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Cyclobutane-Derived Diamines: Synthesis and Molecular Structure

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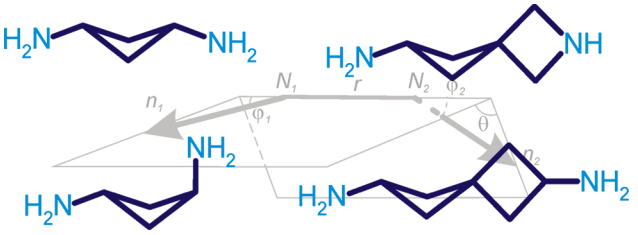
Received June 29, 2010



Cyclobutane diamines (i.e., *cis*- and *trans*-1,3-diaminocyclobutane, 6-amino-3-azaspiro[3.3]heptane, and 3,6-diaminospiro[3.3]heptane) are considered as promising sterically constrained diamine building blocks for drug discovery. An approach to the syntheses of their Boc-monoprotected derivatives has been developed aimed at the preparation of multigram amounts of the compounds. These novel synthetic schemes exploit classical malonate alkylation chemistry for the construction of cyclobutane rings. The conformational preferences of the cyclobutane diamine derivatives have been evaluated by X-ray diffraction and compared with the literature data on sterically constrained diamines, which are among the constituents of commercially available drugs.

Introduction

Restriction of conformational mobility (rigidification) has long been a design principle for the molecules, the basis of whose function is the efficiency of their intermolecular noncovalent interactions. This design principle is especially popular in current drug discovery.[1] Molecular rigidity is widely regarded as one of the most important properties of approved drugs.[2] It has been suggested that the preorganization arising from steric constraint in a drug molecule might contribute to the decrease of the entropy barrier of the intermolecular drug-target interaction, thus increasing the drug's potency and selectivity. Recent studies challenged this hypothesis,[3] but the number of efficient sterically constrained drug molecules continues to increase.[4] Another beneficial feature of sterically constrained molecules (compared to their flexible analogues) is the relative facility of their docking to biological targets, which might be useful for *in silico* drug discovery.[5] And last but not least, the steric constraints might help to assemble spatial arrangements of functional groups involved in the intermolecular interaction which are not attainable in their flexible analogues. This opens the prospects of more efficient involvement of the target functional groups in drug−target interaction.

Synthesis of sterically constrained molecules involves constructing a corresponding rigid molecular scaffold, or the use of presynthesized rigidified building blocks. In drug design, such building blocks as sterically constrained amino acids have often been used.[6] Sterically constrained diamines,

(1) Mann, A. In Practice of Medicinal Chemistry, 3rd ed.; Wermuth, C. G., Ed.; Academic Press/Elsevier: Amsterdam, The Netherlands, 2008; pp 363−379.
(2) Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218–227.
(3) Martin, S. F. *Pure Appl. Chem.* **2007**, *79*, 193–200.
(4) *MDL Drug Data Report* (*MDDR*); Elsevier MDL, version 2009.2
(5) Barril, X.; Solvia, R. In *Structure-Based Drug Discovery: An Overview*; Hubbard, R. E., Ed.; RSC Publishing: Cambridge, UK, 2006; pp 54−96.
(6) (a) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785–2798. (b) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249–262. (c) Shemyakin, M. M.; Ovchinnikov, Y. A.; Ivanov, V. T. *Angew. Chem., Int. Ed.* **1969**, *8*, 492–499. (d) Komarov, I. V.; Grigorenko, A. O.; Turov, A. V.; Khilya, V. P. *Russ. Chem. Rev.* **2004**, *73*, 785–810. (e) Soloshonok, V. A. *Curr. Org. Chem.* **2002**, *6*, 341–364. (f) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145–148. (g) Soloshonok, V. A.; Tang, X. J.; Hruby, V. J.; Meervelt, L. V. *Org. Lett.* **2001**, *3*, 341–343.

DOI: 10.1021/jo101271h Published on Web 08/09/2010

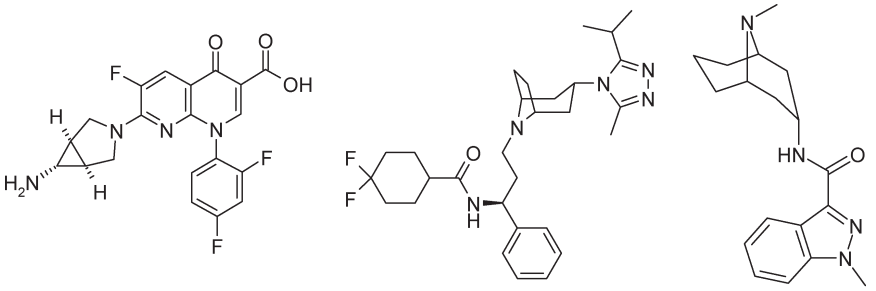


FIGURE 1. Examples of marketed drugs comprising sterically constrained diamine scaffolds.

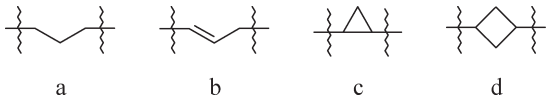


FIGURE 2. Rigidification of a carbon chain (a), double bond (b), cyclopropane (c), and cyclobutane (d) rings.

although they seem to offer similar potential in molecular design,[7] have received much less attention. Figure 1 depicts several examples of marketed drugs possessing diamine scaffolds. These and many other, less successful, examples illustrate the great potential of sterically constrained diamines in drug design and stimulate further studies in this area.

In this paper, we wish to report our results on the synthesis and structural studies of sterically constrained diamines of low molecular weight. Our approach to achieve restriction of the conformational mobility in the diamine molecules was guided by the principle of minimal constitutional changes of flexible parent molecules. Introducing a double bond as well as a cyclopropane ring into an aliphatic chain is widely used to achieve this;[8] however, these constitutional changes considerably disturb the electronic properties, leading to rigidified analogues which differ in chemical reactivity and intramolecular interaction from the flexible counterparts.[9] This drawback is alleviated in cyclobutane derivatives less commonly exploited to date,[10] although the cyclobutane ring retains some flexibility and can be considered as less rigid compared to the cyclopropane fragment[11] (Figure 2).

The structures of 1,3-diaminocyclobutanes **1a** and **1b** are obtained if the design principle shown in Figure 2d is applied to construction of rigidified diamines. Compound **1** was reported first in 1957; it was obtained as a mixture of stereoisomers in ten steps starting from epibromohydrine.[12] A number of examples

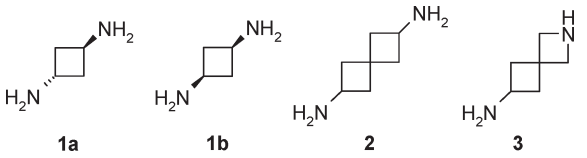


FIGURE 3. Cyclobutane-derived diamines.

illustrating the use of the scaffold **1** in drug discovery were reported since then; in particular, derivatives of diamine **1** were evaluated as inhibitors of kinases CDK1,[13] CDK2, CDK5, GSK-3,[14] and PLK,[13,15] phosphodiesterase PDE4,[16] and the glycine transporter GLyT-1;[17] inhibitors of interactions between Mdm2 and p53 proteins,[18] insecticides, and acaricides.[19]

The design concept described above can be expanded to spirocyclic compounds, e.g. diamines **2** and **3**. Whereas the first synthesis of **2** was described more than a century ago,[20] compound **3** has not been obtained so far (Figure 3).

It should be noted that in order to make selective modification of diamine building blocks possible, it is essential to have one of the nitrogen atoms in their molecules protected (e.g., as Boc derivatives). To the best of our knowledge, no practical approaches to the derivatives of **1**−**3** which allow selective modification of the amino groups have been reported to date.[21] In the present work, we wish to report syntheses of mono-Boc derivatives of each of the diamines **1a**, **1b**, **2**, and **3**.[22] Furthermore, using the results of X-ray diffraction studies, the molecular structures and conformational

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(8) (a) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247–1270. (b) A. Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625–1648. (c) de Meijere, A. *Chem. Rev.* **2003**, *103*, 931–932. (d) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511–542.

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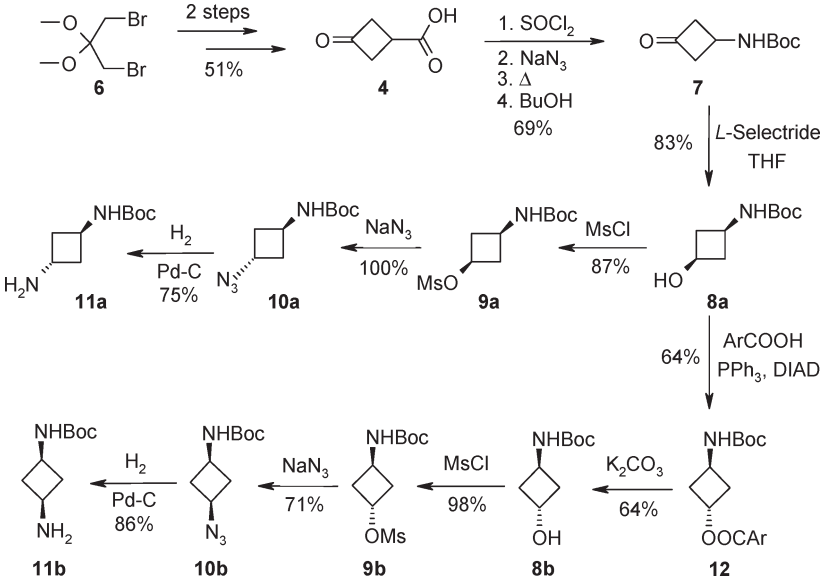
(21) Synthesis of the mono-Boc derivative of **1a** was described without characterization in the patent literature;[16] in this work, an analogous approach is used.

SCHEME 1. Synthesis of the Diamine Derivatives 11a and 11b[a]



[a]Ar is *p*-nitrophenyl (*p*-$O_2NC_6H_4$).

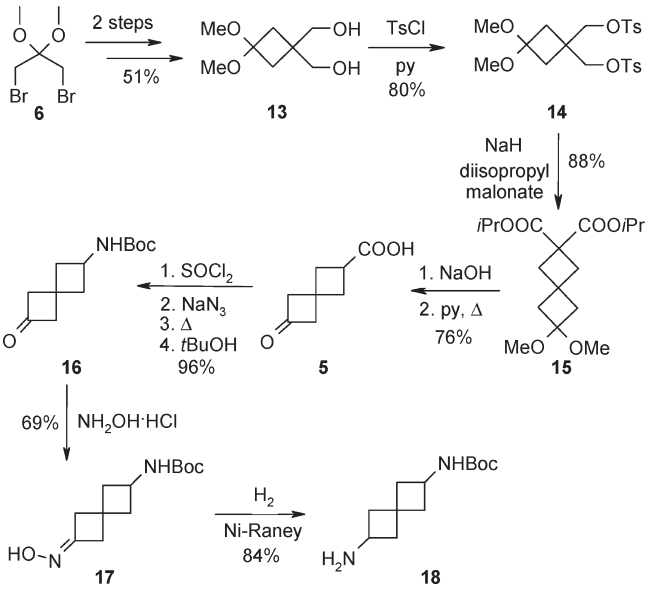
preferences of these diamine building blocks are established and discussed.

Results and Discussion

Synthesis. The synthesis of the monoprotected derivatives of diamines **1** and **2** relies on orthogonal retrosynthetic transformations of the amino functions. Namely, the Curtius rearrangement and reductive amination of the carbonyl compounds can be regarded as the corresponding transforms, ketoacids **4** and **5** therefore being appropriate starting materials.

Among different published syntheses of compound **4**, we considered the method involving double malonate alkylation as the most appropriate for multigram preparation.[23] Curtius rearrangement of an acyl azide obtained from **4** was followed by reaction with *tert*-butanol resulting in the direct formation of *N*-Boc-protected aminoketone **7**.[24] To perform stereoselective transformation of the ketone moiety in **7** to an amino function, compound **7** was first reduced with L-selectride to give alcohol **8a** as a single diastereomer. Compound **8a** was the key intermediate in the synthesis of both isomers **11a** and **11b**. To obtain the trans-isomer **11a**, **8a** was transformed to mesylate **9a**, which underwent S_N2 reaction with sodium azide followed by catalytic hydrogenation to afford **11a** (7 steps, 19% from **6**). Cis-isomer **11b** (9 steps, 7% from **6**) was prepared in an analogous manner starting from alcohol **8b**; the latter was obtained by isomerization of **8a** with a Mitsunobu reaction (Scheme 1).[21]

SCHEME 2. Synthesis of Diamine Derivative 18



An analogous approach was applied to the synthesis of the spirocyclic derivative **18**. In this case, the ketoacid **5** was prepared in five steps from dibromide **6**, using the method reported previously by our group (Scheme 2).[25] Curtius rearrangement of azide obtained from carboxylic acid **5** followed by reaction with *tert*-butanol led to the formation of the *N*-Boc-protected aminoketone derivative **16**. The latter was transformed to oxime **17**, which was reduced catalytically to yield the targeted diamine derivative **18** (9 steps, 15% from **6**).

We have also considered an approach to the synthesis of compound **18** via Fecht's acid dimethyl ester **21** (Scheme 3), which was previously used to obtain the parent diamine **2**.[20]

(22) The preliminary results of this project have been reported previously by our group: Shivanyuk, A. N.; Volochnyuk, D. M.; Komarov, I. V.; Nazarenko, K. G.; Radchenko, D. S.; Kostyuk, A.; Tolmachev, A. A. *Chem. Today* **2007**, *25*, 12–13.

(23) Pigou, P. E.; Schiesser, C. H. *J. Org. Chem.* **1988**, *53*, 3841–3843.

(24) While the work was in progress, an analogous synthesis of compound **7** was reported elsewhere: Kumar, R. J.; Chebib, M.; Hibbs, D. E.; Kim, H.-L.; Salam, N. K.; Hanrahan, J. R.; Johnston, G. A. R. *J. Med. Chem.* **2008**, *51*, 3825–3840.

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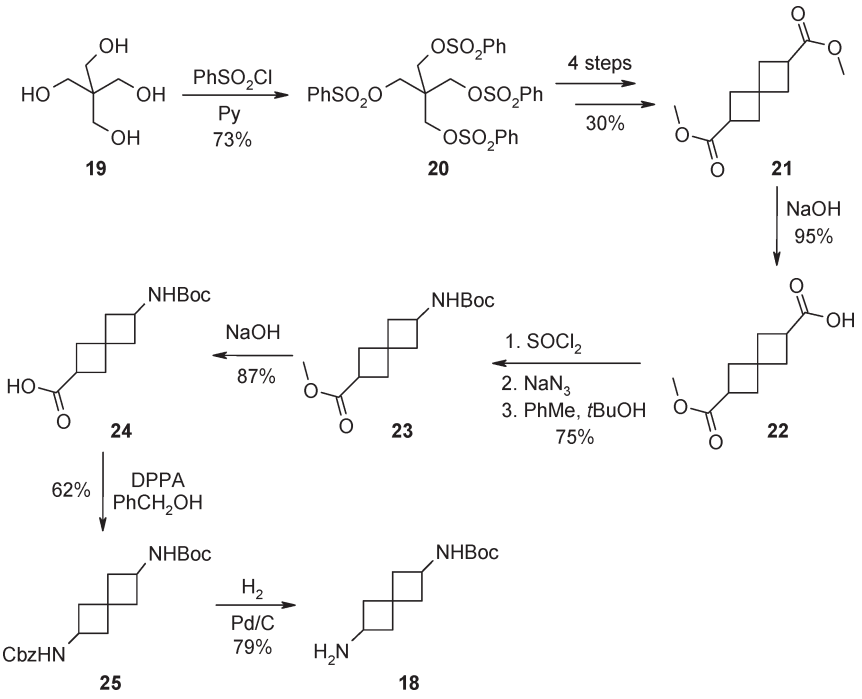
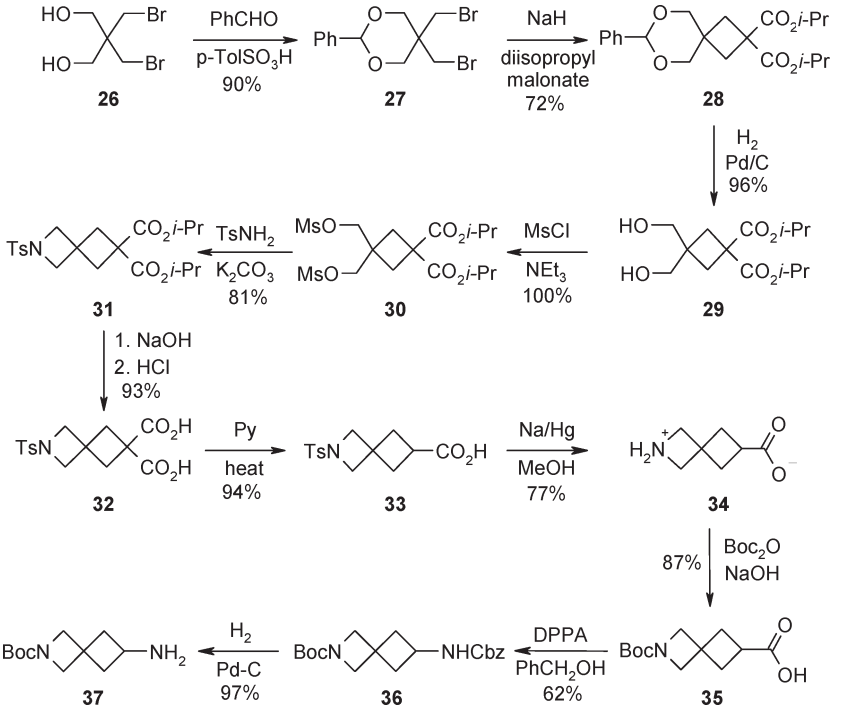
SCHEME 3. Synthesis of the Diamine Derivative 18 via Fecht's Acid Diester 21



SCHEME 4. Synthesis of Diamine Derivative 37



Compound **21** was prepared by using a modified literature procedure.[26] To modify the carboxyl moieties in the molecule of **21** selectively, mild alkaline hydrolysis was performed to afford the monoester **22**. Compound **22** was transformed to the amino acid derivative **23** under classical Curtius rearrangement conditions.[27] Hydrolysis of **23** resulted in the Boc-protected amino acid **24**. To achieve Curtius rearrangement of the remaining carboxyl group in **24**, diphenylphosphoryl azide (DPPA) was used; quenching of the intermediate isocyanate with benzyl alcohol ensured orthogonality

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(27) A slightly different synthesis of **23** has been reported: Jones, B. C. N. M.; Drach, J. C.; Corbett, T. H.; Kessel, D.; Zemlicka, J. *J. Org. Chem.* **1995**, *60*, 6277–6280.

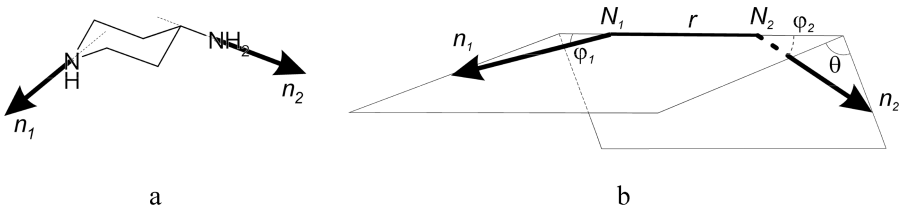

FIGURE 4. (a) Definition of vectors $\boldsymbol{n_1}$, $\boldsymbol{n_2}$ (4-aminopiperidine used as an example); (b) definition of geometric parameters r, φ_1, φ_2, and θ.

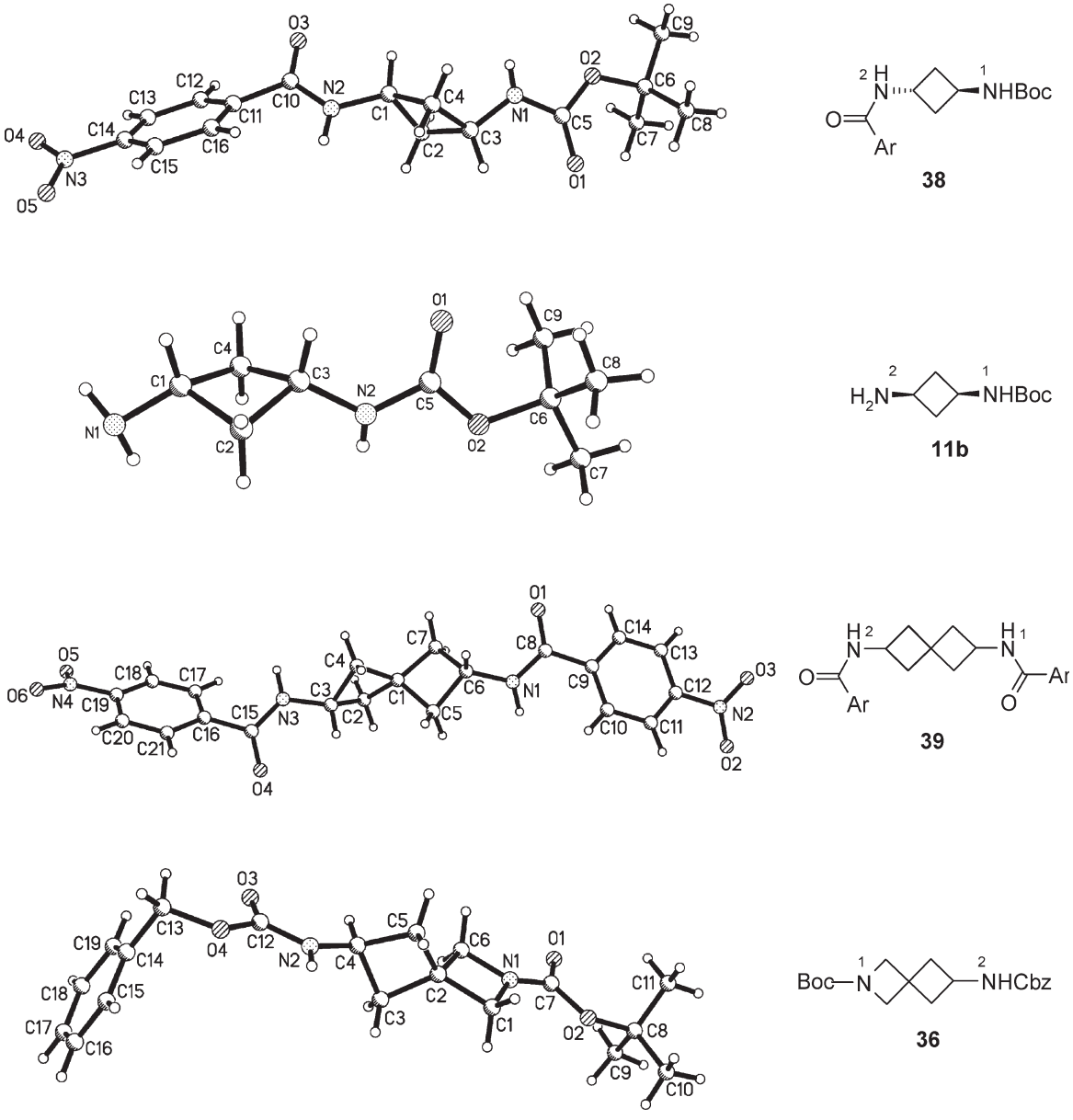

FIGURE 5. Molecular structure of **38**, **11b**, **39**, and **36** (Ar is *p*-$NO_2C_6H_4$).

of the protective groups in the product **25**. Finally, selective monodeprotection of **25** by means of catalytic hydrogenation led to the formation of diamine derivative **18** (7%, 10 steps from **19**). In both syntheses of **18** shown in the Schemes 2 and 3, the product was obtained as a racemate.

A different strategy was developed for the synthesis of diamine derivative **37** (Scheme 4). In this case, the construction of the 2-azaspiro[3.3]heptane core was performed by consequent closure of the cyclobutane and azetidine rings using bis-alkylation of malonate (compound **28**) and tosylamide (compound **31**), respectively. After hydrolysis, decarboxylation, and detosylation, amino acid **34** was obtained.[28] Further steps of the synthesis included Boc-derivatization,

(28) Radchenko, D. S.; Grygorenko, O. O.; Komarov., I. V. *Amino Acids* **2010**, *39*, 515–521.

TABLE 1. Values of the Parameters r, φ_1, φ_2, and θ Obtained from X-ray Diffraction Data on the Sterically Constrained Diamine Derivatives

entry no.	derivative	diamine	r, Å	φ_1, deg	φ_2, deg	θ, deg	ref
1	**44**	piperazine	2.838	23.6	23.6	0.0	33
2	zopiclone	piperazine	2.842	22.3	26.9	177.4	34
3	aripiprazole	piperazine	2.871	25.7	24.2	179.9	35
4	astemizole	4-aminopiperidine	4.261	41.4	25.7	0.6	36
5	demethoxycisapride	4-aminopiperidine	4.242	35.1	19.9	1.2	37
6	**45**	**40**	4.311	27.9	9.0	178.2	38
7	**46**	**40**	4.219	40.1	3.5	166.0	38
8	tropapride[a]	**41**	4.150	50.0	27.3	1.2	39
9	**47**[a]	**42**	4.228	41.4	25.7	0.6	40
10	**48**	**43**	3.072	72.8	68.1	2.1	41
11	**38**	**1a**	4.485	33.4	10.5	179.2	this work
12	**11b**	**1b**	4.585	31.3	30.9	1.8	this work
13	**39**[b]	**2**	6.810	23.3	12.1	112.7	this work
14	**36**	**3**	5.490	5.9	17.9	131.1	this work

[a]Hydrochloride. [b]The data are given for the (a*R*)-isomer.

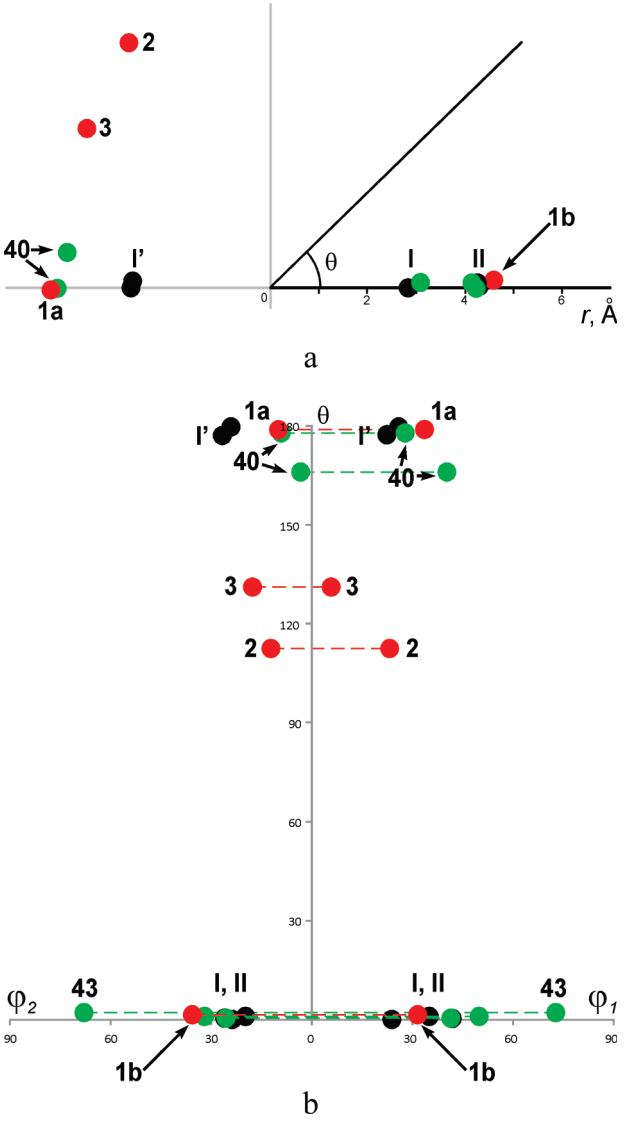

FIGURE 6. The chemical space covered by sterically constrained diamines discussed in this work: (a) $r-\theta$ representation (polar coordinates); (b) $\varphi_1-\theta$ and $\varphi_2-\theta$ representations (shown in the same plot, Cartesian coordinates). Derivatives of piperazine and 4-aminopiperidine are shown in black, the bicyclic diamines **40**−**43** are in green, cyclobutane diamines **1**−**3** are in red. **I** and **I′**: "piperazine" regions ($\theta \approx 0°$ and 180°, respectively). **II**: "4-aminopiperidine" region.

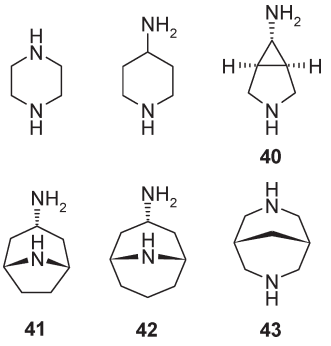

FIGURE 7. Some sterically constrained diamines: constituents of marketed drugs.

Curtius rearrangement, and selective monodeprotection allowing the diamine derivative **37** to be obtained (18%, 11 steps from **26**).

Conformational Preferences. Current rational drug design aims at finding the optimal disposition of the molecular fragments in the potential drug candidates or the scaffolds of which they are constructed. This idea was embodied in the pharmacophore concept, which correlates the potential ligand molecule with a combination of steric and electronic features necessary to ensure optimal interaction with the biological target.[29] From this viewpoint, the diamine scaffolds can be characterized by relative spatial orientation of the amino functions, the role of the carbon framework being reduced to providing this orientation. The disposition of the amino functions of the diamine can be represented by two vectors;[30] namely, the nitrogen atoms (N_1 and N_2) can be regarded as the starting points of the vectors, whereas to define their direction the C−N bond and the bisector C−N−C angle can be used for the primary and secondary amino groups, respectively (Figure 4a). The relative spatial orientation of two vectors $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$ thus obtained for the diamine scaffold can be described by four parameters: the distance between the nitrogen atoms r, the plane angles φ_1 (between vectors $\boldsymbol{n_1}$ and $\boldsymbol{N_2N_1}$) and φ_2 (between $\boldsymbol{n_2}$ and $\boldsymbol{N_1N_2}$),

(29) Wermuth, C.-G.; Langet, T. In *3D QSAR in drug design: theory, methods and applications*; Kubiniyi, H., Ed.; ESCOM Science Publishers: Leiden, Holland, 1993; pp 117−136.

(30) To be more precise, bound unit vectors, see: Tang, K.-T. *Mathematical methods for engineers and scientist 2: vector analysis, ordinary differential equations and Laplace transforms*; Springer-Verlag: Berlin/Heidelberg, Germany, 2007; pp 3−22.

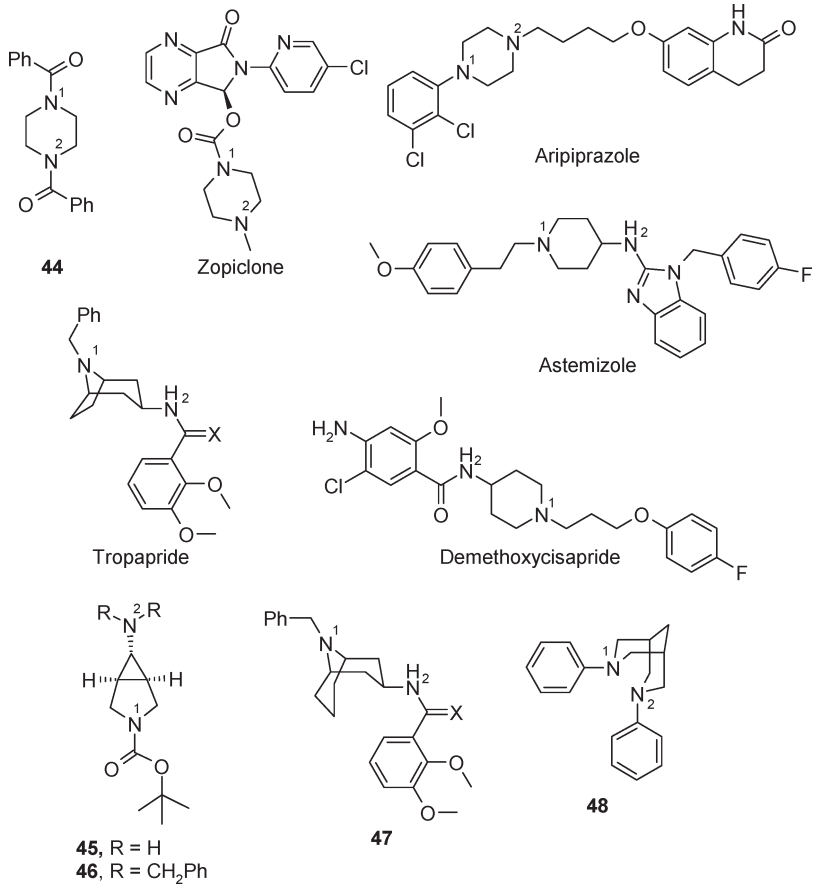

FIGURE 8. Derivatives of sterically constrained diamines studied by X-ray diffraction (literature data).

and the dihedral angle θ defined by vectors $\boldsymbol{n}_1$, $\boldsymbol{N_1N_2}$, and $\boldsymbol{n}_2$ (Figure 4b).[31]

The range of theoretically possible values of φ_1 and φ_2 is between 0° and 180°, although most of the numbers are less than 90°, whereas θ can vary from −180° to 180°. The sign of θ is rather important as it is the only parameter that is affected by the chirality of the diamine molecule. In particular, enantiomers have equal values of r, φ_1, and φ_2, as well as the absolute values of θ, but differ in the sign of θ. It should be noted that all the compounds encountered in this study are either racemic or nonchiral; thus both enantiomers or enantiomeric conformations (respectively) are observed for any set of the values of r, φ_1, φ_2, and $\pm\theta$. In the further discussion, we shall consider only positive values of θ, keeping in mind that the corresponding negative values are also possible.

To establish the above-defined geometrical parameters of the diamine scaffolds **1**−**3**, X-ray diffraction studies of the derivatives **11b**, **36**, **38**, and **39** were performed (Figure 5). All the cyclobutane rings in the molecules of **11b**, **36**, **38**, and **39** adopt puckered conformation (puckering angle is 19.8° (**38**), 29.1° (**11b**), 34.8° (the C(1)−C(2)−C(3)−C(4) torsion angle of **39**), 25.5° (the C(1)−C(5)−C(6)−C(7) torsion angle of **39**), and 29.9° (**36**)), whereas the azetidine ring of **36** is planar within 0.02 Å.

Amino-derived substituents in the cyclobutane rings of **11b**, **36**, **38**, and **39** adopt an equatorial position (except the *tert*-butyloxycarbonylamino group in **38**, which is axial). The values of the corresponding torsion angles are as follows: 147.2(2)° (N(1)−C(1)−C(2)−C(3)) and 143.7(2)° (N(2)−C(3)−C(4)−C(1)), **11b**; 134.1(1)° (N(2)−C(1)−C(4)−C(3)) and 104.7(1)° (N(1)−C(3)−C(4)−C(1)), **38**; −142.4(1)° (C(2)−C(3)−C(4)−N(2)), **36**; and 136.6(1)° (N(1)−C(6)−C(7)−C(1)) and 145.5(1)° (C(1)−C(2)−C(3)−N(3)), **39**.

Amide and carbamate fragments of the diamine derivatives discussed herein exhibit almost perfect planarity (the sum of the bond angles centered at the nitrogen atoms ω_0(N) = 358.5−360°). For **36**, this fact is remarkable as it has been shown previously that the nitrogen atom in many azetidine derivatives tends to be pyramidalized.[32] As could be expected,

(31) In principle, this description can be extended to any conformationally constrained scaffolds possessing two functional groups. It should be noted, however, that due to some flexibility characteristic to any organic molecule (especially to cyclobutane derivatives described in this work), the values of the above-defined geometric parameters can be useful only for semiquantitative considerations. See the Supporting Information for more detailed discussion.

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pyramidalization of the free amino group in **11b** is much more pronounced (ω_0(N) = 341°).

The values of the parameters r, φ_1, φ_2, and θ are summarized in Table 1 and plotted in Figure 6. In addition, the corresponding parameter values were also elucidated from the literature data available for the derivatives of several sterically constrained diamine scaffolds widely used in drug discovery (i.e., piperazine, 4-aminopiperidine, as well as diamines **40**−**43** which are constituents of trovafloxacin, maraviroc, granisetron, and ambasilide, respectively (Figures 7 and 8).

The data in the Table 1 show that the nearly coplanar orientation of $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$ which corresponds to $\theta \approx 0°$ or 180° is frequently encountered in the derivatives of diamines: constituents of marketed drugs. In particular, three regions can be outlined in the $r-\theta$ representation of the chemical space covered by sterically constrained diamines: they correspond to piperazine ($\theta \approx 0°$; $\theta \approx 180°$) and 4-aminopiperidine ($\theta \approx 0°$) derivatives (Figure 6). It should be noted that in the case of parent 4-aminopiperidine, only $\theta \approx 0°$ values are observed, which comply with the equatorial position of the 4-amino substituent. $\theta \approx 180°$ values (which can be referred to the axial position of the substituent) are often met in the derivatives of some bicyclic constrained analogues of 4-aminopiperidine, e.g. diamine **40**.

As could be deduced from Figure 6, the geometric parameters of **1b** derivatives are similar to those of 4-aminopiperidine. This allows one to assume that **1b** might be considered as a 4-aminopiperidine replacement, although comprising an additional rotatable bond. Analogously, trans-isomer **1a** can be regarded as an analogue of a less stable conformation of 4-aminopiperidine with an axial position of the substituent, as also observed in 6-amino-3-azabicyclo[3.1.1]hexane (**40**) derivatives. Diamines **2** and **3** provide access to less explored regions of the chemical space covered by sterically constrained diamines which correspond to noncoplanar, three-dimensional molecular structure.[42]

Conclusions

Practical syntheses of the cyclobutane-derived diamines **1**−**3** as their mono-Boc-protected derivatives which allow selective chemical modification of the amino functions were developed. The chemical space covered by these sterically constrained diamines is analyzed by using the parameters of three-dimensional molecular structures determined by X-ray crystallography. The results of these studies show that monocyclic cyclobutane diamines **1a** and **1b** can be used as surrogates of 4-aminopiperidine, whereas spirocyclic derivatives **2** and **3** open a route into less explored three-dimensional molecular structures.

Experimental Section

***tert*-Butyl (3-Oxocyclobutyl)carbamate (7).** To a solution of the carboxylic acid **4**[23] (50.6 g, 0.44 mol) in CH_2Cl_2 (370 mL) was added $SOCl_2$ (96 mL, 1.32 mol) dropwise upon vigorous stirring. The resulting mixture was refluxed for 1.5 h. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in CCl_4 (2 × 120 mL) and evaporated to remove HCl and $SOCl_2$. The crude product was dissolved in acetone (120 mL), and the resulting solution was added dropwise to a solution of NaN_3 (58.1 g, 0.89 mol) in H_2O (175 mL) at 0 °C over 30 min. The mixture was stirred for 1 h at 0 °C, then ice (600 g) was added, and the product was extracted with Et_2O (3 × 150 mL), dried over $MgSO_4$, and concentrated to 340 mL under reduced pressure. The resulting solution was added to toluene (700 mL), and the mixture was heated to 90 °C. After the residual ether was distilled off, the mixture was stirred at 90 °C for 30 min until evolution of N_2 ceased. Then *tert*-butanol (140 mL) was added, and the mixture was heated at 90 °C for 12 h. After cooling, the solvent was removed under reduced pressure. The crude product (67.9 g) was recrystallized from EtOH; an additional amount was obtained from the mother liquor after dilution with hexane. Yield 57.3 g (69%). White crystals, mp 77−78 °C. For spectral and physical data, see ref 24.

***tert*-Butyl (*cis*-3-Hydroxycyclobutyl)carbamate (8a).** Compound **7** (40 g, 0.216 mol) was dissolved in dry THF (1000 mL) under an argon atmosphere, and the solution was cooled to −78 °C upon stirring. L-Selectride (1 M in THF, 324 mL, 0.324 mol) was added dropwise over 1 h period. The mixture was kept at −78 °C for 1 h, and a solution of NaOH (13.0 g) in H_2O (160 mL) was added dropwise over 30 min followed by 30% aqueous H_2O_2 (120 mL) over 2 h. The resulting mixture was warmed to rt and then diluted with EtOAc (2 L), washed with 10% aqueous Na_2SO_3 and brine, and dried over $MgSO_4$.The solvent was evaporated in vacuo. The crude product (38 g) was purified by recrystallization (hexane−EtOAc (1:1)) to give **8a** (31 g) as yellowish needles. An additional amount of **8a** (2.5 g) was obtained from the mother liquor. The combined yield of the product was 33.5 g (83%). Mp 117 °C. MS (*m*/*z*, EI) 172 ($M^+ - CH_3$), 143 ($M^+ - CO_2$), 87, 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_9H_{17}NO_3$: C 57.73, H 9.15, N 7.48. Found: C 57.68, H 9.01, N 7.73. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, C(C*H*$_3$)$_3$), 1.79 (br s, 2H, 2- and 4-C*H*H), 2.43 (br s, 1H, O*H*), 2.73 (br s, 2H, 2- and 4-CH*H*), 3.63 (br s, 1H, 1-C*H*), 3.99 (quint, J = 6.9 Hz, 1H, 3-C*H*), 4.72 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 28.4 (C(*C*H$_3$)$_3$), 37.3 (*C*H$_2$), 41.8 (*C*(CH$_3$)$_3$), 60.9 (*C*H), 79.7 (*C*H), 155.1 (*C*OOC(CH$_3$)$_3$).

***cis*-3-[(*tert*-Butoxycarbonyl)amino]cyclobutyl Methanesulfonate (9a).** Compound **8a** (44.2 g, 0.236 mol) was dissolved in CH_2Cl_2 (950 mL), triethylamine (49.4 mL, 0.708 mol) was added, and the solution was cooled to −30 °C upon vigorous stirring. Mesyl chloride (21.9 mL, 0.283 mol) was added dropwise over a 20 min period, and the mixture was warmed to ambient temperature, then washed with water (200 mL), 10% aqueous citric acid (200 mL) and brine, dried over Na_2SO_4, and evaporated to yield crude **9a** (59 g). The product was purified by recrystallization (EtOAc) to give **9a** (48.7 g) as yellowish crystals. An additional amount of **8a** (8.8 g) was obtained from the mother liquor. Total yield was 57.5 g (0.205 mol, 87%). Mp 155−156 °C. MS (*m*/*z*, EI) 250 ($M^+ - CH_3$), 122, 79, 55 ($C(CH_3)_3^+$). Anal. Calcd for $C_{10}H_{19}NO_5S$: C 45.27, H 7.22, N 5.28, S 12.08. Found: C 45.06, H 7.51, N 5.54, S 12.33. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.64 (br s, 1H, N*H*), 2.19 (m, 2H, 2- and 4-C*H*H), 2.91 (br s, 2H, 2- and 4-CH*H*), 2.99 (s, 3H, C*H*$_3$SO$_2$), 3.83 (br s, 1H, 3-C*H*), 4.70 (quint, J = 7.1 Hz, 1H, 1-C*H*). ^{13}C NMR ($CDCl_3$) δ 28.4 (C(*C*H$_3$)$_3$), 37.9 (3-*C*H), 38.2 (*C*H$_2$), 39.7 (*C*H$_3$SO$_2$), 67.9 (1-*C*H), 79.9 (*C*(CH$_3$)$_3$), 155.4 (*C*OOC(CH$_3$)$_3$).

***tert*-Butyl (*trans*-3-Azidocyclobutyl)carbamate (10a).** Compound **9a** (55.4 g, 0.209 mol) was dissolved in DMF (570 mL), NaN_3 (57.4 g, 0.863 mol) was added, and the mixture was stirred at 70 °C for 18 h. After cooling, water (1 L) was added, and the mixture was extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with water (2 × 200 mL) and brine, dried over Na_2SO_4, and evaporated to yield **10a** (46.2 g, 100%),

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(42) The 3-Azaspiro[3.3]heptane scaffold has been recently considered as a possible replacement for piperidine, see: (a) Meyers, M. J.; Muizebelt, I.; van Wiltenburg, J.; Brown, D. L.; Thorarensen, A. *Org. Lett.* **2009**, *11*, 3523–3525. (b) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524–3527.

which was used in the next step without further purification. Mp 84 °C. MS (*m*/*z*, CI) 185 ($MH^+ - N_2$), 129 ($MH^+ - N_2 -$ *i*-C_4H_8). Anal. Calcd for $C_9H_{16}N_4O_2$: C 50.93, H 7.60, N 26.40. Found: C 50.59, H 7.26, N 26.03. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H, $C(CH_3)_3$), 2.26 (br s, 2H, CH_2), 2.43 (br s, 2H, CH_2), 4.06 (m, 1H, *CH*), 4.24 (br s, 1H, *CH*), 4.71 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$) δ 28.4 ($C(CH_3)_3$), 37.1 (CH_2), 43.2 (1-*C*H), 52.3(3-*C*H), 79.9 ($C(CH_3)_3$), 154.9 ($COOC(CH_3)_3$).

***tert*-Butyl (*trans*-3-Aminocyclobutyl)carbamate (11a).** Compound **10a** (14.8 g, 65 mmol) was dissolved in MeOH saturated with NH_3 (150 mL), 10% Pd/C (3 g) was added, and H_2 was bubbled through the reaction mixture for 2 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The crude product (12.8 g) was distilled in vacuo to yield **11a** (9.8 g, 48 mmol, 75%) as a clear solid. Bp 102 °C/0.5 mmHg. MS (*m*/*z*, EI) 186 (M^+), 129 ($M^+ - C(CH_3)_3$), 113 ($M^+ - OC(CH_3)_3$). Anal. Calcd for $C_9H_{18}N_2O_2$: C 58.04, H 9.74, N 15.04. Found: C 57.83, H 9.91, N 14.74. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 1.47 (br s, 2H, NH_2), 2.06 (br s, 2H, CH_2), 2.14 (br s, 2H, CH_2), 3.59 (m, 1H, *CH*), 4.15 (br s, 1H, C*H*), 4.73 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 28.4 ($C(CH_3)_3$), 40.4, 42.5, 44.3, 79.3 ($C(CH_3)_3$), 155.3 ($COOC(CH_3)_3$).

***trans*-3-[(*tert*-Butoxycarbonyl)amino]cyclobutyl 4-Nitrobenzoate (12).** To a solution of **8a** (16.3 g, 87 mmol) and *p*-nitrobenzoic acid (16 g, 96 mmol) in dry THF (400 mL) were added triphenylphosphine (34 g, 0.13 mol) and DEAD (25.8 mL, 0.163 mol) subsequently at 0 °C (exothermic reaction upon DEAD addition). The resulting mixture was stirred at rt overnight. The solution formed was concentrated in vacuo, and the residue was subjected to column chromatography on silica gel (hexane−EtOAc (2:1) as an eluent) to afford **12** (18.9 g, 64%) as a white solid. Mp 163−164 °C. MS (*m*/*z*, CI) 237 ($MH^+ - CO_2 - C_4H_8$), 122 ($C_6H_4NO_2^+$). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C 57.14, H 5.99, N 8.33. Found: C 56.94, H 6.39, N 8.02. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, $C(CH_3)_3$), 2.46 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 4.39 (br s, 1H, 3-C*H*), 4.87 (br s, 1H, N*H*), 5.36 (m, 1H, 1-C*H*), 8.20 (dd, 2H, J = 8.0 Hz, C_6H_4), 8.27 (dd, 2H, J = 8.0 Hz, C_6H_4). ^{13}C NMR ($CDCl_3$) δ 29.5 ($C(CH_3)_3$), 38.7 (CH_2), 69.9, 70.1, 81.2 ($C(CH_3)_3$), 124.6, 131.9, 136.6, 151.8, 155.4 ($COOC(CH_3)_3$), 165.5 ($COOC_6H_4NO_2$).

***tert*-Butyl (*trans*-3-Hydroxycyclobutyl)carbamate (8b).** To a mixture of K_2CO_3 (11.7 g, 85 mmol), H_2O (80 mL), and methanol (400 mL) was added compound **12** (18.9 g, 56 mmol). The resulting mixture was refluxed for 1.5 h, cooled, and filtered, and the filtrate was evaporated under reduced pressure. The product **8b** (10.2 g, 64%) was obtained as a white solid that was used in the next step without further purification. Mp 112 °C. MS (*m*/*z*, EI) 172 ($M^+ - CH_3$), 143 ($M^+ - CO_2$), 87, 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_9H_{17}NO_3$: C 57.73, H 9.15, N 7.48. Found: C 57.99, H 9.37, N 7.41. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 1.78 (br s, 2H, CH_2), 2.61 (br s, 1H, O*H*), 2.73 (br s, 2H, CH_2), 3.63 (br s, 1H, 1-C*H*), 3.99 (br s, 1H, 3-C*H*), 4.74 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 28.4 ($C(CH_3)_3$), 37.4 (1-*C*H), 42.3 (CH_2), 60.9 (3-*C*H), 79.7 ($C(CH_3)_3$), 154.9 ($COOC(CH_3)_3$).

***trans*-3-[(*tert*-Butoxycarbonyl)amino]cyclobutyl Methanesulfonate (9b).** Compound **8b** (10 g, 53 mmol) was dissolved in CH_2Cl_2 (100 mL), triethylamine (11.2 mL, 81 mmol) was added, and the solution was cooled to −30 °C upon stirring. Mesyl chloride (5 mL, 64 mmol) was added dropwise over a 20 min period, then the mixture was warmed to ambient temperature, washed with water (30 mL), 10% aqueous citric acid (30 mL), and brine, dried over Na_2SO_4, and evaporated in vacuo to yield **9b** (13.9 g, 98%) as a colorless solid that was used in the next step without purification. Mp 104 °C. MS (*m*/*z*, EI) 250 ($M^+ - CH_3$), 186 ($M^+ - CH_3SO_2$), 143, 122, 79, 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_{10}H_{19}NO_5S$: C 45.27, H 7.22, N 5.28, S 12.08. Found: C 45.15, H 7.47, N 5.17, S 11.80. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 2.42 (br s, 2H, 2- and 4-C*H*H), 2.63 (br s, 2H, 2- and 4-CH*H*), 2.98 (s, 3H, CH_3SO_2), 4.24 (br s, 1H, 3-C*H*), 4.87 (br s, 1H, N*H*), 5.15 (br s, 1H, 1-C*H*). ^{13}C NMR ($CDCl_3$) δ 28.2 ($C(CH_3)_3$), 37.9 (CH_2), 37.9(CH_3SO_2), 42.1 ($C(CH_3)_3$), 72.9 (3-*C*H), 79.8 (1-*C*H), 155.1 (*C*=O).

***tert*-Butyl (*cis*-3-Azidocyclobutyl)carbamate (10b).** Compound **9b** (13.7 g, 52 mmol) was dissolved in DMF (60 mL), NaN_3 (5.03 g, 77 mmol) was added, and the mixture was stirred at 85 °C for 18 h. After cooling, water (110 mL) was added, and the mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with water (2 × 60 mL) and brine, dried over Na_2SO_4, and evaporated in vacuo to yield **10b** (7.8 g, 71%) that was used in the next step without further purification. Mp 95 °C. MS (*m*/*z*, EI) 184 ($M^+ - N_2$), 170 ($M^+ - N_3$), 57 ($C(CH_3)_3$). Anal. Calcd for $C_9H_{16}N_4O_2$: C 50.93, H 7.60, N 26.40. Found: C 51.13, H 7.75, N 26.09. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H, $C(CH_3)_3$), 1.90 (m, 2H, 2- and 4-C*H*H), 2.73 (br s, 2H, 2- and 4-CH*H*), 3.55 (quint, J = 7.3 Hz, 1H, 1-C*H*), 3.85 (br s, 1H, N*H*), 4.69 (br s, 1H, 3-C*H*). ^{13}C NMR ($CDCl_3$) δ 28.3 ($C(CH_3)_3$), 37.1 (CH_2), 43.1 (1-*C*H), 52.3 (3-*C*H), 80.0 ($C(CH_3)_3$), 155.2 ($COOC(CH_3)_3$).

***tert*-Butyl (*cis*-3-Aminocyclobutyl)carbamate (11b).** Compound **10b** (7.66 g, 36 mmol) was dissolved in MeOH saturated with NH_3 (70 mL). The resulting solution was added dropwise to a suspension of Pd/C (2.5 g) in MeOH (70 mL) while H_2 was bubbled through the mixture under ambient pressure. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The crude product (6.1 g) was purified by column chromatography on silica gel (hexane:EtOAc (2:1) as an eluent, R_f 0.51) to give **11b** (5.86 g, 86%) as a white solid. Mp 111−112 °C. MS (*m*/*z*, EI) 129 ($M^+ - C(CH_3)_3$), 113 ($M^+ - OC(CH_3)_3$), 57 ($C(CH_3)_3$). Anal. Calcd for $C_9H_{18}N_2O_2$: C 58.04, H 9.74, N 15.04. Found: C 58.37, H 9.56, N 15.09. ^{1}H NMR ($CDCl_3$) δ 1.41 (br s, 9H, $C(CH_3)_3$), 1.45 (br s, 2H, CH_2), 1.49 (br s, 2H, NH_2), 2.68 (br s, 2H, CH_2), 3.09 (m, 1H, C*H*-NH_2), 3.70 (br s, 1H, C*H*-NHBoc), 4.68 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 28.4 ($C(CH_3)_3$), 38.8, 41.6, 42.9, 79.4, 155.1 (*C*=O).

***tert*-Butyl (6-Oxospiro[3.3]hept-2-yl)carbamate (16).** 6-Oxospiro[3.3]heptane-2-carboxylic acid[25] (**5**) (26 g, 0.169 mol) was dissolved in CH_2Cl_2 (300 mL). $SOCl_2$ (37 mL, 0.51 mol) was added dropwise over a 10 min period upon vigorous stirring. The mixture was refluxed for 1.5 h then cooled to rt, and the solvent was removed under reduced pressure. The residue was dissolved with CCl_4 (2 × 40 mL) and evaporated to remove the residual HCl. The crude product was distilled in vacuo to give colorless oil (25.5 g, bp 112 °C/1 mmHg). It was dissolved in acetone (70 mL), and the solution was added dropwise to a solution of NaN_3 (28.8 g, 0.443 mol) in H_2O (106 mL) at 0 °C over a 30 min period. The mixture was stirred for 1 h at 0 °C, then ice (400 g) was added, and the product was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic extracts were dried over Na_2SO_4, and the solution was concentrated to 60 mL under reduced pressure. The residue was added to toluene (500 mL) and heated to 90 °C. The residue of CH_2Cl_2 was distilled off, and the mixture was stirred at 90 °C for 30 min until evolution of N_2 ceased. Then *tert*-butanol (58 mL) was added, and the mixture was heated at 90 °C for 16 h. After cooling, the solvent was removed in vacuo to give **16** (62 g, 96%) that was used in the next step without further purification. Mp 94 °C. MS (*m*/*z*, EI) 210 ($M^+ - CH_3$), 108 ($M^+ -$ NHBoc). Anal. Calcd for $C_{12}H_{19}NO_3$: C 63.98, H 8.50, N 6.22. Found: C 64.26, H 8.29, N 6.00. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 2.13 (t, J = 11.7 Hz, 0.5 × 2H, C*H*H), 2.13 (t, J = 11.7 Hz, 0.5 × 2H, C*H*H), 2.54 (br s, 2H, CH*H*), 3.03 (s, 2H, CH_2), 3.11 (s, 2H, CH_2), 4.12 (br s, 1H, 2-C*H*), 4.76 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 26.8 ($C(CH_3)_3$), 28.4, 42.7, 58.1, 58.9, 79.5, 154.9 ($COOC(CH_3)_3$), 206.6 (6-*C*=O).

***tert*-Butyl [6-(Hydroxyimino)spiro[3.3]hept-2-yl]carbamate (17).** To a solution of **16** (2 g, 8.8 mmol) and pyridine (2.87 mL, 35.2 mmol) in 2-propanol (15 mL) was added a solution of $NH_2OH\cdot$HCl (0.93 g, 13.4 mmol) in 2-propanol (7 mL). The reaction mixture was refluxed for 3 h, cooled to rt, and evaporated under reduced pressure. The residue was diluted with water (20 mL) and

filtered to give white solid (1.67 g). The crude product was recrystallized from ethanol to give **17** (1.48 g, 69%). Mp 160 °C. MS (*m*/*z*, EI) 209 ($M^+ - 31$), 184 ($M^+ - i$-C_4H_8), 123, 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C 59.98, H 8.39, N 11.66. Found: C 60.24, H 8.07, N 11.54. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 0.5 × 9H, $C(CH_3)_3$), 1.66 (s, 0.5 × 9H, $C(CH_3)_3$), 1.97(td, J = 8.8 and 1.0 Hz, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 4.08 (br s, 1H, N*H*), 4.69 (br s, 1H, O*H*). ^{13}C NMR ($CDCl_3$) δ 28.4 ($C(CH_3)_3$), 29.7, 31.0, 41.0, 43.2, 44.2, 79.6, 154.9 (*C*OO-*t*-Bu), 155.6 (*C*=N).

***tert*-Butyl (6-Aminospiro[3.3]hept-2-yl)carbamate (18). Method A (from 17).** To the solution of **17** (1.48 g, 6.2 mmol) in MeOH saturated with NH_3 (20 mL) was added Raney Ni (0.5 g). The reaction mixture was stirred under 100 psi of H_2 for 3 h. The catalyst was filtered off carefully, and the filtrate was evaporated under reduced pressure. The crude product (1.3 g) was recrystallized from ethanol to give **18** as a white solid (1.16 g, 84%). Mp 119 °C. MS (*m*/*z*, EI) 226 (M^+), 169 ($M^+ - C(CH_3)_3$), 153 ($M^+ - OC(CH_3)_3$). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C 63.69, H 9.80, N 12.38. Found: C 63.69, H 9.80, N 12.38. ^{1}H NMR (DMSO-d_6) δ 1.42 (s, $C(CH_3)_3$), 1.68 (m, 2H, CH_2), 1.79 (t, J = 9.8 Hz, 2H, CH_2), 2.24 (m, 2H, CH_2), 2.39 (m, 2H, CH_2), 3.30 (quint, J = 7.8 Hz, 1H, C*H*), 3.39 (br s, 1H, C*H*), 4.60 (br s, 1H, N*H*). ^{13}C NMR (DMSO-d_6) δ 28.7 ($C(CH_3)_3$), 29.5, 41.6, 42.6, 43.1, 44.2, 45.9, 46.4, 77.9, 154.9 ($COOC(CH_3)_3$).

Dimethyl Spiro[3.3]heptane-2,6-dicarboxylate (21). Fecht acid dimethyl ester **21** was prepared from compound **20**[43] by using a modified literature procedure.[26] Diethyl malonate (255 g, 1.59 mol) was added dropwise to a stirred suspension of NaH (70 g, 1.75 mol) in dry DMF (1.5 L) over 0.5 h. Then compound **20** (300 g, 0.4 mol) was added, and the resulting mixture was heated at 110−120 °C for 20 h, then cooled, diluted with saturated aqueous NH_4Cl (2 L), and extracted with EtOAc (3 × 0.6 L). The combined organic extracts were washed with water (2 × 0.5 L), dried over Na_2SO_4, and evaporated under reduced pressure. The resulting orange oil (150 g) contained approximately 85% of the product (NMR data) and was used in the next step without purification. It was dissolved in EtOH (0.3 L) and added to a solution of NaOH (94 g, 2.35 mol) in EtOH (0.8 L). The mixture was refluxed for 1.5 h, then cooled, and the precipitate was filtered, washed with cold water (50 mL), and dissolved in water (200 mL). The solution was adjusted to pH < 2 with 6 N aqueous HCl and extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude acid (100 g) was used in the next step without purification. It was dissolved in pyridine (1 L), and the solution was refluxed for 14 h. Pyridine was removed in vacuo, and 6 N aqueous HCl was added carefully to the residue to adjust pH < 2. The product was extracted with EtOAc (3 × 100 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude Fecht's acid (42.4 g) was dissolved in MeOH (200 mL), and $SOCl_2$ (67 mL, 0.92 mol) was added dropwise. The resulting mixture was refluxed for 2.5 h, then evaporated under reduced pressure, diluted with CCl_4 (3 × 100 mL), and evaporated again to remove the residual HCl. The crude product was distilled in vacuo (bp 84−89 °C/0.5 mmHg). Compound **21** (25.8 g, 30% from **20**) was obtained as a colorless oil. For spectral and physical data, see ref 26.

6-(Methoxycarbonyl)spiro[3.3]heptane-2-carboxylic Acid (22). Compound **21** (23 g, 108 mmol) was dissolved in EtOH (100 mL) and added to the solution of NaOH (4.33 g, 108 mmol) in EtOH (100 mL). The reaction mixture was refluxed for 1 h, then cooled, the precipitate was filtered, washed with cold water (20 mL), and dissolved in water (100 mL). The solution was adjusted to pH 5−6 with 3 N aqueous HCl and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Compound **22** (20.5 g, 95%) was obtained as a yellow oil that was used in the next step without further purification. For spectral and physical data, see ref 27.

Methyl 6-[(*tert*-Butoxycarbonyl)amino]spiro[3.3]heptane-2-carboxylate (23). To a solution of compound **22** (20.5 g, 0.104 mol) in CH_2Cl_2 (200 mL) was added $SOCl_2$ (30 mL, 0.41 mol) dropwise upon vigorous stirring. The resulting mixture was refluxed for 1 h. After cooling, the solvent was evaporated under reduced pressure. The residue was diluted with CCl_4 (2 × 70 mL) and evaporated to remove the rest of the $SOCl_2$. The crude product was dissolved in acetone (60 mL) and added dropwise to a solution of NaN_3 (19.5 g, 0.3 mol) in H_2O (90 mL) over 30 min. The mixture was stirred at 0 °C for 1 h, then ice (60 g) was added, and the product was extracted with Et_2O (3 × 75 mL). The combined extracts were dried over $MgSO_4$ and concentrated to 60 mL under reduced pressure. The residue was added to toluene (250 mL). After the residual Et_2O was distilled off, the mixture was stirred for 30 min until N_2 evolution ceased. *tert*-Butanol (17 mL) was added, and the mixture was heated at 90 °C for an additional 12 h. After cooling, the solvent was removed in vacuo to give **23** (21.0 g, 75%) pure enough for the next step. For spectral and physical data, see ref 27.

6-[(*tert*-Butoxycarbonyl)amino]spiro[3.3]heptane-2-carboxylic Acid (24). To a solution of **23** (49.6 g, 0.184 mol) in MeOH (200 mL) was added a solution of NaOH (29.5 g, 0.77 mol) in a mixture of MeOH (170 mL) and water (20 mL). The reaction mixture was stirred at rt for 5 h, and the solvent was removed under reduced pressure. Water (100 mL) was added to the residue, and the mixture was adjusted to pH 3−3.5 with 10% aqueous citric acid. The product was extracted with CH_2Cl_2 (4 × 80 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduce pressure. The crude product was recrystallized from EtOH to give **24** (41.1 g, 87%) as a white solid. Mp 101−104 °C. MS (*m*/*z*, EI) 238 ($M^+ - 17$), 55 ($C(CH_3)_3^+$). Anal. Calcd for $C_{13}H_{21}NO_4$: C 61.16, H 8.29, N 5.49. Found: C 60.92, H 8.06, N 5.67. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 1.84 (m, 2H, CH_2), 2.15 (br s, 1H, CH_2), 2.31 (m, 4H, CH_2), 2.47 (br s, 1H, CH_2), 3.02 (quint, J = 8.3 Hz, 1H, 6-C*H*), 3.98 (br s, 1H, C*H*), 4.65 (br s, 1H, N*H*).

Benzyl *tert*-Butylspiro[3.3]heptane-2,6-diylbiscarbamate (25). To a solution of **24** (18.1 g, 70.9 mmol) in toluene (200 mL) were added triethylamine (11.8 mL, 85 mmol) followed by DPPA (16.8 mL, 78 mmol) dropwise. The mixture was heated to 80 °C and stirred at this temperature for 1 h. Next benzyl alcohol (14.7 mL, 0.142 mmol) was added, then the mixture was left for 12−16 h and evaporated under reduced pressure. Aqueous KOH (100 mL, 10%) was added to the residue, and the product was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (50 mL) and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product (19.4 g) was recrystallized from hexane−EtOAc to yield **25** (8.6 g, 62%) as a colorless solid. Mp 132 °C. MS (*m*/*z*, CI) 361 (MH^+), 261 ($MH^+ - CO_2 - C(CH_3)_3$) Anal. Calcd for $C_{20}H_{28}N_2O_4$: C 66.64, H 7.83, N 7.77. Found: C 66.60, H 7.67, N 7.41. ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 9H, $C(CH_3)_3$), 1.84 (m, 2H, 2-CH_2), 2.27 (br s, 2H, 4-CH_2), 2.45 (br s, 2H, CH_2), 4.04 (m, 2H, C*H*), 4.59 (br s, 1H, N*H*), 4.81 (br s, 1H, N*H*), 5.04 (s, 2H, CH_2O), 7.3−7.4 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6) δ 28.4 ($C(CH_3)_3$), 30.8 (CH_2), 41.8 (*C*H), 42.2 (*C*H), 42.8 (CH_2), 43.0 (CH_2), 43.1 (CH_2), 43.2 (CH_2), 66.7 ($CH_2OC_6H_5$), 79.3 ($C(CH_3)_3$), 127.9 (C_6H_5), 128.1 (C_6H_5), 128.4 (C_6H_5), 136.8 (*ipso*-*C* of C_6H_5), 154.9 ($COOCH_2C_6H_5$), 155.4 ($COOC(CH_3)_3$).

***tert*-Butyl (6-Aminospiro[3.3]hept-2-yl)carbamate (18). Method B (from 25).** Compound **25** (15.3 g, 42.5 mmol) was dissolved in EtOH (150 mL), and 10% Pd/C (5 g) was added. The suspension was hydrogenated under 50−70 bar of H_2 at 45 °C for 20 h. The catalyst was filtered of, and the filtrate was evaporated under reduced pressure, diluted with CH_2Cl_2 (150 mL) and washed with 10%

(43) Herzog, H. L. *Org. Synth.* **1951**, *31*, 82.

TABLE 2. The Crystallographic Data and Experimental Parameters for Compounds 11b, 36, 38, and 39

parameter	11b	36	38	39
a, Å	9.9889(7)	8.1775(6)	15.128(3)	9.929(1)
b, Å	11.4918(8)	11.2741(8)	5.980(1)	12.674(1)
c, Å	9.6399(7)	11.5261(7)	19.539(4)	15.774(2)
α, deg	90	74.860(6)	90	90
β, deg	90	71.782(6)	107.58(2)	90.00(1)
γ, deg	90	75.209(6)	90	90
V, Å^3	1106.6(1)	956.7(1)	1684.9(5)	1984.8(3)
F(000)	408	372	712	888
crystal system	orthorhombic	triclinic	monoclinic	monoclinic
space group	$Pna2_1$	$P\bar{1}$	$P2_1/c$	$P2_1/n$
Z	4	2	4	4
μ, mm^{-1}	0.079	0.084	0.099	0.106
D_{calc}, g/cm^3	1.118	1.203	1.322	1.420
$2\Theta_{max}$, grad	60	60	60	60
no. of measured reflcns	6206	11279	17198	12149
no. of independent reflcns	3077	5572	4920	5790
R_{int}	0.033	0.029	0.100	0.042
no. of *R*eflcns with $F > 4\sigma$(F)	1899	1739	1482	1702
no. of parameters	129	233	228	288
R_1	0.054	0.036	0.039	0.037
wR_2	0.134	0.078	0.077	0.067
S	0.954	0.641	0.640	0.625
CCDC no.	778485	778486	778487	778488

aqueous KOH (50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product (10.1 g) was recrystallized from EtOH to give **18** (7.6 g, 34 mmol, 79%) as a white solid. The spectral and physical data are described above.

6-[(*tert*-Butoxycarbonyl)amino]spiro[3.3]heptane-2-carboxylic Acid (35). To the solution of NaOH (0.542 g, 13.6 mmol) in water (25 mL) were added hydrochloride of **34**[28] (2.4 g, 13.5 mmol) and Boc_2O (6.23 mL, 30 mmol). The reaction mixture was stirred at rt for 1.5 h and washed with Et_2O (2 × 10 mL). The aqueous phase was adjusted to pH 3.5−4 with 10% aqueous citric acid and extracted with CH_2Cl_2 (3 × 12 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product (2.9 g) was recrystallized from ethanol (5 mL) to give **35** (2.7 g, 83%) as a white solid. Mp 95−97 °C. MS (m/z, EI) 224 ($M^+ - OH$), 200, 199, 182, 96, 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_{12}H_{19}NO_4$: C 59.73, H 7.94, N 5.80. Found: C 59.90, H 8.22, N 5.53. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, C(CH_3)$_3$), 2.46 (m, 4H, CH_2), 3.01 (quint, J = 8.0 Hz, 1H, CH), 2.73 (br s, 2H, CH_2), 3.69 (s, 2H, CH_2), 3.93 (s, 2H, CH_2), 4.74 (br s, 1H, NH); COOH is not observed due to exchange. ^{13}C NMR ($CDCl_3$) δ 28.4 (C(CH_3)$_3$), 32.5 (2-CH), 34.8 (3-C), 35.8 (CH_2), 61.2 (CH_2), 61.6 (CH), 79.8 ($C(CH_3)_3$), 156.2 ($COOC(CH_3)_3$), 179.4 (CO_2H).

***tert*-Butyl 6-{[(Benzyloxy)carbonyl]amino}azetidine-2-azaspiro-[3.3]heptane-2-carboxylate (36).** Compound **35** (1 g, 4.13 mmol) and triethylamine (0.7 mL, 4.95 mmol) were dissolved in toluene (15 mL). The reaction mixture was heated to 95 °C, then DPPA (1 mL, 4.55 mmol) was added dropwise, and the mixture was stirred for 1.5 h. Then benzyl alcohol (0.9 mL, 8.33 mmol) was added, and the resulting mixture was stirred for 16 h. The solution was evaporated under reduced pressure, and the residue was recrystallized from EtOH to give **36** (0.47 g, 62%) as a white solid. Mp 128−129 °C. MS (m/z, EI) 291 ($M^+ - i$-C_4H_8), 248 ($M^+ - i$-$C_4H_8 - CO_2$). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C 65.88, H 7.56, N 8.09. Found: C 66.17, H 7.51, N 7.84. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, C(CH_3)$_3$), 2.03 (br s, 2H, CH_2), 2.56 (br s, 2H, CH_2), 3.82 (s, 2H, CH_2), 3.93 (s, 2H, CH_2), 4.03 (br s, 1H, 6-CH), 4.92 (br s, 1H, NH), 5.07 (s, 2H, CH_2C$_6$H$_5$), 7.32−7.38 (m, 5H, C$_6$H$_5$). ^{13}C NMR ($CDCl_3$) δ 28.4 (C(CH_3)$_3$), 31.6, 41.4, 41.8, 66.9, 80.1, 128.1, 128.2, 128.6, 136.2, 155.5 (C=O), 156.2 (C=O).

***tert*-Butyl 6-Amino-2-azaspiro[3.3]heptane-2-carboxylate (37).** Compound **36** (50 mg, 0.14 mmol) was dissolved in dry MeOH (7 mL) and 10% Pd/C (30 mg) was added. Hydrogen was bubbled though the mixture over 10 min upon stirring, the catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give **37** (29 mg, 97%) as a white solid. Mp 115 °C. MS (m/z, EI) 212 (M^+), 197 ($M^+ - 15$), 156 ($M^+ - i$-C_4H_8). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C 62.24, H 9.50, N 13.20. Found: C 62.01, H 9.50, N 13.55. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H, C(CH_3)$_3$), 1.72 (br s, 2H, NH_2), 1.80 (m, 2H, CH_2), 2.46 (m, 2H, CH_2), 3.30 (br m, 1H, 6-CH), 3.79 (s, 2H, CH_2), 3.87 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 28.4 (C(CH_3)$_3$), 30.7 (2-CH_2), 43.1 (6-CH), 44.3 (4-C), 44.5 (CH_2), 79.3 ($C(CH_3)_3$), 156.2 (C=O).

***tert*-Butyl {*trans*-3-[(4-Nitrobenzoyl)amino]cyclobutyl}-carbamate (38).** Compound **11a** (200 mg, 1.1 mmol) was dissolved in dioxane (10 mL), and NEt_3 (0.22 mL, 3 mmol) was added followed by 4-nitrobenzoyl chloride (200 mg, 1.1 mmol). The mixture was refluxed for 1.5 h, then diluted with water (20 mL) and filtrered. The precipitate was washed with cold water (5 mL) and ether (10 mL). The crude product was recrystallized from EtOAc (5 mL). Compound **38** (340 mg, 94%) was obtained as a white solid. Mp 240 °C. MS (m/z, CI) 335 (M^+). Anal. Calcd for $C_{16}H_{21}N_3O_5$: C 57.30, H 6.31, N 12.53. Found: C 57.01, H 6.62, N 12.59. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, C(CH_3)$_3$), 2.43 (m, 4H, CH_2), 4.31 (br s, 1H, CH), 4.62 (br s, 1H, CH), 4.81 (br s, 1H, NHBoc), 6.42 (br s, 1H, NHC$_6$H$_4$NO$_2$), 7.95 (dd, 2H, J = 8.0 Hz, C$_6$H$_4$NO$_2$), 8.23 (dd, 2H, J = 8.0 Hz, C$_6$H$_4$NO$_2$). ^{13}C NMR ($CDCl_3$) δ 28.3 (C(CH_3)$_3$), 38.5 (CH_2), 39.2 (CH), 40.2 (CH), 78.2 ($C(CH_3)_3$), 123.7 (CH), 128.0 (CH), 139.9 (C), 149.5 (C), 155.0 ($COOC(CH_3)_3$), 164.3 (COO).

***N*,*N*′-Spiro[3.3]heptane-2,6-diylbis(4-nitrobenzamide) (39).** Compound **18** (310 mg, 1.37 mmol) was dissolved in 3 N HCl (8 mL) and the solution was stirred for 0.5 h. The mixture was evaporated under reduced pressure, diluted with water (2 × 10 mL), and evaporated to remove the residual HCl. The solid was dissolved in preheated dimethylformamide (10 mL), and NEt_3 (0.6 mL, 4.12 mmol) was added followed by 4-nitrobenzoyl chloride (510 mg, 2.74 mmol). The mixture was heated at 80 °C for a 1 h, and then cooled. The product was filtered, then washed with cold water (2 × 25 mL) and ether (20 mL). The crude product was recrystallized from dimethylformamide to give **39** (510 mg, 88%) as orange needles. Mp 289 °C. MS (m/z, CI) 423 ($M^- - 1$). Anal. Calcd for $C_{21}H_{20}N_4O_6$: C 59.43, H 4.75, N 13.20. Found: C 59.27, H 4.70, N 13.51. ^{1}H NMR ($CDCl_3$) δ 2.21 (m, 4H, CH_2), 2.34 (br s, 2H, CH_2), 4.36 (m, 2H, CH),

8.08 (dd, J = 8.0 Hz, 4H), 8.30 (dd, J = 8.0 Hz, 4H), 8.86 (br s, 2H, N*H*). ^{13}C NMR ($CDCl_3$) δ 31.4 ($C(CH_3)_3$), 41.2 (*C*H), 42.1 (CH_2), 42.4 (CH_2), 123.9 (*C*H), 129.2 (*C*H), 140.6 (*C*), 149.5 (*C*), 164.2 (*C*OO).

X-ray Diffraction Studies of 11b, 36, 38, and 39. The crystals for X-ray diffraction studies were obtained by slow crystallization from EtOAc (**11b** and **38**), EtOH (**36**), and dimethylformamide (**39**).

X-ray diffraction studies were performed on an automatic "Xcalibur 3" diffractometer (graphite monochromated Mo Kα radiation, CCD-detector, ω-scanning, $2\theta_{max}$ = 60°). The structure was solved by direct method with the SHELXTL package.[44] The restrains were applied to the lengths of C−C bonds in the *tert*-butyl substituents (1.54(1) Å) for the structure **11b**. Positions of hydrogen atoms were located from electron density difference maps and refined with use of the riding model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and 1.2 for other hydrogen atoms), except the H-atoms at nitrogen which were refined within isotropic approximation. The crystallographic data and experimental parameters are listed in Table 2. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk). The deposition numbers are given in Table 2.

(44) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *A64*, 112–122.

Supporting Information Available: Copies of NMR spectra and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.