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Diastereoselective construction of chiral building blocks for the synthesis of indole alkaloids using an intramolecular Heck reaction

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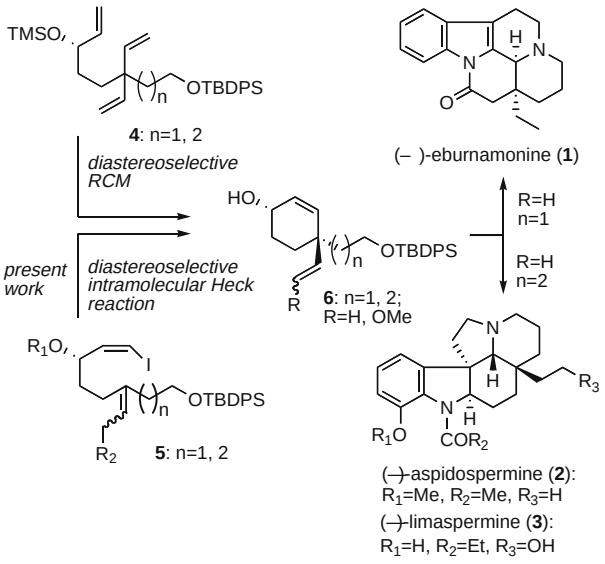
ABSTRACT

Highly diastereoselective construction of the chiral building blocks, with an allylic quaternary carbon stereogenic center, for the synthesis of indole alkaloids has been accomplished by employing a 1,4-chirality transfer via the intramolecular Heck reaction.

Since there are many biologically significant natural and unnatural compounds with quaternary carbon stereogenic center(s), developing new methodologies for the installation of this structural motif is an important issue in organic synthesis.[1] In our previous papers, we described the development of a strategy for constructing the chiral building blocks **6** (n = 1, 2; R = H) with a quaternary center on a cyclohexenol ring by 1,4-chirality transfer via a diastereoselective ring-closing metathesis of **4**,[2] and demonstrated that they can be successfully applied to the asymmetric syntheses of the indole alkaloids (−)-eburnamonine (**1**)[3] (from **6**; n = 1, R = H), (−)-aspidospermine (**2**)[4], and (−)-limaspermine (**3**)[5] (from **6**; n = 2, R = H).

Asymmetric creation of the quaternary center based on the intramolecular Heck (IMH) reaction[6] has been examined by many groups with most of the efforts focusing on the asymmetric IMH reaction using a chiral ligand.[7] However, there have been very few reports of strategies based on the 1,4-chirality transfer via the IMH reaction of acyclic substrates. In 1999, Negishi et al. communicated a methodology for the construction of a quaternary stereogenic center in cycloalkenols by a cyclic carbopalladation–carbonylative esterification, and prepared 3,4,4-trisubstituted cyclohexenols.[8] In the conversion, it was found that 1,4-chirality transfer occurred in as high as 98% diastereoselectivity. During the course of our research on the development of an efficient strategy for the preparation of the chiral building blocks **6** (4,4-disubstituted cyclohexenols),[9] we envisaged that the intramolecular Heck (IMH) reaction (sequential cyclic carbopalladation-reductive elimination) of **5**, possessing a terminal vinyl iodide and trisubstituted alkene moieties, would play a pivotal role in our objective. In this Letter, we report a diastereoselective strategy for assembling the chiral building blocks **6** using the IMH reaction of compounds **5** (Scheme 1).

To investigate the diastereoselectivity of the key IMH reaction, we first prepared the racemic substrates **5a–c**. As the protecting group of the allylic alcohol moiety, we chose *tert*-butyldimethylsilyl (TBS) on the basis of literature precedent.[8] Regioselective reductive coupling of the alkynes **7** (n = 1,2) and the aldehydes with $CrCl_2$ and a catalytic amount of $NiCl_2$ and triphenylphosphine in aqueous DMF[10] produced the allylic alcohols **8a–c**. Claisen rearrangement of the corresponding vinyl ethers gave the aldehydes **9a–c**, which were reacted with lithium trimethylsilylacetylide. The resulting alcohols **10a–c** were protected as TBS ethers to give **11a–c**. They were then treated with NIS and $AgNO_3$[11] to provide the acetylenic iodides which were reduced with diimide, generated



Scheme 1. Strategies of the construction of chiral building blocks for the syntheses of indole alkaloids.

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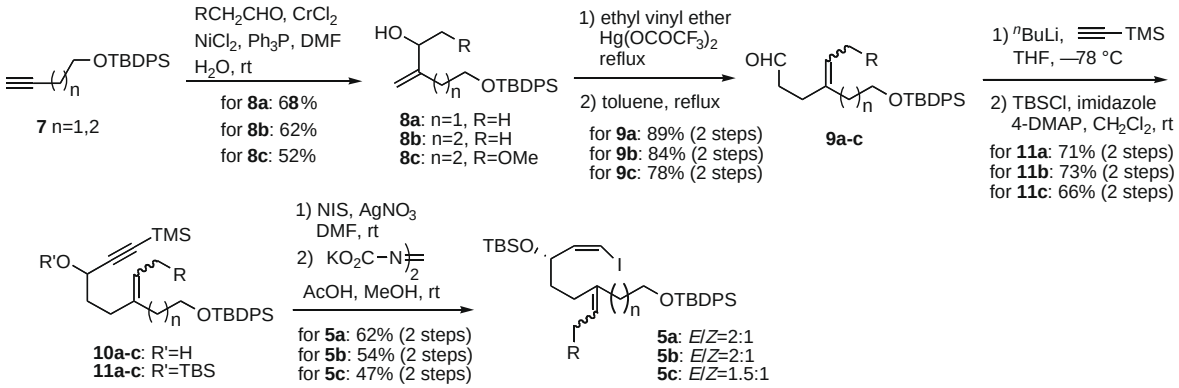
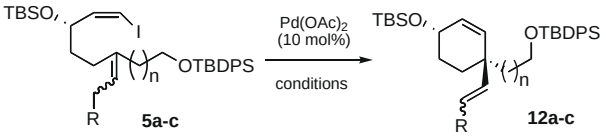


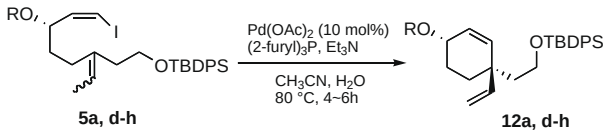
Scheme 2. Preparation of the racemic substrates **5a–c** for the IMH reaction.

Table 1
The IMH reactions of **5a–c**



Entry	5	n	R	Conditions	Yield ,% of 12	de (%)
1	**a**	1	H	(*o*-Tol)$_3$P, Et$_3$N,CH$_3$CN H$_2$O, 80 °C, 6 h	83	94
2	**a**	1	H	(2-Furyl)$_3$P, Et$_3$N,CH$_3$CN H$_2$O, 80 °C, 4 h	96	95
3	**a**	1	H	(2-Furyl)$_3$P, Et$_3$N, CH$_3$CN H$_2$O, 100 °C, 1.5 h	90	95
4	**b**	2	H	(2-Furyl)$_3$P, Et$_3$N,CH$_3$CN H$_2$O, 80 °C, 4 h	94	92
5	**c**	2	OMe	(2-Furyl)$_3$P, Et$_3$N, CH$_3$CN H$_2$O, 80 °C, 3 h	94	95

Table 2
The IMH reactions of **5d–h**



Entry	5	R	12	Yield (%)	de (%)
1	**d**	Me	**d**	89	83
2	**e**	TMS	**g**	89[a]	86[a]
3	**f**	TES	**f**	88	93
4	**g**	H	**g**	52	46
5	**h**	MOM	**h**	85	65

[a] For the desilylated product.

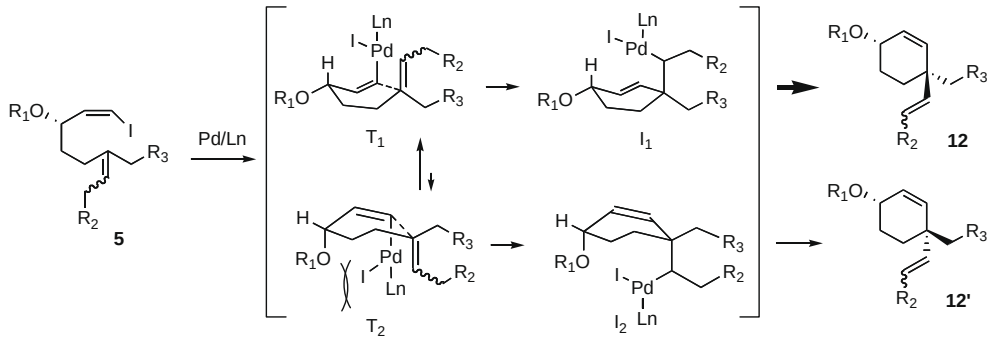
in situ from potassium azodicarboxylate and acetic acid, to give the desired **5a–c** with terminal *Z*-vinyl iodide and trisubstituted alkene (mixture of *E*/*Z* isomers) moieties (Scheme 2).

With the requisite substrates **5a–c** in hand, we then examined the cyclization to find the optimum conditions for obtaining higher yields and diastereoselectivities. The results are summarized in Table 1. Initially, **5a** was treated with Pd(OAc)$_2$ (10 mol %), (*o*-tol)$_3$P, and Et$_3$N in aqueous acetonitrile at 80 °C to give **12a** in 83% yield with 94% de (entry 1). When (2-furyl)$_3$P was used as a ligand, **12a** was obtained in higher yield and diastereoselectivity (entry 2). A higher reaction temperature led to a lower yield of the product (entry 3). Other substrates **5b,c** were treated with the optimized conditions (entry 2) to give the cyclized products **12b,c**[12] in good yields and diastereoselectivities (entries 4 and 5).[13]

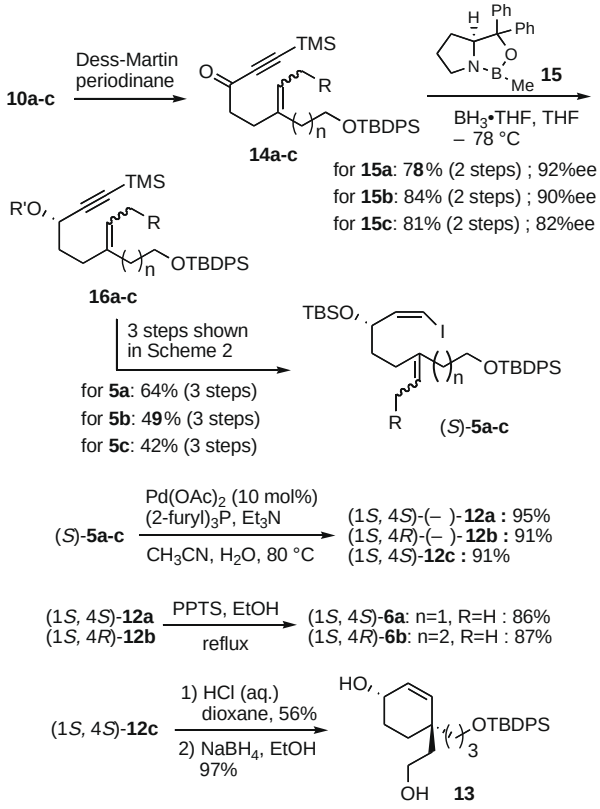
Next, we examined the effect of protecting groups (R in Table 2) on the yield and diastereoselection. The results are shown in Table 2. It was found that the more sterically demanding protecting groups provided higher yields and diastereoselectivities. In the case of **5e,f**, the results were comparable with those of **5a**. When the unprotected and the MOM-protected substrates **5g,h** were used (Table 2), the diastereoselectivity dropped significantly.

The structures of **12a,b** thus obtained were confirmed by the comparison of the ^{1}H and ^{13}C NMR data with those of the optically active authentic compounds[3–5] that were prepared previously by us. As shown in Scheme 3, the cyclization process involves the diastereoselective formation of the intermediate I_1, which subsequently undergoes reductive elimination of the palladium hydride species to give predominantly product **12** via the transition state T_1. The diastereoselection attained in the cyclization step from either the boat-like transition state T_1 or T_2 can be rationalized as a consequence of the allylic strain between the two transition states ($T_1 > T_2$).[8] The decrease in de for **5g,h** (entries 5 and 6 in Table 2) may be due to the internal chelation of the hydroxy and MOM groups with the palladium in the transition state T_2, which would collapse to form the undesired isomer **12′**. The structure of **12c** was deduced from the proposed mechanism (Scheme 3).

To obtain the optically active building blocks **12a–c**, the alkynyl alcohols **10a–c** were oxidized with Dess–Martin periodinane to give the ketones **14a–c**, which were reduced with the chiral oxazaborolidine **15** and BH$_3$·THF[14] to produce the optically active (*S*)-**11a–c** with enantiomeric excesses of 92%, 90%, and 82%, respectively. According to the procedures for racemate synthesis, they were then converted to (*S*)-**5a–c** via three steps, which were subjected to the IMH reactions to give the optically active **12a–c**. On



Scheme 3. Proposed mechanism for the IMH reaction.



Scheme 4. Syntheses of the chiral building blocks.

exposure of **12a,b** to PPTS in ethanol, selective desilylation occurred to give **6a,b** in good yields. The optical rotations of the synthetic **6a,b** (92% and 90% ee, respectively) showed good agreement with those of the authentic materials; for **6a**, $[\alpha]_D^{30}$ −25.6 ($CHCl_3$, *c* 1.10){lit.[3] $[\alpha]_D^{30}$ −27.7 ($CHCl_3$, *c* 1.12)}; for **6b**, $[\alpha]_D^{30}$ −32.7 ($CHCl_3$, *c* 0.50){lit.[4] $[\alpha]_D^{30}$ −36.6 ($CHCl_3$, *c* 0.90)}. The methyl enol ether moiety of **12c** was hydrolyzed with HCl (aq), and the resulting hydroxy aldehyde was reduced with $NaBH_4$ to give the diol **13** {$[\alpha]_D^{30}$ −61.4 ($CHCl_3$, *c* 0.02)}. It could subsequently serve as a useful chiral building block for the synthesis of limaspermine **3** and related alkaloids (Scheme 4).

In summary, a strategy for the preparation of three types of chiral building blocks for the syntheses of the eburna and the aspidosperma indole alkaloids based on a 1,4-chirality transfer via the IMH reaction has been demonstrated. The IMH reaction proceeded with high diastereoselectivity to provide the 4,4-disubstituted cyclohexenols, possessing an allylic quaternary carbon stereogenic center, in excellent yields. The methodology described here holds considerable promise for the synthesis of natural products with quaternary carbon centers.

Acknowledgment

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12. The reaction of **5c** was performed using a mixture of *E*/*Z* isomers (ca. 1.5:1). Attempted reactions for the separated isomers under the same reaction conditions resulted in similar results; for the *E*-isomer, 94%, 95% de; for the *Z*-isomer, 93%, 97% de.
13. *Typical experimental procedure*: To a stirred solution (1.0 M) of **5** (1 equiv) in CH_3CN/H_2O (10:1) were added $Pd(OAc)_2$ (10 mol %), phosphine ligand (20 mol %), and Et_3N (2 equiv), and the resulting mixture was stirred at 80–100 °C for 1.5–6 h. After removal of the solvent, the residue was chromatographed on silica gel column (AcOEt/hexane = 1:20) to give the cyclized product **12**.
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