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Studies towards the synthesis of the marine alkaloid chartelline

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Abstract

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

Keywords

Chartelline C; securines; securamines; biogenetic; Sonogashira coupling

The chartelline marine alkaloids were isolated from the bryozoan *Chartella papyracea* and characterized in the 1980's.^{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 CDCl₃ 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}

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 protocol¹⁷ to give **5** (after *t*-butyl carbamate protection), Scheme 2. Exposure of **5** to standard Sonogashira

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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 the imidazole **16** was undertaken, Scheme 3. The aldehyde **11**¹⁸ was converted into the 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 [MeCOCN₂PO(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 SO₃•pyridine, NEt₃, DMSO in CH₂Cl₂ gave the -diketone **15** (83%). Treatment of **15** with NH₄OAc, (CH₂O)_n in acetic acid at 100 °C, followed by protection of the 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 analog 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 BCl₃/CH₂Cl₂ 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 the acetylene. The indole **5** could now be successfully coupled with the terminal acetylene **19** under standard Sonogashira reaction conditions to give **20** (67%).

Hydrogenation of **20** over Adam's catalyst (PtO₂/H₂/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 the -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 (NH₄OAc, paraformaldehyde, AcOH) the imidazole **23** could be obtained in a 50% yield.

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

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Scheme 1.

(a) NBS, SiO₂, CH₂Cl₂, (b) Boc₂O, NEt₃, DMAP, CH₂Cl₂ 54% over two steps. (c) Acetylene, PdCl₂(PPh₃)₂, CuI, NEt₃, 45 °C. (d) triisopropylsilylacetylene, PdCl₂(PPh₃)₂, CuI, NEt₃, 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) LiAlH₄, THF, -78 °C to rt. (d) Dess-Martin periodinane, CH₂Cl₂, 0 °C, 94% over two steps. (e) Ohira's reagent, MeOH, K₂CO₃, 96%; (f) K₂OsO₄·2H₂O, NMO, Acetone/H₂O, 100%. (g) SO₃·pyr, DMSO, NEt₃, CH₂Cl₂, 83%. (h) NH₄OAc, (CH₂O)_n, AcOH, 100 °C. (i) MOMCl, NEt₃, PhH, 74% over two steps.

Scheme 4.

Scheme 5.

Reagents and conditions: (a) BCl_3 , CH_2Cl_2 , 0°C . (b) TIPSCl , imidazole, $\text{ClCH}_2\text{CH}_2\text{Cl}$, 85°C , 89% over two steps. (c) **5**, $\text{PdCl}_2(\text{PPh}_3)_2$, 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 , $(\text{CH}_2\text{O})_n$, AcOH , 65°C , 50%.