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Efficient synthesis of *cis*-2,6-di-(2-quinolylpiperidine)

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ABSTRACT

An efficient synthesis of *cis*-2,6-di-(2-quinolylpiperidine) has been developed. The key steps involve Wittig reaction of *N*-Cbz-protected *cis*-piperidine-2,6-dicarboxaldehyde (**3**) with 2-(triphenylphosphinylmethyl)quinoline bromide (**4**) and sequential removal of the *N*-Cbz group and double bond reduction. This synthetic procedure provides an efficient preparation for this useful norlobelane analogue.

Introduction

Lobelane (*N*-methyl-*cis*-2,6-diphenethylpiperidine, Fig. 1), a minor piperidine alkaloid of *Lobelia inflata*,[1] has been shown to exhibit good affinity and selectivity for the tetrabenazine (TBZ) binding site on the vesicular monoamine transporter (VMAT2), and is also a potent inhibitor of vesicular dopamine uptake.[2] Structure–activity relationship (SAR) studies indicate that lobelane analogues lacking the *N*-methyl substituent (i.e., norlobelane analogues) retain their affinity for the TBZ binding site on VMAT2, suggesting that the presence of the *N*-methyl group is not critical for interaction with VMAT2. Furthermore, other studies have shown that norlobelane is a potent inhibitor of [^{3}H]DA uptake into striatal vesicles (K_i = 43 nM).[2] SAR studies have also shown that the phenyl moieties in lobelane can be replaced with 1-naphthyl or 2-naphthyl groups, resulting in analogues that are potent and selective inhibitors of VMAT2.[2a] However, such analogues have poor water-solubility and poor drug-like properties. Recent studies have shown that lobelane analogues in which the phenyl moieties have been replaced with heterocyclic rings, such as pyridyl, quinolyl, or indolyl, have improved water-solubility (Fig. 1). Only the quinolyl analogues retained potent VMAT2 inhibitory properties,[3] with quinlobelane (Fig. 1) exhibiting potent inhibition of vesicular [^{3}HDA] uptake (K_i = 51 nM). However, the synthetic procedures utilized in this study were not amenable to the synthesis of 2-quinolyl analogues of norlobelane [e.g., *cis*-2,6-di-(2-quinolylpiperidine); compound **1**, Scheme 1] and its analogues. In order to obtain more drug-like 2-quinolyl analogues of both norlobelane and lobelane for studying both structure–activity and structure–property relationships, a new and efficient synthesis of *cis*-2,6-di-(2-quinolylpiperidine) is now reported, which may be useful for the general synthesis of a wide range of compounds of this type.

Results and discussion

We now report a versatile and efficient method for the preparation of 2-quinolylnorlobelane. Our retrosynthetic approach is outlined in Scheme 1, and is centered around a Wittig reaction for the construction of two double bonds sequentially. The requisite precursor **3** (Scheme 1) can be synthesized from commercial pyridine-2,6-dicarboxylic acid.

The synthesis of target molecule **1** was executed as shown in Scheme 2. Pyridine-2,6-dicarboxylic acid was heated under reflux in methanol containing a few drops of concentrated H_2SO_4 to form

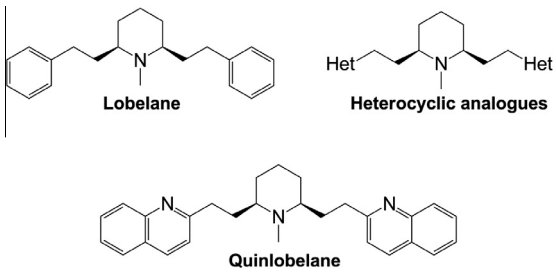

Figure 1. Structures of lobelane, heterocyclic analogs of lobelane and quinlobelane.

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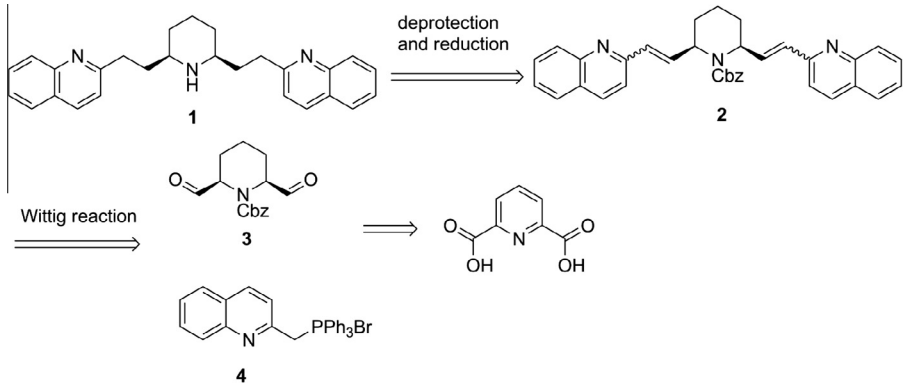
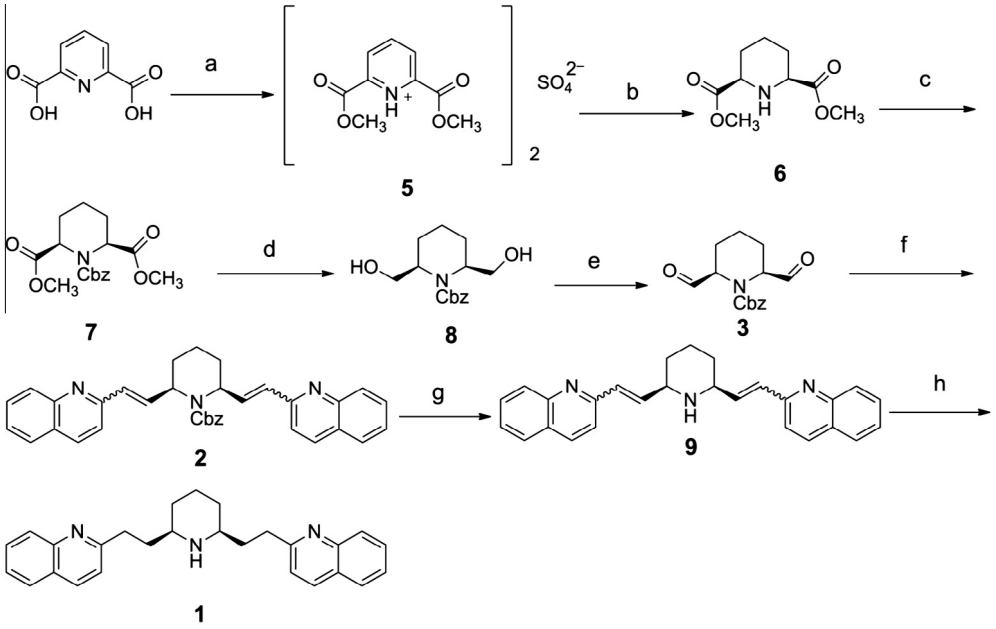
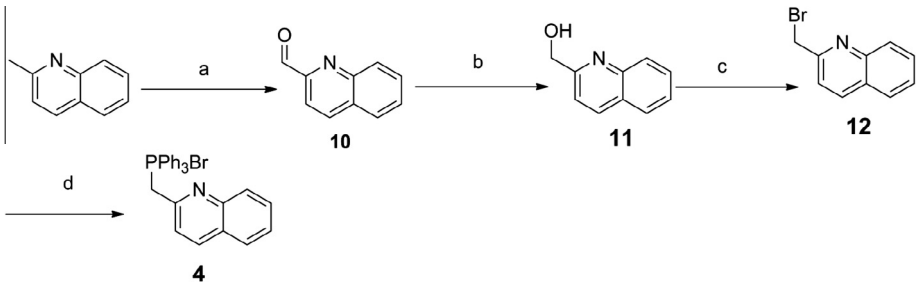


Scheme 1. Retrosynthetic analysis of *cis*-2,6-di-(2-quinolyl piperidine) (**1**).



Scheme 2. Synthetic route to compound **1**. Reagents and conditions: (a) Concd H_2SO_4, MeOH, reflux, 71%; (b) 10% Pd/C, H_2O, rt, 91%; (c) CbzCl, DIPEA, THF, rt, quant; (d) $LiBH_4$, THF, 0 °C→rt, 81%; (e) Swern oxidation, −78 °C; (f) **4**, *tert*-BuOK, THF, rt, 51% (two steps); (g) 6 N HCl, reflux, quant; (h) 10% Pd/C, rt, 75%.



Scheme 3. Synthetic route to compound **4**. Reagents and conditions: (a) SeO_2, solvent-free, 170 °C, 81%; (b) $NaBH_4$, EtOH, rt, 92%; (c) 33% HBr/AcOH, reflux, 98%; (d) PPh_3, toluene, reflux, 95%.

the sulfate salt **5**. Reduction of **5** under 50 psi H_2 pressure followed by crystallization of the crude product from hexane provided the pure *cis*-isomer **6** in 91% yield,[4] which was then protected as its *N*-Cbz derivative **7**. In our original plan, we utilized DIBAL-H for the reduction of **7**, in the hope of obtaining aldehyde **3** in one step. Unfortunately, an unidentified mixture was obtained after work-up of the reaction. To obtain the key intermediate **2**, we reduced ester **7** with $LiBH_4$ to afford alcohol **8**. Then, we explored Dess–Martin periodinane and PCC reactions in our attempts to oxidize compound **8** to the key intermediate **3**. However, only complex mixtures were obtained, which may have been due to facile decomposition of aldehyde **3** during purification by column chromatography. We subsequently found that alcohol **8** could be oxidized efficiently to **3** under Swern conditions.[5] In the Wittig

reaction of **3** with compound **4** (Scheme 3), which is the pivotal step in the synthesis of **1**, we found that it was advantageous to utilize the crude aldehyde **3** directly without further purification to afford the optimal yield of **2** (it is noteworthy that all attempts to obtain a pure sample of compound **3** failed). In our initial attempts to synthesize **2**, THF was used as solvent and *n*-BuLi was utilized as base, and the product was isolated in 6% yield in the two-step procedure. In order to optimize the reaction conditions, other bases were evaluated. The yields obtained by substituting *n*-BuLi with either LiHMDS, NaHMDS, or NaOEt were 8%, 10%, and 11%, respectively, for the two-step synthetic procedure. To our satisfaction, when *tert*-BuOK was used as base, the yield of **2** improved significantly to 51% for the two step reaction.

With the key compound **2** in hand, our initial strategy was to synthesize compound **1** from **2** in one step by removal of the *N*-Cbz group followed by double bond hydrogenation over 20% $Pd(OH)_2$. However, when this procedure was followed, TLC analysis indicated a complex mixture, which proved difficult to purify by column chromatography.

A similar outcome was observed when 10% Pd/C was used. We speculated that these problems might be due to hydrogenolytic ring opening of the piperidine ring under the reduction conditions utilized. In order to circumvent this problem, a strategy involving two separate steps was employed. First, we attempted to reduce the double bonds utilizing Wilkinson's catalysis[6] prior to removal of the *N*-Cbz group; however, no reaction occurred, and the starting material was recovered. Subsequently, we turned to a second strategy, and attempted the removal of the *N*-Cbz group of **2** followed by double bond reduction. We found that 6 N HCl at reflux could be used to deprotect the *N*-Cbz group affording compound **9** in quantitative yield. Hydrogenation of **9** to the desired compound **1** was achieved utilizing 10% Pd/C as catalyst in 75% yield.

Scheme 3 provides the synthetic route to phosphonium salt **4**, which was utilized in the Wittig reaction of compound **3** to **2** (Scheme 2). 2-Methylquinoline was oxidized by SeO_2 at a high temperature (170 °C) under solvent-free conditions to afford aldehyde **10** in good yield. It should be noted that when this oxidation reaction was performed in high boiling points solvents such as 1,4-dioxane, the yield was very low, even after prolonged reaction times. Aldehyde **10** could be reduced by $NaBH_4$ in EtOH to afford carbinol **11** in 92% yield, followed by bromination of **11** in 33% HBr/AcOH to afford bromide **12** in high yield[7] (we found that when compound **10** was brominated with 48% aq HBr, the yield of **12** was only 72% and the reaction required a long time for completion). Compound **12** was then heated under reflux with triphenyl phosphine (PPh_3) in toluene to obtain the desired compound **4** in 95% yield.

Characterization data (^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry) for compounds **1**, **2** and **9** are provided in the References and Notes section[8].

In conclusion, an efficient method for the preparation of *cis*-2,6-di-(2-quinolylpiperidine) (**1**) has been developed. The key step in the synthetic scheme is the introduction of the two 2-quinolyl moieties via Wittig reaction with *N*-Cbz-protected *cis*-piperidine-2,6-dicarboxaldehyde. Other quinolyl analogues of norlobelane and lobeline are currently being prepared utilizing this synthetic procedure, and their biological evaluation is underway.

Acknowledgments

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8. *The spectroscopic data of all known compounds are identical to the reported data.* All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry (HRMS). Selected data (NMR spectra were recorded in $CDCl_3$, ^{1}H at 300 MHz and ^{13} C at 75 MHz): (i) Compound **2**: colorless oil; ^{1}H NMR: δ 7.91 (d, 2H, J = 8.4 Hz), 7.78 (d, 2H, J = 7.5), 7.68–7.60 (m, 4H), 7.48–7.25 (m, 9H), 6.86 (dd, J = 16.2 Hz, 2H), 6.82 (dd, J = 16.2 Hz, 2H), 5.24 (s, 2H), 5.21 (s, 2H), 2.13–1.84 (m, 5H), 1.68–1.63 (m, 1H) ppm; ^{13}C NMR: δ 155.9, 155.8, 148.1, 137.6, 136.8, 136.2, 131.5, 129.6, 129.4, 128.7, 128.3, 128.2, 127.6, 127.4, 126.2, 119.3, 67.8, 52.2, 28.5, 15.6 ppm; HRMS (EI) Calcd for $C_{35}H_{31}N_3O_2$, 525.2416. Found 525.2419 (ii) Compound **9**: viscous oil; ^{1}H NMR: δ 8.10–8.01 (m, 4H), 7.77–7.65 (m, 4H), 7.58–7.45 (m, 4H), 7.26–6.86 (m, 4H), 3.60–3.55 (m, 2H), 2.04–1.86 (m, 3H), 1.63–1.43 (m, 3H); ^{13}C NMR: δ 156.0, 148.2, 139.3, 136.5, 130.8, 129.8, 129.4, 127.6, 127.5, 126.3, 119.0, 59.2, 32.1, 24.7; HRMS(EI) calcd for $C_{27}H_{25}N_3$ 391.2048; Found 391.2045 (iii) Compound **1**: viscous oil; ^{1}H NMR: δ 8.08–7.99 (m, 4H), 7.76–7.79 (m, 2H), 7.62–7.68 (m, 2H), 7.50–7.45 (m, 2H), 7.32–7.26 (m, 2H), 3.11–3.06 (m, 4H), 2.61–2.57 (m, 2H), 2.02–1.94 (m, 4H), 1.78–1.71 (m, 3H), 1.27–1.19 (m, 3H); ^{13}C NMR: δ 162.5, 148.0, 136.6, 129.6, 128.9, 127.7, 126.9, 125.9, 121.6, 56.8, 37.0, 35.9, 32.4, 24.8; HRMS(EI) Calcd for $C_{27}H_{29}N_3$ 395.2361. Found 395.2367.