Published in final edited form as:
Tetrahedron Lett. 2011 April 27; 52(17): 2037–2040. doi:10.1016/j.tetlet.2010.09.086.

Synthetic Studies on the Ambiguine Family of Alkaloids: Construction of the ABCD Ring System

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Abstract

A racemic synthesis of the ABCD ring core of the ambiguines that preserves the tertiary alcohol has been accomplished in convergent synthesis in 10 synthetic steps, in an overall yield of 46% from commercially available 4-bromoindole and *m*-methylanisole.

Keywords

Ambiguine; Hapalindole; Tin (IV) chloride

The ambiguines1›2›3 are a family of indole alkaloids that were first isolated in 1991. They are structurally related to the hapalindoles4›5 family of alkaloids (Figure 1). To date, the ambiguine family has fifteen members (Ambiguines A-O) that are broken down into two subclasses; the tetracyclic and pentacyclic systems.

The tetracyclic ambiguines are structurally the same as the hapalindoles with the exception of the presence of a reverse-prenyl group on C2 of the indole ring. Pentacyclic ambuguines contain a seven-membered ring, which contains either an epoxide, diol, vinyl cyanide, α-hydroxyl ketone or diene functionality. Carbon-13 of ring D, in both families, can either have a methylene carbon (R_1) or chlorine-containing carbon. Likewise, both can either have a hydrogen at the C10 position (R_2) or possess an alcohol at said carbon. The common core for both the hapalindole and ambuguine families for most of their members contains the C13 chlorine containing stereocenter as well as the C10 tertiary alcohol.

The structural complexity and densely functionalized core, has attracted considerable synthetic attention and to date ambiguine H has been conquered by total synthesis.6 We report here, our own preliminary efforts on the synthesis of these intriguing substances.

We envisioned that the pentacyclic core **1** of the ambiguines could arise from an intra-molecular RCM reaction of **2**, which could be assembled through a Mannich reaction with vinyl Grignard and ammonium acetate followed by isonitrile formation from **3** (Scheme 1). Formation of the tetracyclic core **3** was anticipated to arise from the manipulation of **4** and **5**. The C12 quaternary center was envisioned to arise from compound **5**, which could be

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accessed from commercially available *m*-methylanisole and functionalized indole **4** from 2-bromo-6-nitrotoluene.

Following the protocol of Rubottom and Gruber,7 commerically available *m*-methylanisole was converted to **7** utilizing a Birch reduction followed by hydrolysis (Scheme 2). Secondary alcohol **7** was protected with TBSCl and imidazole, followed by treatment with vinylmagnesium bromide to afford the quaternary center substrate as the corresponding TMS-enol ether. Cleavage of the TMS-enol ether with an acetic acid/water/THF mixture afforded racemic **5** in an overall 86% yield for the six steps.

Assembly of tetracycle **11** began with treating racemic **5** with LHMDS and Mander's reagent to give the β-ketoester (Scheme 3). Reduction of the ketone with $NaBH_4$ followed by TMS protection of the resulting alcohol gave **6** in good yields. Treatment of **8** with N-methoxy-methylamine hydrochloride and Me_3Al in THF afforded the Weinreb amide. Subjecting 4-bromo-N-methylindole to lithium-halogen exchange resulted in the corresponding 4-lithium species that was added to the Weinreb amide and worked up under acid conditions and carried on without further purification. Methyl lithium was added to the crude material at −78 °C in THF, warmed to room temperature, and worked up under acidic conditions to afford a 2.5:1 mixture of the secondary alcohol and its corresponding TMS ether. The crude mixture was treated with acetic acid for 45 min, concentrated, and taken into THF and oxidized with Dess-Martin Periodinane to afford **9** in good yields. Dehydration of **9** with TsOH gave the β-methyl, β-indole-exocyclic enone that was subjected to methyl cuprate Michael conditions to afford tricycle **10**. Subjecting **10** to BF_3-etherate afforded tetracycle **11** in an overall yield of 27% from **5** in 11 steps.

Muratake and Natsume8,9 in their total synthesis of hapalindole U employed a dilute (1M) tin (IV) chloride-mediated coupling to form **13**. Treating TMS-enol ether **10** with 4-(2-hydroxy-2-propyl)-N-tosyl-indole **11** with 1 M $SnCl_4$ at −78 °C to afforded tricyle **12** when quenched at −78 °C (Scheme 4).

Murataka's tricycle **14** and our tricyle **11** are similar in structure, with ours being more functionalized. Both routes close the tricycle with BF_3-etherate in THF to give rise to similar tetracycles. Tetracycle **15** was formed in 58% over two steps, whereas tetracycle **11** was formed in 27% over eleven steps clearly showing the advantage of the tin-mediated chemistry. It was thought that utilizing this methodology, which has been used in a variety of alkaloid syntheses,10,11,12,13 we could gain rapid access to the ABCD ring system of the ambigiunes in a more efficient manner than that extant.

Accessing the required 4-(2-hydroxyl-2-propyl)-N-methyl-indole for the tin-mediated coupling was accomplished from 2-bromo-6-nitrotoluene under Leimgruber-Batcho14 conditions to afford **16** in high yields, (Scheme 5). *N*-Methylation of **16** was performed with NaH and methyl iodide in THF to afford **17**. Treatment of **17** under lithium-halogen exchange conditions followed by acetone addition furnished **18** in a 91% yield.

Treatment of **5** with LHMDS followed by TMSCl gave the required TMS-enol ether **19**. A variety of conditions were probed to optimize the coupling of **18** to **19** (Scheme 6 and Table 1). In the event, it was observed that treating indole **18** and TMS-enol ether **19** with fuming tin (IV) chloride in DCM gave the tetracyclic species **20b** in good yields. While we were anticipating the tricycle **20a**, synthesis of **20b** gives the carbon core along with the desired tertiary alcohol at the C10, which is present in several ambiguines.

Further studies into the coupling of **18** and **19** with fuming tin (IV) chloride revealed that the reaction afforded diastereomeric tetracycles **21a** and **21b** (4:1 ratio) (Scheme 7), but not the dehydrated tetracycle as seen in Scheme 4. Quenching the fuming tin (IV) chloride reaction

at −78 °C proved to be essential in forming the tertiary alcohol. When quenching the reaction at any temperate above −50 °C formation of the dehydrated tetracycle **20c** was observed. When **18** and **19** were treated with the 1M tin (IV) chloride solution a similar tricyle as seen in Scheme 4 was formed. Subjecting this tricycle to BF_3-etherate afforded the dehydrated tetracycle **20c**. When performing the same procedure with either the corresponding *N*-Boc or *N*-silyl (TMS, TBS, or TIPS) protecting groups only dehydrated tetracycles were observed. Interestingly, when attempting the reaction on a substrate bearing the *N*-tosyl group under the same conditions, only the tricycle was obtained. Other alkyl protecting groups such as PMB or benzyl groups can be used with the current methodology, however the yields from the coupling reactions are significantly lower, 7% and 11% respectively.

Having accessed the ABCD ring system of the ambiguines, along with the tertiary alcohol at C10, efforts were directed towards gaining access to the same ABCD system with the reverse-prenyl group on C-2 of the indole. Chlorination of the previously described 4-bromoindole with NCS in DMF afforded **22** in excellent yields. Installation of the reverse-prenyl group was accomplished using Danishefsky chemistry15 followed by *N*-methylation of the indole nitrogen to afford **22**. Subjecting **22** to lithium-halogen exchange conditions followed by acetone gave access to **24** in 98% yield.

The coupling of **24** and **19** with fuming tin (IV) chloride was attempted as described previously in Table 1. Unfortunately, no tetracyclic product was observed when subjecting **24** and **19** to any of the previous coupling conditions. Furthermore, only fuming tin (IV) chloride allowed access to the tricycle **25** in 36% yield (Scheme 9). Treating tricycle **25** with BF_3-etherate at room temperature for 24 hours failed to give the desired tetracycle, but rather the dehydrated tetracyclic system. Similar results were obtained when attempting the same methodology on methyl, ethyl, vinyl, and propyl C2 substituted indoles.

In summary, we have shown two methods of accessing the ABCD cores of both the hapalindoles and ambiguines. Utilizing fuming tin (IV) chloride-mediated coupling of tertiary benzylic alcohols of indoles and TMS-enol ethers we have also gained access to more functionalized tetracyclic cores. Current efforts to deploy this methodology for the concise total synthesis of several members of this family of alkaloids are under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This paper is warmly dedicated to Professor Harry H. Wasserman on the occasion of his 90th birthday. We gratefully acknowledge financial support from the National Institutes of Health Grant GM068011.

References and Notes

1. Smitka TA, Bonjouklian R, Doolin L, Jones ND, Deeter JB, Yoshida WY, Prinsep MR, Moore RE, Patterson GM. J Org Chem. 1992; 57:857.
2. Huber U, Moore RE, Patterson GM. J Nat Prod. 1998; 61:1304–1306. [PubMed: 9784177] Raveh A, Carmeli S. J Nat Prod. 2007; 70:196. [PubMed: 17315959]
3. Mo S, Krunic A, Chlipala G, Orjala J. J Nat Prod. 2009; 72:894. [PubMed: 19371071]
4. Moore RE, Cheuk C, Patterson GM. J Am Chem Soc. 1984; 106:6456.
5. Moore RE, Cheuk C, Yang XQ, Patterson GM. J Org Chem. 1987; 52:1036.Moore RE, Cheuk C, Yang XQ, Patterson GM. J Org Chem. 1987; 52:3773.

6. Baran PS, Maimone TJ, Richter JM. Nature. 2007; 446:404. [PubMed: 17377577]
7. Rubottom GM, Gruber JM. J Org Chem. 1977; 42:1051.
8. Muratake H, Natsume M. Tetrahedron Lett. 1989; 30:1815.
9. Muratake H, Natsume M. Tetrahedron. 1990; 46:6331.Muratake H, Natsume M. Tetrahedron. 1990; 46:6343.Muratake H, Kumagami H, Natsume M. Tetrahedron. 1990; 46:6351.
10. Brown MA, Kerr MA. Tetrahedron Lett. 2001; 42:983.Kinsman AC, Kerr MA. J Am Chem Soc. 2003; 125:14120. [PubMed: 14611249]
11. MacKay JA, Bishop RL, Rawal VH. Org Lett. 2005; 7:3421. [PubMed: 16048307]
12. Brailsford JA, Lauchli R, Shea KJ. Org Lett. 2009; 11:5330. [PubMed: 19860385]
13. Tian X, Huters AD, Douglas CJ, Garg NK. Org Lett. 2009; 11:2349. [PubMed: 19432408]
14. Batcho AD, Leimgruber W. Org Synth. 1985; 63:214.
15. Schkeryantz JM, Woo JC, Siliphaivanh P, Depew KM, Danishefsky SJ. J Am Chem Soc. 1999; 121:11964.

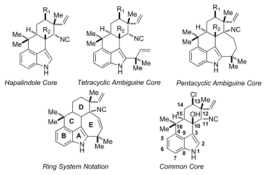
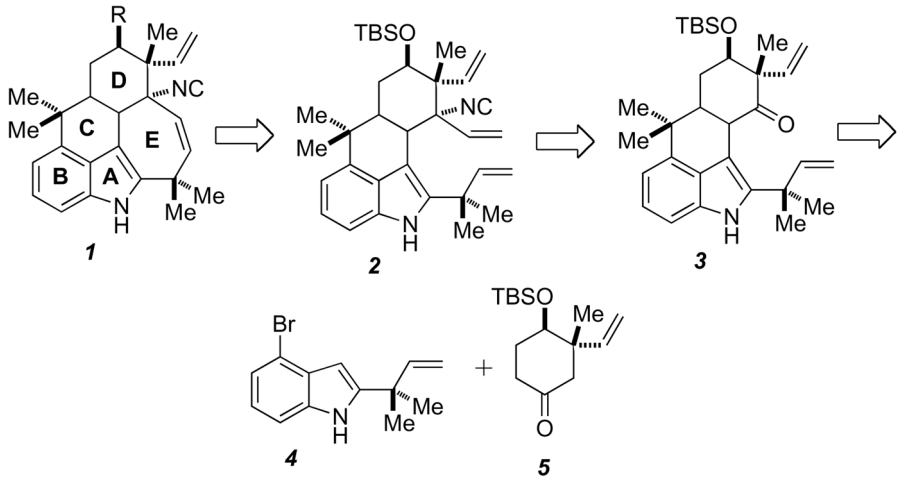
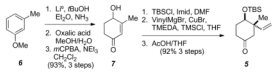


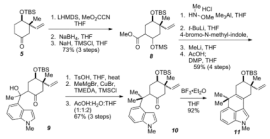
Figure 1.
Hapalindole, Tetracyclic and Pentacyclic Ambiguine Cores.



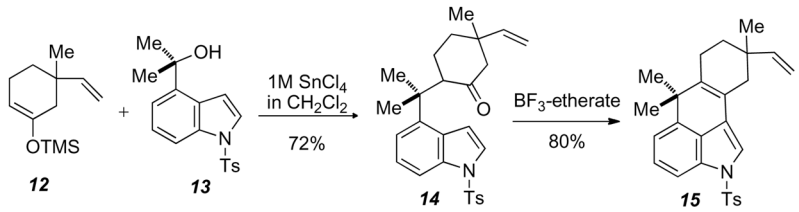
Scheme 1.
Retrosynthetic analysis.



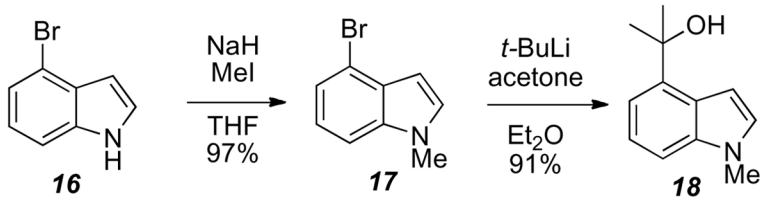
Scheme 2.
Synthesis of substrate **5**.



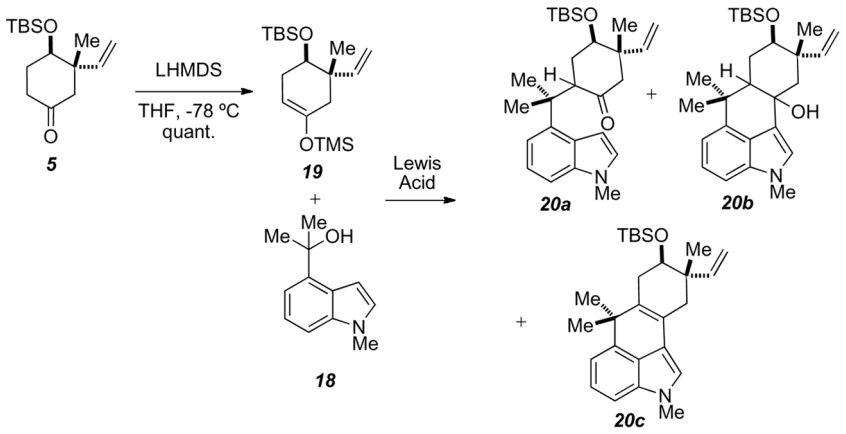
Scheme 3.
Weinreb amide route to tetracycle **11**.



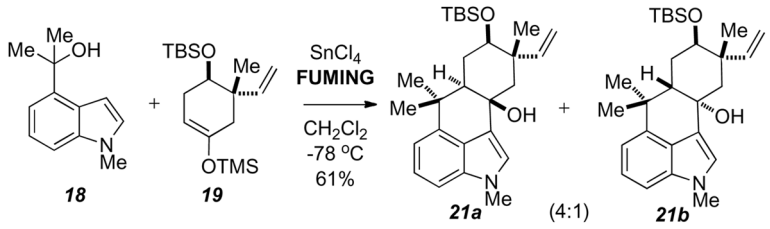
Scheme 4.
Muratake and Natsume tricycle formation



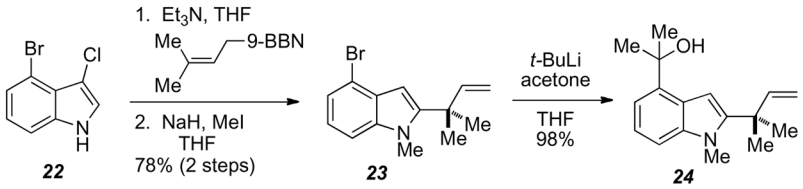
Scheme 5.
Synthesis of indole ***18***.



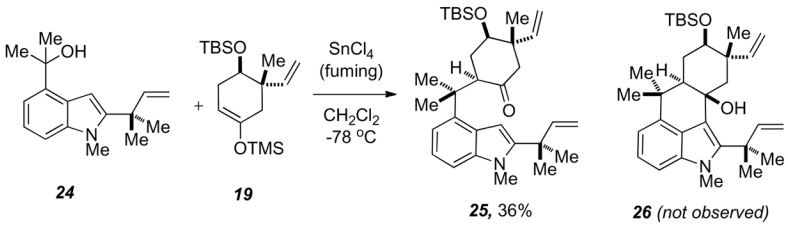
Scheme 6.
Lewis acid-mediated coupling of ***18*** + ***19***.



Scheme 7.
Fuming $SnCl_4$ - mediated tetracycle formation



Scheme 8.
Synthesis of indole **24**.



Scheme 9.
Attempted tetracycle formation

Table 1

Lewis-acid and conditions screened for Scheme 6.

Lewis Acid	Conditions	Product		
		20a	20b	20c
$TiCl_4$ (fuming)	Toluene, −78 °C	7%	X	X
$TiCl_4$ (fuming)	Toluene, −44 °C	X	X	5%
$TiCl_4$ (1 M $PhCH_3$)	Toluene, −78 °C	X	X	X
$TiCl_4$ (1 M $PhCH_3$)	Toluene, −44 °C	X	X	X
$TiCl_4$ (1 M DCM)	DCM, −78 °C	13%	X	X
$TiCl_4$ (1 M DCM)	DCM, −44 °C	X	X	X
$TiCl_4$ (fuming)	DCM, −78 °C	X	X	36%
$TiCl_4$ (fuming)	DCM, −44 °C	X	X	13%
$SnCl_4$ (1 M $PhCH_3$)	Toluene, −78 °C	15%	24%	X
$SnCl_4$ (1 M $PhCH_3$)	Toluene, −44 °C	X	X	X
$SnCl_4$ (1 M DCM)	DCM, −78 °C	83%	X	X
$SnCl_4$ (1 M DCM)	DCM, −44 °C	54%	X	X
$SnCl_4$ (fuming)	DCM, −78 °C	5%	61%	X
$SnCl_4$ (fuming)	DCM, −44 °C	13%	8%	42%