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Graphical Abstract

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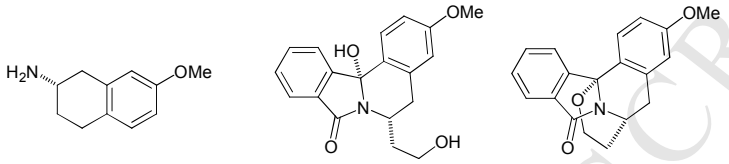

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Synthesis of (*S*)-2-amino-7-methoxytetralin and isoindolo[1,2-a]isoquinolinone derivatives from L-aspartic acid

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ABSTRACT

This paper describes a new total synthesis for (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT,** from L-aspartic acid in an overall yield of 10% over nine steps. The major loss was ascribed to a key intramolecular Friedel-Crafts cyclisation step, which afforded up to 36% yield. Attempts to perform a Friedel-Crafts cyclization of an intermediate phthalimide protected amino alcohol **13** did not give the desired protected **(*S*)-7-MeO-AT**. On the other hand, two new isoindolo[1,2-a]isoquinolinone derivatives **14** and **15,** were isolated in 21 and 11% yield, respectively. The yield of **15** was improved to 70%.

1. Introduction

The pharmacological activity of 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene, AT) 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]

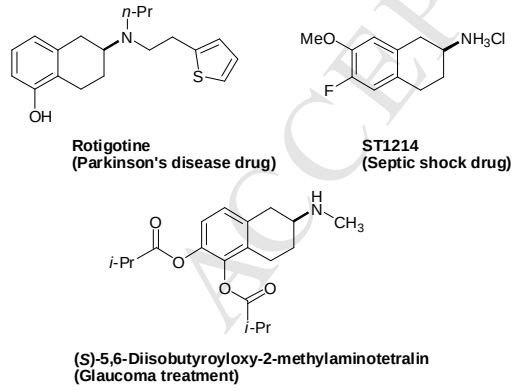
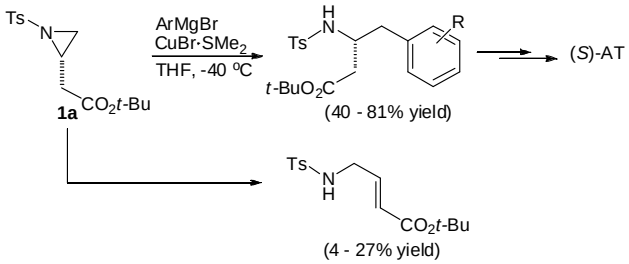


Fig. 1. Pharmacological active 2-aminotetralins.

Today, several enantiopure ATs are used in the treatment of medical conditions like Parkinson's disease,[3] glaucoma[4] and septic shock[5,6] (Fig. 1).

Recently, we reported the synthesis of substituted (*S*)-ATs via ring-opening of aziridine **1a** prepared from L-aspartic acid β-*tert*-butyl ester (see Scheme 1).[7] Unfortunately, this protocol was accompanied with a disturbing elimination reaction. In order to circumvent this side reaction we have tested an alternative chiral C_4-aziridine building block, **1b**, as shown in the protocol described in Scheme 2.



Scheme 1.

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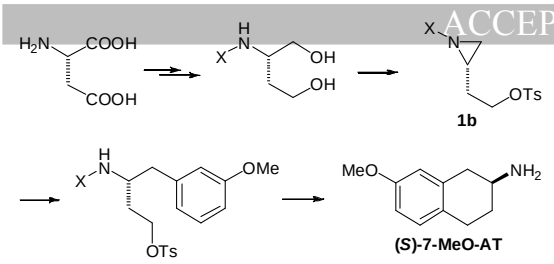


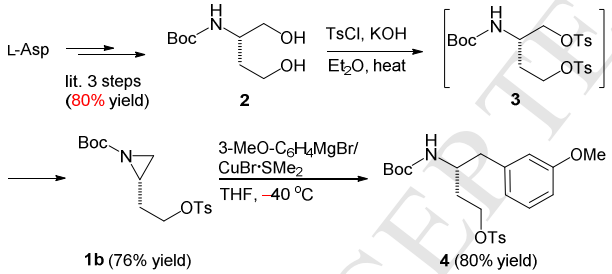
Scheme 2. Strategy for enantioselective synthesis of (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT**, from L-aspartic acid.

In the presented study (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT**, was chosen as the target molecule. The protocol does, however, have the potential to offer ATs with other substituents on the aromatic ring.

2. Results and discussion

2.1. Preparation and ring-opening of aziridine 1b

Natural L-aspartic acid (L-Asp) served as starting material in a three step synthesis to *N*-Boc-diol **2**, following literature procedures (Scheme 3).[8,9] Ring-closing of *N*-Boc-diol **2** to aziridine **1b** was performed according to an adopted procedure described by Wessig and Schwartz.[10] In addition to the intermediate ditosylate **3**, the reaction afforded **1b** as the only cyclized product. This observation was a contrast to the tosylated (or mesylated) *N*-Boc-β-amino alcohols tendency to form oxazolinones.[11,12] We were not able to observe any azetidine formation either, which might occur in some cases where three- and four-membered ring formation are competitive pathways.[13]

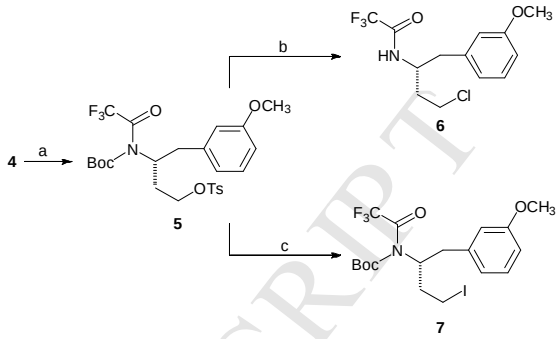


Scheme 3.

Ring-opening reaction of *N*-Boc-aziridine **1b** by a copper aryl nucleophile [from (3-methoxyphenyl)magnesium bromide and CuBr·Me_2S] provided compound **4** in a decent yield. However, the product proved to be somewhat unstable at room temperature. Refluxing of **4** in THF and DCM for 6 hours gave 50% and 23% decomposition respectively. As a consequence, product **4** was stored under an inert atmosphere at −18 °C.

2.2. Intramolecular Friedel-Crafts alkylation

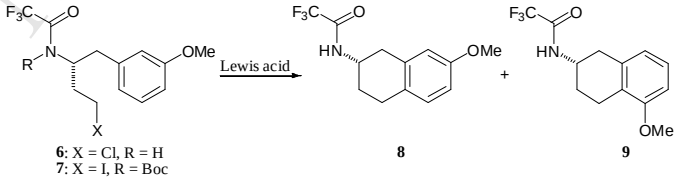
Little is known about the possibilities for intramolecular Friedel-Crafts alkylation of alkyl tosylates, or compounds holding other sulfone based leaving groups (e.g. mesyl or triflate). Initial efforts to ring-close tosylate **4** in the presence of $TiCl_4$ in DCM gave rapid cleavage of the Boc-group even at room temperature. No AT products were observed. A trifluoroacetyl group was therefore introduced to double protect the amine function in **4** (see Scheme 4). Attempted Friedel-Crafts cyclisation of **5** under the same conditions did, however, give cleavage of the Boc-group as well as halogen exchange of the tosyl group, resulting in chloride **6**. A similar exchange has been reported with oxophilic Lewis acids in the presence of alkyl tosylates.[14]



Scheme 4. (a) TFAA, Et_3N, DCM, 0 ºC – rt. 99% yield. (b) $TiCl_4$, DCE, 80 °C, 58% yield. (c) NaI, acetone, 35 °C, 12 h. 78% yield.

The newly formed alkyl chloride **6** could, however, serve as a substrate for a classical Friedel Crafts alkylation reaction. The corresponding iodide **7** was prepared for comparison (see Scheme 4). The results of the cyclisation reactions of chloride **6** and iodide **7** are summarized in Table 1.

Table 1. Intramolecular Friedel-Crafts alkylation



Entry	Substrate	Lewis acid	Conditions, solvent	Ratio[a] **8** : **9**	% yield **8**,[b] (% *ee*)[c]
1	**6**	$AlCl_3$ (2 equiv)	80 °C, 7 h DCE		-[d]
2	**6**	$AlCl_3$ (2 equiv)	83 ºC, 20 h DCE		-[d]
3	**6**	$InBr_3$ (2 equiv)	83 ºC, 20 h DCE	69 : 31	complex mixture
4	**6**	$AlCl_3$ (3 equiv)	100 ºC, 20 h, DCM[e]	83 : 17	36 (99)
5	**6**	$InBr_3$ (2 equiv)	80 ºC, 20 h DCM[e]	68 : 32	<15 (99)
6	**6**	$SnCl_4$ (3 equiv)	80 ºC, 20 h DCM[e]		-[d]
7	**6**	$BF_3{\cdot}Et_2O$ (3 equiv)	80 ºC, 20 h DCM[e]		-[d]
8	**7**	$InBr_3$ (2 equiv)	80 ºC, 18 h DCM[e]	71 : 29	26 (97)

[a] The product ratio was determined by ^{1}H NMR (400 MHz) spectroscopy of the crude product. [b] Isolated yield after purification.
[c] The enantiomeric excess of the products was determined by HPLC analysis.
[d] No reaction. [e] Reaction performed in closed pressure tube.

Two solvents and four Lewis acids were tested. Both, chloride **6** and iodide **7** afforded the desired target molecule **8**. Unfortunately, neither of them provided regioselective reactions, giving significant amounts of the 5-methoxy isomer **9** as well. We did not succeed in finding the optimal conditions for the reactions. The best selectivity (ratio **8** : **9** = 83 : 17) and yield (36 % yield based on ^{1}H NMR of the product mixture) of **8** was obtained with $AlCl_3$ in DCM at 100 °C (closed glass pressure tube) for 20 hours (Table 1, entry 4). The products **8** and **9** were only partly separable by flash chromatography.

Target molecule **(*S*)-7-MeO-AT** is accessible through basic hydrolysis of **8** in quantitative yield.[15]

2.3. Preparation and cyclization of phthalimide protected amino alcohol 13

Harris *et al.*[16] have reported preparation of ATs by ring-closure of phthalimide protected isomer-**13** (see Fig. 2). Treatment of isomer-**13** with TfOH in PhCl at 80 °C gave quantitative yield of ATs in an *ortho* : *para* ratio of 1 : 3. Inspired by their results, we aimed at preparing **(*S*)-7-MeO-AT** from the **13**, which was assumed to be available from **4**.

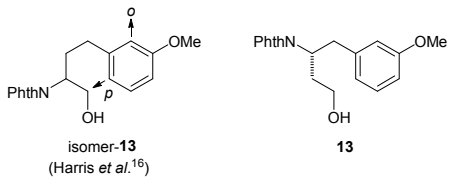
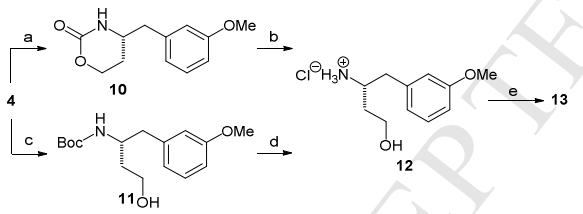


Fig. 2 Phthalimide protected AT precursors.

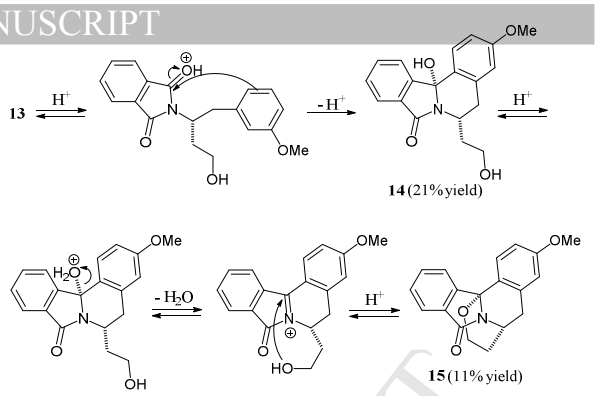
Synthesis of PhthN-alcohol **13** was successfully provided via two alternative routes, according to Scheme 5.



Scheme 5. (a) KOH, DMSO, rt, 29 h, 89% yield. (b) (i) LiOH, MeOH/H_2O, 70 ºC, 2 h. (ii) EtOH/conc HCl, rt, 5 min, 98% yield. (c) SmI_2, H_2O, pyrrolidine, rt, 5 min, 43% yield. (d). Conc HCl/toluene, 65 ºC, 2 h, yield 80% (e) Phthalic anhydride, Et_3N, toluene, 100 °C, 20 h, 87% yield.

Treatment of PhthN-alcohol **13** with TfOH according to the procedure described by Harris *et al.*[16] gave a product mixture which did not appear to contain significant amounts of the desired **(*S*)-7-MeO-AT**. We were, however, able to isolate two main products **14** and **15**, shown in Scheme 6, which were structurally elucidated by NMR experiments (COSY, HSQC, HMBC, NOESY). A mechanistic suggestion for the formation of **14** and **15** is given in Scheme 6.

Compounds **14** and **15** can be classified in the isoindolo[1,2-a]isoquinolinone family. This family contains one known natural



Scheme 6. Suggested mechanism for the formation of compounds **14** and **15**.

product, i.e. (±)-nuevamine, isolated from *Berberis darwinii* Hook species.[17] Several approaches to synthesize derivatives of this class of compounds are known from literature.[18-21] Some of these compounds are considered to have potential biological activities.[22]

During our work we became aware of Selvakumar and Ramanathan's general procedure for preparation of racemic and fused isoindoloisoquinolinone derivatives from a TfOH facilitated intramolecular cyclization of phenethylphthalimides in DCM.[23] Applying their method on **13** (6.8 equiv TfOH, r.t. overnight) yielded **15** in 70% yield. In this reaction we were not able to isolate **14**.

3. Conclusion

A new total synthesis for (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT,** from L-aspartic acid has been developed. The applied protocol afforded protected **(*S*)-7-MeO-AT** in an overall yield of 10% over nine steps. The major loss occurred in the step involving the intramolecular Friedel-Crafts cyclisation, for which only up to 36% yield was obtained, partially due to problems with separation of regioisomeric products.

Attempts to perform Friedel-Crafts cyclization of the phthalimide protected alcohol **13** did not give the desired protected **(*S*)-7-MeO-AT**. On the other hand, this step afforded two new isoindolo[1,2-a]isoquinolinone derivatives **14** and **15**, in 21 and 11% yield, respectively. The yield of **15** of was improved to 70%.

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 calicium 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 Chiralcel OJ (250 x 4.6 mm). ^{1}H 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 ppm 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, NOESY). 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 the MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography.

4.2. Preparation and ring-opening of aziridine 1b

*4.2.1. (S)-tert-Butyl 2-(2-tosyloxy)ethyl)aziridine-1-carboxylate (**1b**).*

The title compound was prepared by adopting a procedure described by Wessig and Schwartz.[10] Diol **2**[8,9] (2.42 g, 11.8 mmol) was dissolved in dry diethyl ether (180 mL) and added tosyl chloride (6.00 g, 31.5 mmol). Pellets of KOH (3.61 g, 65 mmol) were grinded and added instantly to the mixture. After 24 h of reflux, additional KOH (1.00 g, 18 mmol) was added. The reaction was quenched by pouring it over crushed ice (100 g). The organic layer was washed with brine (50 mL) and dried ($MgSO_4$). Purification by flash chromatography (15% EtOAc in *n*-pentane) provided 3.08 g of **1b** as a colorless oil (76 % yield). Data for **1b**: R_f = 0.39 (EtOAc/*n*-hexane, 1:2). $[\alpha]_D^{22}$ +19.3 (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz): δ 7.80 (app d, *J* 8.0 Hz, 2H, tolyl), 7.35 (app d, *J* 8.0 Hz, 2H, tolyl), 4.25-4.12 (m, 2H, CH_2-O), 2.47-2.37 (m, 1H, CH-N), 2.45 (s, 3H, tolyl), 2.27 (d, *J* 6.0 Hz, 1H, C**H**H-N), 1.92 (d, *J* 3.6 Hz, 1H, CH**H**-N), 1.93-1.71 (m, 2H, C**H**$_2$-CH_2O), 1.43 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 162.1 (OC(=O)N), 144.9 (tolyl), 133.0 (tolyl), 129.9 (tolyl), 127.9 (tolyl), 81.4 (*t*-Bu), 68.0 (CH_2-O), 34.3 (CH-N), 31.9 (**C**H_2-CH_2O), 31.4 (CH_2-N), 27.9 (*t*-Bu), 21.6 (tolyl). IR (thin film, NaCl): 2979 (s), 1717 (s), 1598 (m), 1367 (s), 1309 (s), 1222 (s), 1121 (m) cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{23}NNaO_5S$ $(M+Na)^+$ 364.1189, found 364.1200.

*4.2.2. (R)-3-(tert-Butoxycarbonylamino)-4-(3-methoxyphenyl)butyl 4-methylbenzenesulfonate (**4**).*

The title compound was made by adopting a procedure described by Burgaud and co-workers.[24] 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 complete, the reaction was continued with vigorous stirring for 30 min, then titrated utilizing salicylaldehyde as a titration indicator,[25] and used immediately in the following reaction. A solution of Boc-aziridine **1b** (535 mg, 1.57 mmol) and $CuBr{\cdot}Me_2S$ (48 mg, 0.233 mmol, 15 mol %) in dry THF (25 mL) was cooled to −40 °C under argon atmosphere. To the solution, a standardized amount the Grignard solution (3.14 mmol, 2 equiv) was added over a period of 5 min. The reaction mixture was stirred for 2 h and allowed to warm to −10 °C. The reaction mixture was quenched by 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 and dried ($MgSO_4$). Purification performed by flash chromatography (15% EtOAc in *n*-pentane), yielded **4** (564 mg, 80%) as a white crystalline material. Data for **4**: Mp 74 - 77 °C (decomp. gas evolves), R_f = 0.33 (15% EtOAc in *n*-pentane). $[\alpha]_D^{22}$ −8.4 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz): δ 7.77 (app. d, *J* 8.0 Hz, 2H, tolyl), 7.33 (app. d, *J* 8.0 Hz, 2H, tolyl), 7.19 (app. t, *J* 7.8 Hz, 1H, H_{Ar}-5), 6.76 (app. dd, *J* 7.8, 2.6 Hz, 1H, H_{Ar}-4), 6.70 (app. d, *J* 7.8 Hz, 1H, H_{Ar}-6), 6.66 (app. s, 1H, H_{Ar}-2), 4.36 (d, *J* 8.4 Hz, 1H, NH), 4.15-4.02 (m, 2H, H-1), 3.85-3.76 (m, 1H, H-3), 3.78 (s, 3H, CH_3O), 2.85-2.76 (m, 1H, 1H, H-4), 2.69 (dd, *J* 13.2, 6.8 Hz, 1H, H-4), 2.44 (s, 3H, tolyl), 1.96-1.84 (m, 1H, H-2), 1.82-1.66 (m, 1H, H-2), 1.38 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 159.7 (C_{Ar}-3), 155.1 (OC(=O)N), 144.8 (tolyl), 139.0 (C_{Ar}-1), 132.9 (tolyl), 129.9 (tolyl), 129.5 (C_{Ar}-5), 127.9 (tolyl), 121.7 (C_{Ar}-6), 115.0 (C_{Ar}-2), 112.1 (C_{Ar}-4), 79.0 (*t*-Bu), 67.9 (C-1), 55.2 (CH_3O), 48.8 (C-3), 41.0 (C-4), 33.2 (C-2), 28.3 (*t*-Bu), 21.6 (tolyl). IR (KBr): 2929 (m), 1704 (s), 1600 (m), 1490 (s), 1392 (s), 1292 (s), 1175 (s), 1097 (m) cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{32}NO_6S$ $(M+H)^+$ 450.1945, found 450.1946.

4.3. Intramolecular Friedel-Crafts alkylation

*4.3.1. (R)-3-(tert-Butoxycarbonyl)-2,2,2-trifluoro-acetamido-4-(3-methoxyphenyl)butyl 4-methyl-benzenesulfonate (**5**).*

N-Trifluoroacetylation of tosylate **4** was performed according to a general protocol described by Moussa and Romo.[26] Tosylate **4** (450 mg, 1.00 mmol) was dissolved in DCM (20 mL) and cooled to 0 ºC, added Et_3N (280 µL, 2.01 mmol) followed by TFAA (280 µL, 2.01 mmol). After vigorous stirring for 2.5 h at room temperature, the volatiles were removed under reduced pressure. The crude mixture was dissolved in DCM (50 mL), washed with aqueous $NaHCO_3$ (saturated, 25 mL), aqueous citric acid (2% wt, 20 mL) and dried ($MgSO_4$). Removal of the solvent yielded **5** (541 mg, 99%) as a relatively pure colorless oil. Data for **5**: R_f = 0.37 (15% EtOAc in *n*-pentane). $[\alpha]_D^{23}$ +40.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz): δ 7.76 (app. d, *J* 8.4 Hz, 2H, tolyl), 7.33 (app. d, *J* 8.4 Hz, 2H, tolyl), 7.16 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.75 (app. dd, *J* 7.9, 2.2 Hz, 1H, H_{Ar}-4), 6.68 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.64 (app. s, 1H, H_{Ar}-2), 4.75-4.60 (m, 1H, H-3), 4.15-3.90 (m, 2H, H-1), 3.76 (s, 3H, CH_3O), 3.14 (dd, *J* 13.6, 10.4 Hz, 1H, H-4), 2.85 (dd, *J* 13.6, 6.0 Hz, 1H, H-4), 2.43 (s, 3H, tolyl), 2.40-2.29 (m, 1H, H-2), 2.11-2.00 (m, 1H, H-2), 1.39 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 160.5 (q, $^2J_{C,F}$ 39.2 Hz, N**C**(O)CF_3), 159.7 (C_{Ar}-3), 150.8 (Boc), 144.9 (tolyl), 138.2 (C_{Ar}-1), 132.7 (tolyl), 129.9 (tolyl), 129.6 (C_{Ar}-5), 128.0 (tolyl), 121.5 (C_{Ar}-6), 115.3 (q, $^1J_{C,F}$ 287.3, CF_3), 114.5 (C_{Ar}-2), 112.8 (C_{Ar}-4), 86.2 (Boc), 67.1 (C-1), 57.5 (C-3), 55.1 (CH_3O), 38.7 (C-4), 30.9 (C-2), 27.3 (Boc), 21.6 (tolyl). IR (thin film, NaCl): 2985 (m), 1758 (m), 1713 (m), 1600 (m), 1456 (m), 1398 (m), 1261 (m), 1144 (s), 1098 (m) cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{30}F_3NO_7S$ $(M+NH_4)^+$ 563.2033, found 563.2036.

*4.3.2. (R)-N-(4-Chloro-1-(3-methoxyphenyl)butan-2-yl)-2,2,2-trifluoroacetamide (**6**).*

Double protected amine **5** (66 mg, 0.12 mmol) was dissolved in dry 1,2-dichloroethane (3.0 mL). Dropwise to this solution, $TiCl_4$ (40 µL, 0.365 mmol) was added, and the mixture was heated to 80 °C for 2.5 h. After cooling the mixture to room temperature, a phosphate buffer (pH 7, 10 mL, 1 M) was added. The mixture was diluted with DCM (20 mL) and the layers separated. The aqueous layer was extracted with additional DCM (2 × 10 mL). The combined organic layer was dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography (15% EtOAc in *n*-pentane) affording **6** (23 mg, 58%) as white solid. The white solid material could also be recrystallized (*n*-hexane/EtOAc) to fine crystalline needles. Data for **6**: Mp 103 - 104 °C, R_f = 0.51 (15% EtOAc in

n-pentane). $[\alpha]_D^{23}$ −24.6 (c 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.24 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.81 (app. dd, *J* 7.9, 2.4 Hz, 1H, H_{Ar}-4), 6.74 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.70 (app. s, 1H, H_{Ar}-2), 6.31 (d, *J* 7.6 Hz, 1H, NH), 4.44-4.30 (m, 1H, H-2), 3.79 (s, 3H, CH_3O), 3.56 (t, *J* 6.6 Hz, 2H, H-4), 2.97-2.83 (m, 2H, H-1), 2.17-1.95 (m, 2H, H-3). ^{13}C NMR (100 MHz): δ 160.0 (C_{Ar}-3), 156.9 (app. d, $^2J_{C,F}$ 35.7 Hz, C=O), 137.6 (C_{Ar}-1), 129.9 (C_{Ar}-5), 121.6 (C_{Ar}-6), 115.7 (q, $^1J_{C,F}$ 289.3 Hz, CF_3), 114.9 (C_{Ar}-2), 112.6 (C_{Ar}-4), 55.2 (OCH_3), 49.7 (C-2), 41.1 (C-4), 39.9 (C-1), 36.0 (C-3). IR (KBr): 3312 (m), 1704 (s), 1558 (m), 1487 (m), 1439 (m), 1262 (m), 1156 (s), 1056 (m), 699 (m) cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{15}ClF_3NO_2$ $(M+NH_4)^+$ 327.1082, found 327.1078.

*4.3.3. (R)-tert-Butyl 4-iodo-1-(3-methoxyphenyl)-butan-2-yl(2,2,2-trifluoroacetyl)carbamate (**7**)*

The title compound was synthesized by adopting a procedure described by Saplay *et al.*[27] Tosylate **5** (136 mg, 0.249 mmol) was dissolved in acetone (2.0 mL) and added NaI (70 mg, 0.467 mmol). After vigorous stirring at 35 °C for 12 h, the solvent was removed under reduced pressure. The crude mixture was dissolved in water (10 mL) and DCM (15 mL), separated and additionally extracted with DCM (2 × 10 mL). After drying ($MgSO_4$), the solvent was removed, and the residue purified by flash chromatography (10% EtOAc in *n*-pentane). Pure iodide **7** was achieved in 78% yield as slightly yellow oil. Data for **7**: R_f = 0.65 (10% EtOAc in *n*-pentane). $[\alpha]_D^{23}$ +1.95 (c 1.05, CH_2Cl_2). ^{1}H NMR (300 MHz): δ 7.19 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.80-6.72 (m, 2H, H_{Ar}-4 and H_{Ar}-6), 6.70 (app. s, 1H, H_{Ar}-2), 4.75-4.61 (m, 1H, H-2), 3.78 (s, 3H, CH_3O), 3.21-3.01 (m, 3H, H-4 and H-1), 2.91 (dd, *J* 13.7, 6.2 Hz, 1H, H-1), 2.62-2.47 (m, 1H, H-3), 2.27-2.13 (m, 1H, H-3), 1.42 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 160.2 (app. d, $^2J_{C,F}$ 44.9 Hz, **C**(=O)CF_3), 159.8 (C_{Ar}-3), 151.0 (OC(=O)N), 138.3 (C_{Ar}-1), 129.6 (C_{Ar}-5), 121.5 (C_{Ar}-6), 115.4 (q, $^1J_{C,F}$ 288.3 Hz, CF_3), 114.5 (C_{Ar}-2), 112.7 (C_{Ar}-4), 86.2 (CMe_3), 61.3 (C-2), 55.1 (CH_3O), 38.3 (C-1), 35.7 (C-3), 27.4 ((*C*H_3)$_3$C), 0.4 (C-4). IR (thin film, NaCl): 2984 (w), 1759 (m), 1713 (s), 1602 (m), 1586 (m), 1490 (m), 1456 (m), 1372 (m), 1260 (s), 1170 (s), 1043 (w), 836 (m) cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{23}F_3INO_4$ $(M+NH_4)^+$ 519.0962, found 519.0963.

*4.3.4. (S)-2-Trifluoroacetylamino-7-methoxy-1,2,3,4-terahydronaphthalene (**8**) and (S)-2-trifluoroacetylamino-5-methoxy-1,2,3,4-terahydronaphthalene (**9**).*

The intramolecular Friedel-Crafts alkylation of chloride **6** (experiment a, Table 1, entry 4) and iodide **7** (experiment b, Table 1, entry 8) afforded partly inseparable mixtures of **8** and **9**.

(a) Table 1, entry 4: Chloride **6** (22 mg, 0.071 mmol) was dissolved in DCM (5 mL) and added $AlCl_3$ (30 mg, 0.225 mmol). The mixture was heated to 100 °C in a glass pressure tube for 20 h. The mixture was cooled to room temperature and then added an aqueous phosphate buffer (pH 7, 10 mL, 1 M) and DCM (10 mL). The layers were separated and the aqueous phase extracted with additional DCM (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. ^{1}H NMR analysis of the residue showed a product ratio **8** : **9** = 83 : 17. The crude product was purified by flash chromatography (10% EtOAc in *n*-pentane). Impure **8** (7.8 mg, 36% yield, 90% pure, >99% *ee*) was isolated as colorless crystals. The spectroscopic data of **8** was in accordance to data reported by Cecchi *et al.*[28] Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ, *i*-PrOH/*n*-hexane (1:9), 1.0 ml/min, 230 nm, t_R 25.4 min (*S*) and 53.8 min (*R*)). Compound **9** was purified by flash chromatography (10% EtOAc in *n*-pentane) up to 70% purity. Data for **9**: R_f = 0.42 (10% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz): δ 7.13 (app. t, *J* 8.0 Hz, 1H, H-7), 6.71 (app. d, *J* 8.0 Hz, 1H, H-6), 6.70 (app. d, *J* 8.0 Hz, 1H, H-8), 6.24 (br, 1H, NH), 4.40-4.27 (m, 1H, H-2), 3.83 (s, 3H, CH_3O), 3.17 (dd, *J* 16.2, 5.0 Hz, 1H, H-1), 2.97-2.67 (m, 3H, H-1 and H-4), 2.16-2.04 (m, 1H, H-3), 1.94-1.80 (m, 1H, H-3). ^{13}C NMR (100 MHz): δ 157.3 (C-5), 156.7 (app. d, $^2J_{C,F}$ 36.7 Hz, C=O), 134.1 (C-8a), 126.8 (C-7), 123.9 (C-4a), 121.5 (C-8), 115.8 (app. d, $^1J_{C,F}$ 288.6 Hz, CF_3), 107.7 (C-6), 55.3 (CH_3O), 45.9 (C-2), 35.0 (C-1), 27.5 (C-3), 20.7 (C-4). HRMS (ESI) calcd for $C_{13}H_{15}F_3NO_2$ $(M+H)^+$ 274.1049, found 274.1053.

(b) Table 1, entry 8: Iodide **7** (42 mg, 0.084 mmol) was dissolved in DCM (6 mL) and added $InBr_3$ (55 mg, 0.155 mmol). The mixture was heated to 80 °C in a pressure glass tube for 18 h. The mixture was cooled to room temperature and added an aqueous phosphate buffer (pH 7, 10 mL, 1 M) and DCM (10 ml). The layers were separated and the aqueous phase extracted with additional DCM (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. ^{1}H NMR analysis of the residue showed a product ratio **8** : **9** = 71 : 29. The crude product was purified by flash chromatography (10% EtOAc in *n*-pentane). Impure **8** (6.4 mg, 26% yield, 93% pure, 97% *ee*) was isolated as colorless crystals.

4.4. Preparation and cyclization of phthalimide protected amino alcohol 13

*4.4.1. (R)-4-(3-Methoxybenzyl)-1,3-oxazinan-2-one (**10**).*

Tosylate **4** (0.502 g, 1.12 mmol) was dissolved in DMSO (24 mL) and added KOH (0.302 g, 5.38 mmol). The mixture was stirred at room temperature for 29 h. An aqueous phosphate buffer solution was added (pH 7, 12 mL) to quench excess KOH, and then poured into a mixture of H_2O (150 mL), brine (150 mL) and EtOAc (200 mL). The layers were separated and the aqueous layer extracted with additional EtOAc (3 × 150 mL). The combined organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and the residue purified by flash chromatography (EtOAc) affording **10** (0.220 g, 89%) as white solid. Data for **10**: Mp 80 - 84 °C, R_f = 0.22 (EtOAc). $[\alpha]_D^{23}$ +51.5 (*c* 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.26 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.82 (app. dd, *J* 7.9, 2.5 Hz, 1H, H_{Ar}-4), 6.77 (app. d, *J* 7.6 Hz, 1H, H_{Ar}-6), 6.72 (app. s, 1H, H_{Ar}-2), 5.06 (br, 1H, NH), 4.36 (dt, *J* 11.2, 4.2 Hz, 1H, H-6), 4.22 (td, *J* 10.9, 2.8 Hz, 1H, H-6), 3.81 (s, 3H, CH_3O), 3.76-3.67 (m, 1H, H-4), 2.89 (dd, *J* 12.5, 6.9 Hz, 1H, C**H**HPh), 2.66 (dd, *J* 13.4, 8.7 Hz, 1H, CH**H**Ph), 2.09-1.98 (m, 1H, H-5), 1.86-1.74 (m, 1H, H-5). ^{13}C NMR (100 MHz): δ 160.1 (C_{Ar}-3), 153.7 (C-2), 137.5 (C_{Ar}-1), 130.1 (C_{Ar}-5), 121.4 (C_{Ar}-6), 115.1 (C_{Ar}-2), 112.4 (C_{Ar}-4), 65.5 (C-6), 55.2 (CH_3O), 52.1 (C-4), 42.9 (CH_2Ph), 27.5 (C-5). IR (KBr): 3253 (m), 2939 (m), 1699 (s), 1602 (m), 1584 (m), 1489 (m), 1434 (m), 1293 (m), 1154 (m), 1092 (m), 1043 (m), 781 (m), 736 (m) cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ $(M+H)^+$ 222.1125, found 222.1130.

*4.4.2. (R)-tert-Butyl 4-hydroxy-1-(3-methoxyphenyl)butan-2-ylcarbamate (**11**).*

The title compound was synthesized by adopting a procedure described by Ankner and Hilmersson.[29] Tosylate **4** (211 mg, 0.47 mmol) was instantaneous deprotected by the addition of a solution of SmI_2 (28 mL, 0.1 M, 2.8 mmol) in THF, water (150 mg, 8.33 mmol) and pyrrolidine (0.46 mL, 5.51 mmol), under vigorous stirring. After 10 min, the reaction mixture was diluted with diethyl ether (30 mL) and treated with an aqueous solution of potassium sodium tartrate and potassium carbonate (25 mL, 10% w/v each). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). Purification by flash chromatography (25 to 40% EtOAc in *n*-pentane) afforded **11** (59 mg, 43%) as a colorless viscous oil. Data for **11**: R_f = 0.24 (40% EtOAc in *n*-pentane). $[\alpha]_D^{23}$ –13.1 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.21 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.78 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-4), 6.77 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.73 (app. s, 1H, H_{Ar}-2), 4.49 (d, *J* 8.9 Hz, 1H, NH), 4.10 (m, 1H, H-2), 3.70-3.55 (m, 2H, H-4), 3.80 (s, 3H, CH_3O), 3.20 (br, 1H, OH), 2.79 (d, *J* 6.7 Hz, 2H, H-1), 1.95-1.75 (m, 1H, H-3), 1.70-1.55 (m, 1H, H-3), 1.42 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 159.8, 157.0, 139.4, 129.6, 121.8, 115.1, 112.1, 80.0, 59.0, 55.3, 48.0, 41.7, 38.1, 28.4. IR (neat): 3366 (m), 2937 (w), 1686 (s), 1521 (s), 1488 (m), 1452 (m), 1365 (m), 1262 (s), 1156 (s), 1044 (s), 1029 (s) cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{26}NO_4$ $(M+H)^+$ 296.1856, found 296.1856.

*4.4.3. (R)-3-Amino-4-(3-methoxyphenyl)butan-1-ol hydrochloride (**12**).*

(a) Hydrochloride **12** was synthesized from the cyclic carbamate **10** by adopting a procedure described by Curtis *et al.*[30] Cyclic carbamate **10** (197 mg, 0.89 mmol) was dissolved in MeOH/H_2O (8 mL, 1:1) and added LiOH (178 mg, 7.43 mmol). The mixture was under vigorous stirring heated at 70 °C for 2 h. The solvent was removed under reduced pressure and the residue dissolved in diethyl ether (30 mL) and water (15 mL). The layers were separated and the aqueous phase extracted with DCM (4 × 20 mL). The combined organic layer was concentrated under reduced pressure. The residue was redissolved in abs ethanol (10 mL) and added conc hydrochloric acid (0.5 mL). The resultant mixture was stirred for 5 min at room temperature, and then the solvent removed under reduced pressure. Attempts with diethyl ether trituration did not yield the expected solid product. However, hydrochloride **12** (202 mg, 98%) was isolated as a pale yellow oil and used without further purification. Data for **12**: $[\alpha]_D^{23}$ +16.7 (*c* 0.9, abs EtOH). ^{1}H NMR (400 MHz, D_2O): δ 7.37 (t, *J* 7.8 Hz, 1H, H_{Ar}-5), 7.00-6,93 (m, 2H, H_{Ar}-4, H_{Ar}-6), 6.92 (app. s, 1H, H_{Ar}-2), 3.84 (s, 3H, CH_3O), 3.80-3.59 (m, 3H, H-1 and H-3), 3.06 (dd, *J* 14.1, 6.6 Hz, 1H, H-4), 2.91 (dd, *J* 14.1, 8.0 Hz, 1H, H-4), 1.98-1.83 (m, 2H, H-2). ^{13}C NMR (100 MHz, D_2O): δ 159.9 (C_{Ar}-3), 138.1 (C_{Ar}-1), 131.0 (C_{Ar}-5), 122.9 (C_{Ar}-6), 115.7 (C_{Ar}-2), 113.6 (C_{Ar}-4), 59.0 (C-1), 56.0 (CH_3O), 52.2 (C-3), 39.0 (C-4), 34.3 (C-2). IR (KBr): 2885 (br), 1602 (m), 1489 (m), 1264 (m), 1156 (m), 1046 (s), 875 (w), 781 (s), 744 (m), 698 (s) cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{18}NO_2$ $(M–Cl)^+$ 196.1332, found 196.1335.

(b) Compound **12** was alternatively synthesized from *N*-Boc-alcohol **11** by adopting a procedure described by Prashad *et al.*[31] *N*-Boc-alcohol **11** (32 mg, 0.11 mmol) was dissolved in toluene (5 ml) and conc HCl (1 mL), and heated to 65 ºC for 2 hours. Evaporation of the solid under reduced pressure gave 20 mg of **12** (80% yield).

*4.4.4. (R)-2-(4-Hydroxy-1-(3-methoxyphenyl)-butan-2-yl)isoindoline-1,3-dione (**13**).*

Phth protection of the amine group in **12** was performed according to a procedure described by Liu *et al.*[32] HCl-salt **12** (178 mg, 0.767 mmol) and phthalic anhydride (116 mg, 0.783 mmol) was dissolved in toluene (10 mL), and added triethylamine (214 µL, 1.53 mmol). The mixture was refluxed for 2 h, and then stirred at 100 °C for 18 h. The reaction mixture was allowed to cool to room temperature and added DCM (30 mL). The resulting mixture was successively washed with aqueous citric acid (10% wt, 10 mL), water (10 mL), and aqueous $NaHCO_3$ (saturated, 10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacou. Purification of the crude by flash chromatography (EtOAc/*n*-pentane, 1:1) yielded **13** (217 mg, 87% yield) as a colorless oil. Data for **13**: R_f = 0.28 (EtOAc/*n*-pentane, 1:1). $[\alpha]_D^{23}$ +136.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.80-7.71 (m, 2H, Phth), 7.71-7.60 (m, 2H, Phth), 7.10 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.77 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.72 (app. s, 1H, H_{Ar}-2), 6.66 (app. dd, *J* 7.9, 2.4 Hz, 1H, H_{Ar}-4), 4.81-4.66 (m, 1H, H-2), 3.72-3.63 (m, 1H, H-4), 3.69 (s, 3H, CH_3O), 3.62-3.50 (m, 1H, H-4), 3.40 (dd, *J* 13.8, 10.0 Hz, 1H, H-1), 3.12 (dd, *J* 13.8, 6.3 Hz, 1H, H-1), 2.44-2.28 (m, 1H, H-3), 2.12-1.96 (m, 1H, H-3). ^{13}C NMR (100 MHz): δ 168.8 (Phth), 159.6 (C_{Ar}-3), 139.6 (C_{Ar}-1), 133.9 (Phth), 131.6 (Phth), 129.4 (C_{Ar}-5), 123.2 (Phth), 121.2 (C_{Ar}-6), 114.1 (C_{Ar}-2), 112.4 (C_{Ar}-4), 59.6 (C-4), 55.1 (CH_3O), 50.0 (C-2), 38.4 (C-1), 34.7 (C-3). IR (thin film, NaCl): 3460 (m), 2934 (m), 1770 (m), 1699 (s), 1602 (m), 1394 (m), 1263 (m), 1086 (m), 872 (m), 782 (m), 721 (s) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}NO_4$ $(M+H)^+$ 326.1387, found 326.1383.

*4.4.5. Preparation of diol **14** and ether **15**.*

Cyclization of phthalimide **13** was performed by adopting a procedure described by Harris *et al.*[16] Phthalimide **13** (22.8 mg, 0.070 mmol) was dissolved in anhydrous chlorobenzene (1 mL) and added triflic acid (12.5 µL, 0.141 mmol). The reaction mixture was heated to 80 °C for 4 h. Quenching of the room tempered mixture was done by the addition of a phosphate buffer solution (pH 7, 10 mL, 1 M). Extraction with DCM (3 × 15 mL), drying over $MgSO_4$ and removal of the solvent under reduced pressure, resulted in a yellow crude mixture. Isolation of the two main products **14** (4.8 mg, 21% yield) and **15** (2.3 mg, 11% yield), both colorless oils, was performed by column chromatography (2 colums: EtOAc, then 5% MeOH in DCM).

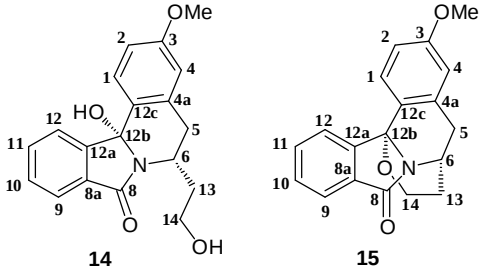


Fig. 4. Numbering of **14** and **15** with respect to ^{1}H and ^{13}C NMR interpretation.

Data for **14**: R_f = 0.31 (5% MeOH in DCM). $[\alpha]_D^{20}$ -0.5 (*c* 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.88 (app. d, *J* 7.7 Hz, 1H, H-12), 7.61-7.55 (m, 1H, H-11), 7.54 (d, *J* 8.7 Hz, 1H, H-1), 7.40-7.31 (m, 2H, H-9 and H-10), 6.74 (dd, *J* 8.7, 2.6 Hz, 1H, H-2), 6.64 (d, *J* 2.6 Hz, 1H, H-4), 5.27 (s, 1H, 12b-OH), 4.69-4.60 (m, 1H, H-6), 3.87-3.64 (m, 2H, H-14), 3.77 (s, 3H, CH_3O), 3.05 (dd, *J* 15.8, 6.5 Hz, 1H, H-5), 2.88 (dd, *J* 15.8, 5.2 Hz, 1H, H-5), 2.29-2.11 (m, 1H, H-13), 1.94-1.78 (m, 1H, H-13). ^{13}C NMR (100 MHz): δ 168.4 (C=O), 159.5 (C-3), 147.8 (12a), 135.3 (4a), 132.3 (C-11), 130.4 (8a), 129.2 (C-10), 128.5 (12c), 127.7 (C-1), 123.2 (C-9), 123.0 (C-12), 113.9 (C-4), 112.5 (C-2), 87.1 (C-12b), 68.9 (C-14), 55.3 (CH_3O), 46.5 (C-6), 34.7 (C-5), 34.3 (C-13). Configuration (6*R*, 12b*S*) was determined by NOESY analysis. IR (KBr): 3403 (m), 1682 (s), 1610 (m), 1467 (m), 1389 (m), 1256 (m), 1111 (m), 1035 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}NO_4$ $(M+H)^+$ 326.1387, found 326.1395.

Data for **15**: R_f = 0.48 (5% MeOH in DCM). $[\alpha]_D^{23}$ +40.8 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 8.02 (app. d, *J* 7.4 Hz, 1H, H-12), 7.87 (app. d, *J* 7.4 Hz, 1H, H-9), 7.69 (d, *J* 8.5 Hz, 1H, H-1), 7.65 (app. t, *J* 7.4 Hz, 1H, H-11), 7.55 (app. t, *J* 7.4 Hz, 1H, H-10), 6.81 (dd, *J* 8.5, 2.7 Hz, 1H, H-2), 6.72 (d, *J* 2.7 Hz, 1H, H-4), 4.99 (app. t, *J* 5.4 Hz, 1H, H-6), 3.85-3.79 (m, 2H, H-14), 3.80 (s, 3H, CH_3O), 3.51 (dd, *J* 17.2, 6.8 Hz, 1H, H-5), 2.95 (d, *J* 17.2 Hz, 1H, H-5), 2.32-2.17 (m, 1H, H-13), 1.69 (app. d, *J* 12.0 Hz, 1H, H-13). ^{13}C NMR (100 MHz): δ 166.9 (C=O), 159.6 (C-3), 144.9 (12a), 138.7 (4a), 131.6 (C-11), 130.4 (8a), 129.8 (C-10), 128.0 (C-1), 124.6 (12c), 124.1 (C-9), 123.3 (C-12), 112.8 (C-4), 112.8 (C-2), 85.3 (C-12b), 59.2 (C-14), 55.3 (CH_3O), 41.6 (C-6), 34.4 (C-5), 31.1 (C-13). Configuration (6*R*, 12b*S*) was determined by NOESY analysis. IR (KBr): 3442 (w), 2919 (m), 1781 (s), 1607 (m), 1429 (m), 1244 (m), 1036 (m) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ $(M+H)^+$ 308.1281, found 308.1292.

*4.4.6. Preparation of ether **15** adopting Selvakumar and Ramanathan's general procedure.*[23]

Phthalimide **13** (0.164 g, 0.50 mmol) was dissolved with stirring in dry dichloromethan (15 mL) and added triflic acid (0.3 mL, 3.39 mmol) via syringe at room temperature. The resulting wine red solution was stirred overnight and quenched with water (10 mL) followed by sodium bicarbonate (1.5 g). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 15 mL). The combined organic extract was washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed under vacuum. The residue was purified by flash chromatography (EtOAc/*n*-hexane, 1:1) to yield **15** (0.108 g, 70% yield) as a viscous colorless oil. The spectroscopic data was in accordance with the data reported above. $[\alpha]_D^{20}$ +73.9 (*c* 1.02, CH_2Cl_2).

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