hz, d, J=11.9 Hz, d, J=13.5 Hz), 6-H_2], 4.65—4.80, 5.20—5.22 and 5.22—5.40 (total 1H, intensity ratio 1 : 3 : 10, each br, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 20.1 (t), 27.1 (t), 28.0 (q), 28.2 (q), 43.0 (t), 43.7 (d), 81.8 (s), 82.6 (s), 116.5 (s), 152.8 (s), 153.6 (s). *Anal.* Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found: C, 58.01; H, 8.00; N, 13.36.

Di-*tert*-butyl 3-Cyano-1,2,5,6-tetrahydropyridazine-1,2-dicarboxylate (10) Colorless oil. MS *m/z* 209 [(MH−Boc)$^+$], 109 [(MH_2−2Boc)$^+$]. IR (neat) cm^{-1}: 2231 (CN), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 and 1.55 (total 18H, intensity ratio 9 : 11, each s, *t*-Bu), [2.17 and 2.21 (total 1H, intensity ratio 1 : 1, each dd, J=4.8, 4.8 Hz), 2.41—2.57 (1H, m) 5-H_2], 2.98—3.22 and 4.29—4.48 (each 1H, m, 6-H_2), 6.04—6.18 (1H, dd, J=4.8, 4.8 Hz, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 22.7 (t), 28.0 (q), 28.1 (q), 41.5 (t), 82.3 (s), 84.8 (s), 113.9 (s), 115.1 (s), 128.0 (d), 150.7 (s), 154.0 (s). HR-MS *m/z*: 209.1160 (Calcd for $C_{10}H_{15}N_3O_2$: 209.1164), 109.0642 (Calcd for $C_5H_7N_3$: 109.0640).

Di-*tert*-butyl 3-(*tert*-Butoxycarbonylaminomethyl)hexahydropyri-

dazine-1,2-dicarboxylate (12) Colorless oil. MS *m/z* 415 (M^+). IR (neat) cm^{-1}: 3423 (NH), 1722, 1693 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.38—1.59 and 1.66—1.83 (28H, m and 3H, m, *t*-Bu×3, 4-H_2, 5-H_2), 2.77—3.48 (3H, m, 3-H, 6-H_2), 3.83—4.45 (2H, m, CH_2NHBoc), 4.70—4.95, 4.95—5.47 and 5.47—5.85 (total 1H, intensity ratio 1 : 10 : 4, each br, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.3 and 19.8 (each t), 23.9, 24.1 and 24.8 (each t), 28.2 (q), 28.3 (q), 28.4 (q), 39.6 and 40.1 (each t), 42.8 and 45.5 (each t), 52.5 and 54.4 (each d), 78.9 (s), 79.1 (s), 81.5 (s), 154.0 (s), 155.1 (s), 156.0 (s). HR-MS *m/z*: 415.2628 (Calcd for $C_{20}H_{37}N_3O_6$: 415.2682).

(±) Hexahydropyridazine-3-carboxylic Acid Trifluoroacetic Acid (13) A mixture of **9** (621 mg, 2 mmol) and 6 M HCl (20 ml) was refluxed for 24 h under argon atmosphere, and then evaporated *in vacuo*. The residue was desalted by ion-exchange chromatography on a Dowex 1×4 (50—100 mesh, CH_3COO^- form) column with water. After addition of AcOH (1 ml) to the eluent, the eluent was concentrated to dryness. 10% CF_3COOH was added to the obtained residue, and the mixture was evaporated *in vacuo* to give the crude trifluoroacetate, which was recrystallized from EtOH–AcOEt. White powder, 454 mg, 93% yield, mp 146—147 °C. MS (FAB) *m/z* 131 [(MH−TFA)$^+$]. IR (KBr) cm^{-1}: 3292, 3080, 2970 (OH, NH), 1724, 1664 (C=O). ^{1}H-NMR (D_2O) δ: 1.81—1.90, 1.90—1.95 and 2.07—2.16 (2H, m, 1H, m, 1H, m, 4-H_2, 5-H_2), 3.12—3.18 and 3.25—3.31 (each 1H, m, 6-H_2), 3.92 (1H, dd, J=8.0, 4.3 Hz, 3-H), ^{13}C-NMR (D_2O) δ: 20.1 (t), 25.1 (t), 45.7 (t), 56.6 (d), 117.1 (q_F, $^1J_{CF}$=291.7 Hz), 163.7 (q_F, $^2J_{CF}$=35.1 Hz), 174.6 (s). *Anal.* Calcd for $C_{17}H_{11}F_3N_2$: C, 34.43; H, 4.54; N, 11.47. Found: C, 34.52; H, 4.43; N, 11.27.

Di-*tert*-butyl 3-Cyano-5-oxohexahydropyridazine-1,2-dicarboxylate (17) To a solution of azodicarboxylate (**4**, 2.30 g, 10 mmol) in CH_2Cl_2 (10 ml) was added 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**14**, 90%, 2.38 ml, 11 mmol) at room temperature, and the mixture was stirred for 30 min. A solution of TMSCN (2.00 ml, 15 mmol) in CH_2Cl_2 (30 ml) and then a solution of $BF_3\cdot$OEt (0.63 ml, 5 mmol) in CH_2Cl_2 (10 ml) were added to the stirring mixture at −40 °C under argon atmosphere. The mixture was stirred under the conditions for 24 h. 2% $NaHCO_3$ aqueous solution (100 ml) was added to the mixture, and the aqueous mixture was vigorously stirred at room temperature for 1 h. The mixture was extracted with $CHCl_3$ (100 ml×3). The organic layer was washed with water (200 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using $CHCl_3$–MeOH (100 : 1) to give **17** (3.06 g, 94% yield). Colorless needles, mp 129—130 °C (from benzene–hexane). MS (FAB) *m/z* 326 (MH^+). IR (KBr) cm^{-1}: 2247 (CN), 1747, 1723 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.50, 1.51 and 1.55 (total 18H, intensity ratio 1 : 2 : 7, each s, *t*-Bu×2), 2.84—2.98 (2H, m, 4-H_2), 3.57—4.04, 4.45—4.62 and 4.74 (total 2H, intensity ratio 10 : 3 : 7, m, br, d, J=18.1 Hz, 6-H_2), 4.98—5.23 and 5.23—5.53 (total 1H, intensity ratio 3 : 7, m, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 27.8 and 28.0 (each q), 28.1 (q), 39.9 and 40.1 (each t), 43.9 and 45.8 (each d), 55.8 and 56.0 (each t), 83.5 (s), 84.0 (s), 116.3 (s), 152.2 (s), 153.4 (s), 199.4 (s). *Anal.* Calcd for $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.91. Found: C, 55.51; H, 7.00; N, 13.07.

$NaBH_4$ Reduction of 3-Cyano-5-oxohexahydropyridazine (17) $NaBH_4$ (567 mg, 15 mmol) was added to a stirred solution of **17** (3.25 g, 10 mmol) in EtOH (150 ml) at −0 °C, and the reaction mixture was stirred until disappearance of the starting material. Cold water (10 ml) was added to the mixture, the aqueous mixture was acidified with AcOH (the range of the pH value: 5—6). The whole mixture was evaporated, and water (100 ml) was added to the residue. The obtained aqueous mixture was extracted with AcOEt (300 ml×3). The combined organic layer was washed with water (200 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using AcOEt–hexane to give **18** and **19**.

LiAl(O*t*-Bu)$_3$H Reduction of 3-Cyano-5-oxohexahydropyridazine (17) A solution of **17** (3.25 g, 10 mmol) in dry THF (70 ml) was slowly added to a stirred solution of LiAl(O*t*-Bu)$_3$H (5.09 g, 20 mmol) in THF (80 ml) at −20 °C under argon atmosphere, and the mixture was stirred for 3 h under the same conditions. An aqueous solution of NH_4Cl (1.75 g) in water (20 ml) was slowly added to the mixture, and the aqueous mixture was acidified with 2 M HCl (the range of the pH value: 5—6). The obtained precipitate was filtered off, well washed with THF (100 ml). The filtrate was concentrated and extracted with AcOEt (300 ml×3). The combined organic layers were washed with water (200 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel using AcOEt–hexane to give **18** and **19**.

Di-*tert*-butyl *cis*-3-Cyano-5-hydroxyhexahydropyridazine-1,2-dicarboxylate (18) Colorless plates, mp 160—162 °C (from benzene–hexane). MS (FAB) *m/z* 328 (MH^+). IR (KBr) cm^{-1}: 3491 (OH), 2242 (CN), 1721, 1696 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.49 and 1.52 (total 18H, intensity ratio 2 : 3, each s, *t*-Bu×2), 2.01 and 2.16 (1H, ddd, J=14.4, 6.6, 3.0 Hz and 1H, dd, J=14.4, 1.4 Hz, 4-H_2), 2.58—2.82 and 2.82—2.98 (total 1H, intensity ratio 2 : 9, each br, OH), 3.02, 3.08—3.39 and 4.34 (total 2H, intensity ratio 5 : 2 : 7, d, J=14.2 Hz, m, d, J=14.2 Hz, 6-H_2), 4.03—4.22 (1H, m, 5-H), 5.03—5.09 and 5.27—5.30 (total 1H, intensity ratio 2 : 7, each m, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 27.9 (q), 28.2 (q), 32.6 (t), 39.0 and 41.2 (each d), 49.4 (t), 62.1 (d), 82.4 (s), 82.7 (s), 117.4 (s), 152.7 (s), 155.2 (s). *Anal.* Calcd for $C_{15}H_{25}N_3O_5$: C, 55.03; H, 7.70; N, 12.84. Found: C, 55.10; H, 7.52; N, 12.78.

Di-*tert*-butyl *trans*-3-Cyano-5-hydroxyhexahydropyridazine-1,2-dicarboxylate (19) Colorless prisms, mp 103—105 °C (from benzene–hexane). MS (FAB) *m/z* 328 (MH^+). IR (KBr) cm^{-1}: 3498 (OH), 2249 (CN), 1718, 1687 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 and 1.49 (total 18H, intensity ratio 5 : 1, each s, *t*-Bu×2), 1.78, 2.23 and 2.27—2.44 (total 2H, intensity ratio 4 : 3 : 1, ddd, J=16.7, 13.1, 5.7 Hz, ddd, J=13.3, 2.1, 2.1 Hz, m, 4-H_2), [2.60, 2.66—2.79 (total 1H, intensity ratio 2 : 1, dd, J=11.7, 11.2 Hz, m), 4.22 and 4.38 (total 1H, intensity ratio 1 : 5, dd, J=12.6, 4.6 Hz and dd, J=13.1, 4.4 Hz), 6-H_2], 3.17—3.29 and 3.49—3.66 (total 1H, intensity ratio 1 : 7, each br, OH), 4.04—4.15 (1H, m, 5-H), 5.21—5.30 and 5.30—5.48 (total 1H, intensity ratio 1 : 3, each br, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 28.0 (q), 28.1 (q), 35.1 and 35.7 (each t), 43.6 and 45.2 (each d), 49.6 and 51.2 (each t), 62.0 (s), 82.5 (s), 83.2 (s), 116.4 (s), 152.6 (s), 153.8 (s). *Anal.* Calcd for $C_{15}H_{25}N_3O_5$: C, 55.03; H, 7.70; N, 12.84. Found: C, 54.98; H, 7.51; N, 12.74.

***cis*-1-(2,4-Dinitrophenyl)-5-hydroxyhexahydropyridazine-3-carboxylic Acid (22)** A solution of *cis*-**18** (981 mg, 3 mmol) in AcOH (30 ml) and 6 M HCl (30 ml) was heated at 120 °C (bath temp.) for 24 h and then evaporated *in vacuo*. The obtained residue was dissolved in water (15 ml). Saturated $NaHCO_3$ aqueous solution (15 ml) and a solution of 1-fluoro-2,4-dinitrobenzene (1.15 ml, 9 mmol) in EtOH (25 ml) were added to the aqueous mixture at 0 °C, the whole mixture (pH 7—8) was stirred at room temperature for 2 h. After addition of 1% $NaHCO_3$ aqueous solution (45 ml) at 0 °C, the mixture was washed with ether (50 ml×2), acidified with 2 M HCl (pH 3), and then extracted with ether (50 ml×3). The organic layer was washed with brine (100 ml×4), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel using ether–MeOH to give **22**. Yellow prisms, mp 200 °C (decomp., from EtOH–ether–hexane), 92% yield. MS *m/z* 312 (M^+). IR (KBr) cm^{-1}: 3392 (OH, NH), 1733, 1610 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.32 (1H, ddd, J=12.0, 11.9, 11.0 Hz, 4-H*ax*), 2.20 (1H, ddd, J=12.0, 3.5, 3.2 Hz, 4-H*eq*), 2.80 (1H, dd, J=11.0, 11.0 Hz, 6-H*ax*), 3.34 (1H, ddd, J = 11.9, 11.9, 3.0 Hz, 3-H), 3.71—3.80 (1H, m, 5-H), 3.98 (1H, dd, J=11.8, 4.8 Hz, 6-H*eq*), 5.09 (1H, d, J=11.9 Hz, NH), 5.20—5.45 (1H, br, OH), 7.22 (1H, d, J=9.4 Hz, 6′-H in Ph-H), 8.19 (1H, ddd, J=9.4, 2.7, 0.5 Hz, 5′-H in Ph-H), 8.33 (1H, dd, J=2.7, 0.5 Hz, 3′-H in Ph-H), 12.54—13.20 (1H, br, COOH). ^{13}C-NMR (DMSO-d_6) δ: 36.9 (t), 52.5 (t), 56.0 (d), 63.7 (d), 115.2 (d), 121.7 (d), 127.2 (d), 136.4 (s), 137.5 (s), 147.1 (s), 171.8 (s). *Anal.* Calcd for $C_{11}H_{12}N_4O_7$: C, 42.31; H, 3.87; N, 17.94. Found: C, 42.32; H, 3.92; N, 17.87.

***trans*-1-(2,4-Dinitrophenyl)-5-hydroxyhexahydropyridazine-3-carboxylic Acid (23)** The title compound was prepared from **19** in a similar manner to that described for **22**. Yellow powder, mp 164—165 °C (from EtOH–ether–hexane), 72% yield. MS *m/z* 312 (M^+). IR (KBr) cm^{-1}: 3415 (OH, NH), 1720, 1608 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.70 (1H, dd, J=11.5, 10.8 Hz, 4-H*ax*), 1.87 (1H, ddd, J=13.1, 3.1, 3.1 Hz, 4-H*eq*), 3.38 and 3.77—3.83 (each 1H, d, J=12.4 Hz, br, 6-H_2), 3.73 (1H, ddd, J=11.2, 11.1, 3.0 Hz, 3-H), 4.05—5.14 (1H, m, 5-H), 5.09—5.14 (1H, br, OH), 5.18 (1H, d, J=11.2 Hz, NH), 7.18 (1H, d, J=9.4 Hz, 6′-H in Ph-H), 8.15 (1H, dd, J=9.4, 2.5 Hz, 5′-H in Ph-H), 8.30 (1H, d, J=2.5 Hz, 3′-H in Ph-H), 12.24—12.95 (1H, br, COOH). ^{13}C-NMR (DMSO-d_6) δ: 34.0 (t), 60.2 (t), 61.8 (d), 72.2 (d), 115.1 (d), 121.8 (d), 126.9 (d), 135.4 (s), 136.8 (s), 148.1 (s), 172.7 (s). *Anal.* Calcd for $C_{11}H_{12}N_4O_7$: C, 42.31; H, 3.87; N, 17.94. Found: C, 42.63; H, 3.97; N, 17.65.

Di-*tert*-butyl *trans*-5-Chloro-3-cyanohexahydropyridazine-1,2-dicarboxylate (24) A mixture of **18** (0.57 g, 1.73 mmol), CCl_4 (2.6 ml) and PPh_3 (0.76 g, 2.86 mmol) in dry THF (2.6 ml) was stirred at 20 °C under argon atmosphere for 3 d, and then evaporated *in vacuo*. The residue was treated with a mixed solvent of AcOEt, $CHCl_3$ and hexane (5, 21, 14 ml). After filtration off for removal of the precipitate (Ph_3PO), the obtained filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane–AcOEt to give **24**. Colorless prisms, mp 119—120 °C (from hexane), 70% yield. MS *m/z* 345, 347 (M^+). IR (KBr) cm^{-1}: 2256 (CN), 1712 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.49, 1.50 and 1.51 (total 18H, each s, intensity ratio 4 : 7 : 1, *t*-Bu×2), 2.06 and 2.46 (each 1H, ddd, J=13.5, 12.0,

5.5 Hz and ddd, J=13.5, 2.1, 2.1 Hz, 4-H_2), 2.74—3.09, 4.32—4.44 and 4.60 (total 2H, intensity ratio 6 : 1 : 5, m, m and dd, J=13.3, 3.9 Hz, 6-H_2), 4.13—4.27 (1H, m, 5-H), 5.11—5.30 and 5.30—5.54 (total 1H, intensity ratio 3 : 7, each br, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 27.9 (q), 28.1 (q), 36.9 (t), 44.2 (d), 48.3 (t), 49.8 (d), 82.8 (s), 83.4 (s), 116.7 (s), 152.3 (s), 152.9 (s). *Anal.* Calcd for $C_{15}H_{24}ClN_3O_4$: C, 52.10; H, 7.00; N, 12.15. Found: C, 52.27; H, 6.95; N, 12.21.

Di-*tert*-butyl *cis*-5-Chloro-3-cyanohexahydropyridazine-1,2-dicarboxylate (25) The title compound was prepared from **19** in a similar manner to that described for **24**. Colorless prisms, mp 129—130 °C (from benzene–hexane), 60% yield. MS m/z 345, 347 (M^+). IR (KBr) cm^{-1}: 2245 (CN), 1728, 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.49, 1.53 and 1.54 (total 18H, intensity ratio 3 : 3 : 4, each s, *t*-Bu×2), 2.30—2.34 (2H, m, 4-H_2), 3.20—3.54, 4.35 and 4.54 (total 2H, intensity ratio 5 : 1 : 4, m, d, J=14.2 Hz and dd, J=14.4, 1.8 Hz, 6-H_2), 4.24—4.32 (1H, m, 5-H), 5.05—5.25 and 5.25—5.43 (total 1H, intensity ratio 4 : 1, each br, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 27.9 (q), 28.1 and 28.2 (each q), 33.6 and 33.8 (each t), 38.7 (d), 49.3 (t), 50.7 and 50.9 (each d), 82.5 (s), 83.2 (s), 116.6 (s), 152.5 (s), 152.7 (s). *Anal.* Calcd for $C_{15}H_{24}ClN_3O_4$: C, 52.10; H, 7.00; N, 12.15. Found: C, 52.04; H, 6.75; N, 12.12.

***trans*-5-Chloro-1-(2,4-dinitrophenyl)hexahydropyridazine-3-carboxylic Acid (27)** The title compound was prepared from **24** in a similar manner to that described for **22**. Yellow prisms, mp 186—189 °C (decomp., from EtOH–ether–hexane), 81% yield. MS m/z 330, 332 (M^+). IR (KBr) cm^{-1}: 3263 (OH, NH), 1736, 1608 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.98—2.19 (2H, m, 4-H_2), 3.55—3.75, 3.95—4.22 (each 1H, br, 6-H_2), 3.80 (1H, ddd, J=11.0, 11.0, 3.5 Hz, 3-H), 4.84 (1H, br, 5-H), 5.39 (1H, d, J=11.1 Hz, NH), 7.24 (1H, d, J=9.5 Hz, 6′-H in Ph-H), 8.19 (1H, dd, J=9.5, 2.7 Hz, 5′-H in Ph-H), 8.36 (1H, d, J=2.7 Hz, 3′-H in Ph-H), 12.9 (1H, br s, COOH). ^{13}C-NMR (DMSO-d_6) δ: 34.7 (t), 51.9 (t), 52.4 (d), 55.0 (d), 115.1 (d), 121.8 (d), 127.2 (d), 136.6 (s), 137.4 (s), 147.5 (s), 171.8 (s). *Anal.* Calcd for $C_{11}H_{11}ClN_4O_6$: C, 39.95; H, 3.35; N, 16.94. Found: C, 40.07; H, 3.47; N, 16.79.

Di-(−)-menthyl 3-Cyano-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (29) The title compound was prepared as a mixture of the diastereomers from **3** and menthyl carboxylate (**28**)[28] in a similar manner to that described for **6**. Colorless oil, 99% yield. MS m/z 473 (M^+). IR (neat) cm^{-1}: 2245 (CN), 1713 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.67—1.15 (24H, m, 2′-isopropyl-H×2, 5′-Me×2, 4′-H_2×2), 1.29—1.57 (4H, br, 3′-H_2×2), 1.62—2.21 (8H, m, 2′-H×2, 5′-H×2, 6′-H_2×2), 3.61—4.00 and 4.35—4.82 (1H, m, 3H, m, 6-H_2×2, 1′-H×2), 5.27—5.73 (1H, br, 3-H), 5.85 (1H, br s, 4-H), 6.11 (1H, br s, 5-H).

Hydrogenation of 29 with 70% $HClO_4$ Compound **29** was hydrogenated in EtOH and worked up as described for **9** to give **30** and **31**.

Di-(−)-menthyl (3*R*)-3-Cyanohexahydropyridazine-1,2-dicarboxylate (30) Colorless prisms, mp 108—109 °C (from hexane). MS (FAB) m/z 476 (MH^+). IR (KBr) cm^{-1}: 2251 (CN), 1716 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.67—1.15 (24H, m, 2′-isopropyl-H×2, 5′-Me×2, 4′-H_2×2), 1.23—1.56 (4H, m, 3′-H_2×2), 1.60—2.20 (12H, m, 2′-H×2, 5′-H×2, 6′-H_2×2, 4-H_2, 5-H_2), [2.73—3.08 (1H, m), 4.19 and 4.34 (total 1H, intensity ratio 1 : 4, each d, J=13.5 and 11.7 Hz), 6-H_2], 4.50—4.76 (2H, m, 1′-H×2), 5.13—5.48 (1H, br, 3-H). $[\alpha]_D^{25}$ −26.8 (c=0.95, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{45}N_3O_4$: C, 68.18; H, 9.54; N, 8.83. Found: C, 68.12; H, 9.34; N, 8.81.

Di-(−)-menthyl (3*S*)-3-Cyanohexahydropyridazine-1,2-dicarboxylate (31) Colorless prisms, mp 50—51 °C (from hexane). MS (FAB) m/z 476 (MH^+). IR (KBr) cm^{-1}: 2249 (CN), 1732, 1709 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.15 (24H, m, 2′-isopropyl-H×2, 5′-Me×2, 4′-H_2×2), 1.30—1.57 (4H, m, 3′-H_2×2), 1.62—2.19 (12H, m, 2′-H×2, 5′-H×2, 6′-H_2×2, 4-H_2, 5-H_2), [2.75—3.18 (1H, m), 4.17 and 4.33 (total 1H, intensity ratio 2 : 3, each d, J=12.8 and 11.5 Hz), 6-H_2], 4.50—4.77 (2H, m, 1′-H×2), 5.12—5.44 (1H, br, 3-H). $[\alpha]_D^{25}$ −82.9 (c=0.97, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{45}N_3O_4$: C, 68.18; H, 9.54; N, 8.83. Found: C, 67.99; H, 9.23; N, 8.67.

(3*R*)-Hexahydropyridazine-3-carboxylic Acid Trifluoroacetic Acid (32) The title compound was prepared from **30** in a similar manner to that described for **13**. White powder, mp 145—147 °C (from EtOH–AcOEt) (lit.[14] mp 147—149 °C), 95% yield. IR (KBr) cm^{-1}: 3442, 3292, 3080 (OH, NH), 1720, 1664 (C=O). $[\alpha]_D^{22}$ −11.6 (c=0.97, MeOH).

(3*S*)-Hexahydropyridazine-3-carboxylic Acid Trifluoroacetic Acid (33) The title compound was prepared from **31** in a similar manner to that described for **13**. White powder, mp 145—147 °C (from EtOH–AcOEt) (lit.[16] mp 149—151 °C), 91%. IR (KBr) cm^{-1}: 3442, 3292, 3080 (OH, NH), 1720, 1664 (C=O). $[\alpha]_D^{28}$ +11.6 (c=1.03, MeOH).

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