Tetrahedron 66 (2010) 8982–8991

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of substituted (*S*)-2-aminotetralins via ring-opening of aziridines prepared from L-aspartic acid β-*tert*-butyl ester

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ARTICLE INFO

Article history:
Received 21 June 2010
Received in revised form 15 August 2010
Accepted 6 September 2010
Available online 21 September 2010

Keywords:
Chiral pool
L-Aspartic acid
Aziridine
Friedel–Crafts cyclisation
(*S*)-2-Aminotetralins

ABSTRACT

This paper describes the total synthesis of the hydrochloride salts of (2*S*)-2-amino-7-methoxytetralin (**21**-**HCl**) and (2*S*)-2-amino-6-fluoro-7-methoxytetralin (**ST1214**), from a common enantiomerically pure aziridine **4b**, which was available from L-aspartic acid β-*tert*-butyl ester. The synthesis of **21**-**HCl** and **ST1214** proceeded in nine steps and 5 and 6% overall yields, respectively. Key steps are the regioselective ring-opening of **4b** with ArMgBr/CuBr·SMe_2 and the intramolecular Friedel–Crafts cyclisation providing α-tetralone. Substituted naphthalenes were formed as side products in the latter reaction.

1. Introduction

The pharmacological activity of 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene) was first described by Bamberger and Filehne in 1889.[1] Since then a large number of articles and patents, mostly describing studies of the physiological properties of this class of compounds, have appeared.[2] Today, several enantiopure 2-aminotetralins (AT) are used in the treatment of medical conditions like Parkinson's disease,[3] glaucoma,[4] and septic shock[5,6] (Fig. 1).

The availability of substituted AT building blocks in high enantiomeric purity for the synthesis and biological testing has been limited to less general methods and/or to non-cost efficient methods. AT in enantiomeric pure forms have been obtained by optical resolution of starting materials to enantiopure precursors,[7–9] and from optical resolution of racemic AT.[10,11] Various chemo enzymatic protocols have also been successfully utilized in the synthesis of enantiopure AT.[12–14] Starting from substituted 2-tetralones, stereoselective catalytic hydrogenation of prochiral enamides and ene carbamates have been performed with chiral catalysts, typically complexes of ruthenium[15–17] or rhodium.[18–20] Naturally occurring α-amino acids like L-aspartic acid,[21,22] L-phenylalanine,[23] and L-tyrosine[23] have been used in multi-step reactions to construct optically pure AT.

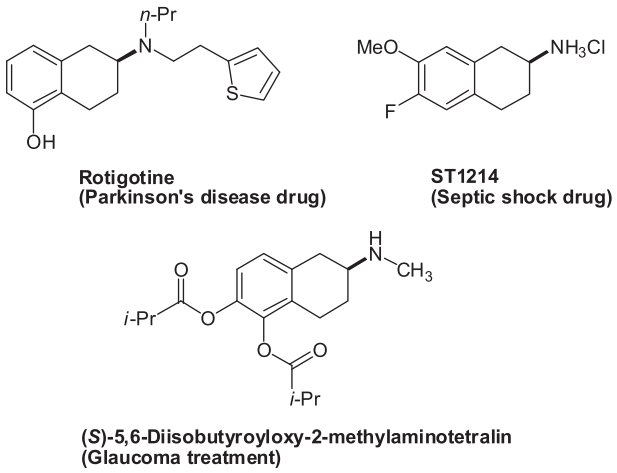

Fig. 1. Pharmacological active 2-aminotetralins.

Herein, we report a new chiral pool synthesis of substituted AT starting from L-aspartic acid β-*tert*-butyl ester (**1**, see Scheme 1). The strategy applies regioselective ring-opening of the corresponding, and activated aziridino *tert*-butyl ester **4** with various substituted aryl nucleophiles to compounds **5**–**8**. This provides a potentially basis for the preparation of a variety of substituted and enantiopure AT with (*S*)-configuration. A Friedel–Crafts cyclisation, reductive deoxygenation of the ring carbonyl group, and finally

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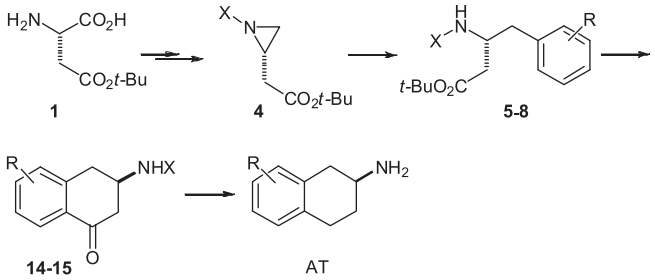
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.09.025



Scheme 1. General protocol for asymmetric synthesis of substituted (*S*)-2-amino-tetralins starting from L-aspartic acid β-*tert*-butyl ester.

removal of the *N*-protecting group complete the synthesis of substituted AT.

Four target molecules **21**–**23** and **ST1214** (see Fig. 2), differing in the aromatic substituent pattern, were chosen to test the general synthetic route shown in Scheme 1. Two steps in the synthesis appear to be central: (i) the regioselective ring-opening of the enantiopure aziridine **4** with substituted aryl nucleophile, and (ii) the intramolecular Friedel–Crafts cyclisation to form a α-tetralone. Two *N*-protected aziridines **4a**[24] and **4b** (see Scheme 2) were chosen to be tested in the former step. The *N*-benzyloxycarbonyl (Cbz) and *N*-*p*-toluenesulfonyl (Ts) are, in general, complimentary protecting groups for amines,[25a,b] but also activate (electron-withdrawing groups) the aziridine for ring-opening reactions.[26] The bulky *tert*-butyl ester group in **4a**,**b** was selected to protect the carbonyl moiety against nucleophilic attack.[25c] The target molecules have an electron-rich aromatic ring in common, which should be beneficial for a successful intramolecular Friedel–Crafts cyclisation to form α-tetralone.

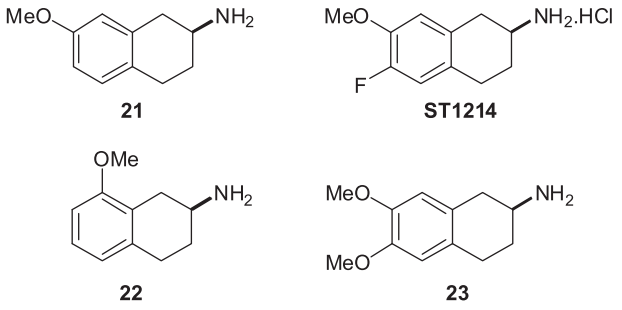
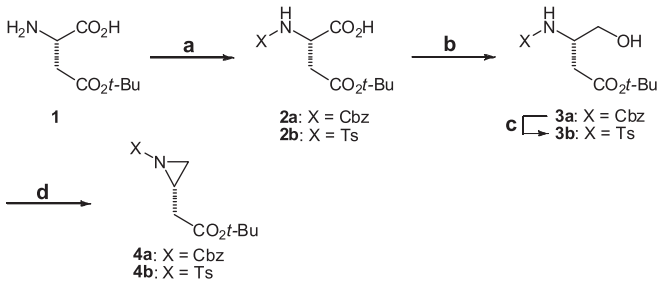


Fig. 2. Target molecules.



Scheme 2. (a) (i) Me_3SiCl, (ii) Et_3N, TsCl, **2b** (84% yield); (b) (i) *i*-BuOCOCl, NMM, DME, −15 °C, (ii) $NaBH_4$, **3a** (89% yield), **3b** (0% yield); (c) (i) H_2, 10% Pd/C, abs EtOH, rt, (ii) TsCl, DMAP, Et_3N, DCM, rt, **3b** (84% yield); (d) DEAD, Ph_3P, THF, 0 °C, **4a** (71% yield), **4b** (90% yield).

2. Results and discussion

2.1. Preparation of activated aziridino *tert*-butyl esters 4a and 4b from L-aspartic acid β-*tert*-butyl ester (1)

Aziridines **4a**[24] and **4b** were prepared from respective L-apartic acid derivatives as described in Scheme 2. The *N*-protected analogues of **1** were either purchased (**2a**, X=Cbz) or synthesized (**2b**, X=Ts) via a modified protocol described by Barlos et al. (Scheme 2).[27] The Cbz amino alcohol **3a** was obtained from a sodium borohydride reduction of **2a**, via an in situ formed mixed anhydride intermediate, in 89% yield.[28] To our surprise, a similar attempt to reduce the Ts protected amino acid **2b** to **3b** did not work at all. Thus, other well-known methods for reduction of amino acids were tested: (i) the combined sodium borohydride/iodine reducing system described by McKennon et al. failed to provide **3b**,[29] (ii) reduction with borane (6 equiv) afforded **3b** in modest 25% yield (best result),[30] and (iii) conversion of **2b** to an *N*-acylbenzotriazole,[31] which was further treated with sodium borohydride, resulted in ca. 20% yield of **3b**.[32] The low yield observed in the latter method was primarily due to difficulties in the *N*-acylbenzotriazole preparation, and not the reduction itself. An alternative attempt to achieve alcohol **3b** in acceptable yield was made by a de- and reprotection sequence starting from alcohol **3a** (see step c, Scheme 2). Catalytic hydrogenolysis over Pd/C and subsequent *N*-tosylation gave **3b** in 84% overall yield.

Aziridines **4a** and **4b** were prepared from respective amino alcohols in a Mitsunobu-type reaction by adopting a procedure described by Lapinsky and Bergmeier, in 71 and 90% yields, respectively (see Scheme 2).[33]

An alternative Mitsunobu reagent system to the classical diethyl azodicarboxylate (DEAD)—triphenylphosphine (Ph_3P) reagents is 1,1′-(azodicarbonyl)piperidine (ADDP)—tributylphosphine (*n*-Bu_3P).[34] The latter system has been reported to provide higher yields in the Mitsunobu reaction for compounds with $pK_a>11$. Test reactions with **3a** (predicted $pK_a=11.33\pm0.46$)[35] resulted, however, in lower yields of **4a** (up to 28%), and the ADDP/*n*-Bu_3P system was not evaluated any further.

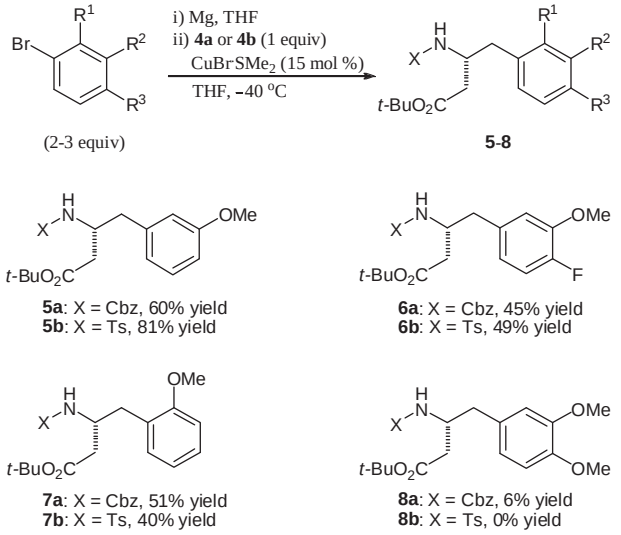
In the 'normal' Mitsunobu reaction, the hydrazine side product (formed in stoichiometric amount) might be a troublesome waste in the purification step.[36] Recently, an organocatalytic Mitsunobu-type reaction, using catalytic amounts of DEAD was reported by But and Toy.[37] In their protocol, stoichiometric amounts of iodosobenzene diacetate, $PhI(OAc)_2$, as an oxidant converts the hydrazine side product back to the DEAD. By utilizing this system, only a catalytic amount of DEAD (0.1 equiv) is required, and easily removable iodobenzene and acetic acid are formed together with triphenylphosphine oxide as by-products. Unfortunately, in our hands, applying the organocatalytic system with amino alcohol **3b** provided only stoichiometric amounts of **4b** with respect to DEAD, i.e., up to 10% yield.

2.2. Nucleophilic ring-opening of aziridines 4a and 4b

Recently, Song et al. reported the reactivity of the Cbz protected aziridine **4a** with various *N*-, *O*- and *S*-nucleophiles in pseudopeptide synthesis.[24] Excellent regioselectivity was observed for *N*- and *S*-nucleophiles with attack entirely at the less substituted aziridine carbon. For *O*-nucleophiles, in combination with an activating Lewis acid ($BF_3\cdot OEt_2$), the regioselectivity in the ring-opening reaction was poor and varied from 1:1 to 3:1. The report did not mention results with carbon nucleophiles.

The regioselective ring-opening of **4a** and **4b** with aryl cuprates were performed in accordance to an adopted literature procedure, described by Burgaud et al.[38] The cuprate was prepared from an arylmagnesium bromide (ArMgBr) and a catalytic amount of $CuBr\cdot SMe_2$ at −40 °C. Initial experiments revealed that stoichiometric control of the Grignard reagent was crucial for the outcome of the reaction. Therefore, freshly prepared ArMgBr solutions were always standardized by titration utilizing salicylaldehyde phenylhydrazone as an indicator.[39] The results from reacting aziridine **4a** and **4b** with ArMgBr/$CuBr\cdot SMe_2$ (ArMgBr prepared from four bromobenzenes: 3-bromoanisole, 2-fluoro-5-bromoanisole, 2-bromoanisole, and 4-bromoveratrole) are presented in Scheme 3.

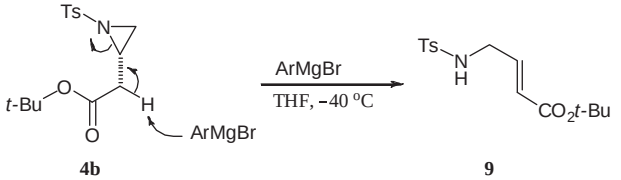
In all cases the ring-opening reaction gave only one regioisomer, formed by attack at the less substituted aziridine carbon, as observed by ^{1}H NMR spectroscopic analysis of the crude product. In general, 2 equiv of the respective Grignard reagent was required to reach acceptable yields. Attempts with 1.0–1.5 equiv of the nucleophile resulted in low yields, and in some cases failed to provide any product at all. In gram scale experiments, we found it convenient to add 3 equiv of the reagent due to a significantly lower conversion. Compounds **5a** and **5b** were isolated in 60 and 81% yields, respectively, and represent the most successful ring-opening reactions of aziridines **4a**,**b** (see Scheme 3). For compounds **6a**,**b** and **7a**,**b** the yields were typically 40–50%. Reactions with the highly electron-rich veratrole nucleophile, prepared from 4-bromoveratrole, proved to be challenging and afforded **8a** in only 6% yield, whereas **8b** was not detected at all.



Scheme 3. Nucleophilic ring-opening of aziridines **4a**,**b** with various aryl cuprates.

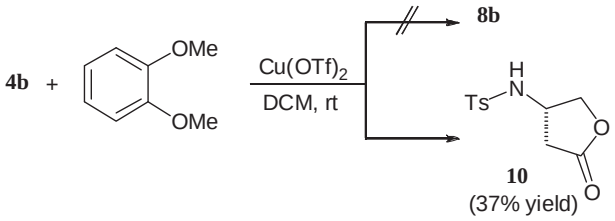
In all reactions with the *N*-Cbz aziridine **4a**, various amounts of benzyl alcohol (up to 23%) were observed in the crude reaction mixture. This occurrence can probably be explained by the fact that the Cbz group is not fully compatible with Grignard reagents. We did also observe various amounts of biaryls (Wurtz coupling products), which are known side products in this type of reactions, especially for electron-rich arenes.[40]

In the ring-opening reactions of **4b**, various amounts of *N*-Ts alkene **9** were isolated as side product (4–27% yield, see Scheme 4). A suggested mechanism for the base promoted reaction is shown in Scheme 4. However, a mechanism involving aziridinyl anions followed by a 1,2-H shift, as recently reviewed by Florio and Luisi, cannot be excluded.[41]



Scheme 4. Base promoted ring-opening of Ts-aziridine **4b**.

Because of the unsuccessful attempts to synthesize dimethoxy analogues **8a** and **8b**, another approach was also tested. Aziridine **4b** was reacted with veratrole under the addition of an azaphilic Lewis acid {$Cu(OTf)_2$[42] or $BF_3{\cdot}OEt_2$[43]}. From the reaction mixtures containing several unidentified products, only lactone **10**[44] was isolated and characterized (Scheme 5).

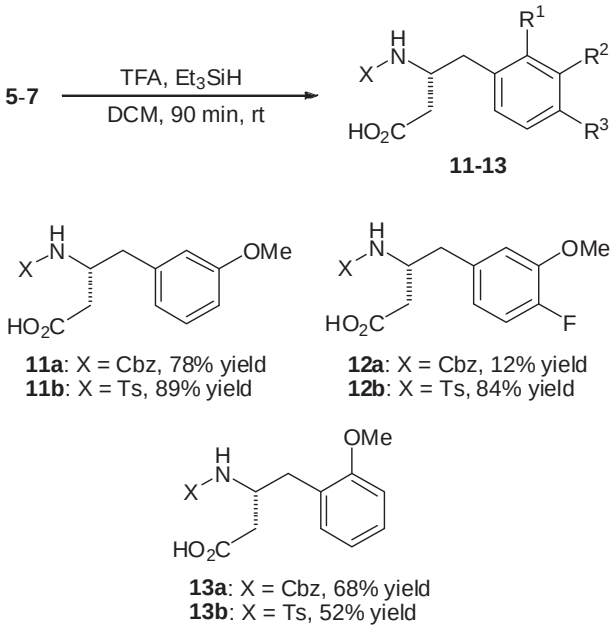


Scheme 5. Lewis acid catalyzed lactonization of aziridine **4b**.

2.3. Intramolecular Friedel–Crafts cyclisation

The attempted intramolecular Friedel–Crafts cyclisation of *tert*-butyl ester **5b**, adopting a recent literature procedure utilizing 1.1 equiv of dimethylchlorosilane (Me_2HSiCl) and 10 mol % of indium tribromide ($InBr_3$) as reagents at 80 °C,[45] failed to give the desired α-tetralone **14b**. Me_2HSiCl is reported to react with *tert*-butyl ester on the expense of its silane proton, forming a chlorosilyl ester, $RCO_2Si(Cl)Me_2$. The latter compound mimics an acid chloride and, in combination with $InBr_3$, a Friedel–Crafts acylation was expected. Decreasing the reaction temperature to 50 °C was also unsuccessful and resulted in a gradual decomposition of **5b**. These negative results forced us to look for other mild procedures for Friedel–Crafts acylation, preferably described to work at ambient, or lower, reaction temperatures.

Finally, we ended up with literature methods using carboxylic acid as substrate. A selective cleavage of *tert*-butyl esters **5a**,**b**, **6a**,**b**, and **7a**,**b** to respective carboxylic acids was performed in accordance to a procedure described by Mehta et al.,[46] where triethylsilane is used as a carbocation scavenger in the presence of trifluoroacetic acid (TFA) in DCM (see Scheme 6). Except for the preparation of **12a**, the yields varied in the range of 52–89%.



Scheme 6. Transforming *tert*-butyl esters to carboxylic acids.

The low isolated yield obtained for **12a** (12%) was primarily due to difficulties with purification of the compound, and not the reaction itself.

The intramolecular Friedel–Crafts cyclisation of **11a**,**b**, **12b**, and **13a**,**b** was evaluated by using two reported methods: method A (reagents: $PCl_5/SnCl_4$),[21] and method B {reagents: trifluoroacetic anhydride (TFAA)—trifluoroacetic acid (TFA)}.[47] The reagents given

for method A are well known from the literature to perform a range of Friedel–Crafts acylation reactions with related substrates,[21,48–50] and were chosen after an initial screening of alternative chlorinating reagents (oxalyl chloride, thionyl chloride) and Lewis acids ($AlCl_3$, $BF_3{\cdot}OEt2$, TMSOTf). A summary of the more promising results from the work with carboxylic acids **11a**,**b** and **12b** are presented in Table 1. The results clearly demonstrate that we did not succeed in finding optimal conditions for the reaction. The best results were obtained by applying method A at 0 °C providing α-tetralones **14a** (Table 1, entry 2), **14b** (entry 4) and **15b** (entry 8) in 28, 40, and 41% isolated yields, respectively. At room temperature, cyclisation of **11b** (entry 3) resulted in significant amounts of *p*-$TsNH_2$, and naphthalenes **16**[51] and **18**.[52] We rationalise that formation of the side products to go through two competitive (regioselective) reaction pathways I (**11b**→**14b**→**16**) and II (**11b**→**14b′**→**18**) as shown in Scheme 7. Aromatization of the two regioisomeric α-tetralones **14b** and **14b′** is expected to proceed through a keto-enol equilibrium, and from elimination of the respective enol tautomer. Since **14b′** or its enol tautomer was never detected in the reaction mixtures, we assume that the enol form of **14b′** is the major tautomer in pathway II, which is stabilized through a hydrogen bond and lined up for a rapid elimination to form naphthalene **18** (see Scheme 7).

The Friedel–Crafts cyclisations of **11b** applying method B resulted in decreased product regioselectivity {78:22 (pathway ratio I:II), entries 5 and 6} compared to method A (95:5, entry 3). The constant pathway I:II ratio (78:22), accompanied with decreased yield of **14b** (from 23 to 9% yield) and increased formation of **16** with prolonged reaction time (from 30 min to 16 h, entries 5 and 6, respectively), supports our mechanistic proposal given in Scheme 7.

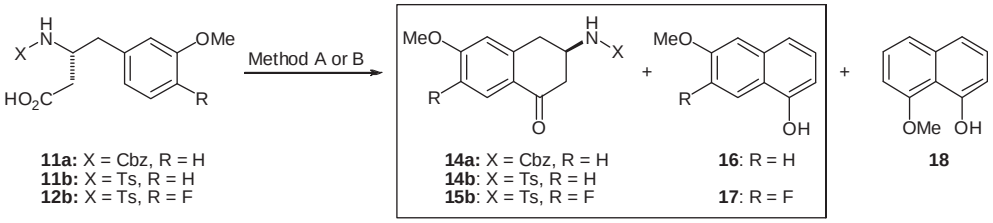
The intramolecular cyclisation of **12b**, either by method A or B, appears to be regiospecific, i.e., only follow pathway I, forming mixtures of α-tetralone **15b** and naphthalene **17** (entries 7, 8, and 9). Aromatization of **15b** to **17** is expected to follow the same mechanism as described in Scheme 7.

Attempted Friedel–Crafts cyclisation reactions of carboxylic acids **13a** and **13b**, either by using method A or B, provided only traces of α-tetralone.

2.4. Reductive deoxygenation and deprotection of *N*-protected α-tetralone to substituted AT

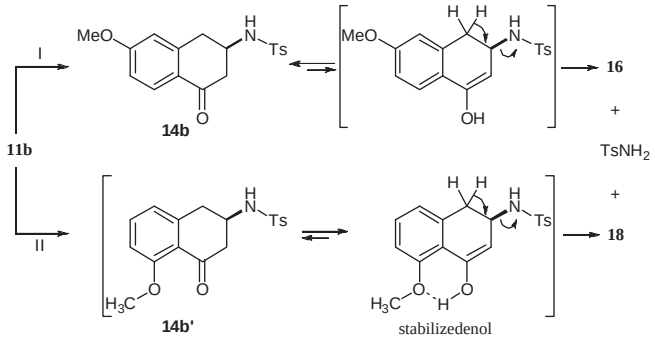
Reductive removal of the ring carbonyl group in α-tetralones **14b** and **15b** were performed by a catalytic hydrogenolysis (Pd/C) at medium pressure (5 atm H_2) by adopting a literature procedure (see Scheme 8).[22] The enantiomeric excess of **19** was determined to

Table 1
Intramolecular Friedel–Crafts cyclisation

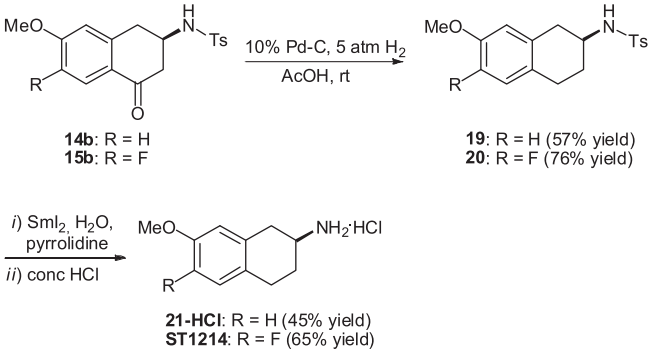


Entry	Substrate	Method	Conditions	Pathway I:II ratio[a]	Product	Yield[b] (%)
1	**11a**	A	0° (30 min)→rt (3 h)	97:3	**14a**	25
2	**11a**	A	0 °C (4 h)	97:3	**14a**	28
3	**11b**	A	0 °C (1 h)→rt (3 h)	95:5	**14b**	27[c]
4	**11b**	A	0 °C (6 h)	91:9	**14b**	40
5	**11b**	B	rt (30 min)	78:22	**14b**	23
6	**11b**	B	rt (16 h)	78:22	**14b**	9
7	**12b**	A	0 °C (1 h)→rt (3 h)	100:0	**15b**	39[d]
8	**12b**	A	0 °C (4 h)	100:0	**15b**	41
9	**12b**	B	0 °C (4 h)	100:0	**15b**	29

[a] The pathway ratio (regioselectivity ratio) was determined by ^1H NMR (400 MHz) spectroscopic analysis of the crude product. For substrate **11b**: pathway I is the sum of compounds **14b**+**16**, and pathway II is compound **18**.
[b] Isolated yield.
[c] Isolated side products: **16** (30% yield) and **18** (3% yield).
[d] Isolated side product: **17** (30% yield).



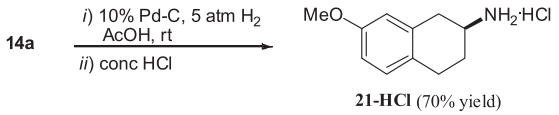
Scheme 7. Side products formed in the Friedel–Crafts cyclisation of **11b** via pathway I and II.



Scheme 8. Reductive removal of carbonyl group and deprotection of *N*-tosyl group.

be 99% by chiral HPLC analysis (Chiralpack AD). The instantaneous deprotection of tosylamides **19** and **20** to **21**-**HCl** and **ST1214**, respectively, were performed by a one-step SmI_2 protocol recently developed by Ankner and Hilmersson (see Scheme 8).[53]

The *N*-Cbz tetralone **14a** was simultaneously deoxygenated and deprotected by catalytic hydrogenolysis (Scheme 9). Treatment of the liberated amine with hydrochloric acid yielded target molecule **21**-**HCl** (70% yield, two steps). Tosylation of **21**-**HCl** provided a sample of tosylate **19** for the purpose of chiral HPLC analysis. High enantiopurity was also found here (99% ee), indicating no problems with racemization.



Scheme 9. Reductive deoxygenation and N-deprotection.

3. Conclusion

It has been demonstrated that chiral aziridines, obtained from L-aspartic acid β-*tert*-butyl ester, can be applied as chiral building blocks in the synthesis of various substituted (2*S*)-2-aminotetralins in highly enantiopure form in line with the general synthetic route presented in Scheme 1. The total synthesis of two of four selected target molecules, differing in the aromatic substituent pattern was accomplished in nine steps and 5–6% overall yields. The key steps are the regioselective ring-opening of aziridines **4a**,**b** with ArMgBr/CuBr·SMe_2 and the intramolecular Friedel–Crafts cyclisation providing α-tetralone. Both steps showed some limitations due to formation of side products. The ring-opening reaction worked for three of four anisoles ArMgBr/CuBr·SMe_2, yielding only one regioisomer by attack at the less substituted aziridine carbon atom and isolated in 40–81% yields. Optimal conditions for the Friedel–Crafts cyclisation were not found, since significant amounts of substituted naphthalenes (up to 33% yield) were formed, presumably from the desired α-tetralones (obtained in ca. 40% yield).

4. Experimental

4.1. General

All reactions were performed under an argon or nitrogen atmosphere. Tetrahydrofuran (THF) was distilled under nitrogen atmosphere from Na/benzophenone. Dichloromethane was distilled under nitrogen from calcium hydride. Melting points were determined on a Buchi 535 apparatus and are uncorrected. TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 312 nm and a 5% alcoholic molybdophosphoric acid for detection. Silica gel for flash chromatography was purchased from Merck. Optical rotations were measured with a Perkin–Elmer 241 Polarimeter. Enantiomeric excesses were determined by HPLC analysis, using Daicels column Chiralpak AD (250×4.6 mm). ^1H and ^{13}C NMR spectra (Bruker Advance DPX instruments 300/75 MHz and 400/100 MHz) were obtained from solutions of $CDCl_3$, and chemical shifts are in parts per million and referenced to TMS via the lock signal of the solvent. ^1H and ^{13}C NMR signals were assigned by 2D correlation techniques (COSY, HSQC, HMBC). IR spectra were run on a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography. The elemental analyses were performed at the Mikroanalytisches labor Beller, Göttingen, Germany.

4.2. Preparation of activated aziridino *tert*-butyl esters 4a and 4b from L-aspartic acid β-*tert*-butyl ester (1)

Commercially available (*S*)-2-Amino-4-*tert*-butoxy-4-oxobutanoic acid (**1**) and (*S*)-(Benzyloxycarbonylamino)-4-*tert*-butoxy-4-oxobutanoic acid (**2a**) were purchased from Aldrich and used without any further purification.

*4.2.1. (S)-4-tert-Butoxy-2-(4-methylphenyl-sulfinimido)-4-oxobutanoic acid (**2b**).* The title compound **2b** was prepared according to a modified literature procedure.[27] In the original paper amino acids were tritylated to give *N*-trityl amino acids. Here, the amino function in **1** was protected with a tosyl group. To a stirred solution of **1** (1.00 g, 5.29 mmol) in anhydrous DCM (12 mL) was added chlorotrimethylsilane (670 μL, 5.28 mmol) at room temperature. The reaction mixture was heated under a gentle reflux for 2 h, and then allowed to attain room temperature. Triethyl amine (1.50 mL, 10.8 mmol) and a solution of *p*-toluenesulfonyl chloride (1.01 g, 5.30 mmol) in anhydrous DCM (5 mL) were added, and the resultant mixture stirred for 2 h at room temperature. The reaction was quenched by addition of MeOH (0.8 mL) and concentrated under reduced pressure. The residue was dissolved in 5% aqueous K_2CO_3 (50 mL) to ensure pH>9. After washing with diethyl ether (100 mL), the aqueous layer was acidified with 10% aqueous citric acid (80 mL, pH 2–3) and then extracted with EtOAc (3×100 mL). The combined EtOAc layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from EtOAc/*n*-hexane (1:1) to afford pure **2b** (1.44 g, 84% yield) as white crystals. Data for **2b**: mp 127–130 °C. $[\alpha]_D^{23}$ +47.6 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz): δ 7.74 (app. d, 2H, *J* 8.0 Hz, tolyl), 7.29 (app. d, 2H, *J* 8.0 Hz, tolyl), 5.70 (d, 1H, *J* 8.0 Hz, NH), 4.17–4.10 (m, 1H, H-2), 2.89 (dd, 1H, *J* 17.0, 4.2 Hz, H-3), 2.73 (dd, 1H, *J* 17.0, 5.0 Hz, H-3), 2.42 (s, 3H, PhCH_3), 1.44 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 175.9 (C-1), 169.7 (C-4), 143.9 (tolyl), 136.7 (tolyl), 129.8 (tolyl), 127.2 (tolyl), 82.6 (*t*-Bu), 52.0 (C-2), 38.7 (C-3), 28.0 (*t*-Bu), 21.5 (PhCH_3). IR (KBr): 3333 (br), 2983 (s), 1760 (s), 1716 (s), 1600 (w), 1371 (s), 1162 (s) cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{20}NO_6S$ $(M-H)^-$ 342.1017, found 342.1010.

*4.2.2. (S)-tert-Butyl 3-(benzyloxycarbonylamino)-4-hydroxybutanoate (**3a**).* Reduction of **2a** to **3a** was performed according to a general procedure described by Rodriguez et al.[28] To a cold (−15 °C) solution of **2a** (5.00 g, 15.5 mmol) in anhydrous DME (125 mL), were successively added *N*-methyl morpholine (NMM) (1.75 mL, 15.9 mmol) and isobutyl chloroformate (2.10 mL, 16.1 mmol). After 5 min, the mixture was filtrated, and the precipitate washed with additional DME (2×20 mL). The filtrate and the washings were combined and cooled to −15 °C. A solution of sodium borohydride (1.80 g, 47.6 mmol) in water (13 mL) was added in one portion, producing a strong evolution of gas, which ceased rapidly. After 5 min, water (125 mL) was added to the mixture, and the stirring continued for 1 h. The mixture was extracted with EtOAc (4×125 mL) and dried ($MgSO_4$). The concentrated crude was purified by flash chromatography [50% EtOAc in petroleum ether (bp 60–80 °C)] to afford **3a** (4.25 g, 89% yield) as a colorless oil. Spectroscopic data of **3a** was comparable with reported data.[54] R_f (EtOAc/*n*-hexane, 1:2)=0.13. $[\alpha]_D^{23}$ −9.8 (*c* 1.1, EtOH), {lit. $[\alpha]_D^{23}$ −8.7 (*c* 1.1, EtOH)}.[54] ^1H NMR (400 MHz): δ 7.39–7.27 (m, 5H, Ph), 5.60 (d, 1H, *J* 7.6 Hz, NH), 5.09 (s, 2H, PhCH_2), 4.08–3.99 (m, 1H, H-3), 3.67 (d, 2H, *J* 4.8 Hz, H-4), 2.95 (br, 1H, OH), 2.61–2.48 (m, 2H, H-2), 1.42 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 171.0 (C-1), 156.2 (O*C*(=O)N), 136.3 (Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 81.3 (*t*-Bu), 66.8 (PhCH_2), 64.3 (C-4), 50.0 (C-3), 37.2 (C-2), 27.9 (*t*-Bu). IR (KBr): 3342

(br), 2978 (m), 1727 (s), 1533 (m), 1368 (s), 1255 (s), 1158 (s), 1061 (s) cm^{-1}. MS (ESI) 332.2 $(M+Na)^+$.

*4.2.3. (S)-tert-Butyl4-hydroxy-3-(4-methylphenyl-sulfonamido)butanoate (**3b**).* The Cbz group in **3a** was removed under neutral conditions (10% Pd/C, 1 atm H_2, abs EtOH) by following an adopted literature procedure given by Park et al.[55] The released amino group was tosylated in accordance to the general procedure described by Gandon et al.[56] *N*-Cbz alcohol **3a** (4.50 g, 14.6 mmol) was dissolved with stirring in abs EtOH (80 mL). Pd/C (10%, 100 mg) was added, the flask was evacuated and then an atmosphere of hydrogen was secured. The mixture was stirred under balloon pressure of hydrogen for 22 h (reaction complete according to TLC). The mixture was filtered through Celite, the filter cake was washed with abs EtOH, and the combined filtrate and washings were evaporated to dryness. The residue was re-dissolved in anhydrous DCM (40 mL) and added DMAP (170 mg, 1.39 mmol) and triethyl amine (4.00 mL, 28.9 mmol). The resultant stirred mixture was cooled to 0 °C, and a solution of *p*-toluensulfonyl chloride (2.80 g, 14.7 mmol) in anhydrous DCM (15 mL) was slowly added over a period of 50 min. The reaction mixture was allowed to warm to room temperature, and then stirred for further 12 h. Water (100 mL) and additional DCM (100 mL) were added. The layers were separated and the aqueous phase extracted with DCM (2×50 mL). The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and residue purified by flash chromatography {50% EtOAc in pet. ether (bp 60–80 °C)} to afford **3b** (4.05 g, 84% yield) as a viscous oil that solidified after a few days. Data for **3b**: mp 58–60 °C. R_f (EtOAc/pet. ether, 1:1)=0.35. $[\alpha]_D^{23}$ +21.5 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.78 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.31 (app. d, 2H, *J* 8.3 Hz, tolyl), 5.59 (d, 1H, *J* 6.4 Hz, NH), 3.64–3.53 (m, 3H, H-3, and H-4), 2.44 (dd, 1H, *J* 16.0, 4.0 Hz, H-2), 2.43 (s, 3H, PhCH_3), 2.37 (dd, 1H, *J* 16.2, 5.8 Hz, H-2), 2.32 (t, 1H, *J* 6.0 Hz, OH), 1.40 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 170.9 (C-1), 143.6 (tolyl), 137.5 (tolyl), 129.8 (tolyl), 127.1 (tolyl), 81.9 (*t*-Bu), 64.1 (C-4), 52.1 (C-3), 37.2 (C-2), 28.0 (*t*-Bu), 21.5 (PhCH_3). IR (KBr): 3580 (m), 3477 (m), 3296 (m), 3244 (s), 2984 (m), 1706 (s), 1365 (s) 1151 (s) cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{24}NO_5S$ $(M+1)^+$ 330.1370, found 330.1374.

Aziridines **4a** and **4b** were synthesized from their respective amino alcohols **3a**,**b** via an adoptet Mitsunobu reaction described by Lapinsky and Bergmeier.[33]

*4.2.4. (S)-Benzyl 2-(2-tert-butoxy-2-oxoethyl)-aziridine-1-carboxylate (**4a**).* Triphenylphosphine (800 mg, 3.05 mmol) was added to a stirred solution of *N*-Cbz alcohol **3a** (0.955 mg, 2.90 mmol) in anhydrous THF (24 mL). The mixture was cooled to 0 °C and diethyl azodicarboxylate (DEAD) (470 μL, 3.02 mmol) added dropwise over a period of 5 min. The reaction mixture was stirred for 5 h at 0 °C. The mixture was concentrated and the residue purified by flash chromatography (10% EtOAc in *n*-hexane) to provide pure aziridine **4a** (600 mg, 71% yield) as a colorless oil. Data for **4a**: R_f (10% EtOAc in *n*-hexane)=0.15. $[\alpha]_D^{23}$ +19.5 (*c* 0.76, MeOH), {lit. $[\alpha]_D$ +23.7 (*c* 0.76, MeOH)}.[24]

*4.2.5. (S)-tert-Butyl 2-(1-tosylaziridin-2-yl)acetate (**4b**).* Ts-aziridine **4b** was synthesized in accordance to the procedure described for preparation of aziridine **4a**. The crude product was purified by flash chromatography (20% EtOAc in *n*-hexane) to afford **4b** (84–90% yield) as colorless crystals. Data for **4b**: R_f (20% EtOAc in *n*-hexane)=0.27. Mp 56–57 °C. $[\alpha]_D^{23}$ +10.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.84 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.33 (app. d, 2H, *J* 8.3 Hz, tolyl), 3.14–3.02 (m, 1H, N–C*H*), 2.69 (d, 1H, *J* 7.0 Hz, NCH_2), 2.44 (s, 3H, PhCH_3), 2.44 (dd, 1H, *J* 16.4, 6.4 Hz, C(=O)CH_2), 2.36 (dd, 1H, *J* 16.4, 6.3 Hz, C(=O)CH_2), 2.13 (d, 1H, *J* 4.5 Hz, NCH_2), 1.39 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 169.0 (C=O), 144.5 (tolyl), 134.9 (tolyl), 129.7 (tolyl), 128.1 (tolyl), 81.5 (*t*-Bu), 37.8 (C(=O)CH_2), 36.1 (N–*C*H), 32.7 (N–CH_2), 28.0 (*t*-Bu), 21.6 (PhCH_3). IR (KBr): 2973 (m), 1717 (m), 1598 (m) 1156 (m) cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{21}NNaO_4S$ $(M+Na)^+$ 334.1084, found 334.1093.

4.3. Nucleophilic ring-opening of aziridines 4a and 4b

Aziridines **4a** and **4b** were ring opened with various ArMgBr/$CuBr\cdot SMe_2$ through an adopted literature procedure.[38] The concentration of generated aryl Grignard reagents in THF was determined in accordance to the literature, utilizing salicylaldehyde phenylhydrazone as a titration indicator.[39] The concentration of ArMgBr was typically kept in the range of 1.0–1.1 M.

*4.3.1. (R)-tert-Butyl3-(benzyloxycarbonylamino)-4-(3-methoxyphenyl)butanoate (**5a**).* A solution of 3-bromoanisole (1.50 mL, 11.8 mmol) in anhydrous THF (8.5 mL) was added slowly to magnesium turnings (280 mg, 11.5 mmol) over a period of approximate 10 min. Once the addition was completed, the reaction was continued with vigorous stirring for 30 min, then titrated[39] and used immediately in the following reaction.

Copper bromide/dimethylsulfide complex ($CuBr\cdot SMe_2$) (60 mg, 0.29 mmol) was added to a solution of Cbz-aziridine **4a** (575 mg, 1.97 mmol) in anhydrous THF (24 mL) under argon atmosphere. The solution was cooled to −40 °C and added the standardized solution of (3-mehoxyphenyl)magnesium bromide in THF (1.0 M, 3.94 mL, 3.94 mmol) over a period of 5 min. The reaction was stirred for 1.5 h and allowed to warm to −10 to 0 °C. The reaction mixture was quenched with aqueous NH_4Cl (saturated, 30 mL), warmed up to room temperature and extracted with diethyl ether (4×50 mL). The combined organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was analyzed by ^{1}H NMR spectroscopy to determine the regioisomeric ratio and, thereafter purified by flash chromatography (10% EtOAc in *n*-hexane), to yield **5a** (470 mg, 60% yield) as a colorless oil. Data for **5a**: R_f (15% EtOAc in *n*-pentane)=0.31. $[\alpha]_D^{23}$ +13.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.40–7.30 (m, 5H, Ph), 7.19 (t, 1H, *J* 7.8 Hz, H_{Ar}-5), 6.80–6.74 (m, 2H, H_{Ar}-4, and H_{Ar}-6), 6.73 (br s, 1H, H_{Ar}-2), 5.36 (d, 1H, *J* 7.2 Hz, NH), 5.08 (s, 2H, PhCH_2), 4.30–4.10 (m, 1H, H-3), 3.77 (s, 3H, OCH_3), 2.93 (dd, 1H, *J* 13.2, 5.6 Hz, H-4), 2.80 (dd, 1H, *J* 13.2, 8.0 Hz, H-4), 2.43 (dd, 1H, *J* 15.6, 5.6 Hz, H-2), 2.35 (dd, 1H, *J* 15.8, 5.8 Hz, H-2), 1.45 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 170.9 (C-1), 159.7 (C_{Ar}-3), 155.6 (O*C*(=O)N), 139.2 (C_{Ar}-1), 136.6 (Ph), 129.5 (C_{Ar}-5), 128.5 (Ph), 128.0 (2C, Ph), 121.7 (C_{Ar}-6), 114.8 (C_{Ar}-2), 112.2 (C_{Ar}-4), 81.2 (*t*-Bu), 66.5 (PhCH_2), 55.1 (OCH_3), 49.4 (C-3), 40.3 (C-4), 38.5 (C-2), 28.1 (*t*-Bu). IR (thin film, NaCl): 3339 (br), 2977 (m), 1724 (s), 1491 (s), 1261 (s), 1153 (s), 1045 (s) cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{29}NNaO_5$ $(M+Na)^+$ 422.1938, found 422.1942.

*4.3.2. (R)-tert-Butyl 4-(3-methoxyphenyl)-3-(4-methylphenylsulfonamido)butanoate (**5b**).* The title compound was prepared from **4b** and (3-methoxyphenyl)magnesium bromide/$CuBr\cdot SMe_2$ in accordance with the procedure described for preparation of **5a**. The crude product was purified by flash chromatography (20% EtOAc in *n*-hexane) to afford **5b** (68–81% yield) as colorless oil. Data for **5b**: R_f (20% EtOAc in *n*-hexane)=0.24. $[\alpha]_D^{23}$ +19.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz): δ 7.61 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.21 (app. d, 2H, *J* 8.4 Hz, tolyl), 7.13 (t, 1H, *J* 7.9 Hz, H_{Ar}-5), 6.73 (dd, 1H, *J* 8.0, 2.2 Hz, H_{Ar}-4), 6.60 (d, 1H, *J* 7.6 Hz, H_{Ar}-6), 6.51 (app. s, 1H, H_{Ar}-2), 5.22 (d, 1H, *J* 8.2 Hz, NH), 3.73 (s, 3H, OCH_3), 3.75–3.61 (m, 1H, H-3), 2.78 (dd, 1H, *J* 13.5, 7.3 Hz, H-4), 2.71 (dd, 1H, *J* 13.6, 6.7 Hz, H-4), 2.41 (dd, 1H, *J* 16.4, 4.6 Hz, H-2), 2.40 (s, 3H, PhCH_3), 2.33 (dd, 1H, *J* 16.5, 6.0 Hz, H-2), 1.44 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 170.7 (C-1), 159.7 (C_{Ar}-3), 143.2 (tolyl), 138.5 (C_{Ar}-1), 137.5 (tolyl), 129.6 (tolyl), 129.5 (C_{Ar}-5), 127.0 (tolyl), 121.6 (C_{Ar}-6), 114.6 (C_{Ar}-2), 112.4 (C_{Ar}-4), 81.5 (*t*-Bu), 55.1 (OCH_3), 52.0 (C-3), 40.6 (C-4), 38.9 (C-2), 28.1

(*t*-Bu), 21.5 (PhCH$_3$). IR (thin film, NaCl): 3288 (br), 2977 (s), 1731 (s), 1601 (m) 1163 (m), 1093 (m) cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{29}NNaO_5S$ (M+Na)$^+$ 442.1659, found 442.1661.

*4.3.3. (R)-tert-Butyl 3-(benzyloxycarbonylamino)-4-(4-fluoro-3-methoxyphenyl)butanoate (**6a**).* The title compound was prepared from **4a** and (4-fluoro-3-methoxyphenyl)magnesium bromide/CuBr·SMe$_2$ in accordance to the procedure described for preparation of **5a**. Purification of the crude mixture by flash chromatography (10% EtOAc in *n*-pentane), provided **6a** (45% yield) as a white crystalline material. Data for **6a**: R_f (10% EtOAc in *n*-pentane)=0.10. Mp 46–48 °C. $[\alpha]_D^{23}$ +14.3 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.39–7.28 (m, 5H, Ph), 6.96 (dd, 1H, *J* 11.2, 8.0 Hz, H$_{Ar}$-5), 6.78 (app. d, 1H, *J* 7.2 Hz, H$_{Ar}$-2), 6.71–6.63 (m, 1H, H$_{Ar}$-6), 5.37 (d, 1H, *J* 8.4 Hz, NH), 5.08 (d, 1H, *J* 12.4 Hz, PhC*H*$_2$), 5.06 (d, 1H, *J* 12.4 Hz, PhC*H*$_2$), 4.22–4.08 (m, 1H, H-3), 3.83 (s, 3H, OCH$_3$), 2.90 (dd, 1H, *J* 13.2, 6.4 Hz, H-4), 2.79 (dd, 1H, *J* 13.2, 7.6 Hz, H-4), 2.44 (dd, 1H, *J* 15.8, 5.4 Hz, H-2), 2.35 (dd, 1H, *J* 15.8, 5.8 Hz, H-2), 1.45 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 170.9 (C-1), 155.6 (O*C*(=O)N), 151.4 (d, $^1J_{CF}$ 244.3 Hz, C$_{Ar}$-4), 147.5 (d, $^2J_{CF}$ 10.9 Hz, C$_{Ar}$-3), 136.5 (Ph), 134.0 (d, $^4J_{CF}$ 3.9 Hz, C$_{Ar}$-1), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 121.5 (d, $^3J_{CF}$ 6.6 Hz, C$_{Ar}$-6), 115.9 (d, $^2J_{CF}$ 18.2 Hz, C$_{Ar}$-5), 114.3 (C$_{Ar}$-2), 81.3 (*t*-Bu), 66.6 (PhCH$_2$), 56.2 (OCH$_3$), 49.5 (C-3), 39.9 (C-4), 38.5 (C-2), 28.1 (*t*-Bu). IR (thin film, NaCl): 3325 (br), 2977 (w), 1724 (s), 1610 (w), 1518 (s), 1152 (s), 1120 (s) cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{28}FNNaO_5$ (M+Na)$^+$ 440.1844, found 440.1847.

*4.3.4. (R)-tert-Butyl 4-(4-fluoro-3-methoxyphenyl)-3-(4-methylphenylsulfonamido)butanoate (**6b**).* The title compound was prepared from **4b** and (4-fluoro-3-methoxyphenyl)magnesium bromide/CuBr·SMe$_2$ in accordance with the procedure described for preparation of **5a**. Purification of the crude mixture by flash chromatography (15% EtOAc in *n*-pentane), afforded **6b** (49% yield) as a colorless oil. Data for **6b**: R_f (20% EtOAc in *n*-hexane)=0.25. $[\alpha]_D^{23}$ +34.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.54 (app. d, 2H, *J* 8.0 Hz, tolyl), 7.18 (app. d, 2H, *J* 8.0 Hz, tolyl), 6.86 (dd, 1H, *J* 11.2, 8.0 Hz, H$_{Ar}$-5), 6.57–6.48 (m, 2H, H$_{Ar}$-2, and H$_{Ar}$-6), 5.27 (d, 1H, *J* 8.4 Hz, NH), 3.76 (s, 3H, OCH$_3$), 3.71–3.60 (m, 1H, H-3), 2.78 (dd, 1H, *J* 13.8, 6.4 Hz, H-4), 2.66 (dd, 1H, *J* 13.8, 7.8 Hz, H-4), 2.50–2.30 (m, 2H, H-2), 2.41 (s, 3H, PhC*H*$_3$), 1.44 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 170.7 (C-1), 151.4 (d, $^1J_{CF}$ 244.8 Hz, C$_{Ar}$-4), 147.5 (d, $^2J_{CF}$ 10.8 Hz, C$_{Ar}$-3), 143.3 (tolyl), 137.3 (tolyl), 133.4 (d, $^4J_{CF}$ 3.9 Hz, C$_{Ar}$-1), 129.5 (tolyl), 126.9 (tolyl), 121.3 (d, $^3J_{CF}$ 6.6 Hz, C$_{Ar}$-6), 115.8 (d, $^2J_{CF}$ 18.2 Hz, C$_{Ar}$-5), 114.0 (C$_{Ar}$-2), 81.6 (*t*-Bu), 55.9 (OCH$_3$), 52.3 (C-3), 40.2 (C-4), 40.0 (C-2), 28.1 (*t*-Bu), 21.4 (PhCH$_3$). IR (thin film, NaCl): 3290 (br), 2978 (m), 1728 (s), 1611 (m) 1519 (s), 1151 (m) cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{32}FN_2O_5S$ (M+NH$_4$)$^+$ 455.2010, found 455.2012.

*4.3.5. (R)-tert-Butyl 3-(benzyloxycarbonylamino)-4-(2-methoxyphenyl)butanoate (**7a**).* The title compound was prepared from **4a** and (2-methoxyphenyl)magnesium bromide/CuBr·SMe$_2$ in accordance with the procedure described for preparation of **5a**. Purification of the crude mixture by flash chromatography (10% EtOAc in *n*-pentane), afforded **7a** (51% yield) as a white crystalline material. Data for **7a**: R_f (25% EtOAc in *n*-hexane)=0.19. Mp 42–43 °C. $[\alpha]_D^{23}$ +16.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.37–7.25 (m, 5H, Ph), 7.20 (app. t, 1H, *J* 8 Hz, H$_{Ar}$-4), 7.11 (app. d, 1H, *J* 7 Hz, H$_{Ar}$-6), 6.87 (app. t, 1H, *J* 7 Hz, H$_{Ar}$-5), 6.83 (app. d, 1H, *J* 8 Hz, H$_{Ar}$-3), 5.45 (d, 1H, *J* 8.2 Hz, NH), 5.03 (s, 2H, PhC*H*$_2$), 4.30–4.18 (m, 1H, H-3), 3.80 (s, 3H, OCH$_3$), 3.00–2.80 (m, 2H, H-4), 2.43 (d, 2H, *J* 5.7 Hz, H-2), 1.45 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 171.0 (C-1), 157.6 (C$_{Ar}$-2), 155.7 (O*C*(=O)N), 136.8 (Ph), 131.3 (C$_{Ar}$-6), 128.4 (Ph), 128.0 (Ph), 127.9 (2C, Ph, and C$_{Ar}$-5), 126.2 (C$_{Ar}$-1), 120.6 (C$_{Ar}$-4), 110.4 (C$_{Ar}$-3), 80.8 (*t*-Bu), 66.3 (PhCH$_2$), 55.2 (OCH$_3$), 49.0 (C-3), 39.4 (C-2), 34.6 (C-4), 28.1 (*t*-Bu). IR (KBr): 3342 (br), 2977 (m), 1723 (s), 1602 (m), 1587 (m), 1495 (s), 1246 (s), 1151 (s) cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{30}NO_5$ (M+1)$^+$ 400.2118, found 400.2111.

*4.3.6. (R)-tert-Butyl 4-(2-methoxyphenyl)-3-(4-methylphenylsulfonamido)butanoate (**7b**).* The title compound was prepared from **4b** and (2-methoxyphenyl)magnesium bromide/CuBr·SMe$_2$ in accordance with the procedure described for preparation of **5a**. Purification of the crude mixture by flash chromatography (10% EtOAc in *n*-pentane) provided **7b** (30–40% yield) in a mixture with start material **4b**. Data for **7b**: ^{1}H NMR (400 MHz): δ 7.51 (app. d, 2H, *J* 8.4 Hz, tolyl), 7.16–7.14 (m, 1H, H$_{Ar}$-4), 7.12 (app. d, 2H, *J* 8.4 Hz, tolyl), 6.90 (dd, 1H, *J* 7.4, 1.8 Hz, H$_{Ar}$-6), 6.77 (dd, 1H, *J* 7.4, 0.9 Hz, H$_{Ar}$-5), 6.73 (dd, 1H, *J* 8.2, 1.0 Hz, H$_{Ar}$-3), 5.50 (d, 1H, *J* 7.2 Hz, NH), 3.75 (s, 3H, OCH$_3$), 3.77–3.67 (m, 1H, H-3), 2.80 (dd, 1H, *J* 13.6, 8.0 Hz, H-4), 2.71 (dd, 1H, *J* 13.6, 6.4 Hz, H-4), 2.54 (dd, 1H, *J* 16.4, 4.0 Hz, H-2), 2.41 (dd, 1H, *J* 16.4, 7.2 Hz, H-2), 2.37 (s, 3H, PhC*H*$_3$), 1.46 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 170.8 (C-1), 157.2 (C$_{Ar}$-2), 142.7 (tolyl), 137.3 (tolyl), 131.3 (C$_{Ar}$-6), 129.4 (tolyl), 127.2 (C$_{Ar}$-4), 126.9 (tolyl), 125.0 (C$_{Ar}$-1), 120.8 (C$_{Ar}$-5), 110.4 (C$_{Ar}$-3), 81.1 (*t*-Bu), 55.2 (OCH$_3$), 51.5 (C-3), 40.2 (C-2), 34.8 (C-4), 28.1 (*t*-Bu), 21.5 (PhCH$_3$). HRMS (ESI) calcd for $C_{22}H_{29}NNaO_5S$ (M+Na)$^+$ 442.1659, found 442.1662.

*4.3.7. (R)-tert-Butyl 3-(benzyloxycarbonylamino)-4-(3,4-dimethoxyphenyl)butanoate (**8a**).* The title compound was prepared from **4a** and (3,4-dimethoxyphenyl)magnesium bromid/CuBr·SMe$_2$ in accordance with the procedure described for preparation of **5a**. The crude product was purified flash chromatography (two columns: first with 20% EtOAc in *n*-hexane, and then 2% abs EtOH in DCM) to afford **8a** (ca. 6% yield) as colorless crystalline material. Data for **8a**: R_f (2% abs EtOH in DCM)=0.20. Mp 75–77 °C. $[\alpha]_D^{23}$ +9.6 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.38–7.28 (m, 5H, Ph), 6.79 (d, 1H, *J* 8.4 Hz, H$_{Ar}$-5), 6.75–6.65 (m, 2H, H$_{Ar}$-2 and H$_{Ar}$-6), 5.36 (d, 1H, *J* 8.4 Hz, NH), 5.09 (s, 2H, PhC*H*$_2$), 4.22–4.10 (m, 1H, H-3), 3.86 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 2.90 (dd, 1H, *J* 13.4, 6.2 Hz, H-4), 2.77 (dd, 1H, *J* 13.6, 8.0 Hz, H-4), 2.44 (dd, 1H, *J* 15.8, 5.4 Hz, H-2), 2.36 (dd, 1H, *J* 16.0, 5.6 Hz, H-2), 1.46 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 171.0 (C-1), 155.6 (O*C*(=O)N), 148.9 (C$_{Ar}$-3), 147.8 (C$_{Ar}$-4), 136.6 (Ph), 130.2 (C$_{Ar}$-1), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 121.4 (C$_{Ar}$-6), 112.4 (C$_{Ar}$-2), 111.2 (C$_{Ar}$-5), 81.2 (*t*-Bu), 66.6 (PhCH$_2$), 55.9 (OCH$_3$), 55.8 (OCH$_3$), 49.6 (C-3), 39.8 (C-4), 38.5 (C-2), 28.1 (*t*-Bu). IR (KBr): 3373 (m), 2978 (m), 1717 (s), 1694 (s), 1589 (w), 1524 (s), 1252 (m), 1150 (m) cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{31}NNaO_6$ (M+Na)$^+$ 452.2044, found 452.2050.

*4.3.8. (E)-tert-Butyl 4-(4-methylphenylsulfon-amido)but-2-enoate (**9**).* The title compound was isolated in various amounts (4–27% yield) from the ring-opening reactions of aziridine **4b** with ArMgBr/CuBr·Me$_2$S. Data for **9**: colorless crystalline material. Mp 63–65 °C. ^{1}H NMR (400 MHz): δ 7.75 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.31 (d, 2H, *J* 8.4 Hz, tolyl), 6.63 (dt, 1H, *J* 15.7, 5.3 Hz, H-3), 5.84 (dt, 1H, *J* 15.7, 1.7 Hz, H-2), 5.20 (br s, 1H, NH), 3.74–3.68 (m, 2H, H-4), 2.42 (s, 3H, PhC*H*$_3$), 1.44 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 165.0 (C-1), 143.7 (tolyl), 140.9 (C-3), 136.8 (tolyl), 129.8 (tolyl), 127.1 (tolyl), 124.8 (C-2), 80.8 (*t*-Bu), 43.8 (C-4), 28.0 (*t*-Bu), 21.5 (PhCH$_3$). IR (KBr): 3265 (m), 2978 (m), 1712 (s), 1651 (m) 1598 (m), 1451 (m), 1321 (s), 1159 (m) cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{25}N_2O_4S$ (M+NH$_4$)$^+$ 329.1530, found 329.1532.

4.4. Deprotection of *tert*-butyl ester

Deprotection of the *tert*-butyl ester group in **5a**,**b**, **6a**,**b**, and **7a**,**b** to **11a**,**b**, **12a**,**b**, and **13a**,**b**, respectively, was performed according to an adopted procedure described by Mehta et al.[46]

*4.4.1. (R)-3-(Benzyloxycarbonylamino)-4-(3-methoxyphenyl)butanoic acid (**11a**).* A solution of *N*-Cbz *tert*-butyl ester **5a** (470 mg, 1.18 mmol) in anhydrous DCM (3.2 mL) was added triethylsilane

(500 μL, 3.10 mmol), and then trifluoroacetic acid (1.6 mL) dropwise. The reaction was stirred vigorously for 90 min at room temperature. Evaporation under reduced pressure afforded a white solid material, which was recrystallized from petroleum ether/EtOAc (5:3), to afford pure **11a** (316 mg, 78%). Data for **11a**: mp 88–92 °C. $[\alpha]_D^{23}$ +20.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz): *δ* 7.38–7.28 (m, 5H, Ph), 7.20 (t, 1H, *J* 7.8 Hz, H_{Ar}-5), 6.80–6.70 (m, 3H, H_{Ar}-2, H_{Ar}-4, and H_{Ar}-6), 5.31 (d, 1H, *J* 8.4 Hz, NH), 5.09 (d, 1H, *J* 12.4 Hz, PhC*H*$_2$), 5.07 (d, 1H, *J* 12.3 Hz, PhC*H*$_2$), 4.35–4.10 (m, 1H, H-3), 3.76 (s, 3H, OCH_3), 2.95 (dd, 1H, *J* 12.4, 5.7 Hz, H-4), 2.80 (dd, 1H, *J* 13.4, 7.8 Hz, H-4), 2.64–2.48 (m, 2H, H-2). ^{13}C NMR (100 MHz): *δ* 176.6 (C-1), 159.7 (C_{Ar}-3), 155.7 (O*C*(=O)N), 138.8 (C_{Ar}-1), 136.3 (Ph), 129.6 (C_{Ar}-5), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 121.7 (C_{Ar}-6), 114.8 (C_{Ar}-2), 112.3 (C_{Ar}-4), 66.8 (Ph*C*H$_2$), 55.5 (OCH_3), 49.0 (C-3), 40.1 (C-4), 37.2 (C-2). IR (KBr): 3341 (s), 2960 (br), 1700 (s), 1535 (m), 1261 (m), 1053 (m) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{21}NNaO_5$ $(M+Na)^+$ 366.1312, found 366.1318.

*4.4.2. (R)-4-(3-Methoxyphenyl)-3-(4-methylphenyl-sulfonamido) butanoic acid (**11b**).* The title compound was prepared from **5b** in accordance with the procedure described for preparation of **11a**. The crude product was purified by flash chromatography (EtOAc in *n*-pentane, gradient: 20–40%). This afforded **11b** in 89% yield as a colorless crystalline material. Data for **11b**: mp 79–81 °C. $[\alpha]_D^{23}$ +36.1 (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz): *δ* 7.60 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.21 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.13 (app. t, 1H, *J* 8 Hz, H_{Ar}-5), 6.73 (app. d, 1H, *J* 8 Hz, H_{Ar}-4), 6.61 (d, 1H, *J* 7.6 Hz, H_{Ar}-6), 6.51 (m, 1H, H_{Ar}-2), 5.51 (d, 1H, *J* 8.4 Hz, NH), 3.73 (s, 3H, OCH_3), 3.80–3.66 (m, 1H, H-3), 2.85 (dd, 1H, *J* 13.7, 7.4 Hz, H-4), 2.74 (dd, 1H, *J* 13.7, 7.0 Hz, H-4), 2.58 (d, 2H, *J* 5.3 Hz, H-2), 2.40 (s, 3H, PhC*H*$_3$). ^{13}C NMR (100 MHz): *δ* 176.2 (C-1), 159.8 (C_{Ar}-3), 143.4 (tolyl), 138.2 (C_{Ar}-1), 137.0 (tolyl), 129.7 (tolyl), 129.7 (C_{Ar}-5), 127.0 (tolyl), 121.6 (C_{Ar}-6), 114.6 (C_{Ar}-2), 112.5 (C_{Ar}-4), 55.1 (OCH_3), 51.6 (C-3), 40.5 (C-4), 37.9 (C-2), 21.5 (Ph*C*H$_3$). IR (KBr): 3203 (br), 1699 (s), 1598 (m), 1493 (m), 1337 (m), 1158 (m), 1090 (m) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{20}NO_5S$ $(M-H)^-$ 362.1068, found 362.1066.

*4.4.3. (R)-3-(Benzyloxycarbonylamino)-4-(4-fluoro-3-methoxyphenyl)butanoic acid (**12a**).* The title compound was prepared from **6a** in accordance with the procedure described for preparation of **11a**. The crude product was purified by flash chromatography (EtOAc in *n*-pentane, gradient: 20–100%). This afforded **12a** in 12% yield as a colorless crystalline material. Data for **12a**: mp 96–98 °C. $[\alpha]_D^{23}$ +18.2 (*c* 0.5, CH_2Cl_2), ^1H NMR (300 MHz): *δ* 7.40–7.19 (m, 5H, Ph), 6.97 (dd, 1H, *J* 11.2, 8.2 Hz, H_{Ar}-5), 6.78 (d, 1H, *J* 7.8 Hz, H_{Ar}-2), 6.73–6.63 (m, 1H, H_{Ar}-6), 5.27 (d, 1H, *J* 8.3 Hz, NH), 5.09 (d, 1H, *J* 12.3 Hz, $PhCH_2$), 5.06 (d, 1H, *J* 12.3 Hz, $PhCH_2$), 4.30–4.13 (m, 1H, H-3), 3.83 (s, 3H, OCH_3), 2.94–2.86 (m, 1H, H-4), 2.83 (dd, 1H, *J* 13.6, 7.7 Hz, H-4), 2.68–2.50 (m, 2H, H-2). ^{13}C NMR (100 MHz): *δ* 177.4 (C-1), 156.5 (O*C*(=O)N), 151.6 (d, $^1J_{CF}$ 245.0 Hz, C_{Ar}-4), 147.6 (d, $^2J_{CF}$ 11.3 Hz, C_{Ar}-3), 135.6 (Ph), 133.2 (d, $^4J_{CF}$ 3.9 Hz, C_{Ar}-1), 128.7 (Ph), 128.5 (Ph), 128.1 (Ph), 121.5 (d, $^3J_{CF}$ 5.6 Hz, C_{Ar}-6), 116.1 (d, $^2J_{CF}$ 18.0 Hz, C_{Ar}-5), 114.3 (br, C_{Ar}-2), 67.6 (Cbz), 56.2 (OCH_3), 49.2 (C-3), 39.9 (C-4), 37.5 (C-2). IR (KBr): 3332 (m), 2933 (br), 1698 (s), 1539 (s) 1518 (s), 1453 (m), 1420 (m), 1276 (s), 1217 (m), 1152 (m), 1055 (m) cm^{-1}.

*4.4.4. (R)-4-(4-Fluoro-3-methoxyphenyl)-3-(4-methylphenylsulfonamido)butanoic acid (**12b**).* The title compound was prepared from **6b** in accordance with the procedure described for preparation of **11a**. The crude product was purified by flash chromatography (EtOAc in *n*-pentane, gradient: 20–40%). This provided **12b** in 84% yield as a colorless crystalline material. Data for **12b**: mp 90–95 °C. $[\alpha]_D^{23}$ +58.5 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz): *δ* 7.52 (app. d, 2H, *J* 8.1 Hz, tolyl), 7.18 (app. d, 2H, *J* 8.1 Hz, tolyl), 6.86 (dd, 1H, *J* 11.0, 8.6 Hz, H_{Ar}-5), 6.53 (d, 2H, *J* 9.6 Hz, H_{Ar}-2, and H_{Ar}-6), 5.49 (d, 1H, *J* 8.4 Hz, NH), 3.76 (s, 3H, OCH_3), 3.75–3.64 (m, 1H, H-3), 2.83 (dd, 1H, *J* 13.8, 6.4 Hz, H-4), 2.72 (dd, 1H, *J* 13.8, 8.1 Hz, H-4), 2.72–2.58 (m, 2H, H-2), 2.41 (s, 3H, PhC*H*$_3$). ^{13}C NMR (100 MHz): *δ* 175.9 (C-1), 151.5 (d, $^1J_{CF}$ 245.0 Hz, C_{Ar}-4), 147.5 (d, $^2J_{CF}$ 10.8 Hz, C_{Ar}-3), 143.6 (tolyl), 136.9 (tolyl), 133.1 (d, $^4J_{CF}$ 3.9 Hz, C_{Ar}-1), 129.5 (tolyl), 126.8 (tolyl), 121.3 (d, $^3J_{CF}$ 6.8 Hz, C_{Ar}-6), 115.9 (d, $^2J_{CF}$ 18.3 Hz, C_{Ar}-5), 114.0 (d, $^3J_{CF}$ 2.1 Hz, C_{Ar}-2), 55.9 (OCH_3), 51.9 (C-3), 40.2 (C-4), 38.5 (C-2), 21.5 (Ph*C*H$_3$). IR (KBr): 3300 (br), 2924 (m), 1729 (s), 1613 (m) 1521 (s), 1160 (m) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{19}FNO_5S$ $(M-H)^-$ 380.0973, found 380.0981.

*4.4.5. (R)-3-(Benzyloxycarbonylamino)-4-(2-methoxyphenyl)butanoic acid (**13a**).* The title compound was prepared from **7a** in accordance with the procedure described for preparation of **11a**. The crude product was recrystallized from EtOAc/petroleum ether (4:6) to afford **13a** (68% yield) as a colorless crystalline material. Data for **13a**: mp 87–90 °C. $[\alpha]_D^{23}$ +20.9 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz): *δ* 7.39–7.25 (m, 5H, Ph), 7.21 (app. t, 1H, *J* 8 Hz, H_{Ar}-4), 7.12 (app. d, 1H, *J* 7 Hz, H_{Ar}-6), 6.88 (app. t, 1H, *J* 7 Hz, H_{Ar}-5), 6.84 (app. d, 1H, *J* 8 Hz, H_{Ar}-3), 5.52 (d, 1H, *J* 8.2 Hz, NH), 5.05 (s, 2H, PhC*H*$_2$), 4.32–4.17 (m, 1H, H-3), 3.78 (s, 3H, OCH_3), 2.95 (d, 2H, *J* 6.8 Hz, H-4), 2.70–2.40 (m, 2H, H-2). ^{13}C NMR (100 MHz): *δ* 177.0 (C-1), 157.5 (C_{Ar}-2), 155.8 (O*C*(=O)N), 136.6 (Ph), 131.4 (C_{Ar}-6), 128.5 (Ph), 128.2 (C_{Ar}-4), 128.0 (2C, Ph), 125.8 (C_{Ar}-1), 120.7 (C_{Ar}-5), 110.7 (C_{Ar}-3), 66.6 (Ph*C*H$_2$), 55.2 (OCH_3), 48.7 (C-3), 37.7 (C-2), 34.3 (C-4). IR (KBr): 3329 (s), 2936 (br), 1693 (s), 1537 (s), 1245 (s), 1113 (m) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{21}NNaO_5$ $(M+Na)^+$ 366.1312, found 366.1312.

*4.4.6. (R)-4-(2-Methoxyphenyl)-3-(4-methylphenyl-sulfonamido) butanoic acid (**13b**).* The title compound was prepared from **7b** in accordance with the procedure described for preparation of **11a**. The product was attempted purified by flash chromatography (EtOAc/petroleum ether, 1:1). However, we were not able to separate **13b** from Ts-lactone **10**. The yield of **13b** was estimated to 52% from ^1H NMR analysis. Data for **13b**: ^1H NMR (400 MHz): *δ* 7.53 (app. d, 2H, *J* 8.4 Hz, tolyl), 7.22–7.14 (m, 1H, H_{Ar}-4), 7.14 (app. d, 2H, *J* 8.4 Hz, tolyl), 6.93 (dd, 1H, *J* 7.4, 1.8 Hz, H_{Ar}-6), 6.83–6.77 (m, 1H, H_{Ar}-5), 6.73 (dd, 1H, *J* 8.4, 0.8 Hz, H_{Ar}-3), 5.65 (d, 1H, *J* 7.6 Hz, NH), 3.74 (s, 3H, OCH_3), 3.82–3.70 (m, 1H, H-3), 2.83 (dd, 1H, *J* 13.6, 7.8 Hz, H-4), 2.77 (dd, 1H, *J* 13.6, 6.8 Hz, H-4), 2.65 (dd, 1H, *J* 16.6, 6.2 Hz, H-2), 2.59 (dd, 1H, *J* 16.6, 6.6 Hz, H-2), 2.38 (s, 3H, PhC*H*$_3$). ^{13}C NMR (100 MHz): *δ* 176.4 (C-1), 157.1 (C_{Ar}-2), 143.1 (tolyl), 136.9 (tolyl), 131.3 (C_{Ar}-6), 129.5 (tolyl), 128.3 (C_{Ar}-4), 126.9 (tolyl), 125.2 (C_{Ar}-1), 120.9 (C_{Ar}-5), 110.4 (C_{Ar}-3), 55.2 (OCH_3), 51.2 (C-3), 38.9 (C-2), 34.8 (C-4), 21.5 (Ph*C*H$_3$).

4.5. Intramolecular Friedel–Crafts cyclisation

The intramolecular Friedel–Crafts cyclisations of **11a**,**b** and **12b** and attempted cyclisations of **13a**,**b**, were conducted by following two reported methods: method A (reagents: $PCl_5/SnCl_4$),[21] and method B {reagents: trifluoroacetic anhydride (TFAA)—trifluoroacetic acid (TFA)}.[47] The synthesis of **14a** from **11a** is shown as a general example for method A, and preparation of **14b** from **11b** is shown as a general example for method B.

*4.5.1. Method A:[21] (R)-benzyl 7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-ylcarbamante (**14a**).* *N*-Cbz-acid **11a** (300 mg, 0.870 mmol) was dissolved in anhydrous DCM (12 mL), cooled to 0 °C and added PCl_5 (200 mg, 0.960 mmol) in one portion. After vigorous stirring for 1 h, $SnCl_4$ (120 μL, 1.03 mmol, 1.2 equiv) was added, and the reaction mixture stirred for an additional 5 h at 0 °C. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ (50 mL), warmed to room temperature, and extracted with DCM (5×50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. The crude product was analyzed by ^1H NMR

spectroscopy to determine the regioisomeric ratio and, thereafter, purified by flash chromatography (EtOAc/*n*-hexane, 2:1) to afford **14a** (80 mg, 28% yield) as colorless crystals. Data for **14a**: R_f (EtOAc/*n*-hexane, 1:2)=0.15. Mp 115–117 °C. $[\alpha]_D^{23}$ +3.1 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz): δ 8.01 (d, 1H, *J* 8.8 Hz, H-5), 7.38–7.28 (m, 5H, Ph), 6.86 (dd, 1H, *J* 8.8, 2.4 Hz, H-6), 6.72 (d, 1H, *J* 2.4 Hz, H-8), 5.09 (s, 2H, PhCH_2), 4.88–4.64 (m, 1H, NH), 4.43–4.27 (m, 1H, H-2), 3.86 (s, 3H, OCH_3), 3.29 (d, 1H, *J* 15.2 Hz, H-1), 3.02–2.84 (m, 2H, H-1, and H-3), 2.66 (dd, 1H, *J* 16.6, 8.2 Hz, H-3). ^{13}C NMR (100 MHz): δ 194.4 (C-4), 164.2 (C-7), 155.5 (OC(=O)N), 143.0 (C-8a), 136.2 (Ph), 129.7 (C-5), 128.6 (2C, Ph), 128.1 (Ph), 125.7 (C-4a), 113.8 (C-6), 113.4 (C-8), 66.9 (PhCH_2), 55.5 (OCH_3), 47.3 (C-2), 44.6 (C-3), 36.3 (C-1). IR (KBr): 3392 (m), 1690 (s), 1668 (s), 1598 (s), 1542 (m), 1441 (w), 1249 (m), 1105 (m) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}NO_4$ $(M+H)^+$ 326.1387, found 326.1380.

4.5.2. Method B:[47] *(R)-N-(7-methoxy-4-oxo-1,2,3,4-tetrahydro-naphthalene-2-yl)-4-methyl-benzenesulfonamide (**14b**).* To an ice-cooled stirred solution of Cbz-acid **11b** (110 mg, 0.30 mmol) in anhydrous DCM (2.0 mL) was added dropwise TFAA (70 μL, 1.5 equiv). The mixture was then added TFA (2.0 mL) and vigorously stirred for 30 min. The reaction was quenched by the addition of aqueous saturated $NaHCO_3$ (40 mL) and DCM (40 mL). The layers were separated and the aqueous phase extracted with additional DCM (2×40 mL). The combined organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was analyzed by ^{1}H NMR spectroscopy to determine the regioisomeric ratio. Recrystallization from MeOH provided 24.4 mg of **14b** (23% yield) as a white solid. Data for **14b**: R_f (EtOAc/*n*-hexane, 1:2)=0.16. Mp 164–166 °C. $[\alpha]_D^{23}$ −59.0 (*c* 1.0, DMF). ^{1}H NMR (400 MHz): δ 7.95 (d, 1H, *J* 8.7 Hz, H-5), 7.73 (app. d, 2H, *J* 8.0 Hz, tolyl), 7.31 (app. d, 2H, *J* 8.0 Hz, tolyl), 6.84 (dd, 1H, *J* 8.7, 2.4 Hz, H-6), 6.63 (d, 1H, *J* 2.3 Hz, H-8), 4.78 (d, 1H, *J* 7.9 Hz, NH), 3.99–3.88 (m, 1H, H-2), 3.85 (s, 3H, OCH_3), 3.20 (dd, 1H, *J* 16.2, 3.6 Hz, H-1), 2.94 (dd, 1H, *J* 16.0, 8.2 Hz, H-1), 2.69 (dd, 1H, *J* 16.9, 3.8 Hz, H-3), 2.48 (dd, 1H, *J* 16.8, 8.9 Hz, H-3), 2.44 (s, 3H, PhCH_3). ^{13}C NMR (100 MHz): δ 193.5 (C-4), 164.3 (C-7), 143.9 (tolyl), 142.5 (C-8a), 137.5 (tolyl), 129.9 (tolyl), 129.7 (C-5), 127.0 (tolyl), 125.7 (C-4a), 114.0 (C-6), 113.4 (C-8), 55.6 (OCH_3), 49.6 (C-2), 45.1 (C-3), 37.3 (C-1), 21.6 (PhCH_3). IR (KBr): 3243 (m), 2962 (w), 1668 (s), 1600 (s), 1461 (m), 1160 (s), 1089 (m) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{19}NNaO_4S$ $(M+Na)^+$ 368.0927, found 368.0925.

*4.5.3. (R)-N-(6-Fluoro-7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-yl)-4-methylbenzene-sulfonamide (**15b**).* The title compound was prepared from **12b**. The crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1:2). Data for **15b**: white crystalline material. Mp 173–175 °C (decomp.). R_f (EtOAc/*n*-hexane, 1:2)=0.14. $[\alpha]_D^{23}$ −53.8 (*c* 0.5, DMF). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (s, 1H, NH), 7.71 (app. d, 2H, *J* 8.0 Hz, tolyl), 7.50 (d, 1H, *J* 11.6 Hz, H-5), 7.39 (app. d, 2H, *J* 8.0 Hz, tolyl), 7.08 (d, 1H, *J* 8.4 Hz, H-8), 3.90 (s, 3H, OCH_3), 3.70–3.58 (m, 1H, H-2), 3.06 (dd, 1H, *J* 16.0, 4.0 Hz, H-1), 2.90 (dd, 1H, *J* 16.0, 8.8 Hz, H-1), 2.58–2.46 (m, 2H, H-3), 2.39 (s, 3H, PhCH_3). ^{13}C NMR (100 MHz): δ 193.3 (C-4), 151.8 (d, $^2J_{CF}$ 11.2 Hz, C-7), 150.5 (d, $^1J_{CF}$ 245.2 Hz, C-6), 142.7 (tolyl), 139.3.5 (d, $^4J_{CF}$ 3.0 Hz, C-8a), 138.2 (tolyl), 129.7 (tolyl), 126.4 (tolyl), 124.9 (d, $^3J_{CF}$ 4.8 Hz, C-4a), 113.6 (d, $^3J_{CF}$ 8.4 Hz, C-8), 112.3 (d, $^2J_{CF}$ 17.8 Hz, C-5), 56.4 (OCH_3), 49.0 (C-2), 44.0 (C-3), 35.5 (C-1), 21.0 (PhCH_3). IR (KBr): 3242 (m), 2959 (w), 2360 (w), 1670 (s), 1613 (s), 1515 (m), 1450 (m), 1316 (s), 1159 (s), 1086 (m) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{22}FN_2O_4S$ $(M+NH_4)^+$ 381.1279, found 381.1277.

*4.5.4. 7-Fluoro-6-methoxynaphthalen-1-ol (**17**).* Compound **17** was isolated as a side product in the Friedel–Crafts cyclisation of **12b** (Table 1, entry 7). Data for **17** (colorless oil): R_f (*n*-hexane/EtOAc, 2:1)=0.56. ^{1}H NMR (400 MHz): δ 7.81 (d, 1H, *J* 12.5 Hz, H-8), 7.32 (app. d, 1H, *J* 8 Hz, H-4), 7.24 (app. t, 1H, *J* 8 Hz, H-3), 7.18 (d, 1H, *J* 8.4 Hz, H-5), 6.71 (app. d, 1H, *J* 8 Hz, H-2), 5.13 (br s, 1H, OH), 4.00 (s, 3H, OCH_3). ^{13}C NMR (100 MHz): δ 152.0 (d, $^1J_{CF}$ 248.5 Hz, C-7), 151.0 (d, $^4J_{CF}$ 12.5 Hz, C-1), 148.3 (d, $^2J_{CF}$ 13.9 Hz, C-6), 132.5 (d, $^4J_{CF}$ 1.5 Hz, C-4a), 125.8 (d, $^6J_{CF}$ 2.4 Hz, C-3), 119.4 (d, $^5J_{CF}$ 1.8 Hz, C-4), 119.0 (d, $^3J_{CF}$ 8.2 Hz, C-8a), 108.0 (d, $^3J_{CF}$ 2.1 Hz, C-5), 107.5 (C-2), 107.0 (d, $^2J_{CF}$ 19.7 Hz, C-8), 56.0 (OCH_3). IR (KBr): 3297 (br), 1642 (m) 1525 (s), 1492 (m), 1430 (m), 1296 (s), 1189 (m), 1164 (s), 1148 (s) cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{10}FO_2$ $(M+H)^+$ 193.0659, found 193.0659.

4.6. Reductive deoxygenation and deprotecting of *N*-protected α-tetralone to substituted AT

*4.6.1. (S)-N-(7-Methoxy-1,2,3,4-tetrahydro-naphthalene-2-yl)-4-methylbenzenesulfonamide (**19**).* Reductive removal of the ring carbonyl group in **14b** was performed in accordance with an adopted literature procedure.[22] A solution of **14b** (94 mg, 0.27 mmol) in AcOH (30 mL) was hydrogenated at 5 atm and room temperature for 38 h using 10% Pd/C (50 mg) as catalyst. After an initial filtration through Celite and concentration under reduced pressure, the crude product was purified by flash chromatography (20% EtOAc in *n*-pentane) to afford **19** (51 mg, 57% yield) as colorless crystalline needles. Data for **19**: R_f (20% EtOAc in *n*-hexane)=0.14. Mp 126–128 °C. $[\alpha]_D^{23}$ −80.7 (*c* 1.0, CH_2Cl_2). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane (1/9), 1.0 mL/min, 230 nm): 99% ee, t_R 28.7 (*S*) and 30.3 (*R*) min. ^{1}H NMR (400 MHz): δ 7.77 (app. d, 2H, *J* 8.3 Hz, tolyl), 7.31 (app. d, 2H, *J* 8.3 Hz, tolyl), 6.96 (d, 1H, *J* 8.4 Hz, H-5), 6.69 (dd, 1H, *J* 8.4, 2.8 Hz, H-6), 6.47 (d, 1H, *J* 2.8 Hz, H-8), 4.44 (br d, 1H, *J* 8.1 Hz, NH), 3.74 (s, 3H, OCH_3), 3.71–3.57 (m, 1H, H-2), 2.92 (dd, 1H, *J* 16.2, 5.0 Hz, H-1), 2.79–2.68 (m, 2H, H-4), 2.57 (dd, 1H, *J* 16.2, 7.5 Hz, H-1), 2.44 (s, 3H, PhCH_3), 1.98–1.84 (m, 1H, H-3), 1.79–1.63 (m, 1H, H-3). ^{13}C NMR (100 MHz): δ 157.7 (C-7), 143.4 (tolyl), 138.0 (C-8a), 134.4 (tolyl), 129.7 (tolyl), 129.7 (C-5), 127.0 (tolyl), 127.0 (C-4a), 113.8 (C-8), 112.8 (C-6), 55.2 (OCH_3), 49.4 (C-2), 36.7 (C-1), 29.7 (C-3), 25.9 (C-4), 21.5 (PhCH_3). IR (KBr): 3318 (s), 3052 (w), 3009 (w), 2938 (m), 2836 (m), 1609 (s), 1505 (s), 1456 (m), 1422 (m), 1322 (s), 1161 (s), 1251 (s), 1062 (m), 811 (m) cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; S, 9.67. Found: C, 64.83; H, 6.35; N, 4.18; S, 9.78.

*4.6.2. (S)-N-(6-Fluoro-7-methoxy-1,2,3,4-tetra-hydronaphthalene-2-yl)-4-methylbenzene-sulfonamide (**20**).* The title compound was prepared from **15b** (45 mg, 0.12 mmol) in accordance to the procedure described for preparation of **19**. The crude product was purified by flash chromatography (25% EtOAc in *n*-pentane) to afford **20** (33 mg, 76% yield) as colorless crystalline needles. Data for **20**: R_f (25% EtOAc in *n*-hexane)=0.28. Mp 139–142 °C. $[\alpha]_D^{23}$ −79.6 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.77 (app. d, 2H, *J* 8.4 Hz, tolyl), 7.31 (d, 2H, *J* 8.4 Hz, tolyl), 6.75 (d, 1H, *J* 12.0 Hz, H-5), 6.51 (d, 1H, *J* 8.4 Hz, H-8), 4.59 (d, 1H, *J* 7.6 Hz, NH), 3.81 (s, 3H, OCH_3), 3.75–3.67 (m, 1H, H-2), 2.91 (dd, 1H, *J* 16.2, 5.0 Hz, H-1), 2.78–2.62 (m, 2H, C-4), 2.58 (dd, 1H, *J* 16.2, 7.6 Hz, H-1), 2.44 (s, 3H, PhCH_3), 1.93–1.83 (m, 1H, H-3), 1.75–1.63 (m, 1H, H-3). ^{13}C NMR (100 MHz): δ 151.0 (d, $^1J_{CF}$ 244.9 Hz, C-6), 145.8 (d, $^2J_{CF}$ 11.1 Hz, C-7), 143.5 (tolyl), 138.0 (tolyl), 129.8 (tolyl), 128.9 (d, $^4J_{CF}$ 3.4 Hz, C-8a), 127.4 (d, $^3J_{CF}$ 6.0 Hz, C-4a), 127.0 (tolyl), 115.7 (d, $^2J_{CF}$ 17.8 Hz, C-5), 113.9 (d, $^3J_{CF}$ 2.0 Hz, C-8), 56.3 (OCH_3), 49.2 (C-2), 36.2 (C-1), 29.2 (C-3), 26.0 (d, $^4J_{CF}$ 1.3 Hz, C-4), 21.6 (PhCH_3). IR (KBr): 3314 (m), 2943 (w), 1520 (s), 1425 (m), 1323 (s), 1292 (m), 1159 (s), 1108 (m), 1030 (w) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{20}FNNaO_3S$ $(M+Na)^+$ 372.1040, found 372.1036.

*4.6.3. (S)-2-Amino-7-methoxy-1,2,3,4-tetrahydro-naphthalene hydrochloride (**21**·**HCl**).* The title compound was prepared from *N*-Cbz α-tetralone **14a** (80 mg, 0.25 mmol) in accordance to the procedure described for preparation of **19**, and by treating the crude product with a concd hydrochloric solution (2 mL). Concentration of the latter solution under reduced pressure provided the crude hydrogen

chloride salt **21**-**HCl**, which was further recrystallized from abs EtOH to afford pure **21**-**HCl** (37 mg, 70% yield) as a white solid. Data for **21**-**HCl**: $[\alpha]_D^{23}$ −64.9 (*c* 0.5, MeOH), {lit. $[\alpha]_D^{20}$ −66.1 (*c* 0.5, MeOH)}.[57] The enantiomeric excess was determined to be 99% by chiral HPLC analysis, after a derivatization of **21**-**HCl** to tosylate **19**. The procedure for the latter reaction is shown below.

To an ice-cooled solution of **21**-**HCl** (21 mg, 0.098 mmol) in anhydrous pyridine (2 mL) was added *p*-TsCl (29 mg, 0.152 mmol), and the resultant mixture was stirred for 2.5 h at 0 °C. The mixture was allowed to warm to room temperature, and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:2) to provide pure **19** (8 mg, 25% yield) as a colorless crystalline material. Spectroscopic data was consistent with data presented earlier for the compound (see chapter 4.6.1). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane (1/9), 1.0 mL/min, 230 nm): 99% ee, t_R 28.7 (*S*), and 30.3 (*R*) min.

*4.6.4. (S)-2-Amino-7-methoxy-1,2,3,4-tetrahydro-naphthalene hydrochloride (**21**-**HCl**).* Instantaneous cleavage of the tosyl protecting group in **19** was performed in accordance with an adopted literature procedure.[53] To a solution of SmI_2 (8.0 mL, 0.1 M, 0.81 mmol, 10.7 equiv) in THF was added *N*-tosylamide **19** (25 mg, 0.076 mmol, 1 equiv) followed by water (40 μL, 30 equiv) and pyrrolidine (130 μL, 20 equiv) under a nitrogen atmosphere. The reaction was completed after few seconds. The resulting mixture was diluted with diethyl ether (6 mL) and treated with an aqueous solution of potassium sodium tartrate and potassium carbonate (10 mL, 10% w/v each). The aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude amine was re-dissolved in 96% EtOH (3 mL) and concd hydrochloric solution (1 mL), before evaporation of the solvent. Discoloration of crude **21**-**HCl** was done by treatment with active carbon in 96% EtOH (5 mL) at 40 °C for 15 min. Finally, the HCl salt was recrystallized from abs EtOH yielding **21**-**HCl** as a colorless solid (7.2 mg, 45% yield). Data for **21**-**HCl**: $[\alpha]_D^{23}$ −64.6 (*c* 0.5, MeOH), {lit. $[\alpha]_D^{20}$ −66.1 (*c* 0.5, MeOH)}.[57]

*4.6.5. (S)-2-Amino-6-fluoro-7-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride (**ST1214**).* Cleavage of tosyl group in **20**, and then HCl precipitation of the liberated amine to form **ST1214** (65% yield), was performed in accordance to the procedure described for preparation of **21**-**HCl** (chapter 4.6.4). Data for **ST1214**: $[\alpha]_D^{23}$ −50.9 (*c* 1.0, H_2O), {lit. $[\alpha]_D$−52.5 (*c* 1.0, H_2O)}.[58]

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.025.

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