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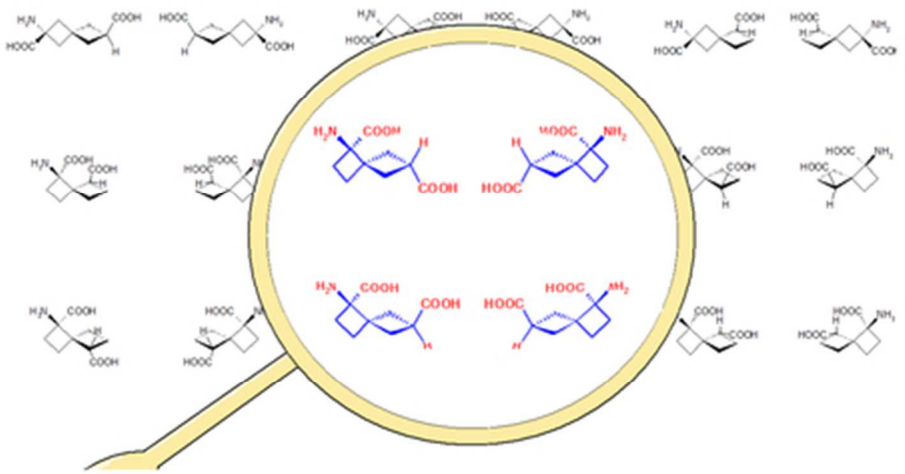

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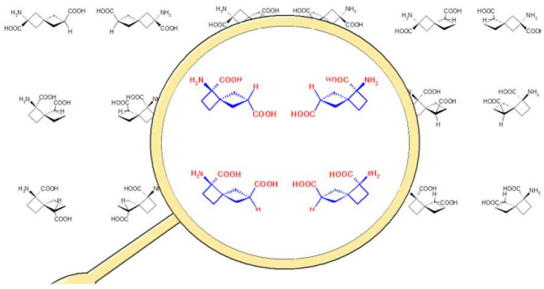
Conformationally restricted glutamic acid analogues: stereoisomers of 1-aminospiro[3.3]heptane-1,6-dicarboxylic acid

Anton V. Chernykh, Dmytro S. Radchenko, Oleksandr O. Grygorenko, Dmitriy M. Volochnyuk, Svitlana V. Shishkina, Oleg V. Shishkin and Igor V. Komarov

A synthetic strategy to construct spiro[3.3]heptane core functionalised at the 1,6-positions gave access to all stereoisomeric 1-aminospiro[3.3]heptane-1,6-dicarboxylic acids.



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Conformationally restricted glutamic acid analogues: stereoisomers of 1-aminospiro[3.3]heptane-1,6-dicarboxylic acid

Anton V. Chernykh,[a, b] Dmytro S. Radchenko,[a, c] Oleksandr O. Grygorenko,[c] Dmitriy M. Volochnyuk,[b] Svitlana V. Shishkina,[d] Oleg V. Shishkin[d] and Igor V. Komarov[c,]*

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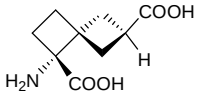
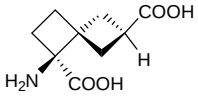
All four stereoisomers of the title compound (**1a–d**) were prepared, starting from a common precursor, 3-oxocyclobutanecarboxylic acid. Lewis acid-catalyzed rearrangement of a 8-oxadispiro[2.0.3.1] octane-6-carboxylic acid derivative was used as the key synthetic step to construct properly functionalized spiro[3.3]heptane skeleton. A stabilized oxaphosphetane intermediate of the Wittig reaction was detected along the synthetic route. Separation of the diastereomeric intermediates allowed obtaining each target compound as a single stereoisomer. The target compounds are all analogues of the glutamic acid; they mimic glutamate in a large array of restricted conformations, which might be used in mechanistic studies or in systematic search for biologically active compounds.

Introduction

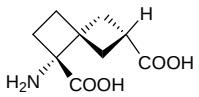
Sets of isomeric functionalized derivatives of small conformationally restricted molecular frameworks (scaffolds) were shown to be useful in design of the molecules used to map receptor binding sites[1,2] and in systematic search for leads in drug design.[3-5] A term "stereolibrary" was coined for such compound sets where only relative position of the functional groups in space varies while molecular topology is the same along all the members of the sets.[6] Spirocyclic scaffolds are especially attractive for the design of the stereolibraries, as they might ensure vide variety of spatial disposition of the functional groups, and consequently, allow constructing chemically diverse compound sets.[7-10] For example, based on the spiro[3.3]heptane scaffold, one can construct nine enantiomeric pairs of rigid glutamic acid analogues, which differ in position and relative orientation of the carboxylic and aminocarboxylate moieties.[11] Conformationally restricted glutamic acid analogues of such type might be used to map the glutamate receptor binding sites, in mechanistic studies of the enzymes which act on glutamate, and ultimately, in the search for biologically active compounds using different systematic approaches.[6,12-15] In this paper we report on the synthesis and stereochemical assignment of novel spiro[3.3]heptane-based glutamic acid analogues – the stereolibrary composed of 1-aminospiro[3.3]heptane-1,6-dicarboxylic acids **1a**–**d**.



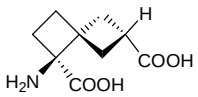
1a



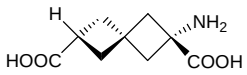
1b



1c



1d



1e

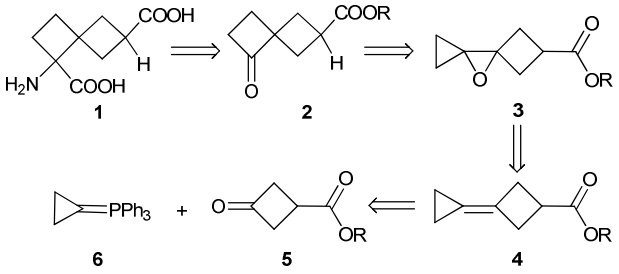
1f

Results and discussion

By now, synthesis of only two of the eighteen theoretically possible members of the spiro[3.3]heptane-based library of the glutamate analogues was reported,[11] namely, (a*S*)- and (a*R*)-2-amino-spiro[3.3]heptane-2,6-dicarboxylic acids (**1e** and **1f**, respectively). Their synthesis was based on simple malonate chemistry, but cannot be adapted to the 1,6-isomers. Completely different strategy was chosen in the present work, highlighted by the retrosynthetic analysis shown in the Scheme 1.

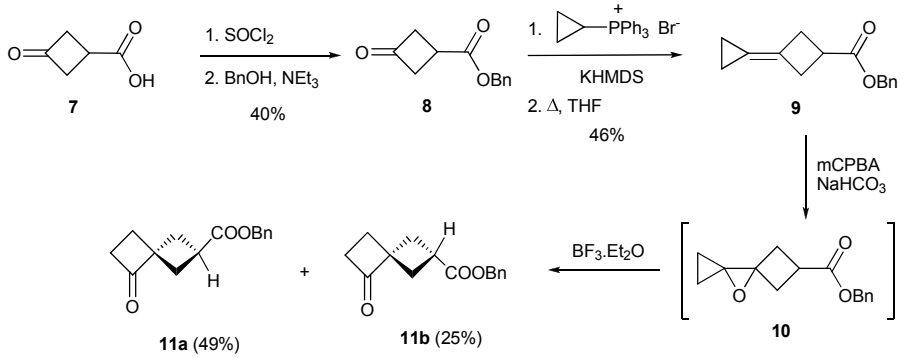
In our approach to compounds **1a**–**d**, a modified Strecker reaction was proposed for construction of the aminocarboxylate moiety in the late steps of the synthesis. Corresponding retrosynthetic transformation led to the ketoester **2** – a key intermediate of the synthesis. Compound **2**, in turn, could be obtained by rearrangement of the epoxide **3**. Oxaspiro[2.2]pentanes (like **3**)

can be prepared either by Corey-Chaykovsky reaction with cyclopropyldiphenyl sulfonium ylide[16] or by epoxidation of the corresponding alkene (**4**), which can be obtained by Wittig olefination with phosphorus ylide **6**.[17] Both approaches led to the ketoester **5** as the starting material, which is readily accessible from commercially available 3-oxocyclobutanecarboxylic acid (**7**). Benzyl group (R in the scheme 1) would be an optimal choice for the protection of the carboxylic moiety: it would diminish the volatility of the intermediate alkene **4**, as well as allow for UV detection of the intermediate products upon chromatographic purifications.

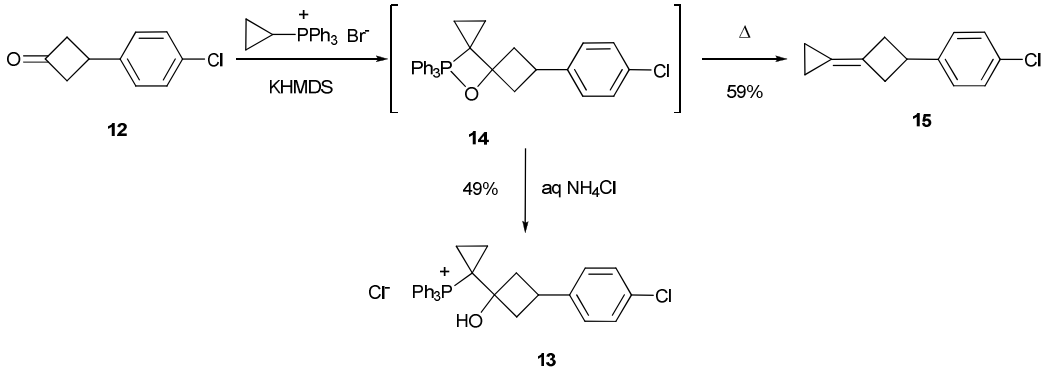


Scheme 1 Retrosynthetic analysis of the targeted 1-aminospiro[3.3]heptane-1,6-dicarboxylic acids

The retrosynthetic scheme should consider a possibility to isolate all four target compounds **1a–d** as the single stereoisomers. To achieve this, we decided to use separation of diastereomeric intermediates at the appropriate stages of the synthesis. Compound **2** could be obtained as a mixture of diastereomers, so the first separation could be done at this step. Resolution of enantiomers of the amino acid precursors synthesized further on could be achieved by the use of a chiral auxiliary; Strecker reaction with a chiral amine (*e. g.* (*S*)-phenylglycinol) proved to be an efficient tool for that purpose in the cyclobutane series.[18] Implementation of the above retrosynthetic plan started with esterification of the acid **7** *via* the corresponding acid chloride (Scheme 2). The method for the synthesis of cyclobutanones reported by Carreira et al.,[19] based on the Corey-Chaykovsky reaction of **8** with cyclopropyldiphenyl sulfonium ylide (KHMDS, THF, -40 °C, 4h, then LiI, 50 °C, 15h, one-pot) failed in our hands, a very complex mixture of unidentified compounds was isolated. Therefore, we explored an alternative sequence based on the Wittig olefination with ylide **6**. Our initial attempts to introduce the ketoester **8** into this transformation were also unfruitful. Therefore, we performed a more detailed study of this reaction using ketone **12** as the model substrate. This ketone and its olefination product turned to be not volatile and did not contain ester moiety which complicated optimization of the reaction conditions with the ketoester **8**. Reaction of **12** under the standard Wittig olefination conditions gave an unexpected product **13** (Scheme 3), the structure of which was determined by an X-Ray diffraction study (Figure 1). Presumably, the salt **13** formed by protonation of the corresponding oxaphosphetane **14** upon the work-up of the reaction mixture with aqueous NH_4Cl. Oxaphosphetanes are usually unstable; the increased stability of **14** towards decomposition to alkene **15** and triphenylphosphine oxide can be explained by high steric strain in the molecule of **15**. It should be noted that although examples of stable oxaphosphetanes are known in the literature,[20] in all the cases reported to date the stabilization was achieved through electronic effects.



Scheme 2 Preparation of the key intermediate, compound **11**.



Scheme 3 Model study of the Wittig olefination with a cyclobutanone derivative **12**.

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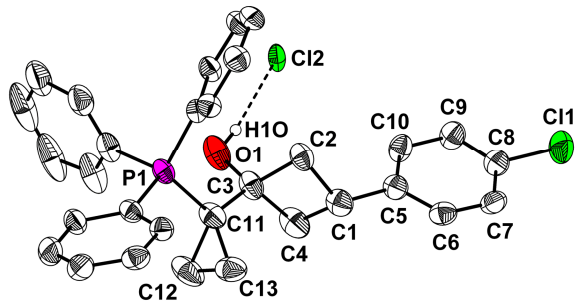


Fig 1 ORTEP diagram of the compound **13** (thermal ellipsoids are shown at 30% probability level)

Transformation of **14** into the alkene **15** was achieved at elevated temperature by heating at reflux in THF. Application of these conditions to the ketoester **8** led to the formation of alkene **9**, which was isolated in 46% yield. Epoxidation of **9** with MCBPA was accompanied by partial rearrangement of the epoxide **10** to ketone **11**. Therefore, compound **10** was not isolated but treated with $BF_3{\cdot}Et_2O$ to give a 2 : 1 mixture of diastereomers **11a** and **11b**, which were separated by column chromatography. The stereochemical configuration of **11a,b** was established by 1D- and 2D-NOESY experiments (Figure 2, see the Electronic supplementary information for details).

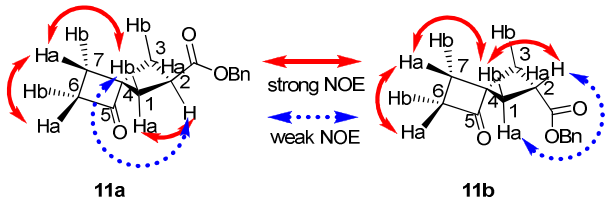
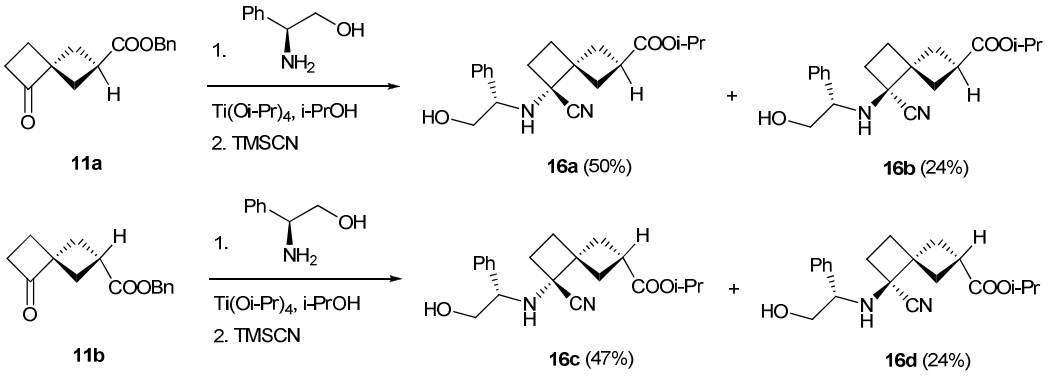


Fig 2 Significant correlations in the NOESY spectra of **11a,b**

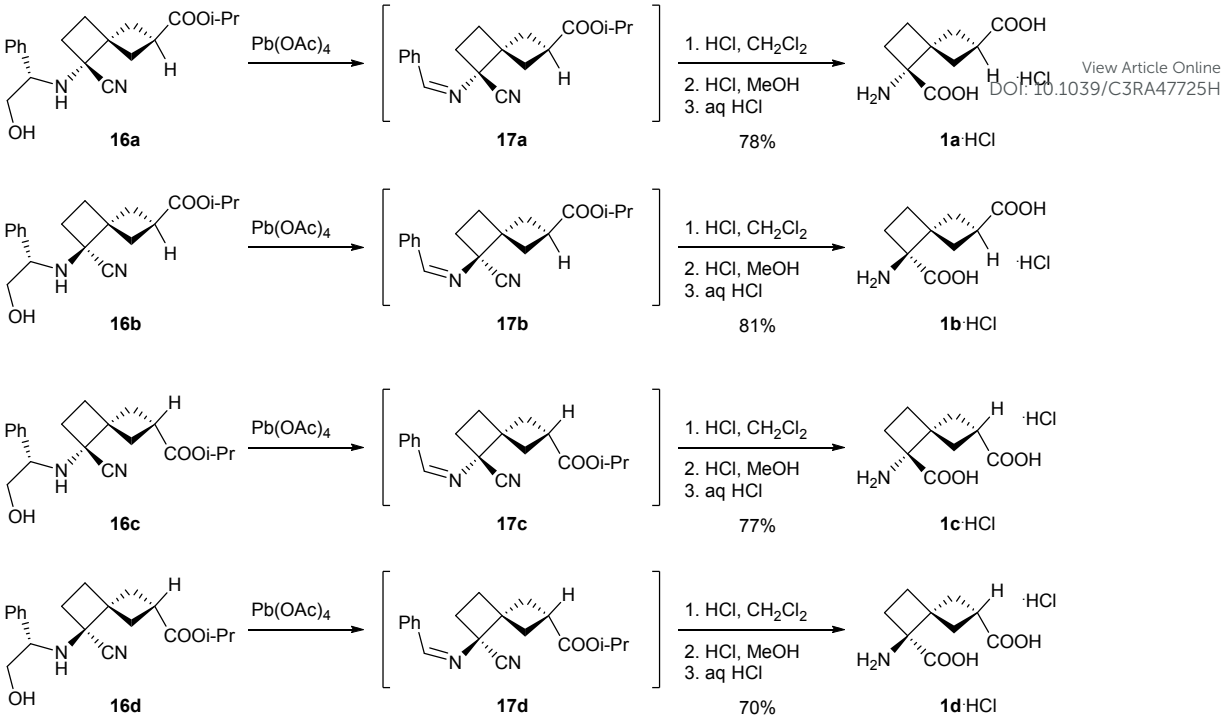
Reaction of **11a** with (*S*)-phenylglycinol under various conditions followed by treatment with TMSCN-MeOH was accompanied by partial transesterification and resulted in an equilibrium mixture of the corresponding aminonitriles and cyanohydrins with COOBn (68%) and COOMe (32%) ester groups, which were difficult to separate. Therefore, we used $Ti(Oi\text{-}Pr)_4$ in *i*-PrOH as water scavenger and mild Lewis acidic catalyst for the first step of the reaction, *i. e.* imine formation. The reaction was also accompanied by transesterification; after addition of TMSCN, a mixture of diastereomers **16a** and **16b** was obtained (Scheme 4). The diastereomers were separated by column chromatography. Compounds **16a** and **16b** appeared to be unstable: formation of the starting ketone **11a** and epimerization were observed upon standing for a few days. Therefore, both **16a** and **16b** were subjected to the next step immediately after the separation. Compounds **16c** and **16d** were obtained from **11b** in an analogous manner.

Further transformation of **16a–d** included cleavage of the (*S*)-phenylglycinol residue with $Pb(OAc)_4$ (Scheme 5). The intermediate imines **17a–d** were not isolated, and immediately subjected to hydrolysis. Under reflux in aqueous HCl, hydrolysis of the nitrile moiety in **16** was too slow presumably due to considerable steric hindrance. Therefore, we used a three-step reaction sequence including formation of imidoyl chloride (HCl – CH_2Cl_2), imidoester (HCl – MeOH), and final hydrolysis to carboxylic acid (aqueous HCl). Imine and ester moieties were also hydrolyzed at this step to give amino acids **1a–d**, which were isolated as hydrochlorides in 70–83% yields (based on **16a–d**).

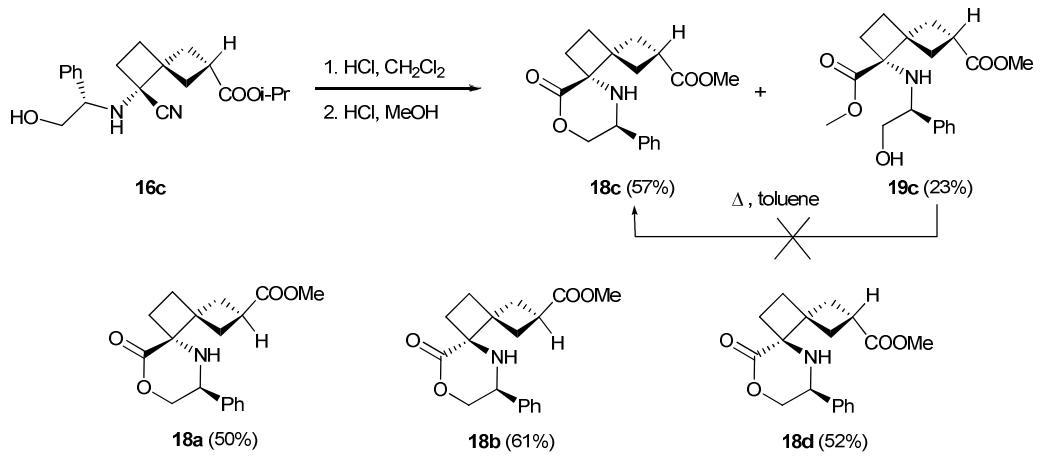
In order to determine the absolute configuration of the aminonitriles **16a-d**, tricyclic derivatives **18a-d** were synthesized (Scheme 6) *via* imidoester formation followed by cyclization. After the work-up of the reaction mixture, a mixture of **18** and methyl esters **19** were obtained; in the case of **16c**, the corresponding ester **19c** was isolated and characterized. No substantial transformation of **19c** to **18c** was observed during pro-



Scheme 4 Synthesis of aminonitriles **16a–d** bearing the chiral auxiliary.



Scheme 5 Final steps of the synthesis of **1a-d**.



Scheme 6 Final steps of the synthesis of **18a-d** and **19c**.

longed heating in toluene. Therefore, the tricyclic derivatives **18a-d** were separated from the corresponding esters **19** by column chromatography. Crystals suitable for X-Ray diffraction studies was obtained for compounds **18a-c**. The results of their X-Ray crystallographic analysis, combined with the 1D- and 2D-NOESY experiments for the ketoesters **11a** and **11b** mentioned above allowed us to deduce eventually the stereoconfiguration of final spirocyclic glutamic acid analogues **1a**–**d** (see the Electronic supplementary information for details in structural and stereochemical assignments of compounds **11a**,**b** by 1D and 2D-NOESY experiments, compounds **18a-c** by X-ray crystallography, and discussion).

Conclusions

The Lewis acid-catalyzed rearrangement of a 8-oxadispiro [2.0.3.1]octane skeleton proved to be efficient for constructing 1,6-functionalised spiro[3.3]heptanes. Using this strategy, rigid spirocyclic glutamic acid analogues **1a**–**d** were synthesized in eight laboratory steps, starting from the common precursor, 3-oxocyclobutanecarboxylic acid. Separation of the diastereomeric intermediates along the synthetic pathway allowed isolation of the target compounds as the single enantiomers. The synthesized stereolibrary **1a**–**d** might be useful as a tool in mechanistic studies of enzymes or receptors for which glutamic acid is the substrate or the ligand, respectively. Easy functionalization of the spiro[3.3]heptane scaffold might also be of use in medicinal chemistry, in the systematic search for biologically active compounds derived from this three-dimensional molecular framework.

Experimental section

General

Solvents were purified according to the standard procedures. Compound **7** was purchased from commercial sources; compound **12**[21] and cyclopropyltriphenylphosphonium bromide[22] were prepared using the procedures reported in the literature. 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, and all 2D 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 GCMS instrument with electron impact ionization (EI).

Benzyl 3-oxocyclobutane-1-carboxylate (8)

To a mixture of benzyl alcohol (113 mL, 1.09 mol) and triethylamine (122 mL, 0.874 mol) in CH_2Cl_2 (400 mL), a solution of 3-oxocyclobutanecarbonyl chloride[23] (57.9 g, 0.437 mol) in CH_2Cl_2 (200 mL) was added at 5 ºC. The resulting solution was stirred at room temperature for 15 min, and then poured into water. Organic phases was washed with 10% aq. citric acid, saturated aq. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, evaporated, and distilled *in vacuo*. The unreacted benzyl alcohol was distilled off first (50ºC / 1 mmHg), followed by benzyl 3-oxocyclobutanecarboxylate **8** (100ºC / 1 mmHg). The yield was 35.2 g (0.172 mol, 40%). Yellow oil. Bp 100 ºC (1 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) 3.19 – 3.34 (m, 3H), 3.34 – 3.49 (m, 2H), 5.20 (s, 2H), δ 7.29 – 7.45 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.4, 51.6, 67.0, 128.3, 128.5, 128.6, 135.5, 173.8, 203.4. MS (GCMS) 204 (M^+), 91 ($C_7H_7^+$). Anal. Calcd. for $C_{12}H_{12}O_3$ C 70.58, H 5.92. Found C 70.36, H 6.17.

(1-(3-(4-Chlorophenyl)-1-hydroxycyclobutyl)cyclopropyl)-triphenylphosphonium chloride (13)

To a suspension of cyclopropyltriphenylphosphonium bromide (2.19 g, 5.71 mmol) in THF (25 mL), KHMDS (0.5 M in toluene, 12.6 mL, 6.28 mmol) was added at –30 ºC under an argon atmosphere. The orange solution was stirred for 2h at rt, and then a solution of 3-(4-chlorophenyl)cyclobutanone **12** (0.928 g, 5.14 mmol) in THF (10 mL) was slowly added at –78 ºC. The reaction mixture was stirred at -78 °C for 1 h, slowly warmed up to rt overnight, and then poured into cold saturated aq. NH_4Cl. The mixture was extracted with $CHCl_3$, the organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was recrystallized from EtOAc-CH_3CN, the precipitate of (1-(3-(4-chlorophenyl)-1-hydroxycyclobutyl)cyclopropyl)triphenyl-phosphonium chloride **13** was filtered and washed with EtOAc. The yield was 1.46 g (2.81 mmol, 49%). White solid. Mp 139–140 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 15.7 Hz, 2H), 1.81 (d, J = 7.2 Hz, 2H), 2.37 (t, J = 10.7 Hz, 2H), 2.48 – 2.63 (m, 2H), 2.78 – 2.90 (m, 1H), 7.12 – 7.18 (m, 2H), 7.24– 7.33 (m, 2H), 7.45 (br s, 1H), 7.60 – 7.68 (m, 6H), 7.69 – 7.78 (m, 3H), 7.87– 8.01 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.0, 22.4 (d, J = 77.2 Hz), 32.2, 43.4 (d, J = 4.7 Hz), 73.3 (d, J = 2.2 Hz), 119.7 (d, J = 87.1 Hz), 128.4, 128.8, 129.8 (d, J = 12.5 Hz), 131.8, 134.5 (d, J = 2.8 Hz), 135.5 (d, J = 9.5 Hz), 143.2. MS (LCMS) 484/486 ($MH^+ - Cl^-$). Anal. Calcd. for $C_{31}H_{29}Cl_2OP \cdot CH_3CN$ C 70.72, H 5.75, Cl 12.65, N 2.50. Found C 70.39, H 5.71, Cl 12.43, N 2.74.

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Chloro-4-(3-cyclopropylidenecyclobutyl)benzene (15)

To a suspension of cyclopropyltriphenylphosphonium bromide (2.67 g, 6.96 mmol) in THF (30 mL), KHMDS (0.5 M in toluene, 15.3 mL, 7.65 mmol) was added at –30 ºC under argon atmosphere. The orange solution was stirred at rt for 2h, and then a solution of 3-(4-chlorophenyl)cyclobutanone **12** (1.13 g, 6.26 mmol) in THF (57 mL) was added slowly at –78ºC. The reaction mixture was stirred at -78 °C for 1h, then slowly warmed up to rt overnight, refluxed for 3h, and poured into cold saturated aq. NH_4Cl. The mixture was extracted with EtOAc, the organic phase was dried over Na_2SO_4, filtered and evaporated. The brown oil was treated with hexane, the solution was decanted and evaporated. The crude product was purified by column chromatography (hexane as an eluent). The yield was 0.75 g (3.66 mmol, 59%). Colorless oil. TLC: R_f = 0.58 (hexanes; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, J = 1.9 Hz, 4H), 2.85 – 2.98 (m, 2H), 3.15 – 3.29 (m, 2H), 3.61 (quint, J = 8.2 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 2.3, 35.3, 39.2, 77.2, 111.7, 123.7, 128.0, 128.5, 131.7, 144.7. MS (GCMS) 204/206 (M^+), 169 ($M^+ - Cl^-$). Anal. Calcd. for $C_{13}H_{13}Cl$ C 76.28, H 6.40, Cl 17.32. Found C 76.66, H 6.21, Cl 17.39.

Benzyl 3-cyclopropylidenecyclobutanecarboxylate (9)

To a suspension of cyclopropyltriphenylphosphonium bromide (50.6 g, 0.132 mol) in THF (570 mL), KHMDS (0.5 M in toluene, 290 mL, 0.145 mol) was added at –30 ºC under argon atmosphere. The orange solution was stirred for 2h at rt and then a solution of benzyl 3-oxocyclobutane-1-carboxylate **8** (24.2 g, 0.119 mol) in THF (200 mL) was added slowly at –78 ºC. The reaction mixture was stirred at -78 °C for 1 h, slowly warmed up to room temperature overnight, refluxed for 3h, and then poured into cold saturated saturated aq NH_4Cl. The mixture was extracted with EtOAc, the organic phase was dried over Na_2SO_4, filtered and evaporated. The brown oil was treated and decanted with hexane – EtOAc (10 : 1) (3×110 mL), and the combined organic extracts were evaporated. The crude product was purified form by column chromatography (Hexanes – EtOAc (20 : 1) as an eluent). The yield was 12.5 g (54.8 mmol, 46%). Colorless oil. TLC: R_f = 0.435 (hexanes : EtOAc 20:1; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 4H), 2.97 – 3.07 (m, 2H), 3.07 – 3.18 (m, 2H), 3.21 – 3.33 (m, 1H), 5.18 (s, 2H), 7.28– 7.44 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 2.2, 34.0, 34.8, 66.3, 112.5, 122.6, 128.2, 128.2, 128.6, 136.2, 175.2. MS (GCMS) 228 (M^+), 137 ($M^+ - C_7H_7$), 91 ($C_7H_7^+$). Anal. Calcd. for $C_{15}H_{16}O_2$ C 78.92, H 7.06. Found C 79.10, H 7.36.

Benzyl (2*s*,4*r*)-5-oxospiro[3.3]heptane-2-carboxylate (11a) and benzyl (2*r*,4*s*)-5-oxospiro[3.3]heptane-2-carboxylate (11b)

To a cooled (0 ºC) solution of benzyl 3-cyclopropylidenecyclo-butanecarboxylate **9** (8.5 g, 37.2 mmol) in CH_2Cl_2 (160 mL), a solution of *meta*-chloroperoxybenzoic acid (9.83 g (85%), 48.4 mmol) in CH_2Cl_2 (150 mL) was added dropwise. The reaction was monitored by TLC (EtOAc/Hex 1:10). After the reaction was

complete (*ca.* 30 min), the mixture was washed with 10% aq. Na_2SO_3 (twice) and saturated aq. $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The resulting oil was dissolved in dry diethyl ether and cooled to 0 ºC. $BF_3 \cdot Et_2O$ (0.53 g, 3.73 mmol) was added slowly to the solution dropwise, and the mixture was stirred at 0 ºC for 15 min. The organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated to give a crude mixture of two diastereomers **11a,b** at 3:2 ratio (NMR data). Both isomers were obtained in pure form by column chromatography (cyclohexane – EtOAc (4 : 1) as an eluent). The chromatographic separation yielded 4.47 g (18.3 mmol, 49%) of *trans*-isomer **11a** (eluted first) and 2.27 g (9.29 mmol, 25%) of *cis*-isomer **11b**.

11a: Colorless oil. TLC: R_f = 0.52 (cyclohexane : EtOAc 4:1; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (t, *J* = 8.5 Hz, H7a, H7b), 2.33 (t, *J* = 10.6 Hz, H1b, H3b), 2.54 (t, *J* = 10.6 Hz, H1a, H3a), 2.88 (t, *J* = 8.5 Hz, H6a, H6b), 3.15 (quint, *J* = 8.6 Hz, H2), 5.06 (s, CH_2Ph), 7.19 – 7.38 (m, C_6H_5). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4 (C7), 32.8 (C2), 32.9 (C1, C3), 43.1 (C6), 60.1 (C4), 66.4 (CH_2Ph), 128.1 (C_6H_5), 128.3 (C_6H_5), 128.6 (C_6H_5), 136.0 (C_6H_5), 174.3 (COOBn), 213.4 (C5). MS (GCMS) 244 (M^+), 91 ($C_7H_7^+$). Anal. Calcd. for $C_{15}H_{16}O_3$ C 73.75, H 6.60. Found C 73.94, H 6.66.

11b: Colorless oil. TLC: R_f = 0.45 (cyclohexane : EtOAc 4:1; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (t, *J* = 8.4 Hz, H7a, H7b), 2.19 – 2.34 (m, H1b, H3b), 2.63 – 2.77 (m, H1a, H3a), 2.89 (t, *J* = 8.5 Hz, H6a, H6b), 3.00 – 3.15 (m, H2), 5.08 (s, CH_2Ph), 7.21 – 7.36 (m, C_6H_5). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.7 (C7), 31.9 (C2), 33.3 (C1, C3), 43.2 (C6), 59.5 (C4), 66.3 (CH_2Ph), 128.1 (C_6H_5), 128.2 (C_6H_5), 128.5 (C_6H_5), 135.9 (C_6H_5), 173.7 (COOBn), 210.8 (C5). MS (GCMS) 244 (M^+), 91 ($C_7H_7^+$). Anal. Calcd. for $C_{15}H_{16}O_3$ C 73.75, H 6.60. Found C 73.51, H 6.38.

Isopropyl (2*S*,4*r*,5*R*)-5-cyano-5-(((*S*)-2-hydroxy-1-phenylethyl)amino)spiro[3.3]heptane-2-carboxylate (16a) and Isopropyl (2*R*,4*r*,5*S*)-5-cyano-5-(((*S*)-2-hydroxy-1-phenylethyl)amino)spiro[3.3]heptane-2-carboxylate (16b)

Compound **11a** (1.50 g, 6.14 mmol), *S*-α-phenylglycinol (1.01 g, 7.37 mmol) and 2-propanol (20mL) were placed into a 50 mL, two-necked flask equipped with a magnetic stirrer and calcium chloride drying tube. Titanium isopropylate (4.36 g (4.57 mL), 15.35 mmol) was added to the solution. After stirring at rt for 3h, TMSCN (1.83 g, 2.46 mL; **caution – toxic**! perform all the operations under a fumehood!), 18.45 mmol) was added. The reaction mixture was stirred at rt overnight, and then poured into EtOAc (350 mL). The mixture was diluted with water (350 mL), shaken, and the precipitate was filtered. The organic layer was dried over Na_2SO_4 and evaporated to give a crude mixture of two diastereomers (3 : 2 by NMR). Separation of isomers by column chromatography (cyclohexane – EtOAc (2 : 1) as an eluent) yielded a mixture of **16a** with benzyl alcohol (eluted first) (1.25 g, 84% purity by NMR, 3.07 mmol, 50%) and a pure **16b** (eluted second) (0.50 g, 1.46 mmol, 24%). Compound **16a** was used in the next step without any additional purification.

16a: Yellow oil. TLC: R_f = 0.46 (cyclohexane – EtOAc 2 : 1; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.2 Hz, 6H), 1.38 – 1.48 (m, 1H), 1.61 – 1.72 (m, 1H), 1.84 – 1.96 (m, 2H), 2.14 (dd, *J* = 12.0, 6.7 Hz, 1H), 2.29 (dd, *J* = 12.3, 6.8 Hz, 1H), 2.41 (br s, 2H), 2.55 – 2.66 (m, 1H), 2.85 (t, *J* = 9.7 Hz, 1H), 3.03 – 2.92 (m, 1H), 3.52 – 3.64 (m, 1H), 3.76 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.05 (dd, *J* = 9.1, 4.0 Hz, 1H), 4.95 – 5.06 (m, 1H), 7.22 – 7.44 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 29.4, 30.3, 30.7, 33.2, 34.2, 46.9, 60.8, 62.4, 67.1, 68.0, 121.2, 127.8, 128.1, 128.6, 140.6, 174.7. MS (LCMS) 343 (MH^+).

16b: Yellow oil. TLC: R_f = 0.34 (cyclohexane : EtOAc 2:1; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.2 Hz, 6H), 1.96 – 2.25 (m, 8H), 2.32 – 2.41 (m, 1H), 2.42 – 2.54 (m, 1H), 2.67 – 2.54 (m, 1H), 3.60 – 3.70 (m, 1H), 3.75 (dd, *J* = 11.0, 4.4 Hz, 1H), 4.00 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.90 – 5.03 (m, 1H), 7.29 – 7.47 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 29.4, 30.0, 30.9, 32.4, 33.8, 47.4, 59.7, 61.6, 66.5, 67.9, 120.5, 127.9, 128.5, 128.9, 140.1, 174.8. MS (LCMS) 343(MH^+). Anal. Calcd. for $C_{20}H_{26}N_2O_3$ C 70.15, H 7.65, N 8.18. Found C 70.40, H 7.33, N 8.47.

Isopropyl (2*R*,4*s*,5*R*)-5-cyano-5-(((*S*)-2-hydroxy-1-phenylethyl)amino)spiro[3.3]heptane-2-carboxylate 16c

A mixture of **16c** with benzyl alcohol (1.28 g, 77% of **16c** by (NMR data), 2.87 mmol, 47%) was obtained analogously to **16a** from **11b** and used in the next step without any additional purification. Yellow oil. TLC: R_f = 0.38 (cyclohexane – EtOAc 2:1; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (dd, *J* = 6.2, 1.0 Hz, 6H), 1.49 (t, *J* = 9.8 Hz, 1H), 1.64 – 1.74 (m, 1H), 1.86 – 2.03 (m, 2H), 2.02 – 2.13 (m, 1H), 2.19 – 2.31 (m, 1H), 2.49 (dd, *J* = 11.6, 8.5 Hz, 1H), 2.57 – 2.92 (m, 3H), 2.94 – 3.05 (m, 1H), 3.61 (t, *J* = 10.0 Hz, 1H), 3.73 (dd, *J* = 10.9, 3.3 Hz, 1H), 4.07 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.95 – 5.09 (m, 1H), 7.19 – 7.50 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 30.0, 31.0, 31.8, 34.3, 45.6, 60.1, 62.2, 67.1, 68.2, 77.2, 120.8, 127.9, 127.9, 128.4, 140.6, 175.0. MS (LCMS) 343(MH^+).

Isopropyl (2*S*,4*s*,5*S*)-5-cyano-5-(((*S*)-2-hydroxy-1-phenylethyl)amino)spiro[3.3]heptane-2-carboxylate (16d)

Compound **16d** (0.5 g, 1.46 mmol, 24%) was obtained analogously to **16b** from **11b**. Yellow oil. TLC: R_f = 0.28 (cyclohexane : EtOAc 2:1; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (dd, *J* = 5.6, 3.8 Hz, 6H), 1.97 – 2.18 (m, 4H), 2.18 – 2.26 (m, 1H), 2.26 – 2.34 (m, 1H), 2.34 – 2.58 (m, 3H), 2.64 (dd, *J* = 11.5, 8.0 Hz, 1H), 2.89 – 3.00 (m, 1H), 3.59 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.69 (dd, *J* = 10.8, 4.5 Hz, 1H), 3.90 (dd, *J* = 7.4, 4.7 Hz, 1H), 4.93 – 5.05 (m, 1H), 7.25 – 7.47 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 29.51, 29.57, 31.3, 31.9, 34.5, 46.0, 58.5, 60.8, 66.4, 68.2, 120.4, 127.5, 128.2, 128.8, 139.9, 174.8. MS (LCMS) 343 (MH^+). Anal. Calcd. for $C_{20}H_{26}N_2O_3$ C 70.15, H 7.65, N 8.18. Found C 69.93, H 7.81, N 8.06.

The ratio of **16c** and **16d** in the crude mixture was 3:2 (NMR data).

(1*R*,4*r*,6*S*)-1-Amino-spiro[3.3]heptane-1,6-dicarboxylic acid (1a), hydrochloride

Compound **16a** (0.62 g, 84% by NMR), 1.53 mmol) was dissolved in CH_2Cl_2–MeOH (1 : 1) (40 mL). The resulting solution was cooled to 0ºC, and $Pb(OAc)_4$ (1.21 g, 2.73 mmol) was added quickly. After 10 min at 0 ºC, saturated aq $NaHCO_3$ (50 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic extract was filtered and the precipitate was washed with CH_2Cl_2 (15 mL). The combined organic phases were

dried over Na_2SO_4 and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and saturated with gaseous HCl for 20 min at 0 ºC. MeOH (5 mL) was added, and the resulting mixture was saturated with HCl for another 20 min at 0 ºC. The reaction mixture was stirred overnight at ambient temperature, and then evaporated. The residue was dissolved in 6 *N* aq HCl (30 mL) and refluxed for 2h, then washed with Et_2O (3×15 mL), evaporated, dissolved in water (15 mL). This solution was made alkaline with an excess of NaOH and evaporated to dryness. The residue was dissolved in 6 *N* aq HCl and evaporated to dryness again. The resulting residue was dissolved in dry ethanol (15 mL), and the precipitate was filtered off. The filtrate was concentrated *in vacuo* and the resulting solid was recrystallized from 2-propanol to give hydrochloride of **1a** (0.28 g, 1.19 mmol, 78 %). White solid. Mp 213–215 ºC (dec). $[\alpha]_D^{20}$ = – 13.6 (c 0.5, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 2.14 – 2.46 (m, 6H), 2.50 – 2.60 (m, 1H), 2.68 (t, *J* = 11.1 Hz, 1H), 3.02 – 3.12 (m, 1H). ^{13}C NMR (126 MHz, D_2O) δ 24.5, 30.7, 32.0, 32.2, 33.9, 44.7, 62.2, 172.4, 179.7. MS (LCMS) 200 ($MH^+ - Cl^-$). Anal. Calcd for $C_9H_{14}ClNO_4$ C 45.87, H 5.99, Cl 5.04, N 5.94. Found C 45.49, H 6.31, Cl 4.77, N 5.90.

(1*S*,4*r*,6*R*)-1-Amino-spiro[3.3]heptane-1,6-dicarboxylic acid (1b), hydrochloride

Compound **1b** (0.14 g, 0.59 mmol, 81%) was obtained from **16b** analogously to **1a**. White solid. Mp 212–214 ºC (dec). $[\alpha]_D^{20}$ = + 10.0 (c 0.5, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 2.14 – 2.46 (m, 6H), 2.50 – 2.60 (m, 1H), 2.68 (t, *J* = 11.1 Hz, 1H), 3.02 – 3.12 (m, 1H). ^{13}C NMR (126 MHz, D_2O) δ 24.6, 30.7, 32.0, 32.3, 34.0, 44.8, 62.3, 172.4, 179.7. MS (LCMS) 200 ($MH^+ - Cl^-$). Anal. Calcd for $C_9H_{14}ClNO_4$ C 45.87, H 5.99, Cl 5.04, N 5.94. Found C 45.60, H 5.91, Cl 5.26, N 5.71.

(1*R*,4*s*,6*R*)-1-Amino-spiro[3.3]heptane-1,6-dicarboxylic acid (1c), hydrochloride

Compound **1c** (0,28 g, 1.19 mmol, 83%) was obtained analogously to **1a** from **16c** (0.64 g, 77% by NMR, 1.44 mmol). White solid. Mp 224–226 ºC (dec). $[\alpha]_D^{20}$ = +13.2 (c 0.5, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 2.16 – 2.36 (m, 5H), 2.38 – 2.51 (m, 2H), 2.53 – 2.61 (m, 1H), 3.13 – 3.26 (m, 1H). ^{13}C NMR (126 MHz, D_2O) δ 24.7, 29.6, 30.8, 33.1, 34.8, 42.6, 61.9, 172.6, 179.1. MS (LCMS) 200 ($MH^+ - Cl^-$). Anal. Calcd for $C_9H_{14}ClNO_4$ C 45.87, H 5.99, Cl 5.04, N 5.94. Found C 45.66, H 6.05, Cl 5.04, N 5.52.

(1*S*,4*s*,6*S*)-1-Amino-spiro[3.3]heptane-1,6-dicarboxylic acid (1d), hydrochloride

Compound **1d** (0.12 g, 0.51 mmol, 70%) was obtained analogously to **1a** from **16d** (0.25 g, 0.73 mmol). White solid. Mp 224–226 ºC (dec). $[\alpha]_D^{20}$ = – 17.2 (c 0.5, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 2.16 – 2.36 (m, 5H), 2.38 – 2.51 (m, 2H), 2.53 – 2.61 (m, 1H), 3.13 – 3.26 (m, 1H). ^{13}C NMR (126 MHz, D_2O) δ 24.7, 29.6, 30.8, 33.1, 34.8, 42.6, 61.9, 172.6, 179.1. MS (LCMS) 200 ($MH^+ - Cl^-$). Anal. Anal. Calcd for $C_9H_{14}ClNO_4$ C 45.87, H 5.99, Cl 5.04, N 5.94. Found C 46.03, H 6.06, Cl 5.17, N 6.31.

Methyl (2*S*,4*r*,5*R*,7*S*)-10-oxo-7-phenyl-9-oxa-6-azadispiro-[3.0.5.2]dodecane-2-carboxylate (18a)

16a (0.62 g, 84% by NMR, 1.53 mmol) was dissolved in CH_2Cl_2 (20 mL) and saturated with gaseous HCl for 20 min at 0ºC. MeOH (5 mL) was added, and the resulting mixture was saturated with HCl for another 20 min at 0ºC. The reaction mixture was stirred overnight at ambient temperature, and then evaporated. The residue was treated wih CH_2Cl_2 (20 mL). The resulting solution was washed with saturated aq. $NaHCO_3$ and dried over Na_2SO_4. Then the solvent was evaporated and the crude product was purified form by column chromatography (Cyclohexane – EtOAc (2 : 1) as an eluent). The yield of **18a** was 0.24 g (0.76 mmol, 50%). White solid. Mp 130–131 ºC. TLC: R_f = 0.50 (cyclohexane : EtOAc 2:1; UV). $[\alpha]_D^{20}$ = – 3.11 (c 0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 – 1.75 (m, 1H), 1.83 – 1.99 (m, 2H), 2.16 (dd, *J* = 11.3, 5.8 Hz, 1H), 2.28 – 2.37 (m, 3H), 2.68 – 2.78 (m, 1H), 2.91 – 3.05 (m, 2H), 3.69 (s, 3H), 4.14 (t, *J* = 10.7 Hz, 1H), 4.26 (dd, *J* = 10.6, 3.2 Hz, 1H), 4.31 (dd, *J* = 10.8, 3.1 Hz, 1H), 7.30 – 7.43 (m, 3H), 7.46 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.7, 31.7, 32.8, 34.3, 35.6, 49.2, 51.9, 54.3, 65.0, 74.2, 127.3, 128.8, 129.0, 138.1, 171.1, 176.0. MS (LCMS) 316 (MH^+). Anal. Calcd for $C_{18}H_{21}NO_4$ C 68.55, H 6.71, N 4.44. Found C 68.37, H 6.93, N 4.26.

Methyl (2*R*,4*r*,5*S*,7*S*)-10-oxo-7-phenyl-9-oxa-6-azadispiro-[3.0.5.2]dodecane-2-carboxylate (18b)

Compound **18b** (0.14 g, 0.44 mmol, 61%) was obtained from **16b** (0,25 g, 0.73 mmol) analogously to **18a**. White solid. Mp 142–143 ºC. TLC: R_f = 0.41 (cyclohexane : EtOAc 2:1; UV). $[\alpha]_D^{20}$ = + 12.89 (c 0.18, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 – 1.75 (m, 1H), 1.88 (t, *J* = 9.6 Hz, 1H), 2.13 – 2.23 (m, 1H), 2.25 – 2.38 (m, 3H), 2.39 – 2.50 (m, 1H), 2.52 – 2.69 (m, 2H), 3.03 – 3.17 (m, 1H), 3.70 (s, 3H), 4.21 – 4.43 (m, 3H), 7.30 – 7.51 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.2, 30.5, 31.6, 32.3, 35.4, 49.8, 52.1, 53.9, 65.8, 74.7, 127.2, 129.1, 129.2, 137.4, 170.6, 175.8. MS (LCMS) 316 (MH^+). Anal. Calcd for $C_{18}H_{21}NO_4$ C 68.55, H 6.71, N 4.44. Found C 68.70, H 6.52 N 4.29.

Methyl (2*R*,4*s*,5*R*,7*S*)-10-oxo-7-phenyl-9-oxa-6-azadispiro-[3.0.5^5.2^4]dodecane-2-carboxylate (18c)

Compound **18c** (0.26 g, 0.82 mmol, 57%) was obtained analogously to **18a** from **16c** (0.64 g, 77% (by NMR), 1.44 mmol). White solid. Mp 111–111 ºC. TLC: R_f = 0.49 (cyclohexane : EtOAc 2:1; UV). $[\alpha]_D^{20}$ = –30.28 (c 0.455, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 – 1.85 (m, 2H), 1.95 – 2.06 (m, 2H), 2.22 – 2.33 (m, 2H), 2.34 – 2.43 (m, 1H), 2.73 – 2.81 (m, 1H), 2.89 (t, *J* = 10.0 Hz, 1H), 3.00 – 3.10 (m, 1H), 3.69 (s, 3H), 4.20 – 4.31 (m, 3H), 7.31 – 7.42 (m, 3H), 7.48 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.5, 31.3, 32.6, 33.9, 34.8, 47.3, 51.9, 54.2, 64.5, 74.3, 127.4, 128.8, 129.0, 138.2, 170.9, 175.7. MS (LCMS) 316 (MH^+). Anal. Calcd for $C_{18}H_{21}NO_4$ C 68.55, H 6.71, N 4.44. Found C 68.42, H 6.58, N 4.14.

Methyl (2*S*,4*s*,5*S*,7*S*)-10-oxo-7-phenyl-9-oxa-6-azadispiro-[3.0.5^5.2^4]dodecane-2-carboxylate (18d)

Compound **18d** (0.12 g, 0.38 mmol, 52%) was obtained analogously to **18b** from **16d** (0.25 g, 0.73 mmol). White solid. Mp 79–80 ºC. TLC: R_f = 0.40 (cyclohexane : EtOAc 2:1; UV). $[\alpha]_D^{20}$ = +32.2 (c 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 – 1.77 (m, 1H), 1.89 (t, *J* = 9.9 Hz, 1H), 1.95 – 2.06 (m, 1H), 2.16 – 2.45 (m, 4H), 2.54 – 2.70 (m, 2H), 3.18 – 3.04 (m, 1H),

3.72 (s, 3H), 4.25 – 4.39 (m, 2H), 4.51 – 4.64 (m, 1H), 7.30 – 7.44 (m, 3H), 7.48 (d, J = 5.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.0, 30.1, 30.2, 32.4, 36.7, 48.4, 52.1, 53.4, 65.4, 74.8, 127.5, 128.9, 129.1, 137.6, 170.7, 176.0. MS (LCMS) 316 (MH^+). Anal. Calcd for $C_{18}H_{21}NO_4$ C 68.55, H 6.71, N 4.44. Found C 68.90, H 6.41, N 4.63.

Dimethyl (1*R*,4*s*,6*R*)-1-(((S)-2-hydroxy-1-phenylethyl)amino)-spiro[3.3]heptane-1,6-dicarboxylate (19c)

Compound **19c** (0.11 g, 0.32 mmol, 22%) was obtained from **16c** during chromatographic purification of **18c**. White solid. Mp 68–69 ºC.TLC: R_f = 0.36 (cyclohexane : EtOAc 2:1; UV). $[\alpha]_D^{20}$ = + 25.2 (c 0.46, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 – 1.52 (m, 1H), 1.90 – 2.07 (m, 4H), 2.07 – 2.21 (m, 2H), 2.64 – 2.74 (m, 1H), 2.89 – 3.02 (m, 1H), 3.45 – 3.57 (m, 1H), 3.57 – 3.65 (m, 2H), 3.69 (s, 3H), 3.77 (s, 3H), 7.20–7.41 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.1, 30.5, 31.6, 33.1, 34.8, 45.5, 51.9, 52.1, 61.7, 67.6, 67.7, 127.3, 127.5, 128.5, 142.6, 175.4, 175.8. MS (LCMS) 348 (MH^+). Anal. Calcd for $C_{19}H_{25}NO_5$ C 65.69, H 7.25, N 4.03. Found C 65.47, H 7.04, N 3.85.

X-Ray diffraction studies

X-Ray diffraction studies were performed on an automatic «Xcalibur 3» diffractometer (graphite monochromated MoK_α radiation, CCD-detector, ω-scanning). The crystals were obtained by slow evaporation of the solutions in MeCN (**13**) or cyclohexane – EtOAc (**18a**, **18b** and **18c**). The structure was solved by direct method using SHELXTL package.[24] Positions of hydrogen atoms were located from electron density difference maps and refined using riding model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and 1.2 for other hydrogen atoms). In the case of **18a–c**, hydrogen atoms at N(1) were refined using isotropic model. The crystallographic data and experimental parameters are listed in Electronic supplementary information, Table S1. 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 S1.

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