JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis and Structural Analysis of Angular Monoprotected Diamines Based on Spiro[3.3]heptane Scaffold

Anton V. Chernykh,[†,‡] Dmytro S. Radchenko,*[,‡,§] Oleksandr O. Grygorenko,[∥] Constantin G. Daniliuc,[⊥] Dmitriy M. Volochnyuk,[†] and Igor V. Komarov[‡,§]

[†]Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska 5, Kyiv 02660, Ukraine

[‡]Enamine Ltd., Alexandra Matrosova Street 23, Kyiv 01103, Ukraine

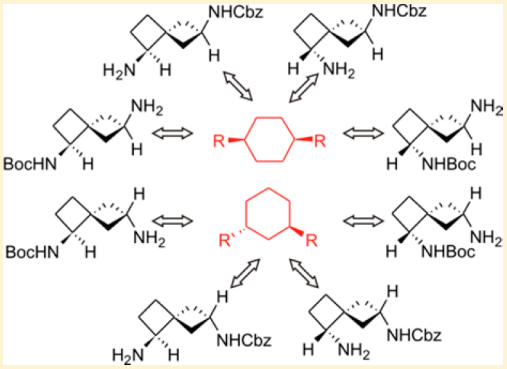
[§]Institute of High Technologies, Taras Shevchenko National University of Kyiv, Volodymyrska 60, Kyiv 01601, Ukraine

[∥]Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska 64, Kyiv 01601, Ukraine

[⊥]Westfalische Wilhelms-Universitat Munster, Institute of Organic Chemistry, Corrensstrasse 40, Munster 48149, Germany

Supporting Information

ABSTRACT: The synthesis of all stereoisomers of spiro[3.3]heptane-1,6-diamines suitably protected for use as building blocks in drug discovery is reported. Structural analysis revealed the similarity between the spiro[3.3]-heptane and cyclohexane scaffolds. Comparison of the distance between functional groups and their spatial orientation proved that (1*S*,4*r*,6*R*)- and (1*R*,4*r*,6*S*)-1,6-disubstituted spiro[3.3]heptanes can be considered as restricted surrogates of *cis*-1,4-disubstituted cyclohexane derivatives. Similarly, (1*S*,4*s*,6*R*)- and (1*R*,4*s*,6*S*)-1,6-disubstituted spiro[3.3]heptanes are the restricted surrogates of *trans*-1,3-disubstituted cyclohexanes. Such replacement can be recommended for use in optimization of ADME parameters of lead compounds in drug discovery.



INTRODUCTION

Saturated carbo- and heterobicyclic systems, in particular, spirocyclic derivatives, can be frequently found among natural biologically active compounds;[1,2] they are also attractive molecular frameworks (scaffolds) used in contemporary drug design.[3−5] The bicyclic scaffolds were shown to allow wide variation of the nature and relative orientation of the substituents that might be of use in fine-tuning the pharmacodynamic and pharmacokinetic parameters of the derivatives during lead identification.[6] Spirocyclic scaffolds composed of small rings (three- or four-membered) might offer another opportunity to obtain the leads in a preorganized, conformationally restricted "biologically active" conformation, thus enhancing the chances to improve efficiency and selectivity of the drug−target interaction.[7−10]

Previously, we have reported the synthesis of spiro[3.3]-heptane and azaspiro[3.3]heptane derivatives as well as their evaluation as 4-aminopiperidine surrogates.[11,12] Also, small-ring containing heteroatom-substituted azaspiro[3.3]heptanes were proposed as restricted surrogates of piperidine, piperazine, morpholine, or thiomorpholine derivatives (Figure 1a).[13,14] Furthermore, substitution of the heterospirocyclic analogues for the six-membered heterocyclic residues in biologically active compounds was shown to advantageously alter the metabolic stability of the compounds.[15] In the present study, we developed this concept further and report on a library of doubly functionalized spiro[3.3]heptane derivatives which might be used as conformationally restricted surrogates of 1,3- or 1,4-substituted cyclohexanes (Figure 1b).

Numerous biologically active compounds and approved drugs contain mono- or disubstituted cyclohexane motifs in the molecules. Mucolytic agents Bromhexine (**1**), introduced by Boehringer Ingelheim in 1963 and still widely used nowadays,[16,17] or its metabolite Ambroxol (**2**)[18,19] could be the examples. Recently, 1,3- and 1,4-disubstituted cyclohexane diamine derivatives (for example, compound **3**)[20] were evaluated as antitubercular agents (Figure 1c).

To the best of our knowledge, a vast majority of the spiro[3.3]heptane derivatives known to date are mono- or "linearly" 2,6-substituted. The examples are axially chiral spiro[3.3]heptane-2,6-diamine, which has been known since 1936,[21,22] or glutamic acid analogues, based on the spiro[3.3]-heptane scaffold.[23] Simple "angularly" 1,5- and 1,6-functionalized spiro[3.3]heptanes are much less studied; rare examples are described mainly in patent literature.[24] Here, we disclose our synthetic approach to novel 1,6-disubstituted spiro[3.3]-heptane derivatives, namely, all the isomers of monoprotected 1,6-spiro[3.3]heptane diamines—the building blocks which can be directly used in constructing analogues of the cyclohexane-

Received: February 11, 2015
Published: March 13, 2015

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981

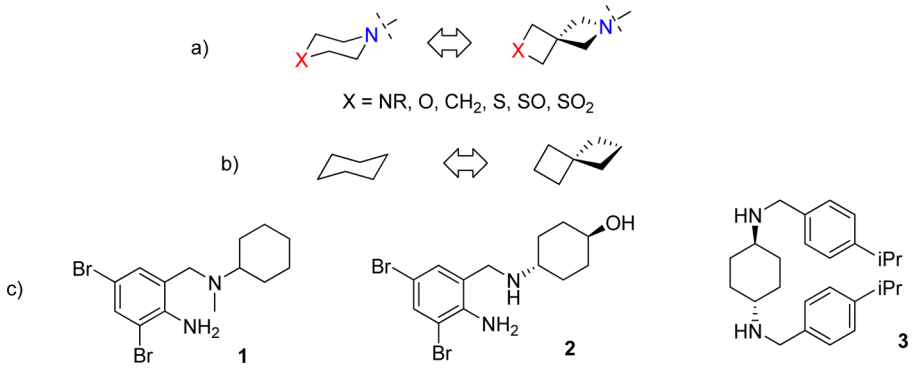


Figure 1. Spirocyclic surrogates of heterocyclic (a) and carbocyclic saturated six-membered rings (b) and examples of cyclohexane-containing biologically active compounds (c).

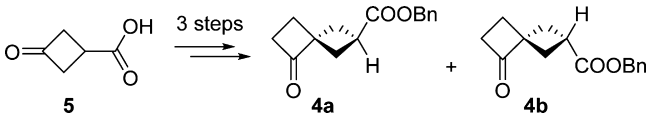
derived biologically active compounds or generally in drug design.

RESULTS AND DISCUSSION

Synthesis. Each of the target compounds has four stereoisomeric forms, and we wanted to obtain them in an optically pure form. In order to achieve this goal, we decided to commence the synthesis from appropriate diastereomeric starting compounds and then use a stereoselective transformation employing a chiral auxiliary at the appropriate step of the synthesis.

Recently, we described diastereomeric ketoesters **4a** and **4b** (Scheme 1), easily prepared from commercially available

Scheme 1. Synthesis of Starting Ketones 4a and 4b



ketoacid **5** and separated by column chromatography.[25] Compounds **4a**,**b** are functionalized in the 1,6-positions suitably to prepare the target compounds.

The carbonyl group in **4a**,**b** was used as a convenient "handle" to attach the chiral auxiliary. Formation and subsequent reduction of imines with either (*R*)-phenylglycinol or (*R*)-phenylethylamine that we tried first gave an inseparable mixture of diastereoisomeric amine derivatives. The progress was achieved when the ketoesters were converted into the imine derivatives using Ellman's sulfinamide auxiliary (*R*)-*t*-BuS(O)NH_2 or (*S*)-*t*-BuS(O)NH_2 and Ti(O*i*-Pr)$_4$ as a Lewis acid catalyst and mild dehydrating agent.[26] Scheme 2 shows the overall strategy, exemplifying it on the synthesis of **12a** and **13a** starting from **4a** and (*R*)-*t*-BuS(O)NH_2. Following the same synthetic scheme, other stereoisomers were prepared, using other combinations of the starting keto-ester and chiral auxiliary: **12b** and **13b** – from **4a** and (*S*)-*t*-BuS(O)NH_2; **12c** and **13c** – from **4b** and (*R*)-*t*-BuS(O)NH_2; and **12d** and **13d** – from **4b** and (*S*)-*t*-BuS(O)NH_2.

The subsequent reduction of imine **6a** with $NaBH_4$ proceeded with good stereoselectivity installing successfully the new chiral carbon center. The diastereomer **7aa** was the major product in the synthesis, with the ratio of **7aa**:**7ab** = 9:1 (by ^{1}H NMR of the crude mixture); it was easily purified by column chromatography. Two-step hydrolysis of compound **7aa** gave the amino acid **9a**. The latter was protected at the nitrogen atom as a Boc-derivative **10a** and subjected to the Curtius rearrangement using benzyl alcohol to quench the intermediate isocyanate, leading to the benzyl carbamate protection at the second nitrogen atom. Both of the protecting groups in compound **11a** could then be selectively removed by hydrogenolysis or acidic hydrolysis to form compounds **12a** or **13a**, respectively.

The absolute configuration of the products was established by X-ray diffraction study performed with diastereomeric derivatives **8a**–**8d**.[27]

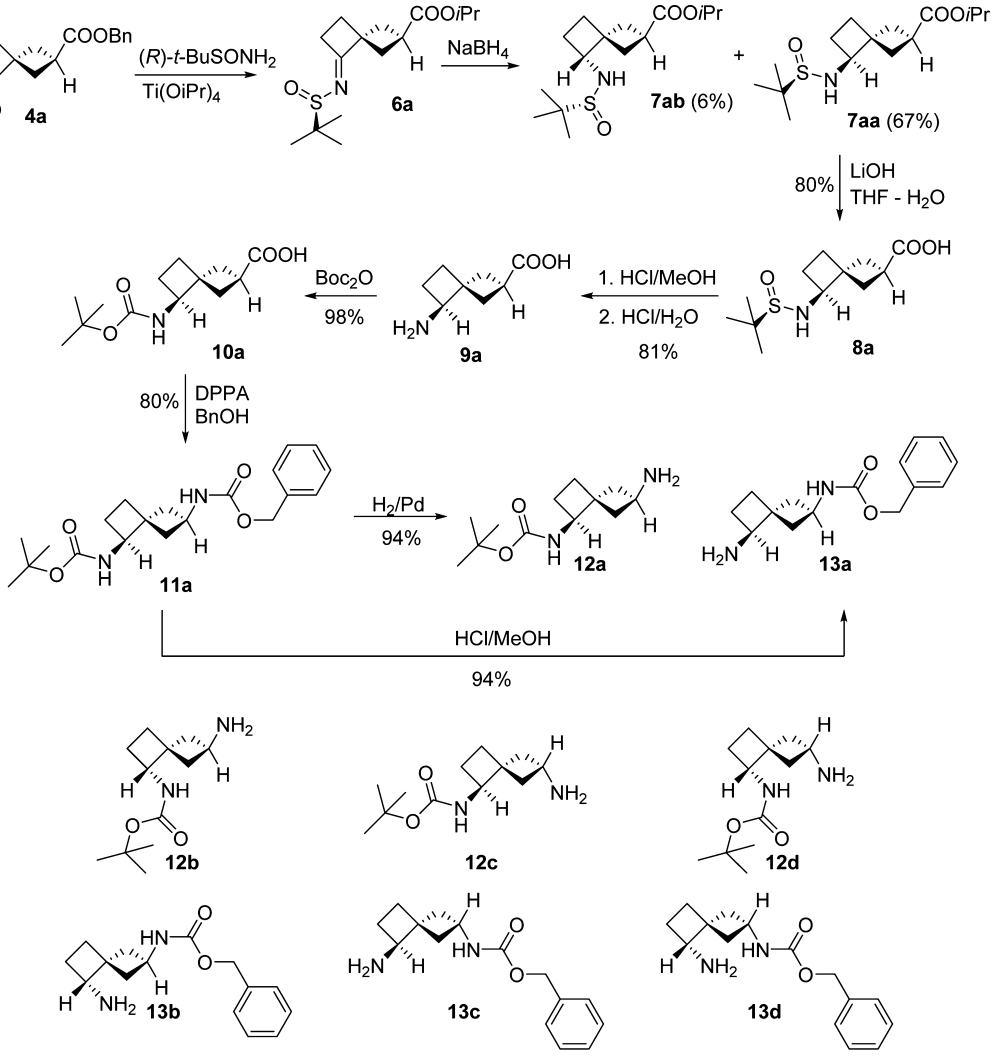
Structure Analysis. The structural relationship between disubstituted cyclohexane and spiro[3.3]heptane derivatives is obvious from considering simple molecular models, but in order to assess this relationship in a quantitative way, we relied on a geometrical approach used by us previously for bicyclic diamines and other molecules.[6,11,28] In this approach, conformation of a scaffold can be characterized by relative spatial orientation of exit vectors $\mathbf{n}_1$ and $\mathbf{n}_2$ defined by the functional groups attached (Figure 2). The attachment points C^1 and C^2 are used as the starting points of these vectors, whereas, to define their direction, the C^1–FG^1 and C^2–FG^2 bonds are used. In turn, the relative orientation of the vectors $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$ is described by four geometric parameters: the distance r between the atoms C^1 and C^2, the plane angles φ_1 (between vectors $\boldsymbol{n}_1$ and $\mathbf{C^2C^1}$) and φ_2 (between $\boldsymbol{n}_2$ and $\mathbf{C^1C^2}$), and the dihedral angle θ defined by vectors $\boldsymbol{n}_1$, $\mathbf{C^1C^2}$, and $\boldsymbol{n}_2$. It can be seen that the values of φ_1 and φ_2 close to 0° are characteristic of a "linear" relative disposition of the substituents attached to the scaffold, whereas θ close to 0° (or 180°) corresponds to the "flattened" structures. On the contrary, the values of θ, φ_1, and φ_2 far from these extreme limits show a "three-dimensional", "non-flattened" nature of the scaffold. It should be noted that the angle θ is the only parameter that distinguishes enantiomers: for these, the absolute values of θ are the same, but the signs are opposite. In further discussion, we will consider only the absolute values of θ, keeping in mind that the values have opposite signs for the enantiomeric pairs.

Geometric parameters r, θ, φ_1, and φ_2 obtained for 1,6-disubstituted spiro[3.3]heptane scaffolds from X-ray data for the compounds **8a**–**8d**, together with the literature data for some other mono- and bicyclic scaffolds,[29−31] are given in Table 1 and illustrated in Figure 3 in different coordinates. For the choice of C^1 and C^2 atoms to be not deliberate, we put $\varphi_1 > \varphi_2$.

The results reflect the fact that four relative spatial orientations of the substituents are possible for 1,6-

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981

Scheme 2. Synthesis of Monoprotected Spiro[3.3]heptane Diamines 12a and 13a and the Structures of All the Monoprotected Diamines Prepared by This Approach



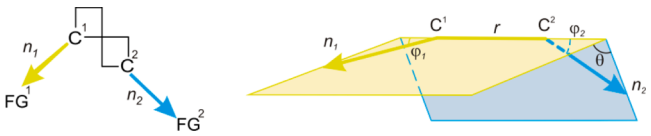


Figure 2. Definition of geometric parameters r, θ, φ_1, and φ_2.

Table 1. Values of Geometric Parameters r, θ, φ_1, and φ_2 for the Compounds 8, 11−17

entry no.	compound	r, Å	φ_1, deg	φ_2, deg	$\|\theta\|$, deg	ref.
1	**8a**	3.59	77	46	25	this work
2	**8b**	3.59	76	46	25	
3	**8c**	3.44	81	30	151	
4	**8d**	3.41	81	30	151	
5	**14**	4.12	33	21	140	11
6	**15**	2.12	32	31	4	
7	**16**	2.14	63	40	180	
8	**17**	2.51	34	34	2	28
9	**18**	2.53	81	35	118	28
10	**19**	2.94	27	25	171	29
11	**20**	2.95	68	27	3	30

disubstituted spiro[3.3]heptane scaffolds (two enantiomeric pairs), each corresponding to one of the stereoisomers **8a−8d**. These orientations have similar values of r (3.41−3.59 Å), φ_1 (76−81°), and φ_2 (30−46°), but differ significantly in the θ values. As might be expected, the two enantiomeric pairs differ only by the sign of the θ angle: ± 25° for **8a,b** and ±151° for **8c,d**, respectively.

It would be of interest to compare the obtained values of geometric parameters with the data for other related disubstituted cores. In particular, the 1,6-disubstituted spiro[3.3]heptane scaffold has the value of r intermediate between 2,6-disubstituted spiro[3.3.]heptane (4.12 Å), (compound **14**) and 1,4-disubstituted cyclohexanes (2.94−2.95 Å) (compounds **19** and **20**). In the r−θ plot, the data points for **8c,d** are located between the points for **14** and *trans*-1,4-disubstituted cyclohexane **19**, whereas, for **8a,b**, the closest data point corresponds to *cis*-**20** (Figure 3a). There is also a similarity in these coordinates for compounds **8c,d** and *trans*-1,3-disubstituted cyclohexane **18**, *trans*-1,3-disubstituted cyclobutane **16**, as well as for the compounds **8a,b** and the corresponding *cis*-isomers **15** or **17**.

The situation is different if the values of φ_1 and φ_2 angles are also considered (Figure 3b). The 2,6-disubstituted spiro[3.3]-

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981

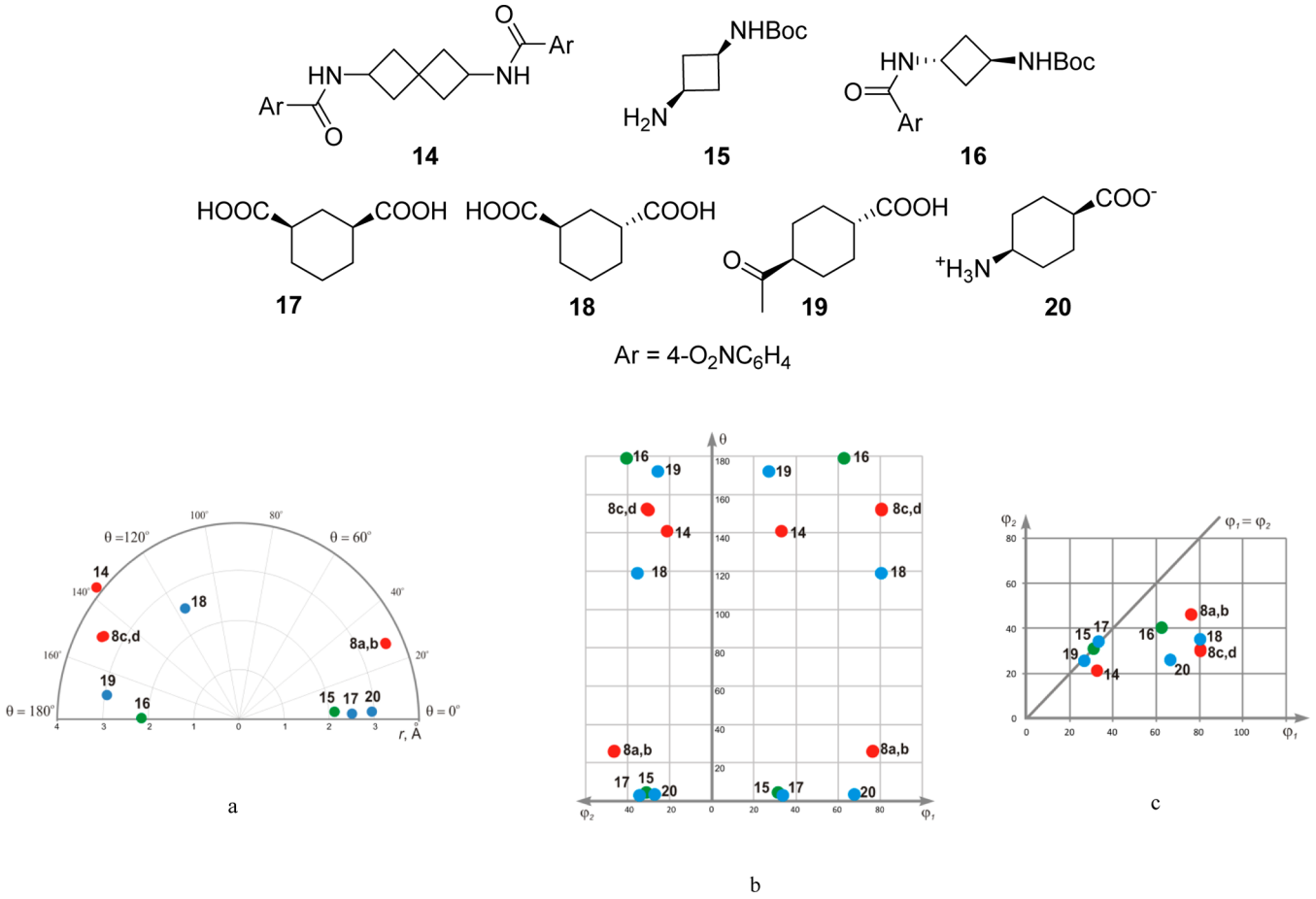


Figure 3. Chemical space covered by scaffolds discussed in this work: (a) r–θ representation (polar coordinates); (b) φ_1–θ and φ_2–θ representations (shown in the same plot, Cartesian coordinates); (c) φ_1–φ_2 representations (Cartesian coordinates).

heptane **14** and all isomers of disubstituted monocyclic scaffolds which have a (pseudo)equatorial orientation of both the substituents (i.e., *cis*-1,3-disubstituted cyclobutane **15**, *cis*-1,3-disubstituted cyclohexane **17**, and *trans*-1,4-disubstituted cyclohexane **19**) show only little difference between φ_1 and φ_2 values—a feature which reflects the similar surroundings of the two substituent attachment points in each case. However, there is significant difference in φ_1 and φ_2 values for the 1,6-disubstituted spiro[3.3]heptanes **8a**–**8d**; this is obviously the consequence of the scaffold dissymmetry. This resembles the situation with isomeric scaffolds in **16**, **18**, and **20**, which have the two substituents mounted on the cycloalkane ring in (pseudo)equatorial and (pseudo)axial positions, respectively. This fact is better illustrated in Figure 3c: the data points for **10**, **16**, **18**, and **20** are close to one another, but far from the $\varphi_1 = \varphi_2$ line, which is characteristic for dissymmetric disubstituted scaffolds. In this view, the *trans*-1,3-disubstituted cyclohexane **18** can be considered as a possible analogue for **8c**,**d**, and *cis*-1,4-disubstituted cyclohexane **20** for **8a**,**b**. It should be noted, however, that, due to some conformational flexibility, the substituents in the scaffolds present in **18** and **20** can change their positions from equatorial to axial and vice versa, which is impossible for **8a**–**8d** (Figure 4). Therefore, the (1*S*,4*r*,6*R*)- and (1*R*,4*r*,6*S*)-1,6-disubstituted spiro[3.3]heptanes (present in **8a**,**b**) can be considered as conformationally rigid replacements fixing equatorial and axial positions of the substituents for *cis*-1,4-disubstituted cyclohexanes, and (1*S*,4*s*,6*R*)- and (1*R*,4*s*,6*S*)-

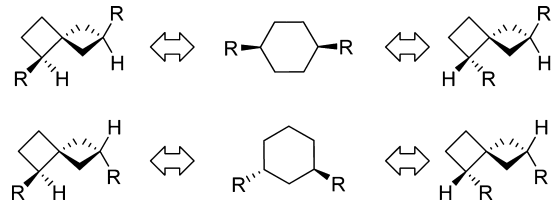


Figure 4. Spiro[3.3]heptane scaffold as cyclohexane framework analogue.

isomers (present in **8c**,**d**) for *trans*-1,3-disubstituted cyclohexanes.

CONCLUSIONS

Expedient synthesis of all stereoisomers of spiro[3.3]heptane-1,6-diamines monoprotected by *t*-butyloxycarbonyl or benzyloxycarbonyl groups is reported. Structural analysis of the spirocyclic scaffold in the intermediates, studied in this work by X-ray crystallography in comparison with the reference compounds described in the literature, revealed the similarity between the spiro[3.3]heptane and cyclohexane scaffolds. This might allow isosteric replacement of *cis*-1,4-disubstituted cyclohexane derivatives with the conformationally restricted analogues, (1*S*,4*r*,6*R*)- and (1*R*,4*r*,6*S*)-1,6-disubstituted spiro[3.3]heptanes. Similarly, (1*S*,4*s*,6*R*)- and (1*R*,4*s*,6*S*)-spiro[3.3]heptanes can be the restricted surrogates of *trans*-1,3-disubstituted cyclohexanes. The replacement can be recom-

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974–3981

mended for use in optimization of pharmacokinetic and pharmacodynamic characteristics of lead compounds in drug discovery.

EXPERIMENTAL SECTION

General. Solvents were purified according to the standard procedures. Compound 7 was purchased from commercial sources; compounds **4a** and **4b** were prepared using the procedures reported in the literature.[25] Melting points were measured on an automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230−400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR spectra were recorded at 499.9 or 400.4 MHz for protons and 124.9 or 100.4 MHz for carbon-13. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. MS analyses were done on an LCMS instrument with chemical ionization (CI) or a GCMS instrument with electron impact ionization (EI). HRMS spectra were recorded on an HPLC system interfaced to an LTQ Orbitrap equipped with electrospray (ESI) ion source. All compound names were generated using ChemBioDraw.

(2*R*,4*r*,5*S*)-5-(((*R*)-*tert*-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylic Acid (8a). *Isopropyl (2R,4r,5S)-5-(((R)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7aa**) and Isopropyl (2S,4r,5R)-5-(((R)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7ab**).* Titanium isopropylate (5.86 g (6.14 mL), 20.62 mmol) was added to the solution of compound **4a** (1.44 g, 5.89 mmol) and (*R*)-2-methylpropane-2-sulfinamide (2.14 g, 17.66 mmol) in 2-propanol (20 mL) under an argon atmosphere. The mixture was refluxed for 3 days. After cooling to ambient temperature, $NaBH_4$ (0.22 g, 5.79 mmol) was added to this solution in three portions. The reaction mixture was stirred at rt overnight, and then poured into EtOAc (250 mL). The mixture was diluted with water (250 mL), shaken, and filtered. The organic layer was dried over Na_2SO_4 and evaporated to give a crude mixture of two diastereomers (90:10 by NMR). Separation of isomers by column chromatography (hexane−EtOAc−Et_3N = 3:1:0.2 as an eluent) gave inseparable mixture of **7aa** and benzyl alcohol (eluted first) (1.39 g, 85% purity by NMR, 3.93 mmol, yield 67%) and **7ab** (eluted second) (0.10 g, 0.33 mmol, yield 6%). Compound **7aa** was used in the next step without additional purification.

7aa: Colorless oil. TLC: R_f = 0.37 (hexane:EtOAc:Et_3N = 3:1:0.2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.95 (dt, J = 12.4, 6.2 Hz, 1H), 3.61 (d, J = 9.1 Hz, 1H), 3.57−3.50 (m, 1H), 3.15−3.04 (m, 1H), 2.51 (t, J = 9.7 Hz, 1H), 2.30 (t, J = 9.7 Hz, 1H), 2.23−1.98 (m, 3H), 1.80−1.70 (m, 1H), 1.55−1.69 (m, 2H), 1.29−1.10 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 175.5, 67.4, 58.7, 55.7, 46.1, 34.9, 33.0, 30. 6, 29.0, 26.1, 22.7, 21.9. MS (LCMS) 302 (MH^+).

7ab: White solid. mp 79−80 °C (hexane−EtOAc). TLC: R_f = 0.29 (hexane:EtOAc:Et_3N = 3:1:0.2). $[\alpha]_D^{20}$ = −31.12 (c 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.95 (dt, J = 12.3, 6.1 Hz, 1H), 3.61−3.56 (m, 1H), 3.34 (d, J = 7.3 Hz, 1H), 2.83 (p, J = 8.3 Hz, 1H), 2.51 (t, J = 10.4 Hz, 1H), 2.26−2.14 (m, 3H), 2.13−2.02 (m, 1H), 1.76−1.56 (m, 3H), 1.27−1.10 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 174.9, 67.6, 57.7, 55.9, 45.9, 35.3, 33.5, 30.6, 28.9, 27.9, 22.8, 21.8. MS (LCMS) 302 (MH^+).

A mixture of **7aa** and benzyl alcohol (1.39 g, 85% purity by NMR, 3.93 mmol) was dissolved in 20 mL of THF and was added to 50 mL of a cooled (0 °C) aqueous solution of $LiOH·H_2O$ (1.65 g, 39.30 mmol). The reaction mixture was stirred at the same temperature for 2 h, diluted with water (20 mL), and extracted with EtOAc (50 mL). The aqueous layer was separated, acidified with aq. $NaHSO_4$, and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was recrystallized from EtOAc. The yield was 0.81 g (3.13 mmol, 80%). White solid. mp 186 °C (EtOAc). $[\alpha]_D^{20}$ = +14.08 (c 0.2575, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.00 (d, J = 8.6 Hz, 1H), 3.58 (q, J = 8.2 Hz, 1H), 3.24−3.12 (m, 1H), 2.57 (t, J = 10.4 Hz, 1H), 2.34 (t, J = 10.7 Hz, 1H), 2.28−2.20 (m, 1H), 2.18−2.06 (m, 2H), 1.82−1.72 (m, 1H), 1.71−1.57 (m, 2H), 1.24 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 180.1, 58.8, 56.1, 46.1, 35.1, 32.8, 30.8, 29.0, 26.1, 22.8. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{12}H_{22}NO_3S$ 260.1315; Found 260.1313.

(2*S*,4*r*,5*R*)-5-(((*S*)-*tert*-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylic Acid (8b). *Isopropyl (2S,4r,5R)-5-(((S)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7ba**) and Isopropyl (2R,4r,5S)-5-(((S)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7bb**).* A mixture of **7ba** and benzyl alcohol (3.72 g, 93% purity by NMR, 11.49 mmol, 69% yield) was obtained from **4a** (4.06 g, 16.64 mmol) analogously to **7aa** and used in the next step without additional purification. **7bb** (0.2 g, 0.66 mmol, 4%) was obtained analogously to **7ab** as well.

7ba: Colorless oil. R_f = 0.37 (hexane:EtOAc:Et_3N = 3:1:0.2). NMR/LCMS data are consistent with the data for its enantiomer, compound **7aa**.

7bb: White solid. mp 77−79 °C (hexane−EtOAc). TLC: R_f = 0.29 (hexane:EtOAc:Et_3N = 3:1:0.2). $[\alpha]_D^{20}$ = +30.26 (c 0.335, $CHCl_3$). NMR/LCMS data are consistent with the data for its enantiomer, compound **7ab**.

Compound **8b** (2.54 g, 9.81 mmol, 85%) was obtained from a mixture of **7ba** and benzyl alcohol (3.72 g, 93% purity by NMR, 11.49 mmol) analogously to **8a**. White solid. mp 186 °C (EtOAc). $[\alpha]_D^{20}$ = −11.08 (c 0.25, $CHCl_3$). NMR/HRMS data are consistent with the data for its enantiomer, compound **8a**.

(2*S*,4*s*,5*S*)-5-(((*R*)-*tert*-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylic Acid (8c). *Isopropyl (2S,4s,5S)-5-(((R)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7ca**) and Isopropyl (2R,4s,5R)-5-(((R)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7cb**).* A mixture of **7ca** and benzyl alcohol (1.34 g, 86% purity by NMR, 3.83 mmol, 56% yield) was obtained from **4b** (1.67 g, 6.84 mmol) analogously to **7aa** and used in the next step without additional purification. **7cb** (0.15 g, 0.50 mmol, 7%) was obtained analogously to **7ab** as well.

7ca: Colorless oil. TLC: R_f = 0.32 (hexane:EtOAc:Et_3N = 3:1:0.2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.97 (dt, J = 12.5, 6.2 Hz, 1H), 4.11 (s, 1H), 3.70−3.56 (m, 1H), 3.02−2.86 (m, 1H), 2.66−2.53 (m, 1H), 2.26−2.08 (m, 3H), 2.01 (t, J = 10.1 Hz, 1H), 1.84 (t, J = 9.8 Hz, 1H), 1.81−1.61 (m, 2H), 1.32−1.10 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 175.5, 67.6, 55.4, 55.4, 44.5, 34.7, 33.0, 30.9, 29.2, 24.5, 22.7, 21.7. MS (LCMS) 302 (MH^+).

7cb: White solid. mp 103−104 °C (hexane−EtOAc). TLC: R_f = 0.19 (hexane:EtOAc:Et_3N = 3:1:0.2). $[\alpha]_D^{20}$ = −29.44 (c 0.2825, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.96 (dt, J = 12.3, 6.2 Hz, 1H), 3.52 (q, J = 7.9 Hz, 1H), 3.33 (d, J = 7.5 Hz, 1H), 2.98 (p, J = 8.8 Hz, 1H), 2.51 (t, J = 10.0 Hz, 1H), 2.35−2.24 (m, 1H), 2.18 (t, J = 10.3 Hz, 1H), 2.11−2.01 (m, 1H), 2.01−1.92 (m, 1H), 1.91−1.81 (m, 1H), 1.79−1.66 (m, 2H), 1.29−1.15 (m, 15H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 174.7, 67.6, 56.8, 56.1, 45.6, 34.6, 33.1, 31.1, 29.3, 28.2, 22.8, 21.9. MS (LCMS) 302 (MH^+).

Compound **8c** (0.82 g, 3.17 mmol, 83%) was obtained from a mixture of **7ca** and benzyl alcohol (1.34 g, 86% purity by NMR, 3.83 mmol) analogously to **7ca**. White solid. mp 149 °C (EtOAc). $[\alpha]_D^{20}$ = −18.74 (c 0.275, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$); δ: 5.01 (s, 1H), 3.71−3.52 (m, 1H), 3.07−2.91 (m, 1H), 2.78−2.61 (m, 1H), 2.27−2.07 (m, 3H), 2.01 (t, J = 10.3 Hz, 1H), 1.84 (t, J = 10.0 Hz, 1H), 1.81−1.71 (m, 1H), 1.67−1.55 (m, 1H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 178.8, 56.2, 56.0, 44.4, 35.4, 33.0, 30.6, 29.6, 24.5, 23.0. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{12}H_{22}NO_3S$ 260.1315; Found 260.1312.

(2*R*,4*s*,5*R*)-5-(((*S*)-*tert*-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylic Acid (8d). *Isopropyl (2R,4s,5R)-5-(((S)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7da**) and Isopropyl (2S,4s,5S)-5-(((S)-tert-Butylsulfinyl)amino)spiro[3.3]heptane-2-carboxylate (**7db**).* A mixture of **7da** and benzyl alcohol (1.48 g, 80% purity by NMR, 3.93 mmol, 57%) was obtained from **4b** (1.67 g, 6.84 mmol) analogously to **7aa** and used in the next step without additional purification. **7db** (0.13 g, 0.43 mmol, 6%) was obtained analogously to **7ab** as well.

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981

7da: Colorless oil. TLC: R_f = 0.32 (hexane:EtOAc:Et_3N = 3:1:0.2). NMR/LCMS data are consistent with the data for its enantiomer, compound **7ca**.

7db: White solid. mp 103−104 °C (hexane−EtOAc). TLC: R_f = 0.19 (hexane:EtOAc:Et_3N = 3:1:0.2). $[\alpha]_D^{20}$ = +31.81 (*c* 0.2625, $CHCl_3$). NMR/LCMS data are consistent with the data for its enantiomer, compound **7cb**.

Compound **8d** (0.86 g, 3.32 mmol, 85%) was obtained from a mixture of **7da** and benzyl alcohol (1.48 g, 80% purity by NMR, 3.93 mmol) analogously to **8a**. White solid. mp 149 °C (EtOAc). $[\alpha]_D^{20}$ = +22.43 (*c* 0.3, $CHCl_3$). NMR/HRMS data are consistent with the data for its enantiomer, compound **8c**.

(1*S*,4*r*,6*R*)-6-Carboxyspiro[3.3]heptan-1-aminium Chloride (9a). Compound **8a** (0.6 g, 2.32 mmol) was dissolved in 8 mL of 2 M methanolic HCl solution. The reaction mixture was stirred at room temperature for 1.5 h. The solution was evaporated and redissolved in 30 mL of 6 M aqueous HCl solution. The aqueous phase was washed twice with $CHCl_3$ (15 mL), the organic phase was discarded, and the aqueous extract was refluxed for 10 min. The solution was evaporated. The crude product was recrystallized from *i*-PrOH. The yield was 0.36 g (1.88 mmol, 81%). White solid. mp 226 °C (*i*-PrOH) (dec). $[\alpha]_D^{20}$ = +7.91 (*c* 0.3233, MeOH). ^{1}H NMR (500 MHz, D_2O), δ: 3.58 (t, *J* = 7.5 Hz, 1H), 3.03 (tt, *J* = 9.5, 6.5 Hz, 1H), 2.59−2.46 (m, 1H), 2.42−2.31 (m, 1H), 2.25−2.09 (m, 3H), 2.05−1.96 (m, 1H), 1.93−1.74 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O), δ: 179.8, 51.9, 42.3, 34.8, 32.5, 30.5, 29.5, 21.5. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{14}NO_2$ 156.1019; Found 156.1019.

(1*R*,4*r*,6*S*)-6-Carboxyspiro[3.3]heptan-1-aminium Chloride (9b). Compound **9b** (1.34 g, 6.99 mmol, 86%) was obtained from **8b** (2.1 g, 8.10 mmol) analogously to **9a**. White solid. mp 226 °C (*i*-PrOH) (dec). $[\alpha]_D^{20}$ = −8.57 (*c* 0.1433, MeOH). NMR/HRMS data are consistent with the data for its enantiomer, compound **9a**.

(1*S*,4*s*,6*S*)-6-Carboxyspiro[3.3]heptan-1-aminium Chloride (9c). Compound **9c** (0.33 g, 1.72 mmol, 76%) was obtained from **8c** (0.58 g, 2.24 mmol) analogously to **9a**. White solid. mp 243 °C (*i*-PrOH) (dec). $[\alpha]_D^{20}$ = +36.30 (*c* 0.1, MeOH). ^{1}H NMR (500 MHz, D_2O), δ: 3.49 (t, *J* = 7.6 Hz, 1H), 3.16−3.03 (m, 1H), 2.32 (t, *J* = 9.5 Hz, 1H), 2.24−2.09 (m, 4H), 2.04 (t, *J* = 10.4 Hz, 1H), 1.96−1.75 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O), δ: 179.6, 50.9, 41.3, 34.9, 32.1, 31.4, 28.8, 21.8. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{14}NO_2$ 156.1019; Found 156.1017.

(1*R*,4*s*,6*R*)-6-Carboxyspiro[3.3]heptan-1-aminium Chloride (9d). Compound **9d** (0.38 g, 1.98 mmol, 73%) was obtained from **8d** (0.7 g, 2.70 mmol) analogously to **9a**. White solid. mp 243 °C (*i*-PrOH) (dec). $[\alpha]_D^{20}$ = −26.55 (*c* 0.3067, MeOH). NMR/HRMS data are consistent with the data for its enantiomer, compound **9c**.

(2*R*,4*r*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)spiro[3.3]heptane-2-carboxylic Acid (10a). Compound **9a** (0.33 g, 1.72 mmol) was dissolved in 15 mL of saturated aq. $NaHCO_3$. To this solution was added Boc_2O (1.13 g, 5.16 mmol) in 15 mL of THF. The reaction mixture was stirred for 24 h and was diluted with 20 mL of water. The aqueous phase was washed with EtOAc (30 mL), acidified with aq. $NaHSO_4$, and extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was recrystallized from a Hexane−EtOAc mixture. The yield was 0.43 g (1.68 mmol, 98%). White solid. mp 111 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = +9.07 (*c* 0.275, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD), δ: 3.98−3.79 (m, 1H), 2.97−2.77 (m, 1H), 2.61−2.45 (m, 1H), 2.32 (t, *J* = 8.7 Hz, 1H), 2.25−2.12 (m, 1H), 2.11−1.96 (m, 2H), 1.76−1.61 (m, 3H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD), δ: 179.3, 158.0, 80.0, 54.1, 46.7, 37.0, 34.2, 32.2, 29.5, 28.8, 24.6. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{21}NO_4Na$ 278.1363; Found 278.1360.

(2*S*,4*r*,5*R*)-5-((*tert*-Butoxycarbonyl)amino)spiro[3.3]heptane-2-carboxylic Acid (10b). Compound **10b** (1.44 g, 5.64 mmol, 87%) was obtained from **9b** (1.24 g, 6.47 mmol) analogously to **10a**. White solid. mp 111 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = −11.44 (*c* 0.1875, $CHCl_3$). NMR/HRMS data are consistent with the data for its enantiomer, compound **10a**.

(2*S*,4*s*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)spiro[3.3]heptane-2-carboxylic Acid (10c). Compound **10c** (0.39 g, 1.53 mmol, 97%) was obtained from **9c** (0.30 g, 1.57 mmol) analogously to **10a**. White solid. mp 164 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = +12.10 (*c* 0.1625, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD), δ: 3.85−3.64 (m, 1H), 3.07−2.91 (m, 1H), 2.50 − (m, 2H), 2.15−1.94 (m, 3H), 1.92−1.81 (m, 1H), 1.80−1.63 (m, 2H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD), δ: 178.9, 157.9, 80.0, 52.7, 46.3, 36.2, 33.4, 32.5, 29.9, 28.8, 25.2. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{21}NO_4Na$ 278.1363; Found 278.1361.

(2*R*,4*s*,5*R*)-5-((*tert*-Butoxycarbonyl)amino)spiro[3.3]heptane-2-carboxylic Acid (10d). Compound **10d** (0.45 g, 1.76 mmol, 96%) was obtained from **9d** (0.35 g, 1.83 mmol) analogously to **10a**. White solid. mp 164 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = −13.01 (*c* 0.3025, $CHCl_3$). NMR/HRMS data are consistent with the data for its enantiomer, compound **10a**.

Benzyl *tert*-Butyl ((1*S*,4*r*,6*R*)-Spiro[3.3]heptane-1,6-diyl)dicarbamate (11a). Compound **10a** (0.25 g, 0.98 mmol), triethylamine (0.41 mL, 2.94 mmol), and DPPA (0.23 mL, 1.08 mmol) were dissolved in toluene (20 mL). The reaction mixture was slowly heated to 100 °C (oil bath) and stirred for 1 h. Benzyl alcohol (0.3 mL, 2.90 mmol) was added to the solution, and the resulting mixture was stirred overnight at the same temperature. The reaction mixture was cooled, poured into EtOAc (25 mL), and washed with water. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was recrystallized from a Hexane−EtOAc mixture. The yield was 0.28 g (0.78 mmol, 80%). White solid. mp 134 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = −32.81 (*c* 0.2175, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD), δ: 7.42−7.21 (m, 5H), 5.02 (s, 2H), 3.99−3.78 (m, 2H), 2.73−2.63 (m, 1H), 2.46−2.33 (m, 1H), 2.12−1.99 (m, 1H), 1.98−1.86 (m, 1H), 1.82−1.28 (m, 13H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD), δ: 188.1, 157.7, 138.4, 129.4, 128.9, 128.7, 80.1, 67.2, 53.8, 44.1, 42.9, 41.9, 37.6, 28.9, 28.8, 25.2. HRMS (ESI-Orbitrap) *m*/*z*: [M − Boc]$^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1598; Found 261.1594.

Benzyl *tert*-Butyl ((1*R*,4*r*,6*S*)-Spiro[3.3]heptane-1,6-diyl)dicarbamate (11b). Compound **11b** (1.42 g, 3.94 mmol, 80%) was obtained from **10b** (1.25 g, 4.90 mmol) analogously to **11a**. White solid. mp 134 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = +30.69 (*c* 0.3525, $CHCl_3$). NMR/HRMS data are consistent with the data for its enantiomer, compound **11a**.

Benzyl *tert*-Butyl ((1*S*,4*s*,6*S*)-Spiro[3.3]heptane-1,6-diyl)dicarbamate (11c). Compound **11c** (0.39 g, 1.08 mmol, 74%) was obtained from **10c** (0.37 g, 1.45 mmol) analogously to **11a**. White solid. mp 113 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = −55.63 (*c* 0.3775, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD), δ: 7.50−7.12 (m, 5H), 5.03 (s, 2H), 4.05−3.90 (m, 1H), 3.87−3.71 (m, 1H), 2.28−2.05 (m, 3H), 2.06−1.90 (m, 2H), 1.87−1.61 (m, 3H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD), δ: 158.0, 157.9, 138.4, 129.4, 128.9, 128.7, 80.0, 67.2, 52.7, 43.8, 42.6, 41.0, 37.9, 29.5, 28.8, 25.7. HRMS (ESI-Orbitrap) *m*/*z*: [M − Boc]$^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1598; Found 261.1597.

Benzyl *tert*-Butyl ((1*R*,4*s*,6*R*)-Spiro[3.3]heptane-1,6-diyl)dicarbamate (11d). Compound **11d** (0.45 g, 1.25 mmol, 78%) was obtained from **10d** (0.41 g, 1.61 mmol) analogously to **11a**. White solid. mp 113 °C (Hexane−EtOAc). $[\alpha]_D^{20}$ = +54.16 (*c* 0.29, $CHCl_3$). NMR/HRMS data are consistent with the data for its enantiomer, compound **11c**.

***tert*-Butyl ((1*S*,4*r*,6*R*)-6-Aminospiro[3.3]heptan-1-yl)carbamate (12a).** Compound **11a** (0.12 g, 0.33 mmol) was dissolved in dry methanol (5 mL), and 5% Pd/C (30 mg) was added. Hydrogen was bubbled though the mixture over 1 h upon stirring, the catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give **12a** (0.07 g, 0.31 mmol, 94%). Colorless oil. $[\alpha]_D^{20}$ = +24.90 (*c* 0.1225, CH_3OH). ^{1}H NMR (500 MHz, CD_3OD), δ: 3.95−3.82 (m, 1H), 3.26−3.12 (m, 1H), 2.74−2.58 (m, 1H), 2.48−2.32 (m, 1H), 2.13−1.98 (m, 1H), 1.84−1.74 (m, 1H), 1.73−1.56 (m, 4H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD); δ: 157.9, 80.0, 54.1, 44.4, 44.1, 43.4, 39.0, 29.0, 28.8, 25.1. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{23}N_2O_2$ 227.1754; Found 227.1751.

***tert*-Butyl ((1*R*,4*r*,6*S*)-6-Aminospiro[3.3]heptan-1-yl)carbamate (12b).** Compound **12b** (0.15 g, 0.66 mmol, 96%) was

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981

obtained from **11a** (0.25 g, 0.69 mmol) analogously to **12a**. Colorless oil. $[\alpha]_D^{20}$ = −24.20 (*c* 0.14, CH_3OH). NMR/HRMS data are consistent with the data for its enantiomer, compound **12a**.

***tert*-Butyl ((1*S*,4*s*,6*S*)-6-Aminospiro[3.3]heptan-1-yl)-carbamate (12c).** Compound **12c** (0.09 g, 0.40 mmol, 95%) was obtained from **11c** (0.15 g, 0.42 mmol) analogously to **12a**. Colorless oil. $[\alpha]_D^{20}$ = +32.25 (*c* 0.5, CH_3OH). ^1H NMR (500 MHz, CD_3OD), *δ*: 3.88−3.70 (m, 1H), 3.30−3.20 (m, 1H), 2.22−2.04 (m, 3H), 1.92−1.63 (m, 5H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD), *δ*: 158.0, 79.9, 53.0, 43.8, 43.7, 43.0, 39.8, 29.9, 28.8, 25.7. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{23}N_2O_2$ 227.1754; Found 227.1751.

***tert*-Butyl ((1*R*,4*s*,6*R*)-6-Aminospiro[3.3]heptan-1-yl)-carbamate (12d).** Compound **12d** (0.10 g, 0.44 mmol, 94%) was obtained from **11d** (0.17 g, 0.47 mmol) analogously to **12a**. Colorless oil. $[\alpha]_D^{20}$ = −32.88 (*c* 0.545, CH_3OH). NMR/HRMS data are consistent with the data for its enantiomer, compound **12c**.

(1*S*,4*r*,6*R*)-6-(((Benzyloxy)carbonyl)amino)spiro[3.3]heptan-1-aminium Chloride (13a). Compound **11a** (0.13 g, 0.36 mmol) was dissolved in 5 mL of 2 M methanolic HCl solution. The reaction mixture was stirred at room temperature for 1.5 h, and then the solution was evaporated. The crude product was recrystallized from *i*-PrOH. The yield was 0.10 g (0.34 mmol, 94%). White solid. mp 71 °C (*i*-PrOH). $[\alpha]_D^{20}$ = −187.21 (*c* 0.27, H_2O). ^1H NMR (500 MHz, D_2O), *δ*: 7.42−7.10 (m, 5H), 4.88 (s, 2H), 3.91−3.75 (m, 1H), 3.62−3.42 (m, 1H), 2.69−2.51 (m, 1H), 2.49−2.29 (m, 1H), 2.25−2.07 (m, 1H), 2.04−1.70 (m, 5H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O), *δ*: 157.3, 136.4, 128.7, 128.3, 127.7, 66.7, 52.3, 41.4, 40.0, 39.9, 35.2, 29.3, 21.9. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1598; Found 261.1593.

(1*R*,4*r*,6*S*)-6-(((Benzyloxy)carbonyl)amino)spiro[3.3]heptan-1-aminium Chloride (13b). Compound **13b** (0.17 g, 0.57 mmol, 98%) was obtained from **11b** (0.21 g, 0.58 mmol) analogously to **13a**. White solid. mp 71 °C (*i*-PrOH). $[\alpha]_D^{20}$ = +187.70 (*c* 0.3, H_2O). NMR/HRMS data are consistent with the data for its enantiomer, compound **13a**.

(1*S*,4*s*,6*S*)-6-(((Benzyloxy)carbonyl)amino)spiro[3.3]heptan-1-aminium Chloride (13c). Compound **13c** (0.14 g, 0.47 mmol, 94%) was obtained from **11c** (0.18 g, 0.50 mmol) analogously to **13a**. White solid. mp 58 °C (*i*-PrOH). $[\alpha]_D^{20}$ = −120.60 (*c* 0.2775, H_2O). ^1H NMR (500 MHz, D_2O), *δ*: 7.39−7.08 (m, 5H), 4.90 (s, 2H), 3.94−3.74 (m, 1H), 3.58−3.36 (m, 1H), 2.32−2.04 (m, 3H), 2.04−1.73 (m, 5H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O), *δ*: 157.2, 136.4, 128.7, 128.3, 127.7, 66.7, 50.6, 41.0, 39.6, 38.8, 36.7, 28.6, 22.4. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1598; Found 261.1593.

(1*R*,4*s*,6*R*)-6-(((Benzyloxy)carbonyl)amino)spiro[3.3]heptan-1-aminium Chloride (13d). Compound **13d** (0.12 g, 0.40 mmol, 95%) was obtained from **11d** (0.15 g, 0.42 mmol) analogously to **13a**. White solid. mp 58 °C (*i*-PrOH). $[\alpha]_D^{20}$ = +120.19 (*c* 0.3, H_2O). NMR/HRMS data are consistent with the data for its enantiomer, compound **13c**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra, HRMS for new compounds, and data for single-crystal X-ray analysis of compounds **8a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +49 0159 02900799. Fax: +49 721 608 44823. E-mail: dmitry.radchenko@gmail.com (D.S.R.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Enamine Ltd., Kyiv, Ukraine. We acknowledge Denis V. Bylina for carrying out HRMS analysis.

■ REFERENCES

(1) Lacoske, M. H.; Theodorakis, E. A. *J. Nat. Prod.* **2014**, DOI: 10.1021/np500757w.
(2) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661.
(3) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673−3682.
(4) Rosenberg, S.; Leino, R. *Synthesis* **2009**, *2009*, 2651−2673.
(5) Grygorenko, O. O.; Radchenko, D. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Komarov, I. V. *Chem. Rev.* **2011**, *111*, 5506−5568.
(6) Grygorenko, O. O.; Prytulyak, R.; Volochnyuk, D. M.; Kudrya, V.; Khavryuchenko, O. V.; Komarov, I. V. *Mol. Diversity* **2012**, *16*, 477−487.
(7) Mann, A. Conformational Restriction and/or Steric Hindrance in Medicinal Chemistry. In *The Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Elsevier: Amsterdam, 2008; pp 363−379.
(8) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622−4628.
(9) Ding, J.; Fraser, M. E.; Meyer, J. H.; Bartlett, P. A.; James, M. N. G. *J. Am. Chem. Soc.* **1998**, *120*, 4610−4621.
(10) Meyer, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4600−4609.
(11) Radchenko, D. S.; Pavlenko, S. O.; Grygorenko, O. O.; Volochnyuk, D. M.; Shishkina, S. V.; Shishkin, O. V.; Komarov, I. V. *J. Org. Chem.* **2010**, *75*, 5941−5952.
(12) Radchenko, D. S.; Grygorenko, O. O.; Komarov, I. V. *Amino Acids* **2010**, *39*, 515−521.
(13) Burkhard, J. A.; Guerot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944−1947.
(14) Burkhard, J. A.; Guerot, C.; Knust, H.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 66−69.
(15) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524−3527.
(16) Gent, M.; Knowlson, P.; Prime, F. *Lancet* **1969**, *294*, 1094−1096.
(17) Grange, J. M.; Snell, N. J. *J. Ethnopharmacol.* **1996**, *50*, 49−53.
(18) Liu, J.; Chen, X.; Hu, Y.; Cheng, G.; Zhong, D. *J. Pharm. Biomed. Anal.* **2010**, *51*, 1134−1141.
(19) Schraven, E.; Koss, F.; Keck, J.; Beisenherz, G. *Eur. J. Pharmacol.* **1967**, *1*, 445−451.
(20) Juyal, V.; Kapoor, E.; Kumar, V.; Ram, V.; Tripathi, V.; Bhagat, S. *Toxicol. Int.* **2014**, *21*, 69−71.
(21) Janson, S. E.; Pope, W. J. *Proc. R. Soc. A* **1936**, *154*, 53−60.
(22) Wynberg, H.; Houbiers, J. P. M. *J. Org. Chem.* **1971**, *36*, 834−842.
(23) Radchenko, D. S.; Grygorenko, O. O.; Komarov, I. V. *Tetrahedron: Asymmetry* **2008**, *19*, 2924−2930.
(24) Kawai, A.; Nakao, K. Spiroalkylhydroxyureas for use as lipoxygenase inhibitors. PCT Int. Appl. WO 9418158 A1, 1994.
(25) Chernykh, A. V.; Radchenko, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Shishkina, S. V.; Shishkin, O. V.; Komarov, I. V. *RSC Adv.* **2014**, *4*, 10894−10902.
(26) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995.
(27) Cambridge Crystallographic Data Centre deposition numbers are 1052954−1052957.
(28) Yarmolchuk, V. S.; Mukan, I. L.; Grygorenko, O. O.; Tolmachev, A. A.; Shishkina, S. V.; Shishkin, O. V.; Komarov, I. V. *J. Org. Chem.* **2011**, *76*, 7010−7016.
(29) van Koningsveld, H. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *40*, 1857−1863.
(30) Newman, J. M.; Thompson, H. W.; Lalancette, R. A. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2002**, *58*, o693−o696.

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981

(31) Ávila, E. E.; Mora, A. J.; Delgado, G. E.; Ramírez, B. M.; Bahsas, A.; Koteich, S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2004**, *60*, o759−o761.

DOI: 10.1021/acs.joc.5b00323
J. Org. Chem. 2015, 80, 3974−3981