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Synthesis of enantiopure 3-amino-1-azaspiro[4.5]decan-8-ones by halonium promoted cyclization of amino-tethered cyclohexenes

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Abstract—Haloaminocyclization reactions of polysubstituted γ-aminocyclohexenes give 3-amino-1-azaspiro[4.5]decan-8-one derivatives. The stereocontrol, chemoselectivity (*N*-attack vs *O*-attack), and influence of the halonium ion are discussed.

1. Introduction

The 1-azaspiro[4.5]decane framework is found in some natural products isolated in the last decade.[1–5] Among these the immunosupressant FR901483[1] and the antimuscarinic TAN1251 derivatives[2] incorporate an oxygenated function at C-8 (Fig. 1). For this reason, there has been a growing interest over the last few years in the development of synthetic methodologies to achieve enantiopure 3-amino-1-azaspiro-[4.5]decan-8-ones, which can be envisaged as advanced building blocks for the synthesis of the aforementioned natural compounds, since they incorporate two of their rings and possess suitable functionalities for assembling the rest of the skeleton.

Several procedures have been described for the preparation of enantiopure compounds with the target framework I (Scheme 1), but, apart from the pioneering work of Snider,[6] in which the key step consists of an intramolecular nitrone/alkene cycloaddition, followed by reduction of the labile

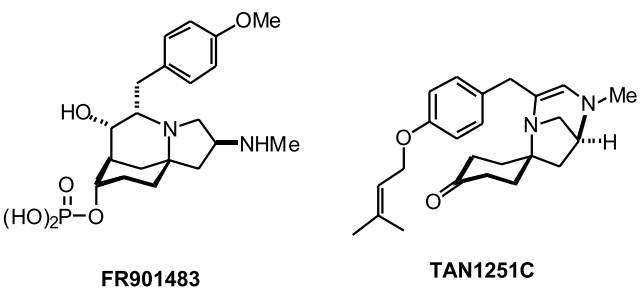
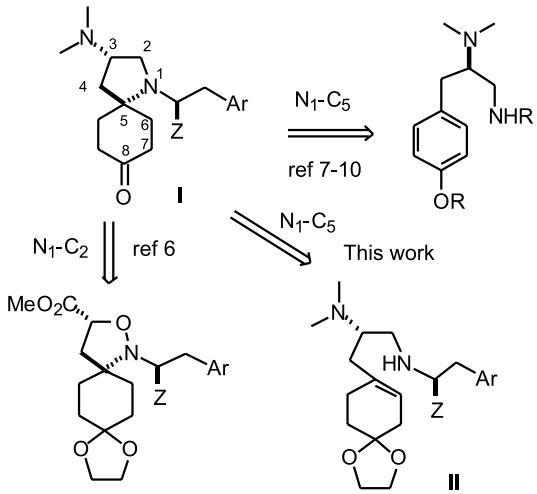


Figure 1.



Scheme 1. Synthesis of enantiopure 3-amino-1-azaspiro [4.5]decan-8-ones.

N–O bond and lactamization, all other approaches (Sorensen,[7] Ciufolini,[8] Wardrop,[9] and Honda[10]) are based on the oxidative azaspirocyclization of tyrosine derivatives to give the corresponding 4,4-disubtituted cyclohexadienones, which after hydrogenation give compounds of type **I**.

In this paper, we describe the studies about a new synthetic entry to these azabicyclic compounds, based on the electrophilic addition of halonium ions to cyclohexene compounds (γ-aminoalkenes of type **II**, see Scheme 2) embodying a 2,3-diaminopropyl side chain, in which the nucleophilic ω-nitrogen of the amine can act as a neighboring group to promote a haloaminocyclization and render enantiopure 3-amino-1-azaspiro[4.5]decan-8-ones.[11] The alkyl side chain incorporates an additional nitrogen atom at the β-position, also linked to a stereogenic center, it

Keywords: FR901483; azaspiro compounds; oxazines; nitrogen heterocycles; cyclization.

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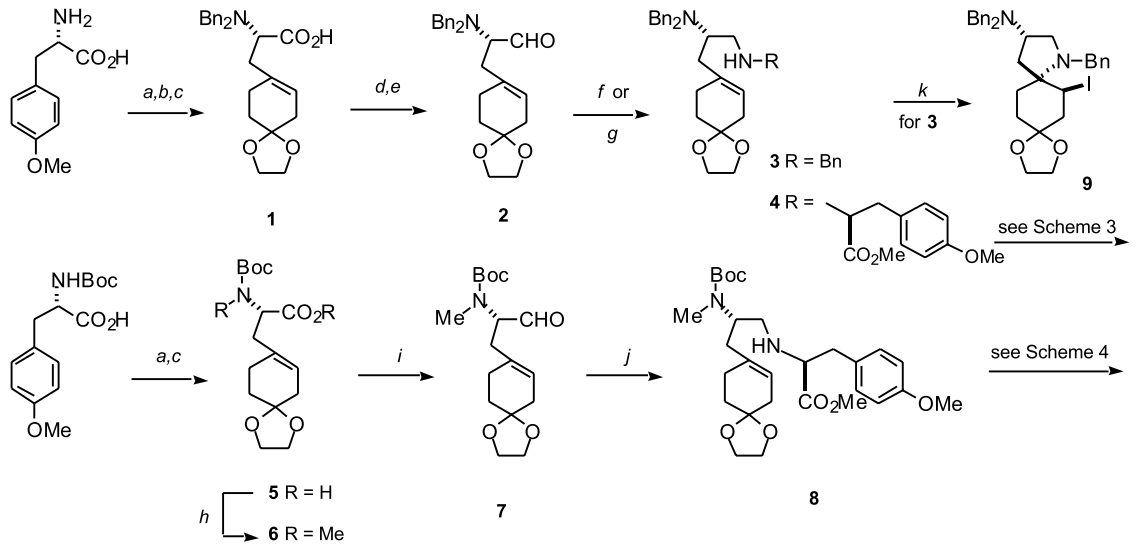


Scheme 2. *Reagents and conditions*: (a) Li, NH_3, EtOH, −78°C; (b) BnBr, K_2CO_3, EtOH, 69%; (c) $(CH_2OH)_2$, $BF_3{\cdot}Et_2O$, THF, 73%; (d) $LiAlH_4$, Et_2O; (e) DMSO, $(COCl)_2$; (f) $BnNH_2$, $MgSO_4$, CH_2Cl_2; then $NaBH_4$, MeOH (78% for three steps); (g) (diOMe)-L-tyrosine, $MgSO_4$, CH_2Cl_2; then $NaBH_4$, MeOH, 80%; (h) MeI, NaH, DMF, 63%; (i) DIBAL-H, toluene, −78°C; (j) as g, 64% for two steps; (k) I_2, $NaHCO_3$, CH_2Cl_2–H_2O, room temperature (19%).

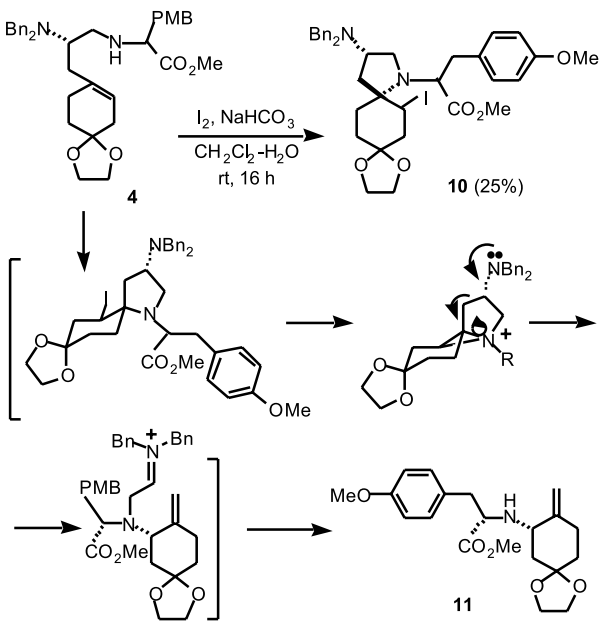
being noteworthy that the two nitrogen atoms come from two different tyrosine units. Although halocyclizations with a nitrogen as an intramolecular nucleophile is a well-known process,[12] amine compounds are scarcely used[13] and there are few precedents for the synthesis of azaspiro derivatives.[14]

2. Results and discussion

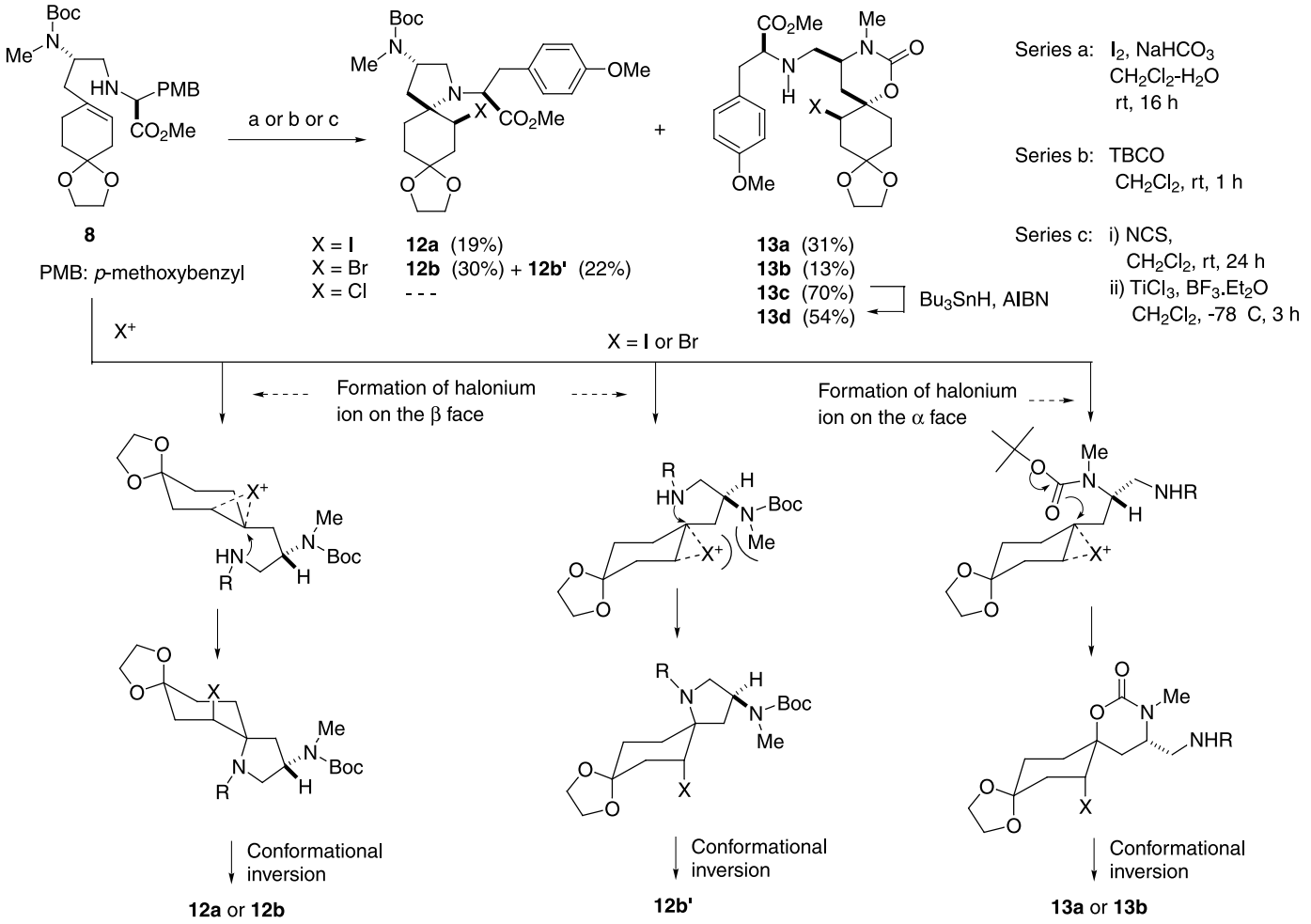
The studies were first carried out using the cyclohexene derivative **3** as a model and then with compounds **4** and **8**, all of which were synthesized from tyrosine derivatives by a Birch reduction to afford the corresponding dihydroanisole, in which the enol ether was converted into the ethylene acetal to avoid the migration of the double bond of the cyclohexene ring formed (Scheme 2). The carboxylic acid of this first unit of tyrosine, in which the amino group had been previously protected either as the dibenzylamino derivative (i.e **1**) or the N(Boc)Me compound (i.e. **5**), was converted to the corresponding aldehyde (compounds **2** and **7**).[15] The preparation of the substrates **3**, **4**, and **8** was concluded with a reductive amination, either with benzylamine to afford **3** or with another tyrosine unit to give compounds **4** and **8**. Having prepared the precursors, we began to study the haloaminocyclization reaction.[16,17]

On reacting with iodine the unsaturated amine **3** afforded the iodo azaspiro derivative **9**, although in low yield, as the result of a 5(N)-*exo-trig* cyclization.[18] The process involves the formation of two new stereocenters: the C(5) spiro center and the C(6) incorporating the halogen atom. The structure of **9** was assigned using a combination of COSY, NOESY, HMQC, and HMBC experiments. The remaining materials formed in this reaction were not identified, making it impossible to discount the formation of other compounds and evaluate any possible diastereoselection in the iodonium ion formation step (see below).

We next directed our attention to the study of the reaction of unsaturated amine **4**, which incorporates a new stereocenter, with iodine. Using the same reaction conditions as above, the azaspiro derivative **10** (25% yield), with the same stereochemistry in C(3) and C(5) as that of the natural products embodying this substructure, was isolated. In this series, the unexpected methylenecyclohexanone **11** was also isolated in some runs (see Scheme 3). The formation of the rearranged compound **11** can be explained by the intramolecular genesis of an aziridinium salt, which is a substrate that undergoes a Grob fragmentation[19] to furnish a compound with a β-aminoiminium salt side chain that is lost after several equilibrium processes[20] to render the secondary amine **11**. The first halo-amination product of this



Scheme 3. Iodine-promoted process upon aminoalkene **4**



Scheme 4. Cyclization processes promoted by halonium ions upon aminoalkene **8**.

Table 1. ^{13}C NMR Chemical shifts of 3-amino-1-azaspiro[4.5]decan-8-ones

	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	NMe	C-2′	CH_2Ar	Other
9[a]	52.0	54.8	33.4	65.3	39.4	46.7	108.8	32.5	21.4	–	64.3/64.6	51.4	[a]
12a[a]	46.8	53.5	34.8	66.2	40.4	46.4	108.3	33.0	24.8	29.2	64.3/64.6	38.1	[b]
12b[a]	47.0	51.7	32.8	66.6	56.3	44.5	108.0	32.8	27.7	28.7	64.4/64.6	37.4	[c]

In ppm relative to TMS. Recorded in $CDCl_3$ at 75.4 MHz. Assignments based on HSQC experiments.
[a] 54.8 $(CH_2Ar)_2$, 128.4/128.6 (*m*-Ar), 128.0/128.1 (*o*-Ar), 126.6/126.7 (*p*-Ar), 139.4/140.3 (*ipso*-Ar).
[b] 28.5, 79.5, 155.8 (NBoc), 51.2, 171.8 (CO_2Me), 59.0 (CH), 55.2, 113.8, 129.7, 130.1, 158.2 (4-$OMeC_6H_4$).
[c] 28.5, 79.5, 155.8 (NBoc), 51.2, 173.7 (CO_2Me), 58.9 (CH), 55.2, 113.7, 129.9, 130.1, 158.1 (4-$OMeC_6H_4$).

latter process is a diastereomer of **10**, indicating that the initial electrophilic attack upon alkene **4** is not stereoselective.

To avoid the unwanted neighboring of the N–C(4) we changed the protecting group of the nitrogen bonded to this carbon from NBn_2 to N(Boc)Me. Treatment of cyclohexene **8** with iodine gave azaspiro derivative **12a** together with the oxazinone **13a**, the latter resulting again from an undesired reaction pathway in which the carbamate unit reacts intramolecularly with the halonium ion intermediate[21] (Scheme 4).

Finally, the haloaminocyclization from **8** was carried out using 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) as a source of bromonium ions.[22] In this case the cyclization product was formed in 52% yield as a mixture of diastereoisomers (**12b**, **12b′**), the oxazinone **13b** being formed only in 13%. Additionally, we attempted the cyclization through the *N*-chloroamine corresponding to amine **8**. When treated with $TiCl_3$ and BF_3Et_2O it gaves exclusively the oxazinone **13c** in 70% yield, which was characterized after a reductive step (Bu_3SnH, AIBN) that gave **13d**. The formation of **13c** implies an ionic mechanism instead of the desired radical process involving an *N*-aminyl species.[23]

The fact that the aforementioned halonium promoted processes differ according to the facial diastereoselection of the halonium attack upon the cyclohexene ring can be explained as follows. When the formation of the cyclic halonium intermediate occurs on the β face, the transition state associated with the nitrogen attack upon this intermediate is favored, while when the cyclic halonium ion is formed on the α face the aminocyclization is disfavored for steric reasons, and hence the attack of the oxygen atom of the carbamate unit is now the preferred process, as depicted in Scheme 4. In the reaction promoted by the bromonium species, smaller than the iodonium species, the process of azaspirocyclization leading to **12b′** compites with that of oxacyclization leading to **13b**. In all cases the cleavage of the cyclic halonium ions takes place via a transition state in which the nucleophile approaches the carbon from the side opposite to the bond that is to be broken and *trans* stereoisomers are exclusively formed. Although these processes are not diastereoselective, it is true that in the bromo derivative series, if the halogen was removed, compounds **12b** (5*R* configuration) and **12b′** (5*S*) are precursors of the same azaspiro compound in which carbon C-5 is not a stereogenic atom.

The NMR chemical shifts of synthesized bicyclic compounds (for ^{13}C NMR data, see Tables 1 and 2) allows the assignment of their constitution, the absolute configuration of either azaspirodecanes or oxazinones being established from the NOESY data taking into account the known *S* configuration of the other stereogenic centers. Compounds of oxazinone type (**13**) show NMR data[24] similar to that of the corresponding azaspiroderivatives (**9**, **10**, **12**) except in the absence of the methyl signal corresponding to the *N*-Boc, but maintaining a carbonyl group of carbamate type, which is slightly more upfield (δ 153.5), as well as the signal attributable to the stereogenic methine carbon of the reduced unit of tyrosine, which appears at δ 3.35 instead of δ 4.85 for the azaspiro compounds. The signal of the *N*-Me group is diagnostic for compounds **13** (δ_H 2.95 and δ_C 33.0), considering the values in the azaspiro derivatives (δ_H 2.85 and δ_C 29.0).

In summary, we have shown that enantiopure aminoalkene **8** undergoes competitive halonium-promoted cyclizations giving N- or O-cyclised products. From a synthetic standpoint the bromoaminocyclization reaction is of interest since although it furnishes azaspiro compound **12b** as a diastereoisomeric mixture, both diastereomers could be useful as intermediates for the synthesis of TAN1251 derivatives, in which the azaspiro carbon is not a stereogenic center.[25]

Table 2. ^{13}C NMR Chemical shifts of 3-methyl-4-[(3*S*)-3-methoxycarbonyl-4-(4-methoxyphenyl)-2-azabutyl]-1-oxa-3-azaspiro[5.5]undecan-2,9-diones

	C-2	NMe	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	CH_2N	CH	CH_2Ar
13a[a]	153.5	32.8	53.3	29.9	78.3	34.5	44.6	107.4	31.7	28.3	49.2	63.3	39.1
13c[b]	153.5	32.8	53.0	31.2	79.2	61.6	40.9	106.9	29.1	26.4	49.3	63.3	39.1
13d[c]	154.3	33.0	53.5	35.5	76.1	29.8	30.8	108.2	30.0	27.8	49.5	63.5	39.1

In ppm relative to TMS. Recorded in $CDCl_3$ at 75.4 MHz. Assignments based on HSQC experiments.
[a] 51.9, 174.9 (CO_2Me), 55.2, 113.8, 129.3, 130.2, 158.3 (4-$OMeC_6H_4$).64.5/64.8 (OCH_2).
[b] 51.8, 174.8 (CO_2Me), 55.1, 113.7, 129.2, 130.1, 158.2 (4-$OMeC_6H_4$).64.4/64.7 (OCH_2).
[c] 51.8, 174.9 (CO_2Me), 55.2, 113.8, 129.3, 130.2, 158.4 (4-$OMeC_6H_4$).64.2/64.4 (OCH_2).

3. Experimental

3.1. General

For general procedures, see Ref. 11.

3.1.1. (2*S*)-2-(*N*,*N*-Dibenzylamino)-3-(4-oxocyclohex-1-enyl)propanoic acid ethyelene acetal (1). *O*-Methyl-L-tyrosine hydrochloride (12.5 g, 54.2 mmol) was submitted to the Birch reduction, following the previously reported procedure to give lithium (2*S*)-2-amino-3-(4-methoxy-2,5-dihydrophenyl)propanoate.[26] To a solution of the above dihydroanisole in EtOH (200 mL) were added K_2CO_3 (18.7 g, 135.4 mmol) and benzyl bromide (21.9 mL, 184.1 mmol) and the mixture was stirred at reflux temperature for 7 h. The reaction mixture was filtered, the solvent removed, and the residue taken up with CH_2Cl_2 (200 mL). The solution was washed with brine (2×200 mL), dried, and concentrated. The residue was purified by chromatography (SiO_2, CH_2Cl_2 to 8:2 CH_2Cl_2–MeOH) to give (2*S*)-2-dibenzylamino-3-(4-methoxy-2,5-dihydrophenyl)propionic acid (14.1 g, 69%): IR (NaCl) 2830–3029, 1699, 1666, 1605, 1217 cm^{-1}; ^1H NMR (200 MHz) δ 2.44–2.60 (m, 4H), 2.68–2.81 (m, 2H), 3.59 (s, 3H, OCH_3), 3.65 (m, 1H, H-2), 3.71 and 3.88 (2d, *J*=14.8 Hz, 2H each, CH_2Ar), 4.57 (m, 1H, H-3′), 5.48 (m, 1H, H-6′), 7.28–7.36 (m, 10H, Ar); ^{13}C NMR (50 MHz) 28.7 and 29.3 (C-3′, C-6′), 36.0 (C-3), 54.0 (OCH_3), 54.3 (CH_2Ar), 58.9 (C-2), 90.3 (C-5′), 121.0 (C-2′), 127.3 (*p*-Ar), 128.3 (*o*-Ar), 129.0 (*m*-Ar), 131.6 (C-1′), 138.5 (*ipso*-Ar), 152.7 (C-4′), 176.9 (CO_2H).

To a solution of the above enolether (2.0 g, 5.3 mmol) in THF (10 mL) at 0°C were added ethylene glycol (1.18 mL, 21.2 mmol) and $BF_3{\cdot}Et_2O$ (0.13 mL, 1.1 mmol). After stirring overnight, the reaction mixture was poured into cooled saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (5×100 mL). The dried organic extracts were concentrated to give a residue, which was purified by chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2–MeOH 98:2) to afford **1** (1.57 g, 73%) as a solid; ^1H NMR (200 MHz, $CDCl_3$) 1.75 (t, *J*=7 Hz, 2H, H-5′), 1.99 (m, 2H, H-6′), 2.30 (m, 2H, H-3′), 2.59 (d, *J*=7.4 Hz, 2H, H-3), 3.61 (t, *J*=7.4 Hz, 1H, H-2), 3.73 and 3.90 (2d, *J*=13.8 Hz, 2H each, CH_2Ar), 4.03 (m, 4H, CH_2O), 5.44 (m, 1H, H-2′), 7.27–7.39 (m, 10H, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$) 26.5 (C-6′), 31.0 (C-5′), 35.8 (C-3′), 36.4 (C-3), 54.2 (CH_2Ar), 59.1 (C-2), 64.4 (CH_2O), 108.1 (C-4′), 122.0 (C-2′), 127.3 (*p*-Ar), 128.3 (*o*-Ar), 129.1 (*m*-Ar), 133.6 (C-1′), 138.5 (*ipso*-Ar), 177.0 (C-1). Anal. calcd for $C_{25}H_{29}NO_4{\cdot}1/2H_2O$: C 72.09, H 7.26, N 3.36. Found: C 72.16, H 7.09, N 3.41.

3.1.2. (2*S*)-2-(*N*,*N*-Dibenzylamino)-3-(4-oxocyclohex-1-enyl) propanal ethylene acetal (2). To a solution of $LiAlH_4$ (224 mg, 5.9 mmol) in Et_2O (12 mL) at 0°C was added the acid **1** (2.0 g, 4.9 mmol) and the mixture was stirred at room temperature overnight. Successively, H_2O (0.2 mL), 15% aqueous NaOH (0.2 mL) and H_2O (0.7 mL were slowly added at 0°C. The mixture was filtered through Celite, dried and concentrated to give (2*S*)-2-(*N*,*N*-dibenzylamino)-3-(4-oxocyclohex-1-enyl)propanol ethylene acetal (2.0 g), which was used in the next step without purification: ^1H NMR (200 MHz, $CDCl_3$) 1.74 (tm, *J*=6.5 Hz, 2H), 1.90 (dd, *J*=12.3, 9 Hz, 1H), 2.11 (m, 2H), 2.25 (m, 2H), 2.44 (dm, *J*=12.3 Hz, 1H), 2.96 (m, 2H), 3.43 and 3.84 (2d, *J*=14 Hz, 2H each), 3.96 (m, 4H), 5.36 (m, 1H), 7.20–7.36 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 27.4 (C-6′), 31.0 (C-5′), 32.9 (C-3), 35.7 (C-3′), 53.0 (CH_2Ar), 56.8 (C-2), 60.8 (CH_2OH), 64.3 (OCH_2), 107.7 (C-4′), 121.1 (C-2′), 127.1 (*p*-Ar), 128.4 (*o*-Ar), 128.9 (*m*-Ar), 134.3 (C-1′), 139.2 (*ipso*-Ar).

A solution of oxalyl chloride (0.13 mL, 1.5 mmol) and DMSO (0.18 mL, 2.5 mmol) in CH_2Cl_2 (10 mL) cooled at −78°C was stirred for 5 min. A solution of the above alcohol (500 mg, 1.3 mmol) in CH_2Cl_2 (2 mL) was slowly added and, after 30 min at −78°C, triethylamine (0.71 mL, 5.1 mmol) was added and the mixture was allowed to warm to room temperature. The solution was poured into H_2O (10 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The organic extracts were washed with brine (3×50 mL), dried and concentrated to give aldehyde **2** (505 mg), which was used without purification: ^1H NMR (200 MHz, $CDCl_3$) 1.75 (t, *J*=7 Hz, 2H), 2.01 (m, 2H), 2.28 (m, 2H), 2.45 (d, *J*=8 Hz, 2H), 3.41 (t, *J*=8 Hz, 1H), 3.79 (s, 4H), 4.00 (m, 4H), 5.40 (m, 1H), 7.26–7.38 (m, 10H), 9.76 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 27.2 (C-6′), 31.1 (C-5′), 32.3 (C-3), 35.9 (C-3′), 54.4 (C-2), 64.4/64.6 (CH_2O), 107.8 (C-4′), 121.8 (C-2′), 127.2 (*p*-Ar), 128.3 (*o*-Ar), 128.8 (*m*-Ar), 134.0 (C-1′), 139.3 (*ipso*-Ar).

3.1.3. (2*S*)-*N*-Benzyl-2-(*N*,*N*-dibenzylamino)-3-(4-oxocyclohex-1-enyl)propanamine ethyelene acetal (3). To a solution of aldehyde **2** (488 mg, 1.25 mmol) in CH_2Cl_2 (5 mL) at 0°C were added anhydrous $MgSO_4$ (300 mg, 2.50 mmol) and benzaldehyde (0.14 mL, 1.25 mmol). The mixture was stirred at room temperature for 4 h, filtered through Celite, and concentrated to give the crude imine. To a stirred solution of this imine (1.25 mmol) in MeOH (5 mL) was slowly added $NaBH_4$ (94 mg, 2.50 mmol) at 0°C. The mixture was stirred at room temperature for 4 h and quenched by addition of H_2O (15 mL). After removal of MeOH, the aqueous phase was extracted with CH_2Cl_2 (4×15 mL). The dried organic extracts were purified by chromatography (Al_2O_3, 1:1 CH_2Cl_2–hexane), to give **3** (470 mg, 78% from acid **1**): $[\alpha]_D$=+56.2 (*c* 0.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, COSY, HSQC, HMBC): 1.70 (m, 2H, H-5′), 1.91 (dd, *J*=13.6, 12 Hz, 2H, H-3, NH), 2.07 (m, 2H, H-6′), 2.22 (m, 2H, H-3′), 2.44 (d, *J*=13.6 Hz, 1H, H-3), 2.54 (dd, *J*=12.8, 5 Hz, 1H, H-1), 2.67 (dd, *J*=12.8, 9.2 Hz, 1H, H-1), 2.98 (m, 1H, H-2), 3.44 and 3.73 (d, *J*=13.6 Hz, 2H each, CH_2N), 3.47 and 3.62 (2d, *J*=13.5 Hz, 1H each, CH_2NH), 3.95 (m, 4H, CH_2O), 5.29 (m, 1H, H-2′), 7.21–7.28 (m, 15H, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$) 27.5 (C-6′), 31.2 (C-5′), 34.5 (C-3), 35.8 (C-3′), 49.7 (C-1), 53.4 (CH_2N), 53.5 (CH_2NH), 55.2 (C-2), 64.4 (CH_2O), 108.0 (C-4′), 120.8 (C-2′), 126.7/126.9 (*p*-Ar), 128.0/128.2 (*o*-Ar), 128.8 (*m*-Ar), 135.2 (C-1′), 140.1/140.8 (*ipso*-Ar). Anal. calcd for $C_{32}H_{38}N_2O_2{\cdot}1/3H_2O$: C 78.66, H 7.97, N 5.73. Found: C 78.49, H 7.95, N 5.77.

3.1.4. Methyl (2*S*,5*S*)-5-(*N*,*N*-dibenzylamino)-2-(4-methoxyphenyl)methyl-6-(4-oxocyclohex-1-enyl)-3-azahexanoate ethylene acetal (4). Operating as above, from aldehyde **2** (505 mg, 1.3 mmol) and methyl ester of

O-methyl-L-tyrosine (319 mg, 1.5 mmol) in CH_2Cl_2 (3 mL) and after reduction with $NaBH_4$, **4** (592 mg, 80%) was isolated after chromatography (Al_2O_3, CH_2Cl_2): $[\alpha]_D$=+21.8 (*c* 0.21, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, COSY, HSQC, HMBC) 1.62 (m, 2H, H-5′), 1.81 (dd, *J*=13.2, 9.6 Hz, 2H, H-6, NH), 1.93 (m, 2H, H-6′), 2.17 (m, 2H, H-3′), 2.31 (dm, *J*=13.2 Hz, 1H, H-6), 2.40 (dd, *J*=11.8, 8 Hz, 1H, H-4), 2.52 (dd, *J*=11.8, 4.8 Hz, 1H, H-4), 2.74 (dd, *J*=13.6, 8.1 Hz, 1H, CH_2Ar), 2.81 (m, 1H, H-5), 2.87 (dd, *J*=13.6, 5.4 Hz, 1H, CH_2Ar), 3.33 (m, 1H, H-2), 3.37 and 3.56 (2d, *J*=13.2 Hz, 2H each, NCH_2Ar), 3.58 (s, 3H, CO_2CH_3), 3.73 (s, 3H, OCH_3), 3.89 (m, 4H, CH_2O), 5.20 (m, 1H, H-2′), 6.81 (d, *J*=8.8 Hz, 2H, *m*-ArOMe), 7.06 (d, *J*=8.8 Hz, 2H, *o*-ArOMe), 7.09–7.20 (m, 10H, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$) 27.5 (C-6′), 31.2 (C-5′), 35.0 (C-6), 35.8 (C-3′), 38.8 (CH_2Ar), 48.2 (C-4), 51.8 (CO_2CH_3), 53.5 (NCH_2Ar), 55.2 (OCH_3), 56.1 (C-5), 63.8 (C-2), 64.4 (CH_2O), 108.0 (C-4′), 114.0 (*m*-ArOMe), 120.8 (C-2′), 126.9 (*p*-Ar), 128.2/128.8 (*o*,*m*-Ar), 129.5 (*ipso*-ArOMe), 130.4 (*o*-ArOMe), 135.2 (C-1′), 139.9 (*ipso*-Ar), 158.5 (*p*-ArOMe), 174.4 (C-1). Anal. calcd for $C_{36}H_{44}N_2O_5 \cdot 1/4H_2O$: C 73.38, H 7.61, N 4.75. Found: C 73.31, H 7.64, N 4.73.

3.1.5. (2*S*)-2-*tert*-Butoxycarbonylamino-3-(4-oxocyclohex-1-enyl)propanoic acid ethyelene acetal (5). Ammonia (225 mL) was added to a cooled (−78°C) solution of *O*-methyl-*N*-*tert*-butoxycarbonyl-L-tyrosine (5 g, 16.9 mmol) in EtOH (50 mL). Small chips of lithium (705 mg, 101.6 mmol) were added with vigorous stirring until the solution was a persistent deep blue, and stirring was maintained for 90 min. The cooling bath was removed, the ammonia was allowed to evaporate overnight, and the reaction mixture was concentrated, the residue was taken up with 5% aqueous $NaHSO_4$ until pH 5 and the aqueous solution was extracted with CH_2Cl_2 (4×200 mL). The dried organic extracts were concentrated to give crude (2*S*)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-2,5-dihydrophenyl) propanoic acid (4.69 g, 93%); ^1H NMR (200 MHz, $CDCl_3$, two rotamers in a 3:2 ratio), major rotamer: 1.44 (s, 9H), 2.25 (m, 2H), 2.25–2.75 (m, 2H), 2.75 (m, 2H), 3.55 (s, 3H), 4.39 (m, 1H), 4.90 (d, *J*=6 Hz, 1H), 4.95 (m, 1H), 5.67 (d, *J*=6 Hz, 1H). For the minor rotamer: 3.57 (s, 3H), 4.61 (m, 1H), 5.53 (m, 1H).

Ethylene glycol (0.39 mL, 7.1 mmol) and $BF_3 \cdot Et_2O$ (44 μL, 0.35 mmol) were added at 0°C to a solution of the above acid (526 mg, 1.8 mmol in THF (6 mL) and the mixture was stirred at room temperature overnight. H_2O was added (25 mL) and the mixture was extracted with CH_2Cl_2 (5×25 mL). The dried organic extracts were concentrated to give **5** (541 mg, 93%), which was used directly in the next step: ^1H NMR (300 MHz, $CDCl_3$, 50°C) 1.44 (s, 9H, $C(CH_3)_3$), 1.77 (t, *J*=6.6 Hz, 2H, H-5′), 2.21 (t, *J*=6.9 Hz, 2H, H-6′), 2.27 (m, 2H, H-3′), 2.34 (dd, *J*=14.1, 8.7 Hz, 1H, H-3), 2.53 (m, 1H, H-3), 3.98 (s, 4H, CH_2O), 4.40 (m, 1H, H-2), 4.99 (d, *J*=7.8 Hz, 1H, NH), 5.43 (m, 1H, H-2′), 6.39 (s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 26.9 (C-6′), 28.3 ($C(CH_3)_3$), 31.0 (C-5′), 35.7 (C-3′), 39.9 (C-3), 51.7 (C-2), 64.3 (CH_2O), 80.1 ($C(CH_3)_3$), 107.8 (C-4′), 122.8 (C-2′), 132.5 (C-1′), 155.5 (NCO_2), 176.3 (C-1). Anal. calcd for $C_{16}H_{25}NO_6$: C 58.70, H 7.70, N 4.28. Found C 58.55, H 7.82, N 4.11.

3.1.6. Methyl (2*S*)-2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-3-(4-oxocyclohex-1-enyl)propanoate ethylene acetal (6). To a cooled (0°C) solution of acid **5** (400 mg, 1.2 mmol) in DMF (4 mL) NaH (117 mg, 4.9 mmol) and methyl iodide (0.38 mL, 6.1 mmol) were added and the solution was stirred overnight at room temperature. 5% aqueous $NaHSO_4$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (5×30 mL). The dried organic extracts were concentrated and purified by chromatography (SiO_2, CH_2Cl_2) to give **6** (272 mg, 63%): $[\alpha]_D$=−17.0 (*c* 0.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 55°C) 1.45 (s, 9H, $C(CH_3)_3$), 1.75 (m, 2H, H-5′), 2.12–2.23 (m, 2H, H-6′), 2.23 (m, 2H, H-3′), 2.42 (dd, *J*=14.4, 11.1 Hz, 1H, H-3), 2.57 (dd, *J*=14.4, 6.9 Hz, 1H, H-3), 2.79 (s, 3H, NCH_3), 3.70 (s, 3H, CO_2CH_3), 3.94 (s, 4H, CH_2O), 4.14 (dd, *J*=14.1, 6.9 Hz, 1H, H-2), 5.96 (m, 1H, H-2′); ^{13}C NMR (75.5 MHz, $CDCl_3$), major/minor rotamers, 26.5/26.9 (C-6′), 28.2 ($C(CH_3)_3$), 30.2/30.5 (NCH_3), 30.9/31.1 (C-5′), 35.7/35.6 (C-3′), 36.3/36.6 (C-3), 51.9 (CO_2CH_3), 55.8/58.0 (C-2), 64.2/64.1 (CH_2O), 80.0/80.5 ($C(CH_3)_3$), 107.6/107.5 (C-4′), 121.4/121.8 (C-2′), 133.2/132.8 (C-1′), 155.8/154.9 (NCO_2), 172.1/171.9 (C-1). Anal. calcd for $C_{18}H_{29}NO_6 \cdot 1/4H_2O$: C 60.07, H 8.26, N 3.89. Found: C 60.15, H 8.49, N 3.98.

3.1.7. (2*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3-(4-oxocyclohex-1-enyl)propanal ethylene acetal (7). To a solution of ester **6** (65 mg, 0.18 mmol) in toluene (1 mL) at −78°C was added dropwise DIBALH (0.27 mL, 1 M in hexane). After the mixture was stirred for 2.5 h, MeOH (0.2 mL) was added and the temperature was raised until room temperature, brine (15 mL) was added and the mixture extracted with CH_2Cl_2 (5×15 mL). The dried organic extracts were concentrated (temperature of bath below 30°C to avoid racemization) to give aldehyde **7** (58 mg), which was used directly in the next step. IR (NaCl) 2927, 1738, 1692, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.45 (s, 9H), 1.76 (m, 2H), 2.23 (m, 2H), 2.52–2.80 (m, 4H), 2.81 and 2.90 (2 s, 3H), 3.96 (s, 4H), 4.45 (dd, *J*=14.1, 6.9 Hz, 1H), 5.38 (m, 1H), 9.60 (s, 1H).

3.1.8. Methyl (2*S*,5*S*)-5-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-2-(4-methoxyphenyl)methyl-6-(4-oxocyclohex-1-enyl)-3-azahexanoate ethylene acetal (8). Operating as above from **2**, using aldehyde **7** (58 mg, 0.18 mmol) and the methyl ester of *O*-methyl-L-tyrosine (31 mg, 0.15 mmol) the corresponding imine was formed, which was reduced with $NaBH_4$ (14 mg, 0.37 mmol). After work-up and purification by chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2–MeOH 95:5) amine **8** (50 mg, 64%) and the alcohol coming from the reduction of aldehyde **7** (20 mg) were isolated. $[\alpha]_D$=+3.3 (*c* 0.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 55°C) 1.44 (s, 9H, $C(CH_3)_3$), 1.72 (m, 2H, H-5′), 1.96–2.14 (m, 4H, H-6′, H-6), 2.20 (m, 2H, H-3′), 2.45 (dd, *J*=12, 9.3 Hz, 1H, H-4), 2.55 (brs, 3H, NCH_3), 2.63 (dd, *J*=12, 5.4 Hz, 1H, H-4), 2.79 (dd, *J*=13.8, 7.5 Hz, 1H, CH_2Ar), 2.89 (dd, *J*=13.8, 6 Hz, 1H, CH_2Ar), 3.41 (dd, *J*=7.5, 6 Hz, 1H, H-2), 3.65 (s, 3H, CO_2CH_3), 3.77 (s, 3H, OCH_3), 3.93 (s, 4H, CH_2O), 4.18 (m, 1H, H-5), 5.26 (m, 1H, H-2′), 6.80 (dm, *J*=8.6 Hz, 2H, *m*-Ar), 7.07 (dm, *J*=8.6 Hz, 2H, *o*-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$, two rotamers) 26.8/26.9 (C-6′), 28.3 ($C(CH_3)_3$), 31.0/31.1 (C-5′), 35.5/35.7 (C-3′), 37.8/38.0 (C-6), 38.4/39.0 (CH_2Ar), 49.3/49.6 (C-4),

51.4/51.6 (CO_2CH_3), 51.8/52.4 (C-5), 53.9/55.0 (OCH_3), 62.8/63.0 (C-2), 64.2 (CH_2O), 78.8/79.3 ($C(CH_3)_3$), 107.7/107.8 (C-4′), 113.6/113.7 (*m*-Ar), 120.4/120.8 (C-2′), 129.1/129.4 (*ipso*-Ar), 130.0 (*o*-Ar), 133.8/134.3 (C-1′), 155.8/155.9 (NCO_2), 158.1/158.2 (*p*-Ar), 174.6 (C-1). Anal. calcd for $C_{28}H_{42}N_2O_7 \cdot 1/4H_2O$: C 64.29, H 8.19, N 5.35. Found: C 64.19, H 8.19, N 5.31.

3.1.9. (3*S*,5*R*,6*S*)-1-Benzyl-3-(*N*,*N*-dibenzylamino)-6-iodo-1-azaspiro[4.5]decan-8-one ethyelene acetal (9). To a solution of amine **3** (50 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) and 5% aqueous $NaHCO_3$ (1 mL) was added dropwise a solution of I_2 (26 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL). After stirring at room temperature overnight, 10% aqueous $Na_2S_2O_3$ (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The dried organic extracts were concentrated and the residue was purified by chromatography (Al_2O_3, 75:25 hexane–CH_2Cl_2) to give **9** (12 mg, 19%); ^{1}H NMR (500 MHz, $CDCl_3$, COSY, NOESY, HSQC, HMBC) 1.58–1.61 (m, 1H, H-10), 1.68–1.71 (m, 2H, H-9, H-10), 1.79–1.82 (m, 1H, H-9), 2.13 (d, *J*=8 Hz, 2H, H-4), 2.35 (t, *J*=13 Hz, 1H, H-7ax), 2.46 (t, *J*=10.5 Hz, 1H, H-2), 2.55 (dt, *J*=13, 4 Hz, 1H, H-7eq), 2.99 (dd, *J*=10.5, 3 Hz, 1H, H-2), 3.13 and 3.91 (2d, *J*=13 Hz, 1H each, CH_2Ar), 3.46 (m, 1H, H-3), 3.55 and 3.81 (2d, *J*=14.5 Hz, 2H each, $(CH_2Ar)_2$), 3.93 (m, 4H, CH_2O), 4.77 (dd, *J*=13, 4 Hz, H-6ax), 7.20–7.50 (m, 15H, Ar); ^{13}C NMR, see Table 1.

3.1.10. (3*S*,5*R*,6*S*)-3-(*N*,*N*-Dibenzylamino)-6-iodo-1-[(1*S*)-1-(methoxycarbonyl)-2-(4-methoxyphenyl)ethyl]-1-azaspiro[4.5]decan-8-one ethylene acetal (10). Operating as above, starting from **4** (30 mg, 0.05 mmol) and after chromatography (Al_2O_3, 3:1 hexane–CH_2Cl_2), iodo derivative **10** (9 mg, 25%) was isolated; ^{1}H NMR (200 MHz, $CDCl_3$) 1.48–1.69 (m, 4H), 2.00 (m, 2H), 2.27 (t, *J*=13.5 Hz, 1H, H-7ax), 2.51 (dm, *J*=13.5 Hz, H-7eq), 3.10 (m, 2H), 3.28–3.45 (m, 2H), 3.45 (m, 1H), 3.46 (s, 3H, CO_2CH_3), 3.54 (m, 1H), 3.67 and 3.76 (2d, *J*=15 Hz, 2H each, CH_2Ar), 3.77 (s, 3H, OCH_3), 3.89 (m, 4H, CH_2O), 4.72 (dd, *J*=13.5, 3.8 Hz, 1H, H-6ax), 6.78 (d, *J*=8.7 Hz, 2H, *m*-ArOMe), 7.12 (d, *J*=8.7 Hz, 2H, *o*-ArOMe), 7.26–7.42 (m, 10H, Ar).

In some runs, 4-methylene-3(*S*)-[(1*S*)-1-(methoxycarbonyl)-2-(4-methophenyl)ethylamino]cyclohexanone ethylene acetal (**11**) was also isolated (~10% yield): ^{1}H NMR (500 MHz, $CDCl_3$, COSY, HSQC, HMBC, NOESY) 1.53 (t, *J*=6.5 Hz, 2H, H-6), 1.76 (dd, *J*=13, 5.5 Hz, 1H, H-2), 1.84 (m, 2H, H-2, H-5), 1.96 (dt, *J*=12, 6.5 Hz, 1H, H-5), 2.76 (dd, *J*=13.5, 9 Hz, 1H, CH_2Ar), 2.98 (dd, *J*=13.5, 5.5 Hz, 1H, CH_2Ar), 3.23 (t, *J*=5.5 Hz, 1H, H-3), 3.43 (dd, *J*=9, 5.5 Hz, 1H, CHN), 3.68 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 3.89 (m, 4H, CH_2O), 4.61 and 4.76 (2 brs, 1H each, $=CH_2$), 6.81 (d, *J*=8.5 Hz, 2H, *m*-Ar), 7.11 (d, *J*=8.5 Hz, 2H, *o*-Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$) 28.4 (C-5), 36.1 (C-6), 38.8 (CH_2Ar), 41.0 (C-2), 51.8 (CO_2CH_3), 55.2 (OCH_3), 57.1 (C-3), 60.2 (CHN), 64.1/64.3 (CH_2O), 108.3 (C-1), 109.9 ($=CH_2$), 113.7 (*m*-Ar), 126.9 (*ipso*-Ar), 130.2 (*o*-Ar), 146.5 (C-4), 158.3 (*p*-Ar), 174.8 (CO_2Me).

3.1.11. Cyclization of 8 promoted by iodine. Operating as above, starting from **8** (100 mg, 0.19 mmol), using 74 mg (0.29 mmol) of I_2, and after chromatography (Al_2O_3, hexane to EtOAc), azaspiro derivative **12a** (22 mg, 19%) and oxazinone **13a** (35 mg, 31%) were isolated. (3*S*, 5*R*,6*S*)-3-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-6-iodo-1-[(1*S*)-1-(methoxycarbonyl)-2-(4-methoxyphenyl) ethyl]-1-azaspiro[4.5]decan-8-one ethylene acetal (**12a**): ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY, HSQC, HMBC) 1.47 (s, 9H, $C(CH_3)_3$), 1.59 (m, 2H, H-10), 1.66 and 1.75 (2m, 1H each, H-9), 1.87 (tm, *J*=9.6 Hz, 1H, H-4), 2.16 (m, 1H, H-4), 2.23 (t, *J*=13.2 Hz, 1H, H-7ax), 2.50 (ddd, *J*=13.2, 4, 2.8 Hz, 1H, H-7eq), 2.89 (s, 3H, NCH_3), 3.09 (d, *J*=8 Hz, 2H, CH_2Ar), 3.14 (dd, *J*=9.2, 4.8 Hz, 1H, H-2), 3.50 (s, 3H, CO_2CH_3), 3.52 (t, *J*=8 Hz, 1H, CHCO), 3.55 (t, *J*=9.2 Hz, 1H, H-2), 3.78 (s, 3H, OCH_3), 3.90 (m, 4H, CH_2O), 4.71 (dd, *J*=13.2, 4 Hz, 1H, H-6), 4.90 (m, 1H, H-3), 6.81 (d, *J*=8.7 Hz, 2H, *m*-Ar), 7.13 (d, *J*=8.7 Hz, 2H, *o*-Ar); ^{13}C NMR, see Table 1. (4*S*,6*S*,7*R*)-7-Iodo-3-methyl-4-[(3*S*)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2-aza-butyl]-1-oxa-3-azaspiro[5.5]undecan-2,9-dione ethylene acetal (**13a**): ^{1}H NMR (400 MHz, $CDCl_3$, COSY, NOESY, HSQC, HMBC) 1.45 (m, 1H, H-11), 1.59 (m, 1H, H-10ax), 1.81 (ddd, *J*=14, 6.8, 4 Hz, 1H, H-10eq), 2.01 (m, 1H, H-11), 2.02 (m, 1H, H-5), 2.20 (t, *J*=13.6 Hz, 1H, H-8ax), 2.45 (ddd, *J*=13.6, 4.4, 2.8 Hz, 1H, H-8eq), 2.49 (m, 1H, CH_2N), 2.48 (m, 1H, H-5), 2.82 (dd, *J*=13.6, 7.6 Hz, 1H, CH_2Ar), 2.92 (dd, *J*=13.6, 6 Hz, 1H, CH_2Ar), 2.96 (s, 3H, NCH_3), 2.99 (dd, *J*=12, 5.2 Hz, 1H, CH_2N), 3.27 (m, 1H, H-4), 3.39 (dd, *J*=8, 5.6 Hz, 1H, CHCO), 3.70 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 3.94 (m, 4H, CH_2O), 4.54 (dd, *J*=13.6, 4.4 Hz, 1H, H-7), 6.83 (d, *J*=8.6 Hz, 2H, *m*-Ar), 7.13 (d, *J*=8.6 Hz, 2H, *o*-Ar); ^{13}C NMR, see Table 2. HRMS calculated from $C_{24}H_{33}IN_2O_5$ 588.1332, found 588.1292.

3.1.12. Cyclization of 8 promoted by TBCO. To a solution of **8** (50 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added 2,4,4,6-tetrabromo-2,5-cyclohexadienone (82 mg, 0.20 mmol) and the reaction mixture was stirred at room temperature overnight. CH_2Cl_2 (8 mL) was added and the organic layer was washed with saturated aqueous Na_2CO_3 (2×10 mL). The dried organic extracts were concentrated and purified by chromatography (Al_2O_3, hexane to EtOAc) to give a partially separable mixture of 6-bromoazaspiro derivatives **12b** (30 mg, 30%) and **12b′** (22 mg, 22%) and the oxazinone **13b** (12 mg, 13%). (3*S*,5*R*,6*S*)-6-Bromo-3-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-1-[(1*S*)-1-(methoxycarbonyl)-2-(4-methoxyphenyl)ethyl]-1-azaspiro [4.5]decan-8-one ethylene acetal (**12b**): ^{1}H NMR (500 MHz, $CDCl_3$, COSY, HMQC) 1.47 (s, 9H, $C(CH_3)_3$), 1.53–1.60 (m, 2H, H-10), 1.66 (m, 2H, H-9), 2.05 (m, 3H, H-7ax, H-4), 2.33 (dm, *J*=11.1 Hz, 1H, H-7eq), 2.85 (s, 3H, NCH_3), 3.05 (m, 2H, CH_2Ar), 3.17 (m, 1H, H-2), 3.46 (m, 1H, H-2), 3.53 (s, 3H, CO_2CH_3), 3.61 (m, 1H, CHCO), 3.78 (s, 3H, OCH_3), 3.91 (m, 4H, CH_2O), 4.51 (dd, *J*=13.2, 3.6 Hz, 1H, H-6), 4.84 (m, 1H, H-3), 6.81 (dm, *J*=8.7 Hz, 2H, *m*-Ar), 7.12 (dm, *J*=8.7 Hz, 2H, *o*-Ar); ^{13}C NMR, see Table 1. Anal. calcd for $C_{28}H_{41}BrN_2O_7$: C 56.28, H 6.92, N 4.69. Found: C 56.07, H 7.05, N 4.36.

3.1.13. Cyclization of 8 through its *N*-chloroamine. To a solution of **8** (125 mg, 0.24 mmol) in CH_2Cl_2 (6 mL) was added *N*-chlorosuccinimide (34 mg, 0.26 mmol) at 0°C. The reaction mixture was stirred at room temperature for 24 h

and concentrated to give the corresponding *N*-chloroamine. To a cooled (−78°C) solution of this compound (0.24 mmol) in degassed CH_2Cl_2 (5 mL) and under argon atmosphere were added $TiCl_3$ (48 mg, 0.31 mmol) and $BF_3{\cdot}Et_2O$ (33 μL, 0.27 mmol). After being stirred for 3 h at this temperature, the reaction mixture was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (5×15 mL). The dried organic extracts were concentrated to give a residue which was purified by chromatography (Al_2O_3, hexane to EtOAc), to give 83 mg (70%) of (4*S*,6*S*,7*R*)-7-chloro-3-methyl-4-[(3*S*)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2-azabutyl]-1-oxa-3-azaspiro[5.5]undecan-2,9-dione (**13c**): ^{1}H NMR (300 MHz, $CDCl_3$) 1.48 (m, 1H), 1.56 (m, 1H), 1.75–1.81 (m, 1H), 1.86–2.00 (m, 1H), 2.02 (m, 1H), 2.28 (dq, *J*=13.8, 2.2 Hz, 1H. H-8eq), 2.44–2.54 (m, 2H), 2.95 (s, 3H, NCH_3), 2.98 (m, CH_2N), 3.36 (m, 2H), 3.70 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 3.96 (m, 4H, CH_2O), 4.24 (dd, *J*=11.4, 4.5 Hz, 1H, H-7), 6.82 (dm, *J*=8.7 Hz, 2H), 7.11 (dm, *J*=8.7 Hz, 2H); ^{13}C NMR, see Table 2. HRMS calculated from $C_{24}H_{33}ClN_2O_7$ 496.1976, found 496.1979.

3.1.14. (4*S*)-3-Methyl-4-[(3*S*)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2-azabutyl]-1-oxa-3-azaspiro[5.5]undecan-2,9-dione (18). To a solution of AIBN (3 mg, 0.015 mmol) in benzene (1 mL) was added Bu_3SnH (21 μL, 0.077 mmol) and heated to reflux temperature. A solution of **17** (17 mg, 0.031 mmol) in benzene (1 mL) was added and the reaction mixture was maintained at this temperature for 2.5 h, and concentrated. The residue was purified by chromatography (SiO_2, hexane–CH_2Cl_2 1:1 to CH_2Cl_2–MeOH 95:5) to give **18** (8 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.54–1.73 (m, 6H), 1.88–1.92 (m, 2H), 1.96 (dd, *J*=14, 11 Hz, 1H, H-5), 2.06 (qd, *J*=13, 4.5 Hz, 1H, H-7eq), 2.45 (dd, *J*=12, 3 Hz, 1H, CH_2N), 2.79 (dd, *J*=14, 7.5 Hz, 1H, CH_2Ar), 2.88 (m, 1H, CH_2Ar), 2.89 (dd, *J*=12, 5.5 Hz, 1H, CH_2N), 2.94 (s, 3H, NCH_3), 3.35 (m, 2H, H-4, CHCO), 3.68 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 3.94 (m, 4H, CH_2O), 6.82 (d, *J*=8.5 Hz, 2H, *m*-Ar), 7.07 (d, *J*=8.5 Hz, 2H, *o*-Ar).

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