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Stereoselective synthesis of dendrobate alkaloid (+)-241D and its C-4 epimer

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ABSTRACT

An efficient stereoselective synthesis of dendrobate alkaloid (+)-241D and its C-4 epimer was achieved from the inexpensive, commercially available starting material decanal (**10**) in an overall yield of 21.9% and 21.1%, respectively. This synthesis utilizes the key steps of Maruoka asymmetric allylation, one-pot epoxidation followed by nucleophilic addition of an organomagnesium reagent (Forsyth's protocol) and subsequent functional group transformations.

Substituted piperidines are among the most ubiquitous heterocyclic building blocks in both natural products and synthetic compounds with important biological activities.[1] Simple 2,6-disubstituted piperidines (solenopsins and isosolenopsins), isolated from fire ant venom, are reported to possess a broad range of activities such as necrotic, insecticidal, antibacterial, antifungal, and anti-HIV.[2] 4-hydroxy-2,6-disubstituted piperidine alkaloid, dendrobate alkaloid 241D, isolated from methanolic skin extracts of Panamanian poison frogs *Dendrobates speciosus* and *Dendrobates pumilio*, possesses potent biological activity.[3] Synthetic racemic alkaloid 241D and the parent 4-piperidone **3** (Fig. 1) were found to be potent inhibitors for binding of perhydrohistrionicotoxin to nicotinic receptor channels of electroplax membranes.[4] In addition, it has also been found that racemic alkaloid 241D blocks the action of acetylcholine by a non-competitive blockade of the nicotinic receptor channel complex.[5]

Owing to the challenges posed by the substitution pattern and also due to the remarkable biological properties, the synthesis of these compounds has attracted much attention. As a consequence of the central role played by the ring system, a number of total syntheses of these compounds in racemic and optically active forms have been established.[6] Despite the availability of many synthetic methods for this class of compounds, there still exists a need to develop procedures more efficient than those currently in existence. In continuation of our ongoing studies on the synthesis of bioactive natural products,[7] we became interested in various cis-2,4,6-trisubstituted piperidine alkaloids. In this Letter, we report a new approach to the stereoselective synthesis of dendrobate alkaloid (+)-241D (**1**) and its C-4 epimer (**2**) based on the route shown in Scheme 1, which makes use of Forsyth's, Marouka asymmetric allylation as a key reaction step in the overall sequence.

In an earlier study from our laboratory we had demonstrated the versatility of Keck allylation and Grubb's cross metathesis reactions for the synthesis of the putative 2,6-disubstituted piperidine alkaloids,[7a] which were isolated from the venom of fire ants of genus *Solenopsis*. Our retrosynthetic strategy for the present synthesis relies on the Maruoka asymmetric allylation approach starting from decanal and Forsyth's protocol. As shown in Scheme 1, initial disconnection of **1** revealed fragment **6**, which could be subjected to reductive amination and diastereoselective cyclization to realize the target molecule. The key step in this synthesis would utilize one-pot epoxidation followed by the nucleophilic attack of an organomagnesium reagent (Forsyth's protocol) onto the appropriately functionalized 1,2-diol **7**, without being affected by its diastereoselectivity. The brevity of this analysis along with the structural simplicity of the precursors makes this route attractive for implementation.

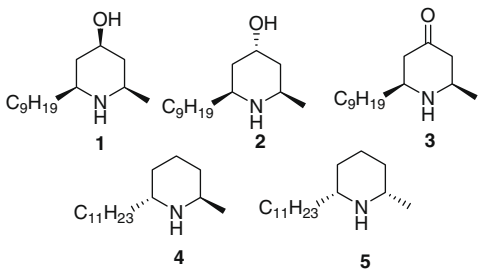

Figure 1. Representative examples of 2,6-disubstituted piperidine alkaloids.

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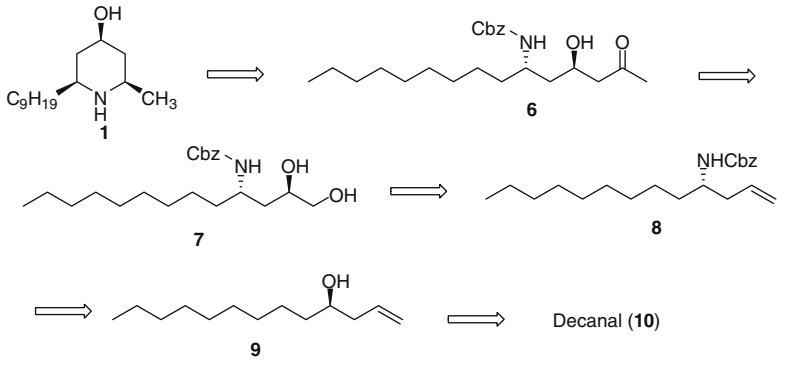
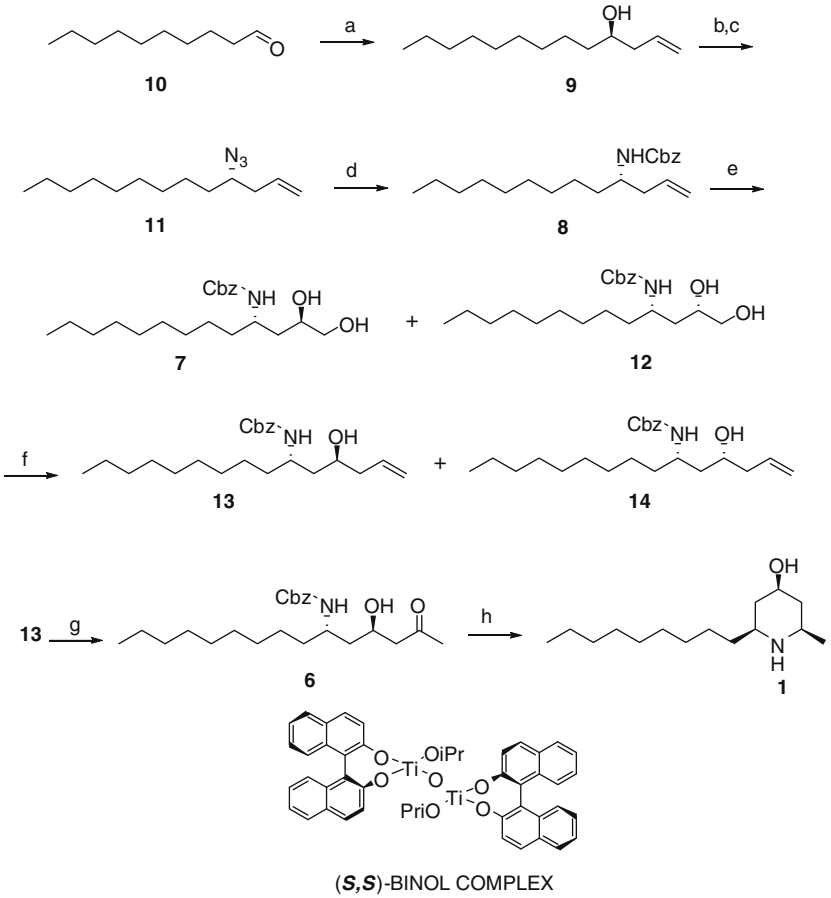


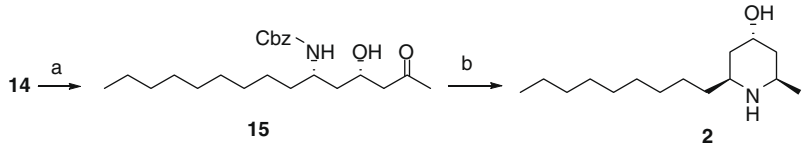
Scheme 1. Retrosynthetic analysis of **1**.

The total synthesis based on the above-mentioned plan was initiated with decanal (**10**) which was subjected to an enantioselective Maruoka allylation using titanium complex (***S,S***)-BINOL and allyltri-*n*-butyltin to furnish the homoallylic alcohol **9** in 84% yield with an excellent enantioselectivity of 98% ee (determined by chiral HPLC).[8] Protection of homoallylalcohol **9** as the tosyl ester (TsCl, pyridine, DMAP, CH_2Cl_2, 92% yield)[9] followed by reaction with NaN_3 in DMF at 70 °C led to the azide intermediate **11** in good yields (79%).[9] The azide **11** was then reduced to an amine using $LiAlH_4$ followed by protection with Cbz-Cl to afford the protected homoallylamine **8**.[10] Sharpless asymmetric dihydroxylation of **8** with Ad-mix-β in (1:1) aq *t*-BuOH at 0 °C afforded diols **7** and **12** in 80:20 ratio as an inseparable diastereomeric mixture in 87% yield,[11] whose diastereomeric ratio was determined by chiral HPLC.[12]

Although homoallylic alcohols are generally prepared in a common multistep sequence from 1,2-diols (generally diol converted to epoxide in two-step sequence followed by nucleophilic opening), we found that the one-pot epoxidation and nucleophilic opening sequence for 1,2-diols (Forsyth's protocol) gave higher yields and resulted in a cleaner overall reaction. Thus, diol mixture **7** and **12** was subjected to one-pot epoxidation followed by ring opening with vinyl magnesium bromide (Forsyth's protocol) to afford homoallyl alcohols **13** and **14** as separable diastereomers in



Scheme 2. Synthesis of alkaloid (+)-241D. Reagents and conditions: (a) $TiCl_4$, TIP, Ag_2O, (*S,S*) BINOL, allyltributyl tin, DCM, 0 °C, 24 h, 84%; (b) TsCl, pyridine–DCM (1:1), 0 °C to rt, 6 h, 92%; (c) NaN_3, DMF, 70 °C, 3 h, 79%; (d) $LiAlH_4$, THF, 0 °C to rt, 1 h then satd $NaHCO_3$, Cbz-Cl, 90%; (e) AD mix-β, *t*-BuOH–H_2O (1:1), 0 °C to rt, 48 h, 87%; (f) NaH, tosylimidazole, THF, 0 °C, 0.5 h then CuI, vinyl magnesium bromide(1 M), −20 °C, 1 h, 70%; (g) $PdCl_2$, CuCl, O_2, THF–H_2O (10:1), rt for 3 h, 85%; (h) 10% Pd/C, H_2, EtOAc, overnight, 77%.



Scheme 3. Synthesis of C-4 epimer of alkaloid (+)-241D. Reagents and conditions: (a) $PdCl_2$, CuCl, O_2, THF–H_2O (10:1), rt for 3 h, 83%; (b) 10% Pd/C, H_2, EtOAc, overnight, 76%.

70% yield.[13] These diastereomers were separated by the flash chromatography to yield pure compounds **13** and **14**. A Wacker oxidation of **13** gave the corresponding carbonyl compound **6** in 85% yield.[14] The absence of olefinic signals and the presence of a methyl singlet at δ 2.13 in ^{1}H NMR confirmed the Wacker oxidation product **6**. Finally, reductive amination followed by diastereoselective cyclization in the presence of 10% Pd/C in ethyl acetate under H_2 atmosphere led to the title compound **1** in 77% yield (Scheme 2).[15] The spectral data obtained were in good agreement with those reported in the literature [optical rotation of **1** is +3.2° (*c* 0.3, MeOH)].[6]

Having achieved a reliable synthesis of the key homoallylic alcohol intermediate **14**, we proceeded to use this compound for the preparation of C-4 epimer of alkaloid (+)-241D (**2**). Accordingly, the double bond present in **14** was converted into ketone **15** using Wacker oxidation protocol ($PdCl_2$, CuCl, O_2, THF–H_2O (10:1), rt). Reductive amination followed by diastereoselective cyclization of **15** with 10% Pd/C in ethyl acetate afforded **2** as a single diastereomer in 76% yield and with properties consistent with literature values[6] (Scheme 3). All the intermediate compounds were well characterized by IR, NMR, and mass spectral techniques.[16]

In conclusion, we have developed an efficient stereoselective protocol for the preparation of dendrobate alkaloid **1** and its C-4 epimer **2** by employing Maruoka asymmetric allylation and Forsyth's reaction sequence as the key steps. This general synthetic route demonstrates its versatility toward the synthesis of highly functionalized piperidines and also paves the way for the structurally related analogs. On the basis of the route described herein, further work toward preparation of the library of 2,4,6-piperidinol analogs for biological analysis is in progress in our laboratory.

Acknowledgments

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16. *Spectral data for selected compounds*: Compound **6**: White solid, mp 95–97 °C $[\alpha]_D^{25}$ −2.8 (*c* 0.75, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.22 (m, 5H), 5.13–4.98 (m, 3H), 4.14–3.97 (m, 1H), 3.86–3.67 (m, 1H), 2.68–2.31 (m, 2H), 2.13 (s, 3H), 1.60–1.12 (m, 18H), 0.88 (t, 3H, *J* = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.6, 157.0, 136.6, 128.4, 128.0, 66.7, 64.4, 50.2, 48.3, 42.8, 35.4, 31.9, 30.8, 29.6, 29.5, 29.4, 26.2, 22.7, 14.2. FABMS: *m*/*z* 392 $[M+1]^+$.
Compound **13**: White solid, mp 92–94 °C $[\alpha]_D^{25}$ +1.6 (*c* 1.08, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H), 5.88–5.68 (m, 1H), 5.16–4.96 (m, 4H), 4.91–4.78 (br d, 1H), 3.88–3.72 (m, 1H), 3.71–3.54 (m, 1H), 2.29–2.05 (m, 2H), 1.57–1.15 (m, 18H), 0.88 (t, 3H, *J* = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 136.4, 135.2, 128.4, 128.1, 128.0, 117.0, 66.9, 66.8, 48.3, 43.4, 41.7, 35.6, 29.6, 29.5, 29.3, 26.2, 22.7, 14.2. FABMS: *m*/*z* 376 $[M+1]^+$.
Compound **8**: White Solid, mp 60–62 °C $[\alpha]_D^{25}$ −11 (*c* 1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H), 5.83–5.64 (m, 1H), 5.12–4.98 (m, 2H), 4.63–4.52 (br d, 1H), 3.76–3.60 (m, 1H), 2.32–2.08 (m, 2H), 1.56–1.12 (m, 16H), 0.88 (t, 3H, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 136.7, 134.2, 128.4, 128.0, 117.8, 66.4, 50.5, 39.5, 34.6, 31.9, 29.6, 29.3, 25.9, 22.7, 14.2. IR (KBr): ν_{max} 3312, 2920, 2851, 1686, 1348.56, 1265, 1123 cm^{-1}; FABMS: *m*/*z* 332 $[M+1]^+$.