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Iminoiodane mediated aziridination of α-allylglycine: access to a novel rigid arginine derivative and to the natural amino acid enduracididine

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Abstract—The synthesis of fully protected aminodihydrohistidines in optically pure form is described starting from allylglycine derivatives. These compounds represent novel conformationally constrained analogues of arginine, one of them being, in addition, a protected form of the marine natural product, enduracididine. The key step of the strategy is a one-pot copper-catalyzed aziridination of *t*-butyl (*S*)-*N*-(9-phenyl-9*H*-fluoren-9-yl)allylglycinate ((*S*)-**16**) with 2-trimethylsilylethanesulfonamide in the presence of iodosylbenzene.

The conformational restriction of flexible bioactive molecules is a well known technique for increasing their intrinsic activity or their selectivity for a particular receptor subtype or enzyme isoform.[1,2] Such rigid ligands can also lead to greater lipophilicity and/or increased stability toward metabolic enzymes, both factors contributing to improved bioavailability of a given active substance. A case in point is arginine (**1**), the endogenous substrate of NO synthase, of which a number of conformationally restricted analogues have been prepared over the past years with these considerations in mind. Such rigid analogues have generally taken three forms. In the first, the essential guanidine function (or an isosteric equivalent) is incorporated in a chain-terminating heterocycle. These include, for instance, the N^{δ}–N^{ω} ethylene bridged analogue **2**[3] and the 2-aminopyrimidine derivative **3**[4] (Fig. 1).

In the second class of compounds, the 3-carbon tether is locked into a more rigid conformation either by introduction of a double bond (i.e. **4**)[5] or by incorporation as a ring (i.e., the guanidinophenylalanine derivative **5**).[5,6] Another approach to rigid arginine analogues consists in linking one of the nitrogen atoms of the guanidine functionality to one of the methylene groups. One such molecule is the piperidine derivative **6**, designed in this case to be a specific thrombin inhibitor.[7] Alternatively, a compound in which the terminal amino function is bonded to the methylene backbone would force arginine to adopt a highly folded conformation as opposed to the extended conformations exhibited by compounds **2**–**6**. Interestingly, such a compound, the aminodihydrohistidine **7** (enduracididine), has been isolated from natural sources. Thus, **7** was identified in 1968 as a component of a peptide antibiotic enduracidin,[8a] itself isolated from *Streptomyces fungicidicus*.[8b,c] Several years later, enduracididine was also shown to be a component of the antibiotic minosaminomycin, isolated from a plant source, *Lonchocarpus*

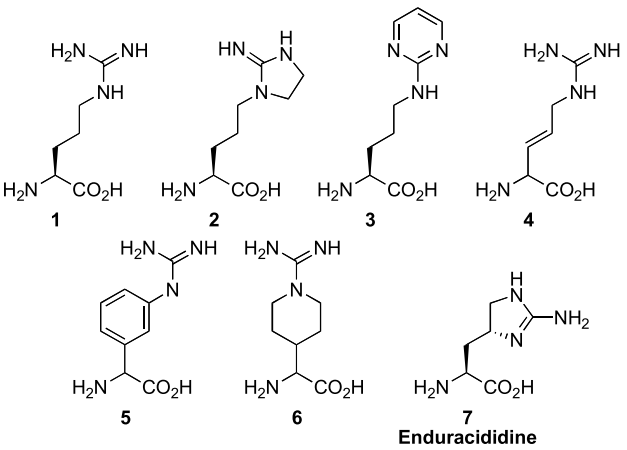

Figure 1. Arginine and rigid derivatives.

Keywords: Arginine mimetic; Allylglycine; Aziridine; Aziridination; Iminoiodane.
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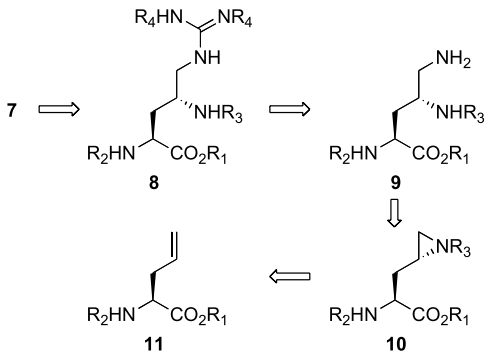
sericeus.[9] More recently, this amino acid has been identified in the cytotoxic fraction of extracts of a marine ascidian, *Leptoclinides dubius*.[10] While it has been reported that the structure of enduracididine was established by X-ray crystallography,[8a] the only published preparation of this compound was by way of a Bamberger cleavage of methyl histidinate which yielded a 1:1 mixture of enduracididine and its (4*S*) isomer.[11]

Thus, with the double incentive of preparing a new conformationally restricted arginine analogue and a natural product, we set about to develop a synthesis of enduracididine (in fact, a protected form of this molecule suitable for insertion in small biologically active peptide derivatives to furnish novel peptidomimetics). A retrosynthetic analysis of this compound (Scheme 1) suggested that it could be obtained from the guanidino derivative **8**, which in turn could be constructed from the diamine **9** for which purpose a variety of reagents are available.[12] The diamino compound **9** could then be prepared by amine (or equivalent) promoted opening of the aziridine **10** itself formed by diastereoselective aziridination of L-allylglycine **11**. The key step in this pathway then was the preparation of aziridine **10** from a suitably protected allylglycine derivative.

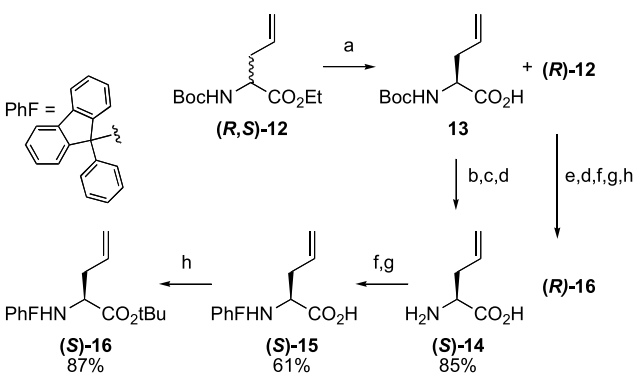


Scheme 1. Retrosynthetic analysis.

Interestingly, while both the epoxide[13] and cyclopropane[14] analogues of aziridine **10** have been described, derivatives of **10** itself have not.[15] A particularly attractive way of achieving this would be by application of the iminoiodane-mediated copper (I or II)-catalyzed aziridination of olefins.[16,17] In addition, the iminoiodane derived from trimethylsilylethanesulfonamide ($SesNH_2$) seemed particularly suited to this purpose as the Ses protecting group can be removed under mild conditions (F^-) avoiding possible racemization of the amino acid.[18] On the other hand, the application of this copper-catalyzed aziridination procedure to a nitrogen-containing olefinic substrate presented a certain challenge since it could be anticipated that the copper I or II salt would be sequestered by this nitrogen atom, thereby inhibiting the desired reaction. Indeed, while the copper-catalyzed iminoiodane-mediated aziridination procedure has been successfully used recently as a key step in the total synthesis of a number of natural products starting from non-nitrogenous substrates,[17] only very few examples[19,20] have been reported of this reaction being applied to nitrogen-containing starting materials. In this paper then, we report the results of our study in this regard and subsequent application to the synthesis of protected enduracididine **7**.

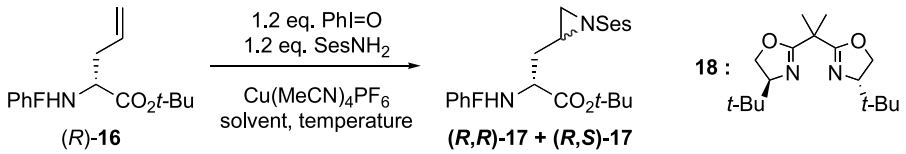
The optically pure starting allylglycine substrates were prepared by enzymatic resolution of racemic ethyl *N*-Boc-allylglycinate **12** using α-chymotrypsin (Scheme 2).[21] This procedure afforded (*S*)-*N*-Boc-allylglycine **13** with 98% optical purity and the unreacted isomer (*R*)-**12** (ee=94%). The choice of protecting groups for the carboxylic acid and amine functionalities of **13** was made based on the following considerations. Firstly, since in the retrosynthetic scheme we planned to generate a diamino intermediate **9**, protection of the carboxylic acid with a bulky *t*-butyl group was deemed necessary to prevent lactamization during this step. Secondly, while the *N*-Boc group may be considered both sufficiently bulky and electron-withdrawing to minimize the aforementioned possibility of copper sequestration during the aziridination step, preliminary experiments showed that the yield of aziridination products was very low.[22] The phenylfluorenyl group was considered a suitable choice in this case, combining both a large steric hindrance around the nitrogen atom with the possibility of selective removal. Thus, the Boc protecting group of compound **13** was removed by treatment with trifluoroacetic acid in dichloromethane (Scheme 2). The resulting free amino acid (*S*)-**14** was then transiently esterified by reaction with trimethylsilyl chloride. Treatment of the product in situ with 9-bromo-9-phenylfluorene in the presence of lead (II) nitrate[23] then provided after methanolic work-up the *N*-phenylfluorenyl (NPhF)-protected derivative (*S*)-**15**. Finally, reaction of the latter with *t*-butyl 2,2,2-trichloroacetimidate[24] yielded the desired fully protected (*S*)-allylglycine **16**. Similar treatment of ethyl (*R*)-*N*-Boc-allylglycine **12** then led to (*R*)-**16**. HPLC analysis of (*S*)-**16** and (*R*)-**16** using a chiral column (C-18 Waters Symmetry) showed that no epimerization had occurred during these deprotection/protection steps.

The (*R*) isomer of **16** was first used to optimize the copper-catalyzed aziridination of the double bond. We have previously demonstrated that the aziridination of a wide range of olefins can be achieved using a convenient one-pot procedure.[25] Thus, by simply mixing 1 equiv. of (*R*)-**16**, 1.2 equiv. of PhI=O and of $SesNH_2$ in the presence of 25 mol% of $Cu(CH_3CN)_4PF_6$ in acetonitrile at room



Scheme 2. Preparation of allylglycine derivatives. (a) α-chymotrypsin.[21] (b) TFA, CH_2Cl_2, rt, 2 h. (c) HCl, EtOH. (d) Propylene oxide, EtOH, reflux, 7 h. (e) 6 N HCl, reflux, 18 h. (f) TMSCl, CH_2Cl_2, reflux, 2 h. (g) PhFBr, $Pb(NO_3)_2$, CH_2Cl_2, rt, 84 h. (h) $Cl_3CC(=NH)O$*t*-Bu, cyclohexane, CH_2Cl_2, rt, 72 h.

Table 1. 'One-pot' copper-catalyzed aziridination of allylglycine derivative (*R*)-**16**



Entry	$Cu(CH_3CN)_4PF_6$	Solvent	Temperature	% Yield[a]	Diastereomeric ratio (*R*,*R*): (*R*,*S*)
1	25 mol%	CH_3CN	rt	32 (67)	65:35
2	25 mol%	C_6H_6	rt	26 (45)	67:33
3	25 mol%	CH_2Cl_2	rt	24 (44)	70:30
4	25 mol%	CH_3CN	5 °C	30 (74)	63:37
5	25 mol%	CH_3CN	45 °C	25 (53)	67:33
6	50 mol%	CH_3CN	rt	28 (60)	66:34
7	25 mol%+35 mol% **18**	CH_3CN	rt	23	70:30
8	25 mol%+35 mol% **18**	CH_3CN	−20 °C	16	75:25

[a] Yields in parentheses based on consumed substrate.

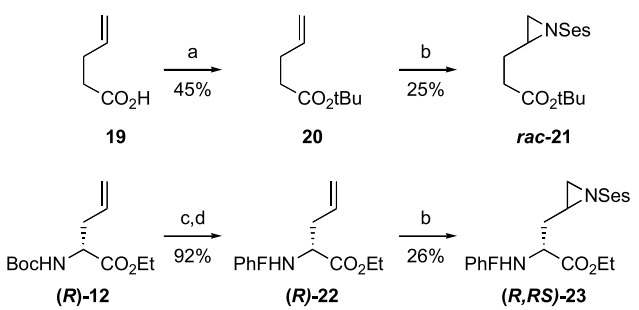
temperature, the desired *N*-Ses aziridine **17** was obtained in 32% overall yield (67% yield based on recovered starting material) (Table 1, entry 1). The aziridination was moderately diastereoselective providing a 65:35 ratio (as determined by ^1H NMR) of the (2*R*,4*R*) and (2*R*,4*S*) isomers, respectively, which could not be separated at this stage (see below for the determination of the absolute configurations).

Several attempts were made to improve the yield and/or the diastereoselectivity of the aziridination but all proved somewhat unsatisfactory. Thus (Table 1), while use of benzene or dichloromethane as the reaction solvent gave moderately higher diastereoselectivities (34 and 40%, respectively), this was at the detriment of yields (26 and 24%, respectively) (entries 2, 3). No substantial changes in yields and diastereoselectivities were observed when the reaction was run at colder (5 °C) or warmer (45 °C) temperatures (entries 4, 5). Unexpectedly, doubling the quantity of copper catalyst led to a slightly decreased aziridine yield (entry 6).

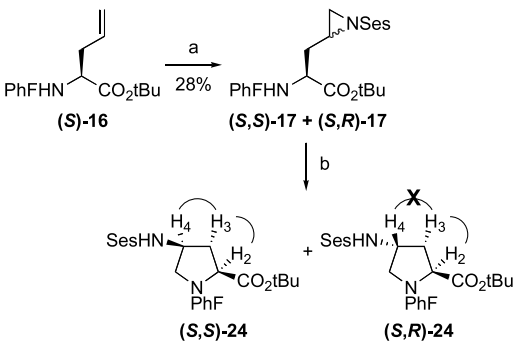
Evans has shown that high stereoselectivities can be obtained when the iminoiodane-mediated aziridination reaction of simple olefins (styrene, cinnamates) is conducted in the presence of chiral bis(oxazoline) catalysts.[26] When 35 mol% of such a ligand (the *t*-butyl derivative **18**) was added to the aziridination reaction medium of (*R*)-**16**, some improvement in diastereoselectivity was observed both at room temperature (40% de, entry 7) and at −20 °C (50% de, entry 8) but again, at the expense of overall product yield (23 and 16%, respectively).

In order to verify whether the presence of a nitrogen atom in the olefinic substrate was responsible for the relatively low aziridination yields, the same aziridination procedure was applied to *t*-butyl 4-pentenoate **20** (prepared by DCC/DMAP promoted esterification of carboxylic acid **19** by *t*-butanol) (Scheme 3). The yield of aziridine **21** (25%) was in fact no better than that starting from the analogous amine-containing substrate (*R*)-**16**, indicating that the nitrogen atom is most probably not interfering with the reaction. Moreover, when the bulky *t*-butyl ester of allylglycine **16** was replaced by a smaller ethyl ester as in (*R*)-**22** (prepared by selective removal of the *N*-Boc group of (*R*)-**12** followed by protection of the resulting amine with a phenylfluorenyl group),[23b] the yield of the corresponding aziridine (*R*)-**23** was again quite low (26%) and, in addition, no diastereoselectivity was observed. These results, combined with our previous observations,[18,27] strongly suggest that the bulky amine and carboxylic acid blocking groups of allylglycine **16** are not the source of the low yields of aziridinated product. The latter is more likely attributable to the previously described poor reactivity of terminal monosubstituted olefins under these conditions. The combined presence of both sterically demanding substituents does, however, appear to be necessary to ensure some diastereoselectivity in the aziridination step.

Since, despite many attempts, neither the yield nor the diastereoselectivity of the aziridination of (*R*)-allylglycine derivative **16** could be further improved, the best reaction conditions were now applied to (*S*)-**16** having the same C-2 configuration as arginine and enduracididine. As expected then, 'one-pot' aziridination of (*S*)-**16** with $SesNH_2$ provided an inseparable 7:3 mixture of aziridines **17** in 28% yield (65% based on consumed starting material) (Scheme 4). Attribution of the C-4 configuration of each isomer was made possible after intramolecular aziridine ring opening by the secondary amine of **17**, the resulting cyclized products being more amenable to NMR analysis. Thus, when the diastereomeric mixture of aziridines **17** was heated at 110 °C for 70 h in DMF, two major compounds were obtained. Separation of the compounds by column chromatography afforded the *cis* 4-aminoproline (*S*,*S*)-**24** in 46% yield[28] and the diastereomeric *trans*-4-aminoproline



Scheme 3. Aziridination of test substrates. (a) *t*-BuOH, DCC, DMAP, CH_2Cl_2, rt, 20 h. (b) $SesNH_2$ PhI=O, 25 mol% $Cu(CH_3CN)_4PF_6$, CH_3CN, rt, 16 h. (c) HCl_g, CH_2Cl_2, rt, 5 h. (d) PhFBr, K_3PO_4, CH_3NO_2, rt, 72 h.



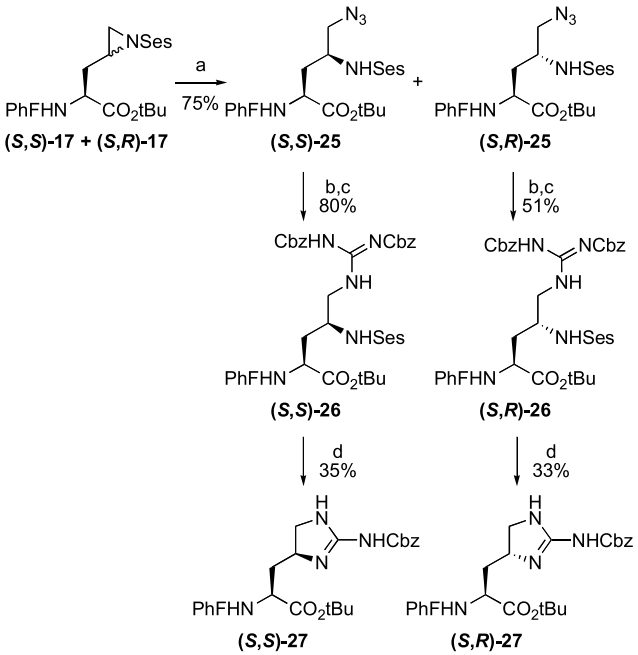
Scheme 4. Determination of the stereochemistry. (a) Conditions for step b in Scheme 3. (b) DMF, 110 °C, 70 h.

derivative (*S*,*R*)-**24** in 17% yield. The configuration of the Ses-amino group of the major compound (*S*,*S*)-**24** was clearly established by ^{1}H NMR NOESY and NOEDIFF experiments. Thus, while no direct correlation was observed between H-2 and H-4, strong NOE effects between H-2 and H-3 on one hand and H-3 and H-4 on the other hand were evident, indicating a *cis* relationship between H-2 and H-4. No such correlation could be observed between H-3 and H-4 in the minor product, though H-2 and H-3 were still strongly correlated, thereby corroborating the H-2/H-4 *trans* relationship in (*S*,*R*)-**24**. Based on these results, it may be deduced that the major diastereomer formed by aziridination of (*S*)-**16** is the (2*S*,4*S*) isomer and that of (*R*)-**16** the (2*R*,4*R*) isomer.

In order to prepare the required diamino intermediate of type **9**, opening of the aziridine ring of compound **17** (a mixture of the (*S*,*S*) and (*S*,*R*) isomers) by azide anion was then investigated (Scheme 5). Careful control of the reaction conditions was required in order to minimize the aforementioned intramolecular aziridine ring opening (heating with NaN_3 in DMF at 65 °C for 80 h in the presence of boron trifluoride etherate). The ^{1}H NMR spectrum of the crude reaction mixture showed that two major ring-opened products **25**, separated and purified by a combination of column chromatography on silica gel and HPLC, had been formed in a ratio identical to that of the diastereomeric components of starting material **17** (7:3). The major compound could thus be assigned the (2*S*,4*S*) configuration and the minor compound the (2*S*,4*R*) configuration.

The synthesis of the target rigid arginine derivatives was completed as shown in Scheme 5. Thus, reduction of the azide function of compound (*S*,*S*)-**25** with triphenylphosphine in the presence of water afforded the intermediate amine[29] which was reacted directly with *S*-methyl *N*,*N*′-bis(benzyloxycarbonyl)isothiourea[30] to give the protected guanidine derivative (*S*,*S*)-**26** in 80% yield. Treatment of this compound with cesium fluoride in DMF at 90 °C for 24 h then provided in one step the dihydroaminoimidazole derivative (*S*,*S*)-**27**, HPLC of which showed a diastereomeric purity of 99%. Identical treatment of (*S*,*R*)-**25** provided compound (*S*,*R*)-**27** (de of 98%). The latter is a protected form of enduracididine **7**.

In summary, we have described herein the first application of the one-pot copper-catalyzed iminoiodane-mediated



Scheme 5. End of the synthesis. (a) NaN_3, $BF_3{\cdot}OEt_2$, DMF, 65 °C, 80 h. (b) PPh_3, THF, H_2O, reflux, 20 h. (c) MeSC(=NCbz)NHCbz, $HgCl_2$, DMF, Et_3N, rt, 84 h. (d) CsF, DMF, 90 °C, 24 h.

aziridination procedure to an α-allylglycine derivative. This subsequently permitted the preparation of novel rigid analogues of arginine (i.e. **27**) starting from the stereoisomeric aziridinated products **17**. Interestingly, the (2*S*,4*R*)-isomer of **27** is a protected form of a marine natural product, enduracididine **7**. The present methodology therefore represents a versatile approach for the preparation of this compound, its isomers and its analogues.[31]

1. Experimental

1.1. General

Melting points were measured in capillary tubes on a Büchi B-540 apparatus and are uncorrected. IR spectra of samples were obtained either as KBr pellets or as films with a Nicolet 205 FT-IR or Fourier Perkin–Elmer 1600 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were determined on a Bruker AC 200 (200 MHz), AC 250 (250 MHz) or Aspect 3000 (300 MHz) instrument. ^{1}H and ^{13}C NMR chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High-resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Optical rotations were determined with a JASCO P-1010 polarimeter. Thin-layer chromatography was performed on silica gel 60 plates with a fluorescent indicator. The plates were visualized with UV light (254 nm) and with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on silica gel 60 (230–240 mesh) at medium pressure (200 mbar). All solvents were distilled and stored over 4 Å molecular sieves before use. All reagents were purchased from the Aldrich Chemical Co.

and were used without further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette.

1.1.1. (*S*)-*N*-(*t*-Butyloxycarbonyl)allylglycine (13) and ethyl (*R*)-*N*-(*t*-butyloxycarbonyl)allylglycinate ((*R*)-12). These compounds were obtained by selective enzymatic saponification of the (*S*) enantiomer of racemic ethyl *N*-(*t*-butyloxycarbonyl)allylglycinate ((*R*,*S*)-**12**) with α-chymotrypsin following the procedure of Schricker et al.[21] The optical purity (ee) of each compound was determined by HPLC on a reverse phase C-18 Waters Symmetry column (4.6×250 mm) after derivatization using *o*-phthaldialdehyde and *N*-acetylcysteine as described.[32] Compound **13**: $[\alpha]_D^{22}$ +13 (c 1.15, MeOH), ee=98%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.50–2.70 (m, 2H), 4.40–4.52 (m, 1H), 4.95–5.05 (m, 1H, exchangeable with D_2O), 5.10–5.33 (m, 2H), 5.62–5.78 (m, 1H). Compound (*R*)-**12**: $[\alpha]_D^{22}$ −10 (c 0.92, MeOH), ee=94%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, 3H, *J*=7.1 Hz), 1.48 (s, 9H), 2.50–2.60 (m, 2H), 4.27 (q, 2H, *J*=7.1 Hz), 4.42–4.52 (m, 1H), 5.10–5.28 (m, 3H, 1H, exchangeable with D_2O), 5.60–5.88 (m, 1H).

1.1.2. (*S*)-Allylglycine ((*S*)-14). To a solution of compound **13** (2.7 g, 12.7 mmol) in dichloromethane (12 mL) held at 0 °C was slowly added trifluoroacetic acid (9.7 mL, 127 mmol). After completion of the addition, the reaction mixture was stirred for 2 h at rt and then evaporated to dryness under vacuum. The residue was dissolved in ethanol (20 mL), 4 N HCl (3 mL) was added and the solution was once again evaporated to dryness, leaving (*S*)-**14** hydrochloride as a white powder (1.9 g, 98%): mp 206–208 °C.

A sample of the latter (500 mg, 3.3 mmol) in absolute ethanol (6.6 mL) was treated with propylene oxide (1.15 mL, 16.5 mmol), the mixture was refluxed for 7 h, cooled and the white precipitate of (*S*)-**14** was collected by filtration and washed with ether (324 mg, 85%). ESMS *m*/*z* 116 $(MH)^+$; ^{1}H NMR (300 MHz, D_2O) δ 2.53–2.72 (m, 2H), 3.80 (dd, 1H, *J*=5.1, 7.1 Hz), 5.23–5.32 (m, 2H), 5.69–5.85 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 35.5, 54.6, 121.1, 131.9, 174.7.

1.1.3. (*S*)-*N*-(9-Phenyl-9*H*-fluoren-9-yl)allylglycine ((*S*)-15). To a suspension of (*S*)-allylglycine (*S*)-**14** (300 mg, 2.61 mmol) in anhydrous dichloromethane (5 mL) was added trimethylsilyl chloride (0.35 mL, 2.75 mmol). The reaction mixture was stirred at rt for 10 min and then refluxed for 2 h. The solution was cooled to rt, triethylamine (0.73 mL, 5.22 mmol) was added followed after 15 min by addition of lead (II) nitrate (0.59 g, 1.79 mmol) and of a solution of 9-bromo-9-phenylfluorene (1.14 g, 3.56 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 84 h at rt. Methanol (2.5 mL) was added, and after 2 h stirring, the mixture was filtered through Celite. The filtrate was evaporated in vacuo and the residue was chromatographed on silica gel (heptane–ethyl acetate 4:1 followed by 1:1) to afford compound (*S*)-**15** as a colorless solid (566 mg, 61%); mp 59–61 °C (lit.[23a] mp 63–64 °C); $[\alpha]_D^{23}$ − 152 (c 1.01, $CHCl_3$); IR (film) 2957, 2926, 1710, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93–2.06 (m, 1H), 2.38–2.50 (m, 1H), 2.70 (t, 1H, *J*=5.4 Hz), 5.10–5.24 (m, 2H), 5.42–5.58 (m, 1H), 7.18–7.70 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.5, 54.9, 72.7, 120.5, 120.6, 124.9, 125.6, 125.9, 127.9, 128.2, 128.6, 128.9, 129.3, 129.4, 140.3, 141.3, 143.0, 146.6, 148.3, 174.7. HRESMS *m*/*z* 378.1466 $(M+Na)^+$ ($C_{24}H_{21}NO_2$+Na requires 378.1470).

1.1.4. *t*-Butyl (*S*)-*N*-(9-phenyl-9*H*-fluoren-9-yl)allylglycinate ((*S*)-16). To a solution of compound (*S*)-**15** (150 mg, 0.42 mmol) in dichloromethane (1 mL) was added a solution of *t*-butyl 2,2,2-trichloroacetimidate (184 mg, 0.84 mmol) in cyclohexane (0.85 mL). The reaction mixture was stirred for 72 h at rt, filtered through Celite and evaporated to dryness under vacuum. The residue was dissolved in dichloromethane (1 mL), treated again with the same quantity of reagent in cyclohexane and stirred for another 60 h. The residue obtained after filtration and evaporation was purified by chromatography on silica gel (heptane–ethyl acetate 19:1), affording compound (*S*)-**16** as a pale yellow solid (172 mg, 87%): mp 54–55 °C; $[\alpha]_D^{22}$ −173 (c 1.13, $CHCl_3$); IR (film) 3312, 2977, 1724, 1448 cm^{-1}; ESMS *m*/*z* 434 $(M+Na)^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.21–2.32 (m, 2H), 2.71 (t, 1H, *J*=5.8 Hz), 3.12 (br s, 1H), 5.02–5.10 (m, 2H), 5.68–5.89 (m, 1H), 7.20–7.50 (m, 11H), 7.68–7.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 40.4, 56.0, 73.2, 80.7, 117.3, 119.9, 125.5, 126.3, 127.2, 127.9, 128.3, 134.7, 140.3, 141.0, 145.1, 149.5, 149.6, 174.6. Anal. calcd for $C_{28}H_{29}NO_2$: C, 81.72; H, 7.10; N, 3.40. Found: C, 81.99; H, 7.17; N, 3.13.

1.1.5. *t*-Butyl (*R*)-*N*-(9-phenyl-9*H*-fluoren-9-yl)allylglycinate ((*R*)-16). A suspension of compound (*R*)-**12** (2.6 g, 10.7 mmol) in 6 N HCl was refluxed for 18 h. The reaction mixture was cooled and evaporated to dryness under vacuum by repeated co-evaporation with ethanol, affording (*R*)-allylglycine as the hydrochloride salt ((*R*)-**14** HCl) in quantitative yield. Treatment of this compound in the same manner as for (*S*)-**14** HCl provided compound (*R*)-**16** identical in all respects to (*S*)-**16** except for the optical rotation: $[\alpha]_D^{22}$ +152 (c 5.0, $CHCl_3$).

1.1.6. *t*-Butyl (2*R*,2′*RS*)-2-*N*-[(9-phenyl-9*H*-fluoren-9-yl)amino]-3-[*N*-(2-trimethylsilylethanesulfonyl)aziridin-2′-yl]propanoate ((*R*,*RS*)-17). To a suspension of activated 3 Å molecular sieves (250 mg) in acetonitrile (1.3 mL) were successively added compound (*R*)-**16** (310 mg, 0.75 mmol) and $Cu(CH_3CN)_4PF_6$ (70 mg, 0.19 mmol). A mixture of 2-trimethylsilylethanesulfonamide (178 mg, 0.98 mmol) and iodosylbenzene (217 mg, 0.98 mmol) was then introduced in five portions over a period of 1.5 h. The reaction mixture was stirred overnight at room temperature then filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (heptane–ethyl acetate 19:1 then 9:1) to afford the *N*-(Ses)aziridines (*R*,*RS*)-**17** (142 mg, 32%) as an inseparable 7:3 mixture of diastereoisomers: IR (film) 1725, 1449, 1323 cm^{-1}; ESMS *m*/*z* 591 $(MH)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05, 0.07 (2s, 9H), 1.05–1.15 (m, 2H), 1.20 (s, 9H), 1.25–1.45 (m, 1H), 1.8–2.05 (m, 2H), 2.4–2.7 (m, 2H), 2.75–3.1 (m, 3H), 7.2–7.45 (m, 11H), 7.65–7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, −1.8, 9.4, 10.0, 28.0, 32.9, 33.6, 37.0, 37.5, 37.9, 48.7, 49.0,

54.6, 73.2, 81.5, 119.9, 120.1, 120.2, 125.6, 126.2, 126.4, 127.4, 128.0, 128.1, 128.3, 128.4, 128.5, 140.1, 141.2, 144.5, 144.7, 148.9, 149.2, 174.1, 174.2. Anal. calcd for $C_{33}H_{42}N_2O_4SSi$: C, 67.07; H, 7.16; N, 4.74; S, 5.43. Found: C, 67.27; H, 7.38; N, 4.56; S, 5.34.

1.1.7. *t*-Butyl (2*S*,2′*RS*)-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)-amino-3-[*N*-(2-trimethylsilylethanesulfonyl)aziridin-2′-yl]propanoate ((*S*,*RS*)-17). Following the same procedure as for the preparation of (2*R*,4*RS*)-**17**, compound (*S*)-**16** (2.39 g, 5.8 mmol) in acetonitrile (25 mL) containing 3 Å molecular sieves (3.75 g) was treated with $Cu(CH_3CN)_4PF_6$ (0.63 g, 1.68 mmol) and a mixture of $SesNH_2$ (1.37 g, 7.6 mmol) and iodosylbenzene (1.7 g, 7.7 mmol) in five portions. After the usual work-up, the crude product was purified by chromatography on silica gel (ethyl acetate 1:19 then 1:9) affording compound (*S*,*RS*)-**17** as a 7:3 mixture of diastereomers (0.95 g, 28%) whose spectral characteristics were identical to those of compound (*R*,*RS*)-**17**.

1.1.8. *t*-Butyl 4-pentenoate (20). A solution of 4-pentenoic acid (1 g, 10 mmol), *t*-butanol (2.2 g, 40 mmol) and DMAP (20 mg, 0.16 mmol) in dichloromethane (5 mL) was treated at 0 °C with DCC (2.25 g, 11 mmol). The reaction mixture was stirred for 15 min at 0 °C and then for 20 h at rt. The precipitate was removed by filtration through Celite, the filtrate was evaporated under vacuum, the residue was taken up in dichloromethane (20 mL) and washed successively with 0.1 M HCl (2×20 mL), saturated aqueous $NaHCO_3$ (20 mL) and water (2×20 mL). The organic phase was dried over $MgSO_4$, the solvent was evaporated and the residue was chromatographed on silica gel affording compound **20**[33] as a colorless oil (710 mg, 45%): IR (film) 2979, 2932, 1732, 1153 cm^{-1}; ESMS *m*/*z* 179 $(M+Na)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.31–2.35 (m, 4H), 4.96–5.10 (m, 2H), 5.73–5.92 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.2, 29.2, 34.8, 80.3, 115.3, 137.1, 172.6.

1.1.9. *t*-Butyl (*R*,*S*)-3-[*N*-(2-trimethylsilylethanesulfonyl)-aziridin-2′yl]propanoate (*rac*-21). Following the same procedure as for the preparation of **17**, compound **20** (211 mg, 1.35 mmol) in acetonitrile (5.3 mL) containing 3 Å molecular sieves (0.7 g) was treated with $Cu(CH_3CN)_4PF_6$ (126 mg, 0.34 mmol) and a mixture of $SesNH_2$ (318 mg, 1.75 mmol) and iodosylbenzene (385 mg, 1.75 mmol) in five portions. After the usual work-up, the crude product was purified by chromatography on silica gel (ethyl acetate–heptane 1:4), affording compound *rac*-**21** as an orange oil (115 mg, 25%): IR (film) 3297, 2954, 1729 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.10–1.17 (m, 2H), 1.44 (s, 9H), 1.62–1.75 (m, 1H), 1.90–2.02 (m, 1H), 2.13 (d, 1H, *J*=4.6 Hz), 2.38 (t, 2H, *J*=7.0 Hz), 2.60 (d, 1H, *J*=7.0 Hz), 2.73–2.82 (m, 1H), 3.04–3.12 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −1.9, 9.8, 26.9, 28.2, 32.6, 33.7, 38.0, 48.9, 80.9, 171.8. HRESMS *m*/*z* 358.1481 $(M+Na)^+$ ($C_{14}H_{29}NO_4SSi+Na^+$ requires 358.1484).

1.1.10. Ethyl (*R*)-*N*-(9-phenyl-9*H*-fluoren-9-yl)allylglycinate ((*R*)-22). HCl gas was bubbled through a solution of compound (*R*)-**12** (4.0 g, 16.4 mmol) in dichloromethane (50 mL) for 75 min. The reaction mixture was stirred at rt for 5 h and then evaporated to dryness under vacuum affording ethyl (*R*)-allylglycinate hydrochloride (3.0 g, 100%): mp 89–91 °C; $[\alpha]_D^{26}$ +1 (c 0.65, MeOH); IR (film) 3406, 2981, 1744, 1487 cm^{-1}; ESMS *m*/*z* 144 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J*=7.1 Hz), 2.75–2.95 (m, 2H), 4.05–4.35 (m, 3H), 5.26 (dd, 1H, *J*=1.5, 10.1 Hz), 5.33 (dd, 1H, *J*=1.5, 16.9 Hz), 5.75–5.95 (m, 1H), 8.70–8.90 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 34.6, 52.9, 62.6, 121.5, 130.3, 168.8.

A solution of this compound (500 mg, 2.78 mmol) in nitromethane (5 mL) was then treated with potassium phosphate (1.18 g, 5.54 mmol) and 9-bromo-9-phenylfluorene (1.07 g, 3.3 mmol). The reaction mixture was stirred at rt for 72 h, ethanol (2 mL) was added and after 5 min of stirring, the mixture was filtered through Celite. The filter pad was washed with ethyl acetate, the filtrate and washings were combined, evaporated to dryness under vacuum and the residue was purified by column chromatography on silica gel (heptane–ethyl acetate 19:1), affording (*R*)-**22** as a pasty solid (985 mg, 92%): $[\alpha]_D^{22}$ +195 (c 2.01, $CHCl_3$); IR (film) 3314, 3062, 2979, 1729, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J*=7.1 Hz), 2.10–2.29 (m, 2H), 2.65–2.73 (m, 1H), 2.93 (br s, 1H), 3.58–3.70 (m, 1H), 3.70–3.82 (m, 1H), 4.97–5.01 (m, 1H), 5.01–5.05 (m, 1H), 5.61–5.76 (m, 1H), 7.13–7.72 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 39.9, 55.7, 60.5, 73.1, 117.7, 119.9, 120.0, 125.5, 126.3, 127.3, 127.5, 127.9, 128.4, 134.4, 140.3, 141.1, 144.9, 147.0, 149.3, 175.7. HRESMS *m*/*z* 406.1793 $(M+Na)^+$ ($C_{26}H_{25}NO_2+Na^+$ requires 406.1783).

1.1.11. Ethyl (2*R*,2′*RS*)-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)-amino-3-[*N*-(2-trimethylsilylethanesulfonyl)aziridin-2′-yl]propanoate ((*R*,*RS*)-23). Following the same procedure as for the preparation of **17**, compound (*R*)-**22** (210 mg, 0.55 mmol) in acetonitrile (2.2 mL) containing 3 Å molecular sieves (0.3 g) was treated with $Cu(CH_3CN)_4PF_6$ (50 mg, 0.134 mmol) and a mixture of $SesNH_2$ (131 mg, 0.72 mmol) and iodosylbenzene (156 mg, 0.71 mmol) in five portions. After the usual work-up and chromatography of the residue on silica gel (ethyl acetate–heptane 1:9 then 1:5), compound (*R*,*RS*)-**23** was obtained as a 1:1 mixture of diastereomers (80 mg, 26%): IR (film) 3310, 2953, 1730, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.07 (s, 9H), 0.80–1.13 (m, 10H), 1.30–1.60 (m, 2H), 1.77–2.00 (m, 2H), 1.87 (d, 1H, *J*=4.4 Hz), 2.06 (d, 1H, *J*=4.4 Hz), 2.43 (d, 1H, *J*=7.0 Hz), 2.63–3.2 (m, 9H), 3.63–3.87 (m, 4H), 7.08–7.47 (m, 22H), 7.66–7.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 9.5, 10.0, 30.5, 32.7, 33.3, 37.0, 37.1, 37.2, 37.3, 48.8, 49.0, 54.2, 54.4, 61.1, 73.1, 120.0, 120.2, 125.5, 126.2, 126.4, 127.5, 127.6, 128.2, 128.4–128.7, 140.1, 141.4, 144.3, 144.5, 148.5, 148.6, 148.9, 149.0, 175.2, 175.3. HRESMS *m*/*z* 585.2200 $(M+Na)^+$ ($C_{31}H_{38}N_2O_4SSi+Na^+$ requires 585.2219).

1.1.12. *t*-Butyl (2*S*,4*S*)- and (2*S*,4*R*)-1-*N*-(9-phenyl-9*H*-fluoren-9-yl)-4-*N*-(2-trimethylsilylethanesulfonyl)-aminoproline ((*S*,*S*)-24 and (*S*,*R*)-24, respectively). A solution of compound (*S*,*RS*)-**17** (147 mg, 0.25 mmol) in DMF (2 mL) was heated at 110 °C for 70 h. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (heptane–ethyl acetate 7:1) affording by order of elution compounds

(*S*,*S*)-**24** and (*S*,*R*)-**24**. Compound (*S*,*S*)-**24**: (67 mg, 46%): $[\alpha]_D^{25}$ +102 (c 0.91, $CHCl_3$); IR (film) 3274, 2956, 1720, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 1.00–1.10 (m, 2H), 1.26 (s, 9H), 1.60–1.70 (m, 1H), 1.95–2.05 (m, 1H), 2.85–2.95 (m, 2H), 3.04 (dd, 1H, *J*=1.7, 10.7 Hz), 3.12 (dd, 1H, *J*=4.4, 9.7 Hz), 3.30 (d, 1H, *J*=9.7 Hz), 3.85–3.95 (m, 1H), 6.37 (d, 1H, *J*=10.3 Hz), 7.10–7.20 (m, 1H), 7.20–7.50 (m, 8H), 7.50–7.60 (m, 2H), 7.60–7.65 (m, 1H), 7.75–7.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8, 10.7, 28.0, 38.5, 50.3, 53.5, 56.7, 59.4, 76.0, 81.4, 120.0, 120.4, 126.7, 127.0, 127.5, 127.6, 127.7, 128.2, 128.5, 128.7, 128.9, 139.4, 141.9, 142.4, 145.5, 148.1, 176.3. HRESMS *m*/*z* 591.2675 $(MH)^+$ ($C_{33}H_{43}N_2O_4SSi$ requires 591.2713).

Compound (*S*,*R*)-**24** (25 mg, 17%): $[\alpha]_D^{22}$ +18 (c 0.66, $CHCl_3$); IR (film) 3271, 2926, 2854, 1735, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.85–0.95 (m, 2H), 1.29 (s, 9H), 1.50–1.70 (m, 1H), 1.95–2.10 (m, 1H), 2.58 (t, 1H, *J*=9.0 Hz), 2.80–2.90 (m, 2H), 3.32 (dd, 1H, *J*=1.8, 9.7 Hz), 3.52 (dd, 1H, *J*=6.4, 9.0 Hz), 4.02 (d, 1H, *J*=8.9 Hz), 4.05–4.20 (m, 1H), 7.05–7.45 (m, 8H), 7.50–7.60 (m, 3H), 7.60–7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9, 10.8, 28.0, 40.0, 49.5, 52.1, 55.1, 60.3, 76.5, 80.5, 120.0, 120.3, 126.4, 126.8, 127.5, 127.6, 127.9, 128.1, 128.6, 128.7, 128.8, 140.3, 141.0, 142.6, 146.9, 147.6, 174.3. HRESMS *m*/*z* 591.2714 $(MH)^+$ ($C_{33}H_{43}N_2O_4SSi$ requires 591.2713).

1.1.13. *t*-Butyl (2*S*,4*S*)- and (2*S*,4*R*)-5-azido-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)amino-4-*N*-(2-trimethylsilylethanesulfonyl)aminopentanoate ((*S*,*S*)-25 and (*S*,*R*)-25, respectively). To a solution of compound (*S*,*RS*)-**17** (870 mg, 1.47 mmol) in DMF (12 mL) were successively added under argon at rt solid sodium azide (400 mg, 6.15 mmol) and boron trifluoride etherate (0.75 mL, 6.1 mmol). The mixture was heated at 65 °C for 80 h, and after cooling to rt, water (120 mL) was added. The solution was extracted with ethyl acetate (3×200 mL), the organic extracts were combined, dried over $MgSO_4$ and evaporated. A first purification of the residue by column chromatography on silica gel (ethyl acetate–heptane 1:7) provided (*S*,*S*)-**25** and (*S*,*R*)-**25** as a mixture (760 mg, ~75%) contaminated with a small amount of the aminoproline derivative **24**. The isomeric azides were partially separated by careful chromatography on silica gel using ethyl acetate–toluene (1:18) as eluting solvent. Pure (*S*,*S*)-**25** (major diastereomer) was finally obtained by preparative HPLC of the enriched fraction on a PrepPak Deltapak C18 cartridge (15 μm, 100 Å, 47×250 mm) using 35:65 isocratic H_2O+0.1% CH_3CO_2H/CH_3CN+0.1% CH_3CO_2H: $[\alpha]_D^{25}$ −134 (c 1.0, $CHCl_3$); IR (film) 3286, 2926, 2103, 1728, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.05–1.15 (m, 2H), 1.25 (s, 9H), 1.50–1.60 (m, 1H), 1.70–1.80 (m, 1H), 2.65–2.75 (m, 1H), 2.85–3.05 (m, 2H), 3.08 (dd, 1H, *J*=6.1, 12.4 Hz), 3.18 (dd, 1H, *J*=5.8, 12.4 Hz), 3.45–3.60 (m, 1H), 7.20–7.50 (m, 11H), 7.70–7.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8, 10.6, 28.0, 35.9, 50.0, 52.4, 54.2, 54.5, 73.3, 82.0, 120.1, 120.4, 126.0, 126.2, 126.4, 127.6, 128.2, 128.3, 128.8, 129.0, 140.3, 141.3, 143.6, 147.9, 148.5, 173.6. HRESMS *m*/*z* 656.2727 $(M+Na)^+$ ($C_{33}H_{43}N_5O_4SSi+Na^+$ requires 656.2703).

Minor diastereomer (*S*,*R*)-**25**: IR (film) 3283, 2954, 2929, 2103, 1724, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.00–1.10 (m, 2H), 1.25 (s, 9H), 1.50–1.64 (m, 2H), 2.47 (t, 1H, *J*=6.3 Hz), 2.79–3.03 (m, 3H), 3.28 (dd, 1H, *J*=4.4, 12.5 Hz), 3.35 (br s, 1H), 3.74–3.87 (m, 1H), 4.25 (d, 1H, *J*=9.1 Hz), 7.17–7.47 and 7.67–7.77 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.7, 10.4, 28.0, 38.5, 50.3, 50.8, 53.4, 55.1, 73.2, 81.9, 120.0, 120.3, 125.8, 126.1, 126.2, 127.5, 128.2, 128.6, 128.9, 140.2, 141.1, 144.2, 148.7, 149.2, 174.2. HRESMS *m*/*z* 656.2676 $(M+Na)^+$ ($C_{33}H_{43}N_5O_4SSi+Na^+$ requires 656.2703).

1.1.14. *t*-Butyl (2*S*,4*S*)-5-[*N*′,*N*″-bis(benzyloxycarbonyl)-guanidino]-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)amino-4-*N*-(2-trimethylsilylethanesulfonyl)aminopentanoate ((*S*,*S*)-26). To a solution of compound (*S*,*S*)-**25** (100 mg, 0.16 mmol) in THF (9 mL) was added triphenylphosphine (55 mg, 0.21 mmol) and water (170 μL, 9.4 mmol). The reaction mixture was refluxed for 20 h, the solvent was evaporated and the residue was dried under vacuum. The latter was dissolved in DMF (1.8 mL) and *S*-methyl *N*,*N*′-bis(benzyloxycarbonyl)isothiourea (68 mg, 0.19 mmol), mercuric chloride (52 mg, 0.19 mmol) and triethylamine (66 μL, 0.47 mmol) were added. The reaction mixture was stirred for 84 h at rt, diluted with ethyl acetate (25 mL) and filtered. The filtrate was washed with a 10% aqueous citric acid solution (3×15 mL) and then with saturated aqueous NaCl (2×15 mL), dried over $MgSO_4$ and evaporated under vacuum. Chromatography of the residue on silica gel (ethyl acetate–heptane 1:3) afforded compound (*S*,*S*)-**26** as a pasty white solid (116 mg, 80%): $[\alpha]_D^{24}$ −55 (c 0.51, $CHCl_3$); IR (film) 3333, 2954, 1729, 1642 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.05–1.15 (m, 2H), 1.21 (s, 9H), 1.50–1.60 (m, 1H), 1.65–1.80 (m, 1H), 2.71 (dd, 1H, *J*=3.6, 8.0 Hz), 2.80–3.05 (m, 3H), 3.35–3.45 (m, 1H), 3.60–3.70 (m, 2H), 5.09 (s, 2H), 5.17 (d, 1H, *J*=12.0 Hz), 5.25 (d, 1H, *J*=12.0 Hz), 7.10–7.50 (m, 21H), 7.60–7.70 (m, 3H), 8.55 (t, 1H, *J*=5.3 Hz), 11.7 (br s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −1.9, 10.3, 27.9, 35.6, 44.0, 49.7, 51.9, 54.2, 67.3, 68.4, 73.3, 82.1, 120.0, 120.4, 126.0, 126.1, 126.4, 127.5, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.9, 134.6, 136.7, 140.2, 141.3, 143.5, 147.8, 148.4, 153.7, 156.4, 163.6, 173.6. HRESMS *m*/*z* 940.3763 $(M+Na)^+$ ($C_{50}H_{59}N_5O_8SSi+Na^+$ requires 940.3751).

1.1.15. *t*-Butyl (2*S*,4*R*)-5-[*N*′,*N*″-bis(benzyloxycarbonyl)-guanidino]-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)-4-*N*-(2-trimethylsilylethanesulfonyl)-2,4-diaminopentanoate ((*S*,*R*)-26). Following the same procedure as for the preparation of (*S*,*S*)-**27**, compound (*S*,*R*)-**25** (156 mg, 0.25 mmol) in THF (18 mL) was refluxed for 20 h in the presence of triphenylphosphine (112 mg, 0.43 mmol) and water (350 μL, 19.4 mmol). After evaporation, the residue, dissolved in DMF (3 mL), was treated with *S*-methyl *N*,*N*′-bis(benzyloxycarbonyl)isothiourea (108 mg, 0.3 mmol), mercuric chloride (82 mg, 0.3 mmol) and triethylamine (105 μL, 0.75 mmol) and the reaction mixture was stirred for 60 h at rt. Work up as before followed by chromatography of the residue on silica gel (ethyl acetate–heptane 1:5) provided compound (*S*,*R*)-**26** as a pasty white solid (125 mg, 51%): $[\alpha]_D^{23}$ −38 (c 1.04, $CHCl_3$); IR (film) 3331, 1729, 1641 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s,

9H), 1.00–1.10 (m, 2H), 1.19 (s, 9H), 1.40–1.60 (m, 1H), 1.60–1.80 (m, 1H), 2.30–2.45 (m, 1H), 2.75–3.00 (m, 3H), 3.25–3.30 (m, 1H), 3.80–3.95 (m, 1H), 5.10 (s, 2H), 5.18 (d, 1H, J=12.1 Hz), 5.24 (d, 1H, J=12.1 Hz), 5.43 (d, 1H, J=7.0 Hz), 7.20–7.50 (m, 21H), 7.60–7.70 (m, 2H), 8.40 (t, 1H, J=5.7 Hz), 11.7 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8, 10.5, 28.0, 39.9, 44.1, 50.0, 51.9, 53.5, 67.3, 68.5, 73.2, 81.6, 120.0, 120.3, 125.7, 126.2, 126.6, 127.4, 128.1, 128.4–128.8, 134.6, 136.7, 140.3, 141.1, 144.2, 148.7, 149.4, 153.6, 157.3, 163.4, 174.4. HRESMS m/z 940.3741 $(M+Na)^+$ ($C_{50}H_{60}N_5O_8SSi+Na^+$ requires 940.3751).

1.1.16. *t*-Butyl (2*S*,4′*S*)-3-[2′-*N*-(benzyloxycarbonyl)-aminoimidazolidin-4′-yl]-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)aminopropanoate ((*S*,*S*)-27). A mixture of compound (*S*,*S*)-**26** (281 mg, 0.31 mmol) and cesium fluoride (141 mg, 0.93 mmol) in DMF (3.5 mL) was heated at 90 °C for 24 h. Water (50 mL) was added and the solution was extracted with ethyl acetate (3×50 mL). The organic extracts were combined, dried over $MgSO_4$ and evaporated leaving a crude product which was purified by column chromatography on silica gel (heptane–ethyl acetate 1:1), affording compound (*S*,*S*)-**27** as a viscous oil which slowly solidified (65 mg, 35%). HPLC of an aliquot on a Waters C18 Symmetry column (4.6×250 mm) using water+0.1% CH_3CO_2H/CH_3CN+0.1% CH_3CO_2H as eluting solvents (85:15 to 12:88 gradient over 40 min; 1 mL/min flow rate) indicated that compound (*S*,*S*)-**27** was 99% pure: $[\alpha]_D^{23}$ −96 (c 0.84, $CHCl_3$); IR (film) 3389, 2929, 1724, 1657, 1622 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.50–1.70 (m, 2H), 2.44–2.54 (m, 1H), 3.09 (dd, 1H, J=7.3, 9.3 Hz), 3.22 (br s, 1H), 3.69 (t, 1H, J=9.3 Hz), 4.01–4.14 (m, 1H), 5.05 (d, 1H, J=12.6 Hz), 5.13 (d, 1H, J=12.6 Hz), 6.56–6.84 (br s, 1H), 7.13–7.45 (m, 16H), 7.65–7.75 (m, 2H), 7.80–8.20 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 41.1, 48.1, 51.7, 53.9, 66.5, 73.1, 81.6, 120.0, 120.4, 125.1, 126.2, 126.3, 127.4, 127.7, 127.9, 128.1, 128.4–128.5, 128.9, 137.6, 140.2, 141.1, 144.3, 148.8, 149.0, 163.2, 164.8, 174.4. HRESMS m/z 603.3009 $(MH)^+$ ($C_{37}H_{39}N_4O_4$ requires 603.2971).

1.1.17. *t*-Butyl (2*S*,4′*R*)-3-[2′-*N*-(benzyloxycarbonyl)-aminoimidazolidin-4′-yl]-2-*N*-(9-phenyl-9*H*-fluoren-9-yl)aminopropanoate ((*S*,*R*)-27). Following the same procedure as for the preparation of (*S*,*S*)-**27**, compound (*S*,*R*)-**26** (119 mg, 0.13 mmol) in DMF (1.5 mL) was treated with cesium fluoride (60 mg, 0.4 mmol) for 24 h at 90 °C. Work-up and purification as before afforded compound (*S*,*R*)-**27** as a pasty solid (26 mg, 33%). HPLC analysis of an aliquot under the same conditions as for (*S*,*S*)-**27** showed (*S*,*R*)-**27** to be 98% pure: $[\alpha]_D^{23}$ −100 (c 0.9, $CHCl_3$); IR (film) 2925, 1727, 1652, 1622 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.50–1.65 (m, 1H), 1.65–1.80 (m, 1H), 2.40–2.50 (m, 1H), 3.01 (dd, 1H, J=7.7, 9.7 Hz), 3.36 (t, 1H, J=9.7 Hz), 3.95–4.10 (m, 1H), 5.16 (d, 1H, J=12.5 Hz), 5.23 (d, 1H, J=12.5 Hz), 7.15–7.45 (m, 16H), 7.65–7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 40.4, 47.6, 53.4, 54.5, 67.8, 73.2, 81.8, 120.0, 120.3, 125.2, 126.2, 126.8, 127.5, 128.2, 128.3, 128.6, 128.7, 136.1, 140.4, 141.1, 143.8, 148.4, 149.2, 159.8, 161.1, 174.3. HRESMS m/z 603.3000 $(MH)^+$ ($C_{37}H_{39}N_4O_4$) requires 603.2971).

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