

# Stereodivergent Total Syntheses of (+)-Monomorine I and (+)-Indolizidine 195B

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A simple and efficient stereoselective total syntheses of two natural products (+)-monomorine I and (+)-indolizidine 195B in high yields starting from a readily available alcohol is described. The key step in this synthetic route exploits the judicious use of solvent to enable a closed or open transition state in a nucleophilic addition of Grignard reagent to sulfinimine, giving selective access to two distinct diastereomers required for the formation of the two target natural products.

The indolizidine framework contains a 5,6-fused ring system, with a nitrogen atom at the ring fusion, and is present in a wide range of medicinally and biologically active natural products.<sup>[1–3]</sup> Because of their often potent biological activities, many approaches have been developed for their synthesis.<sup>[4–6]</sup> Indolizidine alkaloids isolated from amphibians and ants have been identified as toxic and noxious molecules, and are believed to play a significant role in the self-defense system of these animals toward microorganisms and predators. Their biological activity is likely to arise from interference with ion channels in nerve and muscles cells.<sup>[7]</sup> In amphibians, indolizidine alkaloids are part of many classes of alkaloids which are accumulated in skin glands, which can be released onto the skin surface of the animal when needed. Structurally identical alkaloids have recently been isolated from ants and after feeding experiments, and it was suggested that the ants could be the amphibian's source of these alkaloids.<sup>[8–11]</sup> The indolizidine alkaloids isolated from ants and amphibians are disubstituted by alkyl chains at the 3,5-positions in most cases. These compounds have proved attractive targets for synthesis,<sup>[12,13]</sup> with a variety of different synthetic strategies towards their synthesis including racemic, diastereoselective and enantioselective approaches.<sup>[14–19]</sup>

(+)-Monomorine I (1) and (+)-indolizidine 195B (2) are two examples of indolizidine natural products isolated from ant and amphibian sources. They have three stereogenic centres at C-3, C-5 and C-9, with *cis*- and *trans* relationships at C-3 and C-5 substituents, respectively (Figure 1).

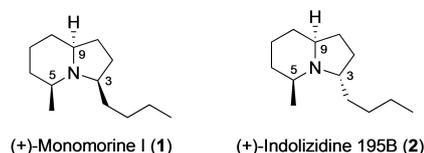


Figure 1. Structures of (+)-monomorine I (1) and (+)-indolizidine 195B (2).

(+)-Monomorine I (1) is a trail pheromone, isolated for the first time in 1973 by Ritter *et al.* from pharaoh's ants (*Monomorium pharaonis* L); a small transparent ant (2 mm) with yellow or light brown colour.<sup>[20]</sup> This ant, which is of tropical origin, is now established in North America and Western Europe. A diastereomer, (+)-indolizidine 195B (2), was isolated by Daly and co-workers in 1986 from the skin secretions of Colombian neotropical poison frogs belonging to the *Dendrobates* family (a genus of poison dart frogs).<sup>[12,13,21–24]</sup> Their interesting structures and stereochemistries have made these common test-beds for synthetic methodologies.<sup>[24]</sup> Herein we report a facile and efficient diastereodivergent synthetic strategy for these two different indolizidines (+)-monomorine I (1) and (+)-indolizidine 195B (2). The stereodivergent route pivots on the key stereocontrolled nucleophilic addition of Grignard reagent to chiral sulfinimine **4** in the presence of two different solvents (coordinating and non-coordinating) to give two different stereochemistry outcomes at the C–N bond formed (Figure 2).

To access (+)-monomorine I (1), our synthetic route began with the preparation of sulfinimine **4** over two steps, which included oxidation of *cis*-4-hexen-1-ol **3** with PCC to give the aldehyde analogue of **3**. This was then condensed with (*S*)-*tert*-butanesulfinamide as a chiral auxiliary using Ellman's protocol,<sup>[25,26]</sup> which afforded the corresponding (*S*<sub>c</sub>)-sulfinimine **4** in good yield (84%) (Scheme 1). The product **4** was reacted

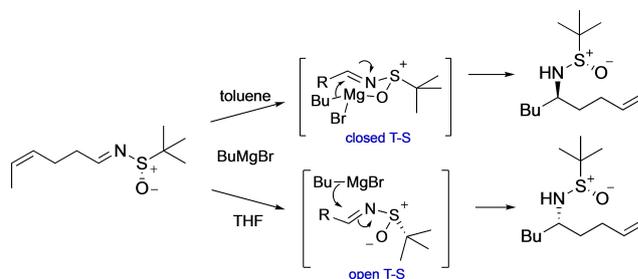
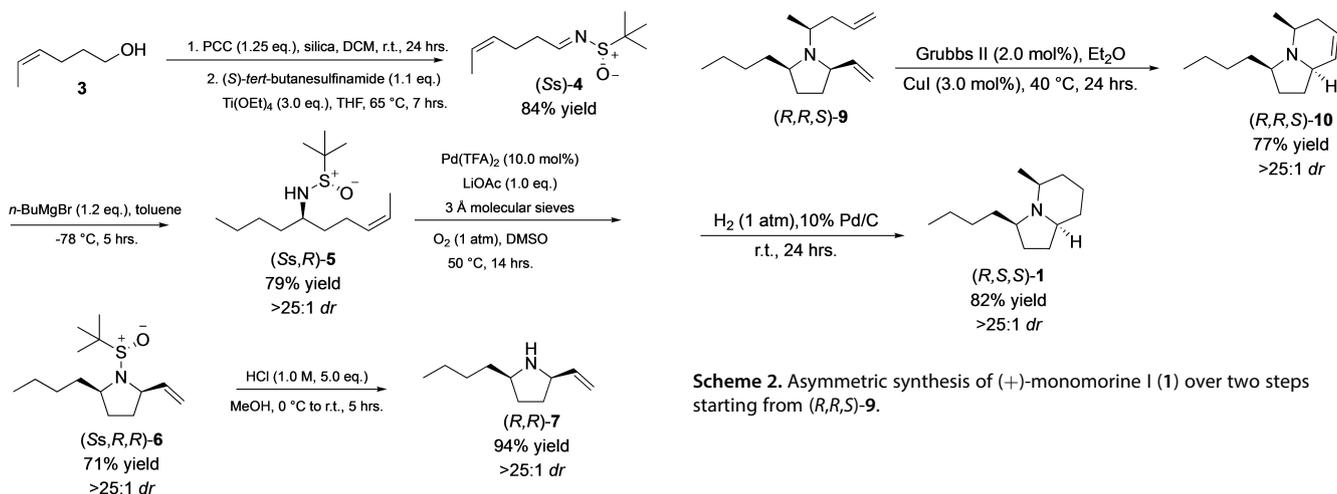


Figure 2. Use of non-coordinating solvent (toluene) favours closed transition state, and coordinating solvent (THF) favours an open transition state in Grignard addition to sulfinimines.<sup>[25,26]</sup>

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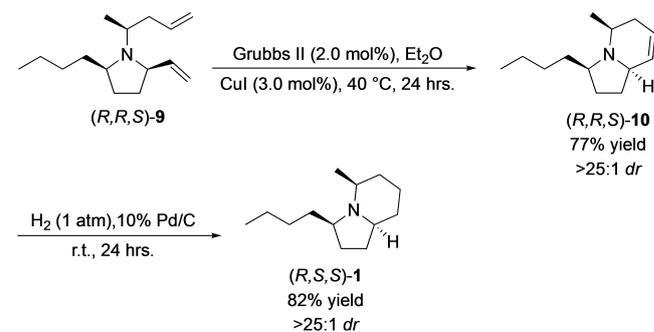
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**Scheme 1.** Synthesis of *cis*-pyrrolidine derivative (*R,R*)-7 starting from *cis*-4-hexen-1-ol **3**.

with *n*-BuMgBr in toluene as a non-coordinating solvent to form the corresponding sulfonamide (*Ss,R*)-**5** in 79% yield with an excellent *dr* (>25:1). The stereochemistry of the new stereocentre (C-3) was assigned as *R* according to the method of Ellman and co-workers,<sup>[25,26]</sup> which is the correct stereochemistry required for the (+)-monomorine natural product **1**. Next, Stahl's Wacker-type oxidative cyclisation<sup>[27]</sup> were then applied on (*Ss,R*)-**5**, which gave the corresponding *cis*-pyrrolidine derivative (*Ss,R,R*)-**6** in a good yield (71%), very high diastereoisomeric ratio (>25:1 *dr*) with the desired stereochemistry at C-9(*S*). Following this, removal of the sulfinyl group of **6** was achieved using acidic conditions, which provided the corresponding amine (*R,R*)-**7** in an excellent yield (94%) and >25:1 *dr* (Scheme 1).

With *cis*-pyrrolidine (*R,R*)-**7** in hand, tosylation of (*R*)-4-penten-2-ol was then performed, which afforded the tosylated alcohol (*R*)-**8** in a good yield (74%). The next step included construction of the stereochemical C-5(*S*) of (+)-monomorine **1** prior to ring closing metathesis to furnish the alkene form (*R,R,S*)-**10**. This was achieved *via* S<sub>N</sub>2 nucleophilic substitution of



**Scheme 2.** Asymmetric synthesis of (+)-monomorine **1** over two steps starting from (*R,R,S*)-**9**.

(*R,R*)-**7** with (*R*)-**8** to prepare the corresponding tertiary amine (*R,R,S*)-**9**, which requires complete stereoinversion on (*R*)-**8** to give the desired C-5(*S*) at (*R,R,S*)-**9**. A range of different reaction conditions were screened for this nucleophilic substitution, to find the best results in terms of yield and diastereoselectivity as described in Table 1.

The formation of **9** proceeds with a variety of bases and solvents with moderate yield (Table 1, Entries 1–5), however the best results were observed using stronger base LiHMDS, which is able to fully deprotonate (*R,R*)-**7** giving a more reactive species towards nucleophilic substitution. This protocol afforded the desired product (*R,R,S*)-**9** as a single diastereoisomer and good yield (73%) (Table 1, Entry 6). Ring closing metathesis was then applied on (*R,R,S*)-**9** in the presence of Grubbs II catalyst, and this provide (*R,R,S*)-**10** in 77% yield with >25:1 *dr*. Finally, hydrogenation of the alkene bond at (*R,R,S*)-**10** was then performed, and the desired natural product (*R,S,S*)-**1** was isolated in 82% yield (20% an overall yield from alcohol **3**) (Scheme 2). The literature reports the specific rotation of **1** as  $[\alpha]_{\text{D}}^{20} = +34$  ( $c = 1.09$ , *n*-hexane),<sup>[28]</sup> which compares favourably with our recorded value  $[\alpha]_{\text{D}}^{23} = +32.9$  ( $c = 1.0$ , *n*-hexane).

To access (+)-indolizidine 195B (**2**), a similar strategy to that used for (+)-monomorine **1** synthesis has been employed apart from the key Grignard addition step. Thus, the desired *trans*-pyrrolidine derivative (*Ss,S,R*)-**13** was obtained in a very

**Table 1.** Optimisation of nucleophilic substitution conditions for synthesis of tertiary amine (*R,R,S*)-**9**.

Entry	Base	Solvent	T [°C]	Yield <sup>[a]</sup>	<i>Dr</i> <sup>[b]</sup>
1	NaHCO <sub>3</sub>	MeCN	82	19	> 10:1
2	NaHCO <sub>3</sub>	THF	66	23	14:1
3	NaHCO <sub>3</sub>	DCM	40	–	–
4	Et <sub>3</sub> N	THF	66	26	10:1
5	Cs <sub>2</sub> CO <sub>3</sub>	THF	66	51	20:1
6	LiHMDS	THF	66	73	> 25:1

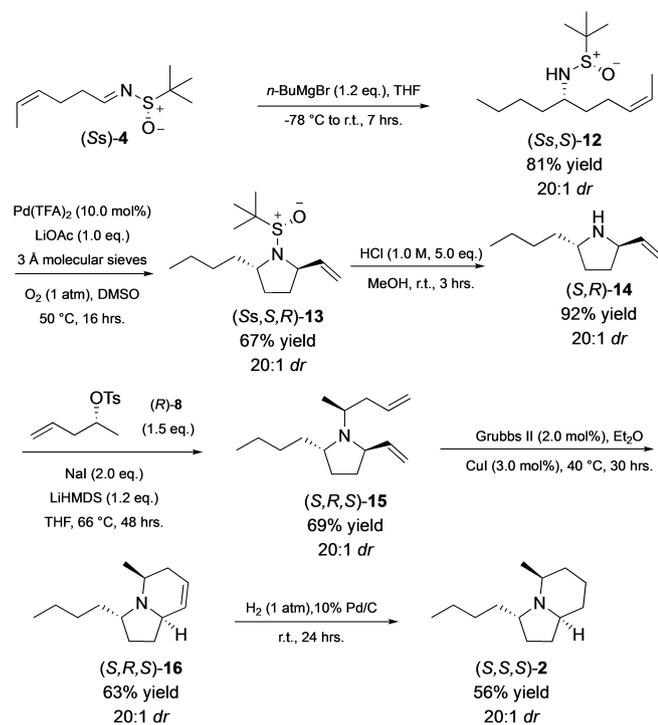
[a] Isolated Yield. [b] The *dr* values were determined by <sup>1</sup>H NMR.

high diastereoisomeric ratio (20:1 *dr*) and 46% overall yield from (*Z*)-4-hexen-1-ol **3** (Scheme 3). This included a nucleophilic addition of *n*-BuMgBr to (*Ss*)-**4** in THF as a coordinating solvent, enabling an open transition state, to form the desired stereochemistry at C–N bond of the sulfinamide formed (*Ss,S*)-**12** in 81% yield. The second C–N bond was formed by Stahl's stereoselective by Wacker oxidation, which provided (*Ss,S,R*)-**13** in 67% yield. In Stahl's paper, it was found that despite the stereochemistry of the sulfinyl group, a methyl group was able direct the stereochemistry of cyclisation, and that a *cis* pyrrolidine was formed. In our case, with a butyl group, we surmise that the extra bulk of the butyl group is not

accommodated in the presumed transition-state, and that instead an alternative transition state delivers a *trans*-substituted pyrrolidine as the major product (Figure 3). We intend to investigate whether this can be applied more generally to the synthesis of *trans* pyrrolidines in future studies. Removal of the sulfinyl group of **13**, nucleophilic substitution of the *trans*-pyrrolidine **14** with tosylate **8** and ring closing metathesis were then carried out as in the prior synthesis to afford the corresponding cyclic alkene (*S,R,S*)-**16** (40% yield over the three steps from **13**). Finally, hydrogenation of (*S,R,S*)-**16** gave (+)-indolizidine 195B (**2**) in 56% yield and 20:1 *dr* (Scheme 3). The specific rotation of our synthetic **2** was found to be  $[\alpha]_D^{25} = +97.4$  ( $c=0.2$ , MeOH), which compares well to the literature, which reports  $[\alpha]_D^{24} = +97.7$  ( $c=0.18$ , MeOH).<sup>[4]</sup>

The confirmation of the relative stereochemistry and absolute configuration of the (+)-monomorine **1** and (+)-indolizidine 195B (**2**) was based on the literature <sup>1</sup>H, <sup>13</sup>C NMR spectra and the specific rotation, respectively.<sup>[28–32]</sup>

In conclusion, stereoselective total syntheses of the indolizidine alkaloids (+)-monomorine **1** and (+)-indolizidine 195B (**2**) have been achieved from alcohol **3** in 20% and 10% overall yields, respectively, which compares well to prior syntheses which range from 2% to 36% and average 11% for asymmetric syntheses. The key step in these syntheses exploits the switching of transition states in the Grignard addition to a sulfinimine to yield to control the stereochemistry of C-3, allowing a stereodivergent route to both natural products.



Scheme 3. Stereoselective synthesis of (+)-indolizidine 195B (**2**).

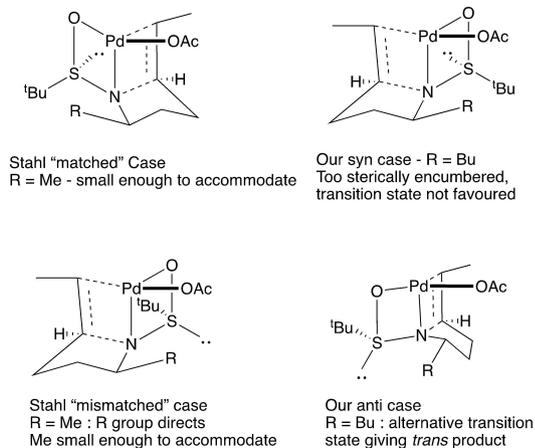


Figure 3. Proposed transition states for R = Me and R = Bu giving rise to *cis* and *trans* pyrrolidine products, respectively.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Chiral auxiliary · Natural Product · Pyrrolidine, Stereodivergent · Sulfinimine

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