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

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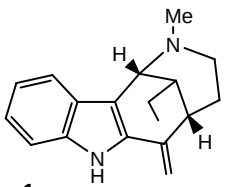
Abstract – Conversion of piperidine (**8**), readily available from the palladium catalyzed tandem cyclization-cross-coupling reaction of indolylborate (**6**) with bromide (**7**), to 1*H*-1,5-methanoazocino[4,3-*b*]indole (**15**) through piperidine (**14**) was investigated.

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.[1] 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**).[2]



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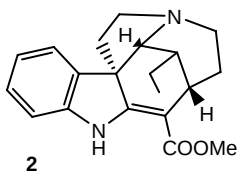

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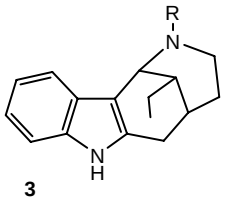

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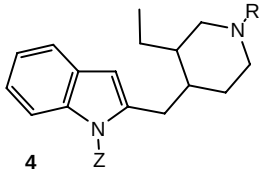


4

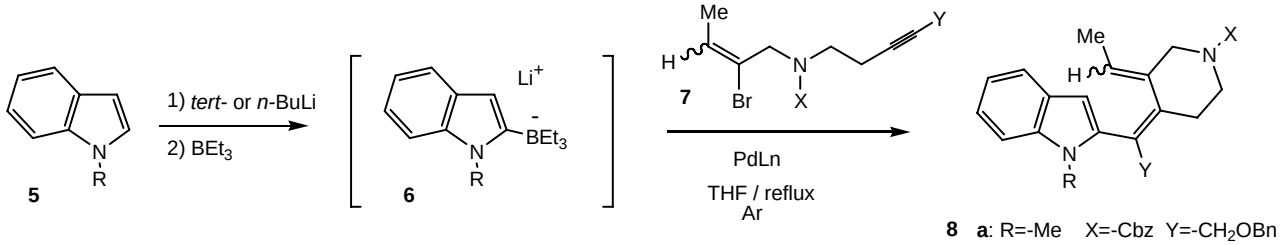
In the course of our investigation to develop the synthetic potential of indolylborate (**6**), readily available *in situ* from indole (**5**),[3] we have previously reported a novel synthesis of ellipticine based on the palladium-catalyzed tandem cyclization-cross-coupling reaction of **6**, which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

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

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,[4] 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.

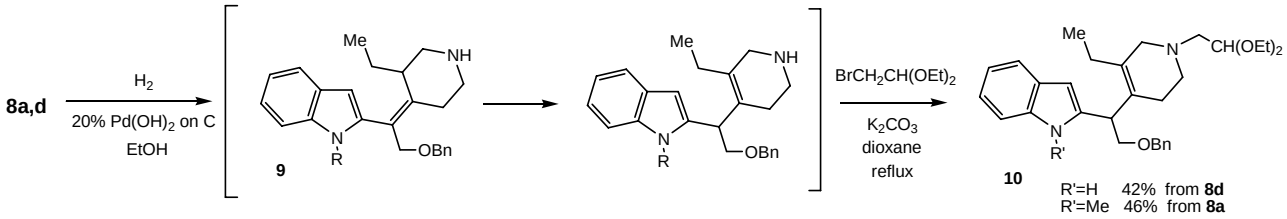
Table Cross-coupling reaction of **6** with **7**



R	**7**	PdLn	Yield(%)[a] of **8**
Me	**7a** (X=Cbz Y=CH_2OBn)	$Pd(OAc)_2$	33 (**8a**)
Me	**7a** (X=Cbz Y=CH_2OBn)	$Pd_2(dba)_3$+4P(*tert*-Bu)$_3$	45 (**8a**)
Me	**7a** (X=Cbz Y=CH_2OBn)	$Pd_2(dba)_3CHCl_3$+4PPh_3	50 (**8a**)
Me	**7b** (X=Cbz Y=TMS)	$Pd_2(dba)_3CHCl_3$+4PPh_3	40 (**8b**)
Me	**7c** (X=Boc Y=TMS)	$PdCl_2$[P(*o*-tol)$_3$]$_2$	55 (**8c**)
OMe	**7a** (X=Cbz Y=CH_2OBn)	$Pd_2(dba)_3CHCl_3$+IMes[b]	49 (**8d**)
OMe	**7a** (X=Cbz Y=CH_2OBn)	$PdCl_2$[P(*o*-Tol)$_3$]$_2$	55 (**8d**)

[a] Yields(%) based on indole (**5**) [b] IMes: 2-imidazolidinylidene

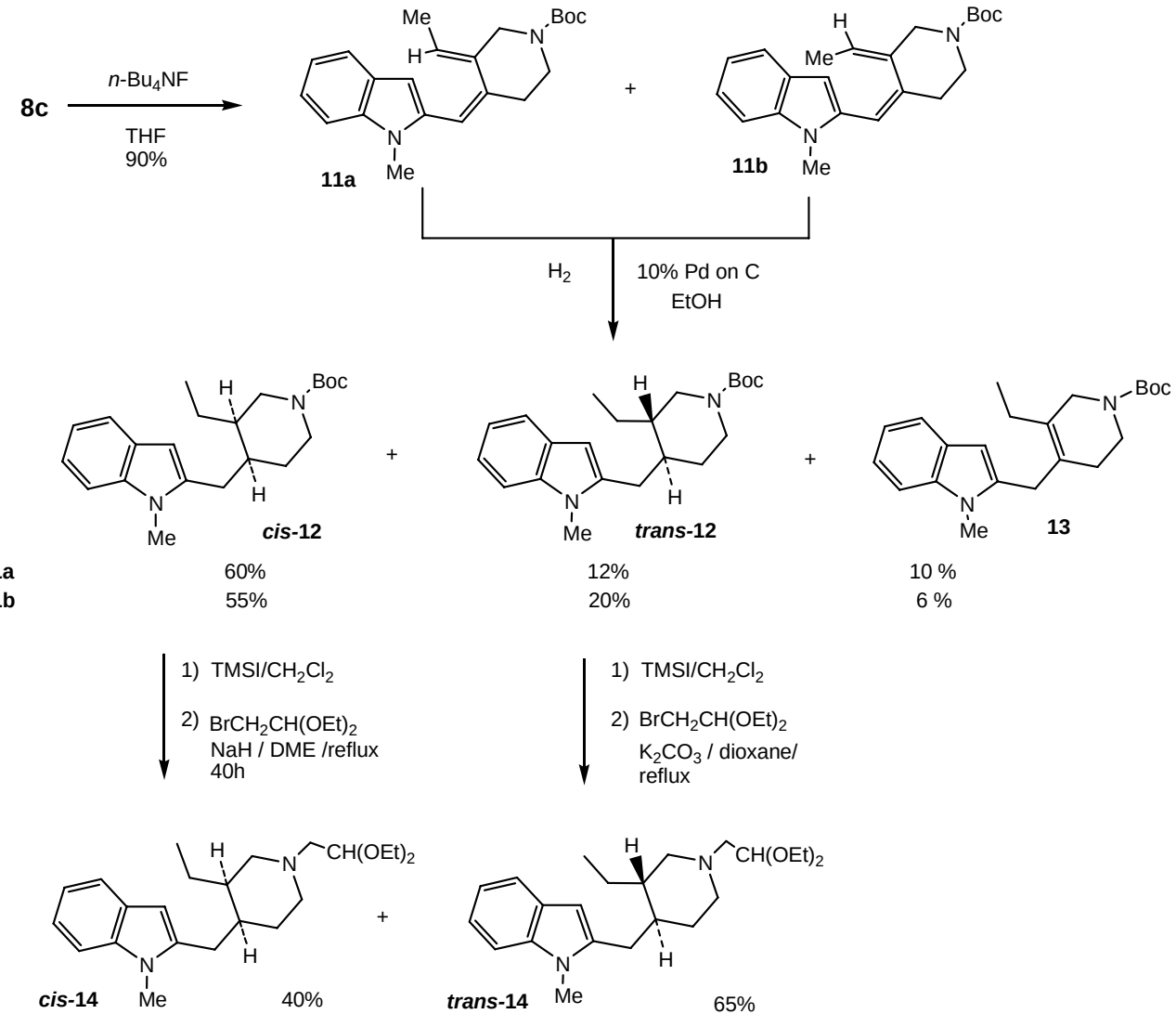
Next, conversion of piperidine (**8**) to **12** was investigated (Scheme 1). When **8a**,**d** were subjected to catalytic hydrogenation under medium pressure, followed by treatment with bromoacetal without purification, we obtained only **10** with both isomerization of the double bond and retention 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

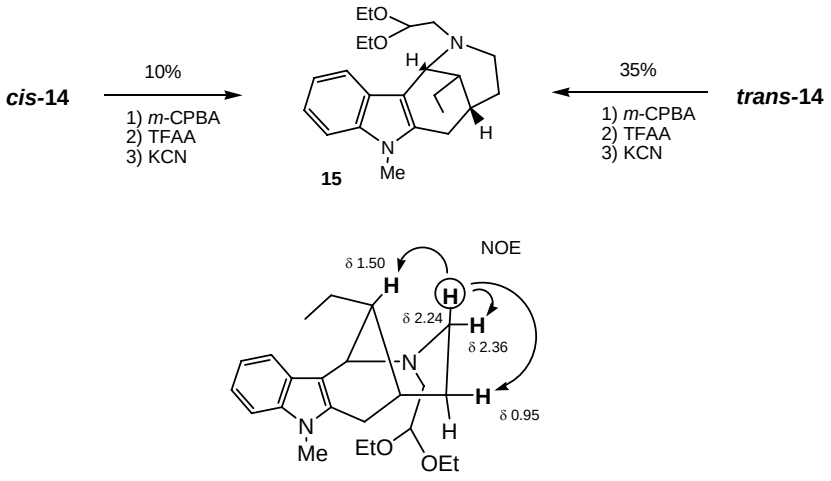
conditions resulted only in the recovery of unchanged **10**, leaving the benzyl group and the double bond intact.

With these results in mind, we then set about the use of piperidine (**11**). Treatment of **8c** with *n*-Bu_4NF 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.[5] 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).[2a] 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*-pieperidines (**4**; Z=Boc, R=Bn) [1) oxidation with *m*-CPBA, 2) addition of TFAA, 3) sequential addition of KCN][2] is known to allow the isolation of the corresponding α–cyanopiperidine derivatives of **4**. Using the same reaction conditions, cyclization reaction of ***trans*-14** was carried out to afford **15** without the isolation of α–cyanopiperidine, but with a somewhat less yield.[6] 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.[2a] 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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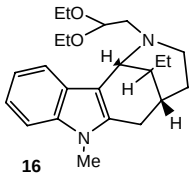
5. ***cis*-14**: ^{1}H-NMR ($CHCl_3$): δ 0.94 (t, 3H, *J*=7.5 Hz), 1.20 (t, 3H, *J*=7.5 Hz), 1.21 (t, 3H, *J*=7.5 Hz), 1.38-1.42 (m, 1H), 1.51-1.67 (m, 5H), 1.91 (br s, 1H), 2.16-2.32 (m, 1H), 2.46 (dd, 1H, *J*=5.1, 13.1 Hz), 2.53 (dd, 1H, *J*=5.1, 13.1 Hz), 2.64-2.76 (m, 3H), 3.51-3.57 (m, 2H), 3.64-3.73 (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}C-NMR ($CHCl_3$): δ 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 $C_{23}H_{36}N_2O_2$: 372.2776. Found: 372.2779.

   ***trans*-14**: ^{1}H-NMR ($CDCl_3$): δ 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}C-NMR ($CDCl_3$): δ 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 $C_{23}H_{36}N_2O_2$: 372.2776. Found: 372.2776.
6. **15**: ^{1}H-NMR (benzene-d_6): δ 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}C-NMR (benzene-d_6): δ 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 $C_{23}H_{34}N_2O_2$: 370.2620. Found: 370.2624. Other products, such as **16** and **17**, were not isolated in the cyclization reaction of **14**.



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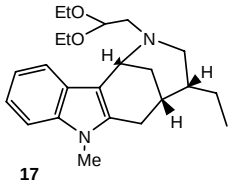

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