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Synthetic studies towards dendridine A: synthesis of *hemi*-dendridine A acetate by Fischer indolization

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ABSTRACT

A short synthesis of *hemi*-dendridine A acetate has been accomplished. The synthesis is based on a modified Fischer indolization that represents a rare example of the single-step synthesis of a 7-oxytryptamine from an *ortho*-oxygenated phenylhydrazine. The synthetic route required developing an efficient synthesis of *N*-acetyl-2-pyrroline, the key coupling partner for the modified Fischer indolization. Some interesting chemistry associated with the abnormal Fischer indolization has been uncovered, whereby two molecules of the phenylhydrazine substrate combined along the abnormal reaction pathway, affording an unusual *N*-phenylindoleamine product.

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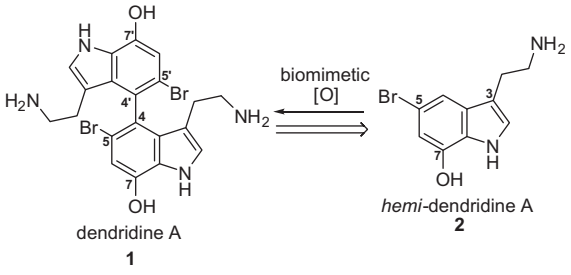
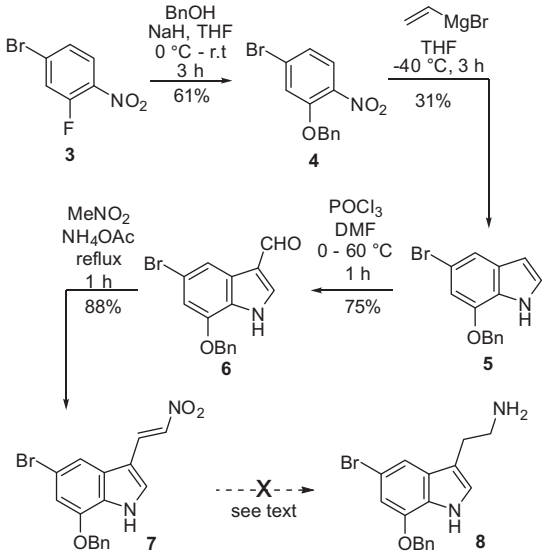
Upon surveying an Okinawan marine sponge *Dictyodendrilla* sp., Kobayashi and co-workers isolated dendridine A (**1**), an optically inactive, C_2-symmetrical bis-tryptamine alkaloid with a rare 4,4′-bisindole moiety (Scheme 1).[1] The only other natural compounds possessing this heterocyclic motif are a series of serotonin derived antioxidants[2] and the biopolymer eumelanin.[3]

In an approach that likely mimics the construction of this natural product in nature, a biomimetic synthesis of **1** was planned using a late-stage oxidative phenolic homocoupling[4,5] of 5-bromo-7-hydroxytryptamine (**2**), which we have termed as *hemi*-dendridine A. Herein, we report our initial studies towards this goal that has culminated in a short synthesis of *hemi*-dendridine A acetate.



Scheme 1. Dendridine A and proposed biomimetic synthesis.

In order to investigate extensively the proposed biomimetic synthesis, our first task was to establish an efficient route to synthetically useful quantities of a suitably protected *hemi*-dendridine A and our initial attempts are outlined in Scheme 2. Commercially available 4-bromo-2-fluoro-1-nitrobenzene (**3**) was subjected to a regioselective S_NAr reaction with the anion of benzyl alcohol,



Scheme 2. Unsuccessful approach.

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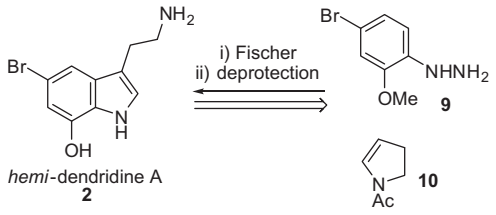
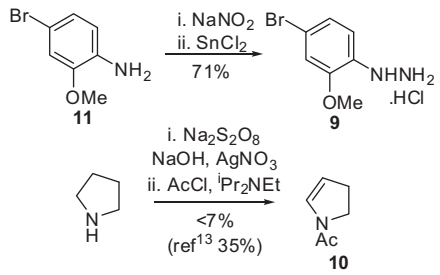
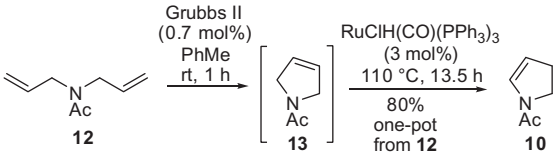


Scheme 3. Planned Fischer route.



Scheme 4. Synthesis of indolization substrates **9** and **10**.



Scheme 5. One-pot synthesis of *N*-acetyl-2-pyrroline (**10**).

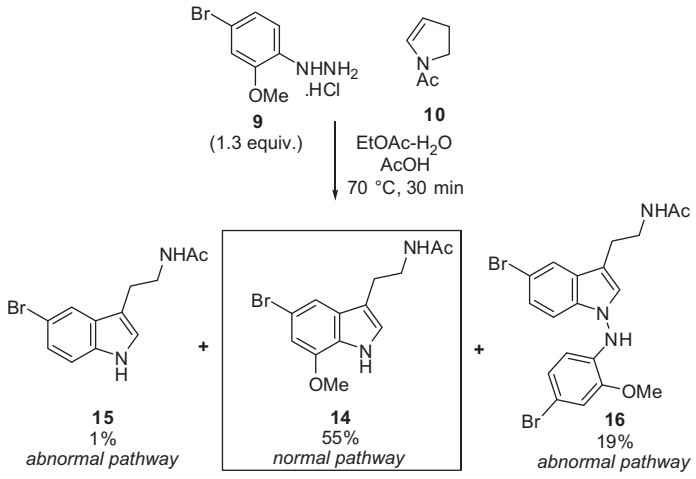
affording **4**. Bartoli indolization[6] of **4** gave 5-bromo-7-benzyloxyindole (**5**) in moderate yield. Straightforward Vilsmeier formylation gave **6** which underwent facile Henry reaction with nitromethane giving **7**, setting the stage for a key reduction that would afford the desired tryptamine **8**.

Our group has previously encountered difficulties in successfully forming brominated tryptamines by reduction of their corresponding nitroalkenes[7] and indeed, this was again the case when attempting the reduction of **7** to **8**, with lithium aluminium hydride[8] and various hydrogenation conditions[9] causing extensive debromination of the indole ring. Using in situ generated BH_3·THF,[10] a reagent that had previously been successful in our hands,[7] resulted in an intractable mixture of products (Scheme 2).

Unperturbed by these negative results, an alternative strategy was sought. A modified Fischer indolization was considered, an idea that was initially avoided due to the propensity of *ortho*-oxygenated phenylhydrazines to form the so-called 'abnormal products' arising from *ipso*-substitution during the sigmatropic rearrangement.[11,12] Nonetheless, our focus turned to this route and a variant of the Fischer indole synthesis reported by Holzapfel[13] seemed appealing, whereby the direct synthesis of tryptamines is achieved from phenylhydrazines and *N*-acyl-2-pyrrolines in a single-step.[14] Pursuing this approach, the two components required were disubstituted phenylhydrazine **9** and *N*-acetyl-2-pyrroline (**10**) (Scheme 3). Commercially available 4-bromo-2-methoxyaniline (**11**) was subjected to a diazotization–reduction sequence, furnishing the desired phenylhydrazine **9** as its hydrochloride salt.[15] *N*-Acetyl-2-pyrroline **10** was accessed from pyrrolidine using the reported modification[13] of the original procedure.[16] However, replicating the reported yield for this step was not possible in our hands, an observation that has been recorded by other research groups[17] (Scheme 4). Due to this issue, a more efficient and reliable route to **10** was sought.

The ring-closing metathesis (RCM) of *N*,*N*′-diallylacetamide (**12**)[18] to *N*-acetyl-3-pyrroline (**13**) is often employed to gauge the efficiency of new metathesis catalysts.[19] Furthermore, since the isomerization of **13** is known[20] to provide *N*-acetyl-2-pyrroline (**10**), it was envisaged combining both of these reactions into one synthetic pathway would provide a straightforward synthesis of **10**. Indeed, it was discovered that the transformation of **12** into **10** could be accomplished in one-pot. When the RCM of **12** was complete (1 h), the reaction mixture was concentrated, then added to a sealed tube containing $RuClH(CO)(PPh_3)_3$[21] and heated to 130 °C for 13.5 h, gratifyingly affording **10** in excellent yield from readily available *N*,*N*′-diallylacetamide (**12**) (Scheme 5). This approach provided synthetically useful quantities of **10** and offers significant advantages over the existing literature procedure.[13,17]

With gram quantities of **9** and **10** secured, the key Fischer indolization could be attempted (Scheme 6). Upon subjecting *N*-acetyl-2-pyrroline (**10**) and a slight excess of phenylhydrazine **9** to standard Fischer reaction conditions, three products were formed. The major product was gratifyingly confirmed as the desired tryptamine **14** arising from the normal Fischer indolization pathway. To



Scheme 6. Fischer indolization.

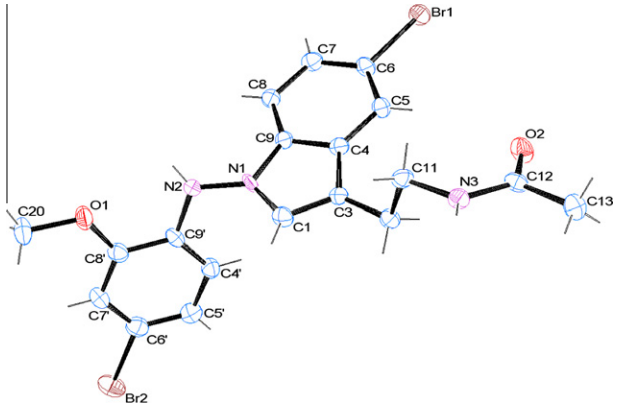
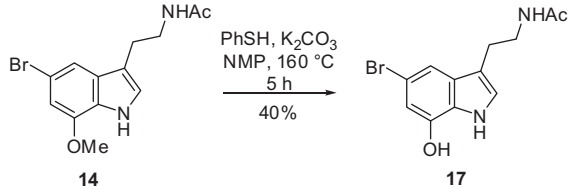


Figure 1. X-ray crystal structure of **16**.[25]



Scheme 7. Synthesis of hemi-dendridine A acetate (**17**).

the best of our knowledge, this is only the second example reporting the synthesis of a tryptamine from an *ortho*-oxygenated phenylhydrazine in a single step.[14g,22] The abnormal Fischer pathway was also operating in this case, as concluded by the isolation of trace amounts of deoxygenated tryptamine **15**.[23] The third compound could not be identified by spectroscopy alone and confirming its assignment as *N*-phenylindoleamine **16**[24] was only possible when X-ray crystals became available (Fig. 1). It can be assumed that the unusual *N*-phenylindoleamine **16** results from a second equiv of phenylhydrazine **9** being incorporated along the abnormal Fischer pathway. All attempts to reduce the yield of abnormal products **15** and **16** by altering the reaction conditions and/or varying the ratio of substrates **9** and **10** were unsuccessful.

Frustratingly, tryptamine **14** resisted all attempts to effect removal of the methoxy group under Lewis acidic conditions, with starting material recovered in all cases. After much investigation, demethylation of tryptamine **14** could be accomplished in acceptable yield using thiophenol and potassium carbonate in NMP at elevated temperature,[26] furnishing 7-hydroxytryptamine **17** (Scheme 7). It was found that dimerization of **17** did not occur spontaneously upon oxidation in air, implying that some enzymatic assistance may be involved in nature's synthesis of these compounds. The oxidative phenolic coupling of *hemi*-dendridine A acetate (**17**) is currently under investigation in our laboratory.

In conclusion, a short route to *hemi*-dendridine A acetate (**17**) has been accomplished using a modified Fischer indolization, providing sufficient quantities of material to investigate extensively the oxidative phenolic homocoupling. We have also reported an efficient synthesis of *N*-acetyl-2-pyrroline (**10**) from *N*,*N*-diallylacetamide (**12**) using a one-pot RCM-isomerization sequence, along with some interesting observations relating to the abnormal Fischer indolization.

Acknowledgements

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Supplementary data

Supplementary data (experimental details for the preparation of *N*-acetyl-2-pyrroline (**10**) and *hemi*-dendridine A acetate (**17**), along with relevant spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.029.

References and notes

1. Tsuda, M.; Takahashi, Y.; Fromont, J.; Mikami, Y.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 1277.
2. Zhang, H. L.; Nagatsu, A.; Sakakibara, J. *Chem. Pharm. Bull.* **1996**, *44*, 874.
3. (a) Pezzella, A.; Vogna, D.; Prota, G. *Tetrahedron* **2002**, *58*, 3681; (b) Pezzella, A.; Panzella, L.; Crescenzi, O.; Napolitano, A.; Navaratnam, S.; Edge, R.; Land, E. J.; Barnone, V.; Ischiad, M. *J. Org. Chem.* **2009**, *74*, 3727. and references cited therein.
4. Scott, A. I. Q. *Rev. Chem. Soc.* **1965**, *19*, 1.
5. For some recent examples of oxidative phenolic homocouplings in natural product synthesis, see: (a) Bringmann, G.; Ledermann, A.; Francois, G. *Heterocycles* **1995**, *40*, 293; (b) Bringmann, G.; Pabst, T.; Busemann, S.; Peters, K.; Peters, E. M. *Tetrahedron* **1998**, *54*, 1425; (c) Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett.* **1999**, *40*, 483; (d) Hüttel, W.; Nieger, M.; Müller, M. *Synthesis* **2003**, 1803; (e) Drochner, D.; Hüttel, W.; Nieger, M.; Müller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 931; (f) Smith, M. J.; Nawrat, C. C.; Moody, C. *J. Org. Lett.* **2011**, *13*, 3396.
6. (a) Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, *9*, 163; (b) For the synthesis of 5-bromo-7-methoxyindole by Bartoli indolization, see: Iyer, P.; Lucas, M. C.; Schoenfeld, R. C.; Villa, M.; Weikert, R. J. US Pat., 20070123527, 2007. *Chem. Abstr.* **2007**, *147*, 31098.
7. Sperry, J. *Tetrahedron Lett.* **2011**, *52*, 4042.
8. Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901.
9. Bernauer, K.; Mahboobi, S. *Helv. Chim. Acta* **1988**, *71*, 2034.
10. Varma, R. S.; Kabalka, G. W. *Synth. Commun.* **1985**, *15*, 843.
11. For some examples of the abnormal Fischer indolization, see: (a) Ishii, H.; Murakami, Y.; Suzuki, Y.; Ikeda, N. *Tetrahedron Lett.* **1970**, *11*, 1181; (b) Ishii, H.; Murakami, Y.; Hosoya, K.; Takeda, H.; Suzuki, Y. Ikeda. N *Chem. Pharm. Bull.* **1973**, *21*, 1481; (c) Ishii, H.; Murakami, Y.; Furuse, T.; Hosoya, K.; Takeda, H.; Ikeda, N. *Tetrahedron* **1991**, *1973*, 29; (d) Ishii, H. *Acc. Chem. Res.* **1981**, *14*, 275; (e) Murakimi, Y.; Takahashi, H.; Nakazawa, Y.; Koshimizu, M.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1989**, *30*, 2099; (f) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1831**, *1994*, 116; (g) Murakimi, Y.; Watanabe, T.; Takahashi, H.; Yokoo, H.; Nakazawa, Y.; Koshimizu, M.; Adachi, N.; Kurita, M.; Tomoko, Y.; Inagaki, T.; Oshishi, M.; Watanabe, M.; Tani, M.; Yokoyama, Y. *Tetrahedron* **1998**, *54*, 45; (h) Murakami, Y.; Yokoo, H.; Yokoyama, Y.; Watanabe, T. *Chem. Pharm. Bull.* **1999**, *47*, 791.
12. Employing 2-sulfonyloxyphenylhydrazones in the Fischer indolization reportedly suppresses the formation of abnormal products (Refs. [11e,g]). For an elegant solution to the abnormal Fischer reaction, see: Szczepankiewicz, B. G.; Heathcock, C. H. *Tetrahedron* **1997**, *53*, 8853.
13. Marais, W.; Holzapfel, C. W. *Synth. Commun.* **1998**, *28*, 3681.
14. There are several variants of the Fischer indolization that deliver tryptamines directly from phenylhydrazines, but we found the preparation and handling of the reagents used in the Holzapfel approach the most convenient. Other methods involve treating phenylhydrazines with different electrophiles: (a) 4-halobutanals (and acetals) (Grandberg synthesis): Grandberg, I. I. *Chem. Heterocycl. Compd (Engl. Transl.)* **1974**, *10*, 501; (b) Castro, J. L.; Matassa, V. G. *Tetrahedron Lett.* **1993**, *34*, 4705; (c) 4-aminobutyraldehyde (and acetals): Spath, E.; Lederer, E. *Ber.* **1930**, *63*, 2102; (d) Hwang, K.-J.; Lee, T.-S. *Synth. Commun.* **1999**, *29*, 2099; (e) Verspui, G.; Elbertse, G.; Sheldon, F. A.; Hacking, M. A. P. J.; Sheldon, R. A. *Chem. Commun.* **2000**, 1363; (f) α-oxygenated lactams: Shono, T.; Matsamura, Y.; Kanazawa, T. *Tetrahedron Lett.* **1983**, *24*, 1259; (g) Palmisano, G.; Danieli, B.; Lesma, G.; Passarella, D. *Tetrahedron* **1989**, *45*, 3583.
15. (a) Crum, J. D.; Sprague, P. W. *Chem. Commun.* **1966**, 417; (b) Guzzo, P. R.; Henderson, A. J.; Nacro, K.; Isherwood, M. L.; Ghosh, A.; Xiang, K. US pat., 20110112122, 2011. *Chem. Abstr.* **2011**, *154*, 459762.
16. Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 4791.
17. Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615.
18. *N*,*N*′-diallylacetamide (**12**) can be routinely prepared on multigram scale by the acetylation of commercially available diallylamine: Barluenga, J.; Nájera, C.; Yus, M. *J. Hetereocycl. Chem.* **1980**, *17*, 917.
19. Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806. and references cited therein.
20. Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.
21. $RuClH(CO)(PPh_3)_3$ gave superior results to the rhodium hydride complex reported in Ref. 20 (a) Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Białoń, J.; Kasperzyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257; (b) Toumi, M.; Couty,

F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270; (c) Kasaya, Y.; Hosi, K.; Terada, Y.; Nishida, A.; Shuto, S.; Arisawa, M. *Eur. J. Org. Chem.* **2009**, 4606.
22. For stepwise syntheses of 7-oxytryptamines from *ortho*-oxygenated phenylhydrazines, see: (a) Vinograd, L. K.; Suvorov, N. N. *Khim. Geterotsikl. Soedin.* **1984**, 1206; (b) Sóti, F.; Incze, M.; Kardos-Balogh, Z.; Kajtár-Peredy, M.; Czántay, C. *Synth. Commun.* **1993**, *23*, 1689; (c) Dubash, N. P.; Mangu, N. K.; Satyam, A. *Synth. Commun.* **2004**, *34*, 1791; (d) Kikuchi, H.; Saito, Y.; Sekiya, J.; Okano, Y.; Saito, M.; Nakahata, N.; Kubohara, Y.; Oshima, Y. *J. Org. Chem.* **2005**, *70*, 8854.
23. Compound **15** was spectroscopically identical to that reported previously: Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V.; Spadoni, G.; Diamantini, G.; Balsamini, C.; Tarzia, G.; Fraschini, F.; Lucini, V.; Nonno, R.; Stankov, B. M. *J. Med. Chem.* **1998**, *41*, 3831.
24. For the synthesis of other *N*-arylindoleamines, see: (a) Wasserman, H. H.; Nettleton, H. R. *Tetrahedron Lett.* **1960**, *7*, 33; (b) Glushkov, V. A.; Berdinskii, I. S. *Khim. Geterotsikl. Soedin.* **1981**, *4*, 488; (c) Reiber, P.; Wakatsuki, Y.; Kisch, H. *Monatsh. Chem.* **1995**, *126*, 1; (d) Satomura, M. *J. Org. Chem.* **1993**, *58*, 3757; (e) Frontana-Uribe, B. A.; Moinet, C.; Toupet, L. *Eur. J. Org. Chem.* **1999**, 419; (f) Messaoudi, S.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2011**, *52*, 2687.
25. Crystallographic data (reference number CCDC 863230) can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk].
26. Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1997**, *38*, 8749.