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Formal synthesis of (±)-perhydrohistrionicotoxin via a stepwise [3+3] annelation strategy

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Abstract—A formal synthesis of (±)-perhydrohistrionicotoxin is described that includes a highly diastereoselective modified Sharpless aziridination and a stepwise [3+3] annelation reaction for the stereoselective construction of the key spiropiperidine motif.

The histrionicotoxin family of alkaloids are isolated from the skins of the brightly coloured poison arrow frogs *Dendrobates histrionicus* and their structures have been determined by Daly and co-workers.[1] The low natural abundance, unique biological profiles and challenging azaspirocyclic architecture of these compounds have rendered them popular targets for organic synthesis.[2,3] In this context, recent work in our laboratories has focused on developing new stereoselective methods for the synthesis of piperidine alkaloids. Specifically, we have developed a [3+3] annelation protocol that comprises the addition of a TMM-equivalent across the C–N bond of an aziridine via the employment of Trost's Pd–TMM complex[4] or an organomagnesium reagent derived from methallyl alcohol[5] (Fig. 1). We report herein, the scope of this strategy for the synthesis of azaspirocyclic piperidines and its application in the formal synthesis of (±)-perhydrohistrionicotoxin **1**. As outlined in Scheme 1, we decided to prepare **1** by intercepting Tanner's intermediate **2**[6] that we envisaged would be made available from spiropiperidine **3** after a [3+3] annelation of aziridine **4**.

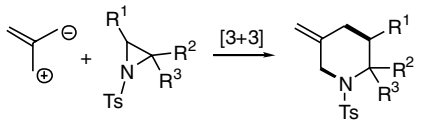
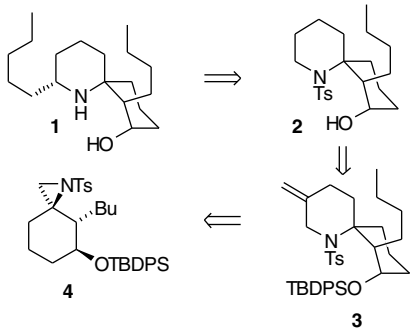


Figure 1.



Scheme 1.

Our first goal was to devise an efficient and stereoselective route to aziridine **4**. Accordingly, we employed a directed addition of *n*-BuLi to epoxide **5** following Wender's protocol[7] and protected the alcohol unit as a TBDPS–ether. Methylenation of ketone **6** using Nysted's reagent proceeded in excellent yield and set the stage for the key stereoselective aziridination reaction. Preliminary efforts focused on the use of a Cu-catalysed nitrene transfer technique,[8] however, we were disappointed to find that aziridination took place to provide **4** in very low yield and with poor levels of diastereocontrol (Scheme 2).

In an effort to improve both the yield and stereoselectivity of the aziridination, we turned our attention to Sharpless' aziridination technique[9] that uses chloramine-T in the presence of an electrophilic Br-source, our results are outlined in Table 1.

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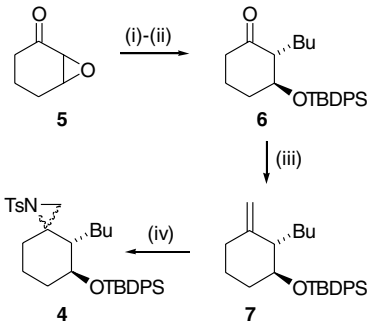
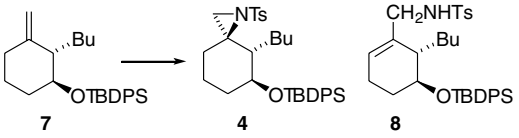


Scheme 2. Reagents and conditions: (i) (a) LDA, THF, −78 °C, 30 min; (b) *n*-BuLi, THF, −20 °C, 20 h; (ii) TBDPSCl, imidazole, DMF, 0 °C to rt, 16 h, 58% (two steps); (iii) Nysted's reagent, $TiCl_4$, THF, 0 °C to rt, 16 h, 98%; (iv) 5 mol % $Cu(OAc)_2$, PhINTs, 4 Å MS, MeCN, 16 h, 15 % (1.5:1 dr).

Table 1.



Entry	Conditions	Yield **4**[b] (%)	Yield **8** (%)
1	TsN(Na)Cl, 20% PTAB,[a] MeCN, 25 °C	26 (99:1)	34
2	TsN(Na)Cl, 20% NBS, MeCN, 25 °C	42 (99:1)	30
3	TsN(Na)Cl, 20% NBS, MeCN, 40 °C	47 (7:1)	31
4	TsN(Na)Cl, 20% NCS, MeCN, 25 °C	20[c]	0

[a] PTAB: phenyltrimethylammonium tribromide.
[b] Diastereomeric ratios are given in parentheses.
[c] A trace amount of the undesired diastereomer was also detected.

Employment of Sharpless' conditions provided an immediate improvement in reaction diastereoselectivity, providing the desired aziridine **4**, albeit in poor yield together with allylic amide **8** as a by-product (entry 1). The stereochemistry of aziridine was confirmed to be the desired *pseudo*-equatorial sulfonamide by NOESY spectroscopy (Fig. 2).[10] We next examined a series of alternative Br-sources and were pleased to find that the yield could be improved by the use of NBS[11] without diminishing reaction stereoselectivity (entry 2). Unfortunately however, the reaction efficiency could not be enhanced further by varying reaction temperature or by using alternative electrophilic halide sources (entries 3 and 4).[12]

With the desired aziridine in hand, we turned our attention to the key piperidine forming reaction. As outlined

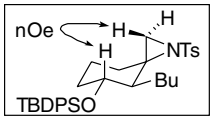
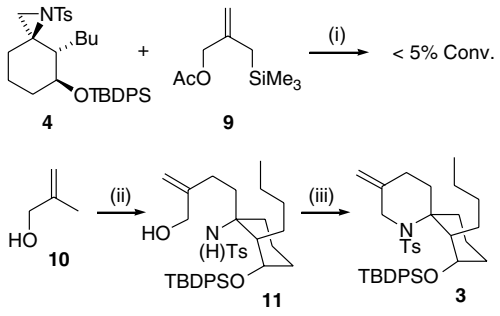


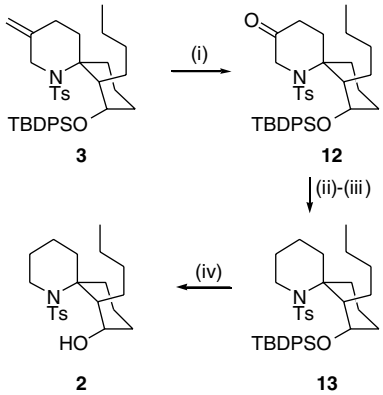
Figure 2.



Scheme 3. Reagents and conditions: (i) (a) 10% $Pd(OAc)_2$, 20% *n*-BuLi, 60% $P(OPr\text{-}i)_3$, 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**9**), THF, reflux, 16 h; (ii) *n*-BuLi, TMEDA, $MgBr_2$, **4**, ether/THF, 3 d, 96%; (iii) 10% $Pd(OAc)_2$, 40% PPh_3, 25% $Ti(OPr\text{-}i)_4$, toluene, reflux, 18 h, 78%.

in Scheme 3, we initially attempted to utilise the Pd-catalysed [3+3] formal cycloaddition reaction to access the spiropiperidine directly, unfortunately however, we could not detect any cycloadduct and the starting aziridine was recovered unchanged. We have recently reported an alternative annelation procedure that involves a stepwise addition–cyclisation sequence.[5] Therefore, double deprotonation of methallyl alcohol **10** and addition of magnesium bromide provided a reagent that underwent efficient addition to aziridine to provide sulfonamide **11** that was cyclised to **3** in the presence of $Ti(OPr\text{-}i)_4$ and a Pd-catalyst.

The remaining steps of the synthesis involved straightforward functional group interconversion processes. As outlined in Scheme 4, oxidative cleavage of olefin in **3** proceeded without incident. Carbonyl reduction to **13** was attempted initially under modified Wolff–Kishner conditions,[13] however, a stepwise hydride reduction followed by Barton deoxygenation was found to be more efficient. Finally, cleavage of silyl ether using TBAF proceeded smoothly to provide spiropiperidine **2**, which had previously been described by Tanner, thus completing the formal synthesis.



Scheme 4. Reagents and conditions: (i) (a) OsO_4, NMO; (b) $NaIO_4$, acetone/H_2O, 1 h, 72%; (ii) $NaBH_4$, MeOH, 1 h, 93%; (iii) (a) NaH, CS_2, MeI, THF, 16 h; (b) AIBN, *n*-Bu_3SnH, benzene, reflux, 20 h, 64% (two steps); (iv) TBAF, THF, 4 d, 98%.

In conclusion, we have described a formal synthesis of perhydrohistrionicotoxin that intercepts Tanner's intermediate in 12 steps. The synthesis includes a highly diastereoselective modified Sharpless aziridination and a stepwise [3+3] annelation reaction for the stereoselective construction of the key spiropiperidine motif.

Acknowledgements

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