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L-Proline derived nitrogenous steroidal systems: an asymmetric approach to 14-azasteroids†

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An efficient chiral pool approach using L-proline to access 14-azasteroids under mild reaction conditions has been described. The key step involves the intramolecular S_N2' cyclization reaction for the construction of critical C-ring in the nitrogen impregnated steroidal architectures bearing unsaturation at $\Delta^{9(11)}$ position. In the endeavour to synthesize some new congeners, the remote electronic impact of the electron donating groups in A ring and heteroatoms like oxygen in B ring, on the propensity of C-ring cyclization was also observed.

Introduction

The total synthesis of natural products and natural product like molecules have been the cynosure among synthetic chemists, as it not only provides opportunity to refine the general strategies delineated previously, but also to innovate new synthetic pathways to accomplish the architecturally complex molecules. In this context, steroids pose an impressive synthetic challenge, owing to their rigid framework with varying levels of functionalization.[1] Steroids with one or more heteroatoms embedded in their skeletons have been an area of considerable interest in the past few years due to their profound pharmacological profile.[2,3] In particular, azasteroids have received much attention owing to their wide range of bioactivities *viz.*, hypotensive,[4a] antifungal,[4b,c] hypocholesterolemic,[4a] antibacterial,[4a,d] GABA receptor antagonists like RU-5135[4e] and neuromuscular blocking agents like pancuronium and chandonium.[4f] Besides, their activities also include inhibition of steroid biosynthesis, which comprises blocking the action of enzyme 5α-reductase involved in the conversion of testosterone (T) to dihydrotestosterone (DHT),[8] thus providing a possible therapeutic approach towards the treatment of prevalent human diseases like benign prostatic hyperplasia,[5] acne, male pattern baldness[6a,b] and alopecia (Fig. 1).[6c] Several azasteroids have also shown antiproliferative activity in breast cancer cell lines.[7]

In view of such broad biological profile, several syntheses of azasteroids with nitrogen at various centers has been reported.[9,10] Most asymmetric strategies utilize the degradation of available chiral steroids followed by reconstruction with simultaneous incorporation of nitrogen.[9l,m] However, ring opening, ring closing sequences generally involve several steps. Besides, no asymmetric synthesis of steroidal systems with nitrogen at 14-position has been accounted.[11] Thus the development of efficient and convergent methodologies towards the asymmetric synthesis of azasteroids is an important area to explore.

Meanwhile, working on the synthesis of heteroatom impregnated natural product like architectures[12] and utilization of amino acids as chiral pool to access biologically important molecules,[13] we thought to employ proline and its derivative as chiral synthon for the incorporation of nitrogen at the desired 14-position and to utilize their inherent chirality to induce specific stereo orientation in the steroidal system for our studies. Thus, we envisioned to have diverse[14] nitrogenous steroidal core **1** with unsaturation at $\Delta^{9(11)}$ as an ideal target.

Results and discussion

As depicted in Scheme 1, the retrosynthetic analysis revealed that the target core **1** could be accomplished from the

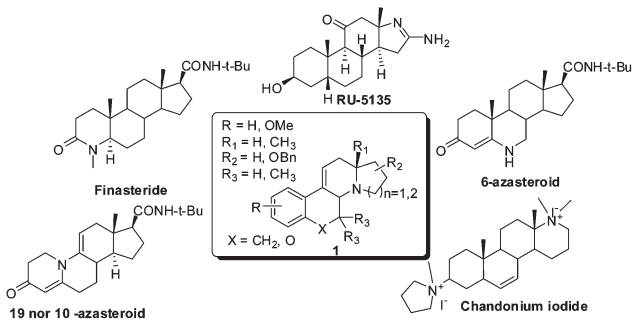

Fig. 1 Representative biologically important azasteroids and our target **1** (14-azasteroids).

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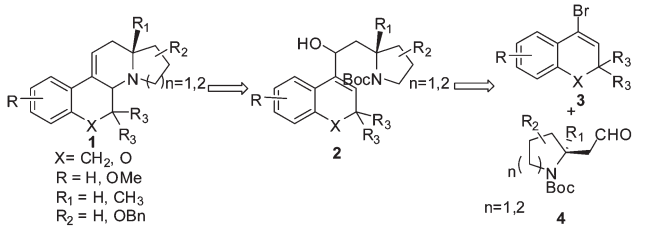


Scheme 1 Retrosynthetic analysis.

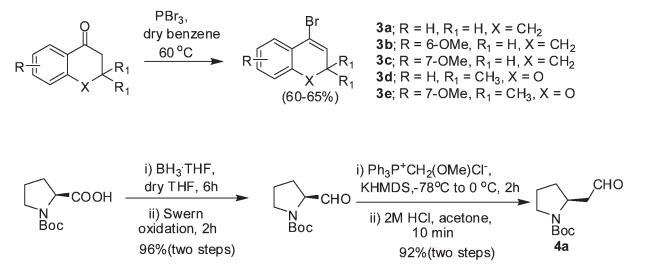
intermediate **2**, which in turn could be obtained by coupling of bromo derivative **3** with L-proline derived aldehyde **4**. The bromo derivatives **3a–e**[15] were obtained by the reaction of substituted/unsubstituted 1-tetralone/chromanone with PBr_3 in dry benzene (Scheme 2), whereas the optically pure aldehyde **4a**[16] was synthesized from commercially available N-(Boc)-S-proline by carboxyl reduction,[17a] Swern oxidation,[17b] Wittig olefination,[17c] and enol ether hydrolysis with 2 M HCl (Scheme 2).

With the starting materials in hand, substrate **3a** was lithiated using *n*-BuLi at −78 °C and was treated with aldehyde **4a** which provided the intermediate carbinols **2a** and **2a′** as two separable diastereoisomers (2 : 1) in 66% yield. However, as the newly generated stereocenter is lost at the cyclization stage, therefore diastereomeric mixture was employed directly without any need for their separation. At this stage, substrates **2a** and **2a′** seemed well poised to undergo *6-endo* trig cyclization to achieve our target cores **1**. Thus, removal of the NHBoc group using 1 : 1 mixture of DCM and TFA at 0 °C followed by treatment with $NaHCO_3$ solution furnished the unsaturated $\Delta^{9(11)}$ 14-azasteroidal core **1a** and **1a′**. Cyclization proceeds through intramolecular S_N2' reaction involving the attack of proline derived pyrrolidine nitrogen atom onto a tetralone derived allylic alcohol.

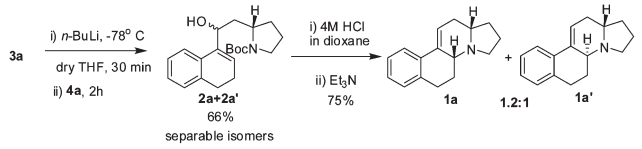
Under optimized conditions, removal of the NHBoc group using 4 M HCl in dioxane followed by cyclization using Et_3N as base afforded the separable mixture of azasteroids **1a** and **1a′** in 1.2 : 1 ratio with 75% yield (Scheme 3).

Thereafter, to explore the scope and limitation of this strategy as well as to introduce diversity in D–ring, optically pure aldehydes **4b**, **4c**, **4d** and **4e** were synthesized (Scheme 4).

Aldehydes **4b**, **4c** and **4d** (eqn 1 and 2; Scheme 4) were prepared from commercially available proline derivatives



Scheme 2 Synthesis of bromo derivatives **3a–e** and optically pure aldehyde **4a**.



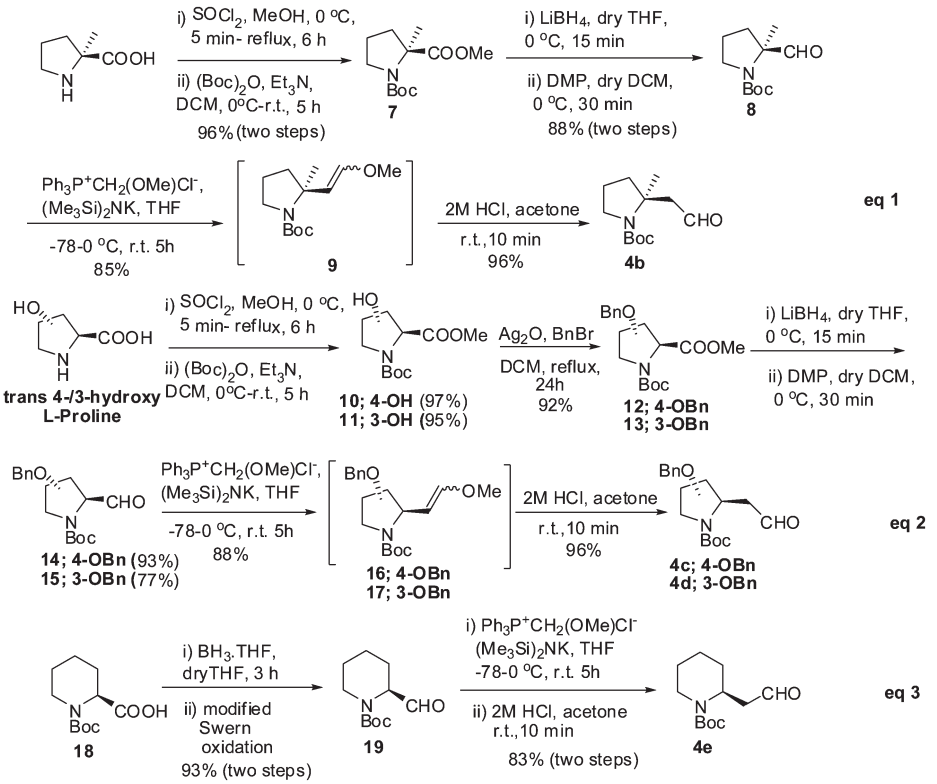
Scheme 3 Synthesis of azasteroids **1a** and **1a′**.

α-methyl- L-proline and *trans*-4-/3-hydroxy L-proline, respectively, using standard reaction conditions. α-methyl- L-proline and *trans*-4-/3-hydroxy L-proline were esterified ($SOCl_2$/MeOH) at 0 °C followed by Boc protection which furnished ester derivatives **7**, **10** and **11**. Benzylation of hydroxyl group in **10** and **11** was performed under neutral reaction conditions using Ag_2O and BnBr to prevent racemization,[18] which provided fully protected L-proline derivatives **12** and **13**, respectively. Reduction of ester moiety in **7**, **12** and **13** using $LiBH_4$ followed by Dess–Martin periodinane (DMP) oxidation provided aldehydes **8**, **14** and **15**, respectively, in good yields. Homologation of aldehydes **8**, **14** and **15** was then performed by employing methoxy methyl triphenyl phosphonium ylide (Ph_3P = CH(OMe) which provided enol ether intermediates **9**, **16** and **17** (an inseparable mixture of *Z* and *E* isomers), respectively. Careful hydrolysis of enol ethers with 2 M HCl in acetone at room temperature provided optically pure aldehydes **4b**, **4c** and **4d** in good yields.[19]

To the best of our knowledge, no reports for the synthesis of enantiomerically pure homologated aldehydes **4b**, **4c** and **4d** are present in literature. However, the optically pure aldehyde **4e**[20] was synthesized from commercially available N-(Boc)-S-pipecolic acid **18** by carboxyl reduction, modified Swern oxidation,[21] Wittig olefination, and enol ether **19** hydrolysis with 2 M HCl (eqn 3; Scheme 4).

Following the similar reaction conditions as shown in Scheme 3, reaction of lithiated bromo derivatives **3** with aldehydes **4a–e** furnished intermediate carbinols **2b–j** in satisfactory yields (55–69%, Table 1). The resulting carbinols **2(b + b′ − j + j′)** were then subjected to previously optimized cyclization conditions (4 M HCl in dioxane followed by Et_3N) which furnished the unsaturated $\Delta^{9(11)}$ 14-azasteroidal skeletons as separable diastereomers **1b + b′**(73%), **1d + d′**(71%), **1e + e′**(76%), **1g + g′**(78%), **1h + h′**(44%) and **1j + j′**(71%) as depicted in Table 1. Unfortunately, substrates **2c + c′**, **2f + f′** and **2i + i′** failed to provide any cyclized product. The reluctance shown by the substrates **2c + c′**, **2f + f′** and **2i + i′** to undergo cyclization could be rationalized by the fact, that the presence of electron donating methoxy (OMe) group at the 3-position (according to steroidal numbering) in A ring and/or the presence of oxygen at 6-position (in B ring) considerably reduces the electrophilicity of the double bond at $\Delta^{8(9)}$ towards nucleophilic attack.

The structural analysis and stereochemical assignment as depicted in unsaturated $\Delta^{9(11)}$ 14-azasteroids **1** (Table 1) were done through incisive analysis of 1D, 2D NMR, *via* ^1H, ^{13}C, (^1H–^1H)/(^1H–^{13}C) COSY and NOESY of selected compounds



Scheme 4 Synthesis of optically pure **4b**, **4c**, **4d** and **4e**.

(see supporting information†). Stereochemistry of the rest of the target structures was assigned analogously.

The *syn* relationship between **13** β-methyl and the C-8 proton in the isomer **1b** was predicted by close observation of its NOESY spectra which showed conspicuous interaction between them along with other visible interactions. The other isomer **1b′** was therefore assigned with having an *anti* relationship between **13** β-methyl and C-8 proton as no such interactions were observed in its NOESY spectra (Fig. 2). Besides, a healthy confirmation comes from the fact that, in cyclic systems, the protons adjacent to the nitrogen atom and on the same side of the N lone pair undergo a strong deshielding effect, whereas the protons on the opposite side are strongly shielded.[22] ^{1}H NMR of **1g** shows only one signal in the region of 3–4 ppm, *i.e.*, at 3.8 ppm, due to the effect of nitrogen lone pair, which is attributable to 15α-H which being *cis* to the lone pair is deshielded. The lack of other signals in this region of the other adjacent protons is consistent of *trans* fusion of the C–D ring system. Thus, the protons at 13*β*, 8*β* and 15*β* are shielded being anti-periplanar to the nitrogen lone pair. However, in contrast, ^{1}H NMR of **1g′** shows two signals in the region of 3–4 ppm, one at 3.53 ppm and another at 3.33 ppm attributable to 15α-H and 8α-H (generated stereocenter), respectively, based on above arguments. A similar trend was observed in other cases too.

We also subjected one of the $\Delta^{9(11)}$ dehydroazasteroid **1g** to hydrogenation conditions (Pd/C, H_2), which furnished fully saturated azasteroid **1g′** in 74% yield. The stereochemical assignment was done on the basis of similar reports in the literature (Scheme 5).[23]

Conclusion

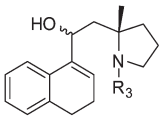
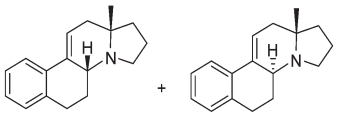
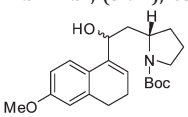
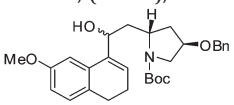
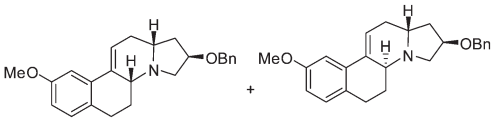
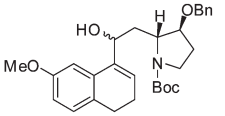
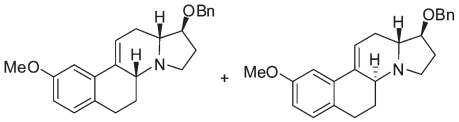
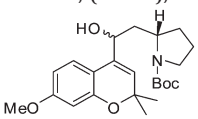
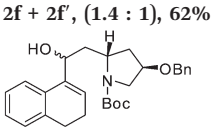
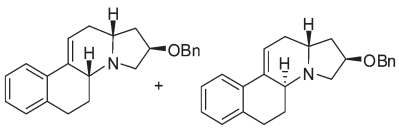
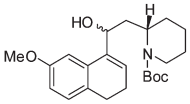
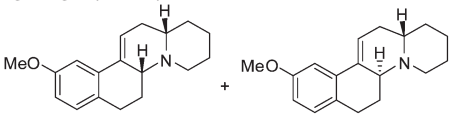
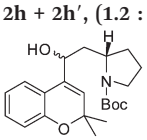
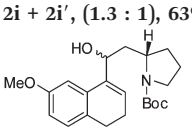
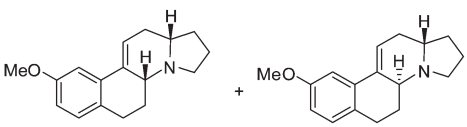
In summary, we have developed a short, efficient and versatile synthetic route towards the synthesis of 14-azasteroids using intramolecular S_N2' cyclization. The developed strategy may prove beneficial to produce several new azasteroidal scaffolds, considering the easy availability of L- as well as D-amino acids. Importantly, the final molecules bear the double bond at $\Delta^{9(11)}$, which could well be exploited to produce a large pool of biologically relevant chiral azasteroids. The biological evaluation of the synthesized molecules is currently underway.

Experimental section

General methods

All dry reactions were carried out under an argon or nitrogen atmosphere in oven-dried glassware using standard gas-light syringes, cannulas and septa. All reagents and solvents were dried prior to use according to standard methods. Commercial reagents were used without further purification unless otherwise stated. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel). Detecting agent used (for TLC) were iodine vapors. Column chromatography was

Table 1 Synthesis of $\Delta^{9(11)}$ 14-azasteroidal skeletons **1**[a]

Entry	Bromo 3	Aldehyde 4	Intermediate Carbinol 2, (d.r.)[b], yield%[c]	Target 1, (d.r.)[b], yield%[c]
1	**3a**	**4b**		
			[d]**2b + 2b′, (3 : 1), 69%**	**1b + 1b′, (1.5 : 1), 73%**
2	**3b**	**4a**		—
			2c + 2c′, (1.5 : 1), 58%	
3	**3c**	**4c**		
			2d + 2d′, (1.4 : 1), 55%	**1d + 1d′, (1.3 : 1), 71%**
4	**3c**	**4d**		
			2e + 2e′, (1.1 : 1), 58%	**1e + 1e′, (1.1 : 1), 76%**
5	**3e**	**4a**		—
			2f + 2f′, (1.4 : 1), 62%	
6	**3a**	**4c**		
			2g + 2g′, (1.3 : 1), 57%	**1g + 1g′, (1.3 : 1), 78%**
7[e]	**3c**	**4e**		
			2h + 2h′, (1.2 : 1), 64%	**1h + 1h′, (1.4 : 1), 44%**
8	**3d**	**4a**		—
			2i + 2i′, (1.3 : 1), 63%	
9	**3c**	**4a**		
			2j + 2j′, (1.3 : 1), 61%	**1j + 1j′, (1.3 : 1), 71%**

[a] Reactions were carried out as depicted in Scheme 3. [b] d.r. was determined from the isolated yield/crude nmr. [c] Combined yield of both diastereoisomers. [d] **2b**, R_3 = Boc; **2b′**, R_3 = H. [e] Products **1h + h′** were inseparable in pure form.

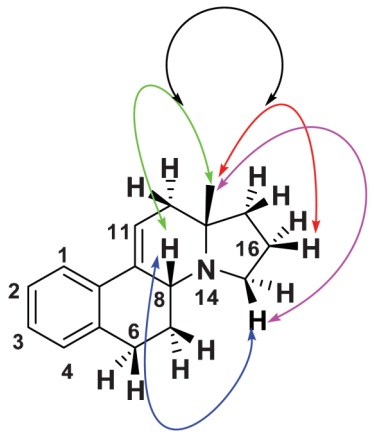


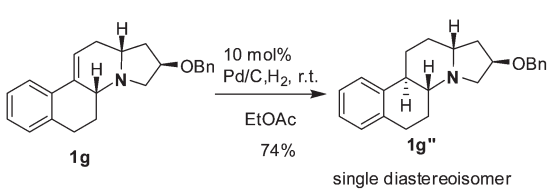
Fig. 2 NOESY interactions as observed in **1b**.

performed over silica gel (230–400 mesh) using freshly distilled solvents. Mass spectra were recorded using electron spray ionization (ESI-MS) or fast atom bombardment spectra (FAB-MS) using argon/xenon as the FAB gas. HRMS spectra were recorded using ESI/Q-TOF conditions. IR spectra were recorded as thin films on salt (NaCl) plates. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (*J* values) are given in hertz (Hz). Chemical shifts are expressed in parts per million.

Typical procedure for *6-endo trig cyclization* (S_N2') to access the azasteroids (4a*R*, 12a*S*)-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1a)

To a solution of allylic alcohol **2a**/**2a**′ (50 mg, 0.14 mmol) in anhydrous dioxane (2 mL) at 0 °C, a solution of HCl in dioxane (4 M, 1 mL) was added; the resulting yellow solution was stirred at r.t for 30 min. Reaction mixture was concentrated and the crude residue was dissolved in methanol (2 mL) and then treated with Et_3N (0.10 mL, 0.73 mmol) at room temperature. Stirring was continued for 15 min. After the completion of reaction, the solvent was removed under vacuum followed by usual workup with DCM/water. The combined organic extracts were washed with brine and dried over Na_2SO_4. The residue was purified by flash column chromatography (230–400 mesh silica) using MeOH : $CHCl_3$ (10 : 90) as eluent which furnished the cyclized products **1a** and **1a**′ (26 mg, 75%) as viscous oil.

For **1a**$[\alpha]_D^{28}$ = +69.58 (c 0.10, $CHCl_3$); R_f 0.58 (10% MeOH in $CHCl_3$) IR (Neat): 2928, 2854, 2362, 1629, 769, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63–7.60 (m, 1H), 7.17–7.08 (m, 3H), 6.37–6.36 (m, 1H), 3.58–3.52 (m, 1H), 3.00–2.90 (m, 3H), 2.48–2.19 (m, 6H), 2.12–2.02 (m, 1H), 2.00–1.90 (m, 1H), 1.87–1.80 (m, 1H), 1.78–1.69 (m, 1H), 1.66–1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 135.3, 133.4, 128.9, 126.8, 125.9, 123.9, 118.6, 63.3, 59.8, 52.4, 32.6, 30.6, 29.1, 28.7, 21.3; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{16}H_{20}N$ 226.159, found 226.159.



Scheme 5 Hydrogenation of **1g**.

(4a*S*,12a*S*)-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1a′)

$[\alpha]_D^{28}$ −3.46 (*c* 0.10, $CHCl_3$); R_f 0.44 (10% MeOH in $CHCl_3$); IR (Neat): 2932, 2347, 1630, 1221, 769, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.47 (m, 1H), 7.18–7.08 (m, 3H), 6.28–6.26 (m, 1H), 3.63–3.60 (m, 1H), 3.34–3.23 (m, 2H), 3.08–2.94 (m, 3H), 2.64–2.55 (m, 1H), 2.41–2.33 (m, 1H), 2.27–2.10 (m, 2H), 2.04–1.88 (m, 3H), 1.71–1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 134.9, 134.5, 128.6, 127.4, 126.2, 123.8, 118.9, 56.9, 54.9, 50.7, 29.7, 29.1, 28.6, 26.2, 21.7; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{16}H_{20}N$ 226.159, found 226.160.

(4a*R*,12a*S*)-12a-methyl-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1b)

As described for **1a**/**1a**′, **2b**/**2b**′ (80 mg, 0.22 mmol) in dioxane (2 mL), 4 M HCl in dioxane (1.5 mL), Et_3N (0.16 mL, 1.1 mmol) in MeOH (2 mL) furnished **1b** and **1b**′ (39 mg, 73%) as viscous colorless oil, **For 1b**, $[\alpha]_D^{28}$ = +31.78 (c 0.22, $CHCl_3$); R_f 0.52 (10% MeOH in $CHCl_3$); IR (Neat): 2924, 2855, 2375, 1634, 1261, 771, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.51 (m, 1H), 7.10–7.02 (m, 3H), 6.24–6.22 (m, 1H), 3.34–3.30 (m, 1H), 3.18–3.11 (m, 1H), 2.90–2.84 (m, 2H), 2.69 (m, 1H), 2.42–2.36 (m, 1H), 2.31–2.27 (m, 1H), 2.18–2.09 (m, 1H), 1.91–1.83 (m, 3H), 1.77–1.64 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4(2C), 132.9, 129.1, 127.1, 126.1, 123.7, 117.4, 59.2, 55.9, 46.9, 38.2, 37.1, 28.8, 28.1, 19.7, 16.5; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{17}H_{22}N$ 240.174, found 240.175.

(4a*S*,12a*S*)-12a-methyl-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1b′)

$[\alpha]_D^{28}$ −9.88 (*c* 0.23, $CHCl_3$); R_f 0.45 (10% MeOH in $CHCl_3$); IR (Neat): 2931, 2373, 1636, 1219, 771, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.51 (m, 1H), 7.17–7.07 (m, 3H), 6.29–6.27 (m, 1H), 3.47–3.44 (m, 1H), 3.42–3.38 (m, 1H), 2.93–2.82 (m, 3H), 2.42–2.31 (m, 2H), 2.15 (dd, 1H, J_1 = 6.9, J_2 = 17.0), 2.02–2.00 (m, 1H), 1.97–1.74 (m, 4H), 1.28(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 134.6, 133.8, 128.9, 127.2, 126.1, 123.5, 117.5, 59.1, 57.9, 53.9, 38.5, 32.2, 30.12, 29.8, 26.4, 20.3; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{17}H_{22}N$ 240.174, found 240.175.

(2*R*,4a*R*,12a*R*)-2-(benzyloxy)-9-methoxy-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1d)

As described for **1a**/**1a**′, **2d**/**2d**′ (80 mg, 0.17 mmol) in dioxane (2 mL), 4 M HCl in dioxane (1.2 mL), Et_3N (0.12 mL, 0.83 mmol) in MeOH (2 mL) furnished **1d** and **1d**′ (43 mg, 71%) as viscous colorless oil, **For 1d**; $[\alpha]_D^{28}$ = +6.76 (c 0.22, $CHCl_3$); R_f 0.57 (3% MeOH in $CHCl_3$); IR (Neat): 2963, 2853, 2361, 1637, 1219, 772, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H), 7.09 (d, 1H, J = 2.5), 7.00 (d, 1H, J = 8.4), 6.73 (dd, 1H, J_1 = 2.5, J_2 = 8.4), 6.32–6.30 (m, 1H), 4.50 (dd, 2H, J_1 = 11.7, J_2 = 17.1), 4.30–4.25 (m, 1H), 3.90–3.83 (m, 1H), 3.80 (s, 3H), 3.04–

2.96 (m, 1H), 2.83–2.66 (m, 3H), 2.45–2.38 (m, 2H), 2.37–2.18 (m, 2H), 2.16–2.12 (m, 1H), 1.82–1.71 (m, 1H), 1.65–1.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 138.2, 135.4, 134.2, 129.9, 128.4 (2C), 127.9, 127.7, 127.6 (2C), 118.4, 113.7, 108.3, 76.9, 71.2, 62.9, 59.6, 57.7, 55.3, 38.6, 32.4, 29.3, 27.8; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{24}H_{28}NO_2$ 362.211, found 362.211.

(2*R*,4a*S*,12a*R*)-2-(benzyloxy)-9-methoxy-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1d′)

$[\alpha]_D^{28}$ = +2.83 (c 0.20, $CHCl_3$); R_f 0.50 (10% MeOH in $CHCl_3$); IR (Neat): 2925, 2356, 1634, 1223, 771, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.30 (m, 5H), 6.70–6.94 (m, 2H), 6.73 (dd, 1H, J_1 = 2.7, J_2 = 8.4), 6.13–6.16 (m, 1H), 4.51 (dd, 2H, J_1 = 11.4, J_2 = 14.1), 4.30–4.27 (m, 1H), 3.80 (s, 3H), 3.56–3.52 (m, 1H), 3.40–3.35 (m, 1H), 3.17 (m, 1H), 3.05–2.96 (m, 1H), 2.91–2.86 (m, 2H), 2.58–2.46 (m, 1H), 2.27–2.24 (m, 1H), 2.11–2.02 (m, 3H), 1.84–1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 138.1, 137.2, 136.6, 129.6, 128.4(2C), 127.7(2C), 127,6, 127.2, 118.9, 113.8, 108.3, 77.2, 71.4, 56.3, 55.5, 55.3, 52.1, 37.7, 31.9, 29.3, 28.0; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{24}H_{28}NO_2$ 362.211, found 362.211.

(2*R*,4a*R*,12a*R*)-2-(benzyloxy)-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1g)

As described for **1a**/**1a′**, **2g**/**2g′** (80 mg, 0.18 mmol) in dioxane (2 mL), 4 M HCl in dioxane (1.2 mL), Et_3N (0.12 mL, 0.90 mmol) in MeOH (2 mL) furnished **1g** and **1g′** (46 mg, 78%) as viscous colorless oil, **For 1g**; $[\alpha]_D^{28}$ = +72.86 (c 0.20, $CHCl_3$); R_f 0.62 (1% MeOH in $CHCl_3$); IR (Neat): 2931, 2801, 2355, 1636, 1218, 771, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–7.50 (m, 1H), 7.28–7.20 (m, 5H), 7.08–7.00 (m, 3H), 6.27–6.25 (m, 1H), 4.43 (dd, 2H, J_1 = 11.3, J_2 = 17.5), 4.24–4.18 (m, 1H), 3.81 (dd, 1H, J_1 = 6.8, J_2 = 9.8), 3.01–2.97 (m, 1H), 2.85–2.83 (m, 1H), 2.82–2.80 (m, 1H), 2.38–2.28 (m, 2H), 2.24–2.17 (m, 2H), 2.12–2.06 (m, 1H), 1.76–1.70 (m, 1H), 1.66–1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 135.4(2C), 133.4, 128.9, 128.4(2C), 127.7(2C), 127.6, 126.9, 126.0, 123.9, 118.1, 76.9, 71.2, 62.9, 59.6, 57.7, 38.6, 32.6, 29.1, 28.6; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{23}H_{26}NO$ 332.200, found 332.201.

(2*R*,4a*S*,12a*R*)-2-(benzyloxy)-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1g′)

$[\alpha]_D^{28}$ −2.83 (*c* 0.22, $CHCl_3$); R_f 0.54 (1% MeOH in $CHCl_3$); IR (Neat): 2939, 2353, 1629, 1212, 759, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 1H), 7.35–7.30 (m, 5H), 7.14–7.07 (m, 3H), 6.12–6.10 (m, 1H), 4.51 (dd, 2H, J_1 = 11.6, J_2 = 14.4), 4.28–4.26 (m, 1H), 3.55–3.51 (m, 1H), 3.33 (dd, 1H, J_1 = 6.3, J_2 = 9.7), 3.11–3.08 (m, 1H), 3.01–2.92 (m, 2H), 2.50–2.41 (m, 1H), 2.28–2.24 (m, 1H), 2.11–2.04 (m, 2H), 1.83–1.73 (m, 2H), 1.60–1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 137.6, 136.0, 134.9, 128.6, 128.4, 127.7, 127.6, 127.0, 125.9, 123.8, 118.8, 77.0, 71.3, 56.3, 55.7, 51.7, 38.0, 31.2, 28.9, 24.8; HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{23}H_{26}NO$ 332.200, found 332.201.

(2*R*,4a*R*,10b*R*,12a*R*)-2-(benzyloxy)-1,2,3,4a,5,6,10b,11,12,12a-decahydrobenzo[*f*]pyrrolo[1,2-a]quinoline (1g′)

To a stirred solution of **1g** (5 mg, 0.015 mmol) in ethyl acetate at r.t. was added Pd/C (10 mol%), and reaction was left stirring for 2 h under H_2 (balloon) at r.t. Reaction mixture was then filtered through silica pad followed by concentration of the organic solvent under vacuum. Flash column chromatogarphy of obtained crude furnished the fully saturated diastereomerically pure azasteroid **1g′** (3.6 mg, 74%) as viscous colorless oil. $[\alpha]_D^{28}$ = +69.16 (c 0.20, $CHCl_3$); R_f 0.82 (1% MeOH in $CHCl_3$); IR (Neat): 2930, 2807, 2357, 1217, 770, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.30 (m, 6H), 7.18–7.10 (m, 3H), 4.51 (dd, 2H, J_1 = 11.5, J_2 = 16.4), 4.27–4.25 (m, 1H), 3.82–3.77 (m, 1H), 2.95–2.92 (m, 2H), 2.65–2.54 (m, 2H), 2.43–2.42 (m, 1H), 2.31–2.29 (m, 1H), 2.28–2.03 (m, 4H), 2.01–1.83 (m, 4H); HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{23}H_{28}NO$ 334.217, found 334.217.

(1*S*,4a*R*,12a*R*)-1-(benzyloxy)-9-methoxy-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1e)

As described for **1a**/**1a′**, **2e**/**2e′** (40 mg, 0.08 mmol) in dioxane (1 mL), 4 M HCl in dioxane (0.6 mL), Et_3N (0.06 mL, 0.42 mmol) in MeOH (1 mL) furnished **1e** and **1e′** (21 mg, 70%) as viscous colorless oil, **For 1e**; $[\alpha]_D^{28}$ = +4.16 (c 0.10, $CHCl_3$); R_f 0.59 (4% MeOH in $CHCl_3$); IR (Neat): 2965, 2863, 2367, 1636, 1218, 772, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 7.09 (d, J = 2.6, 1H), 7.00 (d, J = 8.4, 1H), 6.74 (dd, J_1 = 2.4, J_2 = 8.4, 1H), 6.33–6.31 (m, 1H), 4.54 (dd, J_1 = 11.7, J_2 = 22.6, 2H), 3.92–3.89 (m, 1H), 3.80 (s, 3H), 3.48–3.45 (m, 1H), 3.04–3.00 (m, 1H), 2.85–2.81 (m, 2H), 2.63–2.61 (m, 1H), 2.56–2.42 (m, 1H), 2.31–2.27 (m, 3H), 2.01 (m, 1H), 1.86–1.84 (m, 1H); HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{24}H_{28}NO_2$ 362.211, found 362.214.

(1*S*,4a*S*,12a*R*)-1-(benzyloxy)-9-methoxy-1,2,3,4a,5,6,12,12a-octahydrobenzo[f]pyrrolo[1,2-*a*]quinoline (1e′)

$[\alpha]_D^{28}$ = +1.21 (c 0.05, $CHCl_3$); R_f 0.53 (10% MeOH in $CHCl_3$); IR (Neat): 2923, 2357, 1631, 1222, 771, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.29 (m, 5H), 6.99 (d, J = 8.7, 1H), 6.94 (d, J = 2.3, 1H), 6.74 (dd, J_1 = 2.6, J_2 = 8.2, 1H), 6.14 (m, 1H), 4.54 (dd, J_1 = 11.7, J_2 = 21.2, 2H), 3.86–3.83 (m, 1H), 3.79 (s, 3H), 3.57–3.53 (m, 1H), 3.21–3.18 (m, 1H), 2.97–2.86 (m, 3H), 2.61–2.55 (m, 1H), 2.27–2.34 (m, 3H), 2.02–1.91 (m, 3H); HR-MS $[M + H]^+$ calcd for $C_{24}H_{28}NO_2$ 362.211, found 362.211.

(4a*R*,12a*S*)-9-methoxy-1,2,3,4a,5,6,12,12a-octahydrobenzo[*f*]pyrrolo[1,2-*a*]quinoline (1j)

As described for **1a**/**1a′**, **2j**/**2j′** (80 mg, 0.21 mmol) in dioxane (2 mL), 4 M HCl in dioxane (1.3 mL), Et_3N (0.14 mL, 1.05 mmol) in MeOH (2 mL) furnished **1j**/**1j′** (38 mg, 71%) as viscous colorless oil, $[\alpha]_D^{28}$ = +45.86 (c 0.20, $CHCl_3$); R_f 0.66 (1% MeOH in $CHCl_3$); IR (Neat): 2932, 2811, 2345, 1637, 1218, 771, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02(d, 1H, J = 2.4), 6.93 (d, 1H, J = 8.3), 6.68 (dd, J_1 = 2.3, J_2 = 8.2, 1H), 6.28 (m, 1H), 3.73(s, 3H), 3.49 (m, 1H), 2.93 (m, 1H), 2.79–2.76 (m, 2H), 2.35–2.23 (m, 5H), 1.99–1.90 (m, 2H), 1.78–1.67 (m, 2H), 1.60–1.58 (m, 1H); HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{17}H_{22}NO$ 256.170, found 256.170.

For **1j′**: this isomer was inseparable in pure form.

***tert-butyl* 2-(2-hydroxy-2-(1,2,3,4-tetrahydronaphthalen-1-yl)ethyl)pyrrolidine-1-carboxylate (2a/2a′)**

To a stirred solution of bromo substrate **3a** (300 mg, 1.45 mmol) in anhydrous THF (15 mL) at −78 °C and under N_2, *n*-

BuLi (1.6 M in hexane, 0.90 mL, 1.45 mmol) was added. The resulting yellow solution was stirred at −78 °C for 30 min after which aldehyde **4a** (278 mg, 1.30 mmol) in THF (2 mL) was added and stirred at −78 °C for 1 h followed by overnight stirring at room temperature. It was then quenched with sat. NH_4Cl solution (10 mL), and was extracted with ethyl acetate (3 × 20 mL), washed with brine and dried over Na_2SO_4. The extract was subjected to column chromatography on silica gel and elution with 20% ethyl acetate in hexane furnished alcohol **2a**/**2a′** (325 mg, 66%) as semi solid. For **2a**: $[\alpha]_D^{28}$ = +2.02 (c 0.46, $CHCl_3$); R_f 0.62 (15% EtOAc in hexane), IR (Neat): 3430, 2362, 1559, 1219, 761, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 1H), 7.20–7.13 (m, 3H), 6.25 (m, 1H), 5.23 (s, 1H), 4.70 (s, 1H), 4.30 (br, s, 1H), 3.38–3.34 (m, 2H), 2.74–2.70 (m, 2H), 2.31–2.27 (m, 2H), 2.04–1.81 (m, 4H), 1.74–1.65 (m, 2H),1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 138.4, 136.8, 133.8, 127.6, 126.4, 126.2, 124.2, 122.7, 80.0, 67.9, 66.8, 53.9, 46.5, 42.8. 31.2, 28.4, 28.3, 23.6; ESI-MS *m*/*z* 225 $[M\text{-}OH\text{-}Boc]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{21}H_{29}NO_3$ 343.215, found 343.213.

For **2a′**: $[\alpha]_D^{28}$ −20.62 (*c* 0.24, $CHCl_3$); R_f 0.46 (15% EtOAc in hexane), IR (Neat): 3432, 2359, 1563, 1220, 760, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 1H), 7.22–7.14 (m, 3H), 6.23 (m, 1H), 4.80–4.76 (m, 1H), 4.14–4.11 (m, 1H), 3.34–3.28 (m, 2H), 2.74–2.66 (m, 2H), 2.31–2.25 (m, 2H), 2.07–1.95 (m, 3H), 1.88–1.76 (m, 4H),1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 139.3, 136.9, 133.6, 127.7, 126.5, 126.2, 124.0, 122.6, 79.7, 69.7, 55.9, 54.8, 46.3, 43.4, 32.1, 28.5, 28.3, 23.8; ESI-MS *m*/*z* 225 $[M\text{-}OH\text{-}Boc]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{21}H_{29}NO_3$ 343.215, found 343.214.

(*S*)-*tert*-butyl 2-(2-(3, 4-dihydronaphthalen-1-yl)-2-hydroxyethyl)-2-methylpyrrolidine-1-carboxylate (2b/2b′)

As described for **2a**/**2a′**, **3a** (300 mg, 1.45 mmol) in THF (15 mL), *n*-BuLi (0.9 mL, 1.45 mmol), aldehyde **4b** (295 mg, 1.30 mmol) in THF (2 mL) furnished **2b**/**2b′** (353 mg, 69%) as colorless semisolid. For **2b**: $[\alpha]_D^{28}$ −41.04 (*c* 0.45, $CHCl_3$); R_f 0.56 (15% EtOAc in hexane); IR (Neat): 3428, 3029, 2331, 1569, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (m, 1H), 7.20–7.14 (m, 3H), 6.21 (m, 1H), 4.88 (m, 1H), 3.95–3.42 (m, 3H), 2.71 (t, 2H, *J* = 7.9), 2.28–2.23 (m, 2H), 2.13–2.00 (m, 3H), 1.81–1.76 (m, 3H),1.47 (s, 9H), 1.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.7, 137.0, 136.9, 127.7, 126.6, 126.3, 126.2, 124.9, 123.0, 79.59, 69.2, 62.6, 62.3, 48.7, 48.5, 28.5, 28.3, 26.0, 22.8, 21.7; ESI-MS *m*/*z* 239 $[M\text{-}OH\text{-}Boc]^+$, 340 $[M\text{-}OH]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{22}H_{31}NO_3$ 357.230, found 357.232.

For **2b′**: $[\alpha]_D^{28}$ −49.84 (*c* 0.12, $CHCl_3$); R_f 0.46 (50% EtOAc in hexane); IR (Neat): 3427, 3028, 2329, 1571, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (m, 4H), 6.36 (m, 1H), 5.45 (d, 1H, *J* = 11.3), 3.81–3.71 (m, 2H), 3.56–3.50 (m, 1H), 2.76–2.71 (m, 2H), 2.36–2.27 (m, 3H), 2.03–1.95 (m, 3H), 1.87–1.83 (m, 1H), 1.68–1.59 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.7, 134.3, 132.4, 128.0, 127.1, 126.5, 126.4, 121.8, 73.4, 59.8, 46.1, 40.7, 40.5, 27.9, 25.00, 22.6, 21.3; ESI-MS *m*/*z* 241 $[M\text{-}OH + 1]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{22}H_{31}NO_3$ 357.230, found 357.233.

(2*R*,4*R*)-*tert*-butyl 4-(benzyloxy)-2-(2-hydroxy-2-(7-methoxy-3,4-dihydronaphthalen-1-yl)ethyl)pyrrolidine-1-carboxylate (2d/2d′)

As described for **2a**/**2a′**, **3c** (300 mg, 1.25 mmol) in THF (15 mL), *n*-BuLi (0.78 mL, 1.25 mmol), aldehyde **4c** (358 mg, 1.12 mmol) in THF (2 mL) furnished **2d**/**2d′** (330 mg, 55%) as colorless semisolid, For **2d**: $[\alpha]_D^{28}$ −8.22 (*c* 0.54, MeOH); R_f 0.58 (20% EtOAc in hexane); IR (Neat): 3436, 3021, 2330, 1564, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.30 (m, 5H), 7.04 (d, 1H, *J* = 8.3), 6.90 (s, 1H), 6.67 (dd, 1H, J_1 = 2.2, J_2 = 8.0), 6.25 (m, 1H), 5.01–4.90 (m, 1H), 4.65 (br, s, 1H), 4.47–4.43 (m, 2H), 4.15–4.14 (m, 2H), 3.78 (s, 3H), 3.61–3.58 (m, 1H), 3.44–3.42 (m, 1H), 2.67–2.62 (m, 2H), 2.28–2.21 (m, 2H), 2.04–1.70 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1, 156.7, 138.1, 137.8, 134.6, 128.9, 128.3, 128.1, 127.6, 127.5, 125.0, 111.2, 109.2, 80.3, 76.8, 71.2, 66.9, 55.1, 52.8, 51.1, 43.3, 37.8, 28.3, 27.3, 23.1; ESI-MS *m*/*z* 423 $[M\text{-}t\text{Bu}]^+$, 462 $[M\text{-}OH]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{29}H_{37}NO_5$ 479.267, found 479.268.

For **2d′**: $[\alpha]_D^{28}$ −32.22 (*c* 0.2, $CHCl_3$); R_f 0.46 (20% EtOAc in hexane); IR (Neat): 3433, 2328, 1565, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.30 (m, 5H), 7.06 (d, 1H, *J* = 8.7), 6.92 (s, 1H), 6.68 (d, 1H, *J* = 7.8), 6.24 (m, 1H), 4.73 (br, s, 1H), 4.48 (m, 2H), 4.24 (m, 2H), 4.11–4.08 (m, 1H), 3.78 (s, 3H), 3.54–3.39 (m, 2H), 2.63–2.61 (m, 2H), 2.25 (m, 3H), 2.04–1.80 (m, 3H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1, 155.5, 139.1, 137.9, 134.4, 129.0, 128.3, 128.2, 127.5, 124.9, 110.9, 109.5, 79.9, 76.4, 70.9, 69.9, 55.2, 54.7, 51.3, 43.3, 38.3, 28.4, 27.3, 23.1; ESI-MS *m*/*z* 361 $[M\text{-}OH\text{-}Boc]^+$, 462 $[M\text{-}OH]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{29}H_{37}NO_5$ 479.267, found 479.269.

(2*R*,4*R*)-*tert*-butyl 4-(benzyloxy)-2-(2-(3,4-dihydronaphthalen-1-yl)ethyl)pyrrolidine-1-carboxylate (2g/2g′)

As described for **2a**/**2a′**, **3a** (300 mg, 1.45 mmol) in THF (15 mL), *n*-BuLi (0.90 mL, 1.45 mmol), aldehyde **4c** (416 mg, 1.30 mmol) in THF (4 mL) furnished **2g**/**2g′** (354 mg, 57%) as colorless semisolid, For **2g**: $[\alpha]_D^{28}$ = +19.21 (c 0.50, $CHCl_3$); R_f 0.61 (20% EtOAc in hexane); IR (Neat): 3439, 3018, 2328, 1559, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 6H), 7.06 (m, 3H), 6.16 (m, 1H), 4.93 (br, s, 1H), 4.61 (s, 1H), 4.40 (m, 3H), 4.08–4.06 (m, 2H), 3.51–3.36 (m, 3H), 2.66–2.26 (t, 2H, *J* = 7.8), 2.23–2.20 (m, 2H), 1.66–1.63 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.8, 138.2, 137.8, 136.8, 133.7, 128.4(3C), 127.7(2C), 127.5, 126.4, 126.2, 124.3, 122.7, 80.4,77.2, 71.2, 66.8, 52.9, 51.1, 43.4, 37.8, 28.3, 28.2, 22.7; ESI-MS *m*/*z* 331[M-OH-Boc]$^+$, 432[M-OH]$^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{28}H_{35}NO_4$ 449.257, found 449.258.

For **2g′**:$[\alpha]_D^{28}$ −58.52 (*c* 0.20, $CHCl_3$); R_f 0.56 (20% EtOAc in hexane); IR (Neat): 3436, 3021, 2327, 1579, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 6H), 7.06 (m, 3H), 6.14 (m, 1H), 4.70 (br, s, 1H), 4.41 (s, 2H), 4.18 (s, 1H), 4.02 (m, 1H), 3.80 (m, 1H), 3.47–3.32 (m, 2H), 2.65–2.61 (m, 2H), 2.20 (m, 3H), 1.94 (m, 1H), 1.68 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.6, 139.2, 137.9, 136.9, 133.4, 130.0, 128.9(3C), 127.7(2C), 127.6, 126.2, 124.1, 122.6, 79.9, 76.4, 71.0, 69.8, 54.8, 51.4, 43.4, 38.3, 28.4, 28.2, 22.7; ESI-MS *m*/*z* 331 $[M\text{-}OH\text{-}Boc]^+$, HRMS(ESI/Q-TOF) $[M + H]^+$ calcd for $C_{28}H_{35}NO_4$ 449.257, found 449.259.

(2*R*,3*S*)-*tert*-butyl 3-(benzyloxy)-2-(2-hydroxy-2-(7-methoxy-3,4-dihydronaphthalen-1-yl)ethyl)pyrrolidine-1-carboxylate (2e/2e′)

As described for **2a**/**2a′**, **3c** (300 mg, 1.25 mmol) in THF (15 mL), *n*-BuLi (0.78 mL, 1.25 mmol), aldehyde **4d** (358 mg, 1.12 mmol) in THF (2 mL) furnished **2e**/**2e′** (348 mg, 58%) as colorless semisolid; For **2e**: $[\alpha]_D^{28}$ = +2.23 (c 0.20, MeOH); R_f 0.61 (25% EtOAc in hexane); IR (Neat): 3431, 3019, 2334, 1567, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.27 (m, 5H), 7.05 (d, 1H, J = 8.0), 6.90 (s, 1H), 6.87 (d, 1H, J_1 = 2.1), 6.68 (dd, 1H, J_1 = 2.4, J_2 = 8.1), 6.30–6.27 (m, 1H), 4.70–4.37 (m, 4H), 3.78 (s, 3H), 3.73–3.37 (m, 3H), 2.67–2.61 (m, 2H), 2.30–2.25 (m, 2H), 2.03–1.96 (m, 3H), 1.80–1.70 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.2, 157.1, 138.1, 134.7, 129.0, 128.4(3C), 128.2, 127.6(2C), 127.5(2C), 125.1, 111.4, 109.2, 82.4, 80.3, 70.5, 66.5, 59.2, 55.2, 44.9, 41.3, 28.4, 27.4, 23.2; ESI-MS m/z 423 [M-*t*Bu]$^+$, 462 [M-OH]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{29}H_{37}NO_5$ 479.267, found 479.268.

For **2e′**: this isomer was inseparable from column in pure form.

(*S*)-*tert*-butyl 2-(2-hydroxy-2-(7-methoxy-3,4-dihydronaphthalen-1-yl)ethyl)piperidine-1-carboxylate (2h/2h′)

As described for **2a**/**2a′**, **3c** (300 mg, 1.25 mmol) in THF (15 mL), *n*-BuLi (0.78 mL, 1.25 mmol), aldehyde **4e** (255 mg, 1.12 mmol) in THF (2 mL) furnished **2h**/**2h′** (310 mg, 64%) as colorless semisolid; For **2h**: $[\alpha]_D^{28}$ −2.24 (*c* 0.60, $CHCl_3$); R_f 0.61 (25% EtOAc in hexane); IR (Neat): 3430, 3017, 2331, 1567, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, 1H, J = 8.2), 6.91 (d, 1H, J_1 = 2.6), 6.70 (dd, 1H, J_1 = 2.4, J_2 = 8.1), 6.30 (m, 1H), 4.63 (br, s, 1H), 4.53–4.47 (m, 1H), 4.13–4.03 (m, 1H), 3.80 (s, 3H), 2.84–2.77 (m, 1H), 2.70–2.65 (m, 2H), 2.30–2.26 (m, 2H), 1.74 (m, 2H), 1.53–1.46 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.2, 156.7, 138.2, 134.6, 129.0, 128.2, 125.1, 111.2, 109.2, 80.3, 71.0, 55.2, 46.6, 39.8, 37.2, 29.4, 28.4, 27.4, 25.5, 23.1, 19.2; ESI-MS m/z 331 [M-*t*Bu]$^+$, 370 [M-OH]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{23}H_{33}NO_4$ 387.241, found 387.243.

For **2h′**: $[\alpha]_D^{28}$ −80.34 (*c* 1.20, $CHCl_3$); R_f 0.53 (25% EtOAc in hexane); IR (Neat): 3431, 3019, 2329, 1566, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, 1H, J = 8.1), 6.93 (d, 1H, J_1 = 1.8), 6.69 (dd, 1H, J_1 = 2.5, J_2 = 8.3), 6.23–6.20 (m, 1H), 4.73 (m, 1H), 4.47 (br, s, 1H), 3.92 (m, 1H), 3.80 (s, 3H), 2.76–2.62 (m, 3H), 2.26–2.25 (m, 2H), 1.97–1.93 (m, 2H), 1.63–1.57 (m, 4H), 1.46–1.44 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1, 155.5, 138.7, 134.3, 129.1, 128.2, 125.1, 111.2, 109.5, 79.8, 70.2, 55.3, 48.6, 39.5, 37.2, 29.2, 28.5, 27.3,25.4, 23.2, 19.1; ESI-MS m/z 269 [M-OH-Boc]$^+$, 370 [M-OH]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{23}H_{33}NO_4$ 387.241, found 387.245.

(*S*)-*tert*-butyl 2-(2-hydroxy-2-(7-methoxy-2,2-dimethyl-2*H*-chromen-4-yl)ethyl)pyrrolidine-1-carboxylate (2f/2f′)

As described for **2a**/**2a′**, **3e** (300 mg, 1.11 mmol) in THF (15 mL), *n*-BuLi (0.70 mL, 1.11 mmol), aldehyde **4a** (213 mg, 1.00 mmol) in THF (2 mL) furnished **2f**/**2f′** (278 mg, 62%) as viscous colorless oil; For **2f**: $[\alpha]_D^{28}$ −6.24 (*c* 1.7, MeOH); R_f 0.53 (25% EtOAc in hexane); IR (Neat): 3431, 3014, 2330, 1569, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, 1H, J = 8.0), 6.44–6.41 (m, 2H), 5.67 (s, 1H), 5.40 (d, 1H, J = 3.6), 4.58–4.55 (m, 1H), 4.27 (m, 1H), 3.77 (s, 3H), 3.39–3.35 (m, 2H), 2.00–1.85 (m, 3H), 1.76–1.68 (m, 1H), 1.62–1.58 (m, 2H), 1.50 (s, 9H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.0, 156.7, 154.4, 133.4, 123.7, 122.9, 114.0, 106.3, 102.2, 80.0, 76.0, 65.9, 55.0, 53.6, 46.4, 42.7, 31.1, 28.3, 28.1, 27.1, 23.4 ESI-MS m/z 285 [M-OH-Boc]$^+$, 386 [M-OH]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{23}H_{33}NO_5$ 403.236, found 403.237.

For **2f′**: $[\alpha]_D^{28}$ −26.33 (*c* 1.0, MeOH); R_f 0.42 (25% EtOAc in hexane); IR (Neat): 3437, 3021, 2315, 1585, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, 1H, J = 6.1), 6.44–6.41 (m, 2H), 5.67 (s, 1H), 4.70 (s, 1H), 4.32 (br, s, 1H), 4.10–4.08 (m, 1H), 3.76 (s, 3H), 3.35–3.32 (m, 2H), 2.07–1.98 (m, 1H), 1.86–1.68 (m, 5H), 1.47 (s, 9H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.2, 155.5, 154.6, 134.3, 123.6, 122.9, 113.9, 106.5, 102.3, 79.8, 76.6, 68.8, 56.0, 55.1, 46.4, 43.6, 32.2, 28.5, 28.1, 27.3, 23.7; ESI-MS m/z 285 [M-OH-Boc]$^+$, 386 [M-OH]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{23}H_{33}NO_5$ 403.236, found 403.239.

(*S*)-*tert*-butyl 2-(2-hydroxy-2-(6-methoxy-3,4-dihydronaphthalen-1-yl)ethyl)pyrrolidine-1-carboxylate (2c/2c′)

As described for **2a**/**2a′**, **3b** (300 mg, 1.25 mmol) in THF (15 mL), *n*-BuLi (0.78 mL, 1.25 mmol), aldehyde **4a** (240 mg, 1.12 mmol) in THF (2 mL) furnished **2c**/**2c′** (271 mg, 58%) as viscous colorless oil; For **2c**: $[\alpha]_D^{28}$ −3.24 (*c* 0.7, $CHCl_3$); R_f 0.59 (25% EtOAc in hexane); IR (Neat): 3432, 3016, 2330, 1572, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–7.20 (m, 1H), 6.71–6.70 (m, 2H), 6.11 (m, 1H), 5.20 (s, 1H), 4.64 (br, s, 1H), 4.30 (s, 1H), 3.80 (s, 3H), 3.37–3.34 (m, 2H), 2.72–2.67 (m, 2H), 2.30–2.25 (m, 2H), 2.04–1.85 (m, 4H), 1.71–1.66 (m, 2H), 1.50 (s, 9H); ESI-MS m/z 396 [M + Na]$^+$, 300 [M-OH-*t*Bu]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{22}H_{31}NO_4$ 373.225, found 373.226.

For **2c′**: $[\alpha]_D^{28}$ −23.68 (*c* 0.48, $CHCl_3$); R_f 0.51 (25% EtOAc in hexane); IR (Neat): 3433, 3015, 2329, 1571, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 1H), 6.72–6.70 (m, 2H), 6.10 (m, 1H), 4.73 (s, 1H), 4.12 (s, 1H), 3.80 (s, 3H), 3.31 (m, 2H), 2.71–2.66 (m, 2H), 2.25 (m, 2H), 2.05 (m, 3H), 1.85–1.81 (m, 3H), 1.47 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1(2C), 138.8(2C), 123.8, 121.5, 113.9, 110.8(2C), 79.7, 70.0, 55.9, 55.2, 46.3, 36.6, 32.1, 31.9, 28.8, 28.5, 23.8; ESI-MS m/z 396 [M + Na]$^+$, 300[M-OH-*t*Bu]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{22}H_{31}NO_4$ 373.225, found 373.227.

(*S*)-*tert*-butyl 2-(2-(2,2-dimethyl-2*H*-chromen-4-yl)-2-hydroxyethyl)pyrrolidine-1-carboxylate (2i/2i′)

As described for **2a**/**2a′**, **3d** (300 mg, 1.25 mmol) in THF (15 mL), *n*-BuLi (0.80 mL, 1.25 mmol), aldehyde **4a** (243 mg, 1.14 mmol) in THF (2 mL) furnished **2i**/**2i′** (295 mg, 63%) as viscous colorless oil; For **2i**: $[\alpha]_D^{28}$ −3.67 (*c* 1.2, $CHCl_3$); R_f 0.47 (25% EtOAc in hexane); IR (Neat): 3435, 3018, 2331, 1570, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.08 (m, 2H), 6.88–6.81 (m, 2H), 5.82 (s, 1H), 5.44 (s, 1H), 4.63 (d, 1H, J = 8.6), 4.29 (m, 1H), 3.38 (m, 2H), 2.01–1.60 (m, 6H), 1.52 (s, 9H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.8, 153.2, 133.6, 128.5, 125.6, 122.8, 120.9, 120.4, 116.8, 80.1, 75.7, 65.7, 53.7, 46.5, 42.9, 31.1, 28.4, 28.2, 27.1, 23.5; ESI-MS m/z 255 [M-OH-Boc]$^+$, 317 [M-*t*Bu]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{22}H_{31}NO_4$ 373.225, found 373.226.

For **2i′**: $[\alpha]_D^{28}$ −8.76 (*c* 1.6, $CHCl_3$); R_f 0.42 (25% EtOAc in hexane); IR (Neat): 3437, 3022, 2316, 1595, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.09 (m, 2H), 6.88–6.81 (m, 2H), 5.81 (s, 1H), 4.73 (m, 1H), 4.52 (br, s, 1H), 4.12 (br, s, 1H), 3.34 (m, 2H), 2.08–1.99 (m, 1H), 1.87–1.69 (m, 5H), 1.48 (s, 9H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.7, 153.2, 134.4, 128.6, 125.7, 122.7, 120.7, 120.4, 116.9, 79.8, 75.8, 68.6, 56.1, 46.4, 43.7, 32.4, 28.5, 28.1, 27.2, 23.7; ESI-MS: *m*/*z* 255 [M-OH-Boc]$^+$, 317 [M-*t*Bu]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{22}H_{31}NO_4$ 373.225, found 373.225.

(*S*)-*tert*-butyl 2-(2-hydroxy-2-(7-methoxy-3,4-dihydronaphthalen-1-yl)ethyl)pyrrolidine-1-carboxylate (2j/2j′)

As described for **2a**/**2a′**, **3c** (300 mg, 1.25 mmol) in THF (15 mL), *n*-BuLi (0.78 mL, 1.25 mmol), aldehyde **4a** (240 mg, 1.12 mmol) in THF (2 mL) furnished **2j**/**2j′** (285 mg, 61%) as viscous colorless oil; For **2j**: $[\alpha]_D^{28}$ −4.23 (*c* 0.8, $CHCl_3$); R_f 0.60 (25% EtOAc in hexane); IR (Neat): 3431, 3014, 2331, 1572, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, J = 8.3, 1H), 6.83 (m, 1H), 6.60 (dd, J_1 = 2.5, J_2 = 8.3, 1H), 6.19 (m, 1H), 4.56 (d, J = 8.1, 1H), 4.23 (br, s, 1H), 3.70 (s, 3H), 3.30–3.27 (m, 2H), 2.59–2.54 (m, 2H), 2.21–2.18 (m, 2H), 1.97–1.78 (m, 4H), 1.67–1.50 (m, 3H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1(2C), 138.3, 129.0, 128.1(2C), 124.9, 111.4, 109.2, 80.0, 74.0,70.1, 66.8, 55.1, 53.9, 46.5, 43.4, 31.2, 29.6, 28.4, 27.4, 23.1 ESI-MS: *m*/*z* 396 [M + Na]$^+$, 300 [M-OH-*t*Bu]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{22}H_{31}NO_4$ 373.225, found 373.227.

For **2j′**: $[\alpha]_D^{28}$ −21.14 (*c* 0.54, $CHCl_3$); R_f 0.50 (25% EtOAc in hexane); IR (Neat): 3423, 3012, 2330, 1572, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, J = 7.9, 1H), 6.84 (m, 1H), 6.60 (dd, J_1 = 2.4, J_2 = 8.2, 1H), 6.17 (m, 1H), 4.65 (d, J = 7.4, 1H), 4.04 (br, s, 1H), 3.71 (s, 3H), 3.23 (m, 2H), 2.58–2.53 (m, 2H), 2.18–2.17 (m, 2H), 1.99–1.90 (m, 2H), 1.77–1.60 (m, 4H), 1.39 (s, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1, 155.4, 139.1, 128.2(2C), 124.8, 110.9, 109.4, 79.7, 74.0, 69.9, 55.8, 55.2, 46.3,43.4, 32.3, 28.5, 27.3, 23.1; ESI-MS: *m*/*z* 396 [M + Na]$^+$, 300 [M-OH-*t*Bu]$^+$, HRMS(ESI/Q-TOF) [M + H]$^+$ calcd for $C_{22}H_{31}NO_4$ 373.225, found 373.228.

N-Boc-*trans*-4-hydroxy-L-proline methyl ester (10)

To a stirred slurry of *trans*-4-hydroxy-L-proline (2 g, 8.73 mmol) in methanol (20 mL) was added thionyl chloride (0.70 mL, 9.60 mmol) at 0 °C. After the completion of the addition, the resulting slurry was heated to 60 °C and stirred for 6 h to give a clear light brown solution. The mixture was evaporated under reduced pressure to give methyl ester as a light-brown solid (2.71 g, 98%), which was used in the next step without further purification. Boc_2O (3.68 mL, 15.15 mmol) was added to a stirred suspension of crude methyl ester in CH_2Cl_2 (25 mL). To the mixture was added slowly a solution of triethylamine (4.2 mL, 29.56 mmol). After completion of the starting material as observed by TLC analysis (approximately 3.5 h), the reaction mixture was quenched with 1 N HCl solution (10 mL). The organic layer was separated and evaporated under reduced pressure to give a brown viscous liquid. Purification of the crude over silica gel provided **10** as yellowish syrup (3.63 g, 99%); $[\alpha]_D^{28}$ −66.53 (*c* 1.00, $CHCl_3$); R_f 0.43 (30% EtOAc in hexane); IR (Neat): *v* 3440, 2976, 1746, 1685, 1416, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.47–4.37 (m, 2H), 3.73 (s, 3H), 3.43–3.65 (m, 2H), 2.74–2.63 (m, 1H), 2.34–2.27 (m, 1H), 1.99–2.10 (m, 1H), 1.46 and 1.41 (2s, 9H), rotamers. ESI-MS *m*/*z* 246 [M + H]$^+$.

(2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate (11)

Following similar procedure as for **10**, *trans*-3-hydroxy-L-proline (2 g, 8.73 mmol) provided **11** (3.45 g, 95%, after two steps) as colorless oil; mixture of rotamers, R_f 0.53 (30% EtOAc in hexane); ^1H NMR of major rotamer (300 MHz, $CDCl_3$): δ 4.44–4.19 (m, 2H), 3.75 (s, 3H), 3.66–3.56 (m, 2H), 2.78–2.72 (m, 1H), 2.14–2.03 (m, 1H), 1.95–1.85 (m, 1H), 1.47 and 1.42 (2s, 9H); ESI-MS *m*/*z* 268 [M + Na]$^+$; other paramaters were in full agreement with the literature reports.[24]

(*S*)-1-*tert*-butyl 2-methyl 2-methylpyrrolidine-1,2-dicarboxylate (7)

Following a similar procedure as described for **10**, α-methyl-L-proline (1 g, 7.75 mmol), $SOCl_2$ (0.64 mL, 8.52 mmol), in MeOH (15 mL) and Boc_2O (1.8 mL, 7.6 mmol), Et_3N (2.1 mL, 14.56 mmol) provided **7** (1.80 g, 96%, after two steps) as colorless viscous liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.55–3.42 (m, 2H), 2.15–2.07 (m, 1H), 1.88–1.80 (m, 3H), 1.52–1.47(m, 3H), 1.40 and 1.37 (2s, total 9H), rotamers; ESI-MS *m*/*z* 244 [M + H]$^+$;other paramaters were in agreement with the literature reports.[25]

(2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (12)

To a solution of **10** (1.0 g, 4.08 mmol) in CH_2Cl_2 (15 mL) was added benzyl bromide (0.60 mL, 4.90 mmol), silver oxide (2.83 g, 12.24 mmol) and the mixture was refluxed for 24 h. The contents were filtered (Celite), concentrated and chromatographed over silica gel (10% ethyl acetate in hexane) to obtain **12** (1.25 g, 92%) as colorless viscous liquid; $[\alpha]_D^{28}$ −17.65 (*c* 1.50, $CHCl_3$); R_f 0.65 (30% EtOAc in hexane); IR (Neat): *v* 2978, 1743, 1686, 1419, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.30 (m, 5H), 4.56–4.32 (m, 3H), 4.17–4.10 (m, 1H), 3.72 (s, 3H), 3.70–3.52 (m, 2H), 2.43–2.33 (m, 1H), 2.11–2.02 (m, 1H), 1.45 and 1.41 (2s, 9H), rotamers. ESI-MS *m*/*z* 336 [M + H]$^+$.

(2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-(benzyloxy)pyrrolidine-1,2-dicarboxylate (13)

Following similar procedure as for **12**, **11**(1.0 g, 4.08 mmol), BnBr (0.60 mL, 4.90 mmol) and Ag_2O (2.83 g, 12.24 mmol) furnished **13** (1.25 g, 92%) as colorless oil; mixture of rotamers, ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.27 (m, 5H), 4.67–4.34 (m, 3H), 4.11 (m,1H), 3.72 (s, 3H), 3.68–3.48 (m, 2H), 2.04 (m, 2H), 1.47 and 1.41 (each s, total 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.5, 153.7, 137.4, 128.4, 127.8, 127.7, 127.5, 81.8, 80.8, 79.9, 71.0, 65.1, 64.3, 52.2, 52.1, 44.8, 44.4, 30.8, 29.9, 28.3, 28.2; ESI-MS *m*/*z* 336 [M + H]$^+$.

(2*S*,4*R*)-*tert*-butyl 4-(benzyloxy)-2-formylpyrrolidine-1-carboxylate (14)

To a well stirred solution of **12** (2.0 g, 5.97 mmol) in dry THF (30 mL) at 0 °C was added $LiBH_4$ (138 mg, 6.57 mmol) in portions, the reaction mixture was stirred at r.t. until the completion of reaction (observed from TLC). The reaction

mixture was then quenched with acetone followed by water, after the usual workup (with ethyl acetate and water), the organic layer was concentrated and the alcohol obtained was used for the next step without any purification.

To the ice cooled solution of obtained alcohol (1.8 gm, 5.86 mmol) in dry CH_2Cl_2 (25 mL) was added Dess–Martin periodinane (3.24 gm, 7.62 mmol) and the solution was stirred at r.t. for 2 h. After the completion of reaction, it was quenched with 100 mL solution of $Na_2S_2O_4$ and Na_2CO_3 (1 : 1). After the usual workup with CH_2Cl_2 (25 × 3 mL) and water, the organic layer was concentrated in vacuum and the crude obtained was purified by column chromatography over silica gel (15% ethyl acetate in hexane), which furnished aldehyde **14** (1.65 g, 93%) as colorless viscous liquid; $[\alpha]_D^{28}$ −26.65 (*c* 0.17, $CHCl_3$); R_f 0.69 (30% EtOAc in hexane); IR (Neat): *ν* 3064, 3031, 2977, 2930, 2716, 1704, 1695, 1456, 1397, 1256, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.47, 9.37 (d, *J* = 2.2, 3.5, total 1H), 7.30–7.20 (m, 5H), 4.50–4.40 (dd, J_1 = 11.6, J_2 = 16.8, 2H), 4.27–4.12 (m, 1H), 4.05 (m, 1H), 3.73–3.42 (m, 2H), 2.24–2.08 (m, 1H),1.94–1.81 (m, 1H), 1.39 and 1.35 (2s, 9H), rotamers. ESI-MS *m*/*z* 306 $[M + H]^+$.

(2*S*, 3*S*)-*tert*-butyl 3-(benzyloxy)-2-formylpyrrolidine-1-carboxylate (15)

Following the similar procedure as described for **14**, **13** (2.0 g, 5.97 mmol) furnished **15** (1.65 g, 77%, after two steps) as colorless oil; mixture of rotamers, $[\alpha]_D^{28}$ −30.13 (*c* 0.15, $CHCl_3$); R_f 0.72 (30% EtOAc in hexane); IR (Neat): *ν* 3062, 3031, 2978, 2931, 2716, 1707, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.50 (d, *J* = 24.3, 1H), 7.34–7.32 (m, 5H), 4.63–4.50 (m, 3H), 4.21–4.15 (m,1H), 3.63–3.56 (m, 2H), 2.10–2.06 (m, 1H), 1.94–1.82 (m, 1H), 1.48 and 1.43 (2s, 9H), rotamers; ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 199.7, 199.45, 154.9, 153.8, 137.3, 128.5, 127.9, 127.7, 80.7, 80.4, 79.7, 76.4, 71.2, 70.6, 45.0, 44.7, 31.1, 30.3, 28.2; ESI-MS *m*/*z* 306 $[M + H]^+$.

(*S*)-*tert*-butyl 2-formyl-2-methylpyrrolidine-1-carboxylate (8)

Following similar procedure as described for **14**, **7** (1.0 g, 4.69 mmol), $LiBH_4$ (108 mg, 5.16 mmol) in dry THF (15 mL), followed by DMP (1.77 g, 5.44 mmol) in dry CH_2Cl_2 furnished **8** (780 mg, 88%, after two steps) as colorless syrup; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.29 (d, *J* = 23.9, 1H), 3.60–3.43 (m, 2H), 1.98–1.83 (m, 3H), 1.60–1.44 (m,1H), 1.38–1.26 (m,1 2H), rotamers; ESI-MS *m*/*z* 214 $[M + H]^+$; other paramaters were in good agreement with the literature reports.[25]

(2*S*, 4*R*)-*tert*-butyl 4-(benzyloxy)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (4c)

$(Me_3Si)_2NK$ (1 M, 12.27 mL, 12.27 mmol) was added over a period of 0.5 h under inert atmosphere to a suspension of (methoxymethyl)-triphenyl phosphonium chloride (3.36 g, 9.8 mmol) in anhydrous THF (30 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h and was brought to 0 °C in the next 0.5 h, then a solution of aldehyde **14** (1.5 g, 4.91 mmol) in anhydrous THF was added gradually over 20 min and the reaction mixture was left for 2 h overnight at r.t. with continuous stirring. It was quenched by water and was extracted using ether. Cooling the organic layer to −30 °C led to the crystallization of triphenylphosphine oxide, which was separated by decantation. The resulting organic layer was concentrated to oily residue. Flash chromatography of the residue over silica gel (2 × 15 cm), (68% EtOAc/hexane as eluent), gave enol ethers **16** (1.44 g, 88%) as a colorless oil, which was used further without characterization. To the stirred enol ether **16** (1.44 g, 4.33 mmol), in acetone (10 mL) was added 2 N HCl (3.24 mL, 6.48 mmol) at r.t. and was stirred for 10 min. The reaction mixture was then neutralized by sat. Na_2CO_3 (pH = 7) and extracted with diethylether. The ether layer was dried (over Na_2SO_4) and concentrated, followed by purification on silica gel (100–200 mesh) (using 7% EtOAc/hexane as eluent), which furnished homoprolinal **4c** (1.42 g, 96% yield) as colorless oil, $[\alpha]_D^{28}$ −33.28 (*c* 0.16, $CHCl_3$); R_f 0.70 (20% EtOAc in hexane); IR (Neat): *ν* 3064, 3031, 2978, 2931, 2718, 1701, 1685, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.70 (s, 1H), 7.25 (m, 5H), 4.43 (m, 2H), 4.27 (m, 1H), 4.01 (m, 1H), 3.37–3.33 (m, 2H), 2.95–2.80 (m, 1H), 2.48 (dd, J_1 = 6.4, J_2 = 7.2, 1H), 2.29 (m, 1H), 1.73–1.68 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 200.6, 154.7, 137.8, 128.4, 127.7, 127.6, 80.6, 79.9, 70.8, 51.6, 51.3, 48.7, 37.5, 28.4(3C); ESI-MS *m*/*z* 320 $[M + H]^+$.

(2*R*,3*S*)-*tert*-butyl 3-(benzyloxy)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (4d)

Following the similar procedure as described for **4c**, **15** (750 mg, 2.47 mmol), furnished **4d** (710 mg, 96%) *via* enolether **17** (720 mg, 88%) as colorless syrup; $[\alpha]_D^{28}$ −67.34 (*c* 0.20, $CHCl_3$); R_f 0.72 (20% EtOAc in hexane); IR (Neat): *ν* 3063, 3032, 2978, 2930, 2718, 1706, 1685, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 9.76 (s, 1H), 7.35–7.30 (m, 5H), 4.63–4.54 (m, 2H), 4.38–4.27 (m, 1H), 3.82 (m, 1H), 3.56–3.45 (m, 2H), 2.92–2.71 (m, 1H), 2.44–2.36 (m, 1H), 2.00 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 200.1, 154.1, 137.9, 128.4, 127.6, 82.7, 81.5, 80.1,79.7, 70.7, 57.5, 47.8, 47.1, 44.6, 28.4, mixture of rotamers; ESI-MS *m*/*z* 320 $[M + H]^+$.

(*S*)-*tert*-butyl 2-methyl-2-(2-oxoethyl)pyrrolidine-1-carboxylate (4b)

Following similar procedure asdescribed for **4c**, **8** (1.5 g, 7.04 mmol), $(Me_3Si)_2NK$ (1M, 17.6 mL, 12.27 mmol), (methoxymethyl)-triphenyl phosphonium chloride (5.18 g, 14.04 mmol) in anhydrous THF (30 mL) at −78 °C, furnished **4b** (1.32 g, 96%) as colorless oil *via* enolether **9** (1.46 g, 85%); IR *ν* 2927, 2831, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) Δ 9.73 (s, 1 H), 3.62–3.35 (m, 2 H), 3.11–2.74 (m, 2 H), 2.07–1.79 (m, 4 H), 1.50–1.44 (m, 12 H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 175.8, 154.0, 79.2, 60.5, 51.6, 48.2, 39.3, 28.4, 24.9, 21.8; ESI-MS *m*/*z* 228$[M + H]^+$, other paramaters were in good agreement with the literature reports.[25]

(*S*)-*tert*-butyl 2-formylpiperidine-1-carboxylate (19)

To a stirred solution of commercially available **18** (1.0 g, 4.1 mmol) in THF (2.5 mL) cooled with an ice bath was added BH_3·THF (1.0 M in THF, 6.3 mL, 6.3 mmol). The reaction was warmed to room temperature while stirring. After 3 h the solution was cooled and water (1 mL) was added dropwise. Sodium carbonate (0.8 g) was added and the mixture was vigorously stirred for 30 min. The layers were separated and the aqueous layer was extracted with ether (3 × 3 mL). The

combined ether layers were washed with brine (2.0 mL) and dried (Na_2SO_4). The solvent was evaporated to give oil that was filtered through silica gel using ethyl acetate as eluent. The solvent was evaporated to give an oil that crystallized to intermediate alcohol (product was spectroscopically comparable to the ^{1}H NMR and ^{13}C NMR to literature values)[26] as a white solid, which was used directly in the next step.

A solution of oxalyl chloride (0.218 mL, 2.51 mmol) in CH_2Cl_2 (5.7 mL) under nitrogen was cooled to −78 °C and stirred for 15 min. A solution of DMSO (0.323 mL, 4.57 mmol) in CH_2Cl_2 0.5 mL was added and the solution was stirred for 10 min. A solution of alcohol (0.50 g, 2.09 mmol) in CH_2Cl_2 (2.3 mL) was added dropwise and the reaction was stirred for 1 h at −78 °C. Diisopropylethylamine (1.45 mL, 8.32 mmol) was added dropwise and the mixture was allowed to warm to room temperature. The mixture was washed with 1 M HCl (2 × 2 mL), water (4 × 2 mL), brine (2 × 2 mL) and dried ($MgSO_4$). Concentration of the solvent provided **19** (0.435 g, 98%) as a light yellow oil; $[\alpha]_D^{28}$ −74.31 (*c* 1.5, $CHCl_3$, lit.[27] −77.4, c 1.4, $CHCl_3$); R_f 0.74 (30% EtOAc in hexane), ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 4.57 (m, 1H), 3.93 (m, 1H), 2.92 (m, 1H), 2.18–2.14 (m, 1H), 1.68–1.24 (m, 5H), 1.47 (s, 9H); ESI-MS *m*/*z* 236 $[M + Na]^+$.

(*S*)-*tert*-butyl 2-formylpyrrolidine-1-carboxylate

Spectral data were found to be in good agreement with literature report.[19]

(*S*)-*tert*-butyl 2-(2-oxoethyl)pyrrolidine-1-carboxylate (4a)

Spectral data were found to be in good agreement with literature report.[19]

(*S*)-*tert*-butyl 2-(2-oxoethyl)piperidine-1-carboxylate (4e)

Following the similar procedure as described for **4c**, **19** (1.82 g, 8.50 mmol), $(Me_3Si)_2NK$ (1 M, 21.2 mL, 21.25 mmol), (methoxymethyl)-triphenyl phosphonium chloride (6.29 g, 17.01 mmol) in anhydrous THF (40 mL) at −78 °C to r.t., furnished **4e**[28] (1.73 g, 83%, after two steps) as colorless oil *via* its enol ether (1.78 g, 85%); $[\alpha]_D^{28}$ −53.71 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (dd, J_1 = 2.3, J_2 = 3.0, 1H), 4.84–4.83 (m, 1H), 4.01–3.97 (bd, J = 12.7, 1H), 2.83–2.70 (m, 2H), 2.57–2.50 (m, 1H), 1.76–1.46 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.8, 154.6, 79.9, 45.8, 44.6, 39.2, 28.8, 28.3, 25.2, 18.9; ESI-MS *m*/*z* 228 $[M + H]^+$.

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