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Synthesis of Enantiopure 1-Azaspiro[4.5]decanes by Iodoaminocyclization of Allylaminocyclohexanes

Faïza Diaba,[a] Gemma Puigbó,[a] and Josep Bonjoch*[a]

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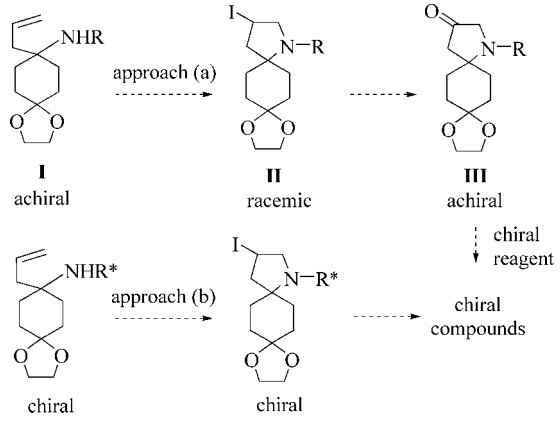
The 5-*endo* iodine-promoted ring closure of 4-allyl-4-(alkylamino)cyclohexanone derivatives gives the corresponding 1-azaspiro[4.5]decanes in good yields. The reaction was tested with enantiopure homoallylamines to evaluate the diastereoselectivity of the process and to provide a route for possible intermediates to the natural products embodying this azabicyclic ring.

Introduction

In the course of our studies related to the immunosupressant FR901483,[1–4] we introduced a new procedure for the synthesis of 1-azaspiro[4.5]decanes[5] that is based on the treatment of homoallylamine **I** with iodine (Scheme 1),[1,6] which promotes the electrophilic cyclofunctionalization of the unsaturated amine to give five-membered ring **II**.[7–10]



Scheme 1.

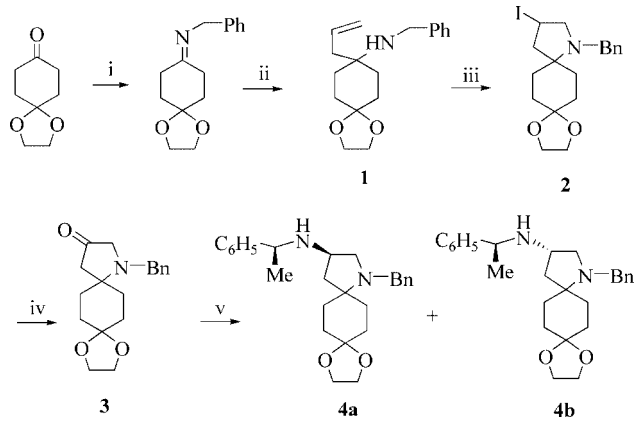
Extending our previous work on iodoaminocyclizations, we report here the use of this procedure for the preparation of enantiopure 1-azaspiro[4.5]decanes, which are potential building blocks in the synthesis of the aforementioned FR901483 as well as TAN1251 derivatives.[11] To achieve this goal, we envisaged two possible approaches: (a) transformation of racemic iodo derivative **II** into achiral compound **III**, which could then be transformed into an enantiopure advanced intermediate or (b) carry out the aminocyclization from an enantiopure homoallylamine and evaluate the stereocontrol induced by the stereogenic center in the side chain upon the newly formed stereogenic center at C-3 of the azaspiro derivative.

Results and Discussion

We explored the first possible approach by synthesizing ketone **III** (R = Bn), an achiral 1-azaspiro[4.5]decane. Required homoallylamine **1** was prepared by a one-pot procedure that involved the formation of an imine from the monoethylene acetal of 1,4-cyclohexanedione and benzylamine, followed by the addition of allylmagnesium bromide (Scheme 2).[3,12] Treatment of **1** with iodine promoted the iodoaminocyclization process to give iodo derivative **2**, which was then oxidized to ketone **3** by using DMSO and silver tetrafluoroborate.[13] The overall sequence worked well and we gained access to achiral functionalized azaspirane **3** in 30% overall yield over the four transformations. The reductive amination of **3** with (*S*)-α-methylbenzylamine gave corresponding secondary amines **4a**,**b**, whose configurations at C-3 were not established, in a nearly equimolecular ratio and a 72% overall yield. Further explorations of approach (a) (e.g. enantioselective reduction of ketone **3** followed by a Fukuyama-Mitsunobu process) were not pursued.

In view of the disappointingly low level of diastereoselectivity observed when the amino group was introduced, we turned to the alternative strategy outlined in Scheme 1. Approach (b) required a chiral homoallylamine such as **9** as the starting material (Scheme 3). Treatment of 1,4-cyclohexanedione monoethylene acetal with (*S*)-2-amino-3-(4-methoxyphenyl)propan-1-ol (**5a**),[14] which was prepared by direct reduction of *O*-methyl-L-tyrosine with $LiBH_4$/TMSCl

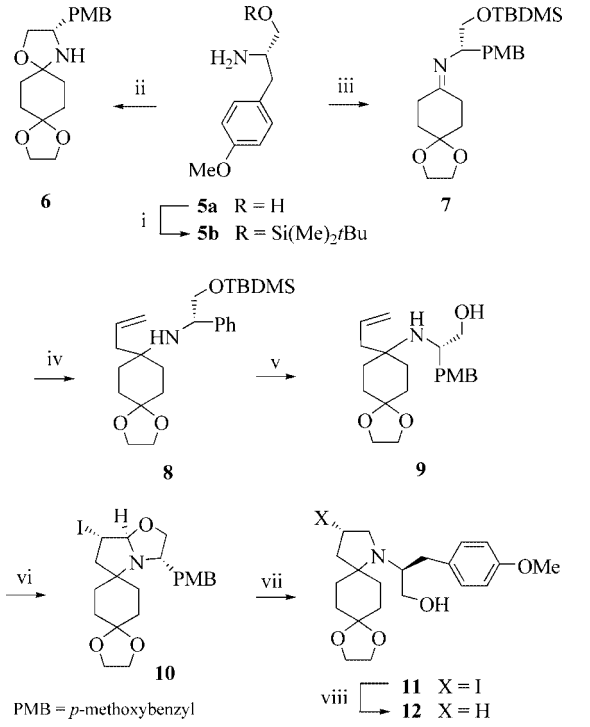
[a] Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona,
Av. Joan XXIII s/n, 08028 Barcelona, Spain
Fax: +34-934024539
E-mail: josep.bonjoch@ub.edu



Scheme 2. Synthesis of enantiopure 3-amino-1-azaspiro[4.5]decan-8-ones: (i) $C_6H_5CH_2NH_2$, 4 Å molecular sieves, CH_2Cl_2, room temp., 5 h; (ii) $CH_2{=}CHCH_2MgBr$, CH_2Cl_2, room temp., 95% for the two steps; (iii) I_2, $NaHCO_3$, CH_2Cl_2/H_2O, room temp., 12 h, 73%; (iv) $AgBF_4$, DMSO, room temp., 12 h, quantitative; (v) (*S*)-1-phenylethylamine, $NaCNBH_3$, THF, room temp., 24 h, 72%.

in 83% yield,[15] gave oxazolidine **6** in excellent yield. As all our attempts to cleave this cyclic hemiaminal (by using allylmagnesium bromide, allyltrimethylsilane, allyltributyltin, and allylcerium chloride) to obtain homoallylamine **9** were unsuccessful, we focused our attention on protected amino alcohol **5b**.[16] Condensation of **5b** with the aforementioned cyclohexanone produced imine **7**, which was treated with allylmagnesium bromide to give homoallylamine **8** in 72% overall yield. Finally, deprotection of **8** by cleavage of the silyl ether group by TBAF gave amino alcohol **9**.

By using the best reaction conditions found for achiral homoallylic amine **1**, we examined the iodine-promoted cyclization from both amines **8** and **9**. Whereas the process from **8** did not proceed, the less sterically demanding deprotected amino alcohol **9** did undergo the aminocyclization process; although, unexpectedly the isolated end product was tricyclic oxazolidine **10**, which was obtained in 62% overall yield for the two successive cyclizations. The formation of **10** probably involved an initial cyclization to afford azaspiranic ring **11** (or a mixture of diastereomers) followed by a neighboring hydroxy group oxidation of the amine to give an iminium intermediate,[17] which was trapped by the hydroxy group to form the oxazolidine ring.[18] On the basis of the small coupling constant (J = 2.8 Hz) observed in the ^{1}H NMR spectrum for the methine protons,[19] we have assigned the stereochemistry of **10** to that shown in Figure 1 with a *trans* relationship between the linked heteroatoms at the pyrrolidine ring. Oxazolidine **10** was reduced ($NaBH_4$)[20] to azaspirane **11** in good yield and then, for analytical purposes, to **12** (Bu_3SnH, AIBN). Although the process seems to be diastereoselective as only diastereomer **10** was isolated, the moderate overall yield of the process (62%) gives room for doubt. The diastereoselectivity could arise from the initial stereocontrolled formation of the iodonium intermediate and its stereocontrolled ring-opening by the amino group. The ring-opening could then be followed by the formation of an iminium ion and attack of



Scheme 3. Reagents and conditions: (i) *t*$BuMe_2SiCl$, imidazole, DMF, room temp., 12 h, 77%; (ii) from **5a**: 1,4-cyclohexanedione monoethylene acetal, 4 Å molecular sieves, CH_2Cl_2, room temp., 2 h, 95%; (iii) from **5b**: 1,4-cyclohexanedione monoethylene acetal, 4 Å molecular sieves, CH_2Cl_2, room temp., 5 h; (iv) $CH_2{=}CHCH_2MgBr$, Et_2O, room temp., 72% for the two steps; (v) TBAF, THF, room temp., 1 h, 84%; (vi) I_2, $NaHCO_3$, CH_2Cl_2/H_2O, room temp., 12 h, 62%; (vii) $NaBH_4$, MeOH, room temp., 2 h, 93%; (viii) Bu_3SnH, AIBN, benzene, reflux, 2 h, 70%.

the hydroxy group on the face opposite to the location of the iodine atom and antiperiplanar to the electron lone pair of the nitrogen atom. Alternatively, and more probably, the nonobservation of other diastereomeric oxazolidines could simply derive from the fact that after the oxidation step, other iminium salt intermediates that were formed could not evolve for steric and/or stereoelectronic reasons and they decomposed in solution upon work up. Thus, this result did not clarify if the stereogenic center in the side chain linked to the nitrogen atom exerted some stereocontrol in the genesis of the new stereogenic center formed at C-3 in the azaspiranic ring.

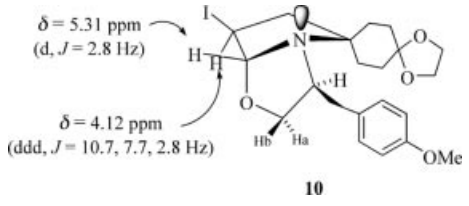
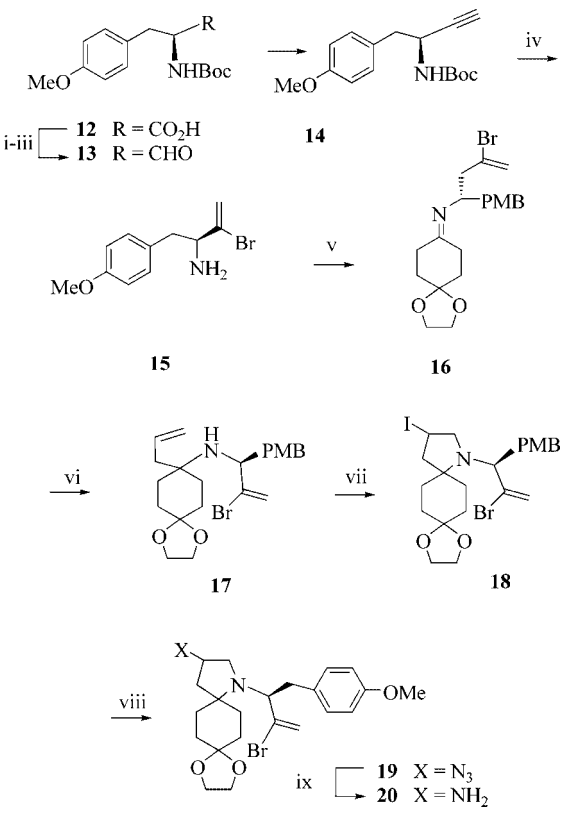


Figure 1. Assignment of the stereochemistry of **10** on the basis of coupling constants.

We then decided to prepare a new type of azaspiranic compound from a homoallylic amine lacking a hydroxy group to prevent the anchimeric process that promotes the oxazolidine ring formation. With this goal in mind, we de-

cided to synthesize vinyl bromide **15** to attempt the iodine-promoted azaspirodecane ring formation, which would also allow us to test the diastereoselectivity of the process and gain access to a valuable intermediate in the synthetic route to FR901683 (Scheme 4).



Scheme 4. Reagents and conditions: (i) MeI, $NaHCO_3$, DMF, room temp., 16 h, 81%; (ii) $LiBH_4$, THF/EtOH, 16 h, 99%; (iii) TEMPO, NaBr, $NaHCO_3$, NaOCl, CH_2Cl_2/H_2O, 0 °C, 2 h, 91%; (iv) $(MeO)_2P(O)CN_2COCH_3$, K_2CO_3, MeOH, room temp., 16 h, 74%; (v) 1,4-cyclohexanedione monoethylene acetal, 4 Å molecular sieves, CH_2Cl_2, room temp., overnight; (vi) $CH_2{=}CHCH_2MgBr$, CH_2Cl_2, room temp., 4 h, 75% for the two steps; (vii) I_2, $NaHCO_3$, CH_2Cl_2/H_2O, room temp., 2 h; (viii) NaN_3, DMF, 50 °C, DMSO, 3 h, 58% for the two steps; (ix) Ph_3P, THF, 1 d, then H_2O, room temp., 3 d, 95%.

Commercially available *O*-methyl-*N*-(*tert*-butoxycarbonyl)-L-tyrosine (**12**) was transformed to corresponding aldehyde **13** by following a reported procedure.[21] Aldehyde **13** was homologated to alkyne **14** with the use of dimethyl 1-diazo-2-(oxopropyl)phosphonate[22] in a basic methanolic solution.[23,24] The hydrobromination of alkyne **14** was carried out with gaseous hydrogen bromide,[25] which resulted in a mixture of regioisomers. Required vinyl bromide **15**, in which the amine group is deprotected, was isolated in 45% overall yield. Condensation of primary amine **15** with 1,4-cyclohexanedione monoethylene acetal was troublesome, and the conversion of **15** to corresponding imine **16** was never complete. Consequently, after treatment with allylmagnesium bromide, homoallylamine **17** was formed together with a small amount of 4-allyl-4-hydroxycyclohexanone acetal.[26]

The aminocyclization of homoallylamine **17** promoted by iodine proved to have a low stereoselectivity; azaspiranic derivatives **18** was isolated as a 3:2 mixture of diastereomers. To gain access to more stable and valuable compounds for the synthesis of FR901483, crude iodides **18** were converted into corresponding amino derivatives **20** by treatment with sodium azide, followed by reduction of azide intermediates **19** with triphenylphosphane. At this stage, both diastereomers at C-3 could be separated, but the absolute configuration was not ascertained. The nearly equimolecular mixture of isolated amines does not reflect the ratio of initially formed iodides **18**. This could be due to the participation of the neighboring nitrogen atom at N-1 in the azide-formation step, which could lead to an aziridinium ion intermediate during the substitution process to a variable extent depending on the configuration of the starting iodide.

In summary, the results reported here demonstrate the utility of iodine-promoted aminocyclization reactions in the elaboration of the azaspirane ring system found in some natural products. Concerning the two approaches studied, we concluded that route (a), which proceeds through achiral azaspiranic ketone **3**, was the most satisfactory as it is shorter than those using chiral starting materials, and additionally, the enantiopure epimeric amino derivatives formed after the reductive amination can be isolated easily. Further studies are needed to determine if the stereocontrol at C-3 can be improved, which would provide a satisfactory synthetic route to enantiopure building blocks with the 3-substituted-1-azaspiro[4.5]decane pattern.[27]

Experimental Section

General: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or Al_2O_3 (ALOX N/UV_{254}, Polygram), and the spots were located with iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). Drying of organic extracts during work up of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si.

4-Allyl-4-benzylaminocyclohexanone Ethylene Acetal (1): To a solution of 1,4-cyclohexanedione monoethylene acetal (10 g, 64 mmol) in CH_2Cl_2 (200 mL) were added benzylamine (8.4 mL, 77 mmol) and 4 Å molecular sieves (20 g). After stirring at room temp. for 4 h, the suspension was filtered through Celite, and the filtrate was concentrated to give the corresponding imine (see Scheme 2): ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.1 (CH_2), 34.1 (CH_2), 34.8 (CH_2), 36.2 (CH_2), 54.4 (CH_2N), 64.3 (CH_2O), 107.8 (C-1), 126.4 (CH), 127.5 (CH), 128.3 (CH), 140.0 (C), 171.7 (CN) ppm. To a solution of this imine in CH_2Cl_2 (100 mL) was added dropwise allylmagnesium bromide (1.28 M in Et_2O, 100 mL, 128 mmol). The mixture was stirred at room temp. overnight, poured into saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic extracts were

washed with brine, dried, and concentrated. After chromatography (Al_2O_3, hexanes/CH_2Cl_2, 1:1), amine **2** (18 g, 98%) was obtained. An analytical sample was obtained by crystallization. M.p. 42–44 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (br. s, 1 H, NH), 1.50–1.75 (m, 6 H), 1.90–2.02 (m, 2 H), 2.26 (d, J = 7.4 Hz, 2 H, CH_2CH), 3.65 (s, 2 H, CH_2Ar), 3.95 (s, 4 H, OCH_2), 5.12 (dm, J = 14.7 Hz, 1 H, *cis*-H), 5.12 (dm, J = 9.3 Hz, 1 H, *trans*-H), 5.85 (ddt, J = 14.7, 9.3, 7.4 Hz, 1 H, *gem*-H), 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.2 and 32.7 (C-2 and C-3), 42.0 (CH_2CH), 45.7 (CH_2Ar), 53.1 (C-4), 64.1 and 64.2 (CH_2O), 109.1 (C-1), 117.9 (=CH_2), 126.7 (*p*-Ar), 128.2 (*o*-Ar and *m*-Ar), 134.1 (=CH), 141.3 (*ipso*-Ar) ppm. IR (neat): $\tilde{\nu}$ = 3300, 1627 cm^{-1}. $C_{18}H_{25}NO_2$ (287.38): calcd. C 75.23, H 8.77, N 4.87; found C 75.36, H 8.83, N 4.85.

1-Benzyl-3-iodo-1-azaspiro[4.5]decan-8-one Ethylene Acetal (2): To a solution of amine **1** (0.5 g, 1.7 mmol) in CH_2Cl_2 (15 mL) and 5% aqueous $NaHCO_3$ (15 mL) was added dropwise a solution of I_2 (0.63 g, 2.5 mmol) in CH_2Cl_2 (15 mL). After stirring at room temp. overnight, saturated aqueous sodium thiosulfite (20 mL) was added. The mixture was extracted with CH_2Cl_2, and the organic extracts were concentrated and purified by chromatography (Al_2O_3, hexanes/CH_2Cl_2, 1:1) to give **2** (0.51 g, 71%) as a yellow liquid, which crystallized on standing. An analytical sample was obtained by crystallization. M.p. 80–81 °C (Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY, HSQC, HMBC): δ = 1.40 (ddd, J = 13.4, 2.5 Hz, 1 H, 6-H_{eq}), 1.60 (td, J = 13.5, 4.0 Hz, 1 H, 7-H_{ax}), 1.64 (td, J = 14.0, 4.5 Hz, 1 H, 9-H_{ax}), 1.71–1.83 (m, 3 H, 7-H_{eq}, 9-H_{eq}, and 10-H_{eq}), 1.86 (td, J = 13.5, 4.0 Hz, 1 H, 6-H_{ax}), 1.90 (td, J = 13.5, 4.0 Hz, 1 H, 10-H_{ax}), 2.32 (dd, J = 14.0, 6.5 Hz, 1 H, 4-H), 2.54 (dd, J = 14.0, 8.5 Hz, 1 H, 4-H), 3.01 (dd, J = 10.5, 6.75 Hz, 1 H, 2-H), 3.06 (dd, J = 10.5, 7.0 Hz, 1 H, 2-H), 3.61 (d, J = 13.5 Hz, 1 H, CH_2Ar), 3.72 (d, J = 13.5 Hz, 1 H, CH_2Ar), 3.94 (s, 4 H, OCH_2), 4.19 (dddd, J = 8.5, 7.0, 6.75, 6.5 Hz, 1 H, 3-H), 7.19–7.33 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8 (C-3), 29.7 (C-10), 30.8 (C-6), 32.2 (C-9), 32.6 (C-7), 47.7 (C-4), 51.1 (CH_2Ar), 61.5 (C-2), 63.1 (C-5), 64.2 and 64.3 (CH_2O), 108.2 (C-8), 126.7 (*p*-Ar), 128.1 (*o*- and *m*-Ar), 140.0 (*ipso*-Ar) ppm. $C_{18}H_{24}INO_2$ (413.28): calcd. C 52.31, H 5.85, N 3.39, I 30.70; found C 52.29, H 5.70, N 3.40, I 30.65.

1-Benzyl-1-azaspiro[4.5]decan-3,8-dione 8-Monoethylene Acetal (3): To a solution of $AgBF_4$ (1.26 g, 6.4 mmol) in DMSO (80 mL) was added dropwise a solution of **2** (2.78 g, 6.7 mmol) in DMSO (60 mL). After stirring at room temp. overnight, triethylamine (1.12 mL, 8.0 mmol) was added and the stirring was maintained for an additional 1 h. The suspension was filtered through Celite, and the filtrate was partitioned between Et_2O and water. The dried organic extracts yielded crude ketone **3** (2 g) in quantitative yield. An analytical sample was obtained by crystallization. M.p. 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54–1.68 (m, 4 H), 1.78–1.89 (m, 2 H), 2.01–2.16 (m, 2 H), 2.46 (s, 2 H, 4-H), 3.07 (s, 2 H, 2-H), 3.75 (s, 2 H, CH_2Ar), 3.96 (s, 4 H, OCH_2), 7.20–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8 (C-6 and C-10), 32.5 (C-7 and C-9), 47.9 (C-4), 52.0 (CH_2Ar), 58.7 (C-2), 61.9 (C-5), 64.3 and 64.4 (CH_2O), 108.0 (C-8), 127.0 (*p*-Ar), 128.1 and 128.3 (*o*- and *m*-Ar), 139.2 (*ipso*-Ar), 213.7 (C-3) ppm. IR (neat): $\tilde{\nu}$ = 1753 cm^{-1}.$C_{18}H_{23}NO_3$ (301.36): calcd. C 71.74, H 7.69, N 4.65; found C 71.92, H 7.74, N 4.67.

Reductive Amination of 3: α-(*S*)-Methylbenzylamine hydrochloride (0.5 g, 3.2 mmol) and portionwise $NaCNBH_3$ (0.25 g, 3.9 mmol) were added to a solution of ketone **3** (0.5 g, 1.6 mmol) in THF (10 mL). After stirring at room temp. for 24 h, water was added, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the organic extracts were dried, concentrated, and purified by chromatography (Al_2O_3, hexane/CH_2Cl_2, 1:1). Firstly, amine **4a** (247 mg, 38%) was eluted, and secondly, amine **4b** (221 mg, 34%) was isolated. **(3*R* or 3*S*)-1-Benzyl-3-[(*S*)-(1-phenylethyl)amino]-1-azaspiro[4.5]decan-8-one Ethylene Acetal (4a):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, J = 6.5 Hz, 3 H, CH_3), 1.32–2.05 (m, 9 H), 2.20 (dd, J = 12.9, 8.3 Hz, 1 H, 4-H), 2.48 (dd, J = 9.4, 5.1 Hz, 1 H, 2-H), 2.68 (dd, J = 9.4, 7.0 Hz, 1 H, 2-H), 3.10 (m, 1 H, 3-H), 3.47 (d, J = 13.1 Hz, 1 H, CH_2N), 3.64 (d, J = 13.1 Hz, 1 H, CH_2N), 3.73 (q, J = 6.5 Hz, 1 H, CHN), 3.94 (m, 4 H, OCH_2), 7.10–7.40 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (CH_3), 28.8 (CH_2), 31.4 (CH_2), 32.6 (CH_2), 32.7 (CH_2), 42.2 (C-4), 52.0 (CH_2N), 52.5 (C-3), 56.0 (CHN), 57.1 (C-2), 62.1 (C-5), 64.2 and 64.3 (OCH_2), 108.6 (C-8), 126.5 (CH), 126.7 (CH), 126.9 (CH), 128.1 (CH), 128.4 (CH), 140.7 (C), 145.5 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{35}N_2O_2$ [M + H] 407.2693; found 407.2692. **(3*R* or 3*S*)-1-Benzyl-3-[(*S*)-*N*-1-phenylethyl)amino]-1-azaspiro[4.5]decan-8-one Ethylene Acetal (4b):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.5 Hz, 3 H, CH_3), 1.26–2.05 (m, 9 H), 2.14 (dd, J = 12.9, 8.5 Hz, 1 H, 4-H), 2.64 (dd, J = 9.4, 4.6 Hz, 1 H, 2-H), 2.70 (dd, J = 9.4, 6.4 Hz, 1 H, 2-H), 3.02 (m, 1 H, 3-H), 3.46 (d, J = 13.3 Hz, 1 H, CH_2N), 3.64 (d, J = 13.3 Hz, 1 H, CH_2N), 3.73 (q, J = 6.5 Hz, 1 H, CHN), 3.92 (m, 4 H, CH_2O), 7.10–7.33 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (CH_3), 28.1 (CH_2), 31.2 (CH_2), 32.4 (CH_2), 32.7 (CH_2), 42.7 (C-4), 51.9 (CH_2N), 52.4 (C-3), 56.4 (CHN), 56.5 (C-2), 61.7 (C-5), 64.1 and 64.2 (CH_2O), 108.5 (C-8), 126.5 (CH), 126.6 (CH), 126.8 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 140.8 (C), 145.4 (C) ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{35}N_2O_2$ [M + H] 407.2693; found 407.2691.

(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)-2-propylamine (5b): *t*$BuMe_2SiCl$ (4 g, 26.5 mmol) and imidazole (3.73 g, 54.8 mmol) were added to a solution of (*S*)-2-amino-3-(4-methoxyphenyl)propanol (**5a**, 4 g, 22.1 mmol) in DMF (40 mL). The mixture was stirred at room temp. for 12 h, and H_2O and Et_2O were then added. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and all organic extracts were dried, concentrated, and purified by chromatography (Al_2O_3, CH_2Cl_2) to afford silyl ether **5b** (5 g, 77%). ^{1}H NMR (300 Hz, $CDCl_3$): δ = 0.06 (s, 6 H, $SiCH_3$), 0.91 (s, 9 H, *t*Bu), 1.40 (br. s, 2 H, NH_2), 2.45 (dd, J = 13.5, 8.4 Hz, 1 H, CH_2Ar), 2.73 (dd, J = 13.5, 5.4 Hz, 1 H, CH_2Ar), 3.05 (m, 1 H, CH), 3.43 (dd, J = 9.7, 6.5 Hz, 1 H, CH_2O), 3.57 (dd, J = 9.7, 4.4 Hz, 1 H, CH_2O), 3.80 (s, 3 H, OCH_3), 6.85 (d, J = 8.6 Hz, 2 H, *m*-Ar), 7.12 (d, J = 8.6 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5 (CH_3Si), 18.1 (CSi), 25.7 (CH_3), 39.3 (CH_2Ar), 54.3 (CH), 55.0 (CH_3O), 67.3 (CH_2O), 113.6 (*m*-Ar), 130.0 (*o*-Ar), 131.0 (*ipso*-Ar), 157.8 (*p*-Ar) ppm.

(*S*)-3-[(4-Methoxyphenyl)methyl]-1,4-oxazaspiro[4.5]decan-8-one Ethylene Acetal (6): To a solution of 1,4-cyclohexanedione monoethylene acetal (0.86 g, 5.5 mmol) in CH_2Cl_2 (6 mL) were added amino alcohol **5a** (1 g, 5.5 mmol) and 4 Å molecular sieves (2 g). After stirring at room temp. for 2 h, the suspension was filtered through Celite, and the filtrate was concentrated to give **6** (1.8 g, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.90 (m, 9 H), 2.63 (dd, J = 13.6, 7.7 Hz, 1 H, CH_2Ar), 2.93 (dd, J = 13.6, 5.9 Hz, 1 H, CH_2Ar), 3.38 (t, J = 7.8 Hz, 1 H, 2-H), 3.61 (dddd, J = 7.8, 7.7, 6.5, 5.9 Hz, 1 H, 3-H), 3.79 (s, 3 H, OMe), 3.84 (dd, J = 7.8, 6.5 Hz, 1 H, 2-H), 3.94 (s, 4 H, OCH_2), 6.84 (d, J = 8.6 Hz, 2 H, *m*-Ar), 7.12 (d, J = 8.6 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8, 31.9, 32.2, 34.6, 38.7, 55.1, 58.8, 64.1, 69.7, 95.1, 108.3, 113.8, 129.7, 130.1, 158.1 ppm. $C_{18}H_{25}NO_4 \cdot 1/2H_2O$ (328.49): calcd. C 65.83, H 7.98 N 4.27; found C 65.93, H 8.04, N 4.09.

(*S*)-4-Allyl-4-(1-[(*tert*-butyldimethylsilyl)oxymethyl]-2-(4-methoxyphenyl)ethylaminocyclohexanone Ethyelene Acetal (8): Following the above procedure for the preparation of **1** with the use of 1,4-cyclohexanedione monoethylene acetal (1 g, 6.4 mmol) and (*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)-2-propylamine (**5**, 2.5 g, 8.3 mmol), corresponding imine **7** was formed. After treatment with allylmagnesium bromide (1 M in Et_2O, 12.8 mL, 12.8 mmol), the crude product was purified by chromatography (CH_2Cl_2/MeOH, 99.5:0.5) to afford **8** (2.2 g, 72%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, CH_3Si), 0.91 (s, 9 H, *t*Bu), 1.30 (br. s, 1 H, NH), 1.40–1.60 (m, 6 H), 1.65 (m, 1 H), 1.75 (m, 1 H), 2.16 (m, 2 H, CH_2CH), 2.64 (dd, J = 13.5, 5.8 Hz, 1 H, CH_2Ar), 2.76 (dd, J = 13.5, 7.1 Hz, 1 H, CH_2Ar), 2.90 (m, 1 H, CHN), 3.31 (dd, J = 9.8, 5.9 Hz, 1 H, CH_2O), 3.45 (dd, J = 9.8, 4.4 Hz, 1 H, CH_2O), 3.79 (s, 3 H, CH_3O), 3.92 (s, 4 H, OCH_2), 5.02 (dd, J = 16.0, 2.2 Hz, 1 H, *cis*-H), 5.03 (dd, J = 10.2, 2.2 Hz, 1 H, *trans*-H), 5.80 (m, 1 H, *gem*-H), 6.82 (d, J = 8.6 Hz, 2 H, *m*-Ar), 7.10 (d, J = 8.6 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 (CH_3Si), 18.2 (CMe_3), 25.9 (CH_3), 30.5 and 30.6 (C-3 and C-5), 33.1 (C-2 and C-6), 39.4 (CH_2Ar), 42.7 (CH_2CH), 53.6 (C-4), 53.8 (CHN), 55.2 (CH_3O), 64.1 (OCH_2CH_2O), 65.5 (CH_2O), 108.8 (C-1), 113.6 (*m*-Ar), 117.3 (=CH_2), 130.4 (*o*-Ar), 131.7 (*ipso*-Ar), 134.8 (=CH), 157.9 (*p*-Ar) ppm. $C_{27}H_{45}NO_4Si$ (475.72): calcd. C 68.17, H 9.53, N 2.94; found C 68.08, H 9.74, N 2.93.

(*S*)-4-Allyl-4-[1-(hydroxymethyl)-2-(4-methoxyphenyl)ethylamino]-cyclohexanone Ethylene Acetal (9): To a solution of ether **8** (2 g, 4.2 mmol) in THF (10 mL) was added a solution of TBAF (1 M in THF, 12.6 mL, 12.6 mmol). After stirring for 1 h at room temp., the reaction was quenched with water and extracted with EtOAc. The dried organic extract was concentrated and purified by chromatography (CH_2Cl_2/MeOH, 100:0 to 97:3) to afford alcohol **9** (1.27 g, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35–1.75 (m, 8 H), 2.20 (m, 2 H, CH_2CH), 2.65 (dd, J = 13.5, 8.3 Hz, 1 H, CH_2Ar), 2.71 (dd, J = 13.5, 6.2 Hz, 1 H, CH_2Ar), 3.02 (m, 1 H, CHN), 3.23 (dd, J = 10.5, 3.3 Hz, 1 H, CH_2O), 3.37 (dd, J = 10.5, 4.1 Hz, 1 H, CH_2O), 3.79 (s, 3 H, OCH_3), 3.92 (s, 4 H, OCH_2), 5.07 (dm, J = 16.5 Hz, 1 H, *cis*-H), 5.09 (dm, J = 10.7 Hz, 1 H, *trans*-H), 5.71 (ddt, J = 16.5, 10.7, 7.3 Hz, 1 H, *gem*-H), 6.84 (d, J = 8.7 Hz, 2 H, *m*-Ar), 7.10 (d, J = 8.7 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.5 and 30.7 (C-3 and C-5), 32.4 and 33.3 (C-2 and C-6), 39.6 (CH_2Ar), 41.8 (CH_2CH), 52.9 (CHN), 54.0 (C-4), 55.1 (CH_3O), 63.2 (CH_2O), 64.0 (OCH_2), 108.4 (C-1), 113.8 (*m*-Ar), 118.1 (=CH_2), 130.2 (*o*-Ar), 130.6 (*ipso*-Ar), 133.9 (=CH), 158.1 (*p*-Ar) ppm. $C_{21}H_{31}NO_4$ (361.46): calcd. C 69.78, H 8.64, N 3.87; found C 69.50, H 8.81, N 3.83.

7-Iodo-3-[(4-methoxyphenyl)methyl]-2,3,4,5,6,7,7a-hexahydropyrrolo[2,1-b]oxazol-5-spirocyclohexanon-4-one Ethylene Acetal (10): Iodine (1.18 g, 4.6 mmol) in CH_2Cl_2 (50 mL) was slowly added to a solution of homoallylamine **9** (0.82 g, 2.27 mmol) in CH_2Cl_2 (30 mL) and 5% aqueous $NaHCO_3$ solution (30 mL). The mixture was stirred at room temp. overnight. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The dried organic extracts were concentrated and purified by chromatography (Al_2O_3, hexane/EtOAc, 8:2) to yield **10** (0.68 g, 62%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.80 (m, 8 H), 2.15 (dd, J = 12.7, 10.7 Hz, 1 H, 6-H), 2.52 (dd, J = 13.6, 7.4 Hz, 1 H, CH_2Ar), 2.71 (dd, J = 13.6, 7.5 Hz, 1 H, CH_2Ar), 2.80 (dd, J = 12.7, 7.5 Hz, 1 H, 6-H), 3.45–3.60 (m, 1 H, 3-H), 3.47 (dd, J = 7.5, 3.4 Hz, 1 H, CH_2O), 3.69 (dd, J = 7.5, 6.6 Hz, 1 H, CH_2O), 3.79 (s, 3 H, CH_3O), 3.89 (s, 4 H, OCH_2), 4.12 (ddd, J = 10.7, 7.7, 2.8 Hz, 1 H, CHI), 5.31 (d, J = 2.8 Hz, 1 H, CHNO), 6.82 (d, J = 8.7 Hz, 2 H, *m*-Ar), 7.12 (d, J = 8.7 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (CHI), 27.6 (C-2′), 32.7 (C-3′), 32.9 (C-5′), 36.0 (C-6′), 40.6 (CH_2Ar), 48.2 (C-6), 55.2 (CH_3O), 58.0 (C-3), 64.2 i 64.3 (OCH_2CH_2O), 64.7 (C-5), 70.7 (C-2), 105.6 (C-7a), 107.7 (C-4′), 113.6 (*m*-Ar), 130.5 (*o*-Ar), 130.9 (*ipso*-Ar), 158.1 (*p*-Ar) ppm. MS (CI): *m*/*z* (%) = 486 (23) $[M + 1]^+$, 374 (100).

(3*S*)-1-[(1*S*)-1-Hydroxymethyl-2-(4-methoxyphenyl)ethyl]3-iodo-1-azaspiro[4.5]decan-8-one Ethylene Acetal (11): $NaBH_4$ (56 mg, 1.5 mmol) was added to a solution of oxazolidine **10** (240 mg, 0.50 mmol) in MeOH (12 mL), and the reaction mixture was stirred at room temp. for 2 h. After quenching with H_2O (20 mL), the solution was extracted with EtOAc (3 × 30 mL). The dried organic extracts furnished **11** (223 mg, 93%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.43–1.99 (m, 8 H), 2.18 (dd, J = 14.0, 8.1 Hz, 1 H, 4-H), 2.40–2.68 (m, 3 H, 4-H and CH_2Ar), 2.91 (m, 1 H, CHN), 3.12–3.39 (m, 4 H, 2-H and CH_2O), 3.79 (s, 3 H, OCH_3), 3.94 (m, 4 H, OCH_2), 4.32 (m, 1 H, 3-H), 6.83 (d, J = 8.6 Hz, *m*-Ar), 7.07 (d, J = 8.6 Hz, *o*-Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7 (C-3), 31.5 and 32.0 (C-6 and C-10), 33.0 and 34.8 (C-7 and C-9), 36.3 (CH_2Ar), 48.0 (C-4), 54.1 (C-2), 55.2 (OCH_3), 56.1 (CHN), 60.5 (CH_2OH), 63.5 (C-5), 64.1 and 64.3 (OCH_2), 108.0 (C-8), 113.8 (*m*-Ar), 129.6 (*o*-Ar), 130.5 (*ipso*-Ar), 158.0 (*p*-Ar) ppm. MS (EI): *m*/*z* (%) = 456 (3), 366 (44), 360 (3), 238 (83), 121 (100), 101 (27), 99 (25), 91 (38).

1-[(1*S*)-1-(Hydroxymethyl)-2-(4-methoxyphenyl)ethyl]-1-azaspiro-[4.5]decan-8-one (12): To a solution of iodide **11** (88 mg, 0.18 mmol) in benzene (3 mL) were added AIBN (2 mg, 0.01 mmol) and Bu_3SnH (0.1 mL, 0.38 mmol). The reaction mixture was heated at reflux for 2 h, cooled, and concentrated. The residue was purified by chromatography (SiO_2, CH_2Cl_2/MeOH, 100:0 to 96:4), to give **12** (46 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$, COSY, HSQC): δ = 1.60–1.94 (m, 12 H), 2.53 (m, 1 H, CH_2Ar), 2.89 (m, 3 H, CH_2Ar and 2-H), 3.22 (m, 2 H, CHN and CH_2O), 3.36 (m, 1 H, CH_2O), 3.79 (s, 3 H, OCH_3), 3.95 (m, 4 H, OCH_2), 6.84 (d, J = 8.6 Hz, 2 H, *m*-Ar), 7.09 (d, J = 8.6 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.1 (C-3), 30.0 (C-6 and C-10), 32.4 and 33.0 (C-7 and C-9), 34.2 (C-4), 35.9 (CH_2Ar), 43.3 (C-2), 55.2 (OCH_3), 56.8 (CHN), 60.3 (CH_2OH), 64.2 and 64.3 (OCH_2), 108.8 (C-8), 113.9 (*m*-Ar), 129.8 (*o*-Ar), 130.6 (*ipso*-Ar), 158.1 (*p*-Ar) ppm. MS (EI): *m*/*z* (%) = 362 (1), 330 (8), 241 (15), 240 (100), 135 (14), 121 (29), 74 (13), 55 (14). $C_{21}H_{31}NO_4$ (361.46): calcd. C 69.77, H 6.45, N 3.07; found C 69.39, H 6.67, N 2.99.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)but-3-yn-2-amine (14): Dimethyl 1-diazo-2-oxopropylphosphonate (2.66 g, 13.8 mmol) in MeOH (20 mL) and K_2CO_3 (2.55 g, 18.4 mmol) were added in sequence to a solution of aldehyde **13** (2.57 g, 9.2 mmol) in MeOH (20 mL) at 0 °C. The reaction mixture was stirred at room temp. overnight, then quenched with saturated aqueous NH_4Cl solution (50 mL), and extracted with CH_2Cl_2 (5 × 50 mL). The dried organic extracts were concentrated and purified by chromatography (SiO_2, CH_2Cl_2) to give **14** (1.87 g, 74%) as a yellowish solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 2.35 (s, 1 H, ≡CH), 2.94 (m, 2 H, 4-H), 3.81 (s, 3 H, OCH_3), 4.68 (m, 1 H, 3-H), 5.07 (m, 1 H, NH), 6.89 (d, J = 8.4 Hz, 2 H, *m*-Ar), 7.24 (d, J = 8.4 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0 [$C(CH_3)_3$], 40.5 (C-4), 43.7 (C-3), 54.8 (OCH_3), 71.9 (≡CH), 79.5 [$C(CH_3)_3$], 82.7 (C-2), 113.4 (*m*-Ar), 128.1 (*ipso*-Ar), 130.4 (*o*-Ar), 154.3 (NHCO), 158.2 (*p*-Ar) ppm. HRMS: calcd. for $C_{16}H_{21}NO_3$ 275.3505; found 275.3521.

(2*S*)-3-Bromo-1-(4-methoxyphenyl)but-3-en-2-amine (15): Hydrogen bromide gas (900 mg, 11.1 mmol) was bubbled through a solution of Et_4NBr (840 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. A solution of amine **14** (1 g, 3.6 mmol) in CH_2Cl_2 (5 mL) was added, and

the reaction mixture was stirred for 24 h, basified with aqueous 1 N NaOH solution, and extracted with $CHCl_3$ (4 × 100 mL). The dried organic extracts were concentrated and purified by chromatography (SiO_2, CH_2Cl_2/MeOH, 100:0 to 99.5:0.5) to yield vinyl bromide **15** (420 mg, 45%) and its regioisomer **15′** –not shown –(159 mg, 17%). **15**: $[\alpha]_D$ = + 38.9 (*c* = 0.59, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.65 (s, 2 H, NH_2), 2.71 and 2.86 (2dd, *J* = 13.5, 6.8 Hz, 1 H each, CH_2), 3.55 (t, *J* = 6.8 Hz, 1 H, CH), 3.78 (s, 3 H, OMe), 5.41 (d, *J* = 1.8 Hz, 1 H, =CH_2), 5.61 (d, *J* = 1.8 Hz, 1 H, =CH_2), 6.83 (d, *J* = 8.7 Hz, 2 H, *m*-Ar), 7.13 (d, *J* = 8.7 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 41.0 (CH_2), 55.1 (OMe), 60.9 (CH), 113.7 (*m*-Ar), 116.4 (=CH_2), 129.8 (*ipso*-Ar), 130.2 (*o*-Ar), 139.9 (=CBr), 158.1 (*p*-Ar) ppm. IR (NaCl): $\tilde{\nu}$ = 3374, 1612, 1512, 1247 cm^{-1}. HRMS: calcd. for $C_{11}H_{14}BrNO$ 256.1452; found 256.1460. (*Z*)-(2*S*)-4-Bromo-1-(4-methoxyphenyl)but-3-en-2-amine (**15′**). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 2 H, NH_2), 2.62 (dd, *J* = 13.5, 8.1 Hz, 1 H, CH_2), 2.82 (dd, *J* = 13.5, 5.1 Hz, 1 H, CH_2), 3.79 (s, 3 H, OMe), 4.06 (ddd, *J* = 8.1, 7.8, 5.1 Hz, 1 H, CH), 6.08 (dd, *J* = 7.8, 6.9 Hz, 1 H, CH=), 6.19 (dd, *J* = 6.9, 0.9 Hz, 1 H, =CHBr), 6.85 (d, *J* = 8.4 Hz, 2 H, *m*-Ar), 7.16 (d, *J* = 8.4 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 41.7 (CH_2), 52.5 (CH), 55.2 (OCH_3), 107.6 (=CHBr), 113.8 (*m*-Ar), 129.8 (*ipso*-Ar), 130.3 (*o*-Ar), 138.6 (CH=), 158.2 (*p*-Ar) ppm.

4-Allyl-4-{*N*-[(*S*)-3-bromo-1-(4-methoxyphenyl)but-3-en-2-yl]-amino}cyclohexanone Ethylene Acetal (17): To a solution of amine **15** (100 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) were added molecular sieves 4 Å (600 mg) and 1,4-cyclohexanedione monoethylene acetal (51 mg, 0.33 mmol). The reaction mixture was heated at reflux, stirred for 4 h, and then filtered through Celite to give a solution of crude imine **16**. To this solution was added allylmagnesium bromide (1 M in Et_2O, 0.36 mL, 0.36 mmol), and the reaction mixture was stirred at room temp. for 4 h, quenched with saturated NH_4Cl aqueous solution (15 mL), and extracted with CH_2Cl_2 (4 × 15 mL). The dried organic extracts were concentrated and purified by chromatography (SiO_2, CH_2Cl_2) to give **17** (106 mg, 75%). $[\alpha]_D$ = + 17.5 (*c* = 0.23, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 1 H, NH), 1.38–1.70 (m, 7 H), 1.77–1.86 (m, 1 H), 2.16 (d, *J* = 7.2 Hz, 2 H, CH_2C=), 2.66 (dd, *J* = 13.5, 6.3 Hz, 1 H, CH_2Ar), 2.77 (dd, *J* = 13.5, 7.5 Hz, 1 H, CH_2Ar), 3.42 (dd, *J* = 7.5, 6.3 Hz, 1 H, CHN), 3.78 (s, 3 H, OMe), 3.90 (s, 4 H, OCH_2), 5.01 (dm, *J* = 18.9 Hz, 1 H, *cis*-H), 5.03 (dm, *J* = 9.3 Hz, 1 H, *trans*-H), 5.35 and 5.53 (2d, *J* = 1.7 Hz, 1 H each, CBr=CH_2), 5.64–5.78 (m, 1 H, *gem*-H), 6.81 (d, *J* = 8.7 Hz, 2 H, *m*-Ar), 7.09 (d, *J* = 8.7 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3 and 30.7 (C-3 and C-5), 32.9 and 33.1 (C-2 and C-6), 42.1 and 42.8 (CH_2C = and CH_2Ar), 54.3 (C-4), 55.2 (OCH_3), 61.2 (CHN), 64.1 (OCH_2), 108.7 (C-1), 113.6 (*m*-Ar), 116.9 (=CH_2), 117.4 (=CH_2), 130.1 (*ipso*-Ar), 130.3 (*o*-Ar), 134.6 (=CH), 141.8 (=CBr), 158.1 (*p*-Ar) ppm. HRMS: calcd. for $C_{22}H_{30}BrN_2O$ 435.1409; found 435.1418.

1-[(*S*)-3-Bromo-1-(4-methoxyphenyl)but-3-en-2-yl]-3-iodo-1-aza-spiro[4.5]decan-8-one Ethylene Acetal (18): A solution of I_2 (252 mg, 0.99 mmol) in CH_2Cl_2 (7.5 mL) was added dropwise to a solution of amine **17** (289 mg, 0.66 mmol) in CH_2Cl_2 (2.5 mL) and 5% aqueous $NaHCO_3$ (7.5 mL). After stirring for 2 h at room temp., 10% aqueous $Na_2S_2O_3$ (20 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), and the organic extracts were concentrated to give a diastereomeric mixture of iodides **18**, which was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC): δ = 1.43–1.61 (m, 3 H), 1.76 (m, 4 H), 1.99 (m, 1 H), 2.05 (m, 1 H, 4-H), 2.50 (m, 1 H, 4-H), 2.85 (dd, *J* = 14.0, 3.6 Hz, 1 H, CH_2Ar), 3.04 (dd, *J* = 14.0, 8.8 Hz, 1 H, CH_2Ar), 3.28 (dd, *J* = 10.2, 3.2 Hz, 1 H, 2-H), 3.52 (dd, *J* = 8.8, 3.2 Hz, 1 H, 2-H), 3.78 (s, 3 H, OCH_3), 3.80 (masked, 1 H, NCH), 3.94 (m, 4 H, CH_2O), 4.16 (m, 1 H, 3-H), 5.40 (d, *J* = 1.4 Hz, 1 H, =CH_2), 5.58 (d, *J* = 1.4 Hz, 1 H, =CH_2), 6.79 (dm, *J* = 8.8 Hz, 2 H, *m*-Ar), 7.11 (dm, *J* = 8.8 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (C-3), 31.6, 31.9, 32.3, 33.3 (CH_2), 38.8 (CH_2Ar), 47.9 (C-4), 55.4 (OCH_3), 56.7 (C-2), 61.0 (C-5), 62.4 (NCH), 64.5 (CH_2O), 107.9 (C-8), 113.7 (*m*-Ar), 117.5 (=CH_2), 130.2 (*o*-Ar), 130.8 (*ipso*-Ar), 138.4 (C=), 157.9 (*p*-Ar) ppm.

1-[(*S*)-3-Bromo-1-(4-methoxyphenyl)but-3-en-2-yl]-3-azido-1-aza-spiro[4.5]decan-8-one Ethylene Acetal (19): NaN_3 (86 mg, 1.32 mmol) was added to a solution of the diastereomeric mixture of iodides **18** (0.66 mmol) in DMF (15 mL) The mixture was stirred at 50 °C for 3 h, the solvent was evaporated, and the crude product was purified by chromatography (SiO_2, CH_2Cl_2) to afford azide **19** (184 mg, 58% from **17**) as a diastereomeric mixture. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (dm, *J* = 12.2 Hz, 1 H), 1.41 (ddd, *J* = 12.6, 6.3, 3.0 Hz, 1 H), 1.51–1.62 (m), 1.66–1.87 (m), 2.06 (dd, *J* = 13.5, 7.5 Hz, 1 H), 2.14 (dd, *J* = 13.5, 7.5 Hz, 1 H), 2.76 (dd, *J* = 13.5, 6.6 Hz, 1 H), 2.82 (dd, *J* = 13.5, 5.7 Hz, 1 H), 2.99 (dd, *J* = 13.8, 8.7 Hz, 1 H), 3.02 (dd, *J* = 14.1, 9.0 Hz, 1 H), 3.12 (dd, *J* = 9.6, 5.1 Hz, 1 H), 3.34 (dd, *J* = 9.6, 4.2 Hz, 1 H), 3.40 (dd, *J* = 9.6, 5.7 Hz, 1 H), 3.59 (dd, *J* = 9.6, 6.0 Hz, 1 H), 3.78 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.79 [m, 2 H, N(1)CH], 3.92 (m, 8 H, CH_2O), 3.93 (m, 2 H, 3-H), 5.39 (d, *J* = 1.8 Hz, 1 H, =CH_2), 5.42 (d, *J* = 1.8 Hz, 1 H, =CH_2), 5.51 (d, *J* = 1.8 Hz, 1 H, =CH_2), 5.65 (d, *J* = 1.8 Hz, 1 H, =CH_2), 6.81 (dm, *J* = 8.1 Hz, 2 H, *m*-Ar), 6.82 (dm, *J* = 8.4 Hz, 2 H, *m*-Ar), 7.11 (dm, *J* = 8.1 Hz, 2 H, *o*-Ar), 7.14 (dm, *J* = 8.4 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9 (CH_2), 31.2 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 37.6 and 38.0 (CH_2Ar), 40.5 (C-4), 50.7 (C-2), 55.2 (OCH_3), 58.0 and 58.1 (C-3), 62.6, 62.7 and 62.8 [C-5 and N(1)CH], 64.3 (CH_2O), 107.9 (C-8), 113.5 (*m*-Ar), 117.6 and 117.8 (=CH_2), 130.0 and 130.1 (*o*-Ar), 130.7 and 130.8 (*ipso*-Ar), 138.0 (C=), 157.9 (*p*-Ar) ppm.

1-[(*S*)-3-Bromo-1-(4-methoxyphenyl)but-3-en-2-yl]-3-amino-1-aza-spiro[4.5]decan-8-one Ethylene Acetal (20): Triphenylphosphane (23 mg, 0.09 mmol) was added to the diastereomeric mixture of azides **19** (14 mg, 0.03 mmol) in THF (2 mL), and the reaction mixture was stirred at room temp. for 24 h. H_2O (0.1 mL) was added and the stirring was maintained for 3 d. The reaction mixture was extracted with 1 N HCl (2 × 5 mL), and the aqueous phase was basified with K_2CO_3 and extracted with CH_2Cl_2 (4 × 10 mL). The dried organic extracts were concentrated and purified by chromatography (SiO_2, CH_2Cl_2/MeOH, 1:0 to 8:2) to yield a mixture of primary amines **20**, from which one diastereomer was isolated in a pure form after an additional chromatographic process. **20a**: $[\alpha]_D$ = + 12.3 (*c* = 0.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC, NOESY): δ = 1.08 (dm, *J* = 12.2 Hz, 1 H), 1.40 (m, 2 H), 1.57 (m 1 H), 1.68 (m, 3 H), 1.78 (m, 2 H), 2.15 (dd, *J* = 13.0, 7.4 Hz, 1 H, 4-H), 2.84 (dd, *J* = 14.0, 6.8 Hz, 1 H, CH_2Ar), 2.87 (m, 1 H, 2-H), 3.00 (dd, *J* = 14.0, 7.6 Hz, 1 H, CH_2Ar), 3.39 (m, 1 H, 3-H), 3.46 (dd, *J* = 8.4, 5.6 Hz, 1 H, 2-H), 3.78 (s, 3 H, OCH_3), 3.80 [m, 1 H, N(1)CH], 3.91 (m, 4 H, OCH_2), 5.42 (d, *J* = 1.8 Hz, 1 H, =CH_2), 5.59 (d, *J* = 1.8 Hz, 1 H, =CH_2), 6.82 (dm, *J* = 8.4 Hz, 2 H, *m*-Ar), 7.15 (dm, *J* = 8.4 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.5 (CH_2), 32.7 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 38.1 (CH_2Ar), 44.7 (C-4), 49.3 (C-3), 54.2 (C-2), 55.2 (OCH_3), 62.6 and 62.7 (C-5 and N(1)CH), 64.3 (CH_2O), 108.1 (C-8), 113.6 (*m*-Ar), 117.5 (=CH_2), 130.1 (*o*-Ar), 131.1 (*ipso*-Ar), 138.8 (C=), 158.0 (*ipso*-Ar) ppm. HRMS: calcd. for $C_{22}H_{31}BrN_2O_3$ 451.4071; found 451.4058. **20b** (from a mixture): ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC, NOESY): δ = 1.20 (m, 1 H), 1.48 (m, 1 H), 1.60 (m, 1 H, 4-H), 1.66 (m), 1.92 (td, *J* = 13.6, 4.0 Hz, 1 H), 2.14 (dd, *J* = 12.8, 7.6 Hz, 1 H, 4-H), 2.41 (br. s, 2

H, NH_2), 2.81 (dd, J = 14.0, 5.6 Hz, 1 H, CH_2Ar), 2.92 (dd, J = 14.0, 9.2 Hz, 1 H, CH_2Ar), 3.09 (dd, J = 8.8, 3.6 Hz, 1 H, 2-H), 3.26 (dd, J = 8.8, 5.2 Hz, 1 H, 2-H), 3.36 (m, 1 H, 3-H), 3.76 [m, 1 H, N(1)CH], 3.79 (s, 3 H, OCH_3), 3.92 (m, 4 H, OCH_2), 5.36 (d, J = 2.0 Hz, 1 H, $=CH_2$), 5.52 (d, J = 2.0 Hz, 1 H, $=CH_2$), 6.81 (dm, J = 8.6 Hz, 2 H, *m*-Ar), 7.11 (dm, J = 8.6 Hz, 2 H, *o*-Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.2 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 35.1 (CH_2), 37.5 (CH_2Ar), 44.6 (C-4), 49.5 (C-3), 54.0 (C-2), 55.4 (OCH_3), 62.7 [C-5 and N(1)CH], 64.5 (CH_2O), 108.3 (C-8), 113.8 (*m*-Ar), 117.5 ($=CH_2$), 130.3 (*o*-Ar), 131.1 (*ipso*-Ar), 139.0 (C=), 158.2 (*ipso*-Ar) ppm.

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[27] For related studies about 5-*endo*-*trig* cyclizations of homoallylic amines in the field of FR901483 synthesis, see ref.[12]

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