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ORGANOCATALYTIC APPROACH TO THE SYNTHESIS OF OPTICALLY ACTIVE 1,2,3-TRISUBSTITUTED AZETIDINES

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ABSTRACT

A concise approach towards trisubstituted optically active azetidines, including a study of the scope and limitations of the synthetic sequence, is reported. The synthesis comprises the L-proline organocatalyzed three component reaction between substituted benzaldehydes, anilines and an enolizable aldehyde, followed by the *in situ* reduction of the resulting β-aminoaldehydes to the corresponding β-aminoalcohols and final intramolecular cyclization of the latter by way of the intermediate tosylates.

Key words: chiral azetidines, enantioselective synthesis, organocatalysis, ring-closing reactions

INTRODUCTION

Nitrogen heterocycles are at the heart of many essential pharmaceuticals and physiologically-active natural products. The azetidines are four-membered nitrogen heterocycles of great interest for fundamental research and useful for practical applications. Much has been learned about the chemical reactivity of these heterocycles since the discovery that the 2-azetidinone ring is a key feature of the β-1actam antibiotics.[1]

These molecules constitute synthetic targets of interest because of their presence in natural products and synthetic intermediates, usefulness as tools in peptidomimetics and nucleic acid chemistry,[2a-e] for their potent biological and pharmaceutical activities[2f,g] and for their use as ligands in organic synthesis.

In fact, ligands with an azetidine moiety have been employed in various asymmetric catalytic processes, including reductions,[3a,b] diethylzinc additions,[3c-f] the Henry reaction,[3g] cycloadditions[3h] and cyclopropanations,[3i] with promissing results. In addition, C_2-symmetric bis(aziridines) have been used as bidentate ligands in transition metal catalyzed reactions.[4]

On the other hand, several natural products characterized by bearing an azetidine core have been isolated; among them, the naturally-ocurring α-aminoacid azetidine-2-carboxylic acid, a powerful proline antagonist in plant tissue cultures,[5] and some of its functionalized derivatives, such as the phytosiderophores nicotianamine[6a,b] and mugineic acid,[6c,d] and the structurally related 2''-nicotianamine, an angiotensin converting enzyme-inhibitor (Figure 1).[6e]

Another group of azetidine bearing natural products include the vioprolides, antifungal and cytotoxic peptolides, exemplified by vioprolide A,[7a] and the polyoxins, such as polyocin A, peptide nucleosides possibly involved in cell wall chitin biosynthesis.[7b,c] Additional representatives of natural azetidines are the

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cytotoxic and antibacterial penaresidines[8] and the related penazetidine A, an inhibitor of protein kinase C.[9] Interestingly, natural products such as gelsemoxonine and okaramine B carry fused polysubstituted azetidine moieties.[10]
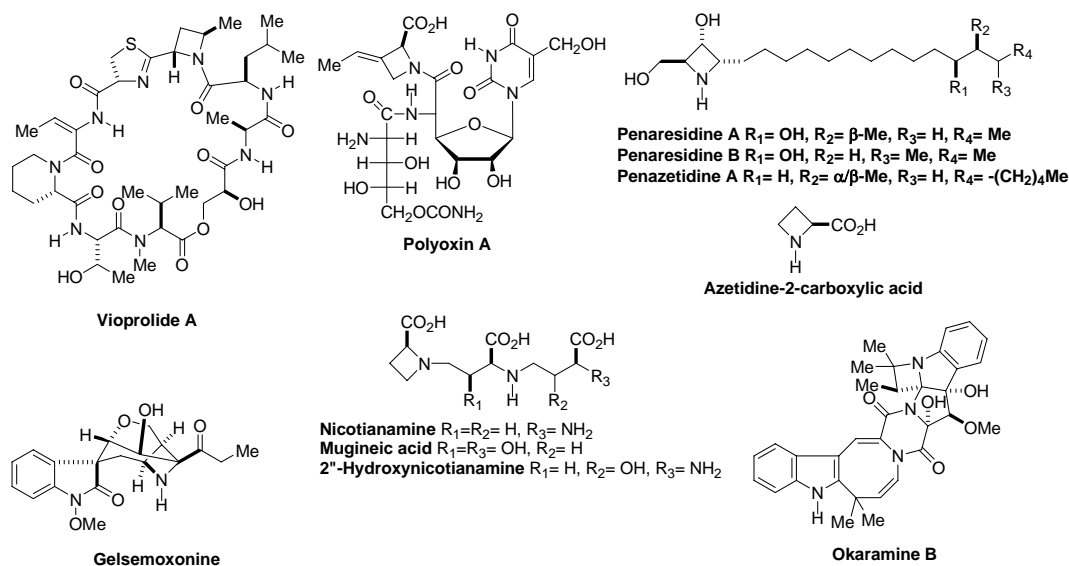

Figure 1. Chemical structures of natural products carrying an azetidine moiety.

The azetidine motif is also found in several synthetic bioactive compounds, including aggrecanase,[11a] thrombin[11b] and β-amyloid cleaving enzyme-1 inhibitors,[11c] as well as N-methyl-D-aspartate receptor[12a] and cholinergic channel modulators,[12b] antiviral agents[12c] and inducers of cytokine production.[12d]

Synthetic approaches towards optically active polysubstituted azetidines have been recently reviewed.[13] These include the cyclization of cyanomethyl-1,2-aminoalcohol derivatives (C_2-C_3 bond formation)[14a-c] and the cyclization of 1,3-aminoalcohols (C_2-N bond formation).[14d-g] Other alternatives are the direct cyclization between primary amines and optically pure 1,3-diol derivatives (C_2-N and C_4-N bond formation),[15a,b] the intramolecular cyclization of 3-amino-1,2-diols ($C_{2/4}$-N bond formation)[15c] and the electrophile-induced intramolecular cyclization of homoallylic amino vinylsilanes ($C_{2/4}$-N bond formation).[15d,e] The metal carbene N–H insertion of chiral α,α'-dialkyl-α-diazoketones ($C_{2/4}$-N bond formation),[16a] the photochemical ring closure of α-(N-methylamino) ketones (C_2-C_3 bond formation) prepared from enantiopure aminodiols[16b] and the deoxygenation of preformed enantiomerically pure β-lactams,[16c-e] have also been employed for that purpose.

However, in terms of synthetic approaches and applications, the azetidines have been comparatively less studied than their lower and higher homologous small-ring saturated single nitrogen heterocycles, the aziridines, pyrrolidines and piperidines. Several authors have pointed out the scarcity of general and efficient methods for the synthesis of enantiopure azetidines.[17] Furthermore, the low number of publications on optically active polysubstituted azetidines also reflects the need of new enantioselective approaches towards these heterocycles.[17b] Marinetti et al.[17c] conjectured that the reason for the lack of progress in the

development of the chemistry of optically active azetidines could be related to synthetic difficulties associated to the formation of the four-membered ring from acyclic derivatives; this is a disfavoured process compared to the analogous construction of sligthly larger and even smaller rings.

Therefore, herein we wish to report our results of the enantioseclective organocatalyzed synthesis of 1,2,3-trisubstituted azetidines employing a direct, tri-component one-pot cross-Mannich based synthesis of β-aminoaldehydes, followed by their *in situ* reduction to their corresponding alcohols and subsequent cyclization by treatment with tosyl chloride and Et₃N, under microwave irradiation.

RESULTS AND DISCUSSION

The Mannich reaction is one of the most important C-C bond-forming reactions for the production of nitrogenous molecules. The organocatalyzed chiral version of the reaction has recently received considerable attention as a source of structurally diverse optically active β-aminocarbonyl compounds (Mannich bases);[18] in this multicomponent process, an (usually aromatic and non-enolizable) aldehyde, an amine and an enolizable carbonyl component react with catalytic amounts of a suitable chiral amine, which forms a chiral enamino intermediate, able to attack the Schiff base obtained *in situ* by condensation of the aldehyde and the amine. Mannich bases have broad usefulness as synthetic building blocks, in the preparation of natural and biologically active products. Proline and proline derivatives have been utilized as highly stereoselective catalysts, in most of these enamine-catalyzed Mannich-type reactions.

Based on pevious work by the group of Hayashi,[19] in the initial experiments (Scheme 1) 4-nitrobenzaldehyde (**1**), propanal as a suitable enolizable aldehyde (**4**) and 3,4-dimethoxyaniline (**2**) were mixed with 20 mol% L-proline as chiral catalyst and subjected to reaction. Under these conditions, the use of NMP as solvent met with failure, while adding 4Å molecular sieves to a mixture of the benzaldehyde and the amine in order to promote pre-formation of the Schiff base (**3**), and reacting the latter at -20ºC with propanal provided only minor amounts of the expected product the β-aminoaldehyde intermediate **5**, which proved to be highly unstable to silica gel column chromatography.
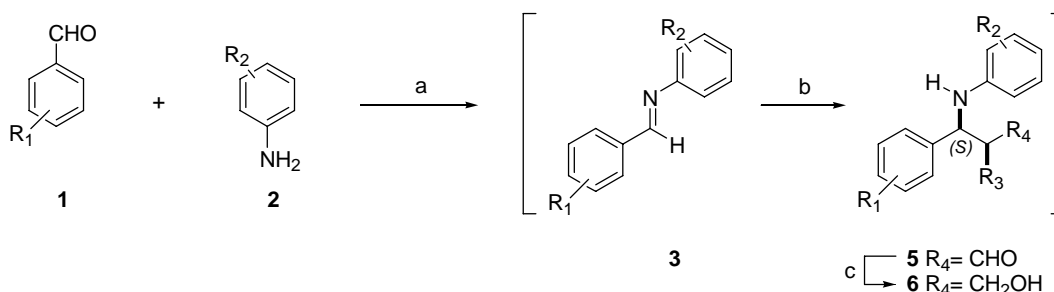

Scheme 1. *Reagents and conditions:* a) L-proline (10 mol%), NMP, MW; b) R₃CH₂CHO (**4**), NMP, -20ºC, 24 h; c) NaBH₄, MeOH, Et₂O, 0ºC, 1 h. Aldehyde **1**:aniline **2**:aldehyde **4**:L-Proline= 1.0:1.1:3.0:0.2. For the identity of R₁, R₂ and R₃, see Table 2.

Therefore, the reaction protocol was modified to include pre-formation of the Schiff base and to avoid isolation of the β-aminoaldehyde. The first modification, which avoided the use of molecular sieves, proved to be more efficient when carried out under microwave irradiation at 70ºC during 1 h than by submitting the mixture to conventional heating. Dropwise treatment of the Schiff base with three equivalents of propanal (**4**) furnished the expected β-aminoaldehyde **5**, which was reduced *in situ* with $NaBH_4$ in MeOH, furnishing the corresponding β-aminoalcohol **6**, which could be uneventfully purified in 62% overall yield.

It was also observed that the reaction solvent played a key role in the yield and outcome of the transformation. Employing anhydrous DMSO, 45% aminoalcohol was recovered, while a 1:1 mixture of DMSO and CH_2Cl_2 gave no useful products and a 2:1 $DMSO/CH_2Cl_2$ solvent furnished important amounts of aldol condensation products. Analogously, 50% yield of β-aminoalcohol was realized when the reaction was carried out in DMF, while a 1:1 mixture of DMF/CH_2Cl_2 yielded mainly the intermediate imine. Therefore, synthesis of the β-aminoalcohols **6** in the experiments to explore the scope and limitations of the sequence were carried out in NMP.

Table 1. Selection of the cyclizing agent.
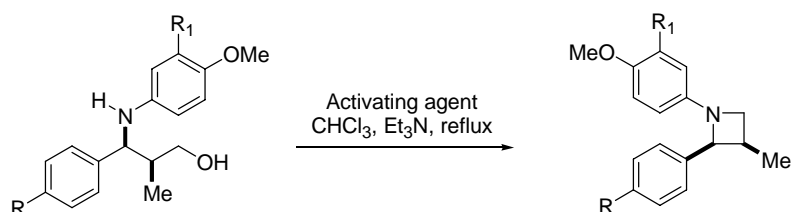
Run Nº	Aminoalcohol	Activating agent	Yield of azetidine (%)	ee of azetidine (%)
1	R= NO$_2$, R$_1$= H	ClCO$_2$Et	33	92
2		TsCl	94	92
3		BzCl	a	
4	R= NO$_2$, R$_1$= OMe	ClCO$_2$Et	27	97
5		TsCl	95	97
6		ClCO$_2$Et	6^b	97
7		TsCl	51^c	
8	R= H, R$_1$= OMe	ClCO$_2$Et	16	91
9		TsCl	69	91
10	R= Cl, R$_1$= OMe	TsCl	90	96
11		BzCl	a	
12		MsCl	55	96

[a]Formation of the benzoate was observed.
[b]Formation of the carbamate was observed (27%).
[c]Under conventional heating.

The amination of alcohols has been performed employing various strategies, which involve converting the carbinol into a suitable leaving group (Mitsunobu, Appel-type halogenation, formationof sulfonates, carbonates and other esters), followed by base-assisted displacement of the latter with the cyclizing nitrogen moiety, as the final step.[20]

In search of new and efficient conditions (Table 1), cyclization through formation of the benzoate ($PhCOCl$-Et_3N) followed by intramolecular displacement of the latter was attempted;[21] however, this resulted in an incomplete sequence, yielding a mixture of products which included the intermediate benzoate (runs 3 and 11). On the other hand, activation of the primary alcohol as the carbonate ($ClCO_2Et$, Et_3N) prior to intramolecular displacement gave several unseparable compounds and low yields of the expected products (runs 1 and 4).

Interestingly, Couty and coworkers[22] reported that chloroformates are able to open the azetidine ring. Finally, reaction with tosyl chloride and Et_3N under microwave irradiation resulted in smooth and clean cyclizations (entries 2, 5, 9 and 10), which successfully competed with the corresponding thermal conditions (entry 7) and with the related $MsCl$-Et_3N process (entry 12),[23] perhaps because in the latter case, the sulfene intermediates generated under the reaction conditions may undergo side reactions lowering product yields or demanding great excesses of the reagent.[24]

Once selected the most suitable cyclizing conditions, the scope and limitations of the synthetic protocol were studied with different benzaldehydes and anilines. It was observed that steric hindrance excerted a major effect on the outcome of the reaction. On the side of the aromatic aldehyde, while the transformation accepted compounds carrying electron withdrawing and electron releasing substituents, the presence of an *ortho* substituent yielded the intermediate imine **3**, which failed to undergo the Mannich reaction (entries 9, 11 and 12), except with the more activated aldehydes (entries 5 and 8), albeit at the expense of reduced yield in the case of the bromoaldehyde of entry 8; *meta*-substituted aldehydes reacted uneventfully (entries 6 and 10). On the other hand, the results of steric effects were more evident on the aniline side. The bulky 2-phenylaniline failed to react (entries 14 and 17), while reaction with α-naphthylamine and 2-methoxyaniline (entries 15 and 16) furnished the corresponding Schiff bases, which failed to further undergo the Mannich reaction with propanal. Finally, it was observed that the synthetic sequence accepts enolizable aldehydes other than propanal, such as phenylpropanal (entry 20).

The configurational assignment of the azetidines was deduced from their ^1H NMR data on the basis of the coupling constants between C_2 and C_3 of the heterocycles, which were obeserved to be between 7.2 and 8.5 Hz. The relative configuration was further confirmed employing NOE experiments. Interestingly, only the 2,3-*cis* diastereomers were obtained.

Yields were moderate for both main stages, the synthesis of the α-aminoalcohol and its cyclization, while enantiomeric excesses of the resulting products were mostly above 90%. A tendency to lower enantiomeric excess values was observed when electron releasing substituents were present in the benzaldehyde derived moiety (entries 8 and 10) of the α-aminoalcohol and/or the starting aniline carried electron withdrawing substituents (entry 18).

Table 2. Synthesis of 1,2,3-trisubstituted azetidines.
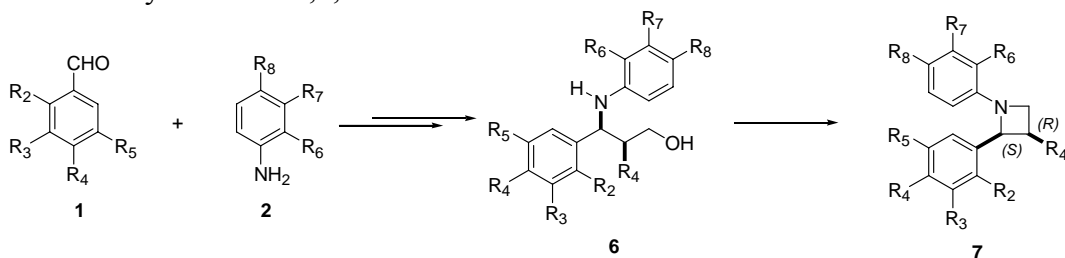
Run Nº	Aldehyde (1)	Aniline (2)	Yield of 6 (%)	Yield of 7 (%)	ee of 7 (%)	$[\alpha]_D$ CHCl$_3$
1	$R_2= R_3= R_4= R_5= H$	$R_6= H,$ $R_7= R_8= OMe$	41	69	91	-191.5 (c= 0.5)
2	$R_2= R_3= R_5= H,$ $R_4= Br$	$R_6= H,$ $R_7= R_8= OMe$	66	15	93	-156.3 (c= 0.2)
3	$R_2= R_3= R_5= H,$ $R_4= Me$	$R_6= H,$ $R_7= R_8= OMe$	52	67	95	-161.9 (c= 0.5)
4	$R_2= R_3= R_5= H,$ $R_4= NO_2$	$R_6= H,$ $R_7= R_8= OMe$	62	57	97	-207.4 (c= 1.0)
5	$R_2= R_3= OMe,$ $R_4= R_5= H$	$R_6= H,$ $R_7= R_8= OMe$	67	70	99	-219.8 (c= 0.5)
6	$R_2= R_4= R_5= H,$ $R_3= OBn$	$R_6= H,$ $R_7= R_8= OMe$	50	45	81	-192.9 (c= 0.32)
7	$R_2= R_3= R_5= H,$ $R_4= Cl$	$R_6= H,$ $R_7= R_8= OMe$	67	90	96	-218.9 (c= 1.1)
8	$R_2= Br, R_3= H,$ $R_4= R_5= OMe$	$R_6= H,$ $R_7= R_8= OMe$	7	36	86	-129.5 (c= 0.12)
9	$R_2= Cl,$ $R_3= R_4= R_5= H$	$R_6= H,$ $R_7= R_8= OMe$	- Imine			
10	$R_2= H,$ $R_3= R_4= R_5= OMe$	$R_6= H,$ $R_7= R_8= OMe$	33	62	68	-143.7 (c= 0.2)
11	$R_2= CF_3,$ $R_3= R_4= R_5= H$	$R_6= H,$ $R_7= R_8= OMe$	- Imine			
12	$R_2= CF_3,$ $R_3= R_4= R_5= H$	$R_6= R_7= H,$ $R_8= OMe$	- Imine			
13	$R_2= R_3= R_5= H,$ $R_4= Cl$	$R_6= R_7= H,$ $R_8= OMe$	35	69	92	-168.7 (c= 1.2)
14	$R_2= R_3= R_5= H,$ $R_4= NO_2$	$R_6= Ph,$ $R_7= R_8= H$	NR			
15	$R_2= R_3= R_5= H,$ $R_4= NO_2$	α-Naphthylamine	Imine			
16	$R_2= R_3= R_5= H,$ $R_4= OMe$	$R_7= R_8= H,$ $R_6= OMe$	Imine			
17	$R_2= R_3= R_5= H,$ $R_4= OMe$	$R_6= Ph,$ $R_7= R_8= H$	NR			
18	$R_2= R_3= R_5= H,$ $R_4= OMe$	$R_6= R_7= H,$ $R_8= CO_2Et$	21	34	83	-174.3 (c= 0.3)
19	$R_2= R_3= R_5= H,$ $R_4= NO_2$	$R_6= R_7= H,$ $R_8= OMe$	62	94	93	-223.4 (c= 1.1)
20	$R_2= R_3= R_5= H,$ $R_4= NO_2$	$R_6= R_7= H,$ $R_8= OMe$	56[a]	36	97	-196.7 (c= 0.4)

[a]Reaction with 3-phenylpropanal.

EXPERIMENTAL

FT-IR spectra were determined employing a Perkin One spectrophotometer as thin films held between NaCl cells. The ^{1}H and ^{13}C-NMR spectra were acquired in CDCl$_3$ in a Bruker Avance spectrometer (300.13 and 75.48 MHz for ^{1}H and ^{13}C, respectively), with tetramethylsilane (TMS) as internal standard. The chemical shifts are reported in ppm downfield from TMS and coupling constants (J) are expressed in Hertz. DEPT 135 and DEPT 90 experiments aided the interpretation and assignment of the fully decoupled ^{13}C NMR spectra. In special cases, NOE and 2D-NMR experiments (COSY, HMBC and HMQC) were also employed.

Microwave-assisted reactions were performed in a CEM Discover microwave oven. Optical rotation data were obtained with a Jasco DIP 1000 photopolarimeter, employing a 1.0 dm cell. HPLC enantiomeric excess determinations were carried out with a Varian Prostar 210 liquid chromatograph equipped with two pumps, a manual injector fitted with a 20 μL loop and a Varian Prostar 325 variable dual-wavelength UV-Vis detector, set at 254 nm. The chromatographic separations were performed with a 250 × 4.6 mm Chiralcel OD column, employing a 90:10 mixture of hexane:2-propanol as mobile phase, delivered at 1 mL/min. The chromatograms were recorded and analyzed employing Varian Galaxie v. 6.0 software.

The reactions were carried out under dry nitrogen or argon atmosphere, employing oven-dried glassware. Anhydrous DMF was obtained by heating the PA grade product over BaO for 4 h, followed by distillation under reduced pressure; anhydrous Et$_3$N was prepared by atmospheric pressure distillation after refluxing the reagent 4 h over CaH$_2$; absolute MeOH was accessed by refluxing the solvent over clean magnesium turnings and distilling from the resulting magnesium ethoxide; anhydrous CH$_2$Cl$_2$ and CHCl$_3$ were prepared by a 4 h reflux of the solvent over P$_2$O$_5$ followed by distillation; anhydrous solvents were stored in dry Young ampoules. All other reagents were acquired from Aldrich Chemical Co., and used as received.

All new compounds gave single spots on TLC plates run in different hexane-EtOAc solvent systems. Chromatographic spots were detected by exposure to UV light (254 nm), followed by spraying with ethanolic *p*-anisaldehyde/ sulfuric acid reagent and careful heating of the plates for improving selectivity. Flash column chromatographic purifications were carried out employing silica gel 60 H. Elution was carried out with hexane-EtOAc mixtures, under positive pressure and employing stepwise gradient of solvent polarity techniques.

Typical experimental procedure for the synthesis of amino alcohols: A solution of the benzaldehyde (1.0 equiv.), the aniline (1.1 equiv.) and L-proline (0.2 equiv.) in NMP (2 mL) was submitted to microwave irradiation at 70ºC for 30 min.; then, the mixture was cooled to -20ºC and treated dropwise with a solution of propanal (3.0 equiv.) in NMP (1.5 mL). Stirring continued for 20 h at this temperature, when a 1:1 mixture of MeOH and Et$_2$O (4 mL) was added, the mixture was placed at 0ºC, and treated with NaBH$_4$ (3.0 equiv.). After 60 min., the reaction was diluted with phosphate buffer pH= 7.0 (10 mL) and the organic

materials were extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over Na_2SO_4 and, after removal of the volatile materials under reduced pressure, the remaining oily residue was chromatographed.

Typical experimental procedure for the synthesis of azetidines: DMAP (cat.), Et_3N (4 equiv.) and TsCl (2.5 equiv.) were successively added to a solution of the amino alcohol (1 equiv.) in $CHCl_3$ (2 mL) and the mixture was subjet to microwave irradiation at 70ºC for 1 h. Then, brine (10 mL) was added and the organic materials were extracted with EtOAc (4 × 20 mL). The organic phases were then combined and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was submitted to chromatography.

(2*S*,3*R*)-1-(3,4-Dimethoxyphenyl)- 3-methyl-2- (4-nitrophenyl)azetidine: IR (film, ν): 2957, 2850, 1598, 1465, 1452, 1343, 1239, 1221, 1140, 1027, 849, 823 and 745 cm^{-1}; ^{1}H NMR δ: 0.89 (d, *J*= 7.3, 3H), 2.95 (ddd, *J*=3.0, 7.3 and 8.3, 1H), 3.61 (dd, *J*= 3.0 and 6.4, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.92 (dd *J*= 6.4 and 7.3, 1H), 5.07 (d, *J*= 8.3, 1H), 5.86 (dd, *J*= 2.6 and 8.6, 1H), 6.03 (d, *J*= 2.6, 1H), 6.71 (d, *J*= 8.6, 1H), 7.52 (d, *J*= 8.7, 2H) and 8.23 (d, *J*= 8.7, 2H); ^{13}C NMR δ: 16.2, 29.9, 55.8, 56.7, 57.0, 68.6, 97.7, 103.5, 112.9, 123.6 (2C), 127.5 (2C), 142.2, 146.2, 147.2, 147.5 and 149.9.

(2*S*,3*R*)-2-(4-Chlorophenyl)- 1-(4-methoxyphenyl)- 3-methylazetidine: IR (film, ν): 2956, 2846, 1615, 1486, 1451, 1337, 1297, 1245, 1179, 1087, 841 and 785 cm^{-1}; ^{1}H NMR δ: 0.89 (d, *J*= 7.3, 3H), 2.84 (ddd, *J*= 2.8, 7.3 and 8.6, 1H), 3.55 (dd, *J*= 2.8 and 6.7, 1H), 3.72 (s, 3H), 3.83 (dd, *J*= 6.7 and 7.3, 1H), 4.85 (d, *J*= 8.6, 1H), 6.28 (d, *J*= 8.9, 2H), 6.67(d, *J*= 8.9, 2H) and 7.17-7.30 (m, 4H); ^{13}C NMR δ: 16.1, 30.0, 55.8, 56.9, 68.8, 113.3 (2C), 114.6 (2C), 128.2 (2C), 128.4 (2C), 132.7, 138.3, 146.2 and 152.5.

(2*S*,3*R*)-1-(4-Methoxyphenyl)- 3-methyl-2- (4-nitrophenyl) azetidine: IR (film, ν): 2960, 1605, 1513, 1462, 1346, 1243, 1233, 1179, 1109, 1037 and 819 cm^{-1}; ^{1}H NMR δ: 1.00 (d, *J*= 6.6, 3H), 2.21 (ddd, *J*=3.2, 6.6 and 8.0, 1H), 3.31 (dd, *J*= 3.2 and 5.3, 1H), 3.54-3.67 (m, 1H), 3.58 (s, 3H), 4.62 (bs, 1H), 6.40 (bd, *J*= 9.0, 2H), 6.61 (d, *J*= 9.0, 2H), 7.44 (d, *J*= 8.7, 2H) and 8.11 (d, *J*= 8.7, 2H); ^{13}C NMR δ: 13.2, 42.4, 47.9, 55.8, 77.3, 114.9 (2C), 115.0 (2C), 123.4 (2C), 127.5 (2C), 140.2, 147.2, 150.0 and 152.7.

(2*S*,3*R*)-2-(2,3-Dimethoxyphenyl)- 1-(3,4-dimethoxyphenyl)- 3-methyl azetidine: IR (film, ν): 2958, 2834, 1612, 1586, 1514, 1480, 1345, 1276, 1239, 1139, 1072, 1028, 1010 822, 783 and 755 cm^{-1}; ^{1}H NMR δ: 0.85 (d, *J*= 7.4, 3H), 2.84 (ddt, *J*= 2.8, 7.4 and 7.5, 1H), 3.48 (dd, *J*= 2.8 and 7.5, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 3.76-3.80 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 5.16 (d, *J*= 8.5, 1H), 5.86 (dd, *J*= 2.6 and 8.5, 1H), 6.05 (d, *J*= 2.6, 1H), 6.62 (d, *J*= 8.2, 1H), 6.79 (dd, *J*= 1.8 and 8.2, 1H) and 9.93-7.04 (m, 2H); ^{13}C NMR δ: 16.2, 29.7, 55.7 (2C), 56.7, 57.4, 60.4, 65.5, 97.8, 103.6, 111.2, 113.0, 120.6, 123.7, 133.3, 141.7, 145.5, 147.5, 149.8 and 152.2.

(2*S*,3*R*)-1-(3,4-Dimethoxyphenyl)- 3-methyl- 2-phenylazetidine: IR (film, ν): 2956, 2925, 2935, 1613, 1586, 1514, 1452, 1352, 1239, 1138, 1028, 823, 743 and 702 cm⁻¹; ¹H NMR δ: 0.83 (d, *J*= 7.2, 3H), 2.79 (ddd, *J*= 2.8, 7.2 and 7.9, 1H), 3.49 (dd, *J*= 2.8 and 6.9, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.80 (dd, *J*= 6.9 and 7.2, 1H), 4.93 (d, *J*= 7.9, 1H), 5.84 (dd, *J*= 2.6 and 8.6, 1H), 6.00 (d, *J*= 2.6, 1H), 6.63 (d, *J*= 8.6, 1H) and 7.19-7.28 (m, 5H); ¹³C NMR δ: 16.2, 35.5, 53.6, 55.8, 56.7, 56.8, 79.3, 100.5, 110.0, 115.5, 126.8 (2C), 127.9 (2C), 137.5, 140.3, 145.0 and 150.9.

(2*S*,3*R*)-2-(4-Bromophenyl)- 1-(3,4-dimethoxyphenyl)- 3-methylazetidine: IR (film, ν): 2932, 1607, 1578, 1516, 1490, 1451, 1403, 1262, 1213, 1172, 1041, 1010, 828, 806 and 755 cm⁻¹; ¹H NMR δ: 0.89 (d, *J*= 6.8, 3H), 2.05-2.11 (m, 1H), 3.17 (dd, *J*= 5.1 and 7.7, 1H), 3.31 (dd, *J*= 6.8 and 7.7, 1H), 3.67 (s, 3H), 3.77 (s, 3H), 4.55 (d, *J*= 7.2, 1H), 6.02 (s, 1H), 6.99-7.07 (m, 4H) and 7.35 (d, *J*= 8.5, 2H); ¹³C NMR δ: 12.9, 42.5, 47.9, 55.6, 56.7, 58.2, 96.8, 120.9, 126.4, 128.5, 129.8, 131.6, 133.7, 135.5, 140.7, 140.9, 143.6 and 151.9.

(2*S*,3*R*)-1-(3,4-Dimethoxyphenyl)- 3-methyl-2- (4-methylphenyl)azetidine: IR (film, ν): 2925, 2854, 1712, 1597, 1514, 1453, 1380, 1234, 1164, 1027, 740 and 698 cm⁻¹; ¹H NMR δ: 0.91 (d, *J*= 7.3, 3H), 2.35 (s, 3H), 2.83 (ddd, *J*= 2.5, 7.5 and 7.7, 1H), 3.55 (dd, *J*= 2.5 and 6.6, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 3.85 (dd, *J*= 6.6 and 7.5, 1H), 4.97 (d, *J*= 7.7, 1H), 5.92 (dd, *J*= 2.5 and 8.6, 1H), 6.06 (d, *J*= 2.5, 1H), 6.69 (d, *J*= 8.6, 1H), 7.15 (d, *J*= 8.0, 2H) and 7.22 (d, *J*= 8.0, 2H); ¹³C NMR δ: 16.1, 21.2, 29.9, 55.7, 56.7, 56.9, 69.4, 97.8, 103.5, 113.0, 126.7 (2C), 128.9 (2C), 136.4, 136.5, 141.7, 147.2 and 149.8.

(2*S*,3*R*)-2-[3-(Benzyloxy)phenyl]- 1-(3,4-dimethoxyphenyl)- 3-methyl azetidine: IR (film, ν): 2924, 2851, 1737, 1584, 1513, 1453, 1345, 1239, 1151027, 788 and 697 cm⁻¹; ¹H NMR δ: 0.91 (d, *J*= 7.4, 3H), 2.85 (ddd, *J*= 2.8, 7.4 and 8.0, 1H), 3.55 (dd, *J*= 2.8 and 6.7, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 3.85 (dd, *J*= 6.7 and 7.4, 1H), 4.96 (d, *J*= 8.0, 1H), 5.06 (bs, 2H), 5.93 (dd, *J*= 2.6 and 8.5, 1H), 6.05 (d, *J*= 2.6, 1H), 6.70 (d, *J*= 8.5, 1H), 6.87-6.93 (m, 2H), 7.00 (bs, 1H) and 7.24-7.34 (m, 6H); ¹³C NMR δ: 16.0, 29.7, 55.7, 56.7, 58.0, 69.5, 69.93, 97.8, 103.6, 113.0, 113.2, 113.5, 119.4, 127.6 (2C), 127.9, 128.5 (2C), 129.2, 137.0, 141.5, 141.7, 147.1, 149.8 and 158.9.

(2*S*,3*R*)-2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-3-methylazetidine: IR (film, ν): 2958, 2928, 2849, 1613, 1514, 1452, 1341, 1239, 1139, 1089, 1027, 822, 787 and 714 cm⁻¹; ¹H NMR δ: 0.91 (d, *J*= 7.3, 3H), 2.85 (ddt, *J*= 2.8, 7.7 and 7.9, 1H), 3.55 (dd, *J*= 2.8 and 6.9, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 3.86 (dd, *J*= 6.9 and 7.7, 1H), 4.96 (d, *J*= 7.9, 1H), 5.89 (dd, *J*= 2.6 and 8.7, 1H), 6.03 (d, *J*= 2.6 and 8.7, 1H), 6.70 (d, *J*= 8.7, 1H), 7.26-7.34 (m, 4H); ¹³C NMR δ: 16.1, 55.7, 56.7, 56.9, 68.8, 97.7, 103.5, 113.0, 128.1 (2C), 128.4 (2C), 129.6, 132.7, 138.2, 141.9, 146.8 and 149.9.

(2*S*,3*R*)-2-(2-Bromo- 4,5-dimethoxyphenyl)-1- (3,4-dimethoxyphenyl)-3-methylazetidine: IR (film, ν): 2958, 2849, 1686, 1501, 1140, 1349, 1209, 1028,

790 and 749 cm^{-1}; ^{1}H NMR δ: 0.92 (d, J= 7.3, 3H), 3.00 (ddd, J= 2.6, 7.3 and 7.8, 1H), 3.56 (dd, J= 2.6 and 6.4, 1H), 3.74 (s, 3H), 3.77 (s, 6H), 3.83 (dd, J= 6.4 and 7.3, 1H), 3.88 (s, 3H), 5.04 (d, J= 7.8, 1H), 5.91 (dd, J= 2.4 and 8.5, 1H), 6.05 (d, J= 2.4, 1H), 6.69 (d, J= 8.5, 1H), 7.02 (s, 1H) and 7.06 (s, 1H); ^{13}C NMR δ: 16.0, 29.1, 55.8, 56.2 (2C), 56.6, 56.9, 69.5, 97.9, 103.8, 111.2, 112.2, 112.9, 115.1, 131.0, 142.0, 147.1, 148.4 (2C) and 149.7.

(2S,3R)-2-(3,4,5-Trimethoxyphenyl)- 1-(3,4-dimethoxyphenyl)- 3-methyl azetidine: IR (film, ν): 2955, 2849, 1680, 1588, 1501, 1140, 1349, 1209, 1033 and 795 cm^{-1}; ^{1}H NMR δ: 0.95 (d, J= 7.7, 3H), 2.81 (ddt, J= 2.9, 7.0 and 8.2, 1H), 3.54 (dd, J= 2.9 and 6.6, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.85 (dd, J= 6.6 and 7.0), 3.87 (s, 3H), 4.89 (d, J= 8.2, 1H), 5.96 (dd, J= 2.6 and 8.7, 1H), 6.08 (d, J= 2.6, 1H), 6.57 (s, 2H), 6.72 (d, J= 8.7, 1H); ^{13}C NMR δ: 15.9, 30.1, 55.8, 56.2 (2C), 56.7, 56.9, 60.9, 70.0, 98.0, 103.5 (2C), 103.8, 112.9, 135.5, 136.7, 141.9, 147.3, 149.7 and 153.2 (2C).

(2S,3R)-Ethyl 4-[2-(4-methoxyphenyl)- 3-methylazetidin-1-yl]benzoate: IR (film, ν): 2956, 2925, 2854, 1712, 1597, 1514, 1453, 1380, 1234, 1164, 1027, 740 and 698 cm^{-1}; ^{1}H NMR δ: 0.87 (d, J= 7.2, 3H), 1.31 (t, J= 7.5, 3H), 2.89-3.05 (m, 1H), 3.64 (dd, J= 3.9 and 7.4, 1H), 3.82 (s, 3H), 4.02 (dd, J= 7.4 and 9.5, 1H), 4.29 (q, J= 7.5, 2H), 5.17 (d, J= 8.5, 1H), 6.33 (d, J= 8.8, 2H), 6.89 (d, J= 8.8, 2H), 7.19 (d, J= 8.8, 2H) and 7.82 (d, J= 8.8, 2H). ^{13}C NMR δ: 14.4, 16.0, 30.1, 49.4, 55.3, 56.4, 68.7, 111.0 (2C), 113.8 (2C), 118.8, 127.9 (2C), 129.7 (2C), 130.9, 133.0, 158.9 and 167.0.

(2S,3R)-3-Benzyl-1-(4-methoxy-phenyl)- 2-(4-nitro-phenyl)azetidine: IR (film, ν): 2958, 2849, 1613, 1587, 1514, 1452, 1341, 1239, 1027, 822, 787 and 714 cm^{-1}; ^{1}H NMR δ: 2.55 (t, J=7.3, 2H), 2.77-2.87 (m, 1H), 3.46 (t, J= 7.3, 1H), 3.64 (dd, J= 3.2 and 7.3, 1H), 3.73 (s, 3H), 3.99-4.04 (m, 1H), 6.46-6.49 (m, 2H), 6.77-6.81 (m, 2H) and 7.13-7.34 (m, 9H); ^{13}C NMR δ: 32.7, 32.9, 55.7, 55.8, 56.2, 114.6, 126.0, 128.3, 128.4 (3C), 128.5 (5C), 128.8 (2C), 139.7, 140.1, 141.9, 146.9, and 152.6.

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