Two Types of Stereocontrol in the Formation of Spiro Skeletons *via* a Carbonyl Ene Reaction and a Palladium-catalysed Carbonyl Allylation: a Formal Synthesis of (+)-Perhydrohistrionicotoxin

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Different stereocontrol is observed in the formation of spiro skeletons *via* a carbonyl ene reaction and a palladium-catalysed carbonyl allylation, and a formal synthesis of (+)-perhydrohistrionicotoxin is accomplished.

Histrionicotoxin **1** was isolated from skin extracts of the Colombian poison dart frogs, *Dendrobates histrionicus*.[1] The alkaloid and the fully hydrogenated congener, perhydrohistrioniocotoxin **2**, have become attractive synthetic targets owing to their unusual spiropiperidine structures (Fig. 1), the scarcity of natural sources[2] and their interesting pharmacological properties.[3] Although four asymmetric syntheses of **2** have been reported, the stereocontrol at the three contiguous asymmetric carbon centres was poor (low selectivity or step-wise elaboration).[4]

We describe here two types of stereocontrol in the formation of spiro skeletons *via* a carbonyl ene reaction and a palladium-catalysed carbonyl allylation. An asymmetric formal synthesis of (+)-**2** is also reported *via* a product obtained from the latter reaction.

Our pivotal synthetic strategy is the stereocontrolled construction of three contiguous asymmetric carbon centres *via* a carbonyl ene reaction[5a] or a palladium-catalysed carbonyl allylation[6] based on the chirality at the quaternary carbon centre, constructed by the Pummerer-type reaction of the chiral vinylic sulfoxide,[7] as shown in Scheme 1.

Following the method of Arnold and Holy,[8] cyclopentanone was converted into the bromide **3**, which was lithiated and treated with (−)-menthyl (*S*)-toluene-*p*-sulfinate to give the chiral vinylic sulfoxide **4** (Scheme 2). On treatment of **4** with allylmagnesium bromide, the Pummerer-type reaction proceeded to give the vinylic sulfide **5**. The enantiomeric excess (e.e.) was 90%† and the absolute configuration was assigned tentatively as *S*, after comparison with previous results.[7] The assignment was also confirmed by the successful synthesis of (+)-**2**.‡

The vinylic sulfide **5** was then treated as follows: (1) chemoselective hydroboration–oxidation, (2) mesylation, and (3) cyanation, which afforded the nitrile **6**. The acetal group of **6** was deprotected with toluene-*p*-sulfonic acid monohydrate (*p*-TsOH·H_2O), and then the resulting aldehyde was treated with Wittig reagent to provide the *cis*-olefin exclusively. After isomerization with thiophenol and AIBN to give the *trans*-olefin, the cyano moiety was reduced with diisobutylaluminium hydride (DIBAL) to give aldehyde **7**. Deacetalisation followed by Horner–Emmons reaction of nitrile **6** gave the α,β-unsaturated ester, which was reduced to allylic alcohol **8** on treatment with DIBAL.

The Lewis acid catalysed ene reaction of **7** was performed with Me_2AlCl to give the spiro compound **10** as a single isomer. The stereochemical assignment, however, revealed that the product was the undesired C-6 epimer.§ This result was different from that reported by Snider and coworkers,[5b] and can be explained as follows. In the reaction, the large STol group would be situated at an equatorial site in the six-membered cyclic transition state, as shown in Scheme 3. The formation of **10** *via* the transition state **9a** can be ascribed to the destabilisation of transition state **9b** by the 1,2-diequatorial repulsion between the aldehyde and olefin substituents.[5a]

We then tried palladium catalysed carbonyl allylation of **8**. Masuyama and coworkers[6a] reported that the reaction proceeded with high diastereoselectivity in the intermolecular allylation, but there was less information about the stereochemistry of the intramolecular version and the effect of the chirality at the allylic position. Fortunately, the palladium catalysed intramolecular carbonyl allylation of **8** [$PdCl_2(PhCN)_2$ (10 mol%), $SnCl_2$ (2.5 equiv.), H_2O (12 equiv.), THF] proceeded diastereoselectively to afford **12**

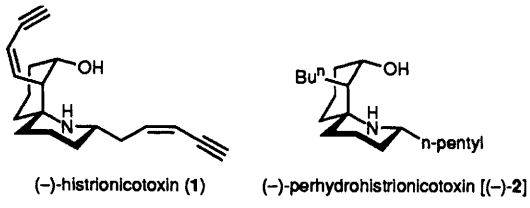
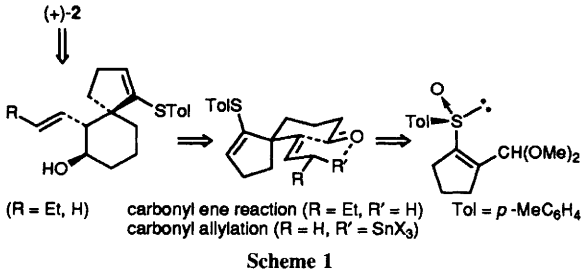
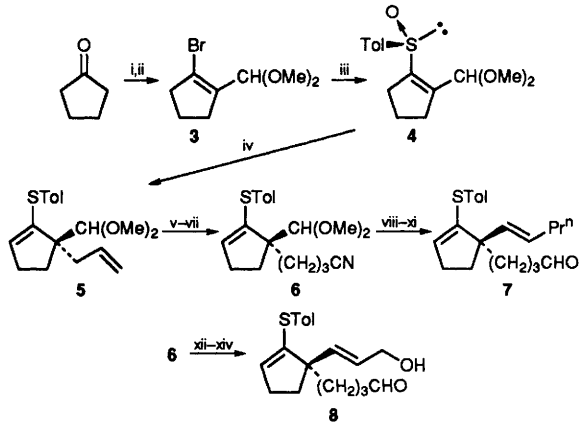


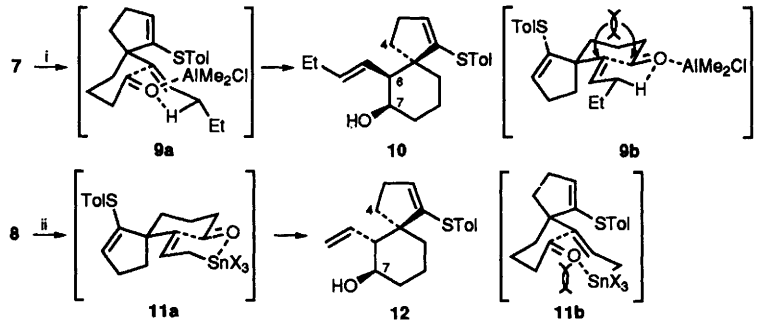
Fig. 1



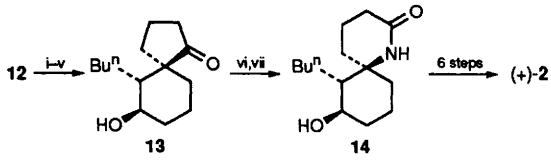
Scheme 1



Scheme 2 *Reagents and conditions*: i, PBr_3, DMF, $CHCl_3$, 0–20 °C, overnight; ii, $CH(OMe)_3$, MeOH, room temp., 1 d (55% in 2 steps). iii, Bu^nLi, (*S*)-(−)-menthyl toluene-*p*-sulfinate, THF, −78 °C, 3 h (86%); iv, allylmagnesium bromide, THF, 0 °C to room temp., 6 h (63%, 90% e.e.); v, 9-borabicyclo[3.3.1]nonane (9-BBN) dimer, THF, 0 °C to room temp., 6 h then 3 mol dm^{-3} NaOH, H_2O_2, 0 °C to room temp., 2 h (85%); vi, methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C, 30 min; vii, KCN, 18-crown-6, MeCN–H_2O, reflux, 6 h (75% in 2 steps); viii, *p*-TsOH·H_2O, acetone, room temp., overnight; ix, $Ph_3P^+Bu^nBr^-$, Bu^nLi, THF, room temp., 4 h (85% in 2 steps); x, PhSH, AIBN, benzene, reflux, 6 h (90%); xi, DIBAL, CH_2Cl_2, −78 °C, 2 h (80%); xii, *p*-TsOH·H_2O, acetone, room temp., overnight; xiii, $(EtO)_2P(O)CH_2CO_2Et$, Bu^tOK, THF, −40 °C, 2 h (80% in 2 steps); xiv, DIBAL, toluene, −78 °C to room temp., 5.5 h (92%)



Scheme 3 *Reagents and conditions*: i, Me_2AlCl, CH_2Cl_2, 0 °C, 3 h (67%); ii, $PdCl_2(PhCN)_2$ (10 mol%), $SnCl_2$, THF–H_2O, room temp., 24 h (60%, **12**: other isomers 83 : 17)



Scheme 4 *Reagents and conditons*: i, methoxymethyl chloride, Pr^i_2EtN, CH_2Cl_2, DMAP, room temp., 10 h (89%); ii, 9-BBN dimer, THF, room temp., 12 h, then 3 mol dm^{-3} NaOH, H_2O_2, 0 °C, 1 h (75%); iii, toluene-*p*-sulfonyl chloride (*p*-TsCl), pyridine, DMAP, CH_2Cl_2, room temp., 1 h (80%); iv, Et_2CuLi, Et_2O, −40 °C, 2 h (74%); v, 10% HCl, MeCN, 60 °C, 2 h (77%); vi, $MeCO_2Na$, NH_2OH·HCl, MeOH, room temp., 2 d (64%); vii, *p*-TsCl, pyridine, benzene, room temp., 12 h (32%)

with the desired stereochemistry, along with two isomers (**12**: other isomers 83 : 17).¶ The stereoselectivity of this reaction may be rationalised as follows. The transition state **11a** would predominate over **11b** owing to the steric interactions between the bulky stannyl group and the axial substituent in **11b**, thereby affording **12** as the major product.

The elaboration of **12** to a known intermediate of (+)-**2** was performed by the following sequence: (1) protection of secondary alcohol, (2) hydroboration–oxidation, (3) tosylation, (4) ethylation, and (5) deprotection of alcohol and ketone to afford ketol **13** (Scheme 4). The spectroscopic data (IR, ^{1}H NMR) of **13** was consistent with data for an authentic sample of racemic **13**. Then ketol **13** was transformed into the amide **14**. The synthesised **14** {$[\alpha]_D^{22}$ +61.2 (*c* 0.61, $CHCl_3$), lit.[4d] $[\alpha]_D^{25}$ +65.1 (*c* 1.00, $CHCl_3$)} was shown to be identical with an authentic racemic sample by comparison of the spectroscopic properties (IR, ^{1}H NMR, MS). Since (+)-**14** leads to (+)-**2** in 6 steps by the method of Takahashi and coworkers,[4d] we achieved a formal synthesis of (+)-**2**.

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Footnotes

† The optical purity of **5** was determined in a similar manner to that reported in ref. 7*b*.

‡ The results may be explained by the *si*-face attack of Grignard reagent *via* coordination of the sulfinyl oxygen with magnesium ion.

§ The stereochemical assignment of compound **10** was established by an NOE observed between C-4 and C-7 protons and the coupling constant of C-7 proton (dd, *J* 12.5, 3.0, 3.0 Hz) at δ 3.76, which shows the existence of an axial–axial coupling and two axial–equatorial ones with *vicinal* protons.

¶ The stereochemistry of compound **12** was confirmed as follows. An NOE was observed between C-4 and C-7 protons and the coupling constant of C-7 proton (ddd, *J* 10.0, 10.0, 4.5 Hz) at δ 3.50 showed the existence of two axial–axial couplings and an axial–equatorial one with *vicinal* protons. The assignment was also confirmed by the synthesis of (+)-**2**.

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