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Preparation and Synthetic Applications of 2-Halotryptamines: Synthesis of Elacomine and Isoelacomine

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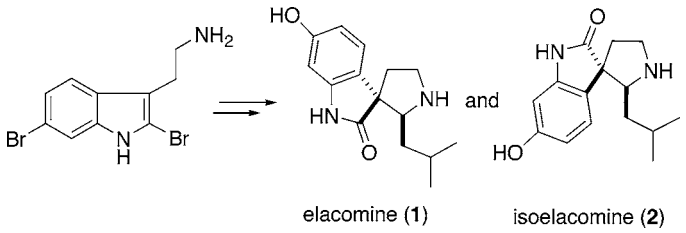
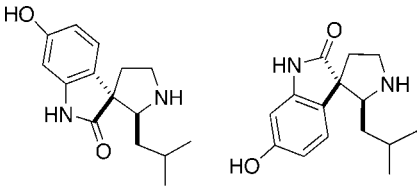
ABSTRACT



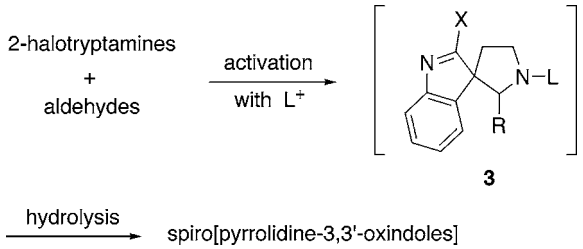
The preparation of 2-halotryptamines from tryptamine is described. New stereoselective intramolecular iminium ion spirocyclization methodology for the construction of spiro[pyrrolidine-3,3′-oxindoles] is outlined in synthetic studies of elacomine (1) and isoelacomine (2).

Elacomine (**1**) and isoelacomine (**2**) are naturally occurring hemiterpene spirooxindole alkaloids isolated from the roots of the shrub *Elaeagnus commutata*. Borschberg and co-workers recently confirmed these structures through synthesis and also established their isolation as naturally occurring racemates.[1] Using tryptamine and tryptophan, these investigators employed a "classical" Pictet−Spengler/oxidative rearrangement approach involving tetrahydro-β-carbolines for constructing the spirooxindole framework.



From a synthetic viewpoint, 2-halo-tryptamine (and -tryptophan) derivatives are potentially useful synthons for the construction of indole-based natural products. For example, aldehyde condensation with 2-halotryptamines in which the α-position is blocked would, in principle, direct subsequent reaction to the β-position and, hence, lead to the formation of spiroannulated 2-haloindolenines **3** (without a priori consideration of stereochemistry) (Scheme 1). The fate of the haloindolenine intermediate could conceivably proceed along several different pathways. One such pathway, hydrolysis, would furnish the desired spirooxindole in a single sequential event. In this communication, we report the direct preparation of 2-halotryptamines **5** and **12**, their use in stereocontrolled spiro[pyrrolidine-3,3′-oxindole] construction,

Scheme 1. Spirocyclization of 2-Halotryptamines



(1) Pellegrin, C.; Weber, M.; Borschberg, H.-J. *Helv. Chim. Acta* **1996**, *79*, 151−168 and references therein.

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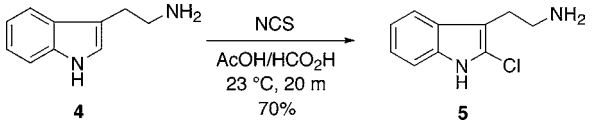
and application to the synthesis of elacomine (**1**) and isoelacomine (**2**).

Although 2-halo-tryptamines are potentially useful intermediates in indole alkaloid synthesis, their synthetic utility has not been previously demonstrated. Surprisingly, a literature search for 2-chloro- and 2-bromotryptamine resulted in no published reports of these compounds.[2,3] Previous investigations from our lab regarding the halogenation and synthesis of tryptamine-based bis(indole) marine natural products[4] led us to the present discovery that the hydrochloride salt of tryptamine (**4**) undergoes efficient regioselective chlorination at the 2-position using NCS in a 10:3 acetic acid/formic acid solution (23 °C) (Scheme 2). The resulting

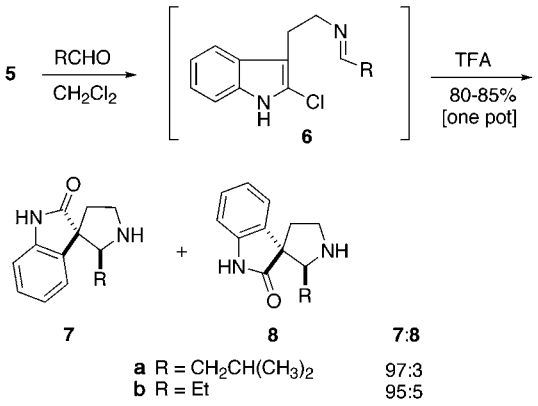
Scheme 2. Preparation of 2-Chlorotryptamine (**5**)



product, 2-chlorotryptamine (**5**)·HCl, mp 173−175 °C, is formed in good yields.[5]

With halotryptamine **5** in hand, our attention next turned to the spirocyclization reaction (Scheme 3). In the event,

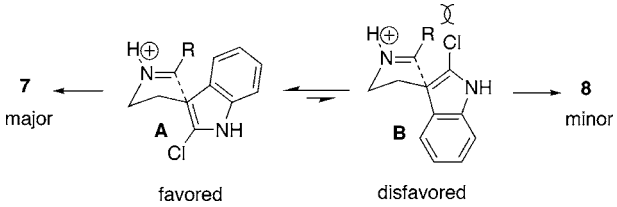
Scheme 3. Stereocontrolled Spirocyclization of 2-Chlorotryptamine (**5**) and Aldehydes



condensation of **5** with isovaleraldehyde (CH_2Cl_2, $MgSO_4$, 2 h, 23 °C) produced Schiff base **6**, which upon activation with TFA (5 equiv, 2 h) afforded 6-deoxyisoelacomine (**7a**) and minor amounts of diastereomeric 6-deoxyelacomine (**8a**) in good overall yield and high diastereoselectivity (97:3). Diastereomers **7a** and **8a** can be separated by flash chromatography and isolated in pure form. The relative stereochemistry of **7a** and **8a** was confirmed by ^{1}H NMR and NOE studies. The major diastereomer resulting from the cyclocondensation reaction orients the R group *trans* to the oxindole carbonyl. Preliminary indications suggest a strong propensity for this stereochemical preference. For example, the less sterically encumbered aldehyde, propionaldehyde, also exhibits high diastereoselection in the spirocyclization of **5** leading to predominantly **7b**.

This stereochemical outcome suggests that the initial iminium ion cyclization leading to the formation of spirochloroindolenine **3** proceeds through an irreversible kinetically controlled pathway (Scheme 4). One possible explana-

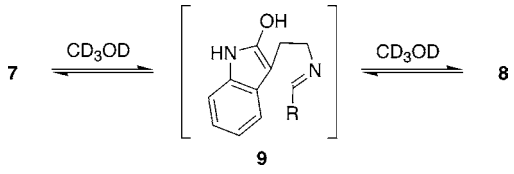
Scheme 4. Stereochemical Rationale



tion for the observed stereoselectivities is minimization of steric interactions in the transition state between the R group and chlorine moiety as depicted by structure **A**. Under the reaction conditions, protonation of the resulting pyrrolidine nitrogen helps prevent an undesirable retro-Mannich process that would lead to an erosion of stereochemical control.

Upon standing for 2−3 days in CD_3OD (23 °C), a 1:1 equilibrium mixture of spirooxindoles **7** and **8** resulted from each corresponding pure diastereomer (Scheme 5). Equilibra-

Scheme 5. Retro-Mannich Equilibration of **7** and **8**



tion via a retro-Mannich type process through an intermediate related to **9** is presumed to be involved. Separate treatment of **7a** and **8a** with methyl chloroformate produced carbamates **10** and **11**, respectively (Scheme 6). These derivatives are configurationally stable in CD_3OD. Although the ^{1}H and ^{13}C NMR spectra for carbamate **10** are characteristically sharp, this is not the case for **11**, which exhibited peak broadening presumably due to restricted rotation.

To synthesize metabolites **1** and **2**, 2,6-dibromotryptamine (**12**) was prepared in 41% yield from tryptamine (**4**)·HBr using 2 equiv of NBS.[6] Condensation of **12** with isovaler-

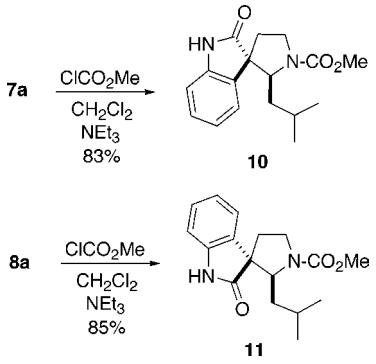
(2) Iodotryptamine has been reported: (a) Kline, T. *J. Heterocycl. Chem.* **1985**, *22*, 505−509. (b) Sintas, J. A.; Vitale, A. A. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 677−684.

(3) Enzymatic chlorination of tryptamine derivatives has been reported: Hölzer, M.; Burd, W.; Riebig, H.-U.; van Pee, K.-H. *Adv. Synth. Catal.* **2001**, *343*, 591−595.

(4) (a) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121−2123. (b) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3185−3187. (c) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2002**, *4*, 941−943.

(5) Similarly, bromination of tryptamine hydrobromide with 1 equiv of NBS proceeded smoothly to afford 2-bromotryptamine (**5a**)·HBr, mp 173−175 °C, in good yields.

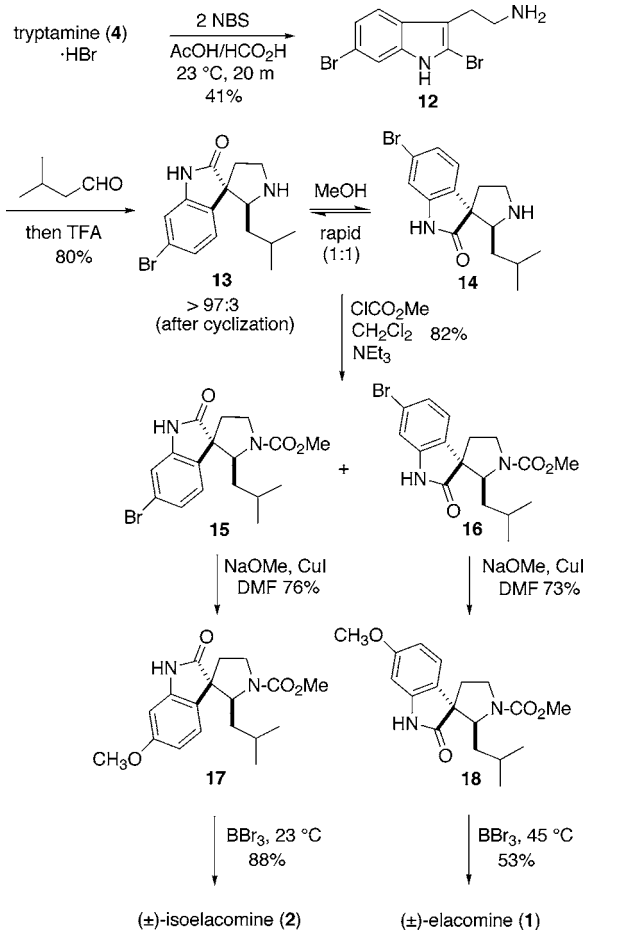
Scheme 6



aldehyde followed by treatment with TFA produced spirooxindole **13** as the major diastereomer (>97:3 as judged after aqueous workup by ^{1}H NMR). Attempts to purify **13** as the free base by flash chromatography resulted in rapid isomerization to **14**. The presence of the 6-bromo substituent in **13** and **14** greatly accelerates the retro-Mannich process (Scheme 5). Since both **1** and **2** were ultimately desired, we decided to convert a mixture of **13** and **14** (rather than reattempt purification of these isomers) to their corresponding spirooxindole carbamates **15** and **16**. As in the case of carbamates **10** and **11**, these derivatives are readily purified by chromatography. Separate copper-catalyzed methoxylation[7] of arylbromides **15** and **16** gave 6-methoxyoxindole derivatives **17** and **18**, respectively, in good yields. Both carbamates **16** and **18** exhibited broadened NMR characteristics similar to those of carbamate **11**, suggesting restricted rotation in these systems as well. Simultaneous cleavage of the carbamate and aryl ether functionalities of **17** with boron tribromide[8] proceeded smoothly at room temperature to give (±)-isoelacomine (**2**). Slightly elevated temperatures and longer reaction times were necessary to effect a similar cleavage in **18** to afford (±)-elacomine (**1**). All spectral data for synthetic **1** and **2** were in agreement with those reported for the corresponding natural product.[1] Slow isomerization of **1** and/or **2** was observed at 23 °C in CD_3OD, and after 3 weeks a 1:1 equilibrium mixture of **1** and **2** was obtained.

One of the major synthetic challenges facing spirooxindole construction is controlling stereochemistry at the quaternary spiro and adjacent alkyl centers. Recently, a number of efforts, some successful, have been made to devise solutions to this problem.[9] Methods that utilize readily available tryptamine- and/or tryptophan-based starting materials, however, have been limited to two "classical" approaches. They are the Pictet−Spengler/oxidative rearrangement sequence involving β-carbolines and the intramolecular Mannich-type condensation of tryptamine- and tryptophan-derived oxindoles. These methods often proceed with modest stereochemical outcomes. We have described a new method that provides direct and rapid access to 2-halotryptamines from which stereocontrolled transformations to spirooxindoles have been demonstrated. Noteworthy is the mild and nonequilibrating conditions used to kinetically form the versatile spirochloroindolenine intermediate **3** and spiro-

Scheme 7. Synthesis of Elacomine (**1**) and Isoelacomine (**2**)



[pyrrolidine-3,3′-oxindole] ring system. Application of this spirocyclization methodology to chiral 2-halotryptophan esters is currently in progress.[10]

Acknowledgment. Financial support from Oregon State University and Chugai Pharmaceutical Co. is gratefully acknowledged. We thank Rodger Kohnert for assistance with NMR data acquisition and Jeff Morre of the Mass Spectrometry Facility of the Environmental Health Science Center (NIEHS P30 ES00210) at Oregon State University for mass spectral data acquisition.

Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for compounds **1**, **2**, **5**, **7**, **8**, and **10**−**18** and representative procedures for the preparation of 2-halotryptamines and spirocyclization reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) 2,4-Dibromotryptamine (**12a**) and 2,5-dibromotryptamine (**12b**) were also obtained from the reaction in 20% yield each.

(7) Miyake, Y.; Kikugawa, Y. *J. Heterocycl. Chem.* **1983**, *20*, 349−352.

(8) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1986**, 249−282.

(9) For a recent review, see: Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209−2219.

(10) Under analogous halogenation conditions, optically active 2-chloro- and 2-bromotryptophan methyl esters can be obtained in good yields from L-tryptophan methyl ester·HX using NCS and NBS, respectively.