Radioactive Isotope Complexation

Norbadione A: Synthetic Approach to the Bis(pulvinic acid) Moiety and Cesium-Complexation Studies

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Following the reactor accident in Chernobyl in 1986, it was noted that several species of fungi contained high levels of

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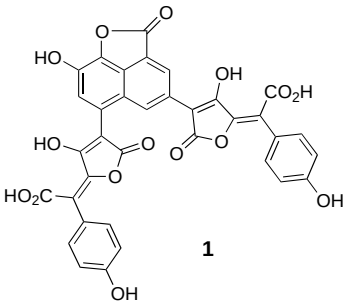
radioactivity, mainly as a result of the radioisotope ^{137}Cs.[1] Among these species was the edible mushroom bay boletus (*Xerocomus badius* (Fr.) Kühn. ex Gilb.). A study by Steglich and co-workers, who had previously isolated badione A and norbadione A (two pigments of the cap cuticle of bay boletus) as their dipotassium salts, showed that these compounds formed complexes with cesium 137.[2,3] A key observation was



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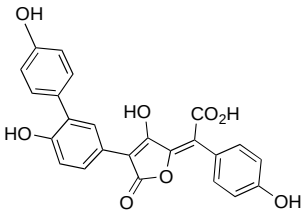

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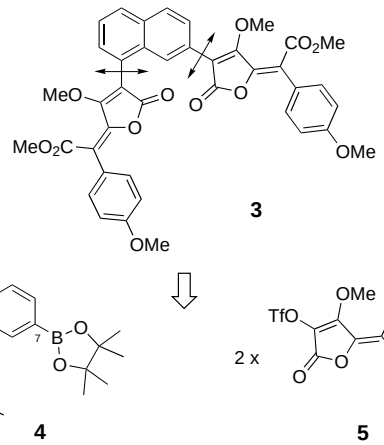
that norbadione A (**1**) is a much better ligand than the simple pulvinic acid derivative atromentic acid (**2**), a characteristic that could be attributed to the presence in its structure of two pulvinic acid chains that are able to participate jointly in the binding of the cesium cation.[4]

Selective complexation of cesium could be of great value for such purposes as the separation of the radionuclide ^{137}Cs from nuclear waste[5] or its removal from contaminated persons.[6] The evaluation of norbadione A and structurally related analogues in these applications was envisaged. Herein we first report a synthetic approach to the bis(pulvinic acid) backbone characteristic of the pigments of the badione group, as illustrated by the synthesis of permethylated analogue **3** (Scheme 1). Second, the complexation properties of the dipotassium salt of norbadione A and of compound **3** were investigated by electrospray tandem MS (ESI MS/MS).[7] The utilization of compound **3** was of particular interest for the evaluation of the degree of cesium complexation specifically by the pulvinic acid moieties, as complexation by the carboxylate moieties could not interfere in this case. Full-scan simple ESI MS spectra were used to investigate the stoichiometries and stability constants of the cesium complexes. Structural information on the cesium complexes was then assessed from neutral loss experiments. Such data are reported for the first time.

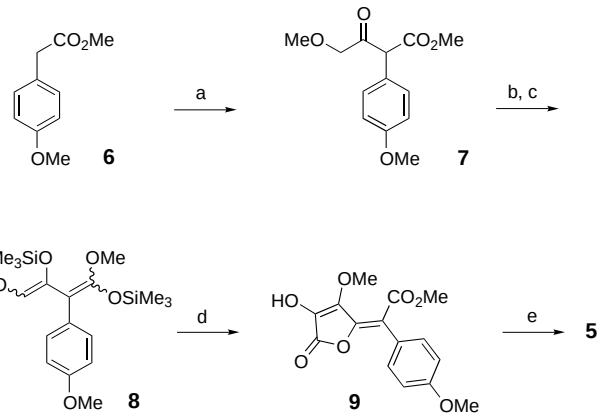
Our approach to the synthesis of **3** was based on the palladium-catalyzed double Suzuki–Miyaura cross coupling of triflate **5** and diboronate **4** (Scheme 1).[8] Such a strategy has the advantage that it should be amenable to the preparation of other analogues in which the distance between the two pulvinic acid chains could be modified simply by changing the diboronate.

The preparation of triflate **5**, described in Scheme 2, relied mainly on the Lewis acid catalyzed Langer cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadiene derivative **8** with oxalyl chloride.[9,10] α-Aryl-β-ketoester **7** was obtained in good yield from the reaction of 2 equivalents of the lithium enolate derived from methyl *para*-anisylacetate (**6**) and methyl



3 **4** **5**

Scheme 1. Retrosynthetic analysis of permethylated analogue **3**. Tf = trifluoromethanesulfonyl.



6 **7** **8** **9** **5**

Scheme 2. Synthesis of triflate **5**. a) **6** (2 equiv), *i*Pr_2NLi (2 equiv), THF, −78 °C, then $MeOCH_2CO_2Me$ (1 equiv), −78 °C→RT, 77%; b) Et_3N, Me_3SiCl, THF, room temperature; c) *i*Pr_2NLi, THF, −78 °C, then Me_3SiCl, −78 °C→RT, 95%; d) oxalyl chloride (1.3 equiv), Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78 °C→RT, 54%; e) Tf_2O, pyridine, CH_2Cl_2, −78 °C→RT, 68%.

methoxyacetate. Ketoester **7** was converted into the bis(silylated) diene **8** in two steps, which proceeded in very good yield on a multigram scale. However, compound **8** did not withstand distillation and was therefore used in the next step without purification. The cyclization of **8** with oxalyl chloride was then carried out under a variety of conditions. The best yield of lactone **9** (54%) was obtained with 1.3 equivalents of oxalyl chloride in the presence of 0.3 equivalents of trimethylsilyl triflate, upon allowing the reaction mixture to warm from −78 °C to room temperature overnight. Only one stereoisomer was obtained. The attribution of the indicated *E* configuration is based on general observations by Langer et al.[9] on the stereochemical outcome of related cyclization reactions and on the preparation of the known compound **10** (see below). Alcohol **9** was readily converted into the corresponding triflate **5** by treatment with triflic anhydride in the presence of pyridine.

A Suzuki–Miyaura reaction of triflate **5** was then carried out using phenylboronic acid in the presence of the catalyst

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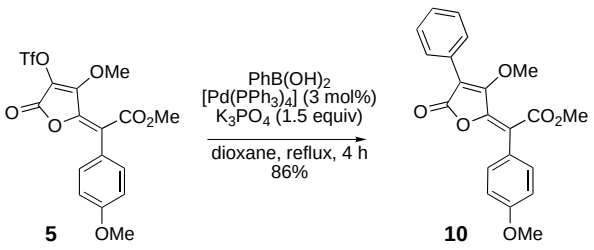
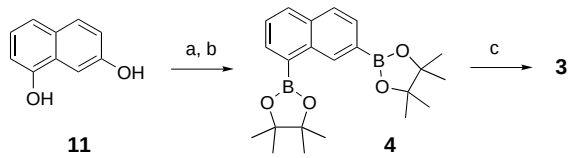


Scheme 3. Preparation of pulvinic acid derivative **10** by the Suzuki–Miyaura reaction of phenylboronic acid with triflate **5**.

$[Pd(PPh_3)_4]$ and the base K_3PO_4 at reflux in dioxane,[11] to afford compound **10** in 86% yield (Scheme 3). The ^1H NMR spectrum of compound **10** was identical to that reported for the *E* isomer of *O*-methylisopinastric acid, which is quite different from that of the *Z* isomer.[12] This allowed us to determine the *E* configuration of the central double bond in alcohol **9** unambiguously.

The preparation of diboronate **4** was carried out in two steps from 1,7-dihydroxynaphthalene (**11**; Scheme 4). Treatment with triflic anhydride in pyridine converted **11** into the corresponding known ditriflate.[13] The procedure described by Masuda and co-workers.[14] for the palladium-catalyzed borylation of aryl triflates with pinacolborane enabled the preparation of diboronate **4** in 45% yield.



Scheme 4. Preparation of permethylated analogue **3** by double Suzuki–Miyaura reaction of diboronate **4** and triflate **5**. a) Tf_2O, pyridine, 95%; b) pinacolborane (6 equiv), $[PdCl_2(dppf)]$ (0.06 equiv), Et_3N (12 equiv), dioxane, 80°C, 13 h, 45%; c) **5** (2 equiv), $[PdCl_2(PPh_3)_2]$ (cat.), aqueous Na_2CO_3, THF, reflux, 3 h, 63%. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

Our initial idea for the preparation of compound **3** through a double Suzuki–Miyaura reaction was to make use of the corresponding diboronic acid as the starting material. However, several attempts to hydrolyze the boronate groups of **4** were unsuccessful. Fortunately, conditions recently described for the palladium-catalyzed cross coupling of vinyl triflates with boronic esters, in the presence of $[PdCl_2(PPh_3)_2]$ as the catalyst and aqueous Na_2CO_3 as the base,[15] were found to be successful for the conversion of diboronate **4** and triflate **5** (2 equiv) into the desired norbadione A analogue **3**, obtained in 63% yield.

ESI MS has been applied previously to the study of metal-ion complexation by a variety of ligands to provide the structures, stoichiometries, and oxidation states of ligand–metal complexes.[16] Several reports have shown the potential of ESI MS for studying the interactions between alkaline cations and ligands.[17] It also appears that ESI MS can be used as a reliable technique for the direct determination of solution binding constants for such noncovalent complexes.[18] These studies have shown good agreement between relative solution-phase and gas-phase ionic abundances of metal complexes present in thermodynamic equilibrium in solution. Recently, ESI MS has allowed the acquisition of solution data such as stoichiometries and stability constants of Ln^{III} complexes of the whole lanthanide series with various di(dialkyltriazinyl)pyridine ligands.[19] ESI MS thus seemed appropriate for the study of the complexation of cesium by the potassium salt of norbadione A or by methylated compound **3**. There have been no reports published that deal with the stability constants of Cs^+ complexes of the potassium salt of norbadione A, which is the naturally occurring form of this compound.

We first studied the complexation behavior of the dipotassium salt of norbadione A (hereafter denoted $NboK_2$) by means of a speciation study. A 10^{-4} M solution of $NboK_2$ in methanol was treated with increasing quantities of cesium chloride.[20] Three different species were identified: free $NboK_2$, observed as the potassium complex $[Nbo+2K+K]^+$ (and as the sodium complex $[Nbo+2K+Na]^+$ of weaker relative intensity),[21] and cesium complexes $[Nbo+2K+Cs]^+$ and $[Nbo+K+2Cs]^+$. The species $[Nbo+3Cs]^+$ was not observed. Its formation might be prevented for steric reasons. Based on the assumption that the ion current in the gas phase quantitatively represents the solution equilibrium, the species distribution was obtained from the total signal response of these singly charged ions in spectra taken at each cesium/norbadione A ratio (see Supporting Information). By doing so, it was possible to plot the speciation curves shown in Figure 1.

As CsCl was added, the quantity of complex $[Nbo+2K+Cs]^+$ present reached a maximum at a 1.2 molar ratio of cesium to ligand, while the quantity of complex $[Nbo+K+2Cs]^+$ increased regularly. The formation of the latter complex is observed even when only small amounts of cesium are present, thus showing that this species is favored.

Neutral loss experiments were also performed to provide structural information about the cesium complexes. The neutral loss of the component $NboK_2$ was only seen from $[Nbo+2K+Cs]^+$ and the neutral loss of the component NboKCs was only seen from $[Nbo+K+2Cs]^+$. This suggests

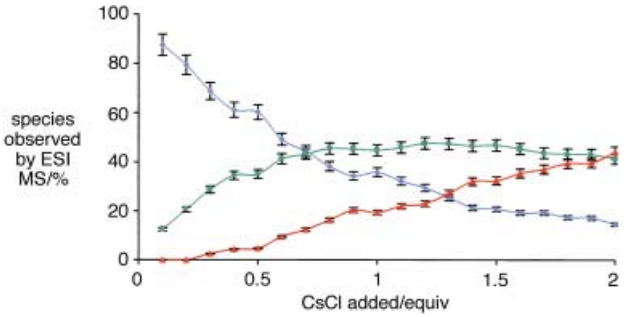


Figure 1. ESI–MS speciation curves of norbadione A dipotassium salt in the presence of cesium chloride in methanol. ◆: free ligand, ■: $[Nbo+2K+Cs]^+$ complex, ▲: $[Nbo+K+2Cs]^+$ complex. Relative abundances are reproducible within 5% from run to run.

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that the norbadione A potassium salt binds to Cs^+ through the pulvinic acid moieties, and that the second Cs^+ binding involves one of the carboxylate groups.

The complexation constant determined by ESI MS for the formation of the complex that contains one cesium cation, as represented in Scheme 5, is $\lg\beta = 4.9 \pm 0.4$.

$$NboK_2 + Cs^+ \xrightarrow{\beta} NboK_2{\cdot}Cs^+ \qquad \beta = \frac{[NboK_2{\cdot}Cs^+]}{[NboK_2][Cs^+]}$$

Scheme 5. Formation of the $NboK_2{\cdot}Cs^+$ complex from norbadione A dipotassium salt.

We also undertook a speciation study on the permethylated analogue **3** by using the same experimental procedure as described above. For reasons of coherence with the first speciation study, 1.2 equivalents of potassium were added to each sample to express the competitive influence of potassium on Cs^+–**3** complex formation (Figure 2). Two different

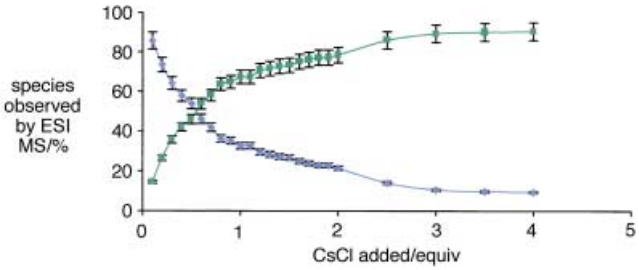

Figure 2. ESI–MS speciation curves of the permethylated analogue **3** in the presence of cesium chloride in methanol. ◆: free ligand, ■: complex $[\mathbf{3}+Cs]^+$. Relative abundances are reproducible within 5% from run to run.

species were identified: free **3**, observed as the potassium complex $[\mathbf{3}+K]^+$, and the cesium complex $[\mathbf{3}+Cs]^+$. The stability constant calculated for the 1:1 complex is $\lg\beta' = 4.6 \pm 0.4$ (Scheme 6). The stability constants of the 1:1 complexes that contain ligands **3** and norbadione A are thus quite similar. These results are in agreement with the structural hypothesis made from the neutral loss experiments whereby the neutral component of the $[Nbo+2K+Cs]^+$ complex is $NboK_2$. We also briefly evaluated the binding selectivity of **3** for Na^+, K^+, and Cs^+. In the presence of 0.8 equivalents of each alkali cation (in total, 2.4 equivalents), we observed a distribution of 60% cesium complex, 24% potassium complex, and 16% sodium complex. This distribution clearly indicates selectivity for cesium over potassium and sodium.

In summary, these results suggest that the complex formed by the dipotassium salt of norbadione A and one cesium cation results from an interaction between this cation and the pulvinic acid moieties of norbadione A. Thus, the structure depicted in Figure 3 might be favored: the cesium ion is held

$$\mathbf{3} + Cs^+ \xrightarrow{\beta'} \mathbf{3}{\cdot}Cs^+$$

Scheme 6. Formation of the $\mathbf{3}{\cdot}Cs^+$ complex from compound **3**.

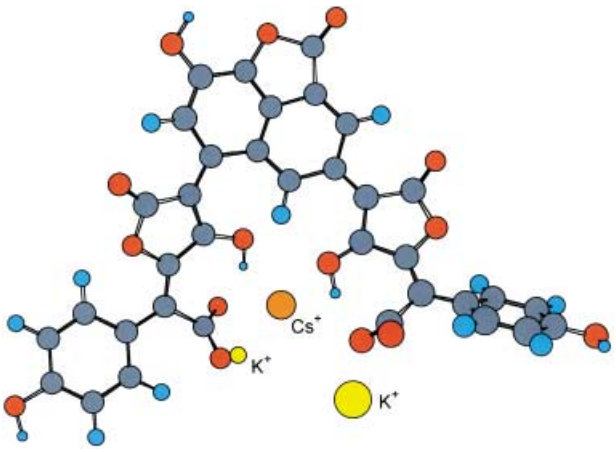

Figure 3. Structural hypothesis for the cesium complex of $NboK_2$ (Chem3D model). One potassium ion is located above the plane of the naphthalene moiety, the other one is located underneath that plane.

in a pseudocavity formed by a special arrangement of the two pulvinic acid moieties. Further work will include a decorporation study of radioactive cesium on animals, by treatment with norbadione A, the development of our synthetic approach towards a total synthesis of norbadione A, and the preparation of analogues designed for the selective complexation of different metal cations.

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Keywords: C–C coupling · cesium · mass spectrometry · metal complexation

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[20] Methanol was preferred to water as the solvent, since decarboxylation reactions readily occur in the ESI source with aqueous solutions.
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