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## STUDIES ON THE PREPARATION OF 1,5-METHANOAZOCINO- INDOLE BASED ON INDOLYLBORATE

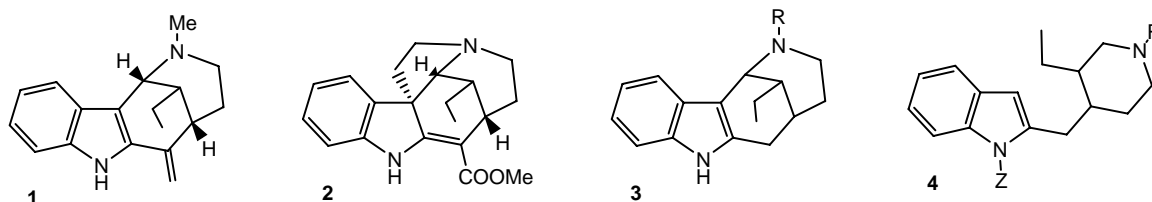
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**Abstract** – Conversion of piperidine (**8**), readily available from the palladium catalyzed tandem cyclization-cross-coupling reaction of indolylborate (**6**) with bromide (**7**), to 1*H*-1,5-methanoazocino[4,3-*b*]indole (**15**) through piperidine (**14**) was investigated.

Uleine (**1**) and tubotaiwine (dihydrocondylocarpine) (**2**) are of a class of alkaloids composed of a 1*H*-1,5-methanoazocino[4,3-*b*]indole core (**3**) as its key feature, and several groups have completed the syntheses **1** and **2** as well as more complex molecules of this class of alkaloids.<sup>1</sup> Among the known synthetic approaches, the cyclization of piperidine (**4**) by way of iminium ions has been developed as a stereoselective method of synthesizing the azocinoindole core (**3**).<sup>2</sup>

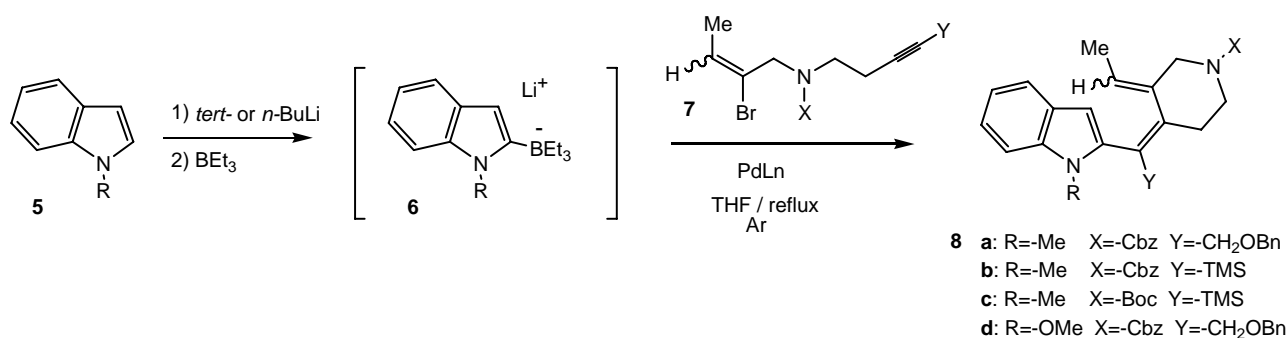


In the course of our investigation to develop the synthetic potential of indolylborate (**6**), readily available *in situ* from indole (**5**),<sup>3</sup> we have previously reported a novel synthesis of ellipticine based on the palladium-catalyzed tandem cyclization-cross-coupling reaction of **6**, which involved the construction of pyridocarbazole core by way of the cyclization of piperidine (**8**; R=Boc, X=Cbz, Y=Me).<sup>4</sup> Thus, facile

availability of **8** from the cross-coupling reaction of **6** with **7** in a one-pot manner prompted us to derive an alternative protocol for the generation of piperidine (**4**). Herein are the results of our preliminary investigation.

Based on the previous protocol,<sup>4</sup> the palladium-catalyzed cross-coupling reaction of **6** was effected with a mixture of (*E/Z*)-bromides (**7**) having sterically hindered group at the acetylenic carbon to give **8** as an inseparable mixture of (*E/Z*)-isomers, but with somewhat less satisfactory yields, as shown in Table.

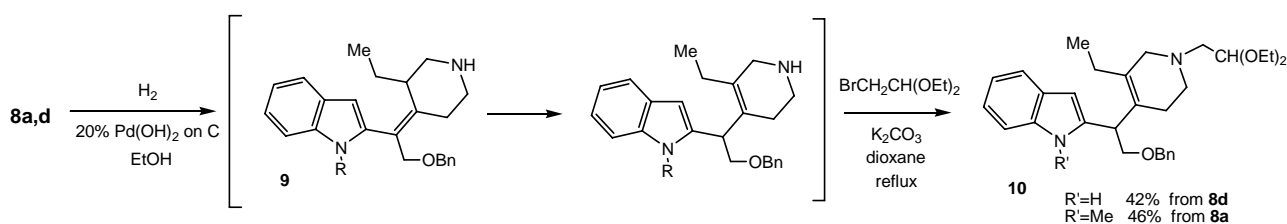
Table Cross-coupling reaction of **6** with **7**



R	<b>7</b>	PdLn	Yield(%) <sup>a</sup> of <b>8</b>
Me	<b>7a</b> (X=Cbz Y=CH <sub>2</sub> OBn)	Pd(OAc) <sub>2</sub>	33 ( <b>8a</b> )
Me	<b>7a</b> (X=Cbz Y=CH <sub>2</sub> OBn)	Pd <sub>2</sub> (dba) <sub>3</sub> +4P( <i>tert</i> -Bu) <sub>3</sub>	45 ( <b>8a</b> )
Me	<b>7a</b> (X=Cbz Y=CH <sub>2</sub> OBn)	Pd <sub>2</sub> (dba) <sub>3</sub> CHCl <sub>3</sub> +4PPh <sub>3</sub>	50 ( <b>8a</b> )
Me	<b>7b</b> (X=Cbz Y=TMS)	Pd <sub>2</sub> (dba) <sub>3</sub> CHCl <sub>3</sub> +4PPh <sub>3</sub>	40 ( <b>8b</b> )
Me	<b>7c</b> (X=Boc Y=TMS)	PdCl <sub>2</sub> [P( <i>o</i> -tol) <sub>3</sub> ] <sub>2</sub>	55 ( <b>8c</b> )
OMe	<b>7a</b> (X=Cbz Y=CH <sub>2</sub> OBn)	Pd <sub>2</sub> (dba) <sub>3</sub> CHCl <sub>3</sub> +IMes <sup>b</sup>	49 ( <b>8d</b> )
OMe	<b>7a</b> (X=Cbz Y=CH <sub>2</sub> OBn)	PdCl <sub>2</sub> [P( <i>o</i> -Tol) <sub>3</sub> ] <sub>2</sub>	55 ( <b>8d</b> )

<sup>a</sup> Yields(%) based on indole (**5**) <sup>b</sup> IMes: 2-imidazolidinylidene

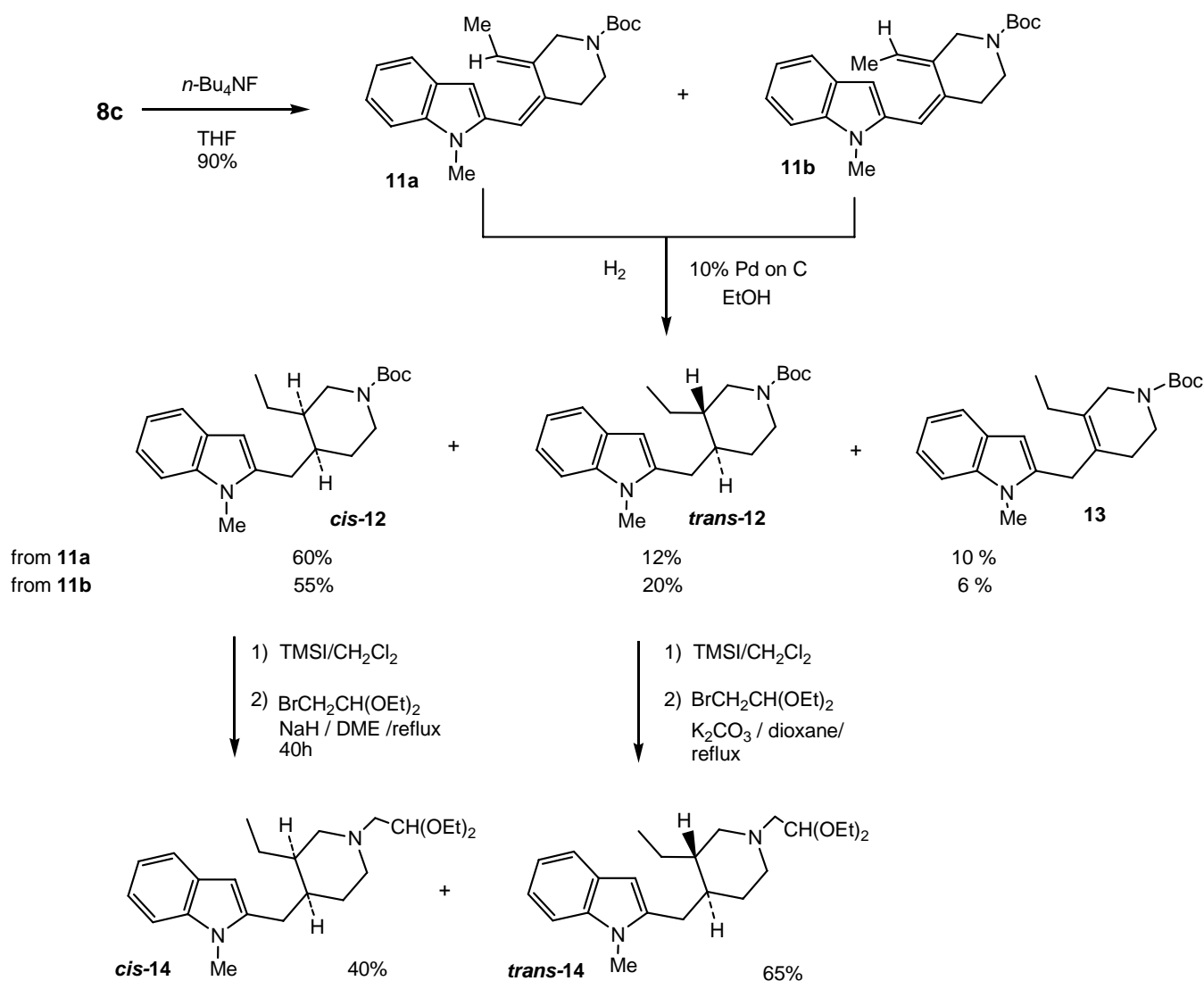
Next, conversion of piperidine (**8**) to **12** was investigated (Scheme 1). When **8a,d** were subjected to catalytic hydrogenation under medium pressure, followed by treatment with bromoacetal without purification, we obtained only **10** with both isomerization of the double bond and retention of the benzyl group. Piperidines (**10**) were probably formed from the rapid reduction of the ethylidene group in **8** leading to **9**, followed by isomerization of the double bond. Attempts to reduce **10** under various



Scheme 1

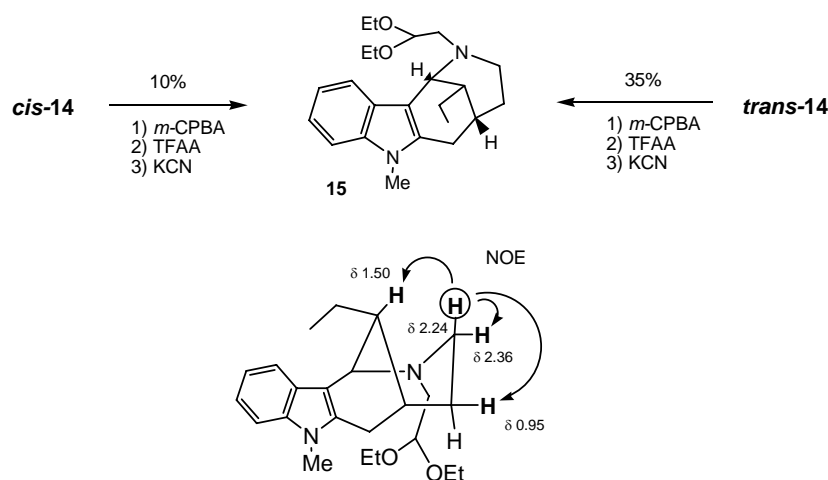
conditions resulted only in the recovery of unchanged **10**, leaving the benzyl group and the double bond intact.

With these results in mind, we then set about the use of piperidine (**11**). Treatment of **8c** with *n*-Bu<sub>4</sub>NF in THF readily afforded a mixture of **11a** and **11b**, separable by medium pressure liquid chromatography. Catalytic hydrogenation of **11a** and **11b**, respectively, using 10%Pd on C in EtOH under 4 atmospheric pressure of hydrogen smoothly proceeded to afford *cis*-**12**, *trans*-**12** and **13** as shown in Scheme 2. Then, *cis*- and *trans*-**12** were respectively subjected to a two-step sequence to *cis*- and *trans*-**14** involving removal of the *N*-Boc group and *N*-alkylation with bromoacetal.<sup>5</sup> The structural assignment of *cis*-**14** and *trans*-**14** was based on a comparison with authentic samples of each isomer, derived from the known piperidines (**4**;Z=H, R=Bn).<sup>2a</sup> The transformation was successful with *trans*-**12** to give *trans*-**14**, whereas the reaction of *cis*-**12** with bromoacetal was sluggish, requiring forced conditions to produce *cis*-**14**.



Scheme 2

Next, the cyclization of piperidines (*cis/trans*-**14**) was investigated (Scheme 3). Cyclization reaction of *cis*- and *trans*-piperidines (**4**; Z=Boc, R=Bn) [1) oxidation with *m*-CPBA, 2) addition of TFAA, 3) sequential addition of KCN]<sup>2</sup> is known to allow the isolation of the corresponding  $\alpha$ -cyanopiperidine derivatives of **4**. Using the same reaction conditions, cyclization reaction of *trans*-**14** was carried out to afford **15** without the isolation of  $\alpha$ -cyanopiperidine, but with a somewhat less yield.<sup>6</sup> On the other hand, the same treatment of *cis*-**14** unexpectedly led to dissatisfactory results in which only a small amount of **15** was obtained, accompanied by a considerable formation of unidentified materials. The results encountered in the cyclization stage of **14** seems to be ascribable to the electron-donating nature of the *N*-methyl group of the indole ring.<sup>2a</sup> Structure of **15** was confirmed based on NOE experiments.



Scheme 3

In summary, we have described an access to piperidines (**14**) by way of **8** readily available from the tandem cyclization-cross-coupling reaction of indolylborate (**6**) with bromide (**7**), and the subsequent conversion of **14** to 1*H*-1,5-methanoazocino[4,3-*b*]indole (**15**). Further investigation is in progress, including the optimization of the cross-coupling reaction using **6** bearing a versatile *N*-protecting group.

## ACKNOWLEDGEMENTS

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5. **cis-14**:  $^1\text{H-NMR}$  ( $\text{CHCl}_3$ ):  $\delta$  0.94 (t, 3H,  $J=7.5$  Hz), 1.20 (t, 3H,  $J=7.5$  Hz), 1.21 (t, 3H,  $J=7.5$  Hz), 1.38-1.42 (m, 1H), 1.51-1.67 (m, 5H), 1.91 (br s, 1H), 2.16-2.32 (m, 1H), 2.46 (dd, 1H,  $J=5.1$ , 13.1 Hz), 2.53 (dd, 1H,  $J=5.1$ , 13.1 Hz), 2.64-2.76 (m, 3H), 3.51-3.57 (m, 2H), 3.64-3.73 (m, 2H), 3.66 (s, 3H), 4.62 (t, 1H,  $J=5.1$  Hz), 6.23 (s, 1H), 7.06 (dt, 1H,  $J=1.0$ , 7.8 Hz), 7.14 (dt, 1H,  $J=1.0$ , 7.8 Hz), 7.26 (d, 1H,  $J=8.0$  Hz), 7.52 (d, 1H,  $J=8.3$  Hz).  $^{13}\text{C-NMR}$  ( $\text{CHCl}_3$ ):  $\delta$  12.4, 15.5, 19.8, 28.1, 29.7, 37.8, 40.4, 53.6, 56.4, 61.4, 61.6, 61.8, 100.2, 101.4, 108.9, 119.4, 119.8, 120.6, 128.0, 137.5, 139.8. HR-MS  $m/z$ : Calcd for  $\text{C}_{23}\text{H}_{36}\text{N}_2\text{O}_2$ : 372.2776. Found: 372.2779.
- trans-14**:  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.95 (t, 3H,  $J=7.5$  Hz), 1.19 (t, 3H,  $J=7.5$  Hz), 1.21 (t, 3H,  $J=7.5$  Hz), 1.20-1.49 (m, 4H), 1.61-1.69 (m, 1H), 1.75-1.85 (m, 2H), 1.93 (dt, 1H,  $J=2.3$ , 11.5 Hz), 2.37 (dd, 1H,  $J=10.1$ , 14.9 Hz), 2.49 (dd, 1H,  $J=5.1$ , 13.2 Hz), 2.53 (dd, 1H,  $J=5.1$ , 13.2 Hz), 2.86 (d, 1H,  $J=10.9$  Hz), 3.08 (d, 1H,  $J=11.5$  Hz), 3.15 (dd, 1H,  $J=2.9$ , 14.9 Hz), 3.51-3.62 (m, 2H), 3.66 (s, 3H), 3.62-3.74 (m, 2H), 4.63 (t, 1H,  $J=5.1$  Hz), 6.23 (s, 1H), 7.06 (t, 1H,  $J=7.8$  Hz), 7.14 (dt, 1H,  $J=1.0$ , 7.8 Hz), 7.25 (d, 1H,  $J=8.0$  Hz), 7.51 (d, 1H,  $J=8.3$  Hz).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  11.3, 15.4, 24.0, 29.7, 30.5, 31.3, 40.0, 42.5, 54.5, 59.3, 61.3, 61.7, 61.9, 100.5, 101.5, 108.8, 119.3, 119.7, 120.5, 127.9, 137.9, 139.6. HR-MS  $m/z$ : Calcd for  $\text{C}_{23}\text{H}_{36}\text{N}_2\text{O}_2$ : 372.2776. Found: 372.2776.
6. **15**:  $^1\text{H-NMR}$  ( $\text{benzene-d}_6$ ):  $\delta$  0.80 (t, 3H,  $J=7.4$  Hz), 0.95 (dd, 1H,  $J=2.9$ , 12.6 Hz), 1.06 (t, 3H,  $J=7.5$  Hz), 1.10 (t, 3H,  $J=7.5$  Hz), 1.30-1.43 (m, 1H), 1.46-1.55 (m, 2H), 1.60-1.69 (m, 2H), 2.24 (dt, 1H,

$J=2.3, 12.1$  Hz), 2.36 (d, 1H,  $J=12.1$  Hz), 2.49 (dd, 1H,  $J=4.0, 13.8$  Hz), 2.69 (s, 3H), 2.67-2.72 (m, 1H), 2.81 (dd, 1H,  $J=6.3, 13.8$  Hz), 3.08-3.15 (m, 1H), 3.28-3.35 (m, 2H), 3.39-3.45 (m, 1H), 3.53-3.60 (m, 1H), 4.30 (d, 1H,  $J=4.0$  Hz), 4.55 (dd, 1H,  $J=4.0, 6.3$  Hz), 6.80 (d, 1H,  $J=8.0$  Hz), 7.11 (t, 1H,  $J=7.5$  Hz), 7.19 (t, 1H,  $J=7.5$  Hz), 8.20 (d, 1H,  $J=8.0$  Hz).  $^{13}\text{C-NMR}$  (benzene- $d_6$ ):  $\delta$  10.9, 15.3, 22.2, 28.5, 29.1, 29.5, 37.4, 45.1, 50.1, 57.1, 58.2, 61.0, 61.8, 101.7, 108.8, 110.0, 115.4, 120.8, 123.0, 123.3, 124.8, 137.0, 152.0. HR-MS  $m/z$ : Calcd for  $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2$ : 370.2620. Found: 370.2624. Other products, such as **16** and **17**, were not isolated in the cyclization reaction of **14**.

