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Towards the Stable Binding of Mercury: Synthesis and Functionalization of Dibenzyldiazabicyclononane Scaffolds

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Dedicated to the memory of Prof. Pius August Schubiger (1945–2024, ETH Zurich and PSI Villigen)

A universally applicable synthesis route for the preparation of functionalized diazabicyclononane compounds was elaborated starting from a readily available 1,5-diphenyl-3,7-diazabicyclo[3.3.1] nonan-9-ol by alkylation of both secondary amines with modified benzyl residues containing a bromo, trimethylstannyl, trimethylsilyl, and pinacolboranyl residue. High yields (65–88 %) were achieved, supporting the intended purpose of these compounds: efficient mercuration reactions to stably bind Hg^{2+}. Finally, the C-9 position of two functionalized diazabicyclononanes was further modified by introducing an azide functionality. This enables the conjugation to biomolecules of interest via click chemistry combined with a tracking by the introduced mercury isotopes.

Introduction

The design of encapsulating systems based on chelating macromolecules to form stable radiometal conjugates continues to be an important part of radiopharmaceutical development for both diagnostic and therapeutic applications in nuclear medicine.[1–4] A critical aspect of radiometal-based radiopharmaceuticals is their stability *in vivo*. Unwanted release of the radiometal ion should be minimal in order to prevent off-target accumulation *in vivo*. Therefore, the radiometal-binding ligand[5] is the key to ensure a high radiometal complex stability, especially when working with radioisotopes of mercury, e.g. $^{197(m)}$Hg.

In the 1960s and early 1970s, radiomercury was produced in reactors, albeit with a low specific activity. Regardless, ^{197}Hg- and ^{203}Hg-labeled chlormerodrin[6,7] was clinically employed for brain, kidney[8–10] and lung[11] imaging. Initially, ^{197}Hg was discussed as substitute for ^{99m}Tc.[12] However, it's use was discontinued by the FDA in 1989.[13] A rapid progress of ^{99m}Tc-radiopharmaceutical development and lack of viable *in vivo* stable mercury compounds led to a substantial decline of radiomercury applications.[14–16] Recently, cyclotron-produced $^{197(m)}$Hg with high specific activity (>500 GBq/μmol) was obtained using monoisotopic Au as target material. This high specific activity allows a safe application with mercury far below toxicity thresholds.[17]

The pair of mercury isotopes $^{197(m)}$Hg allows a diagnostic use as gamma emitter for single photon emission computed tomography (SPECT) medical imaging,[18] and a therapeutic application due to the high number of Auger and conversion electrons (^{197m}Hg: 19, ^{197}Hg: 23). The Auger electron emissions per decay have energies similar to those of ^{125}I, which has already been shown to be effective in inducing cell death by extracellular irradiation.[19–21] With physical half-lives of 23.82 h (^{197m}Hg) and 64.81 h (^{197}Hg)[22] as well as the single stable decay product ^{197}Au, the innate radioisotope pair $^{197(m)}$Hg fulfills the concept of radionuclide theranostics and holds promise for future radiopharmaceutical applications in nuclear medicine.[17,23]

Interest in mercury in modern chemistry is rather low, primarily due to its toxicity.[24] Thus, the research has been traditionally aimed on the detection, speciation determination[25] and removal from the environment.[26,27] More recent research is focused on the site-specific incorporation of organometallic entities into the nucleoside scaffolds,[28,29] their

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chemical transformations of organometallic nucleosides and biological applications.[30] Furthermore, chelation therapies after mercury poisoning are often based on the use of thiol-containing chelators such as dimercaptosuccinic acid.[31] In this case, a rapid clearance from the biological system has the highest priority, not a high long-term stability. However, the latter is a primary requirement for an application as radiopharmaceutical in nuclear medicine.

Bifunctional chelators are mostly considered for radiometals, which are able to encapsulate the radiometal by forming a complex and to provide a link to the tumor target vector molecule.[1–4] In contrast to other metals, organomercury compounds have a mandatory high water tolerance combined with the highest bond dissociation energies for Hg-C_{Ar}-bonds.[32] However, acyclic organomercurials suffer from a significant hydrolysis.[33,34] The application of a three-dimensional 3,7-diazabicyclo[3.3.1]nonane skeleton (also known as bispidine) as cyclic organic backbone furnished with benzyl groups at the nitrogen atoms leads to an organomercury compound which is stable *in vivo* and *in vitro* even at the radiotracer level.[35] The carbon atom at the C-9 position of the 3,7-diazabicyclo[3.3.1]-nonane allows the conjugation to the target vector molecule. However, the introduction of the trimethylstannyl leaving groups in the ortho position of the benzyl side chains, which are required for the prompt electrophilic introduction of (radio)mercury under mild conditions, is a bottleneck of the synthesis. The lithiation, which is prerequisite for the stannylation, led to a mixture of products, e.g. **Hg-I** with alkylated C-9 position, partially in rather low yields combined with a more complicated purification procedure.[35] The XRD analysis of **Hg-I** of this approach is shown in Figure 1.

Our aim was to synthesize new functionalized 3,7-diazabicyclo[3.3.1]nonane derivatives allowing for a fast introduction of (radio)mercury using stannyl, silyl, or boronyl leaving groups in a different synthetic route. We also wanted to avoid product mixtures from side reactions during the introduction of the leaving groups. Additionally, the C-9 position of the 3,7-diazabicyclononane skeleton was functionalized by azidoalkyl groups, allowing a later connection of the pharmacologically relevant targeting vector molecule. Structures of several intermediate compounds of the synthesis route were additionally fully characterized by XRD analyses.

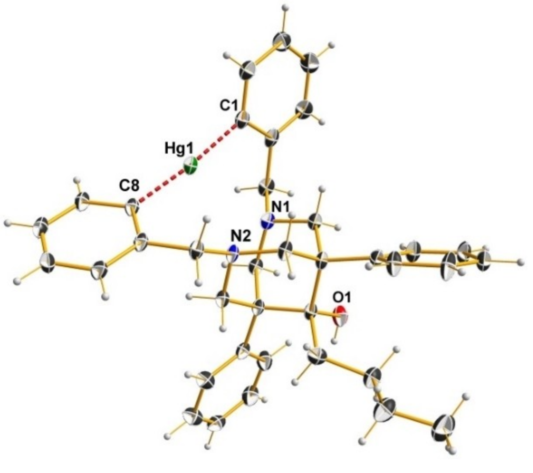
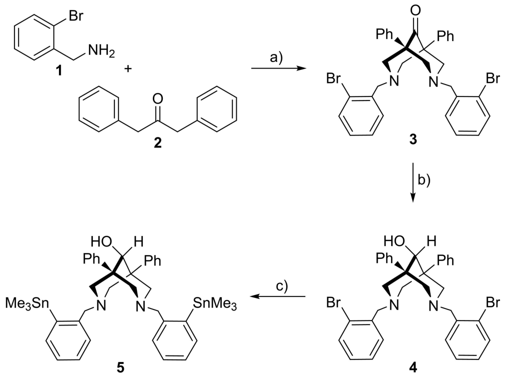


Figure 1. Molecular structure of the mercury-containing diazabicyclononane by-product **Hg-I**[32] (ORTEP plot, 50% probability level at −150 °C; the orientation with the higher occupation of the disordered phenyl ring is shown for better visibility).

Results and Discussion

Based on previous results, a synthetic route was elaborated starting from easily accessible starting materials to obtain the stannyl-functionalized diazabicyclononane **5** without unwanted side reactions. For this purpose, *o*-bromobenzylamine (**1**) was reacted with diphenylacetone (**2**) and formaldehyde under acidic conditions to obtain the functionalized diazabicyclononane skeleton **3** in 64% yield. Subsequently, diazabicyclononane **3** was reduced with $NaBH_4$ to yield alcohol **4** (94%) containing the OH groups at the C-9 position. The last step involved the introduction of the $SnMe_3$ group via the reaction of compound **4** with Me_6Sn_2 under Pd catalysis. Various Pd-catalysts ($Pd(PPh_3)_4$, $PdCl_2$, Pd_2dba_3) were tested, with only Pd_2dba_3 providing the desired product **5**, albeit in a low yield. To prevent decomposition of the Me_3Sn group under acidic conditions, the column chromatography was performed with 1% Et_3N as additive. In contrast to the previously published synthesis using the lithiation step, our synthetic approach provided the stannylated derivative **5** without by-products.[35] The full procedure is expressed in Scheme 1.

However, the synthesis of silylated and the borylated diazabicyclononane compounds was not possible with this route. To access the aforementioned derivatives and to overcome the poor yields of **5**, the basic 1,5-diphenyl-3,7-diazabicyclo[3.3.1] nonan-9-ol (**9**) was prepared starting from 5,7-diphenyl-1,3-diazaadamantan-6-one (**6**), which was treated with $LiAlH_4$ to yield adamantanol **7** (58% yield).[36] The OH group in position C-9 of compound **7** is necessary for a later functionalization, e.g. with biomolecules or dyes. In the next step, the methylene bridge between the two nitrogen atoms was cleaved by double acetylation with acetic anhydride,

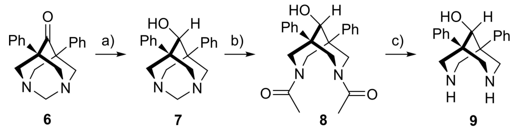


Scheme 1. Preparation of the bromo-functionalized diazabicyclononanes **3** and **4**, followed by the introduction of the Me_3Sn leaving groups to yield **5** for the binding of mercury. Reaction conditions: a) paraformaldehyde, MeOH, Na_2SO_4, acetic acid, 45 °C, 3 d; b) $NaBH_4$, dioxane, MeOH, toluene, rt, overnight; c) Sn_2Me_6, Pd_2dba_3, toluene, 100 °C, overnight.

providing compound **8** in 60% yield. Finally, the acetyl groups were removed with 10 M HCl to yield basic diazabicyclononane **9** in 85% yield (30% yield over 3 steps). The complete reaction pathway is shown in Scheme 2.

Both diazaadamantanes **6** and **7** are part of the synthesis procedure for the basic diazabicyclononane **9**. During the preparation, single crystals of compounds **6** and **7** were obtained for single-crystal XRD analyses. Selected data of the structure determinations of **Hg-I**, **6**, and **7** is compiled in Table 1.

Compound **6** crystallizes in the orthorhombic system with space group *Ima*2. Notably, the asymmetric unit contains halves of two symmetry-independent molecules. One, that expands from O1, is located on a mirror plane (Wyckoff site 4b), the other one around O2 on a twofold axis (Wyckoff site 4a). The molecular structures of the two independent molecules of **6** are shown in Figures 2A and 2B, with the result of a superimposition fit shown in Figure 2C. This fit reveals that the diazabicyclononane cores of both structures are essentially the same, but the phenyl rings are arranged dissimilar along the C2–C6 and the C13–C17 bond (different dihedral angles of the plane through the carbon atoms of the phenyl ring and the plane through O1, C1, C2 compared to O2, C12, C13). Due to the absence of acidic H atoms, the molecules lack any intermolecular forces besides Van-der-Waals interactions. All



Scheme 2. Synthesis of the basic diazabicyclononane compound **9**. Reaction conditions: a) $LiAlH_4$, $THF_{anhydr.}$, 60 °C, 3 h; b) Ac_2O, rt, overnight; c) HCl (10 M), 100 °C, overnight.

Table 1. Selected X-ray structure determination parameters of **Hg-I**, **6**, and **7**.

Compound	Hg-I	6	7
Empirical formula	$C_{37}H_{40}HgN_2O$	$C_{20}H_{20}N_2O$	$C_{20}H_{22}N_2O$
Formula weight	729.30	304.38	306.39
Temperature [K]	123(2)	123(2)	123(2)
Crystal system	triclinic	orthorhombic	triclinic
Space group (number)	$P\bar{1}$ (2)	*Ima*2 (46)	$P\bar{1}$ (2)
a [Å]	9.2613(5)	42.634(6)	11.3542(6)
b [Å]	11.4994(6)	9.524(1)	12.4006(6)
c [Å]	14.8293(7)	7.625(1)	12.5370(5)
α [°]	72.035(2)	90	90.625(2)
β [°]	84.413(2)	90	109.297(2)
γ [°]	87.689(2)	90	105.591(2)
Volume [Å^3], Z	1495.1(1), 2	3096.2(7), 8	1595.0(1), 4
ρ_{calc} [g cm^{-3}]	1.620	1.306	1.276
μ [mm^{-1}]	5.154	0.080	0.078
Goodness-of-fit on F^2	1.034	1.056	1.053
Final *R* indexes[a,b] [$I \geq 2\sigma(I)$]	$R_1 = 0.0288$ $wR_2 = 0.0590$	$R_1 = 0.0487$ $wR_2 = 0.1141$	$R_1 = 0.0605$ $wR_2 = 0.1532$
Final *R* indexes [all data]	$R_1 = 0.0397$ $wR_2 = 0.0631$	$R_1 = 0.0637$ $wR_2 = 0.1234$	$R_1 = 0.0896$ $wR_2 = 0.1809$

[a] $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$; [c] GoF $= S = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

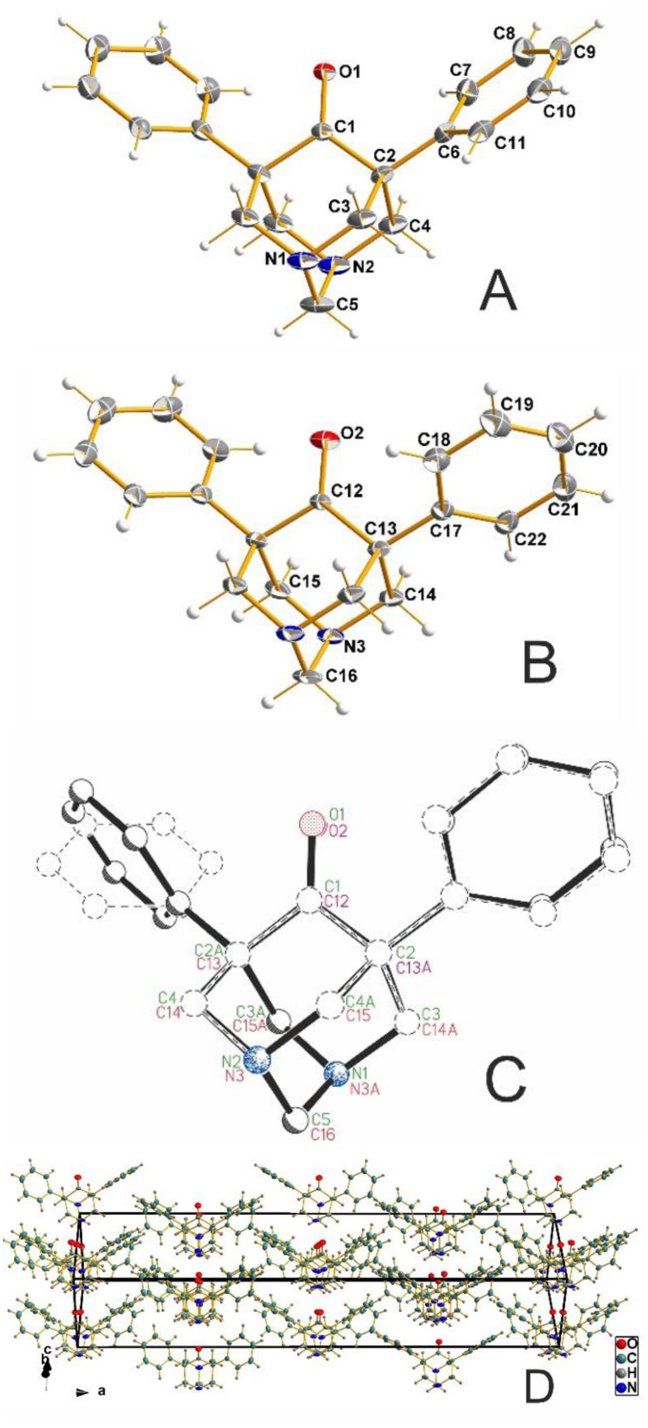


Figure 2. Molecular structure of the compound **6**. (A, B) Thermal ellipsoid plot at the 50% probability level at −150 °C; (C) Superimposition fit of the two symmetry independent molecules; (D) Arrangement of the molecules of **6** in the unit cell.

molecules are packed with the same orientation in the unit cell, see Figure 2D.

A triclinic symmetry with space group $P\overline{1}$ is found in crystals of adamantanol **7**. As in **6**, the asymmetric unit consists of two symmetry-independent molecules presented in Figure 3A and 3B. Their superimposition fit (Figure 3C) reveals the same structure and same orientation of the phenyl rings. Only their arrangement in the unit cell differs. This arrangement gives rise to short O–H···N (neighbouring molecule) contacts, e.g., strong hydrogen bridges with a D–A distance of 2.704(1) Å for O1–H1A···N4 and 2.717(1) Å for O2–H2A···N1′ (′: +x, −1+y, +z). As a result, chains of hydrogen bonded molecules exist in crystals of **7**, see Figure 3D.

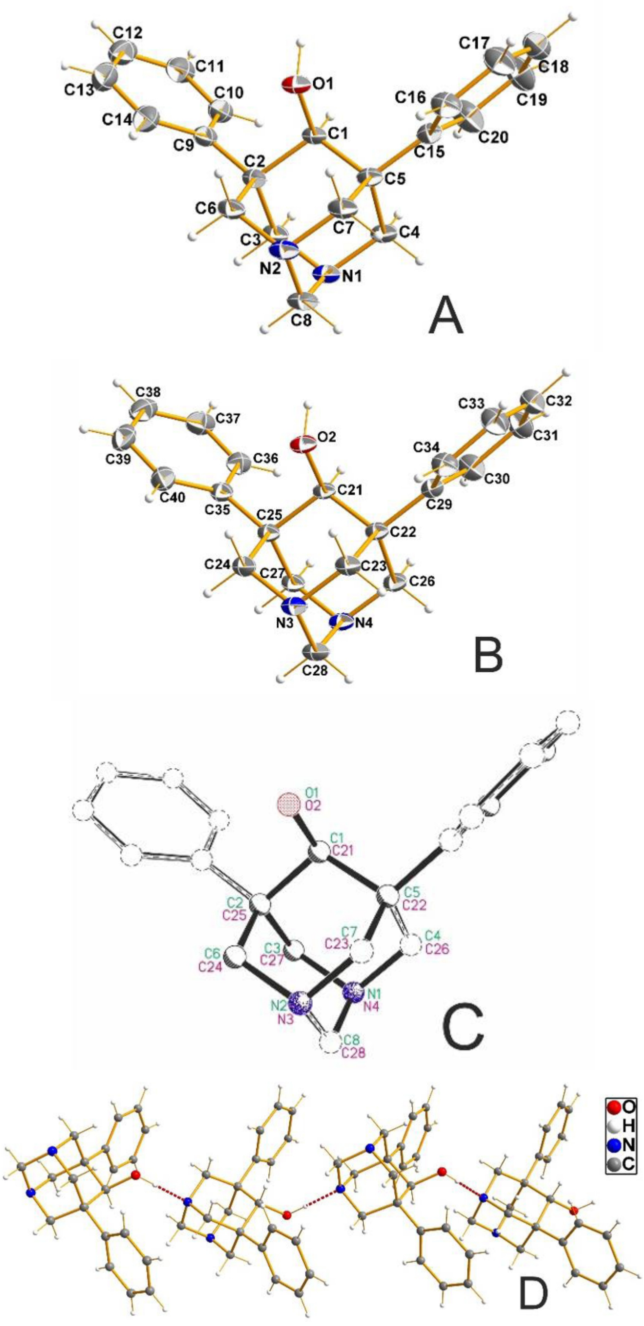
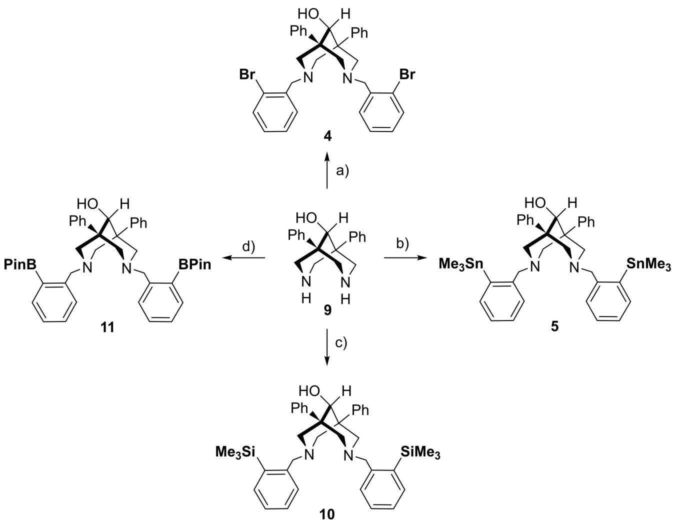


Figure 3. Molecular structure of compound **7**. (A, B) Thermal ellipsoid plot at the 50% probability level at −150 °C; (C) Superimposition fit of the two symmetry independent molecules; (D) Chains of the molecules of **7** interconnected through OH···N′ hydrogen bridges.

Functionalization of the Secondary Amines

Functionalized side arms with leaving groups such as boronate, silyl or stannyl groups are mandatory for a later introduction and stable binding of mercury. Thus, basic 1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (**9**) was used for the introduction of different functionalized side arms. These were based on benzyl groups via *N*-alkylation at both secondary amines leading to the desired *N*-alkylated diazabicyclononanes **4**, **5**, **10**, and **11** in high yields. An overview of the reactions is shown in Scheme 3. As proof-of-concept, *o*-bromo compound **4** was prepared again, now in 88% yield starting from diazabicyclononane **9**, 2-bromobenzyl bromide, and Cs_2CO_3 as base. Other bases such as K_2CO_3 unfortunately resulted in very low yields. Using the same conditions, compound **5** was obtained by the reaction of **9** with 2-(trimethylstannyl)benzyl chloride[37] in a high yield of 70%.

In addition to the stannylated diazabicyclononane **5**, compounds **10** and **11** were prepared and fully characterized. Compound **10** contains two trimethylsilyl and **11** two pinacolboranyl (BPin) leaving groups. To achieve this, diazabicyclononane **9** was reacted with 2-(trimethylsilyl)benzyl chloride[38] using Cs_2CO_3 as base to obtain silyl compound **10** in 65% yield. Diazabicyclononane **11** containing the pinacolborane leaving groups was accessible in a high yield of 69% by the reaction of **9** with 2-bromomethylphenylboronic acid pinacol ester. The purification of **10** and **11** was conveniently accomplished without the addition of Et_3N; a degradation was not observed.



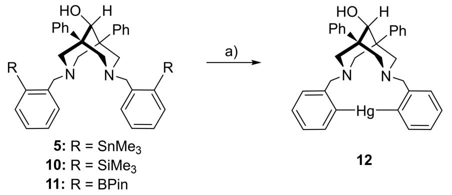
Scheme 3. Preparation of the functionalized diazabicyclononanes **4**, **5**, **10**, and **11** starting from basic diazabicyclononane **9** for the introduction of mercury. Reaction conditions: a) 2-bromobenzyl bromide, Cs_2CO_3, acetonitrile, 80 °C, overnight; b) 2-(trimethylstannyl)benzyl chloride, Cs_2CO_3, acetonitrile, 80 °C, overnight; c) 2-(trimethylsilyl)benzyl chloride, Cs_2CO_3, acetonitrile, 80 °C, overnight; d) 2-bromomethylphenylboronic acid pinacol ester, Cs_2CO_3, acetonitrile, 80 °C, overnight.

Preparation of the Organomercury Compound

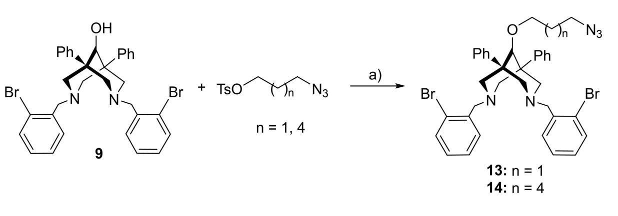
As a proof of concept, all three compounds **5** (Me_3Sn), **10** (Me_3Si), and **11** (BPin) were used to prepare the final organomercurial **12** with $Hg(OAc)_2$ as pointed out in Scheme 4. Compound **12** was obtained in acceptable to high yields depending on the employed leaving group of either $SnMe_3$ (69% yield) or BPin (56% yield). In both cases, the Me groups of the starting compounds **5** or **11** disappeared in the ^1H NMR spectrum. Compound **10**, containing the $SiMe_3$ leaving group, did not react under the chosen conditions. In this case, only starting material **10** and decomposed material were detected.

Functionalization of the Diazabicyclononane C-9 Position

To further functionalize the diazabicyclononane for future applications, e.g., as radiolabeling building block, it is necessary to introduce a "connector" for biologically active molecules. The alcohol function of the C-9 position of the diazabicyclononane skeleton seems to be appropriate despite its reduced reactivity. Different bases (KOH, NaH, KO^{t}Bu, Cs_2CO_3, Et_3N, DIPEA) and solvents (DCM, THF, 1,4-dioxane, DMF) were used to force the alkylation with either 3-azidopropyltosylate or 6-azidohexyltosylate to introduce linkers, suitable for click chemistry applications, e.g., Cu-AAC, SPAAC, or Staudinger Ligation. Anhydrous DMF as solvent, NaH as base in excess at 40 °C and a reaction time of 1 d under an argon atmosphere were identified as optimal reaction conditions, providing the highest yields. The 3-azidopropylated diazabicyclononane **13** was obtained in 38% and the 6-azidohexylated derivative **14** in 30% yield (Scheme 5).



Scheme 4. Mercuration of the functionalized diazabicyclononanes **5**, **10**, and **11**. Reaction conditions: a) $Hg(OAc)_2$, acetonitrile, rt, overnight.



Scheme 5. Functionalization of diazabicyclononane **9** at the C-9 position of the diazabicyclononane skeleton with azidoalkyl groups to obtain both *O*-alkylated diazabicyclononanes **13** and **14** ready for click labeling. Reaction conditions: a) NaH, DMF, 40 °C, 1 d.

Conclusions

A convenient 4-step synthetic route was established to obtain functionalized diazabicyclononanes containing $SnMe_3$, $SiMe_3$, and BPin as leaving groups for the introduction of (radio)mercury. Advantages are the higher yields and the absence of both product mixtures and by-products. The latter are usually formed from the introduction of the $SnMe_3$ leaving group through use of n-BuLi for the Li-halogen-exchange. Furthermore, the convenient access to other leaving groups (e.g., $SiMe_3$, BPin) is possible. Additionally, the purification process for mercury compound **12** is easier using a convenient two-phase washing step with water.

Experimental Section

General

All chemicals were purchased from commercial suppliers and used without further purification unless otherwise specified. Anhydrous DMF, dichloromethane, and THF were purchased from Acros and deuterated solvents were purchased from deutero. Compounds **3**, **4**,[35] **6–9**,[36] 2-trimethylstannylbenzyl chloride[37] and 2-trimethylsilylbenzyl chloride[38] were prepared according to procedures described in the literature. NMR spectra of all compounds were recorded on an Agilent DD2-400 MHz NMR or an Agilent DD2-600 MHz NMR spectrometer with ProbeOne. Chemical shifts of the ^1H, and ^{13}C spectra were reported in parts per million (ppm) using TMS as internal standard for $^1H/^{13}C/^{29}Si$ spectra, $BF_3{\cdot}OEt_2$ for ^{11}B NMR spectra, and $HgCl_2$ for ^{199}Hg NMR spectra. Mass spectrometric (MS) data were obtained on a CMS ExPresseIon (Advion) with MassExpress software by electron spray ionization (ESI). TLC analyses were performed using Merck Silica Gel 60 F_{254} sheets. TLCs were developed by visualization under UV light ($\lambda = 254$ nm). Chromatographic separations were accomplished by using an automated column chromatography system Biotage Isolera Four and appropriate Biotage KP-SIL SNAP silica gel columns. Single crystal X-ray diffraction data was collected with a Bruker Apex Kappa-II CCD diffractometer using graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). Measurements were performed at −150 °C. The structures were solved by direct methods and refined against F^2 by full-matrix least-squares using the program suites from G. M. Sheldrick.[39–41] All non-hydrogen atoms were refined anisotropically; all hydrogen atoms were placed on geometrically calculated positions and refined using riding models. In **Hg-I**, one of the two phenyl rings is disordered, what has been treated in the structure refinement by a split model with two different orientations of the phenyl rings.

Warning! All forms of mercury (inorganic and organic mercury compounds) are highly hazardous if inhaled or if they remain on the skin for more than a short period of time. Avoid poisoning from inhalation, ingestion, and injection or absorption through the skin by using appropriate safety equipment.

Chemical Syntheses

3,7-Bis(2-bromobenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]-nonan-9-ol (4). (alternative approach starting from **9**) Compound **9** (50 mg, 0.17 mmol) and 2-bromobenzyl bromide (100 mg, 0.58 mmol) were dissolved in anhydrous acetonitrile (15 mL), Cs_2CO_3 (115 mg, 0.35 mmol) was added and the reaction mixture was heated at 80 °C overnight. After TLC control, the solvent was removed, the residue was dissolved in chloroform and washed with water (3×20 mL) and brine (20 mL). Afterwards, the organic phase was dried over Na_2SO_4, the solvent was removed and the crude product was purified via automated column chromatography to yield compound **4** as colorless solid (94 mg, 88 %). NMR spectra are in accordance with the previously published (see also SI).[35]

1,5-Diphenyl-3,7-bis(2-(trimethylstannyl)benzyl)-3,7-diazabicyclo-[3.3.1]nonan-9-ol (5). (alternative approach starting from **9**) Compound **9** (100 mg, 0.34 mmol) and 2-(trimethylstannyl)benzyl chloride (228 mg, 0.70 mmol) were dissolved in anhydrous acetonitrile (10 mL), Cs_2CO_3 (111 mg, 0.35 mmol) was added and the reaction mixture was heated to 80 °C and reacted overnight. After TLC control, the solvent was removed, the residue was dissolved in chloroform and washed with water (3×20 mL) and brine (20 mL). Afterwards, the organic phase was dried over Na_2SO_4, the solvent was removed and the crude product was purified via automated column chromatography (silica, eluent: chloroform→ chloroform:ethyl acetate 3:1 containing 1 % Et_3N) to yield compound **5** as colorless solid (190 mg, 70 %).

1,5-Diphenyl-3,7-bis(2-(trimethylsilyl)benzyl)-3,7-diazabicyclo[3.3.1]-nonan-9-ol (10). Compound **9** (100 mg, 0.34 mmol) and 2-(trimethylsilyl)benzyl chloride (140 mg, 0.71 mmol) were dissolved in anhydrous acetonitrile (10 mL), Cs_2CO_3 (122 mg, 0.37 mmol) was added and the reaction mixture was heated to 80 °C and reacted overnight. After TLC control, the solvent was removed, the residue was dissolved in chloroform and washed with water (3×20 mL) and brine (20 mL). Afterwards, the organic phase was dried over Na_2SO_4, the solvent was removed and the crude product was purified via automated column chromatography (silica, eluent: chloroform→ chloroform:ethyl acetate 1:1) to yield compound **10** as colorless solid (136 mg, 65 %).

1,5-Diphenyl-3,7-bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzyl)-3,7-diazabicyclo[3.3.1]nonan-9-ol (11). Compound **9** (69 mg, 0.27 mmol) and 2-bromomethylphenylboronic acid pinacol ester (170 mg, 0.57 mmol) were dissolved in anhydrous acetonitrile (15 mL), Cs_2CO_3 (89 mg, 0.27 mmol) was added and the reaction mixture was heated to 80 °C and reacted overnight. After TLC control, the solids were removed by filtration, the solvent was removed and the residue was purified via automated column chromatography (silica, eluent: ethanol) to yield compound **11** (139 mg, 69 %) as colorless solid.

8,10-Diphenyl-8,9,10,11-tetrahydro-5*H*,7*H*,13*H*-6,10:8,12-dimethanodibenzo[b,m][1]mercura[5,11]diazacyclotetradecin-9-ol (12). Compound **5** (100 mg, 0.12 mmol) was dissolved in acetonitrile (5 mL) and $Hg(OAc)_2$ (40 mg, 0.12 mmol) was added. The mixture was stirred at ambient temperature overnight. Next, the solvent was removed and the crude was purified via column chromatography to yield **12** (58 mg, 69 %) as light yellow solid.

9-(3-Azidopropoxy)-3,7-bis(2-bromobenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane (13). Under Ar, compound **9** (100 mg, 0.158 mmol, 1 eq.) was dissolved in DMF (10 mL) and stirred at 60 °C for 30 min. Next, NaH (60 % in mineral oil, 60 mg, 2.5 mmol, 27 eq.) were added and the mixture allowed to stir at 60 °C for 60 min. Afterwards, 3-azidopropyl tosylate (0.5 mL, 6.6 eq.) was slowly added and the mixture was stirred at 40 °C overnight. After TLC control, the solvent was removed, the residue was dissolved in DCM (20 mL) and washed with water (2×20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (silica, eluent: chloroform:acetone 1:0→4:1). Compound **13** (30 mg, 38 %) was obtained as slightly yellow syrup.

9-(6-Azidohexoxy)-3,7-bis(2-bromobenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane (14). Under Ar, compound **9** (150 mg, 0.24 mmol, 1 eq.) was dissolved in DMF (10 mL) and stirred at 60 °C for 30 min. Next, NaH (60 % in mineral oil, 70 mg, 2.9 mmol, 18 eq.) was added and the mixture allowed to stir at 60 °C for 60 min. Afterwards, 3-azidohexyl tosylate (0.9 mL, 6.6 eq.) was slowly added and the mixture was stirred at 40 °C overnight. After TLC control, the solvent was removed, the residue was dissolved in DCM (20 mL) and washed with water (2 x 20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed and the crude product was pre-purified via column chromatography (silica, eluent: chloroform:acetone 1:0→4:1) and finally with semipreparative HPLC (acetonitrile/water 55 %→80 %). Compound **14** (TFA salt, 55 mg, 30 %) was obtained as colorless solid.

Supporting Information

Characterization data for reaction products, copies of NMR, MS and IR spectra.

CCDC-2207652 (**Hg-I**), CCDC-2227173 (**6**), and CCDC-2227174 (**7**) contain the supplementary crystallographic data. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe http://www.ccdc.cam.ac.uk/structures.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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