Full Paper

Diastereoselective Pictet–Spengler Reactions of a Tethered 2-Aminoimidazole

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The diastereoselective Pictet–Spengler reaction of aminopropyl-2-aminoimidazole with enantiopure aldehydes has been investigated. With amino acid-derived aldehydes, *anti* stereochemistry is favoured, with a diastereoselectivity up to 92 % achievable. The absolute stereochemistry of the products was determined through synthesis of a rigid derivative and from NMR data in combination with molecular modelling. The diastereoselectivity was shown to be dependent on the steric bulk of the amino acid side chain and independent of the nitrogen protecting group. Lewis acids catalysed the reaction but did not affect the diastereoselectivity.

Introduction

The Pictet–Spengler reaction was first discovered in 1911 by Amé Pictet and Theodor Spengler (Fig. 1),[1] and has been found useful for the synthesis of tetrahydo-β-carbolines and tetrahydroisoquinolines and recently been proposed to be a common biosynthetic reaction for the construction of a range of alkaloids.[2]

The reaction has been used to great avail in classic syntheses such as haemultine,[3] manzamine alkaloids,[4] yohimbinoid alkaloids,[5] and ecteinascidin 743.[6]

Although the Pictet–Spengler reaction has been widely studied in indole and benzene chemistry,[7] less is known about the Pictet–Spengler cyclisation of other heterocycles such as imidazoles, an important component of many marine natural products.[8] In 1948, Folkers et al. reported the first example of a Pictet–Spengler reaction between histidine and vitamin B$_6$ to form a tetrahydroimidazopyridine (**1**) (Fig. 2).[9]

Since then, there have been sporadic reports on Pictet–Spengler reactions between various aldehydes and ketones and histamine, histidine or histinol.[10] Notably, these reactions are generally reported as base-catalysed, probably going through a mechanism like that shown in Fig. 3. However, it is possible that base is simply required to avoid the non-nucleophilic imidazolium ion.

We used this reaction to good effect in the concise total synthesis of ageladine A (**3**) and in a range of analogues starting from 2-aminohistamine (**2**) and 4,5-dibromopyrrole carboxyaldehyde or other aryl aldehydes (Fig. 4).[11]

Subsequently, Horne and coworkers used this method with a variety of aliphatic and aromatic aldehydes in the synthesis of imidazoazepine (azulene) analogues (**5**) of ageladine A from 2-aminohomohistamine (**4**), the basic building block for all the oroidin alkaloids (Fig. 5).[12]

Unlike indole- and phenyl-ethylamine, the enantioselective or diastereoselective Pictet–Spengler reaction of imidazoles

has not previously been reported. For tryptamines and phenyl-ethylamines, amino acid aldehydes have been successfully employed for the synthesis of a number of biologically important natural products and been the subject of detailed stereochemical investigations.[13] We reasoned that a stereospecific version of the Pictet–Spengler reaction with imidazoles could provide access to new chiral imidazole alkaloids and be useful in
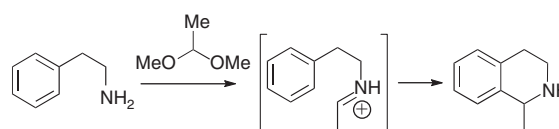

Fig. 1. Pictet–Spengler reaction between phenylethylamine and acetaldehyde dimethyl acetal involving an intermediate iminium ion.
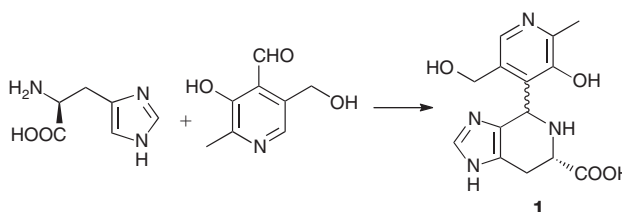

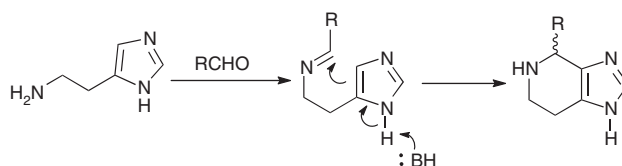**Fig. 2.** Pictet–Spengler reaction of histidine with vitamin B$_6$.

Fig. 3. Proposed base-catalysed mechanism for the Pictet–Spengler reactions of imidazole.
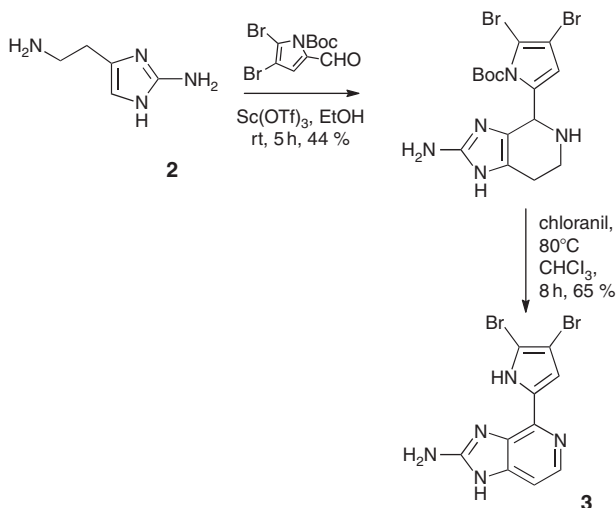
Fig. 4. Concise synthesis of ageladine A using Pictet–Spengler reaction.
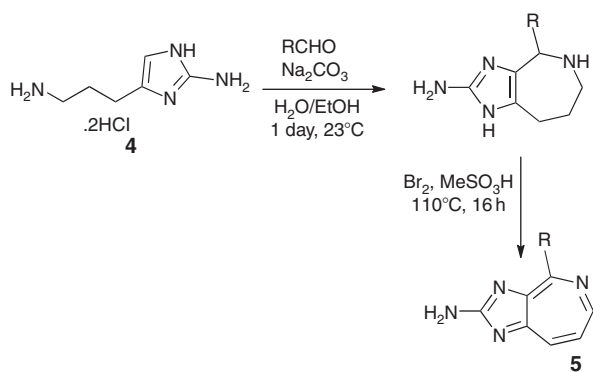

Fig. 5. Synthesis of imidazoazepine analogues of ageladine A using Pictet–Spengler reaction.

the stereospecific synthesis of imidazole-containing natural products such as mikimopine, cucumopine, and analogues.[14] As a first step in this direction, we decided to investigate the potential for diastereoselectivity of the base-catalysed Pictet–Spengler reaction between 2-aminoimidazoles and enantiopure aldehydes (**6**) derived from amino acids.

Result and Discussion

As a starting point, we decided to extend the chemistry developed by Horne using 2-aminohomohistamine (**4**), which was synthesised in three steps from ornithine.[15] A series of amino acid aldehydes (**6**) were synthesised from the corresponding amino acids using the method of Kanellis,[16] except after reduction of the protected amino acid with BH_3-THF, the intermediate alcohols were oxidised using the Dess–Martin reagent.[17] Screening solvents (water, aqueous ethanol, ethanol) and bases (Na_2CO_3, K_2CO_3, triethylamine), we were pleased to see a good yield of the Pictet–Spengler product using triethyamine in alcohol at room temperature (rt). Thus, stirring **4** with Boc-L-alaninal (**6a**) gave the corresponding bicyclic product with a moderate diastereomeric excess (*de*) of 56 % (**7a**/**8a**, Table 1), favouring *anti* stereochemistry over *syn*. Similar results were obtained with other amino acid-derived aldehydes (entries 2–6). The *de* increased from phenylalaninal (72 %) to leucinal (84 %) and valinal (92 %), suggesting that steric factors play an important role. Changing the protecting group from Boc to the less bulky Cbz (entry 7) or ethylcarbamate

(entry 8) groups had little effect on the diastereomeric ratio, suggesting that the protecting group on nitrogen is sufficiently distant from the reaction centre not to influence the geometry of the transition state (TS).

Most Pictet–Spengler reactions are acid-catalysed, with imidazoles being somewhat unusual in being base-catalysed (Fig. 3).[13] We were interested to know if a Lewis acid could improve the diastereoselectivity through complexation of the TS. We previously observed that the combination of Lewis acid and Brønsted base increased the rate of Pictet–Spengler cyclisation in the six-membered ring system.[11] Unfortunately, scandium, indium, and lanthanum did not significantly change the diastereomeric ratio (Table 2) but did increase the rate of the reaction (entries 3–5), with scandium triflate showing marginally better activity than the other two. Temperature can have a dramatic effect on stereoselectivity by favouring the kinetic product and temperature-dependent changes in the diastereoselectivity of the standard Pictet–Spengler reaction of tryptamine with enantiopure aldehydes is known.[18] When we screened reactions at lower temperatures (entries 1 and 2), a small improvement in the diastereomeric ratio was obtained at 0°C but no reaction was observed at −78°C. The reaction was also found to proceed without any catalyst (entry 6), albeit at a slower rate. Base catalysis is evident by comparing entry 1 (Table 1) and entry 6 (Table 2). In the former, the reaction proceeded in 72 % yield in 3–4 h in the presence of triethylamine. The free base, without base catalysis, reacted in a lower yield (67 %) in 8 h but the diastereoselectivity was largely unaffected.

The coupling constant obtained for H10a–H10 for all the major isomers **7** is between 8 and 9 Hz and for minor isomers **8** is between 5 and 6 Hz in [D4]MeOH. This information suggested that all the major and minor products had the same stereochemistry. However, the observed coupling constants and nuclear Overhauser effects (NOEs) could not definitely be used to assign the C10a–C10 dihedral.

To assign the stereochemistry, we prepared rigid tricyclic compounds **10** and **12** by reacting **9** and **11** (derived from D-alaninal) with carbonyldiimidazole in moderate yields (Scheme 1). Poor yields were obtained for the imidazolidinone when the reaction was carried out in the recommended solvent (acetonitrile)[19] but DMF was found suitable. Initial attempts using triphosgene or thiophosgene in dichloromethane (DCM) gave complex mixtures.

The structure of the tricyclic product was confirmed by heteronuclear multiple bond correlation (HMBC) spectroscopy where (H6)$_2$, H10, H10a, and the amide NH showed $^3J_{CH}$ correlations to the urea carbonyl (C8) at 159.5 ppm (Scheme 1, Fig. S1 in the Supplementary Material). Other important $^3J_{CH}$ correlations, including NH, H6a, and H10 to the C10a, and NH and H10a to C10 could also be seen in the 2D NMR (Fig. S1).

Unfortunately, the NMR coupling constants between H10a and H10 (Fig. S2 in the Supplementary Material) were again very similar (6.1 and 7.1 Hz), which did not allow differentiation based on a calculated dihedral using the well-known Karplus relationship.[20] Molecular modelling (simulated annealing) of the tricyclic ureas (**10** and **12**) generated 100 random structures, each minimised to only three possible dihedrals (Fig. S3 in the Supplementary Material). For the (10R*,10aS*)-isomer (**10**), there are three minima for the C10b–C10 dihedral at ~142–144°. For the (10R*,10aR*)-isomer (**12**), similarly three minima are seen but the dihedral ranges from −12 to −20°. The calculated coupling constants (6.8, 7.4 Hz)[20] were not different enough to positively determine the absolute

Table 1. Pictet–Spengler reaction of 4 and amino acid derived aldehydes 6

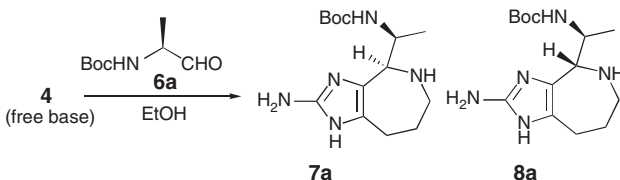$$4 \xrightarrow[\text{rt, 3–4 h}]{\text{TEA, EtOH}} 7 + 8$$
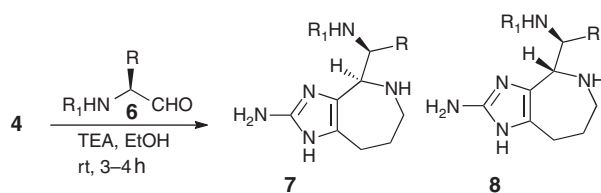
Entry	Aldehyde	Major isomer (*anti*)	Minor isomer (*syn*)	Yield[A] [%]	Ratio[B] (dr[C]) *anti* : *syn* (**7** : **8**)
1	**6a** (S), CHO, NHBoc	**7a**	**8a**	72	78 : 22
2	**6b** (R), CHO, NHBoc	**7b**	**8b**	79	78 : 22
3	**6c** Ph, (S), CHO, NHBoc	**7c**	**8c**	85	86 : 14
4	**6d** (S), CHO, NHBoc	**7d**	**8d**	62	96 : 4
5	**6e** (R), CHO, NHBoc	**7e**	**8e**	71	96 : 4
6	**6f** (S), CHO, NHBoc	**7f**	**8f**	89	92 : 8
7	**6g** (S), CHO, NHCbz	**7g**	**8g**	65	72 : 28
8	**6h** (R), CHO, NHCOOEt	**7h**	**8h**	90	74 : 26

[A]Yield for **7** and **8**.
[B]Ratios calculated using ^{1}H NMR spectrum of the diastereomeric mixture.
[C]Diastereomeric ratio.

stereochemistry but suggested that the major isomer was **10** and that the minor was **12**.

However, the modelling results indicated that the distance between the C10–Me and H10a were quite different. For the (10R^*, 10aR^*) isomer, the distance was ~3.5 Å and for the other isomer, it was ~2.8 Å. These differences should be easily differentiated through the NOE. Thus 1D-rotation frame Overhauser effect (ROE) experiments on compounds **10** and **12** (Fig. S4 in the Supplementary Material), under identical conditions, resulted in enhancement of all neighbouring protons (Fig. 6). Both compounds showed a 0.9 ± 0.05 % ROE from C10–Me to H10, confirming that the ROE experiments were

Table 2. Lewis acid catalysed Pictet–Spengler reaction of **4** (free base) and Boc-ʟ-alaninal

| Entry	Catalyst (20 mol-%)	Temperature [°C]	Time [h]	Yield[A] [%]	Anti : syn[B] **7a** : **8a**
1	Sc(OTf)$_3$	−78	8	0	–
2		0	6	55	81 : 19
3		rt	1	82	77 : 23
4	In(OTf)$_3$	rt	2	75	77 : 23
5	La(OTf)$_3$	rt	1	79	74 : 16
6		rt	8	67	75 : 25

[A]Yield for **7** plus **8**.
[B]Diastereoisomeric ratios calculated using ^{1}H NMR spectroscopy.
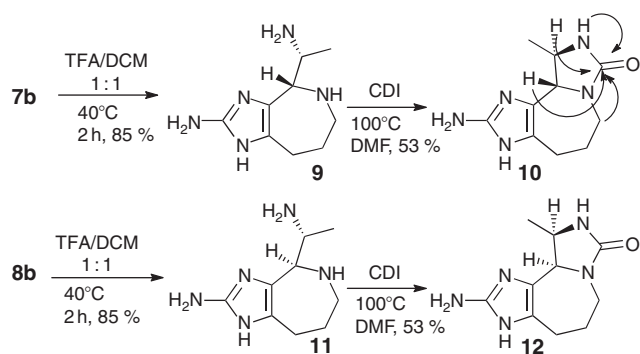
Scheme 1. Synthesis of imidazolinones **10** and **12**; arrows indicate $^3J_{CH}$ correlation observed in the HMBC.
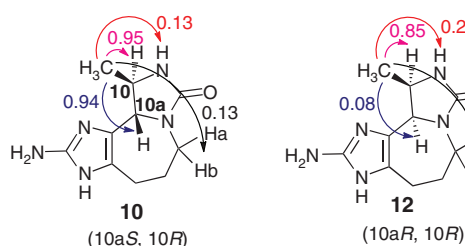
Fig. 6. NOE correlation for major (left) and minor (right) isomers prepared from ᴅ-alanine.

nearly identical. Of particular note was that the major isomer had a 0.94 % enhancement of H10a but for the corresponding minor isomer, the enhancement was 10× smaller, showing that in the major isomer (**10**), the methyl group and H10a are on the same side of the ring (10*R*, 10a*S*). The 1D-ROE measurements confirmed the molecular modelling results, indicating that the (10*R*, 10a*S*)-isomer is the major isomer formed in the Pictet–Spengler reaction of ʟ-alaninal.

The selection for this diastereomer can be rationalised by looking at the putative TS in the Pictet–Spengler reaction. After formation of the imine, base-catalysed nucleophilic attack of the imidazole requires a TS like that shown in Fig. 7. Applying the
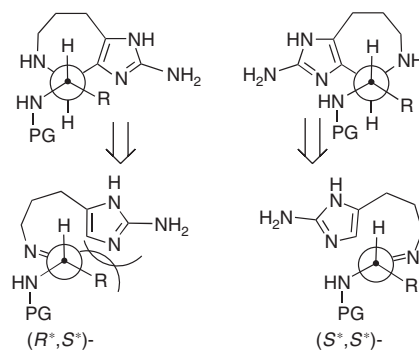
Fig. 7. Putative transition states for the Pictet–Spengler reaction favouring the *anti* TS (PG: protecting group).

Felkin–Anh transition state model, where 'R' is the large substituent, the (*S**, *S**) TS should be favoured. As the protecting group (PG) is remote, it should not affect the TS as observed experimentally (Table 1; entries 2, 7, and 8).

Conclusions

For the first time, the diastereoselective version of the Pictet–Spengler reaction of aminopropyl-2-aminoimidazole has been investigated with enantiopure amino acid-derived aldehydes. The reaction proceeded with good to excellent diastereoselectivity, depending only on the steric bulk of the amino acid side chain. Different protecting groups on nitrogen and various Lewis acids did not change the diastereoselectivity but Lewis acids did accelerate the reaction even in the presence of excess base. Based on detailed NMR experiments and molecular modelling, it was eventually possible to assign *anti* stereochemistry to the major isomer and *syn* to the minor isomer.

Experimental

General Methods

Chloroform, dichloromethane, ethanol, and methanol were obtained from Froline Australia and were fractionally distilled before use from anhydrous potassium carbonate. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. All the reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded in 5-mm Pyrex NMR tubes (Wilmald, USA; 507-PP) on Bruker DPX400 or DRX600 NMR spectrometers, operating at 400 and 600 MHz respectively for protons. Chemical shifts were referenced to the solvent peaks: δ_H 3.31 and δ_C 49.1 for CD$_3$OD, δ_H 7.25 and δ_C 77.01 for CDCl$_3$, and δ_H 2.49 and δ_C 39.5 for [D6]DMSO.

All two-dimensional (2D) spectra were recorded with quadrature detection in both dimensions using time proportional phase incrimination (TPPI). For double-quantum filtered correlation spectroscopy (DQF-COSY) and rotating frame Overhauser effect spectroscopy (ROESY)[21] experiments, 2048 data points were collected in t_2 and 512 in t_1, and between 24 and 80 transients were collected at each increment. Relaxation delays and solvent suppression were as for the 1D spectra. Gradient-selective 1D-ROESY difference spectra were recorded with a continuous-wave pulse equivalent to a 4-kHz spinlock of 250-ms duration using selective refocussing with a Gaussian-shaped pulse.[22] ROE enhancements were measured as a percentage of the irradiated peak and not compensated for offset from the carrier frequency. Carbon–hydrogen

correlation (HSQC) was achieved via a sensitivity-enhanced double INEPT transfer using echo/antiecho-TPPI gradient (80 : 20.1) selection.[23] Two thousand and forty-eight data points were collected in t_2 (128 scans per increment) with a 1.3-s recycle delay with decoupling during acquisition. In t_1, 512 increments were used (10–120 ppm) and the INEPT sequence was optimised for an X–H coupling of 145 Hz. A gradient ratio of 80 : 20.1 was used to select echo/antiecho-TPPI phase sensitivity. HMBC spectra were obtained via zero and double quantum coherence with a low-pass J-filter to suppress one-bond couplings. No decoupling was used during the acquisition and the results were magnitude-calculated. A long-range coupling of 20 Hz was used for HMBC selection. Data were processed using the Bruker *TopSpin* (version 1.4) software. The spectra were zero-filled twice in F1 and once in F2 and processed with either squared sine-bell (π/2- or π/3-shifted) or Lorentzian–Gaussian window functions. The spectra were referenced and phased in both dimensions. A baseline correction was subsequently applied in F2 and F1 if necessary.

Molecular dynamics and minimisation were performed using the *Insight II/Discover3* Molecular Modelling System. The compound was built using the Builder module in *InsightII*, and energy-minimised briefly. Molecular dynamics simulations were performed at 1000 K for 0.1 ns and a structure sampled every 10 ps in order to generate 100 random structures. Each structure was cooled to 200 K over 8 ps using a simulated annealing approach. This was followed by minimisation of each structure, involving steepest descents, conjugate gradients, and quasi-Newton–Raphson minimisation until the final maximum derivative was less than 0.0001 kcal mol^{-1} Å^{-1}. The MMFF94 force field was used in all *Discover3* calculations.[24]

Preparation of 4-(3-Aminopropyl)-1H-imidazol-2-amine 4 dihydrochloride

Compound **4** was synthesised using a method of Horne et al.[15] Ornithine hydrochloride (5 g, 0.029 mol) was dissolved in a dry ethanol (50 mL) and the reaction mixture cooled to 0°C. After 10 min, thionyl chloride (2.83 mL, 0.037 mol) was slowly added to the reaction mixture, keeping the temperature below 5°C. The reaction mixture was then warmed to room temperature and then refluxed for 8 h, after which solvent was removed under reduced pressure yielding ornithine ethyl ester dihydrochloride (5.82 g, 89 %) as a white solid. δ_H (400 MHz, [D6]DMSO) 8.76 (bs, 3H), 8.27 (bs, 3H), 4.16 (m, 2H), 3.94 (t, J 6.6, 1H), 2.79–2.68 (m, 2H), 1.90–1.80 (m, 2H), 1.79–1.58 (m, 2H), 1.21 (t, J 7.4, 3H). Ornithine ethyl ester dihydrochloride was dissolved in water (50 mL) and the solution cooled to 0°C. Sodium amalgam (109.2 g, 0.22 mol) was slowly added to the reaction mixture over a period of 30 min. During the addition, the pH of the reaction mixture was maintained at 1–3 using dropwise addition of 15 % hydrochloric acid. When the pH remained constant and the evolution of gas had ceased, the solution was decanted to remove mercury. The pH of the solution was maintained at 4.5 by addition of 1 M sodium hydroxide. The aldehyde so formed was further heated to 95°C with an aqueous solution of cyanamide (9.6 mL, 0.114 mol) for 2 h. The solvent was removed, leaving behind a thick yellow residue, which was triturated with methanol. The filtrate was concentrated and recrystallised (ethanol) to yield aminopropylimidazole dihydrochloride (1.92 g, 42 %) as a yellow solid. δ_H (400 MHz, [D6]DMSO) 12.33 (s, 1H), 11.79 (s, 1H), 8.31 (bs, 2H), 7.37 (bs, 3H), 6.61 (s, 1H), 2.77–2.65 (m, 2H), 2.50 (t, J 6.7, 2H), 1.88–1.77 (m, 2H). Lit.[15a]

4-(3-Aminopropyl)-1H-imidazol-2-amine 4

To a stirred solution of 4-(3-aminopropyl)-1*H*-imidazol-2-amine dihydrochloride **4** (500 mg, 2.35 mmol) in ethanol (10 mL) was added triethylamine (0.65 mL, 4.71 mmol), the solvent removed under reduced pressure and the dark-brown residue subject to column chromatography over aluminium oxide using a gradient of 10 : 90–35 : 65 (MeOH/DCM saturated with ammonia) to aminopropylimidazole free base (310 mg, 94 %) as a thick yellow liquid.

General Procedure of Pictet–Spengler Cyclisation of 4 (Dihydrochloride Salt)

To a stirred solution of **4** (0.0023 mol) in ethanol (5 mL) was added triethylamine (0.0070 mol) and the reaction mixture stirred at room temperature for 10 min, followed by addition of the aldehyde **6** (0.0027 mol). The reaction mixture was stirred for a further 3–6 h, after which the solvent was removed under reduced pressure and the residue subjected to flash chromatography (silica gel) using a gradient of 5 : 95–15 : 85 (MeOH/DCM saturated with ammonia), collecting **7** and **8** as a mixture (Table 1). Diastereomeric ratios were obtained from NMR spectra and the diastereoisomers separated by more careful flash chromatography (silica gel).

Lewis Acid-catalysed Pictet–Spengler Cyclisation of 4 (Free Base)

To a stirred solution of **4** (free base, 0.0023 mol) in ethanol (5 mL) was added aldehyde **6a** (0.0027 mol) and Lewis acid (20 mol-%) and the reaction mixture stirred at room temperature for 1–8 h. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (silica gel) using a gradient of 5 : 95–15 : 85 (MeOH/DCM saturated with ammonia), yielding a mixture of **7a** and **8a** as a yellowish solid (Table 2). Diastereomeric ratios were obtained from NMR spectra and separated by flash chromatography (silica gel).

In the case of entries 1, 2, and 6 (Table 2), the reactions were carried out on the free base without addition of catalyst or base.

(1′S,4R)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 7a

$[\alpha]_D^{26}$ 21.0 (c 0.053 in EtOH). δ_H (400 MHz, CD$_3$OD) 3.89–4.00 (m, 1H), 3.49 (d, J 8.8, 1H), 3.07–3.18 (m, 1H), 2.85–2.95 (m, 1H), 2.47–2.70 (m, 2H), 1.62–1.86 (m, 2H), 1.43 (s, 9H), 1.06 (d, J 6.6, 3H). δ_C (100 MHz, CD$_3$OD) 157.9, 148.0, 129.9, 127.5, 80.1, 60.7, 48.5, 46.1, 29.7, 28.8, 26.1, 19.3. m/z (high resolution mass spectrometry, HRMS) 296.2078 [M + H]$^+$; C$_{14}$H$_{26}$N$_5$O$_2$ requires 296.2087.

(1′S,4S)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 8a

$[\alpha]_D^{26}$ −9.2 (c 0.003 in EtOH). δ_H (400 MHz, CD$_3$OD) 4.04–4.13 (m, 1H), 3.57 (d, J 5.1, 1H), 3.10–3.20 (m, 1H), 2.83–2.92 (m, 1H), 2.61–2.72 (m, 1H), 2.47–2.57 (m, 1H), 1.71–1.89 (m, 2H), 1.39 (s, 9H), 1.12 (d, J 6.8, 3H). δ_C (100 MHz, CD$_3$OD) 157.5, 148.3, 129.9, 128.2, 80.0, 61.0, 47.8, 30.0, 28.7, 25.7, 17.1. m/z (HRMS) 318.1900 [M + Na]$^+$; C$_{14}$H$_{25}$N$_5$O$_2$Na requires 318.1900.

(1′R,4S)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 7b

$[\alpha]_D^{26}$ −21.7 (c 0.028 in EtOH). δ_H (400 MHz, CD$_3$OD) 3.90–4.00 (m, 1H), 3.50 (d, J 8.8, 1H), 3.07–3.18 (m, 1H), 2.85–2.95

(m, 1H), 2.48–2.69 (m, 2H), 1.63–1.86 (m, 2H), 1.43 (s, 9H), 1.06 (d, J 6.5, 3H). δ_C (100 MHz, CD$_3$OD) 157.8, 148.0, 130.0, 127.5, 80.1, 60.7, 48.5, 46.2, 29.7, 28.8, 26.1, 19.3. m/z (HRMS) 318.1906 [M + Na]$^+$; C$_{14}$H$_{25}$N$_5$O$_2$Na requires 318.1900.

(1′R,4R)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 8b

$[\alpha]_D^{26}$ 8.9 (c 0.002 in EtOH). δ_H (400 MHz, CD$_3$OD) 4.04–4.13 (m, 1H), 3.57 (d, J 5.5, 1H), 3.10–3.20 (m, 1H), 2.83–2.92 (m, 1H), 2.61–2.72 (m, 1H), 2.47–2.57 (m, 1H), 1.71–1.88 (m, 2H), 1.39 (s, 9H), 1.12 (d, J 6.8, 3H). δ_C (100 MHz, CD$_3$OD) 157.5, 148.3, 129.9, 128.2, 80.0, 61.0, 47.8, 30.0, 28.7, 25.7, 17.1. m/z (HRMS) 318.1906 [M + Na]$^+$; C$_{14}$H$_{25}$N$_5$O$_2$Na requires 318.1900.

(1′S,4R)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)-2′-phenylethyl)carbamate 7c

$[\alpha]_D^{26}$ 12.7 (c 0.005 in EtOH). δ_H (400 MHz, CD$_3$OD) 7.09–7.26 (m, 5H), 4.02–4.15 (m, 1H), 3.63 (d, J 8.2, 1H), 3.17–3.25 (m, 1H), 2.77–2.98 (m, 3H), 2.48–2.74 (m, 2H), 1.65–1.93 (m, 2H), 1.26 (s, 9H); δ_C (100 MHz, [D6]DMSO) δ_C 154.5, 146.1, 139.6, 128.8, 127.5, 125.2, 77.0, 58.2, 54.5, 46.9, 36.5, 28.9, 27.9, 23.5. m/z (HRMS) 394.2214 [M + Na]$^+$; C$_{20}$H$_{29}$N$_5$O$_2$Na requires 394.2213.

(1′S,4R)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)-2′-methylpropyl)carbamate 7d

$[\alpha]_D^{26}$ 22.3 (c 0.060 in EtOH). δ_H (400 MHz, CD$_3$OD) 3.77 (dd, J 8.6, 4.3, 1H), 3.68 (d, J 8.6, 1H), 3.12–3.22 (m, 1H), 2.83–2.91 (m, 1H), 2.62–2.72 (m, 1H), 2.48–2.57 (m, 1H), 1.64–1.83 (m, 3H), 1.43 (s, 9H), 0.88 (d, J 3.1, 3H), 0.86 (d, J 3.2, 3H). δ_C (100 MHz, CD$_3$OD) 158.6, 148.0, 129.5, 128.2, 80.0, 57.5, 57.0, 46.3, 30.2, 29.8, 28.8, 26.3, 21.3, 17.1. m/z (HRMS) 346.2206 [M + Na]$^+$; C$_{16}$H$_{29}$N$_5$O$_2$Na requires 346.2213.

(1′R,4S)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)-2′-methylpropyl)carbamate 7e

$[\alpha]_D^{26}$ −21.4 (c 0.032 in EtOH). δ_H (400 MHz, CD$_3$OD) 3.77 (dd, J 8.6, 4.2, 1H), 3.68 (d, J 8.9, 1H), 3.12–3.22 (m, 1H), 2.83–2.91 (m, 1H), 2.62–2.72 (m, 1H), 2.48–2.57 (m, 1H), 1.64–1.83 (m, 3H), 1.43 (s, 9H), 0.88 (d, J 3.2, 3H), 0.86 (d, J 3.2, 3H). δ_C (100 MHz, CD$_3$OD) 158.7, 148.0, 129.6, 128.3, 80.0, 57.5, 57.0, 46.3, 30.2, 29.8, 28.8, 26.3, 21.3, 17.1. m/z (HRMS) 346.2211 [M + Na]$^+$; C$_{16}$H$_{29}$N$_5$O$_2$Na requires 346.2213.

(1′S,4R)-tert-Butyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)-3′-methylbutyl)carbamate 7f

$[\alpha]_D^{26}$ 5.6 (c 0.009 in EtOH). δ_H (400 MHz, CD$_3$OD) 3.91–4.01 (m, 1H), 3.48 (d, J 8.3, 1H), 3.20–3.27 (m, 1H), 2.84–2.95 (m, 1H), 2.59–2.71 (m, 1H), 2.49–2.57 (m, 1H), 1.51–1.89 (m, 4H), 1.43 (s, 9H), 1.15–1.26 (m, 1H), 0.88 (d, J 6.7, 3H), 0.83 (d, J 6.4, 3H). δ_C (100 MHz, CD$_3$OD) 158.3, 148.0, 129.4, 127.9, 79.9, 60.7, 51.1, 46.6, 43.3, 29.6, 28.8, 26.2, 24.2, 22.0. m/z (HRMS) 360.2376 [M + Na]$^+$; C$_{17}$H$_{31}$N$_5$O$_2$Na requires 360.2369.

(1′S,4R)-Benzyl-(1′-(2-amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 7g

$[\alpha]_D^{26}$ 21.9 (c 0.067 in EtOH). δ_H (400 MHz, CD$_3$OD) 7.38–7.21 (m, 5H), 5.07 (s, 2H), 4.09–3.98 (m, 1H), 3.54 (d, J 8.8, 1H), 3.17–3.05 (m, 1H), 2.92–2.79 (m, 1H), 2.70–2.46 (m, 2H), 1.90–1.63 (m, 2H), 1.08 (d, J 6.58, 3H). δ_C (100 MHz, CD$_3$OD) 158.4, 148.2, 138.4, 129.9, 129.5, 129.0, 128.8, 127.5, 67.5, 60.8, 46.2, 29.7, 26.1, 19.3. m/z (HRMS) 330.1923 [M + H]$^+$; C$_{17}$H$_{24}$N$_5$O$_2$ requires 330.1924.

(1′S,4S)-Benzyl (1′-(2-Amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 8g

$[\alpha]_D^{26}$ −1.2 (c 0.018 in EtOH). δ_H (400 MHz, CD$_3$OD) 7.37–7.23 (m, 5H), 5.02 (s, 2H), 424–4.12 (m, 1H), 3.63 (d, J 4.6, 1H), 3.19–3.07 (m, 1H), 2.89–2.77 (m, 1H), 2.71–2.59 (m, 1H), 2.56–2.47 (m, 1H), 1.86–1.70 (m, 2H), 1.14 (d, J 6.9, 3H). δ_C (100 MHz, CD$_3$OD) 157.9, 148.4, 138.3, 130.3, 129.4, 128.9, 128.7, 128.0, 67.3, 60.9, 47.9, 30.0, 25.5, 16.9. m/z (HRMS) 330.1923 [M + H]$^+$; C$_{17}$H$_{24}$N$_5$O$_2$ requires 330.1924.

(1′S, 4R)-Ethyl (1′-(2-Amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 7h

$[\alpha]_D^{26}$ 18.2 (c 0.095 in EtOH). δ_H (400 MHz, CD$_3$OD) 4.13–3.95 (m, 2H), 3.53 (d, J 8.8, 1H), 3.18–3.08 (m, 1H), 2.95–2.87 (m, 1H), 2.69–2.49 (m, 2H), 1.86–1.62 (m, 2H), 1.22 (t, J 7.1, 3H), 1.07 (d, J 6.6, 3H). δ_C (100 MHz, CD$_3$OD) 158.7, 148.2, 130.0, 127.5, 61.8, 60.8, 46.2, 29.7, 26.2, 19.4, 15.0. m/z (HRMS) 268.1768 [M + H]$^+$; C$_{12}$H$_{22}$N$_5$O$_2$ requires 268.1768.

(1′S,4S)-Ethyl (1′-(2-Amino-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-4-yl)ethyl)carbamate 8h

$[\alpha]_D^{26}$ −9.8 (c 0.025 in EtOH). δ_H (400 MHz, CD$_3$OD) 4.20–4.11 (m, 1H), 4.02 (q, J 7.01, 1H), 3.61 (d, J 5.12, 1H), 3.20–3.09 (m, 1H), 2.90–2.81 (m, 1H), 2.72–2.61 (m, 1H), 2.58–2.47 (m, 1H), 1.88–1.71 (m, 2H), 1.19 (t, J 7.01, 3H), 1.13 (d, J 6.86, 3H). δ_C (100 MHz, CD$_3$OD) 158.3, 148.5, 130.4, 128.1, 61.8, 61.1, 48.1, 30.2, 25.6, 17.0, 15.1. m/z (HRMS) 268.1768 [M + H]$^+$; C$_{12}$H$_{22}$N$_5$O$_2$ requires 268.1768.

(1′R,4R)-(1′-Aminoethyl)-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-2-amine 9

Compound 7b (30 mg, 10 mmol) was dissolved in TFA/DCM (3 mL, 1 : 1) and the reaction mixture was heated at 40°C for 3 h, after which the solvent was removed under reduced pressure, leaving a light-brown solid, which was purified by column chromatography (basic alumina) using a gradient of 5 : 95–40 : 60 (MeOH/DCM saturated with ammonia) yielding the deprotected azepinamine 9 (17 g, 85 %) as a thick colourless oil. $[\alpha]_D^{26}$ −14.9 (c 0.013 in EtOH). δ_H (400 MHz, CD$_3$OD) 3.9 (d, J 9.4, 1H), 3.62–3.72 (m, 1H), 3.15–3.24 (m, 1H), 3.04–3.13 (m, 1H), 2.59–2.79 (m, 2H), 1.85–1.96 (m, 1H), 1.64–1.77 (m, 1H), 1.29 (d, J 6.6, 3H). δ_C (100 MHz, CD$_3$OD) 147.8, 126.4, 122.7, 57.0, 45.1, 29.0, 24.6, 16.5. m/z (HRMS) 196.1560 [M + H]$^+$; C$_9$H$_{18}$N$_5$ requires 196.1562.

(1′R,4R)-4-(1′-Aminoethyl)-1,4,5,6,7,8-hexahydroimidazo[4,5-c]azepin-2-amine 11

Compound 8b (30 mg, 10 mmol) was dissolved in TFA/DCM (3 mL, 1 : 1) and the reaction mixture was heated at 40°C for 3 h, after which the solvent was removed under reduced pressure, leaving a light-brown solid, which was purified by column chromatography (basic alumina) using a gradient of

5 : 95–40 : 60 (MeOH/DCM saturated with ammonia) yielding the deprotected azepinamine **11** (17 g, 89 %) as a thick colourless oil. $[\alpha]_D^{26}$ 2.4 (*c* 0.008 in EtOH). δ_H (400 MHz, CD$_3$OD) 4.21 (d, *J* 5.4, 1H), 3.85–3.94 (m, 1H), 3.07–3.16 (m, 1H), 2.73–2.85 (m, 1H), 2.60–2.70 (m, 1H), 1.85–2.02 (m, 1H), 1.33 (d, *J* 6.6, 3H). δ_C (100 MHz, CD$_3$OD) δ_C 148.7, 129.0, 116.8, 55.6, 46.1, 25.3, 23.2, 15.7. *m/z* (HRMS) 196.1559 [M + H]$^+$; C$_9$H$_{18}$N$_5$ requires 196.1562.

(10R,10aS)-2-Amino-10-methyl-4,5,6,9,10,10a-hexahydrodiimidazo[1,5-a:4′,5′-c]azepine-8(3H)-one **10**

To a stirred solution of **9** (16.0 mg, 0.08 mmol) in dry DMF (3 mL) was added 1,1′-carbonyldiimidazole (16.0 mg, 0.09 mmol) and the reaction mixture heated at 100°C for 2 h under an inert atmosphere, after which solvent was removed under reduced pressure and the dark-brown residue obtained subjected to flash chromatography (silica; gradient 5 : 95–20 : 80 MeOH/DCM saturated with ammonia) affording imidazolidinone **10** (8 mg, 45 %) as a pale-yellow powder. $[\alpha]_D^{26}$ 13.4 (*c* 0.004 in EtOH). δ_H (600 MHz, [D6]DMSO) 6.38 (s, 1H), 4.97 (s, 2H), 3.98 (d, *J* 6.1, 1H), 3.91–3.86 (m, 1H), 3.70–3.65 (m, 1H), 2.71–2.65 (m, 1H), 2.57–2.51 (m, 1H), 2.48–2.42 (m, 1H), 1.81–1.75 (m, 1H), 1.58–1.50 (m, 1H), 1.23 (d, *J* 6.1, 3H). δ_C (100 MHz, CD$_3$OD) 162.8, 149.5, 132.4, 129.8, 64.2, 52.2, 44.1, 28.0, 24.9, 22.0. *m/z* (HRMS) 222.1347 [M + H]$^+$; C$_{10}$H$_{16}$N$_5$O requires 222.1355.

(10R,10aR)-2-Amino-10-methyl-4,5,6,9,10,10a-hexahydrodiimidazo[1,5-a:4′,5′-c]azepine-8(3H)-one **12**

To a stirred solution of **11** (12 mg, 0.06 mmol) in dry DMF (3 mL) was added 1,1′-carbonyldiimidazole (11.0 mg, 0.07 mmol) and the reaction mixture heated at 100°C for 2 h under an inert atmosphere, after which solvent was removed under reduced pressure and the dark-brown residue obtained subjected to flash chromatography (silica; gradient 5 : 95–20 : 80 MeOH/DCM saturated with ammonia) affording imidazolidinone **12** (7 mg, 53 %) as a pale-yellow powder. $[\alpha]_D^{26}$ 5.2 (*c* 0.003 in EtOH). δ_H (600 MHz, [D6]DMSO) 6.30 (s, 1H), 4.94 (s, 2H), 4.45 (d, *J* 7.1, 1H), 3.92–3.82 (m, 1H), 3.68–3.59 (m, 1H), 2.37–2.65 (m, 3H), 1.92–1.81 (m, 1H), 1.59–1.48 (m, 1H), 0.84 (d, *J* 6.4, 3H). δ_C (obtained from HMBC and HSQC) (100 MHz, [D6]DMSO) 148.5, 59.9, 48.9, 40.6, 27.2, 23.2, 16.3. *m/z* (HRMS) 222.1354 [M + H]$^+$, C$_{10}$H$_{16}$N$_5$O requires 222.1355.

Supplementary Material

1D and 2D spectra are available on the Journal's website.

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