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Syntheses of three naturally occurring polybrominated 3,3'-bi-1*H*-indoles

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Abstract

The naturally occurring polybrominated indoles 2,2',5,5'-tetrabromo-3,3'-bi-1*H*-indole, 2,2',6,6'-tetrabromo-3,3'-bi-1*H*-indole, and 2,2',5,5',6,6'-hexabromo-3,3'-bi-1*H*-indole were synthesized using a palladium catalyzed, carbon monoxide mediated, double reductive *N*-heterocyclization of 2,3-bis(2-nitro-4(or 5)-bromophenyl)-1,4-butadienes as the key step.

Graphical Abstract

Keywords

polybrominated biindoles; palladium; catalysis; cyclization

Introduction

A small number of 3,3'-bi-1*H*-indoles have been isolated from marine algae and from a terrestrial fungus. The first alkaloid of this kind to be isolated and characterized was 2,2',5,5'-tetrabromo-3,3'-bi-1*H*-indole (**1**) isolated from the cyanobacterium *Rivularia firma* in 1982 (Figure 1).¹ The isomeric alkaloid, 2,2',6,6'-tetrabromo-3,3'-bi-1*H*-indole (**2**) was later isolated from the same species.² More recently 2,2',5,5',6,6'-hexabromo-3,3'-bi-1*H*-indole (**3**) was isolated from the red alga *Laurencia similis*.³ Biindole **3** was shown to be a protein tyrosine phospholipase 1B inhibitor.⁴

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Supporting Information

Supplementary information associated with this article including all experimental procedures and ¹H NMR and ¹³C NMR spectra can be found in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2017.01.103>

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In addition to compounds **1–3**, the sulfur containing alkaloids **4**,⁵ **5–6**,⁶ **7**,⁷ all produced by the red alga *Laurencia brongniartii*, and the polyfunctionalized biindole **8** from the green alga *Chaetomorpha basiretorsa Setchell*⁸ have been isolated. The only example of a 3,3'-bi-1*H*-indole from a terrestrial source is the parent compound isolated from the fungus *Gliocladium catenulatum*.⁹ To the best of our knowledge neither of the polyhalogenated biindoles **1–8** have been prepared synthetically to date.

We have recently disclosed a methodology for the synthesis of 3,3'-biindoles wherein a palladium catalyzed, carbon monoxide mediated, double reductive cyclization of 2,3-bis(2-nitrophenyl)-1,3-butadienes was employed in a key indolization step (Scheme 1).¹⁰ For example, reductive cyclization of 2,3-bis(2-nitrophenyl)-1,3-butadiene (**9**) gave the parent 3,3'-bi-1*H*-indole (**10**) in excellent isolated yield. Herein are described synthetic routes to biindoles **1–3** using a reductive cyclization of 2,3-bis(2-nitro-5/6-bromophenyl)-1,3-butadienes as the key step followed subsequent introduction of the remaining bromine atoms.

Results and Discussion

5-Bromo-2-nitro-1-iodobenzene (**11**) was used as the starting point for the synthesis of alkaloids **1** and **3**. Sonogashira cross-coupling of **11** with trimethylsilylethyne gave **12** (Scheme 2). The silyl group was removed using potassium carbonate in a methanol-diethyl ether mixture to afford **13**. Treatment of **13** with tributyltin hydride in the presence of bis(triphenylphosphine)palladium dichloride furnish vinyl tin derivative **14** with excellent α -selectivity (Scheme 2). No trace of the β -isomer was observed by ¹H NMR of the crude reaction mixture.¹¹ It should be noted that each of the first three steps afforded the desired compound in an excess of 91% yield and a 77% overall yield. Tin compound **14** smoothly underwent homocoupling to give diene **15** using an excess of copper chloride in N,N-dimethylformamide (DMF).¹⁰ Diene **15** was dissolved in DMF and treated with carbon monoxide (pCO = 6 atm, 120 °C) in the presence of a palladium catalyst system consisting of bis(dibenzylideneacetone)palladium (10-mol%) - 1,3-bis(diphenyl)propane (12-mol%) - 1,10-phenanthroline (20-mol%) to give 5,5'-dibromo-3,3'-bi-1*H*-indole **16**.

Biindole (**16**) has previously been prepared by a palladium catalyzed oxidative dimerization of 5-bromoindole,¹² reductive cyclization of **17**,¹³ and a two-step procedure employing a nucleophilic addition of 5-bromoindole (**18**) to 5-bromoisatine (**19**) followed by borane reduction of the intermediate (Scheme 5).¹⁴ The ¹H NMR and ¹³C NMR data recorded for **16** were in complete accordance with the reported values.

The two and four additional bromines in alkaloids **1** and **3** were envisioned to be introduced via bromination of **16** using N-bromosuccinimide (NBS) or bromine. Reactions of **16** with bromine under a variety of conditions did not afford any identifiable product nor was any starting material recovered. 3-Substituted indoles have been selectively brominated in the 2-position using NBS. For example, bromination of 3-methylindole using NBS in carbon tetrachloride (CCl₄) to give 2-bromo-3-methylindole in 97% yield has been reported.¹⁵ Based on this precedence, biindole **16** was treated with 2.0 equivalents of NBS in CCl₄ affording the naturally occurring tetrabrominated alkaloid **1** in 59% yield after

chromatographic purification. Reactions of **16** with 4–6 equivalents of NBS in CCl₄ were not clean and afforded a number of inseparable products with low overall mass balance. However, replacing CCl₄ with a 1:1 mixture of tetrahydrofuran and dichloromethane as the solvent system gave **3** in 46% isolated yield upon treatment with six equivalents of NBS. All analytical data for **1**¹ and **3**³ were in complete agreement with the data reported for the isolated natural products.

A synthetic sequence similar to the one depicted in Scheme 2 was used to prepare the remaining 2,2',6,6'-tetrabrominated alkaloid **2**. 1-(4-Bromo-2-nitrophenyl)ethyne (**20**) served as the starting point for the synthesis of **2** (Scheme 4). Both the regioselective palladium catalyzed hydrostannylation of **20** furnishing vinyl tin **21** and the subsequent copper mediated homocoupling affording diene **22** proceeded uneventfully. Reductive cyclization of **22** furnished 6,6'-dibromo-3,3'-biindole (**23**) in 64% isolated yield. Compound **23** has previously been prepared via a palladium catalyzed oxidative dimerization of 6-bromoindole.¹⁶

Similar to the synthesis of **1**, biindole **23** was treated with 2.0 equivalents of NBS in CCl₄ affording the tetrabrominated biindole alkaloid **2** in 59% yield after chromatographic purification. All analytical data were in complete agreement with the data reported for isolated **2**.¹

Compound **23** was also perceived to be a suitable precursor to the hexabromo substituted natural product **3** via the introduction of the four additional bromines in the 2,2',5,5'-positions, respectively. In the event, treatment of **23** with five equivalents of NBS in a THF-dichloromethane solvent system gave a separable mixture of the expected product **3** together with significant amount of 2,2',5,6,6'-pentabromo-bi-1*H*-indole **24** (Scheme 5). All attempt to increase the yield of **3** at the expense of **24** were unsuccessful. For example, increasing the amount of NBS to eight equivalents gave roughly the same product ratio but in a much diminished yield (Scheme 5). In addition, an attempt to introduce the remaining bromine to the isolated pentabromo-biindole **24** using 3 equivalents of NBS was unsuccessful. The starting material was recovered in high yield (94%) after chromatography.

Precedence for direct regioselective 2,6-dibromination and 2,5,6-tribromination of 3-substituted indoles can be found in the literature. For example, 2,6-dibromination of 3-cyanomethylindole using NBS-SiO₂ in dichloromethane gave 2,6-dibromo-3-cyanomethylindole (81%), 2,5-dibromo-3-cyanomethylindole (3%), and 2,4-dibromo-3-cyanomethylindole (5%).¹⁷ 3-Methylindole afforded selectively 2,6-dibromo-3-methylindole using NBS-SiO₂ in dichloromethane¹⁸ and 3-phenylindole using NBS in acetic acid furnished a 6:1 ratio of 2,6-dibromo-3-phenylindole and 2,5-dibromo-3-phenylindole.¹⁹ In contrast, a 3:4 ratio of 2,6:2,5-dibromination was observed from brominations of methyltryptophan employing NBS in AcOH/HCOOH.²⁰ Tribromination of 3-methylindole with bromine in acetic anhydride gave 2,5,6-tribromo-3-methyl-N-acetylindole.²¹ Based on these previously reported brominations, polybrominations of the parent 3,3'-biindole **10** to give either **2** or **3**, depending on the stoichiometry of the reagents, were also pursued. Thus, 3,3'-biindole **10** was treated with 4.0, 5.1, and 8.0 equivalents of NBS in THF/dichloromethane (Scheme 6). Bromination of **10** proved to be substantially more difficult

and only low yields of product(s) were obtained. Using 4.0 equivalents of NBS gave a mixture of **2** and **24** both in 8% isolated yield. Increasing the amount of NBS to 5.1 equivalents eliminated the formation of biindole **2** but gave instead pentabrominated and hexabrominated compounds **24** and **3**, respectively. Finally, treatment of **10** with 8.0 equivalents of NBS gave **3** in 16% yield. No other products were isolated from the three different bromination reactions of **10**.

In summary, short synthetic routes to three naturally occurring polybrominated 3,3'-bi-1*H*-indoles have been developed. All analytical data of the synthetically derived compounds were in all aspects identical to the naturally occurring biindoles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research highlights

- Syntheses of three polybrominated biindole alkaloids have been completed.
- A palladium catalyzed reductive cyclization was used as key ring-closing step.
- N-Bromosuccinimide was used brominate the biindoles.

Figure 1.
Naturally occurring polyhalogenated 3,3'-bi-1*H*-indoles.

Scheme 1.
Palladium catalyzed double reductive cyclization to 3,3'-biindoles.

Scheme 2.

Synthesis of 2,2',5,5'-tetrabromo- and 2,2',5,5',6,6'-hexabromo-3,3'-bi-1*H*-indole.

Scheme 3.

Scheme 4.

Synthesis of 2,2',6,6'-dibromo-3,3'-bi-1*H*-indole.

Scheme 5.
Polybromination of **23**.

Scheme 6.

Bromination of 3,3'-bi-1*H*-indole (**10**).