Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 6364–6367
Tetrahedron Letters

Studies towards the synthesis of the marine alkaloid chartelline C

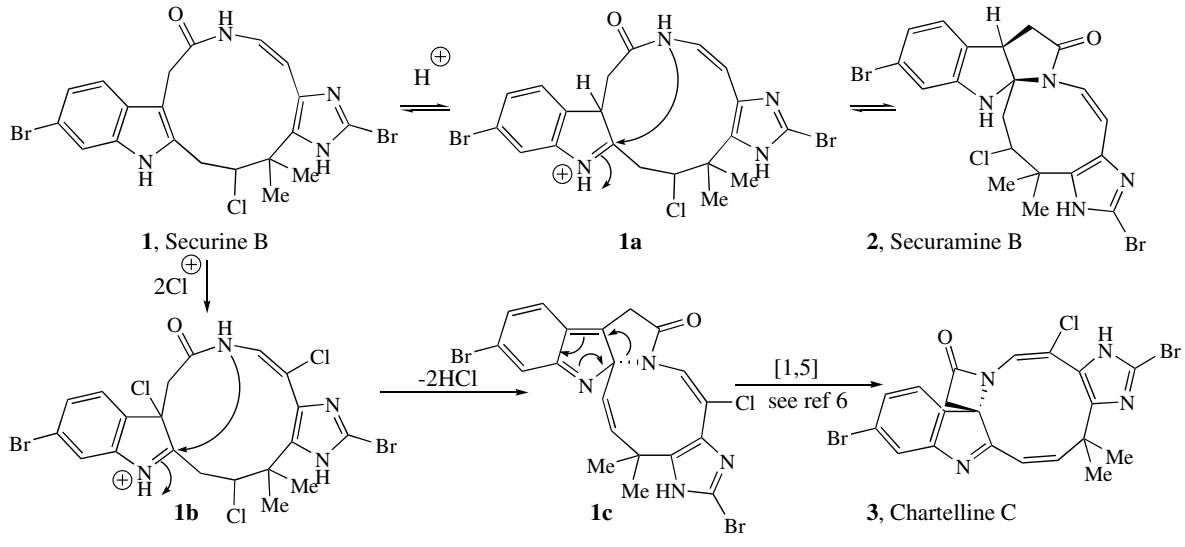
Phillip J. Black, Evan A. Hecker and Philip Magnus*

Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station A5300, Austin, TX 78712-1167, USA

Received 5 June 2007; revised 25 June 2007; accepted 2 July 2007
Available online 30 July 2007

Abstract—2,6-Dibromoindole **5** underwent regioselective Sonogashira coupling at the 2 position with simple acetylenic partners. While, imidazole-acetylene **16** failed to couple to **5**, cyclic carbonate **19** succeeded to give **20**, which was further elaborated into indole-imidazole **23**.

The chartelline marine alkaloids were isolated from the bryozoan *Chartella papyracea* and characterized in the 1980s.[1–3] A related bryozoan *Securiflustra securifrons* also produces the securines and securamines,[4,5] and they are plausible biogenetic precursors to the chartellines. It was reported that solutions of securine B **1** in DMSO-d_6 converted into securamine B **2**, presumably via **1a**, Scheme 1.[4] Redissolving **2** in $CDCl_3$ converted **2** back into **1**. One could imagine that if this isomerization were carried out in the presence of an electropositive source of chlorine, **1** could be converted into chartelline C **3** through the intermediacy of **1b** and **1c**. The transformation of **1c** into **3** can be written as a [1,5]-shift and is a key step in the recently reported biogenetically inspired strategy for the synthesis of **3** by Baran and Shenvi.[6,7] Several other groups have reported on synthetic approaches to chartelline C[6,8–11] as well as related alkaloids.[12,13]



Scheme 1.

Keywords: Chartelline C; Securines; Securamines; Biogenetic; Sonogashira coupling.
* Corresponding author. Tel.: +1 512 471 3966; fax: +1 512 471 7839; e-mail: p.magnus@mail.utexas.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.040

Our plan was also based on the supposition that the spiro-β-lactam in **3** could arise from a late stage oxidative cyclization of a suitable macrolactam.[14] The macrolactam precursor to **1c**, namely, **1**, was envisioned as arising from macrolactamization, and to eventually achieve this a regioselective Sonogashira coupling at the 2-position of a 2-halo-6-bromoindole was required as a starting point. The only selective coupling of an acetylene at the 2-position of an indole that has a 6-bromo substituent was a 2-iodo-6-bromoindole,[7] and since this compound required a six-step synthesis from 6-bromoindole, we were interested to see if a 2,6-dibromoindole exhibited any selectivity in a Sonogashira coupling reaction.

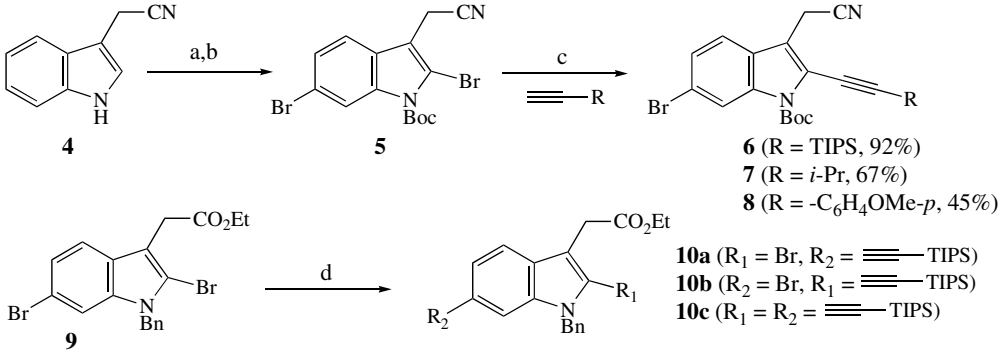
Indole-3-acetonitrile **4**[15,16] was regioselectively brominated using a known protocol[17] to give **5** (after *t*-butyl carbamate protection), Scheme 2. Exposure of **5** to standard Sonogashira coupling reaction conditions proceeded with complete regioselectivity to give the 2-coupled indoles **6**, **7** and **8**, respectively. It was found that the choice of protecting group on the indole nitrogen atom was essential to achieving regioselectivity in the Sonogashira coupling reaction. For example, when an *N*-benzyl-2,6-dibromo indole **9** was subjected to the coupling reaction conditions with triisopropylsilylacetylene, a mixture of **10a**, **10b** and **10c** was obtained in a ratio of 1:2:1.5 and in an overall yield of 72%.

With the indole portion in hand, synthesis of imidazole **16** was undertaken, Scheme 3. Aldehyde **11**[18] was converted into α,β-unsaturated ester **12**[19] (90%) and subjected to deconjugative dimethylation to give **13** (96%). Reduction of **13** followed by oxidation and treatment of the resulting aldehyde with Ohira's reagent [MeCOCN$_2$PO(OEt)$_2$],[20,21] gave the terminal acetylene **14** in 90% yield over three steps.

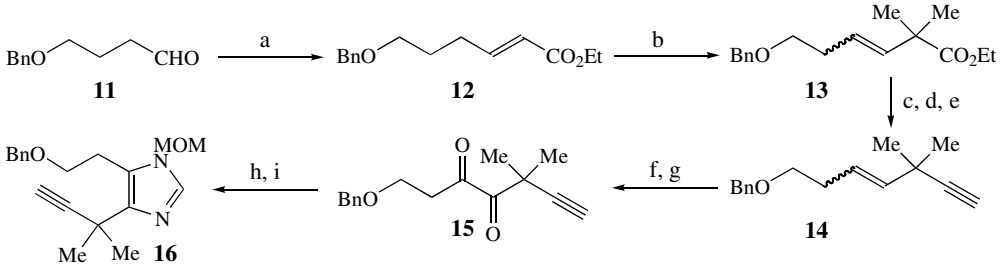
Dihydroxylation of the internal alkene in **14** followed by oxidation of the resulting diol with SO$_3$·pyridine, NEt$_3$, DMSO in CH$_2$Cl$_2$ gave α-diketone **15** (83%). Treatment of **15** with NH$_4$OAc, (CH$_2$O)$_n$ in acetic acid at 100 °C, followed by protection of imidazole NH gave **16** in reproducible yields of 74% from **15**.[22]

Unfortunately, attempts to couple **5** and **16** to give **17**, under a variety of Sonogashira and Castro–Stephens reaction conditions failed, Scheme 4. In light of Baran's reported work[6,7] we revisited this reaction applying their reaction conditions, but no coupling product **17** was observed. Presumably, the more reactive 2-iodo analogue of **5** would have been successful. It was therefore decided to construct the imidazole portion after the acetylenic coupling process.

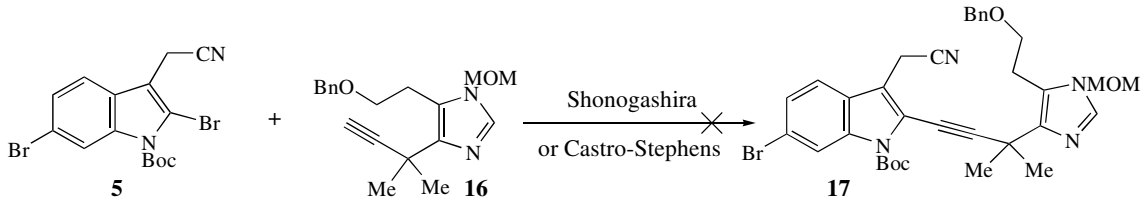
The cyclic carbonate **18** (made from **14** by *vic*-dihydroxylation followed by triphosgene/pyridine) was treated with BCl$_3$/CH$_2$Cl$_2$ and the resulting alcohol protected as its TIPS ether **19** (89% over two steps), Scheme 5. It was necessary to conduct the exchange of the benzyl ether since the benzyl analogue of **20** was not compatible with the *cis*-hydrogenation of acetylene. Indole **5** could now



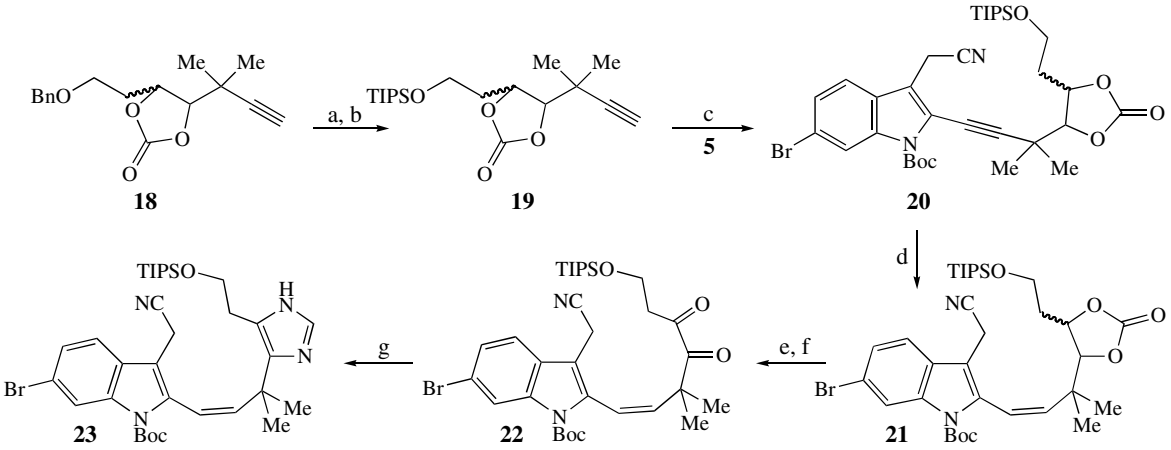
Scheme 2. (a) NBS, SiO$_2$, CH$_2$Cl$_2$. (b) Boc$_2$O, NEt$_3$, DMAP, CH$_2$Cl$_2$ 54% over two steps. (c) Acetylene, PdCl$_2$(PPh$_3$)$_2$, CuI, NEt$_3$, 45 °C. (d) Triisopropylsilylacetylene, PdCl$_2$(PPh$_3$)$_2$, CuI, NEt$_3$, MeCN, 25 °C, 72%, **10a**, **10b** and **10c** in a 1:2:1.5 ratio, respectively.



Scheme 3. Reagents and conditions: (a) triethylphosphonoacetate, NaH, THF, 0 °C, 90%. (b) LiHMDS, HMPA, THF at −78 °C, then MeI and LiHMDS, HMPA, THF at −78 °C, then MeI, 96% for one-pot procedure. (c) LiAlH$_4$, THF, −78 °C to rt. (d) Dess–Martin periodinane, CH$_2$Cl$_2$, 0 °C, 94% over two steps. (e) Ohira's reagent, MeOH, K$_2$CO$_3$, 96%. (f) K$_2$OsO$_4$. 2 H$_2$O, NMO, Acetone/H$_2$O, 100%. (g) SO$_3$·pyr, DMSO, NEt$_3$, CH$_2$Cl$_2$, 83%. (h) NH$_4$OAc, (CH$_2$O)n, AcOH, 100 °C. (i) MOMCl, NEt$_3$, PhH, 74% over two steps.



Scheme 4.



Scheme 5. Reagents and conditions: (a) BCl_3, CH_2Cl_2, 0 °C. (b) TIPSCl, imidazole, $ClCH_2CH_2Cl$, 85 °C, 89% over two steps. (c) **5**, $PdCl_2(PPh_3)_2$, CuI,NEt_3, 25 °C, 67%. (d) H_2, PtO_2 (cat.), EtOH, 60%. (e) NaOH (aq), dioxane. (f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 43% over two steps. (g) NH_4OAc, $(CH_2O)_n$, AcOH, 65 °C, 50%.

be successfully coupled with the terminal acetylene **19** under standard Sonogashira reaction conditions to give **20** (67%).

Hydrogenation of **20** over Adam's catalyst (PtO_2/H_2/EtOH) reduced the acetylenic bond stereoselectively to the *cis*-alkene **21** without competing hydrogenolysis of the 6-Br substituent in the indole ring. Hydrogenation of **20** over 10% Pd/C or Raney Ni reduced the acetylenic bond to the *cis*-alkene but also removed the 6-Br atom. Standard hydrogenation catalysts such as Lindlar's catalyst, Wilkinson's catalyst and Pt/C proved too unreactive, as were transfer hydrogenation and diimide (generated in situ).

Treatment of **21** with NaOH (aq) in dioxane by followed oxidation of the resulting diol with the Dess–Martin periodinane reagent gave α-diketone **22** (43% yield). When **22** was subjected to the earlier imidazole formation conditions, the starting material was destroyed without any imidazole formation. However, by maintaining a lower reaction temperature, with the same reagents (NH_4OAc, paraformaldehyde, AcOH) imidazole **23** could be obtained in a 50% yield.

In summary, the regioselective Sonogashira of 2,6-dibromoindole **5** can be used to synthesize the 2-isoprene-imidazole chain provided imidazole is constructed after the coupling reaction.

Acknowledgement

The NIH (GM 32718) and the Welch Chair (F-0018) are thanked for their support of this research. Kevin Williamson is thanked for his contributions.

References and notes

1. Chevolot, L.; Chevolot, A. M.; Gajhede, M.; Larsen, C.; Anthoni, U.; Christophersen, C. *J. Am. Chem. Soc.* **1985**, *107*, 4542–4543.
2. Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 4709–4712.
3. Nielsen, P. H.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand. Ser. B: Org. Chem. Biochem.* **1988**, *B42*, 489–491.
4. Rahbaek, L.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Petersen, B. O. *J. Org. Chem.* **1996**, *61*, 887–889.
5. Rahbk, L.; Christophersen, C. *J. Nat. Prod.* **1997**, *60*, 175–177.
6. Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714–3717.
7. Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028–14029.
8. Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631–2633.
9. Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025–2027.
10. Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440–441.

11. Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159–3166.
12. Korakas, P.; Chaffee, S.; Shotwell, J. B.; Duque, P.; Wood, J. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12054–12057.
13. Sun, C.; Camp, J. E.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1779–1781.
14. Scott, A. I.; Yoo, S. E.; Chung, S.-K.; Lacadie, J. A. *Tetrahedron Lett.* **1976**, *17*, 1137–1140.
15. Eliel, E. L.; Murphy, N. J. *J. Am. Chem. Soc.* **1953**, *75*, 3589–3590.
16. Yamada, F.; Hashizume, T.; Somei, M. *Heterocycles* **1998**, *47*, 509–516.
17. Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051–1054.
18. Garcia, C.; Martin, T.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 1420–1428.
19. Solladie, G.; Fernandez, I.; Maestro, C. *Tetrahedron: Asymmetry* **1991**, *2*, 801–819.
20. Ohira, S. *Syn. Commun.* **1989**, *19*, 561–564.
21. Roth, G. J.; Liepold, B.; Mueller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59–62.
22. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Part 4A: Five-membered Rings with Two or More Nitrogen Atoms; Pergamon Press, 1984; Vol. 5.