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TOWARDS NEW SILA- OR GERMA-DERIVATIVES OF MOTESANIB

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Abstract – Developing new access to original silylated heterocycles is an emerging challenge in medicinal chemistry. In this paper, we describe a synthesis of silylated and germylated Motesanib analogues relying on a peptide coupling between a nicotinic acid derivative and silylated or germylated heterocycles, prepared according to our previous reports.

Motesanib **1** (AMG 706)[1] is a multikinase inhibitor and antiangiogenic agent, that was tested as an experimental drug candidate (phase III). It is an orally administrated small molecule antagonist of VEGF receptors, platelet-derived growth factor receptors, and stem cell factor receptors.[2] The silicon atom has a large similarity with carbon atom and it was shown that the introduction of silicon in a molecule can impact its biological activity, by modifying metabolism.[3,4] As the search of new therapeutic agents by modification of known compounds appears as a promising way to adjust the biological profile, we were interested in the synthesis of silicon-containing Motesanib derivative (Figure 1), in particular as this compound therapeutic properties seems to be recently challenged for specific indications.[5] Our group has developed a synthetic methodology giving access to a novel family of silylated and germylated binuclear heterocycles.[6] We therefore decided to explore the possibility of including these scaffolds into more elaborated bioactive molecules, such as Motesanib **1**. We describe in this paper our attempts to establish a synthesis route towards silylated derivatives, as well as the extension toward a germylated one.

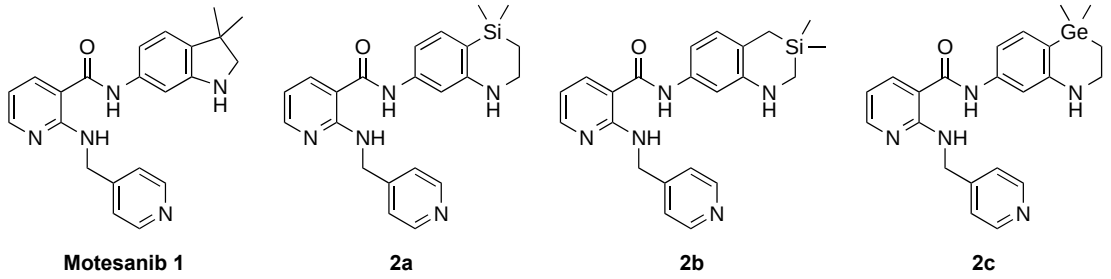
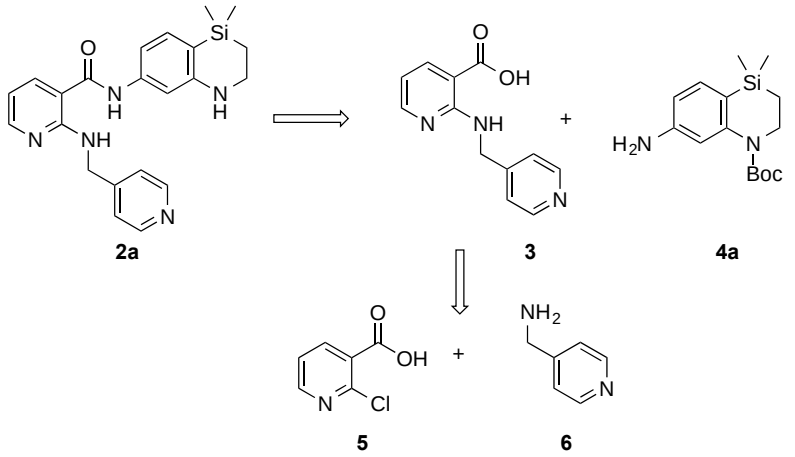


Figure 1. Structures of Motesanib **1** and envisioned derivatives **2**

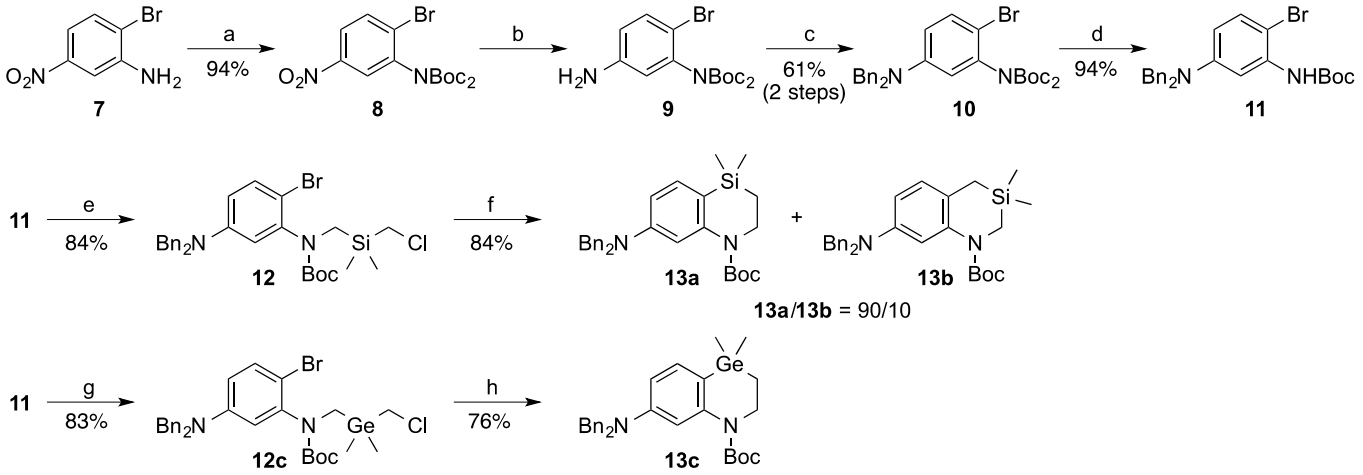
The key step of the retrosynthetic pathway we propose relies on the coupling of the nicotinic acid derivative **3** (from commercially available pyridines **5** and **6**) with aminoazasilines **4** (or germylated analogues). Thus, analogues **2a-c** could be prepared according to the method depicted in Scheme 1 for compound **2a**.



Scheme 1. Retrosynthetic approach of the silicon-containing Motesanib derivative **2a**

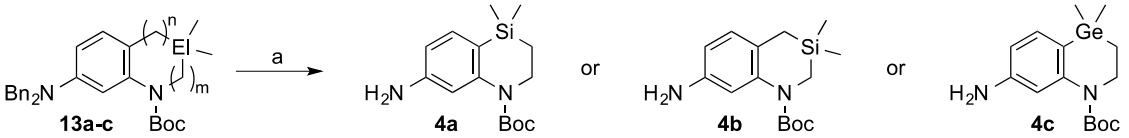
We first focused on the preparation of the silylated and germylated building blocks **4a-c**, assembled following our previous strategy. The access to advanced precursors **13a-c** has already been described (Scheme 2),[6b] and was repeated to provide these compounds on a 10 mmol scale. We do not come back the description of these synthetic routes.

The final coupling in our strategy required the dibenzylamino group in **13a** to be deprotected and this was achieved by catalytic hydrogenolysis. The expected free aniline **4a** was obtained in classical conditions (1 atm H_2, MeOH, Pd/C), but contaminated with 33% of an unidentified side-product resulting from the breakdown of the heterocyclic ring, probably triggered by the solvent. Using non-hydroxylated solvents such as ethyl acetate was inefficient for this reaction, but we significantly improved the results by decreasing the nucleophilic properties of the solvent by replacing MeOH with EtOH. Thus, running the reaction in the presence of 20% Pd/C in ethanol led to the expected product **4a** in 90% yield after 30 minutes. However, this compound turned out to be relatively unstable over time and must be prepared right before use.



Scheme 2. Synthesis of building blocks **13a-c**. Reagents and conditions: (a) Boc_2O, DMAP, CH_2Cl_2, 24 h, rt; (b) Zn, NH_4Cl, acetone, 4 h, reflux; (c) BnBr, NaI, K_2CO_3, DMF, 24 h, rt; (d) K_2CO_3, MeOH, 4 h, rt; (e) $(ClCH_2)_2Si(Me)_2$, NaH, DMF, 3 h, 80 °C; (f) *t*-BuLi, THF, 1 h, -78 °C; (g) $(ClCH_2)_2Ge(Me)_2$, NaH, DMF, 3 h, 80 °C; (h) *t*-BuLi, THF, 1 h, -78 °C.

With the aim to achieve the synthesis of the analogues **4b-c**, we applied the same optimized procedure on their precursors **13b-c**. While the silylated isomer **4b** seemed to be slightly more stable, the germylated compound **4c** behaves as **4a**. However, both were obtained in yields exceeding 90% but had to be freshly prepared before use (Scheme 3).

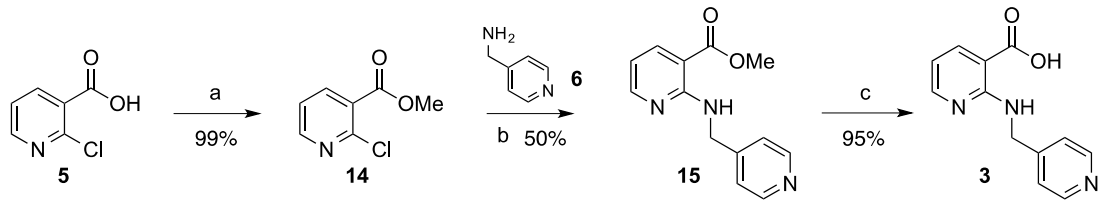


13a: El = Si; n = 0; m = 2
13b: El = Si; n = 1; m = 1
13c: El = Ge; n = 0; m = 2

Scheme 3. Hydrogenolysis of compounds **13a-c**. Reagents and conditions: (a) H_2, Pd/C, EtOH, 30 min, rt.

We then investigated the preparation of the other partner: the nicotinamide derivative **3**. On the first attempts, this latter, was tentatively prepared directly from the 2-chloronicotinic acid **5** and the pyridinylmethanamine **6** on the basis of a succinct note published in 2007.[7a] Since no experimental conditions were available, we tried also conditions inspired from those reported by Wang for the coupling of 4-aminomethyl-7-azaindole and 2-chloro-5-fluoronicotinic acid (*i.e.* $NaHCO_3$ in 1-pentanol at 130 °C during 48 h in a sealed tube).[7b] However, the conversion hardly reached 25%, even in the high concentration conditions suggested by the authors. We also examined various coupling protocols, changing the base, the temperature, the solvent as well as the heating process (sealed tube, oil bath, microwaves). Unfortunately, even in the best conditions, the conversion remained under 30%, and we were not able to isolate a clean sample of the product. We thus decided to protect the acidic moiety of **5**

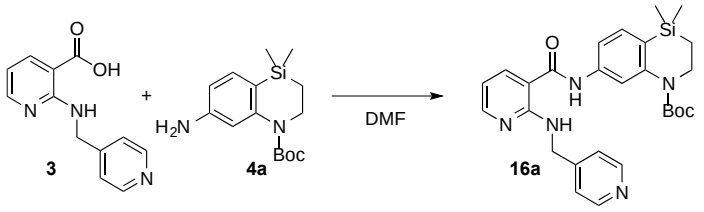
converting it into the corresponding methyl ester **14** (Scheme 4). This transformation was performed quantitatively by reacting **5** with 1.2 equiv. of trimethylsilyldiazomethane in THF/MeOH/hexane at room temperature.[8] Resorting to conditions inspired by the above experiments, the coupling between **6** and **14** was improved, the yield reaching 50% in **15** when heating ester **14** with 3 equiv. of amine **6** under microwave irradiation at 130 °C during 30 minutes in EtOH.



Scheme 4. Synthesis of the nicotinic acid derivative **3**. Reagents and conditions: (a) $TMSCHN_2$, THF MeOH/hexane, 1.5 h, rt; (b) **6**, EtOH, 30 min, 130 °C (μw); (c) NaOH, MeOH/H_2O, 4 h, 80 °C.

At this stage, it was important to evaluate the ability of ester **15** to undergo a direct amidation by aniline derivatives. A model optimization involving **15** and aniline was performed, and led to a satisfying conversion rate of 70% when 4 equiv. of *i*PrMgCl were employed in THF. Applying these conditions to **4a** led to disappointing results. Instead of the expected amide **16a**, only the starting materials or degradation products were recovered even when using *i*PrMgCl in harsher conditions, resorting to Knochel's turbo Grignard reagent *i*PrMgC·LiCl,[9] or changing the base. We thus opted to saponify the ester **15** back to acid **3**, in the perspective of using classical peptide coupling conditions. The results are reported in Table 1 below for aniline **4a**.

Table 1. Conditions of peptide coupling of nicotinic acid derivative **3** with aniline **4a**



entry	equiv. of **3**	conditions	conv. %	isolated yield %
1	1	PyBOP (1 equiv.), TEA (3 equiv.), 45 h, rt	33	-
2	1	PyBOP (1 equiv.), TEA (3 equiv.), 15 h, 80 °C	50	10
3	1	EDC (1.5 equiv.), DIPEA (3 equiv.), 15 h, rt	-	-
4	2	PyBOP (2 equiv.), DIPEA (4 equiv.), 60 h, rt	60	41
5	2	PyBOP (2 equiv.), DIPEA (4 equiv.), 24 h, 80 °C	78	60
6	2	PyBOP (2 equiv.), DIPEA (4 equiv.), 15 h, 150 °C	100	35

The results show that benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP, Castro's reagent) was the appropriate coupling agent in this case, leading to 33-100% conversion, depending on the base employed and the temperature. In the best conditions (Table 1, entry 5), 60% isolated yield could be obtained in the first protected silicon-containing Motesanib derivative **16a**.

Applying the same procedure to the more stable aniline **4b** led to the expected second protected sila-Motesanib derivative **16b** in 65% yield. A further extension was run with the fragile germylated aniline **4c** but the targeted third derivative **16c** was obtained this time in only 22% yield, probably because of the degradation of **4c** during the course of this long (24 h) reaction.

The final step consisted in the deprotection of the nitrogen in the aminoazasiline appendage that was attempted on compound **16a**. The optimal conditions to remove the Boc group consisted in using 5 equiv. of TMSOTf in the presence of 10 equiv. of 2,6-lutidine in dichloroethane at 0 °C for 30 minutes. The product was clearly obtained and could be characterized by ^{1}H NMR. However the free silicon-containing Motesanib derivative turned out to be relatively unstable, both in the presence of alcohol or $CDCl_3$, preventing more detailed analyses.

In conclusion, we have succeeded in the synthesis of two Boc-protected sila-Motesanib and one germa-Motesanib analogues, employing a peptide coupling reaction between a nicotinic acid derivative and a silylated or germylated heterocycle. The binuclear aniline partners incorporating a silicon or germanium atom could be obtained following a general and straightforward protocol based on a rearrangement developed recently by our group. With this preparation of silicon- and germanium-containing Motesanib derivatives, we demonstrated that these scaffolds could be included into elaborated bioactive molecules. The validity of our original hypothesis concerning the bioisostery of silicon for this class of bioactive molecules will now have to be evaluated before new synthetic analogs can be designed and synthetized.

EXPERIMENTAL

General experimental conditions for microwave irradiation procedure

All reactions under microwave irradiation (ν = 2.45 GHz) were performed in oven-dried 10 mL sealable Pyrex tubes equipped with a Teflon coated stirring bar (obtained from CEM) under an argon atmosphere. The irradiation was run in a CEM Discover 1-300W system equipped with build-in pressure measurement sensor and a vertically focused IR temperature sensor.

Synthesis of the methyl 2-chloronicotinate 14 (CAS registry number: 40134-18-7)

Protocol using trimethylsilyldiazomethane: To a solution of 2-chloronicotinic acid **5** (2.0 g, 12.7 mmol) in a mixture THF/MeOH (3:1) (100 mL) was added the solution of trimethylsilyldiazomethane in hexane (2.0 M, 7.6 ml, 15.2 mmol). After 1.5 h at room temperature, 0.2 equiv. of acetic acid was added, then the

reaction mixture was concentrated under reduced pressure to give the crude product, which was engaged directly to the following step without any purification. The ester **14** was isolated as yellow oil (2.16 g, 99%).

Protocol using dimethyl sulfate: To a suspension of 2-chloronicotinic acid **5** (5.0 g, 32 mmol) in acetone (40 mL) were added the potassium carbonate (6.63 g, 48 mmol, 1.5 equiv.) and the dimethyl sulfate (3.35 mL, 35 mmol, 1.1 equiv.). After 20 h at room temperature, the reaction mixture was filtered and rinsed with acetone. The filtrate was then concentrated under reduced pressure and diluted with CH_2Cl_2. The solution was then washed with a saturated aqueous solution of sodium carbonate, dried over Na_2SO_4, filtered and concentrated under reduced pressure, to give the almost clean crude mixture which was purified by distillation under reduce pressure (4.0 g, 71%).

^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.23 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.48 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.3, 153.0, 150.4, 141.8, 128.6, 124.0, 53.4.

Synthesis of the methyl 2-((pyridin-4-ylmethyl)amino)nicotinate 15 (CAS registry number: 474799-48-9)

To a solution of ester **14** (2.16 g, 12.3 mmol) in dry EtOH (7 mL) was added the distillated aminopyridine (3.74 mL, 37.0 mmol, 3.0 equiv.). After 30 min under microwave irradiations (300 W) at 130 °C, the reaction mixture was concentrated under reduced pressure to give the crude product. The excess of aminopyridine was then precipitated by addition of Et_2O. The filtrate was concentrated under reduced pressure and purified by column chromatography (1%-5% MeOH/DCM). The expected product **15** was isolated as a white solid (1.54 g, 50%).

^{1}H NMR (300 MHz, CD_3OD) δ 8.59 (brs, 1H), 8.41 (d, *J* = 6.1 Hz, 2H), 8.14-8.20 (m, 2H), 7.36 (d, *J* = 6.1 Hz, 2H), 6.63 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.78 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.0, 159.5, 154.4, 152.6, 149.9 (2C), 141.5, 123.8 (2C), 113.1, 107.9, 52.6, 44.4; MS (EI, 70 eV) *m/z*: 244 ($M+H^+$), 223, 153 (base), 136.

Synthesis of the 2-((pyridin-4-ylmethyl)amino)nicotinic acid 3 (CAS registry number: 854382-06-2)

To a solution of ester **15** (150 mg, 0.61 mmol) in a mixture EtOH/water (1:1) (12 mL) was added the sodium hydroxide (35 mg, 0.9 mmol, 1.5 equiv.). After 4 h at 80 °C the reaction mixture was quenched with a pH 7 buffer and the resulting solution was concentrated under reduced pressure. The wet solid was dried by coevaporation using toluene (3 times) and dissolved in MeOH, the suspension was filtered and the filtrate concentrated under reduced pressure to give the corresponding carboxylic acid **3** as a yellow solid (134 mg, 95%).

^{1}H NMR (300 MHz, CD_3OD) δ 8.42 (d, *J* = 6.1 Hz, 2H), 8.18 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.95 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.40 (d, *J* = 6.1 Hz, 2H), 6.57 (dd, *J* = 7.5, 5.0 Hz, 1H), 4.73 (s, 2H); ^{13}C NMR (75 MHz,

CD_3OD) δ 174.5, 160.0, 153.1, 150.4, 149.8 (2C), 141.5, 123.9 (2C), 116.7, 112.7, 44.4; **HRMS** (ESI^+): calculated 230.0930 (for $C_{12}H_{12}N_3O_2$, M+H), found. 230.2000.

Synthesis of sila- or germa-Motesanib analogues 16a-c

To a solution of the protected aniline **13a-c**[6b] (1.0 equiv.) in anhydrous EtOH (100 mL/mmol) was added carefully 20% (w/w) of Pd/C. The mixture was then stirred under H_2 atmosphere (rubber balloon) during 30 min, filtered through a Celite pad and washed with EtOH. The mixture was concentrated under reduced pressure to give the expected aniline **4a-c** that required no further purification and was directly introduced to the peptide coupling step.

To a solution of carboxylic acid **3** (2.0 equiv.) in anhydrous DMF (5 mL/mmol) was added the PyBOP reagent (2.0 equiv.), the diisopropylethylamine (4.0 equiv.) and a solution of the silylated/germylated amine **4a-c** (1.0 equiv.) in DMF (5 mL/mmol). After 24 h at 80 °C, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The resulting organic phase was then washed with water (5 times) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was finally purified by flash chromatography on silica gel using the appropriate mixture of eluents.

Sila-Motesanib 16a is obtained from protected aniline **13a** (0.56 mmol) as a yellow solid (153 mg, 0.3 mmol, 54% for two steps).

^1H NMR (300 MHz, CD_3OD) δ 8.42 (d *J* = 6.2 Hz, 2H), 8.12 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.05 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 6.2 Hz, 2H), 6.69 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.76 (s, 2H), 3.84-3.75 (m, 2H), 1.48 (s, 9H), 1.20-1.12 (m, 2H), 0.26 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.9, 158.8, 156.0, 152.8, 152.3, 150.3, 149.9 (2C), 140.9, 138.4, 135.1, 127.8, 123.9 (2C), 119.6, 119.0, 113.1, 112.9, 82.0, 46.4, 44.5, 28.7 (3C), 14.7, -1.1 (2C); **HRMS** (ESI^+): calculated 504.2431 (for $C_{27}H_{34}N_5O_3Si$, M+H), found. 504.2433; **Mp** 59 °C.

Sila-Motesanib 16b is obtained from protected aniline **13b** (0.075 mmol) as colorless oil (25 mg, 0.05 mmol, 64% for two steps).

^1H NMR (300 MHz, CD_3OD) δ 8.42 (d, *J* = 6.0 Hz, 2H), 8.11 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 6.0 Hz, 2H), 7.41-7.38 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.68 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.76 (s, 2H), 3.05 (brs, 2H), 1.94 (s, 2H), 1.46 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.7, 158.8, 156.8, 152.8, 152.1, 149.9, 149.9 (2C), 142.1, 138.2, 137.5, 131.1, 123.9 (brs, 2C), 121.3, 120.3, 113.2, 112.9, 81.7, 44.5, 36.7 (brs), 28.7 (3C), 19.1, -2.89 (2C); **HRMS** (ESI^+): calculated 504.2431 (for $C_{27}H_{34}N_5O_3Si$, M+H), found. 504.2424.

Germa-Motesanib 16c is obtained from protected aniline **13c** (0.20 mmol) as colorless oil (22 mg, 0.04

mmol, 20% for two steps).

^{1}H NMR (300 MHz, CD_3OD) δ 8.28-8.19 (m, 2H), 7.92 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.85 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.21-7.19 (m, 2H), 6.49 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.77 (s, 2H), 3.80-3.73 (m, 2H), 1.48 (s, 9H), 1.44-1.38 (m, 2H), 0.41 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.8, 158.8, 156.1, 152.8, 152.3, 150.1, 149.8 (2C), 140.4, 138.3, 134.8, 130.6, 123.9 (br s, 2C), 120.0, 119.7, 113.0, 112.9, 81.8, 47.3, 44.5, 28.7 (3C), 16.7, -1.8 (2C); **HRMS** (ESI$^+$): calculated 550.1873 (for $C_{27}H_{34}N_5O_3{}^{74}Ge$, M+H), found. 550.1892.

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8. For a large scale application of this reaction, we found that a protocol involving dimethyl sulfate in acetone in the presence of K_2CO_3 gives a reasonable methylation yield (71%); for more details: see experimental part.
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