Diastereoselective Synthesis and Estimation of the Conformational Flexibility of 6-Oxoperhydropyridazine-3-carboxylic Acid Derivatives

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α,β-Didehydroglutamates have been diastereoselectively transformed into 6-oxoperhydropyridazine-3-carboxylic acid derivatives (OPCAs), which constitute a new class of cyclic amino acid derivatives. Acylation at N-1 renders dipeptides which show considerable conformational rigidity. Semiempirical calculations suggest that OPCAs might force peptide turns with different amplitudes depending on the substitution pattern and relative stereochemistry of the substituents of the pyridazinone ring.

Introduction

Biological processes are mainly governed by the interaction of peptides with macromolecular receptors. For these interactions to be successful, the three-dimensional conformation of the peptide chain is of crucial importance. There are considerable efforts to improve the pharmacological properties of natural peptides by structure modifications of the amino acid constituents.[1] However, it is difficult to determine a priori the optimum conformation of a peptide required to obtain the desired biological response. Therefore, new procedures to enforce conformational restrictions in peptides are welcome.

In this context, proline (Pro) occupies a special place among the natural amino acids. The incorporation of stereochemically constrained amino acids into peptides can effectively reduce the populations of possible peptide chain conformations. Accordingly, Pro derivatives have been incorporated into bioactive peptides to study conformational effects.[2] However, the imidic bond formed with the preceding N-terminal amino acid is subject to isomerization, and both *cis* and *trans* isomers occur in solution ($\Delta G° < 2$ kcal/mol).[3] Therefore, numerous Pro mimetics have been developed to control the *cis*:*trans* ratio.[4] In particular, replacement of Pro for its higher homologue pipecolic acid (2-piperidinecarboxylic acid, homoproline) (Pip) promotes significant changes in bioactivity and leads to interesting model compounds for studies on peptide conformations.[5] More recently ϵ-azapipecolic acid (piperazic acid) (Piper) and 2,3,4,5-tetrahydropyridazine-3-carboxylic acid derivatives (PCAs) have attracted attention as highly rigid conformational analogues of proline.[6]

We have considered the possibility of using the closely related[7] 6-oxoperhydropyridazine-3-carboxylic acid derivatives (OPCAs) as templates to control the geometry (β-turn)[8] of a peptide chain. In parallel with Piper derivatives and PCAs, a *trans* conformation ($\omega = 0°$) of the chain would be expected in OPCAs. Furthermore, the stereochemically controlled introduction of different substituents at carbons C-4 and C-5 of the pyridazinone skeleton of OPCAs may help stabilize different ring conformations, which will enforce different dihedral angles (ϕ) for the peptide chain (Figure 1).

Results and Discussion

The synthesis of the *N*-acyl OPCAs **9** and **10** was accomplished starting from the readily obtainable α,β-didehydroglutamates (DDGlu) **3** as common starting materials as outlined in Scheme 1.

Enolization of **1** (KO^{t}Bu, THF, −78 °C) followed by reaction with methylpropiolate (**2a**) gave rise to (*Z*)-**3a**

(1) (a) *Peptide Secondary Structure Mimetics, Tetrahedron*; Kahn, M., Ed.; Tetrahedron Symposia in Print No. 50; Elsevier: New York, 1993; Vol. 49, p 3433. (b) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (c) Giannis, A.; Rübsam, F. *Adv. Drug Res.* **1997**, *29*, 1. (d) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Chem. Biol.* **1999**, *9*, 530. (e) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714.

(2) See for example: (a) Hondrelis, J.; Lonergan, G.; Voliotis, S.; Matsoukas, J. *Tetrahedron* **1990**, *46*, 565. (b) Karenewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Lee, V. G.; Loots, M. J.; Petrillo, E. W. *J. Med. Chem.* **1990**, *33*, 1459. (c) Shuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith, G. F.; Giffordmoore, D. S.; Paschal, J. W.; Gesellchen, P. D. *J. Med. Chem.* **1995**, *38*, 4446. (c) Mierke, D. F.; Pattaroni, C.; Delaet, N.; Toy, A.; Goodman, M.; Tancredi, T.; Motta, A.; Temussi, P. A.; Moroder, L.; Bovermann, G.; Wunsch, E. *Int. J. Pept. Protein Res.* **1990**, *36*, 418. (d) Juvradi, P.; Dooley, D. J.; Humblet, C. C.; Lu, G. H.; Lunney, E. A.; Panek, R. L.; Skeean, R.; Marshall, G. R. *Int. J. Pept. Protein Res.* **1992**, *40*, 163. (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L.; Mishenko, N. *Tetrahedron* **1999**, *55*, 12031. (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L. *Tetrahedron* **1999**, *55*, 12045.

(3) Kern, D.; Schutkowski, M.; Drakenberg, T. *J. Am. Chem. Soc.* **1997**, *119*, 8403.

(4) See: (a) Dummy, P.; Keller, M.; Ryan, D. E.; Rohwedder, B.; Wöhr, T.; Mutter, M. *J. Am. Chem. Soc.* **1997**, *119*, 918. (b) Beausoleil, R.; Sharma, R.; Michnick, S. W.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 6572. (c) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902. (d) Chalmers, D. K.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 5927 and references cited therein.

(5) (a) Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287. (b) Genin, M. J.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 860. (c) Maison, W.; Lützen, A.; Kosten, M.; Schlemminger, I.; Westerhoff, O.; Saak, W.; Martens, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1867.

(6) Xi, N.; Alemany, L. B.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 80.

(7) Both PCAs and OPCAs are six-membered heterocycles with two nitrogen atoms at positions 1 and 2, and C-6 is sp^2 hybridized. The nitrogen at position 1 is sp^2 hybridized in PCAs, while the nitrogen at position 1 is sp^3 hybridized in OPCAs. See the calculations.

(8) (a) Giannis, A.; Kolter, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (c) Kahn, M. *Synthesis* **1993**, 821.

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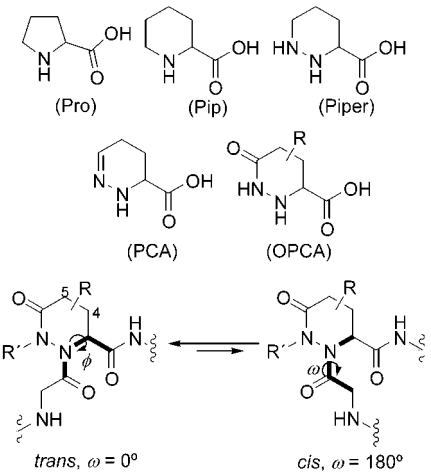


Figure 1.

Scheme 1

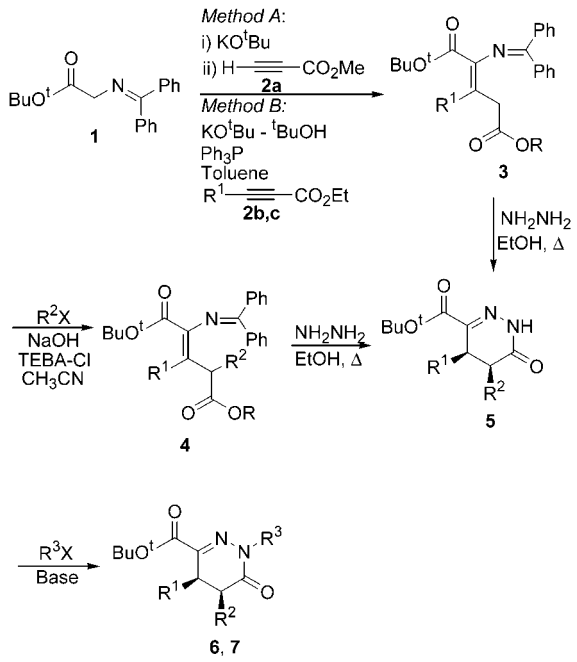


Table 1. Synthesis of 3

no.	R^1	**3** (%)[a]	(*Z*)-**3**:(*E*)-**3**[b]
1	H	**3a** (85)	100:0
2	CH_3	**3b** (90)	65:35
3	Ph	**3c** (85)	30:70

[a] Isolated yield. [b] Determined by integration of the ^{1}H NMR ($CDCl_3$, 300 MHz) of the crude reaction products.

in a thermodynamically driven process.[9] On the other hand, compounds **3b,c** were best prepared[10] by treatment of **1** with alkynoates **2b,c** (1 equiv) in the presence of KO^{t}Bu (0.5 equiv), ^{t}BuOH (0.5 equiv), and Ph_3P (5 mol %). Compounds **3b,c** were obtained as *Z*:*E* mixtures (Scheme 1, Table 1)[11] which could be separated by silica gel chromatography (hexane−Et_2O, 80:20).

Table 2. Synthesis of 4

no.	R^1	R^2	**4** (%)[a]	(*Z*)-**4**:(*E*)-**4**[b]
1	H	CH_3	**4a** (90)	100:0
2	H	Bn	**4b** (90)	100:0
3	CH_3	CH_3	**4c** (85)	65:35
4	CH_3	Bn	**4d** (85)	85:15
5	Ph	CH_3	**4e** (80)	0:100
6	Ph	Bn	**4f** (75)	0:100

[a] Isolated yield [b] Determined by integration of the ^{1}H NMR ($CDCl_3$, 300 MHz) of the crude reaction products

Table 3. Synthesis of 5a−e and 4,5-*cis*-5f,g from 3 and 4

no.	R^1	R^2	**5** (%)[a]	4,5-*cis*:4,5-*trans*[b]
1	H	CH_3	**5a** (85)	
2	H	Bn	**5b** (85)	
3	CH_3	H	**5c** (80)	
4	Ph	H	**5d** (75)	
5	H	H	**5e** (85)	
6	CH_3	CH_3	4,5-*cis*-**5f** (75)	>99:<01
7	CH_3	Bn	4,5-*cis*-**5g** (75)	70:30[c]

[a] Isolated yield. [b] Determined by integration of the ^{1}H NMR ($CDCl_3$, 300 MHz) of the crude reaction products. [c] Separated by silica gel chromatography (hexanes−EtOAc, 80:20).

Alkylation of compounds **3** under solid−liquid PTC conditions took place exclusively at C-4[12,13] (R^2X, NaOH, (TEBA)Cl, acetonitrile), giving rise to compounds **4** as *Z*:*E* mixtures (Table 2). However, it was found that compounds **4** were obtained with the same *Z*:*E* ratio irrespective of the double bond geometry of the starting materials **3b**, thus making unnecessary the separation of isomers (*Z*)-**3b,c** and (*E*)-**3b,c**. The results are gathered in Table 2.

Cyclization (NH_2–NH_2, EtOH) of compounds **3** or **4a,b** (R^1 = H) and **4c,d** (R^1 = CH_3) afforded the 6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylates **5**. However, compounds **4e,f** (R^1 = Ph) did not cyclize under these reaction conditions. In the case of compounds **4c,d**, cyclization to the corresponding 4,5-*cis*-**5f,g** took place in a diastereoselective fashion (Table 3).

This stereochemistry was evidenced by the value of the $^3J_{H4-H5}$ coupling constant (4,5-*cis*-**5f**, $^3J_{H4-H5}$ = 7.0 Hz; 4,5-*cis*-**5g**, $^3J_{H4-H5}$ = 6.5 Hz), which is in agreement with the dihedral angle value estimated for H4−C−C−H5 in compound 4,5-*cis*-**5f**.[14,15]

PM3 calculations carried out for compound 4,5-*cis*-**5f** (R^1 = CH_3, R^2 = CH_3) put forward two minimum-energy conformations of similar energy (ΔH_f(I) = −112.6 kcal/mol, ΔH_f(II) = −113.0 kcal/mol, $\Delta\Delta H_f$ = 0.4 kcal/mol) where the CH_3 groups can adopt either a pseudoaxial or a pseudoequatorial disposition. Dihedral angles H4−C−C−H5 of 44° and 46° were obtained for these conformers. In a similar fashion, calculations carried out for the 4,5-*trans* configuration of **5f** rendered two minimum-energy conformers (ΔH_f(I) = −114.7 kcal/mol, ΔH_f(II) = −114.9 kcal/mol, $\Delta\Delta H_f$ = 0.3 kcal/mol), both with dihedral angles H4−C−C−H5 of 87°. This should correspond to a coupling constant $^3J_{H4-H5}$ smaller than those actually observed for compounds 4,5-*cis*-**5f,g**.

(9) Alvarez-Ibara, C.; Csákÿ, A. G.; Martín, E.; de la Morena, M. J.; Quiroga, M. L. *Tetrahedron Lett.* **1997**, *38*, 4501.

(10) Direct reaction of iminoglycinates **1** and related compounds with alkynoates **2b,c** requires the use of naked enolates. See ref 9.

(11) The assignment of the *E* or *Z* geometry of compounds **3b,c** was based on the comparison of their ^{1}H and ^{13}C NMR spectra with those previously described for closely related compounds. See refs 9 and 12.

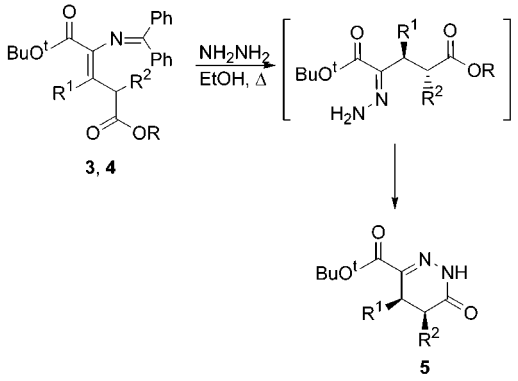
(12) Alvarez-Ibarra, C.; Csákÿ, A. G.; Martín, M. E.; Quiroga, M. L. *Tetrahedron* **1999**, *55*, 7319.

(13) Alvarez-Ibarra, C.; Csákÿ, A. B.; Gómez de la Oliva, C.; Rodríguez, E. *Tetrahedron Lett.* **2001**, *42*, 2129.

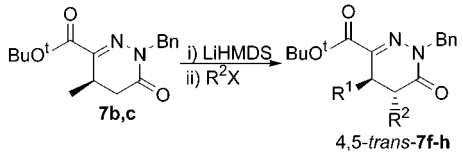
(14) $^3J_{H4-H5}$ and NOE correlations of 4,5-*cis*-**5f** are also to be compared with those obtained for 4,5-*trans*-**6f**.

(15) Further confirmation of the *cis* stereochemical assignment came from NOE experiments carried out on 4,5-*cis*-**5f**. Thus, irradiation of H-5 in the ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) (δ = 2.68, q) gave rise to a 4% NOE enhancement of the signal of H-4 (δ = 3.16, q).

Scheme 2



Scheme 3



4,5-*trans*-**7f**, $R^1 = CH_3$, $R^2 = CH_3$, 95 %, *de* > 98%
4,5-*trans*-**7g**, $R^1 = CH_3$, R^2 = Bn, 90%, *de* > 98%
4,5-*trans*-**7h**, R^1 = Ph, $R^2 = CH_3$, 95%, *de* > 98%

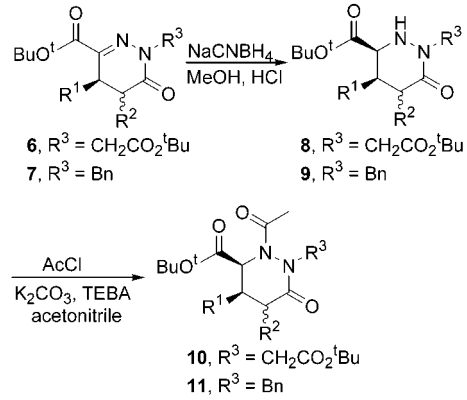
These calculations also put forward a higher stability of **5f** in a 4,5-*trans* configuration than in a 4,5-*cis* configuration. Therefore, the obtention of compound 4,5-*cis*-**5f** from the reaction with hydrazine of the didehydroglutamates **4c,d** can be accounted for by the intermediacy of the more stable *anti* open-chain hydrazone, which affords the 4,5-*cis* products upon cyclization (Scheme 2). This also explains the failure in the cyclization of **4e,f** (R^1 = Ph), as a consequence of the steric hindrance.

Dihydropyridazinones **5** were transformed (Scheme 1) into compounds **6** and **7** by reaction with either ^{t}butylbromoacetate (**6**; LiHMDS, THF, −78 °C) or BnBr (**7**; K_2CO_3, (TEBA)Cl, acetonitrile).

To access the 4,5-*trans* diastereomers of the final compounds **10** and **11**, an alternative strategy for the introduction of the C-5 substituent was devised at this stage (Scheme 3). Therefore, the C-5-unsubstituted dihydropyridazinones **7a,b** were enolized (LiHMDS, THF, −78 °C) and reacted with electrophiles. These alkylations took place *anti* with respect to R^1 (CH_3 or Ph), giving rise to compounds 4,5-*trans*-**7f**−**h**. It is worth mentioning that this strategy allowed for the synthesis of compound **7h** (R^1 = Ph, 4,5-*trans*), whereas the synthesis of the corresponding 4,5-*cis* compound was not possible by cyclization of **4e** with NH_2–NH_2 (vide supra). The 4,5-*trans* stereochemisty of compounds 4,5-*trans*-**7f**−**h** was evidenced by the value of the $^3J_{H4-H5}$ coupling constant (1.5 Hz) and NOE measurements.[16,17]

The OPCAs **8** ($R^3 = CH_2CO_2{}^t$Bu) and **9** (R^3 = Bn) were prepared by reduction of the imino bond of compounds **6** and **7**, which was carried out with $NaCNBH_3$ (MeOH, HCl). It was found that the diastereoselectivity of these transformations was controlled by the substituent at C-4

Scheme 4



of the pyridazinone ring (Scheme 4). Thus, attack of the hydride took place from the opposite side of the ring with respect to R^1, giving rise to high diastereoselectivities in favor of the 3,4-*cis* isomers of compounds **8** and **9** irrespective of the 4,5-stereochemistry of the starting materials. On the other hand, lower diastereoselectivities were found in the reductions of compounds **6a,b** (R^1 = H). The results are gathered in Table 4. The stereochemistry of compounds **8** and **9** was assigned by comparison of their NMR data with those of 3,4-*cis*-4,5-*cis*-**8d**, for which NOE measurements were carried out.[18]

Finally, compounds **10** and **11** were synthesized by acylation of N-1 of the OPCAs **8** and **9** (AcCl, K_2CO_3, (TEBA)Cl, acetonitrile) (Scheme 4).

Compounds **12**−**16** were chosen as simplified models for the conformational study[19] of the OPCAs **10** and **11** (Figure 2).

Molecular mechanics (MM+ force field) calculations were used as a rough estimate[20] of the geometries of the different conformers which were used as inputs for semiempirical (PM3) calculations.[21] Initial minimization (MM+ force field) of compound **12** in an *ω-trans* conformation ($\omega = 0°$) gave rise to a cyclohexanone-like ring, where the substituents at N-1, N-2, and C-3 could adopt either a pseudoequatorial or a pseudoaxial disposition (eight conformers). Independent minimization (PM3) of each of these eight conformers gave rise to three minimum-energy conformations,[22] *ω-trans*-**12a**−**c** (Table 5, entries 1−3). These conformers showed different values for the dihedral angle ϕ. However, the energy difference ($\Delta\Delta H°$) found for conformers *ω-trans*-**12a**−**c** was less than 2 kcal/mol. The same protocol was followed starting from compound **12** in an *ω-cis* ($\omega = 180°$) conformation, giving rise to conformers *ω-cis*-**12a**−**c** (Table 5, entries 4−6) whose energies ($\Delta\Delta H°$) also differed by less than 2 kcal/mol.

The previous conformers estimated for compound **12** by molecular mechanics calculations in either an *ω-cis*

(16) $^3J_{H4-H5}$ and NOE correlations of 4,5-*trans*-**6f** are to be compared with those obtained for 4,5-*cis*-**5f**.

(17) Irradiation of H-5 in the ^{1}H NMR spectrum of **7d** ($CDCl_3$, 300 MHz) (δ = 2.48, qd) gave rise to a 5% NOE enhancement of the signal of CH_3–C-4 (δ = 1.09, d), and no NOE was observed with H-5 (δ = 2.90, qd).

(18) Irradiation of H-3 in the ^{1}H NMR spectrum of **8d** ($CDCl_3$, 300 MHz) (δ = 3.66, d) gave rise to a 4% NOE enhancement of the signal of H-4 (δ = 4.11, ddd).

(19) All calculations were carried out with the Hyperchem 5.0 package, Hypercube, Inc., Ontario, Canada.

(20) Cyclic hydrazones of the type found in PCAs or OPCAs are not parametrized in the MM+ method. The starting geometries calculated by this procedure are approximate and only of qualitative value.

(21) Repulsive forces are not particularly strong in PM3. The conformational energy differences calculated by this method represent lower-end estimates.

(22) The minimum-energy conformation and those which did differ by less than 2.5 kcal/mol were selected for all compounds **12**−**16**. All conformers showed pyramidalized nitrogen atoms for both N-1 and N-2.

Table 4. Synthesis of 8 and 9 from 6 and 7

no.	R^1	R^2	R^3	**6**, **7**	**8**, **9** (%)[a]	de (%)[b]
1	H	CH_3	$CH_2CO_2{}^tBu$	**6a**	3,5-*cis*-**8a** (50)	20
2	H	Bn	$CH_2CO_2{}^tBu$	**6b**	3,5-*cis*-**8b** (45)	20
3	CH_3	H	$CH_2CO_2{}^tBu$	**6c**	3,4-*cis*-**8c** (85)	>98
4	Ph	H	$CH_2CO_2{}^tBu$	**6d**	3,4-*cis*-**8d** (80)	>98
5	H	H	$CH_2CO_2{}^tBu$	**6e**	**8e** (90)	
6	CH_3	CH_3	$CH_2CO_2{}^tBu$	4,5-*cis*-**6f**	3,4-*cis*-4,5-*cis*-**8f** (80)	>98
7	CH_3	Bn	$CH_2CO_2{}^tBu$	4,5-*cis*-**6g**	3,4-*cis*-4,5-*cis*-**8g** (80)	>98
8	CH_3	H	Bn	**7a**	3,5-*cis*-**9a** (90)	>98
9	Ph	H	Bn	**7b**	3,5-*cis*-**9b** (85)	>98
10	H	H	Bn	**7c**	**9c** (95)	
11	CH_3	CH_3	Bn	4,5-*trans*-**7d**	3,4-*cis*-4,5-*trans*-**9d** (85)	>98
12	CH_3	Bn	Bn	4,5-*trans*-**7e**	3,4-*cis*-4,5-*trans*-**9e** (80)	>98
13	Ph	CH_3	Bn	4,5-*trans*-**7f**	3,4-*cis*-4,5-*trans*-**9f** (80)	>98

[a] Isolated yield. [b] Determined by integration of the ^1H NMR ($CDCl_3$, 300 MHz) of the crude reaction products. In entries 3−13 none of the other isomers could be detected by ^1H NMR. [c] Separated by silica gel chromatography (hexanes−Et_2O, 80:20).

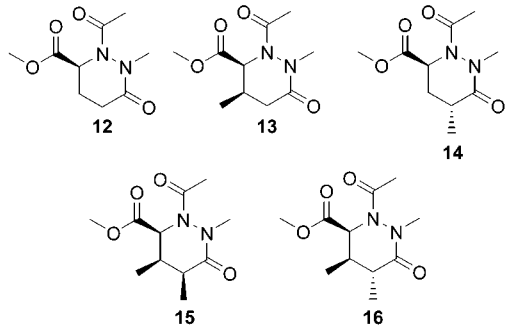
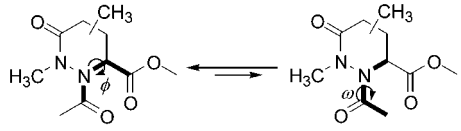


Figure 2.

Table 5. Conformational Preferences in OPCAs 12−16



no.	conformation	ΔH_f[a]	ϕ (deg)	ω (deg)
1	*ω-trans*-**12a**	144.0	140	21
2	*ω-trans*-**12b**	142.2	153	12
3	*ω-trans*-**12c**	143.6	109	30
4	*ω-cis*-**12a**	141.4	143	179
5	*ω-cis*-**12b**	140.7	158	171
6	*ω-cis*-**12c**	142.9	136	131
7	*ω-trans*-**13a**	148.7	140	20
8	*ω-trans*-**13b**	147.1	95	8
9	*ω-cis*-**13a**	146.3	143	179
10	*ω-cis*-**13b**	144.8	111	147
11	*ω-trans*-**14a**	148.1	141	15
12	*ω-cis*-**14a**	145.1	147	165
13	*ω-trans*-**15a**	148.8	136	20
16	*ω-trans*-**15b**	150.9	95	10
17	*ω-cis*-**15a**	146.2	137	177
18	*ω-cis*-**15b**	148.7	109	149
19	*ω-trans*-**16a**	153.3	140	15
20	*ω-trans*-**16b**	150.9	94	10
21	*ω-cis*-**16a**	151.3	142	142
22	*ω-cis*-**16b**	148.3	105	153

[a] PM3 calculation, kcal/mol.

($\omega = 180°$) or an *ω-trans* ($\omega = 0°$) disposition were used as starting geometries to estimate the conformational population of compounds **13**−**16** by replacing H-4 and/or H-5 by methyl and running semiempirical (PM3) calculations. The minimum-energy conformations[22] and geometries thus calculated are gathered in Table 5. Inspection of these data reveals that replacement of H-4 by methyl afforded only two minimum-energy conformations for compounds *ω-cis*-**13** and *ω-trans*-**13** (Table 5, entries 7−10) instead of the three previously obtained for **12** (Table 5, entries 1−6). However, the energy difference ($\Delta\Delta H°$) was again less than 2 kcal/mol. On the other hand, replacement of H-5 in **12** by methyl afforded single minimum-energy conformations for *ω-cis*-**14** and *ω-trans*-**14** (Table 5, entries 11 and 12).[23] Furthermore, the energy difference ($\Delta\Delta H°$) between the *ω-cis* and *ω-trans* conformers of **14** was 2.97 kcal/mol, which corresponds to a rotamer ratio[24] of 99:1 in favor of *ω-trans*-**14**. Replacement of both H-4 and H-5 in **12** gave rise to **15** and **16**. In the case of **15** (Table 5, entries 13−18), the corresponding *ω-trans* conformations were favored over the *ω-cis* conformations, and conformer *ω-trans*-**15b** ($\phi = -95°$) was favored over *ω-trans*-**15a** (conformation ratio 3:97 for *ω-trans*-**15a**:*ω-trans*-**15b**). In a similar fashion, the *ω-trans* conformations were favored over the *ω-cis* conformations for compound **16** (Table 5, entries 19−22). However, opposite to the case of **15**, conformation *ω-trans*-**16a** ($\phi = -140°$) was favored over *ω-trans*-**16b** (conformation ratio 98:2 for *ω-trans*-**16a**:*ω-trans*-**16b**).[25]

These results qualitatively suggest that OPCAs **10** and **11** show a preference for the *ω-trans* geometry and might force peptide turns with different amplitudes (ϕ angle) as a function of the substitution pattern and relative stereochemistry of the substituents of the pyridazinone ring:[26] $\phi \approx 140-145°$ for the C-5-monosubstituted and *trans*-C-4,5-disubstituted derivatives, and $\phi \approx 95°$ for the *cis*-C-4,5-disubstituted ones.

Conclusions

The present study puts forward that OPCAs can be prepared in a highly diastereoselective fashion using readily available α,β-didehydroglutamates as starting materials. This synthesis allows for the mono- or disubstitution of the pyridazinone moiety of OPCAs at carbons C-4 and C-5, which can be obtained at will either in a 4,5-*cis* fashion or in a 4,5-*trans* fashion. Reduction of the C=N bond took place with high diastereoselectivity in favor of the 3,4-*cis* stereochemistry. These compounds can

(23) The complementary stereochemistry, i.e., 3,5-*anti*, was not considered, as compounds **10a,b** and **11a,b** have only been obtained as the corresponding 3,5-*cis* isomers.

(24) Estimated from $\Delta\Delta H° \approx \Delta\Delta G° = -RT \ln K$ at 25 °C.

(25) No significant qualitative modifications of these results with respect to the ϕ or ω angles were observed upon replacement of the methyl group at N-2 by $PhCH_2$ or MeO_2C-CH_2 or by replacement of the methyl groups at C-4 and C-5 by Ph and $PhCH_2$, respectively.

(26) Bock, M. B.; Di Pardo, R. M.; Williams, P. D.; Pettibone, D. J.; Clineschmidt, B. V.; Ball, R. G.; Veber, D. F.; Freidiger, R. M. *J. Med. Chem.* **1990**, *33*, 2321.

be considered as new conformationally constricted amino acids, where the amplitude of the ϕ dihedral angle can be tuned with the substitution pattern of the pyridazinone ring, which may be of use for the design of new peptides with controlled geometries. Although all products herein described are racemic, this procedure can be adapted to the enantioselective preparation of OPCAs making use of chiral auxiliaries.[13]

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. Toluene was distilled after being refluxed over Na/benzophenone. Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. ^1H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR NMR spectra at 50.5 or 75 MHz in $CDCl_3$ solution with TMS as internal reference. Glycine imine **1** was prepared from *tert*-butyl glycinate following the literature procedure.[27] Compound (*Z*)-**3a** was prepared from **1** and **2a** following the previously described procedure.[12]

Addition of Glycine Imine 1 to Alkynoates 2b,c in the Presence of ^{t}BuOH−KO^{t}Bu. General Procedure. To a solution of PPh_3 (5 mg, 17 μmol) in toluene (0.75 mL) were added KO^{t}Bu (18 mg, 0.17 mmol), ^{t}BuOH (16 μL, 0.17 mmol), the corresponding compounds **2b,c** (0.34 mmol), and a solution of the glycine imine **1** (100 mg, 0.34) in toluene (0.75 mL). The mixture was heated at 80 °C for 24 h. The solution was filtered, and the remaining solid material was washed with Et_2O (3 × 0.5 mL). The solvent was evaporated, and the residue was separated by chromatography (hexane−Et_2O, 80:20).

Data for (*Z*)-2-(Benzhydrylideneamino)-3-methylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*Z*)-3b: white solid (59%); mp 88−90 °C (hexane); IR ($CHCl_3$) ν 1869, 1701, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.24 (10H, m), 4.11 (2H, c, ^3J = 7.0 Hz), 3.52 (2H, s), 1.88 (3H, s), 1.23 (3H, t, ^3J = 7.0 Hz), 1.19 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.0, 169.4, 163.3, 129.4, 129.1, 128.0, 1127.9, 81.0, 60.4, 39.7, 27.7, 20.8, 14.2 ppm. Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.65; H, 7.64; N, 3.32.

Data for (*E*)-2-(Benzhydrylideneamino)-3-methylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*E*)-3b: colorless oil (32%); IR ($CHCl_3$) ν 1899, 1716, 1635, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74−7.57 (10H, m), 4.01 (2H, c, ^3J = 7.0 Hz), 3.73 (2H, s), 2.04 (3H, s), 1.10 (3H, t, ^3J = 7.0 Hz), 1.07 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.3, 169.4, 163.4, 132.4, 130.4, 130.1, 129.7, 128.3, 128.0, 80.8, 60.6, 40.9, 27.7, 19.4, 14.1 ppm. Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.72; H, 7.52; N, 3.45.

Data for (*Z*)-2-(Benzhydrylideneamino)-3-phenylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*Z*)-3c: colorless oil (26%); IR ($CHCl_3$) ν 1798, 1657, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72−6.95 (15H, m), 3.99 (2H, c, ^3J = 7.0 Hz), 3.65 (2H, s), 1.30 (9H, s), 1.1 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.9, 169.1, 164.0, 140.6, 132.4, 130.3, 130.0, 129.3, 129.0, 128.7, 128.2, 127.8, 127.6, 126.8, 124.6, 81.7, 60.4, 39.7, 27.9, 14.1 ppm. Anal. Calcd for $C_{32}H_{35}NO_4$: C, 77.24; H, 7.09; N, 2.81. Found: C, 77.35; H, 7.29; N, 2.71.

Data for (*E*)-2-(Benzhydrylideneamino)-3-phenylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*E*)-3c: white solid (60%); mp 92−94 °C (hexane); IR ($CHCl_3$) ν 1895, 1648, 1655 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79−7.43 (15H, m), 4.03 (2H, c, ^3J = 7.0 Hz), 3.66 (2H, s), 1.10 (3H, t, ^3J = 7.0 Hz), 0.79 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 171.0, 170.2, 163.8, 141.3, 140.8, 139.5, 137.0, 130.6, 129.6, 129.5, 129.4, 128.2, 127.9, 127.7, 126.8, 80.7, 60.5, 40.6, 26.9, 13.9 ppm. Anal. Calcd for $C_{32}H_{35}NO_4$: C, 77.24; H, 7.09; N, 2.81. Found: C, 77.55; H, 7.17; N, 2.75.

(27) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

Alkylation of Compounds 3. General Procedure. To a solution of **3** (0.18 mmol) in acetonitrile (1 mL) were added successively the corresponding alkylant R^2X (0.2 mmol), NaOH (0.18 mmol), and (TEBA)Cl (0.02 mmol). The reaction mixture was stirred for 1 h. The resulting suspension was filtered through Celite, and the remaining solid material was washed with Et_2O (3 × 1 mL). Evaporation of the solvent afforded an oil that was purified by column chromatography (hexanes−Et_2O, 80:20).

Data for (*Z*)-2-(Benzhydrylideneamino)-4-methylpent-2-enedioic Acid 1-*tert*-Butyl 5-Methyl Ester, (*Z*)-4a: colorless oil (90%); IR ($CHCl_3$) ν 1879, 1721, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.71−7.35 (10H, m), 6.16 (1H, d, ^3J = 8.0 Hz), 4.01(1H, dc, ^3J = 8.0 Hz, ^3J = 7.0 Hz), 3.70 (3H, s), 1.27 (9H, s), 1.25 (3H, t, ^3J = 7 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 173.6, 170.3, 162.6, 141.2, 139.4, 137.0, 130.5, 129.7, 129.0, 128.8, 127.9, 127.8, 122.5, 80.9, 51.7, 44.7, 27.8, 18.7 ppm. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N 3.56. Found: C, 73.45; H, 7.94; N 3.72.

Data for (*Z*)-2-(Benzhydrylideneamino)-4-benzylpent-2-enedioic Acid 1-*tert*-Butyl 5-Methyl Ester, (*Z*)-4b: colorless oil (90%); IR ($CHCl_3$) ν 1708, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63−7.09 (15H, m), 6.00 (1H, d, ^3J = 10.0 Hz), 3.74 (1H, ddd, ^3J = 10.0 Hz, ^3J = 8.5 Hz, ^3J = 6.5 Hz), 3.70 (3H, s), 3.03 (1H, dd, ^2J = 13.5 Hz, ^3J = 8.5 Hz), 2.85 (1H, dd, ^2J = 13.5 Hz, ^3J = 6.5 Hz), 1.18 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.2, 170.3, 162.2, 142.2, 139.1, 138.4, 136.8, 130.7, 129.5, 129.2, 128.9, 128.7, 128.0, 127.9, 126.5, 122.2, 81.1, 51.7, 45.8, 30.0, 27.7 ppm. Anal. Calcd for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 76.93; H, 6.55; N, 2.88.

Data for (*Z*)-2-(Benzhydrylideneamino)-3,4-dimethylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*Z*)-4c: colorless oil (55%); IR ($CHCl_3$) ν 1715, 1647 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.71−7.40 (10H, m), 4.20−4.05 (3H, m), 1.99 (3H, s), 1.31−1.19 (6H, m), 1.15 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.2, 168.5, 163.5, 140.1, 137.5, 137.0, 133.5, 130.3, 129.6, 129.4, 127.9, 80.8, 60.5, 42.6, 27.7, 14.5, 14.2, 13.8 ppm. Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.15; H, 7.40; N, 3.28.

Data for (*E*)-2-(Benzhydrylideneamino)-3,4-dimethylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*E*)-4c: colorless oil (30%); IR ($CHCl_3$) ν 1710, 1637 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65−7.15 (10H, m), 4.48 (1H, c, ^3J = 7.0 Hz), 4.05 (2H, c, ^3J = 7.0 Hz), 1.60 (3H, s), 1.20 (9H, s), 1.18−1.07 (6H, m) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.2, 169.5, 163.0, 139.5, 130.5, 129.3, 128.6, 128.0, 127.9, 127.8, 81.1, 60.4, 41.1, 27.9, 15.3, 15.0, 14.3 ppm. Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.25; H, 7.30; N, 3.38.

Data for (*Z*)-2-(Benzhydrylideneamino)-4-benzyl-3-methylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*Z*)-4d: colorless oil (73%); IR ($CHCl_3$) ν 1720, 1634 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45−7.17 (15H, m), 4.48 (1H, dd, ^3J = 8.0 Hz, ^3J = 6.5 Hz), 4.10 (2H, c, ^3J = 7.0 Hz), 3.34 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 2.98 (1H, dd, ^2J = 14.0 Hz, ^3J = 6.5 Hz), 2.06 (3H, s), 1.21 (3H, t, ^3J = 7.0 Hz), 1.14 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 173.0, 167.9, 163.5, 140.0, 139.5, 138.3, 136.8, 132.2, 130.2, 129.6, 129.2, 129.1, 128.1, 128.0, 127.8, 127.7, 126.0, 80.1, 60.5, 50.0, 35.2, 27.7, 14.9, 14.1 ppm. Anal. Calcd for $C_{34}H_{39}NO_4$: C, 77.68; H, 7.48; N, 2.66. Found: C, 77.77; H, 7.40; N, 2.63.

Data for (*E*)-2-(Benzhydrylideneamino)-4-benzyl-3-methylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*E*)-4d: colorless oil (13%); IR ($CHCl_3$) ν 1737, 1664 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39−7.18 (15H, m), 5.00 (1H, dd, ^3J = 8.0 Hz, ^3J = 7.0 Hz), 4.14 (2H, c, ^3J = 7.0 Hz), 3.22 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 2.79 (1H, dd, ^2J = 14.0 Hz, ^3J = 7.0 Hz), 1.80 (3H, s), 1.28 (9H, s), 1.21 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.8, 170.0, 163.0, 139.6, 137.9, 137.6, 136.5, 132.6, 130.4, 128.7, 81.0, 60.4, 47.8, 36.1, 27.8, 15.3, 14.1 ppm. Anal. Calcd for $C_{34}H_{39}NO_4$: C, 77.68; H, 7.48; N, 2.66. Found: C, 77.67; H, 7.45; N, 2.69.

Data for (*E*)-2-(Benzhydrylideneamino)-4-methyl-3-phenylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*E*)-4e: colorless oil (85%); IR ($CHCl_3$) ν 1726, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.06 (15H, m), 4.19 (1H, c, ^3J

= 7.0 Hz), 4.01 (2H, c, ^3J = 7.0 Hz), 1.09 (3H, t, ^3J = 7.0 Hz), 1.08 (3H, d, ^3J = 7.0 Hz), 0.60 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.9, 169.7, 164.2, 139.9, 139.7, 138.8, 136.6, 135.2, 130.6, 129.8, 129.7, 128.5, 127.9, 127.6, 126.8, 80.5, 60.6, 42.7, 26.8, 14.5, 14.1 ppm. Anal. Calcd for $C_{33}H_{37}NO_4$: C, 77.47; H, 7.29; N, 2.74. Found: C, 77.57; H, 7.25; N, 2.76.

Data for (*E*)-2-(Benzhydrylideneamino)-4-benzyl-3-phenylpent-2-enedioic Acid 1-*tert*-Butyl 5-Ethyl Ester, (*E*)-4f: colorless oil (85%); IR ($CHCl_3$) ν 1724, 1628 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95−7.01 (20H, m), 4.69 (1H, dd, ^3J = 8.0 Hz, ^3J = 6.5 Hz), 4.03 (2H, c, ^3J = 7.0 Hz), 3.17 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 2.87 (1H, dd, ^2J = 14.0 Hz, ^3J = 6.5 Hz), 1.14 (3H, t, ^3J = 7.0 Hz), 0.67 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.7, 170.4, 164.0, 134.0, 144.9, 140.9, 140.6, 139.7, 139.5, 139.4, 138.6, 136.9, 134.4, 129.1, 129.0, 128.8, 128.0, 127.9, 127.8, 127.6, 127.2, 80.5, 60.6, 49.7, 31.6, 26.8, 14.1 ppm. Anal. Calcd for $C_{39}H_{41}NO_4$: C, 79.70; H, 7.03; N, 2.38. Found: C, 79.78; H, 7.13; N, 2.28.

Cyclization of Compounds 3 and 4 with Hydrazine. General Procedure. To a solution of hydrazine hydrochloride (72 mg, 1.08 mmol) in EtOH (7 mL) were added NaOAc (87 mg, 1.08 mmol) and a solution of compounds **3** and **4** (0.27 mmol) in EtOH (7 mL). The mixture was stirred at reflux temperature for 24 h. At rt was added a saturated solution of NaCl, and the organic layer was decanted. The aqueous layer was extracted with EtOAc (3 × 7 mL), and the combined organic extracts were dried over $MgSO_4$. Evaporation under reduced pressure afforded a residue which was purified by chromatography (hexanes−EtOAc, 80:20).

Data for 5-Methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 5a: white solid (85%); mp 146−148 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3355, 1753, 1628 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.85 (1H, s), 3.07 (1H, dd, ^2J = 15.0 Hz, ^3J = 4.5 Hz), 2.59−2.42 (2H, m), 1.57 (9H, s), 1.27 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.6, 162.2, 144.5, 83.1, 30.5, 28.7, 28.0, 14.9 ppm. Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.49; H, 7.69; N, 13.21.

Data for 5-Benzyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 5b: white solid (85%); mp 128−130 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3340, 1715, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (1H, s), 7.24−7.09 (5H, m), 3.18 (1H, dd, ^2J = 18.0 Hz, ^3J = 8.5 Hz), 2.79 (1H, dd, ^2J = 17.0 Hz, ^3J = 6.0 Hz), 2.68−2.60 (2H, m), 2.41 (1H, dd, ^2J = 17.0 Hz, ^3J = 9.5 Hz) 1.53 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 162.0, 144.5, 137.3, 129.2, 128.7, 126.9, 83.0, 37.3, 35.3, 27.9, 25.3 ppm. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.68; H, 6.96; N, 9.75.

Data for 4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 5c: white solid (80%); mp 100−102 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3413, 1710, 1631 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (1H, s), 3.25 (1H, qd, ^3J = 7.5 Hz, ^3J = 1.5 Hz), 2.62 (1H, dd, ^2J = 17.5 Hz, ^3J = 7.5 Hz), 2.39 (1H, dd, ^2J = 17.5 Hz, ^3J = 1.5 Hz), 1.54 (9H, s), 1.15 (3H, d, ^3J = 7.5 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.7, 161.8, 147.9, 83.0, 33.4, 27.9, 27.2, 16.0 ppm. Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.49; H, 7.70; N, 13.21.

Data for 6-Oxo-4-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 5d: white solid (75%); mp 143−145 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3260, 1701, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (1H, s), 7.25−7.09 (5H, m), 4.42 (1H, dd, ^3J = 8.5 Hz, ^3J = 2.5 Hz), 2.86 (1H, dd, ^2J = 17.5 Hz, ^3J = 8.5 Hz), 2.71 (1H, dd, ^2J = 17.5 Hz, ^3J = 2.5 Hz), 1.40 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.9, 161.8, 145.4, 137.9, 129.2, 127.8, 126.8, 83.2, 38.0, 33.9, 27.9 ppm. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.65; H, 6.60; N, 10.24.

Data for 6-Oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 5e: white solid (85%); mp 146−148 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3410, 1695, 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (1H, s), 2.86 (2H, t, ^3J = 7.5 Hz), 2.54 (2H, t, ^3J = 7.5 Hz), 1.55 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 167.1, 162.1, 144.4, 83.1, 28.0, 26.0, 21.0 ppm. Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.43; H, 7.15; N, 14.10.

Data for 4,5-*cis*-4,5-Dimethyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*cis*-5f: white solid (75%); mp 74−76 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3340, 1713, 1648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (1H, s), 3.16 (1H, q, ^3J = 7.0 Hz), 2.68 (1H, q, ^3J = 7.0 Hz), 1.57 (9H, s), 1.24 (3H, d, ^3J = 7.5 Hz), 1.04 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.5, 161.9, 149.3, 83.0, 34.9, 32.1, 28.0, 10.0, 9.5 ppm. Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.35; H, 8.12; N, 12.34.

Data for 4,5-*cis*-4-Benzyl-5-methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*cis*-5g: colorless oil (75%); IR ($CHCl_3$) ν 3245, 1711, 1628 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.55 (1H, s), 7.59−7.47 (5H, m), 3.52 (1H, dd, ^2J = 14.0 Hz, ^3J = 4.0 Hz), 3.05 (1H, q, ^3J = 6.5), 2.84 (1H, ddd, ^3J = 10.5 Hz, ^3J = 6.5, ^3J = 4.0), 2.63 (1H, dd, ^2J = 14.0 Hz, ^3J = 10.5 Hz), 1.02 (9H, s), 1.09 (3H, d, ^3J = 6.5 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 169.0, 161.8, 149.3, 138.3, 129.8, 129.1, 128.7, 128.6, 128.4, 126.6, 83.0, 46.2, 36.7, 31.0, 28.0, 9.6 ppm. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.50; H, 7.30; N, 9.29.

N-Alkylation of 5 with *tert*-Butyl Bromoacetate. General Procedure. To a stirred solution of compounds **5** (0.47 mmol) in anhydrous THF (1 mL) at −78 °C was added LiHMDS (1 M in THF, 0.94 mL, 0.94 mmol), and the solution was stirred for 2 h. *tert*-Butyl bromoacetate (0.14 mL, 0.94 mmol) was added dropwise, the reaction mixture was stirred for 20 h, and the temperature was slowly raised to rt. H_2O (3 mL) was added, and the organic layer was decanted. The aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic extracts were dried over $MgSO_4$. Evaporation under reduced pressure afforded a residue which was purified by column chromatography (hexanes−EtOAc, 80:20).

Data for 1-*tert*-Butoxycarbonylmethyl-5-methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 6a: white solid (90%); mp 120−122 °C (hexane); IR ($CHCl_3$) ν 1712, 1621 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.46 (2H, s), 3.02 (1H, dd, ^2J = 15.0 Hz, ^3J = 4.5 Hz), 2.64−2.41 (2H, m), 1.54 (9H, s), 1.46 (9H, s), 1.26 (3H, d, ^3J = 6.5 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 169.6, 167.3, 161.9, 144.1, 82.8, 82.1, 51.8, 30.9, 29.3, 28.1, 28.0, 15.2 ppm. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.96; H, 8.11; N, 8.40.

Data for 5-Benzyl-1-*tert*-butoxycarbonylmethyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 6b: white solid (90%); mp 95−97 °C (hexane); IR ($CHCl_3$) ν 1709, 1641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.08 (5H, m), 4.42 (2H, s), 3.17 (1H, dd, ^2J = 13.0 Hz, ^3J = 2.5 Hz), 2.73−2.46 (4H, m), 1.44 (9H, s), 1.40 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.5, 167.3, 161.8, 144.0, 137.6, 129.2, 128.6, 126.8, 82.8, 82.2, 51.9, 37.7, 35.3, 28.0, 27.9, 25.7 ppm. Anal. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.69; H, 7.55; N, 6.90.

Data for 1-*tert*-Butoxycarbonylmethyl-4-methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 6c: white solid (90%); mp 98−100 °C (hexane); IR ($CHCl_3$) ν 1733, 1695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.57 (1H, d, ^2J = 17.0 Hz), 4.35 (1H, d, ^2J = 17.0 Hz), 3.22 (1H, qd, ^3J = 7.0 Hz, ^3J = 2.0 Hz), 2.69 (1H, dd, ^2J = 17.0 Hz, ^3J = 7.0 Hz), 2.43 (1H, dd, ^2J = 17.0 Hz, ^3J = 2.0 Hz), 1.53 (9H, s), 1.45 (9H,s), 1.21 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 167.2, 165.4, 161.5, 147.9, 82.7, 82.0, 51.5, 33.5, 28.0, 27.9, 27.8, 16.0 ppm. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.80; H, 8.06; N, 24.61.

Data for 1-*tert*-Butoxycarbonylmethyl-5-phenyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 6d: colorless oil (90%); IR ($CHCl_3$) ν 1732, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.23 (5H, m), 4.59 (1H, d, ^2J = 17.0 Hz), 4.47 (1H, d, ^2J = 17.0 Hz), 4.39 (1H, dd, ^3J = 9.0 Hz, ^3J = 3.0 Hz), 2.99 (1H, dd, ^2J = 17.5 Hz, ^3J = 9.0 Hz), 2.80 (1H, dd, ^2J = 17.5 Hz, ^3J = 3.0 Hz), 1.48 (9H, s), 1.41 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.1, 165.0, 161.5, 144.8, 138.4, 129.2, 127.7, 127.1, 82.9, 82.3, 51.9, 39.2, 34.4,

28.1, 27.8 ppm. Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.94; H, 7.27; N, 7.21. Found: C, 64.84; H, 7.29; N, 7.26.

Data for 1-*tert*-Butoxycarbonylmethyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 6e: white solid (90%); mp 95−97 °C (hexane); IR ($CHCl_3$) ν 1733, 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.47 (2H, s), 2.87 (2H, t, $^3J = 8.0$ Hz), 2.57 (2H, t, $^3J = 8.0$ Hz), 1.54 (9H, s), 1.46 (1H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 167.3, 166.0, 161.7, 144.3, 82.8, 81.2, 51.7, 28.0, 27.9, 26.2, 21.8 ppm. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.60; H, 7.79; N, 8.95.

Data for 4,5-*cis*-1-*tert*-Butoxycarbonylmethyl-4,5-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*cis*-6f: colorless oil (90%); IR ($CHCl_3$) ν 1738, 1672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, d, $^2J = 17.0$ Hz), 4.35 (1H, d, $^2J = 17.0$ Hz), 3.11 (1H, q, $^3J = 6.5$ Hz), 2.73 (1H, q, $^3J = 6.5$ Hz), 1.56 (9H, s), 1.47 (9H, s), 1.24 (3H, d, $^3J = 6.5$ Hz), 1.09 (3H, d, $^3J = 6.5$ Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.5, 167.4, 161.7, 148.8, 82.7, 82.1, 51.7, 35.2, 32.9, 28.1, 28.0, 10.4, 9.6 ppm. Anal. Calcd for $C_{17}H_{28}N_2O_5$: C, 59.98; H, 8.29; N, 8.23. Found: C, 59.98; H, 8.29; N, 8.23.

Data for 4,5-*cis*-5-Benzyl-1-*tert*-butoxycarbonylmethyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*cis*-6g: colorless oil (90%); IR ($CHCl_3$) ν 1728, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.05 (5H, m), 4.62 (1H, d, $^2J = 18.0$ Hz), 4.36 (1H, d, $^2J = 18.0$ Hz), 3.50 (1H, dd, $^2J = 15.0$ Hz, $^3J = 6.0$ Hz), 3.01−259 (3H, m), 1.50 (9H, s), 1.48 (9H, s), 1.36 (3H, d, $^3J = 7.0$ Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.5, 168.0, 161.6, 149.0, 138.9, 134.5, 129.1, 128.6, 82.7, 81.7, 51.7, 46.5, 36.2, 30.5, 28.1, 27.9, 9.7 ppm. Anal. Calcd for $C_{23}H_{32}N_2O_5$: C, 66.32; H, 7.74; N, 6.73. Found: C, 66.42; H, 7.70; N, 6.70.

N-Alkylation of 5 with Benzyl Bromide. General Procedure. To a stirred solution of compounds **5** (0.47 mmol) in acetonitrile (10 mL) were added K_2CO_3 (260 mg, 1.88 mmol) and (TEBA)Cl (43 mg, 0.19 mmol), and the solution was stirred for 10 min. Benzyl bromide (15 μmL, 0.19 mmol) was added, and the reaction mixture was stirred at reflux temperature for 5 h. The resulting suspension was filtered through Celite, and the remaining solid material was washed with EtOAc (3 × 2 mL). The solvent was evaporated, and the residue was purified by column chromatography (hexanes−EtOAc, 80:20).

Data for 1-Benzyl-4-methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 7a: white solid (95%); mp 81−83 °C (hexane); IR ($CHCl_3$) ν 1685, 1604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34−7.27 (5H, m), 5.09 (1H, d, $^2J = 14.5$ Hz), 4.91 (1H, d, $^2J = 14.5$ Hz), 3.19 (1H, qd, $^3J = 7.0$ Hz, $^3J = 2$ Hz), 2.62 (1H, dd, $^2J = 17.0$ Hz, $^3J = 7.0$ Hz), 2.42 (1H, dd, $^2J = 17.0$ Hz, $^3J = 2.0$ Hz), 1.55 (9H, s), 1.08 (3H, d, $^3J = 7.0$ Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 165.0, 161.7, 147.6, 137.0, 129.0, 128.4, 128.3, 127.5, 126.9, 82.6, 52.8, 34.2, 27.9, 27.7, 16.1 ppm. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found:: C, 67.50; H, 7.30; N, 9.36.

Data for 1-Benzyl-4-phenyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 7b: colorless oil (95%); IR ($CHCl_3$) ν 1709, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12−6.87 (10H, m), 5.09 (1H, d, $^2J = 14.0$ Hz), 4.84 (1H, d, $^2J = 14.0$ Hz), 4.27 (1H, dd, $^3J = 8.5$ Hz, $^3J = 3.0$ Hz), 2.83 (1H, dd, $^2J = 17.0$ Hz, $^3J = 8.5$ Hz), 2.70 (1H, dd, $^2J = 17.0$ Hz, $^3J = 3.0$ Hz), 1.36 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.3, 161.6, 145.1, 137.7, 136.6, 129.0, 128.7, 128.5, 128.4, 127.6, 126.8, 82.8, 52.6, 38.6, 34.8, 27.8 ppm. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.54; H, 6.61; N, 7.60.

Data for 1-Benzyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic acid *tert*-Butyl Ester, 7c: white solid (95%); mp 72−74 °C (hexane); IR ($CHCl_3$) ν 1683, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.17 (5H, m), 4.88 (2H, s), 2.67 (2H, t, $^3J = 8.0$ Hz), 2.38 (2H, t, $^3J = 8.0$ Hz), 1.44 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.5, 161.9, 144.0, 137.0, 128.5, 128.4, 127.6, 126.9, 82.6, 52.6, 27.9, 26.6, 21.7 ppm. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.75; H, 6.90; N, 9.73.

Alkylation of Compounds 7a−c. General Procedure. To a stirred solution of compounds **7a−c** (0.33 mmol) in anhydrous THF (1 mL) at −78 °C was added LiHMDS (1 M in THF, 0.66 mL, 0.66 mmol), and the solution was stirred for 2 h. The corresponding alkylant R^3X (0.66 mmol) was added dropwise, the reaction mixture was stirred for 20 h, and the temperature was slowly raised to rt. H_2O (3 mL) was added, and the organic layer was decanted. The aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic extracts were dried over $MgSO_4$. Evaporation under reduced pressure afforded a residue which was purified by column chromatography (hexanes−EtOAc, 80:20).

Data for 4,5-*trans*-1-Benzyl-4,5-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*trans*-7d: colorless oil (95%); IR ($CHCl_3$) ν 1689, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (5H, m), 5.08 (1H, d, $^2J = 14.0$ Hz), 4.92 (1H, d, $^2J = 14.0$ Hz), 2.90 (1H, cd, $^3J = 7.5$ Hz, $^3J = 1.5$ Hz), 2.48 (1H, cd, $^3J = 7.5$ Hz, $^3J = 1.5$ Hz), 1.56 (9H, s), 1.09 (3H, d, $^3J = 7.5$ Hz), 1.06 (3H, d, $^3J = 7.5$ Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.8, 164.3, 153.0, 130.2, 128.4, 128.2, 127.5, 82.3, 53.0, 35.2, 30.0, 28.0, 16.4, 16.1 ppm. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.39; H, 7.55; N, 8.84.

Data for 4,5-*trans*-1,5-Dibenzyl-4-methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*trans*-7e: colorless oil (90%); IR ($CHDCl_3$) ν 1698, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38−6.97 (10H, m), 5.11 (1H, d, $^2J = 14.5$ Hz), 4.96 (1H, d, $^2J = 14.5$ Hz), 2.97−2.85 (2H, m), 2.62−2.57 (1H, m), 2.44 (1H, dd, $^2J = 13.0$ Hz, $^3J = 11.0$ Hz), 1.55 (9H, s), 0.97 (3H, d, $^3J = 7.5$ Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 167.3, 161.7, 146.9, 137.1, 129.1, 128.6, 128.4, 127.5, 126.9, 82.5, 53.1, 46.7, 36.3, 31.1, 28.0, 15.8 ppm. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.39; H, 7.55; N, 8.84.

Data for 4,5-*trans*-1-Benzyl-5-methyl-4-phenyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 4,5-*trans*-7f: colorless oil (90%); IR ($CHCl_3$) ν 1708, 1685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39−7.18 (10H, m), 5.16 (1H, d, $^2J = 14.0$ Hz), 4.94 (1H, d, $^2J = 14.0$ Hz), 4.00 (1H, d, $^3J = 4$ Hz), 2.78 (1H, cd, $^3J = 7.5$ Hz, $^3J = 4.0$ Hz), 1.41 (9H, s), 1.25 (3H, d, $^3J = 7.5$ Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 168.1, 162,1, 144.4, 137.7, 136.7, 129.0, 128.7, 128.4, 128.2, 127.7, 127.6, 127.0, 82.7, 53.1, 46.7, 40.2, 27.8, 16.9 ppm. Anal. Calcd for for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.97; H, 6.90; N, 7.41.

Reduction of Compounds 6 and 7 with $NaCNBH_3$. General Procedure. To a solution of compounds **6** and **7** (0.32 mmol) in MeOH (1 mL) was added 2 N HCl to pH 2. $NaCNBH_3$ (9.6 mmol) was added in three portions with an interval of 5 min. The acid mixture was stirred for 24 h. The solvent was evaporated, and the aqueous solution was alkalanized with 3 M KOH to pH 12. The mixture was extracted with EtOAc (3 × 3 mL) and the combined extract dried on $MgSO_4$. The solvent was evaporated, and the residue was purified by chromatography (hexanes−EtOAc, 70:30).

Data for 3,5-*cis*-1-*tert*-Butoxycarbonylmethyl-5-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,5-*cis*-8a: colorless oil (50%); IR ($CHCl_3$) ν 3275, 1730, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.88 (1H, s), 4.49 (1H, d, $^2J = 17.0$ Hz), 4.43 (1H, d, $^2J = 17.0$ Hz), 3.75 (1H, t, $^3J = 7.5$ Hz), 2.65−2.52 (3H, m), 1.48 (9H, s), 1.47 (9H, s), 1.27 (3H, d, $^3J = 7.0$ Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.7, 168.0, 167.7, 83.4, 83.2, 60.4, 55.0, 35.7, 32.7, 28.1, 28.0, 15.2 ppm; Anal. Calcd for $C_{16}H_{28}N_2O_5$: C, 58.52; H, 8.59; N, 8.53. Found: C, 58.47; H, 8.62; N, 8.62.

Data for 3,5-*cis*-5-Benzyl-1-*tert*-butoxycarbonylmethyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,5-*cis*-8b: colorless oil (45%); IR ($CHCl_3$) ν 3401, 1728, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (1H, d, $^2J = 14.5$ Hz), 4.66 (1H, d, $^2J = 14.5$ Hz), 4.48 (1H, d, $^3J = 10.5$ Hz), 3.42−3.36 (2H, m), 2.78−2.68 (2H, m), 2.08−1.85 (2H, m), 1.48 (9H, s), 1.47 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.2, 167.5, 167.2, 139.0, 128.5, 128.3, 128.2, 82.9, 82.7, 60.0, 56.5, 35.2, 32.2, 30.4, 27.6, 27.5 ppm. Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. C, 65.42; H, 7.89; N, 7.01.

Data for 3,4-*cis*-1-*tert*-Butoxycarbonylmethyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-8c: white solid (85%); mp 67−69 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3421, 1732, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (1H, d, ^3J = 12.0 Hz), 4.55 (1H, d, ^2J = 17.0 Hz), 3.96 (2H, m), 2.68 (1H, dd, ^2J = 17.0 Hz, ^3J = 6.5 Hz), 2.52 (1H, m), 2.33 (1H, dd, ^2J = 17.0 Hz, ^3J = 4.5 Hz), 1.49 (9H, s), 1.47 (9H, s), 1.06 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 168.9, 168.2, 82.5, 82.2, 59.8, 50.5, 37.4, 31.1, 28.1, 28.0, 14.7 ppm. Anal. Calcd for $C_{16}H_{28}N_2O_5$: C, 58.52; H, 8.59; N, 8.53. Found: C, 58.58; H, 8.55; N, 8.53.

Data for 3,4-*cis*-1-*tert*-Butoxycarbonylmethyl-4-phenyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-8d: colorless oil (80%); IR ($CHCl_3$) ν 3385, 1722, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.16 (5H, m), 4.90 (1H, d, ^3J = 12.0 Hz), 4.55 (1H, d, ^2J = 17.0 Hz), 4.11 (1H, dd, ^3J = 12.0 Hz, ^3J = 5.0 Hz), 4.03 (1H, d, ^2J = 17.0 Hz), 3.66 (1H, td, ^3J = 7.0 Hz, ^3J = 5.0 Hz), 2.87 (1H, dd, ^2J = 17.5 Hz, ^3J = 7.0 Hz), 2.75 (1H, dd, ^2J = 17.5 Hz, ^3J = 5.0 Hz), 1.42 (9H, s), 1.19 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.5, 169.5, 168.2, 138.3, 128.8, 128.2, 127.8, 82.2, 82.2, 60.6, 51.0, 42.8, 35.6, 28.1, 27.8 ppm. Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.55; H, 7.70; N, 7.16.

Data for 1-*tert*-Butoxycarbonylmethyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 8e: white solid (90%); mp 81−83 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3417, 1736, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (1H, d, ^3J = 10.0 Hz), 4.14 (2H, s), 3.78 (1H, dt, ^3J = 10.0 Hz, ^3J = 7.0 Hz), 2.46 (2H, t, ^3J = 7.0 Hz), 2.26 (1H, q, ^2J = 7.0 Hz, ^3J = 7.0 Hz), 2.00 (1H, q, ^2J = 7.0 Hz, ^3J = 7.0 Hz), 1.41 (9H, s), 1.39 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 170.9, 168.3, 82.3, 82.1, 56.3, 50.6, 29.1, 28.1, 28.0, 27.5 ppm. Anal. Calcd for $C_{15}H_{26}N_2O_5$: C, 57.31; H, 8.34; N, 8.91. Found: C, 57.38; H, 8.30; N, 8.81.

Data for 3,4-*cis*-4,5-*cis*-1-*tert*-Butoxycarbonylmethyl-4,5-dimethyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*cis*-8f: colorless oil (80%); IR ($CHCl_3$) ν 3402, 1726, 1659 cm−1; ^1H NMR (200 MHz, $CDCl_3$) δ 4.69 (1H, d, ^2J = 17 Hz), 4.17 (1H, d, ^3J = 4.0 Hz), 3.97 (1H, s), 3.83 (1H, d, ^2J = 17 Hz), 2.79 (1H, q, ^3J = 7.0 Hz), 2.39 (1H, m), 1.45 (9H, s), 1.48 (9H, s), 1.24 (3H, d, ^3J = 7.0 Hz), 0.97 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 171.2. 169.4, 168.4, 82.3, 82.2, 60.9, 50.5, 38.8, 35.4, 28.1, 28.0, 13.0, 8.8 ppm; Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.63; H, 8.83; N, 8.18. Found: C, 59.69; H, 8.80; N, 8.18.

Data for 3,4-*cis*-4,5-*cis*-5-Benzyl-1-*tert*-butoxycarbonylmethyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*cis*-8g: colorless oil (80%); IR ($CHCl_3$) ν 3428, 1728, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.24 (5H, m), 4.65 (1H, d, ^2J = 17.0 Hz), 3.96 (1H, d, ^2J = 17.0 Hz), 3.87 (1H, d, ^3J = 3.5 Hz), 3.58 (1H, dd, ^2J = 14.5 Hz, ^3J = 4.5 Hz), 2.96 (1H, dt, ^3J = 9.0 Hz, ^3J = 4.5 Hz), 2.60 (1H, dd, ^2J = 14.5 Hz, ^3J = 9.0 Hz), 2.29−2.24 (1H, m), 1.49 (9H, s), 1.44 (9H, s), 1.01 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 169.3, 168.4, 139.4, 128.7, 128.6, 126.3, 82.4, 82.3, 61.0, 50.5, 46.5, 32.5, 31.9, 28.1, 28.0, 9.1 ppm. Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.00; H, 8.19; N, 6.69. Found: C, 66.09; H, 8.14; N, 6.67.

Data for 3,4-*cis*-1-Benzyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-9a: white solid (90%); mp 83−85 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3428, 1726, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.26 (5H, m), 4.87 (1H, d, ^2J = 14.5 Hz), 4.43 (1H, d, ^2J = 14.5 Hz), 4.34 (1H, d, ^3J = 10.5 Hz), 3.71 (1H, dd, ^3J = 10.5 Hz, ^3J = 4.5 Hz), 2.60 (1H, dd, ^2J = 16.5 Hz, ^3J = 6.0 Hz), 2.43−2.33 (1H, m), 2.27 (1H, dd, ^2J = 16.5 Hz, ^3J = 5.0 Hz), 1.38 (9H, s), 0.88 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 168.4, 136.7, 128.6, 128.2, 127.5, 82.5, 59.8, 51.6, 37.6, 31.0, 28.0, 14.8 ppm. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.00; H, 7.85; N, 9.29.

Data for 3,4-*cis*-1-Benzyl-4-phenyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-9b: white solid (85%); mp 142−144 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3415, 1730, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17−6.91 (10H, m), 5.05 (1H, d, ^2J = 14.0 Hz), 4.39 (1H, d, ^2J = 14.0 Hz), 4.33 (1H, d, ^3J = 12.0 Hz), 3.96 (1H, dd, ^3J = 12.0 Hz, ^3J = 5.5 Hz), 3.56 (1H, c, ^3J = 5.5 Hz), 2.86 (1H, dd, ^2J = 17.0 Hz, ^3J = 5.5 Hz), 2.75 (1H, dd, ^2J = 17.0 Hz, ^3J = 5.5 Hz), 1.15 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.6, 168.1, 138.0, 136.5, 128.6, 127.9, 127.7, 82.5, 60.6, 51.9, 42.6, 35.9, 27.8 ppm. Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.18; H, 7.17; N, 7.60.

Data for 1-Benzyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 9c: white solid (95%); mp 110−112 °C (hexanes−EtOAc); IR ($CHCl_3$) ν 3288, 1726, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65−7.28 (5H, m), 4.69 (2H, s), 4.37 (1H, d, ^3J = 10.0 Hz), 3.66 (1H, dd, ^3J = 10.0 Hz, ^3J = 7.0 Hz), 2.53 (2H, t, ^3J = 7.0 Hz), 2.23 (1H, q, ^2J = 7.0 Hz, ^3J = 7.0 Hz), 2.05 (1H, q, ^2J = 7.0 Hz, ^3J = 7.0 Hz), 1.46 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9, 170.7, 137.1, 128.5, 128.4, 127.5, 82.3, 56.4, 51.7, 29.4, 27.9, 27.4 ppm. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.24; H, 7.60; N, 9.65.

Data for 3,4-*cis*-4,5-*trans*-1-Benzyl-4,5-dimethyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*trans*-9d: colorless oil (85%); IR ($CHCl_3$) ν 3308, 1711, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34−7.30 (5H, m), 5.05 (1H, ^2J = 14.0 Hz), 4.98 (1H, ^2J = 14.0 Hz), 3.73 (1H, d, ^3J = 7.5 Hz), 3.68 (1H, s), 3.08 (1H, cd, ^3J = 7.5 Hz, ^3J = 1.5 Hz), 2.56 (1H, qd, ^3J = 7.5 Hz, ^3J = 1.5 Hz), 1.25 (9H, s), 1.22 (3H, d, ^3J = 7.5 Hz), 1.10 (3H, d, ^3J = 7.5 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 169.8, 168.9, 136.3, 128.8, 128.0, 127.9, 82.2, 64.1, 52.6, 39.4, 33.9, 28.7, 16.7, 16.1 ppm. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.98; H, 8.20; N, 8.84.

Data for 3,4-*cis*-4,5-*trans*-1,5-Dibenzyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*trans*-9e: colorless oil (85%); IR ($CHCl_3$) ν 3299, 1724, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−6.94 (10H, m), 5.31 (1H, d, ^3J = 10.0 Hz), 5.02 (1H, d, ^2J = 14.5 Hz), 4.82 (1H, d, ^2J = 14.5 Hz), 4.04 (1H, dd, ^3J = 10 Hz, ^3J = 4.5 Hz), 2.86−2.47 (4H, m), 1.47 (9H, s), 0.88 (3H, d, ^3J = 7.5 Hz) ppm. ^{13}C NMR (200 MHz, $CDCl_3$) δ 171.1, 170.1, 137.0, 129.1, 128.5, 127.6, 82.3, 60.4, 53.0, 46.7, 36.3, 31.1, 28.0, 15.8 ppm. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 10.00. Found: C, 73.15; H, 7.66; N, 10.06.

Data for 3,4-*cis*-4,5-*trans*-1-Benzyl-5-methyl-4-phenyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*trans*-9f: colorless oil (85%); IR ($CHCl_3$) ν 3287, 1720, 1653 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44−7.32 (10H, m), 5.0 (1H, s), 4.84 (1H, d, ^2J = 14.0 Hz), 4.49 (1H, d, ^2J = 14.0 Hz), 4.22 (1H, dd, ^3J = 6.0 Hz, ^3J = 1.5 Hz), 3.98 (1H, d, ^3J = 6.0 Hz), 2.94 (1H, m), 1.22 (3H, d, ^3J = 7.5 Hz), 1.05 (9H, s) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.4, 170.6, 136.6, 130.8, 128.7, 128.6, 128.5, 84.0, 66.7, 53.6, 49.9, 36.5, 27.6, 14.2 ppm. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.48; H, 7.36; N, 7.49.

Addition of Acetyl Chloride to 8 and 9. General Procedure. To a stirred solution of compounds **8** and **9** (0.33 mmol) in acetonitrile (4 mL) were added K_2CO_3 (182 mg, 1.32 mmol) and (TEBA)Cl (29 mg, 0.13 mmol), and the solution was stirred for 10 min. Acetyl chloride (94 μmL, 1.32 mmol) was added, and the reaction mixture was stirred at refluxed temperature for 5 h. The resulting suspension was filtered through Celite, and the remaining solid material was washed with EtOAc (3 × 2 mL). The solvent was evaporated, and the residue was purified by column chromatography (hexanes−EtOAc, 80:20).

Data for 3,4-*cis*-2-Acetyl-1-*tert*-Butoxycarbonylmethyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-10a: colorless oil (85%); IR ($CHCl_3$) ν 1740, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (1H, d, ^3J = 9.5 Hz), 4.30 (1H, d, ^2J = 17.0 Hz), 4.18 (1H, d, ^2J = 17.0 Hz), 3.00 (1H, m), 2.39−2.15 (5H, m), 1.50 (9H, s), 1.49 (9H, s), 1.12 (3H, d, ^3J = 7.5 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.9, 172.9, 168.6, 166.1, 82.7, 82.1, 58.3, 54.7, 36.6, 30.8, 28.1, 28.0, 20.8, 16.0 ppm. Anal. Calcd for $C_{18}H_{30}N_2O_6$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.42; H, 8.19; N, 7.50.

Data for 2-Acetyl-1-*tert*-Butoxycarbonylmethyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 10b: colorless oil (85%); IR ($CHCl_3$) ν 1731, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.66 (1H, dd, ^3J = 9.5 Hz, ^3J = 7.0 Hz), 5.03 (1H, d, ^2J = 17.5 Hz), 3.87 (1H, d, ^2J = 17.5 Hz), 3.01 (2H, t, ^3J = 8.0 Hz), 2.72−2.63 (2H, m), 2.19 (3H, s), 1.49 (9H, s), 1.48 (9H, s), ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.0, 173.3, 169.7, 167.2, 83.4, 83.2, 56.8, 54.5, 32.9, 28.7, 28.7, 25.0, 20.3 ppm. Anal. Calcd for $C_{17}H_{28}N_2O_6$: C, 57.29; H, 7.92; N, 7.86. Found: C, 57.19; H, 7.98; N, 7.82.

Data for 3,4-*cis*-4,5-*cis*-2-Acetyl-1-*tert*-Butoxycarbonylmethyl-4,5-dimethyl-6-oxoperhydropyridazine-3- carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*cis*-10c: colorless oil (75%); IR ($CHCl_3$) ν 1735, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (1H, d, ^3J = 9.0 Hz), 5.34 (1H, d, ^2J = 14.5 Hz), 4.86 (1H, d, ^2J = 14.5 Hz), 2.82−2.77 (1H, m), 2.66−2.54 (1H, m), 2.19 (3H, s), 1.51 (9H, s), 1.50 (9H, s), 1.16 (3H, d, ^3J = 7.0 Hz), 0.98 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 173.4, 172.9, 172.3, 168.2, 82.5, 82.1, 60.2, 50.6, 41.2, 36.5, 28.0, 27.9, 22.0, 12.2, 11.5 ppm. Anal. Calcd for $C_{19}H_{32}N_2O_6$: C, 59.36; H, 8.39; N, 7.29. Found: C, 59.25; H, 8.47; N, 7.32.

Data for 3,4-*cis*- 2-Acetyl-1-benzyl-4-methyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-11a: colorless oil (80%); IR ($CHCl_3$) ν 1736, 1696 cm^{-1}; ^1H NMR δ 7.56−7.31 (5H, m), 5.42 (1H, d, ^3J = 9.0 Hz), 5.32 (1H, d, ^2J = 14.5 Hz), 4.64 (1H, d, ^2J = 14.5 Hz), 2.61−2.34 (3H, m), 1.51 (3H, s), 1.45 (9H, s), 0.99 (3H, d, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 172.6, 169.9, 164.7, 139.4, 132.7, 130.2, 128.6, 82.9, 63.8, 55.4, 39.9, 32.7, 28.1, 22.7, 14.1 ppm. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.95; H, 7.44; N, 8.13.

Data for 2-Acetyl-1-benzyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 11b: colorless oil (85%); IR ($CHCl_3$) ν 1736, 1681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.32 (5H, m), 5.52 (1H, t, ^3J = 8.5 Hz), 5.18 (1H, d, ^2J = 14.5 Hz), 4.61 (1H, d, ^2J = 14.5 Hz), 2.59−2.45 (2H, m), 2.17−2.03 (2H, m), 1.56 (3H, s), 1.48 (9H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.8, 174.6, 169.7, 136.2, 129.7, 128.7, 128.1, 82.6, 55.6, 54.6, 31.2, 28.0, 25.0, 20.3 ppm. Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.14; H, 7.20; N, 8.45.

Data for 3,4-*cis*-4,5-*trans*-2-Acetyl-1-benzyl-4,5-dimethyl-6-oxoperhydropyridazine-3-carboxylic Acid *tert*-Butyl Ester, 3,4-*cis*-4,5-*trans*-11c: colorless oil (75%); IR ($CHCl_3$) ν 1735, 1693 cm^{-1}; ^1H NMR δ 7.37−7.25 (5H, m), 5.35 (1H, d, ^3J = 6.0 Hz), 5.05 (1H, d, ^2J = 14.5 Hz), 4.95 (1H, d, ^2J = 14.5 Hz), 2.58 (1H, cd, ^3J = 7.5 Hz, ^3J = 1.0 Hz), 2.35−2.28 (1H, m), 1.54 (3H, s), 1.25 (9H, s), 1.11 (3H, d, ^3J = 7.5 Hz), 1.10 (3H, d, ^3J = 7.5 Hz) ppm; ^{13}C NMR δ 171.3, 169.8, 165.0, 136.7, 130.1, 129.2, 128.4, 128.3, 82.1, 64.0, 53.0, 39.8, 33.2, 29.3, 17.1, 16.5 ppm. Anal. Calcd for C, 65.87; H, 7.56; N, 8.09. Found: C, 65.75; H, 7.54; N, 8.18.

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