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Synthesis and evaluation of novel azetidine analogs as potent inhibitors of vesicular [^{3}H]dopamine uptake

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ABSTRACT

Lobelane analogs that incorporate a central piperidine or pyrrolidine moiety have previously been reported by our group as potent inhibitors of VMAT2 function. Further central ring size reduction of the piperidine moiety in lobelane to a four-membered heterocyclic ring has been carried out in the current study to afford novel *cis*-and *trans*-azetidine analogs. These azetidine analogs (**15a–15c** and **22a–22c**) potently inhibited [^{3}H]dopamine (DA) uptake into isolated synaptic vesicles ($K_i \leqslant 66$ nM). The *cis*-4-methoxy analog **22b** was the most potent inhibitor ($K_i = 24$ nM), and was twofold more potent that either lobelane (**2a**, $K_i = 45$ nM) or norlobelane (**2b**, $K_i = 43$ nM). The *trans*-methylenedioxy analog, **15c** ($K_i = 31$ nM), was equipotent with the *cis*-analog, **22b**, in this assay. Thus, *cis*- and *trans*-azetidine analogs **22b** and **15c** represent potential leads in the discovery of new clinical candidates for the treatment of methamphetamine abuse.

1. Introduction

Methamphetamine (METH) is an addictive psychostimulant drug and its abuse has been steadily rising throughout the last decade to become an escalating worldwide problem. Chronic METH abuse may cause neural damage, which can result in harmful effects on cognitive processes, such as attention and memory. Although there are serious consequences resulting from METH abuse, there are no FDA-approved pharmacological agents available to treat METH addiction.

Psychostimulant abuse is primarily thought to result from alterations in the central dopaminergic system. METH interacts with the vesicular monoamine transporter-2 (VMAT2), promoting vesicular dopamine (DA) release into the cytosol, and also inhibiting monoamine oxidase, both of which result in an increase in cytosolic concentrations of DA. METH also reverses the DA transporter (DAT) to afford elevated synaptic DA concentrations, which is thought to be associated with its abuse liability. Importantly, research has shown that lobeline (Fig. 1), the principal alkaloid in *Lobelia inflata*, potently inhibits [^{3}H]DA uptake into synaptic vesicles, inhibits METH-evoked DA release from rat striatal slices, and attenuates METH-induced behavioral effects in rats.[1–3] However, lobeline is a relatively nonselective drug, and has been shown to interact with several different CNS targets, including $\alpha4\beta2^*$, $\alpha7^*$ and $\alpha6\beta2^*$ containing nicotinic acetylcholine receptors (nAChRs) as well as DAT.

Development of selective, high affinity VMAT2 inhibitors will allow us to test the hypothesis that selective inhibition of VMAT2 function decreases METH reward. Preliminary structure–activity relationship (SAR) studies aimed at selectively targeting VMAT2 initially identified *N*-methyl-2,6-di-(*cis*-phenylethyl)piperidine (lobelane) (Fig. 1, **2a**),[4] a chemically defunctionalized analog of lobeline, as a more potent and selective inhibitor of vesicular DA uptake. Lobelane has negligible affinity for $\alpha4\beta2^*$, $\alpha7^*$ and $\alpha6\beta2^*$ containing nAChRs, and has improved affinity for the [^{3}H]dihydrotetrabenazine binding site on VMAT2compared to lobeline. Preliminary SAR studies with lobelane analogs (Fig. 1) revealed that

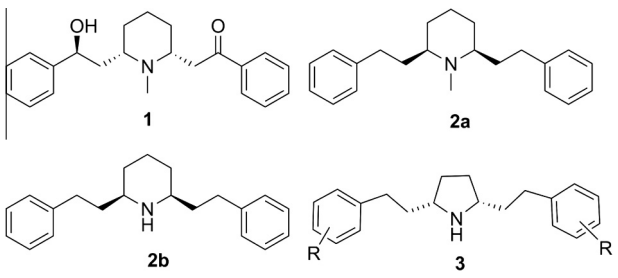

Figure 1. Molecular structures of lobeline (**1**), lobelane (**2a**), norlobelane (**2b**), and pyrrolidineanalogs of norlobelane (**3**).

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aromatic substituted analogs exhibited improved affinity for VMAT2, and also lacked affinity for α4β2*and α7* nicotinic acetylcholine receptors. However, such analogs suffer from poor drug likeness properties, including poor water-solubility. Other SAR studies also indicated that removal of the *N*-methyl substituent in lobelane (Fig. 1, **2a**) to afford norlobelane (Fig. 1, **2b**), did not significantly affect affinity for VMAT2, suggesting that the presence of the *N*-methyl group is not a critical structural requirement for interaction with VMAT2.[5] Based on these observations, a series of pyrrolidino analogs of norlobelane (Fig. 1, **3**) were synthesized and evaluated asVMAT2 inhibitors.[6–8] The results indicated that pyrrolidinonorlobelane analogs were potent inhibitors of vesicular DA uptake.

In order to broaden the scope of the above SAR study, we now have synthesized a series of novel *cis*- and *trans*-azetidine derivatives (**15a**–**15c** and **22a**–**22c**) to assess further the effect of heterocyclic ring size reduction in norlobelane (**2b**). General synthetic approaches to azetidine derivatives have been reported previously.[9–12] In this communication, we report on a highly efficient synthetic route for the preparation of a series of novel *cis*- and *trans*-1,4-disubstituted azetidine derivatives that are structurally related to norlobelane (**2b**). This synthetic route involves a critical Wittig reaction and a selective double bond reduction. The azetidine derivatives obtained were evaluated for their ability to inhibit the uptake of [^{3}H]DA into isolated synaptic vesicles from rat brain.

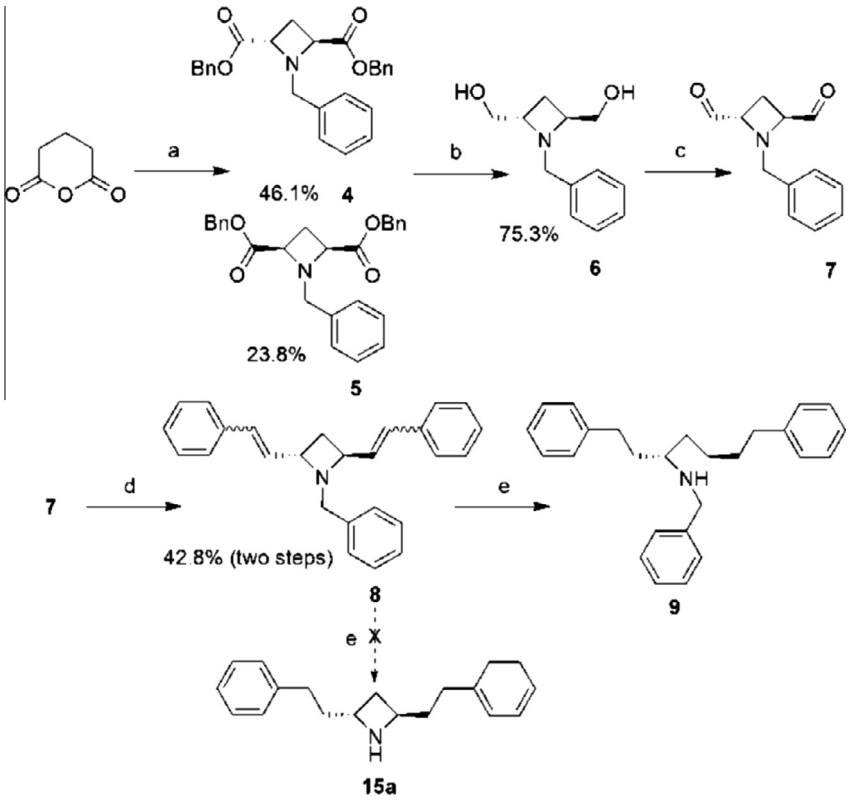
2. Results and discussion

2.1. Chemistry

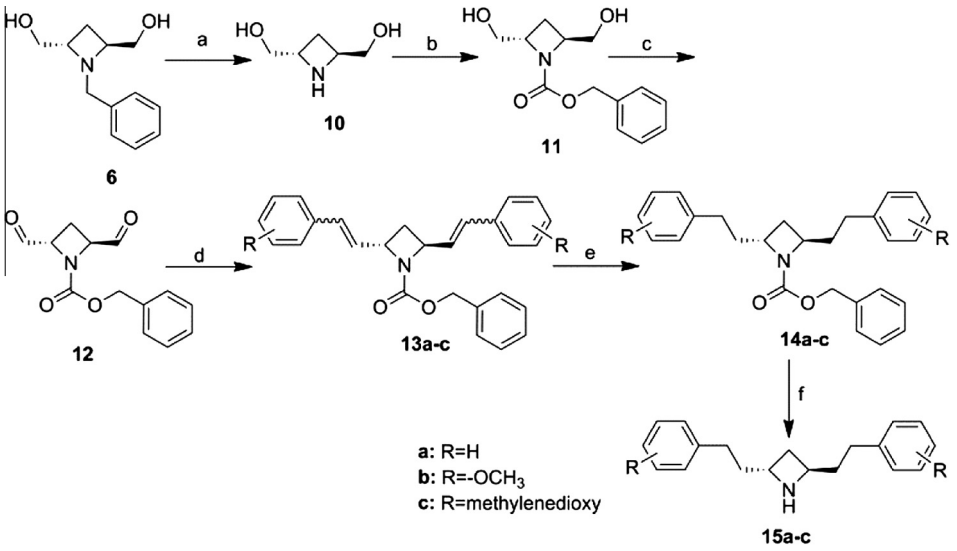
Our initial strategy for the synthesis of azetidine analogs of norlobelane are summarized in Scheme 1. Isomers **4** and **5** were prepared utilizing literature procedures, that is, Baldwin's adaptation of Cromwell's original azetidine synthesis,[13] which involved a four-step reaction sequence. Initially, bromination of glutaric anhydride afforded α,α′-dibromoglutaric anhydride, which was then converted to its diester with benzyl alcohol in the presence of oxalyl chloride in DMF. Subsequent reaction of the benzyl diester with 3 equiv of benzylamine in DMF at 80 °C afforded a mixture of the *trans*- and *cis*-azetidine isomers **4** and **5**, in a 2:1 ratio. Separation and treatment of the (±)-*trans*-isomer **4** with $NaBH_4$ afforded alcohol **6** in 75% yield. When compound **6** was submitted to Dess–Martin oxidation, a complex mixture was obtained and significant decomposition occurred during silica gel column chromatography clean-up; consequently the desired (±)-dialdehyde **7** was not obtained. Based on these findings, compound **6** was subjected to Swern oxidation and the resulting (±)-dialdehyde **7** used directly in a Wittig reaction with benzyl triphenyl phosphonium bromide. After reaction work-up and product purification, the key intermediate **8** was obtained in 42.8% over two steps from **6**. We attempted to effect hydrogenation of the alkene moieties in **8** with simultaneous hydrogenolysis of the *N*-benzyl group.

However, when compound **8** was submitted to hydrogenation with 20% $Pd(OH)_2$, the major product obtained was the ring opened derivative **9**, along with other unidentified by-products. As a result of this failure, we attempted to overcome this difficulty by utilizing sequential steps for the reduction of the double bonds followed by the removal the *N*-benzyl protecting group, respectively, using $NaBH_4$, $CuCl_2/NaBH_4$[6]and then Wilkinson's reagent.[14] Unfortunately, none of the desired product, **15a**, was obtained utilizing this strategy.

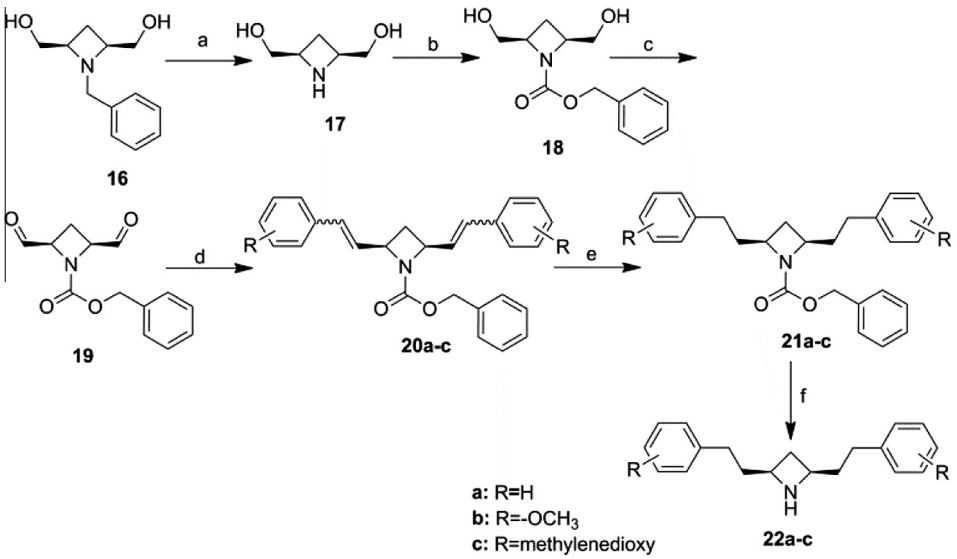
In view of the above problems, we sought an alternative route to the target azetidine derivative **15a**. Thus, instead of utilizing an *N*-benzyl protecting group, the Cbz moiety was used to protect the *N*-atom of **10** after removal of the *N*-benzyl group from **6** with 20% $H_2/Pd(OH)_2$/MeOH(Scheme 2). Treatment of compound **10**



Scheme 1. Reagents and conditions: (a) Ref. 13, four steps; (b) $NaBH_4$, THF/EtOH (3:1), rt; (c) oxalyl chloride, DMSO, TEA, CH_2Cl_2, −78 °C → rt; (d) $C_6H_5CH_2P(C_6H_5)_3Br$, *n*-BuLi, THF, −78 °C → rt; (e) $Pd(OH)_2$, MeOH, H_2, rt.



Scheme 2. Reagents and conditions: (a) 20% $Pd(OH)_2$, MeOH, rt; (b) CbzCl, DIPEA, THF; (c) Swern oxidation,[13] −78 °C → 0 °C; (d) simple and substituted Ph-$CH_2P(C_6H_5)_3Br$, *tert*-BuOK, THF, rt; (e) Wilkinson's reagent, THF/*tert*-BuOH (1:1), 55 °C, H_2; (f) Pd/C, H_2, rt.



Scheme 3. Reagents and conditions: (a) 20% $Pd(OH)_2$, MeOH, rt; (b) CbzCl, DIPEA, THF; (c) Swern oxidation,[13] −78 °C → 0 °C; (d) simple and substituted Ph-$CH_2P(C_6H_5)_3Br$, *tert*-BuOK, THF, rt; (e) Wilkinson's reagent, THF/*tert*-BuOH (1:1), 55 °C, H_2; (f) Pd/C, H_2, rt.

with CbzCl/DIPEA in THF afforded the *N*-CBz protected analogue **11** in 83% yield from **6**. Swern oxidation of alcohol **11**, followed by in situ Wittig reaction with the appropriate aromatic substituted benzyltriphenylphosphonium bromide afforded the unsaturated esters **13a**–**13c** in 64–69% overall yield from **11**. Note, that when *n*-BuLi was used as a base in the Wittig reaction of **12** with benzyltriphenylphosphonium bromide, the yield of **13a** from **11** was only 6%. When compound **13a** was hydrogenated over Pd/C or $Pd(OH)_2$ an unidentified mixture resulted, and the target compound **15a** was not obtained. Attempts failed at initial removal of the *N*-Cbz group of compound **13a** with 6 M HCl prior to hydrogenation. Interestingly, when compound **13a** was treated with $CuCl/NaBH_4$, compound **14a** was obtained, although the yield was only 40%. However, when compounds **13a**–**13c** were each treated with Wilkinson's reagent, intermediates **14a**–**14c** were obtained in 95–98% yield. With the key intermediates **14a**–**14c** in hand, the target compounds **15a**–**15c** were obtained through hydrogenation over 10% Pd/C in 90–93% yield.

When the above procedure was utilized for the synthesis of the *cis*-1,4-disubstituted azetidine analogs from *cis*-intermediate **5**, the target compounds **22a**–**22c** were obtained in comparable yields to the *trans*-isomers, **15a**–**15c**.The *cis*-aromatic substituted azetidine analogs **22a**–**22c** were prepared as described above utilizing the appropriate aromatic substituted benzyltriphenylphosphonium bromide and the cis-*N*-benzyloxycarbonyl-1,4-diformylazetidine isomer **19** (Scheme 3).

The above azetidine analogs were submitted for pharmacological evaluation as their water-soluble hydrochloride salts for their ability to inhibit the uptake of [^{3}H]DA into isolated synaptic vesicles from rat brain. The inhibition constants (K_i) obtained are listed in Table 1. The water-solubilities of the hydrochloride salts of the azetidine analogs were generally slightly improved compared to

Table 1
Inhibition constants (K_i) for analog-induced inhibition of uptake of [^{3}H]DA into synaptic vesicles

Compound[a]	R	VMAT2 [^{3}H]DA uptake, K_i (nM); mean ± SEM[b]
METH	—	2460 ± 8.3
2a	—	45 ± 2.0
2b	—	43 ± 8.0
15a	H	48 ± 2.8
15b	4-OCH_3	66 ± 6.1
15c	3,4-Methylenedioxy	31 ± 7.7
22a	H	62 ± 3.9
22b	4-OCH_3	24 ± 1.5
22c	3,4-Methylenedioxy	55 ± 3.0

[a] All compounds were evaluated as their water-soluble hydrochloride salts.
[b] Each K_i value represents mean ± SEM from four independent experiments, each performed in duplicate. **METH**: Methamphetamine.

the hydrochloride salts of the corresponding norlobelane analogs, and were similar to those of the previously reported hydrochloride salts of the pyrrolidine analogs of norlobelane.[8,15] Interestingly, all of the azetidine analogs exhibited potent inhibition of [^{3}H]DA uptake into isolated synaptic vesicles (K_i = 24–66 nM).

Among the compounds tested, it is interesting to note that the inhibitory activity of the novel *cis*-azetidine derivative **22b** (K_i = 24 nM) was about twofold more potent than that of lobelane (**2a**, K_i = 45 nM) and norlobelane (**2b**, K_i = 43 nM). Comparison of the inhibitory data for **15a** (K_i = 48 nM) and **22a** (K_i = 62 nM), and for **15c** (K_i = 31 nM) and 22c (K_i = 55 nM), indicates that the inhibitory activities of the *trans*-type azetidine derivatives are not different from those of the *cis*-type azetidine derivatives. This lack of difference in inhibition of DA uptake at VMAT2 between the *cis*- and *trans*-azetidine isomers is intriguing, since the *cis*-scaffold is structurally quite different from the *trans*-scaffold with respect to spatial arrangement of the 2,4-diphenethyl substituents. This indicates that the difference in stereochemistry between these analogs is not a critical factor that governs their mode of interaction with their binding site on the cytosolic face of VMAT2, which translocates DA from the cytosol into the vesicle. This phenomenon has also been observed with the structurally related *cis* and *trans* isomers of 2,5-di-(2-phenethyl)-pyrrolidine, which are also equipotent in their ability to inhibit DA uptake at VMAT2.[8,15] These azetidine analogs water solubility is same as the lobelanepiperidine and pyrrolidine compounds.

The above data indicate that these novel azetidine derivatives may represent new 'lead analogs' with pharmacological and physiochemical properties favorable for subsequent drug development.

3. Pharmacological evaluation

3.1. [^{3}H]DA uptake inhibition assay

Inhibition of [^{3}H]DA uptake was conducted using the isolated synaptic vesicle preparations. Briefly, rat striata were homogenized with 10 strokes of a Teflon pestle homogenizer (clearance ~0.003′) in 14 ml of 0.32 M sucrose solution. Homogenates were centrifuged (2000*g* for 10 min at 4 °C), and the resulting supernatants were centrifuged again (10,000*g* for 30 min at 4 °C). Pellets were resuspended in 2 ml of 0.32 M sucrose solution and subjected to osmotic shock by adding 7 ml of ice-cold water to the preparation, followed by the immediate restoration of osmolarity by adding 900 μL of 0.25 M HEPES buffer and 900 μL of 1.0 M potassium tartrate solution. Samples were centrifuged (20,000*g* for 20 min at 4 °C), and the resulting supernatant was centrifuged again (55,000*g* for 1 h at 4 °C), followed by the addition of 100 μL of 10 mM $MgSO_4$, 100 μL of 0.25 M HEPES and 100 μL of 1.0 M potassium tartrate solution prior to the final centrifugation (100,000*g* for 45 min at 4 °C). Final pellets were resuspended in 2.4 ml of assay buffer (25 mM HEPES, 100 mM potassium tartrate, 50 μM EGTA, 100 μM EDTA, 1.7 mM ascorbic acid, 2 mM ATP-Mg^{2+}, pH 7.4). Aliquots of the vesicular suspension (100 μL) were added to tubes containing assay buffer, various concentrations of inhibitor (0.1 nM ~ 10 mM) and 0.1 μM [^{3}H]DA in a final volume of 500 μL. Nonspecific uptake was determined in the presence of Ro4-1284 (10 μM). Reactions were terminated by filtration, and radioactivity retained by the filters was determined by liquid scintillation spectroscopy (Liquid scintillation analyzer; PerkinElmer Life and Analytical Sciences, Boston, MA).

4. Conclusions

In conclusion, we have developed an efficient synthetic approach for the preparation of novel azetidine analogs (**15a–c** and **22a–c**) of norlobelane (**2b**). Conditions were developed for the synthesis of the key intermediate Cbz-protected diphenethylazetedines (**14a–c** and **21a–c**). The *cis*-analog **22b** was the most potent inhibitor of [^{3}H]DA uptake (K_i = 24 nM) and was about twofold more potent than lobelane (**2a**, K_i = 45 nM) and norlobelane (**2b**, K_i = 43 nM). Interestingly, the *trans*-methylenedioxy analog **15c** was equipotent with **22b**. Thus, *cis*- and *trans*-azetidine analogs **22b** and **15c** were considered unique structures and potential leads in the discovery of clinical candidates for the treatment of methamphetamine abuse.

5. Experimental part

5.1. General chemistry

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Anhydrous DCM was obtained via distillation over CaH_2. Silica gel 60 F_{254} thin layer chromatography plates were obtained from Dynamic Adsorbents Inc. Flash chromatography silica gel 60, 40–64 μm, was obtained from Silicycle Ultrapure Silica Gels. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at 500(^{1}H) or at 300(^{1}H)/75(^{13}C) MHz in the indicated deuterated solvents. High resolution (HRMS) mass spectra were obtained using electron impact (EI) ionization techniques ona magnetic sector instrument at a resolution greater than 10,000.

5.2. Synthesis

5.2.1. (±)-*trans*-(1-Benzyl azetidine-2,4-diyl)dimethanol (6)

At 0 °C, (±)-*trans*-benzyl 2,2′-(1-benzylazetidine-2,4-diyl) diacetate (7.5 g, 18.1 mmol) was dissolved in 200 ml THF/EtOH (3:1). $NaBH_4$ (8.2 g, 216 mmol) was added to the stirred solution in portions. After completion of the reaction (as indicated by TLC monitoring) the resulting mixture was acclimated to room temperature. The reaction mixture was diluted with EtOAc and sequentially washed with 1 M citric acid solution and saturated aqueous NaCl solution. The organic phase was separated and the aqueous phase was extracted three times with EtOAc. The organic phases was combined and purified by flash chromatography (DCM/MeOH 5:1) to give pure compound **6** (2.8 g, 75%) as an amorphous solid, which was crystallized from acetone to give a white solid. Mp: 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.35 (m, 5H), 4.06 (d, J = 13.5, 1H), 3.72–3.78 (m, 3H), 3.48–3.60 (m, 4H), 3.05 (br s, 2H), 2.14 (t, J = 6.9, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.7, 128.5, 128.3, 127.5, 62.8, 62.3, 54.1, 21.5 ppm.

5.2.2. (±)-*trans*-Benzyl 2,4-bis(hydroxylmethyl)azetidine-1-carboxylate (11)

Compound **6** (0.52 g, 2.5 mmol) was dissolved in 10 ml of methanol. To this solution was added 0.13 g 20% $Pd(OH)_2$, and the resulting mixture was strongly stirred under 1 atm H_2 at room temperature. After completion of the reaction (determined by TLC monitoring) the reaction mixture was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to afford the crude product, which was used directly in the next step.

The above crude product was dissolved in 15 ml DCM and Cbz-Cl (0.35 ml, 2.5 mmol) was added to the solution. The reaction mixture was cooled to 0 °C and DIPEA was added slowly. Then the reaction was acclimated to room temperature. After the reaction was completed, 30 ml of DCM was added to dilute the mixture, and organic solution was washed with saturated aqueous NH_4Cl solution. The organic phase was then separated and purified by flash chromatography (hexane/EtOAc-1:1 to 1:2) and compound **11** was obtained as an amorphous solid (0.52 g, 82.9%, two steps): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.37 (m, 5H), 5.05–5.15 (m, 2H), 4.28–4.44 (m, 3H), 3.61–3.87 (m, 4H), 2.71 (br s, 1H), 2.14–2.20 (m, 1H), 1.95–2.02 (m, 1H); ^{13}C(75 MHz, $CDCl_3$): δ 156.9, 136.1, 128.8, 128.5, 128.2, 67.6, 66.6, 63.7, 62.2, 61.6, 21.5 ppm. HRMS (EI) calcd for $C_{13}H_{17}NO_4$, 251.1116, found 251.1113.

5.2.3. (±)-*trans*-Benzyl-2,4-distyrylazetidine-1-carboxylate (13a)

5 ml of anhydrous DCM was placed in flask and cooled to −78 0 °C. Oxalyl chloride (0.3 ml, 3.4 mmol) was added to the flask and anhydrous DMSO (0.28 ml, 3.9 mmol) was dropped slowly into the mixture. The solution was stirred for 5 min and compound **11** (0.21 g, 0.85 mmol) was dissolved in 1 ml anhydrous DCM and injected into the reaction mixture. After 1 h, 0.89 ml of anhydrous Et_3N was added to the reaction flask, which was then acclimated to room temperature. Saturated aqueous NH_4Cl solution was used to quench the reaction. The mixture was separated and the aqueous phase was extracted twice with DCM. The organic phases were combined, dried over anhydrous $NaSO_4$, filtered, and the filtrate evaporated to dryness. The resulting crude product was used immediately in the next step.

Benzyltriphenylphosphonium bromide (1.1 g, 2.6 mmol) was suspended in 5 ml anhydrous THF. 2.5 ml of 1 M potassium *tert*-butoxide was added slowly to the mixture. The solution was stirred for 1 h and the above crude aldehyde dissolved in 1 ml DCM was added to the solution. The reaction was stirred for 2 h at room temperature. Saturated aqueous NH_4Cl solution was then added to quench the reaction. 10 ml of EtOAc was added and the mixture was separated. The aqueous phase was extracted twice with EtOAc. The organic phases were combined and purified by flash chromatography (hexane/EtOAc 12:1). Compound **13a** was obtained as colorless oil in 63.9% yield (two steps). ^{1}H NMR (300 MHz, $CDCl_3$):δ 6.99–7.39 (m, 15H), 6.34–6.65 (m, 3H), 5.97–6.04 (m, 1H), 4.94–5.27 (m, 4H), 2.34–2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 136.7, 136.6, 136.5, 133.6, 132.2, 131.4, 130.6, 130.0, 129.4, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.4, 127.9, 127.8, 127.3, 126.8, 66.6, 61.5, 60.3, 56.6, 32.4, 32.2, 31.7, 30.0 ppm; HRMS (EI) calcd for $C_{27}H_{25}NO_2$ 395.1885, found 395.1873.

5.2.4. (±)-*trans*-Benzyl-2,4-bis(4-methoxystyryl)azetidine-1-carboxylate (13b)

The same procedure to that described for the preparation of compound **13a** was utilized. Compound **13b** was obtained as an oil in 65.1% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01–7.45 (m, 11H), 6.76–6.93 (m, 4H), 6.44–6.50 (m, 1H), 5.84–5.92 (m, 1H), 4.83–5.26 (m, 3H), 3.74–3.87 (m, 7H), 2.32–2.38 (m, 2H) ppm. HRMS (EI) calcd for $C_{29}H_{29}NO_4$, 455.2097, found 455.2099.

5.2.5. (±)-*trans*-Benzyl-2,4-bis(2-(benzo[*d*][1,3]dioxol-5-yl)vinyl) azetidine-1-carboxylate (13c)

The same procedure to that described for the preparation of compound **13a** was utilized. Compound **13c** was obtained as an oil in 68.8% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14–7.28 (m, 5H), 6.76–6.91 (m, 6H), 6.42–6.60 (m, 2H), 6.19 (br s, 2H), 5.90–5.97 (m, 4H), 5.19 (d, J = 12.6, 1H), 4.89–4.95 (m, 3H), 2.33–2.39 (m, 2H) ppm. HRMS (EI) calcd for $C_{29}H_{25}NO_6$, 483.1682, found 483.1675.

5.2.6. 5.2.4.(±)-*trans*-Benzyl-2,4-diphenethylazetidine-1-carboxlate (14a)

Compound **13a** (0.13 g, 0.32 mmol) was dissolved in 8 ml THF/*tert*-BuOH (1/1) and 0.05 g tris(triphenylphosphine)-rhodium chloride added to the solution. The mixture was hydrogenated at 55 °C under 1 atm H_2. After the reaction was complete, the mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by flash chromatography (hexane/EtOAc 24:1) and compound **14a** was obtained as a colorless oil in 97.6% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07–7.39 (m, 15H), 5.02–5.16 (m, 2H), 4.26 (br s, 2H), 2.24–2.63 (m, 6H), 1.84–2.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 141.6, 141.5, 137.0, 128.6, 128.5, 128.4, 128.1, 128.1, 128.0, 126.1, 66.4, 59.5, 58.9, 36.0, 35.6, 31.2, 30.8, 28.6 ppm; HRMS (EI) calcd. for $C_{27}H_{29}NO_2$, 399.2198, found 399.2191.

5.2.7. (±)-*trans*-Benzyl-2,4-bis(4-methoxyphenethyl)azetidine-1-carboxylate (14b)

The same procedure to that described for the preparation of compound **14a** was utilized. Compound **14b** was obtained as a colorless oil in 95.3% yield. ^{1}H (300 MHz, $CDCl_3$): δ 7.26–7.37 (m, 4H), 7.00–7.14 (m, 4H),6.78–6.85 (m, 5H), 5.04–5.19 (m, 2H), 4,27 (br s, 2H), 3.73–3.86 (m, 6H),2.46–2.62 (m, 5H), 2.23–2.27 (m, 1H), 1.82–2.07 (m, 4H). HRMS (EI) calcd for $C_{29}H_{33}NO_4$, 459.2410, found 459.2407.

5.2.8. (±)-*trans*-Benzyl-2,4-bis(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl) azetidine-1-carboxylate (14c)

The same procedure to that described for the preparation of compound **14a** was utilized. Compound **14c** was obtained as a colorless oil in 96.1% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.36 (m, 5H), 6.51–6.72 (m, 6H), 5.92 (s, 4H), 5.02–5.16 (m, 2H), 4.23 (br s, 2H), 2.43–2.56 (m, 5H), 2.21 (br s, 1H), 1.97 (d, J = 6.5 Hz, 2H), 1.82–1.88 (m, 2H) ppm. HRMS (EI) calcd for $C_{29}H_{29}NO_6$, 487.1995, found 487.1998.

5.2.9. (±)-*trans*-2,4-Diphenethylazetidine (15a)

Compound **14a** (0.13 g, 0.32 mmol) was dissolved in 10 ml of MeOH containing 0.019 g 10% Pd/C. The mixture was vigorously stirred under 1 atm H_2 at room temperature. TLC was used to monitor the reaction. After the reaction was complete, the solution was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash chromatography (DCM/CH_3OH 15:1) and compound **15a** was afforded as a colorless oil in 93.2% yield; ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.14–7.26 (m, 10H), 4.27 (t, J = 7.5, 1H), 2.70–2.74 (m, 2H), 2.51–2.61 (m, 3H), 2.36–2.40 (m, 2H), 2.10–2.19 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 139.9, 128.8, 128.7, 128.6, 128.4, 126.5, 56.9, 36.1, 31.7, 30.3 ppm. HRMS (EI) calcd for $C_{19}H_{23}N$ 265.1830, found 265.1823.

5.2.10. (±)-*trans*-2,4-bis(4-methoxyphenethyl)azetidine (15b)

The same procedure to that described for the preparation of compound **15a** was utilized. Compound **15b** was obtained as a colorless oil in 91.7% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04–7.08 (m, 4H), 6.73–6.83 (m, 4H), 4.23–4.31 (m, 2H), 3.67–3.84 (m, 6H), 2.64–2.73 (m, 2H), 2.47–2.60 (m, 2H), 2.31–2.43 (m, 2H), 2.12–

2.20 (m, 2H), 1.99–2.10 (m, 2H), 1.24–1.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 131.8, 129.6, 129.4, 114.3, 114.1, 56.9, 55.5, 36.1, 30.8, 30.1 ppm. HRMS (EI) calcd for $C_{21}H_{27}NO_2$, 325.2042, found 325.2039.

5.2.11. (±)-*trans*-2,4-Bis(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)azetidine (15c)

The same procedure to that described for the preparation of compound **15a** was utilized. Compound **15c** was obtained as a colorless oil in 90.4% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58–6.73 (m, 6H), 5.84–5.97 (m, 4H), 3.68–3.77 (m, 2H), 2.29–2.58 (m, 4H), 1.80–2.05 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 145.7, 135.7, 121.2, 109.0, 108.3, 101.0, 55.4, 40.0, 32.2, 30.1 ppm. HRMS (EI) calcd for $C_{21}H_{23}NO_4$, 353.1627, found 353.1631.

5.2.12. *cis*-(1-Benzylazetidine-2,4-diyl) dimethanol (16)

The same procedure to that described for the preparation of compound **6** was utilized, except that *cis*-benzyl 2,2′-(1-benzylazetidine-2,4-diyl) diacetate was utilized in place of *trans*-benzyl 2,2′-(1-benzylazetidine-2,4-diyl) diacetate. Compound **16** was obtained as a white solid, mp 71–73 °C, yield, 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.31 (m, 5H), 3.69 (s, 2H), 3.28–3.31 (m, 6H), 2.75 (br s, 2H), 1.99–2.05 (m, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 138.1, 129.3, 128.7, 127.8, 63.6, 63.3, 61.3, 20.5 ppm.

5.2.13. *cis*-Benzyl-2,4-bis(hydroxylmethyl)azetidine-1-carboxylate (18)

The same procedure to that described for the preparation of compound **11** was utilized. Compound **18** was obtained as a viscous oil, yield, 79.7% (two steps), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.34 (m, 5H), 5.08 (s, 2H), 4.26 (br s, 2H), 3.85 (d, J = 11.5, 2H), 3.60 (br s, 2H), 2.13–2.21 (m, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 157.8, 136.2, 128.7, 128.5, 128.4, 128.1, 67.3, 64.5, 63.8, 60.7, 20.1 ppm. HRMS (EI) calcd for $C_{13}H_{17}NO_4$ 251.1116, found, 251.1116.

5.2.14. *cis*-Benzyl-2,4-distyrylazetidine-1-carboxlate (20a)

The same procedure to that described for the preparation of compound **13a** was utilized. Compound **20a** was obtained as an oil, yield 45.3% (two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.41 (m, 15H), 6.62 (d, J = 15.9, 2H), 6.38 (dd, J_1 = 6.9, J_2 = 15.9, 2H), 5.13 (s, 2H), 4.78–4.85 (m, 2H), 2.75–2.84 (m, 1H), 1.98–2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 136.7, 136.6, 133.7, 131.4, 130.6, 130.0, 128.8, 128.7, 128.5, 128.4, 127.9, 127.8, 127.3, 126.8, 66.6, 60.5, 56.6, 32 ppm.

5.2.15. *cis*-Benzyl-2,4-bis(4-methoxylstyryl)azetidine-1-carboxylate (20b)

The same procedure to that described for the preparation of compound **13a** was utilized. Compound **20b** was obtained as an oil in 50.7% yield (two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.44 (m, 9H), 6.82–6.93 (m, 4H), 6.46–6.58 (m, 2H), 6.19–6.26 (m, 1H), 5.86–5.93 (m, 1H), 5.02–5.18 (m, 3H), 4.70–4.78 (m, 1H), 3.73–3.88 (m, 6H), 2.73–2.83 (m, 1H), 1.90–1.98 (m, 1H) ppm; HRMS (EI) calcd for $C_{29}H_{29}NO_4$, 455.2097, found 455.2089.

5.2.16. *cis*-Benzyl-2,4-bis(2-(benzo[*d*][1,3]dioxol-5-yl)vinyl) azetidine-1-carboxylate (20c)

The same procedure to that described for the preparation of compound **13a** was utilized. Compound **20c** was obtained as an oil in 53.4% yield (two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.27 (m, 5H), 6.94 (s, 1H), 6.72–6.83 (m, 5H), 6.42–6.54 (m, 2H), 6.15–6.22 (m, 1H), 5.85–5.96 (m, 5H), 5.07–5.17 (m, 3H), 4.71–4.74 (m, 1H), 2.73–2.82 (m, 1H), 1.88–1.97 (m, 1H) ppm. HRMS (EI) calcd for $C_{29}H_{25}NO_{6,}$ 483.1682, found 483.1678.

5.2.17. *cis*-Benzyl-2,4-diphenethylazetidine-1-carboxlate (21a)

The same procedure to that described for the preparation of compound **14a** was utilized. Compound **21a** was obtained as an oil in 87.9% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.38 (m, 15H), 5.13 (d, J = 4.5 Hz, 2H), 4.13–4.21 (m, 2H), 2.63–2.68 (m, 4H), 2.25–2.47(m, 3H), 1.88–1.97 (m, 2H), 1.52–1.58 (m, 1H); ^{13}C(75 MHz, $CDCl_3$): δ 158.0, 141.7, 136.9, 128.6, 128.5, 128.5, 128.1, 128.0, 126.0, 66.6, 59.4, 38.6, 31.7, 29.3 ppm. HRMS (EI) calcd for $C_{27}H_{29}NO_2$, 399.2198, found 399.2193.

5.2.18. *cis*-Benzyl-2,4-bis(4-methoxyphenethyl)azetidine-1-carboxa- late (21b)

The same procedure to that described for the preparation of compound **14a** was utilized. Compound **21b** was obtained as an oil in 93.1% yield, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.38 (m, 4H), 7.08 (d, J = 8.1, 4H), 6.80–6.83 (m, 5H), 5.11 (s, 2H), 4.08–4.15 (m, 2H), 3.72–3.85 (m, 6H), 2.56–2.62 (m, 4H), 2.35–2.44 (m, 1H), 2.19–2.30 (m, 2H), 1.83–1.92 (m, 2H), 1.50–1.56 (m, 1H) ppm. HRMS (EI) calcd for $C_{29}H_{33}NO_4$ 459.2410, found 459.2408.

5.2.19. *cis*-Benzyl-2,4-bis(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)azetidine-1-carboxylate (21c)

The same procedure to that described for the preparation of compound **14a** was utilized. Compound **21c** was obtained as an oil in 94.7% yield, ^{1}H NMR(500 MHz, $CDCl_3$): δ 7.26–7.38 (m, 5H), 6.60–6.72 (m, 6H), 5.90 (s, 4H), 5.11 (s, 2H), 4.11–4.13 (m, 2H), 2.55–2.58 (m, 4H), 2.37–2.43 (m, 1H), 2.20–2.24 (m, 2H), 1.82–1.88 (m, 2H), 1.48–1.53 (m, 1H) ppm. HRMS (EI) calcd for $C_{29}H_{29}NO_6$, 487.1995, found 487.1992.

5.2.20. *cis*-2,4-Diphenethylazetidine (22a)

The same procedure to that described for the preparation of compound **15a** was utilized. Compound **22a** was obtained as a viscous oil, yield 87.3%. ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.16–7.29 (m, 10H), 3.59–3.66 (m, 2H), 2.47–2.67 (m, 5H), 2.24–2.32 (m, 1H), 1.75–1.92 (m, 4H),1.51–1. 61 (m, 1H); ^{13}C(75 MHz, $CDCl_3$): δ 142.1, 128.5, 128.4, 125.9, 54.2, 40.6, 33.8, 32.1 ppm. HRMS (EI) calcd for $C_{19}H_{23}N$, 265.1830, found 265.1822.

5.2.21. *cis*-2,4-Bis(4-methoxyphenethyl)azetidine (22b)

The same procedure to that described for the preparation of compound **15a** was utilized. Compound **22b** was obtained as a viscous oil, yield 90.5%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98–7.26 (m, 4H), 6.68–6.81 (m, 4H), 4.13–4.21 (m, 2H), 3.67–3.80 (m, 6H), 2.28–2.71 (m, 8H), 1.89–2.11 (m, 3H), 1.23–1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9, 158.2, 131.9, 129.6, 129.4, 114.2, 114.1, 56.6, 55.6, 55.5, 36.6, 32.0, 30.7 ppm. HRMS (EI) calcd for $C_{21}H_{27}NO_2$, 325.2042, found 325.2044.

5.2.22. *cis*-2,4-Bis(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)azetidine (22c)

The same procedure to that described for the preparation of compound **15a** was utilized. Compound **22c** was obtained asa viscous oil, yield 91.6%. ^{1}H NMR (300 MHz, $CDCl_3$): (300 MHz, $CDCl_3$) 6.59–6.72 (m, 6H), 5.89 (s, 4H), 4.16–4.21 (m, 2H), 2.60–2.68 (m, 2H), 2.29–2.52 (m, 6H), 1.95–2.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 147.8, 146.0, 135.0, 121.8, 109.5, 108.8, 101.3, 55.5, 36.7, 32.0, 30.9 ppm. HRMS (EI) calcd for $C_{21}H_{23}NO_4$, 353.1627, found 353.1623.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.08.001.

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