Research Article

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Synthesis of a high specific activity methyl sulfone tritium isotopologue of fevipiprant (NVP-QAW039)

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The synthesis of a triple tritiated isotopologue of the CRTh2 antagonist NVP-QAW039 (fevipiprant) with a specific activity >3 TBq/mmol is described. Key to the high specific activity is the methylation of a bench-stable dimeric disulfide precursor that is *in situ* reduced to the corresponding thiol monomer and methylated with [$^3H_3$]MeONos having per se a high specific activity. The high specific activity of the tritiated active pharmaceutical ingredient obtained by a build-up approach is discussed in the light of the specific activity usually to be expected if hydrogen tritium exchange methods were applied.

Keywords: tritium; CRTh2 receptor antagonists; NVP-QAV680; NVP-QAW039; fevipiprant; 3-(2-methyl-7-aza-indolyl) acetic acid; chemical cross-linking; [$^3H_3$]methyl nosylate; palladium catalysis; hydrogen isotope exchange

Introduction

Transmembrane chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells (CRTh2) represents an attractive target to address the need for the efficient oral anti-inflammatory treatment of allergic asthma. This receptor recognizes prostaglandin D_2 (**1**, Figure 1) and regulates in a joint system the pathophysiology of several allergic and chronic inflammatory conditions.[1,2] Ever since the discovery of the nonsteroidal anti-inflammatory agent indometacin[3] (**2**, Figure 1) to function as a ligand for CRTh2,[4,5] numerous drug discovery initiatives have been launched aiming to develop orally available CRTh2 antagonists belonging to many different compound classes, currently in the preclinical or early clinical phase.[6] Among these development compounds, medicinal chemistry literature recognizes indol-1-yl acetic acids and indol-3-yl acetic acids as promising drug candidates.[7–10] Recently, the 7-azaindole-3-acetic acid NVP-QAV680 (**3**, Figure 1) was found to be a highly selective compound with low nanomolar functional potency for the *in vitro* inhibition of CRTh2-driven human eosinophil and Th2 lymphocyte activation. This compound progressed into human clinical studies.[11] Further structural and electronic optimization of NVP-QAV680 led to the discovery of the trifluoromethyl derivative NVP-QAW039 (fevipiprant, **4a**, Figure 1), which exhibits improved potency in human eosinophil and Th2 cell assays.[12] Saturation and competition-binding experiments with CHO–CRTh2 cell membranes and [$^3H_3$]QAW039 revealed that fevipiprant is a slowly dissociating CRTh2 antagonist that may afford improved clinical efficacy.[13] The synthesis of the tritium isotopologue of fevipiprant used for these experiments is the subject of this publication. A detailed discussion of the aforementioned kinetic profiling and receptor occupancy studies will be published elsewhere.[14]

Although methods are known, allowing for the synthesis of different deuterium isotopomers of **4a** by site-selective H/D exchange under basic aqueous thermal conditions with microwave irradiation,[15] we desired to develop a safe synthetic approach providing access to a methyl sulfone tritium isotopologue of our next-generation CRTh2 receptor antagonist **4a** without using basic THO as a dangerous tritium source. The rationale behind this goal was to develop a radioligand of fevipiprant that can be used under physiological pH in receptor occupancy experiments without having the risk of THO formation due to the aforementioned weak proton acidity of the methyl sulfone moiety. Thus, a precursor suitable for late-stage introduction of the tritium label as well as well-defined high specific activity was desired. Fontana and coworkers described a strategy for the synthesis of a deuterium-labeled methyl-phenyl-sulfide containing active pharmaceutical ingredient.[16] These authors methylated a volatile, thus easily dimerizing thiol using a low-boiling deuterated methylating agent followed by sulfur oxidation. As such, we speculated if this strategy can be applied

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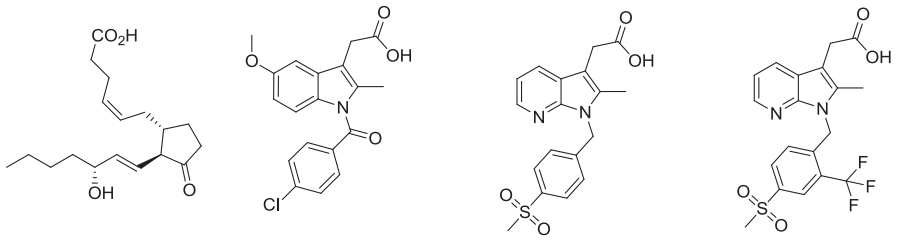
Abbreviations: *AIBN azaisobutyronitrile; BEMP 2-tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; DDT dithiothreitol; NBS *N*-bromo succinimide; NMO *N*-methylmorpholine *N*-oxide; MeONos methyl nosylate; TIPSSH triisopropylsilyl mercaptane.



1 (PGD2) **2** (Indometacin) **3** (NVP-QAV680) **4a** (NVP-QAW039, fevipiprant)

Figure 1. Structures of the potent mediator of allergic inflammation prostaglandin D_2 (PGD_2, **1**), the first nonsteroidal anti-inflammatory agent indomethacin (**2**), and chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells antagonists **3** and **4a** emerging from the Novartis pipeline.

to prepare tritiated isotopomers of prostaglandin D_2 receptor antagonists, which are structurally related to fevipiprant.[9]

A bioconjugation chemistry-inspired approach[17] in which a disulfide such as **5** (Figure 2) serves as a stable precursor for late-state tritium isotope introduction has not been described before in the literature. Our strategy was to cleave **5** by Cleland reduction[18] (step 1) and to trap the released thiol with a high specific activity [$^3H_3$-Me]methyl electrophile[19] (step 2). Subsequent oxidation of the phenyl [$^3H_3$]-methyl sulfide moiety (step 3) and hydrolysis of the ester (step 4) will generate the tritiated radioligand of the active pharmaceutical ingredient in a safe and efficient way. This retrosynthetic analysis also can be applied to any other hydrogen isotope labeling of methyl sulfone moieties, which so far followed the aforementioned strategy of Fontana *et al.*

Results and discussion

Synthesis of compound 5

Two routes A and B (Scheme 1 and Scheme 2, respectively) for the synthesis of the disulfide **5** were tested. While the key step of route B was realized in analogy with the medicinal chemistry synthesis of NVP-QAV680[11] (**3**), route A differs from route B by the sequence when the thio substituent was introduced into the commercially available starting material **6**. Although this difference might appear marginal, route A gave the impression of being superior because the predicted instability of the TIPS protecting group followed by oxidation of the unprotected thiol group should give clean and quick access to the core disulfide of **5**. Indeed, when the silyl-protected thiol functionality was introduced using palladium-catalyzed methods described by Migita[20,21] and Hartwig[22] (Scheme 1, step i) and when the oxidation of the deprotected thiol **8** (step ii) was completed in acidic water[23] (step iii), the disulfide **9** was isolated in 56% yield over two steps. Unfortunately, the radical *bis*-bromination of the methyl group in **9** with NBS was difficult to control, and most likely, the disulfide bridge was cleaved to form an unstable sulfenylbromide[24], which we could not characterize further. This interpretation is supported by the observation that although a relatively clean reaction was observed during in-process control, the crude post-extraction product was not stable on silica when the sulfenylbromide was treated with a weak acid. For this reason we turned our attention to route B, where radical side-chain bromination of **6** followed an established method for the synthesis of **10**.[25] The use of a safer alternative solvent to CCl_4 for this bromination was not investigated. The original radical initiator (benzoyl peroxide) was replaced by what is considered to be less explosive (AIBN). Subsequent alkylation of the pyrrolo nitrogen of the azaindole moiety of heterocycle **11** using electrophile **10** in the presence of a phosphazene base[11] yielded **12** in acceptable yields (71%, step ii). The palladium-catalyzed carbon–sulfur cross-coupling (step iii) tested in route A was successfully applied to the even more functionalized substrate **13**. Under these conditions, silyl-protected **13** was obtained in a good yield (80%). Further deprotection of **13** with alkylammonium fluoride (step iv) gave a mixture of the thiol **14** and the auto-oxidation product **5**. Upon chromatography on silica, both compounds were separated, and the thiol **14** was oxidized to its dimer **5** as developed in route A (step v). The disulfide **5** was characterized as by two-dimensional NMR and mass spectrometry (MS). Fourier transform infrared (FT-IR)

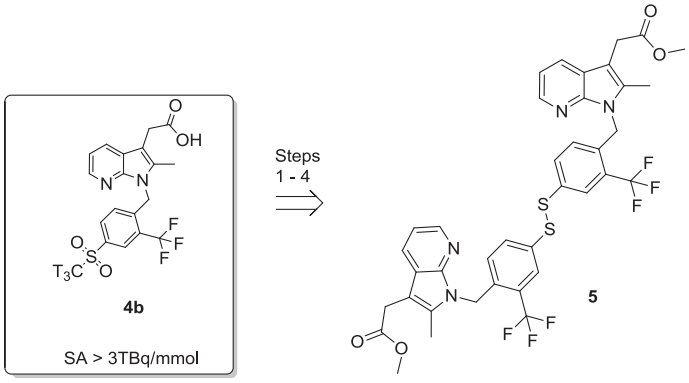
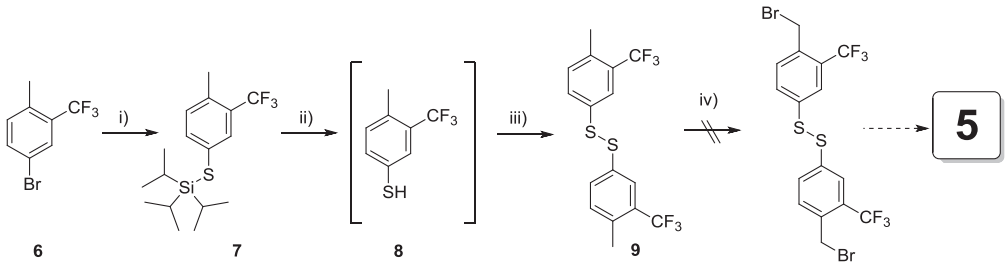
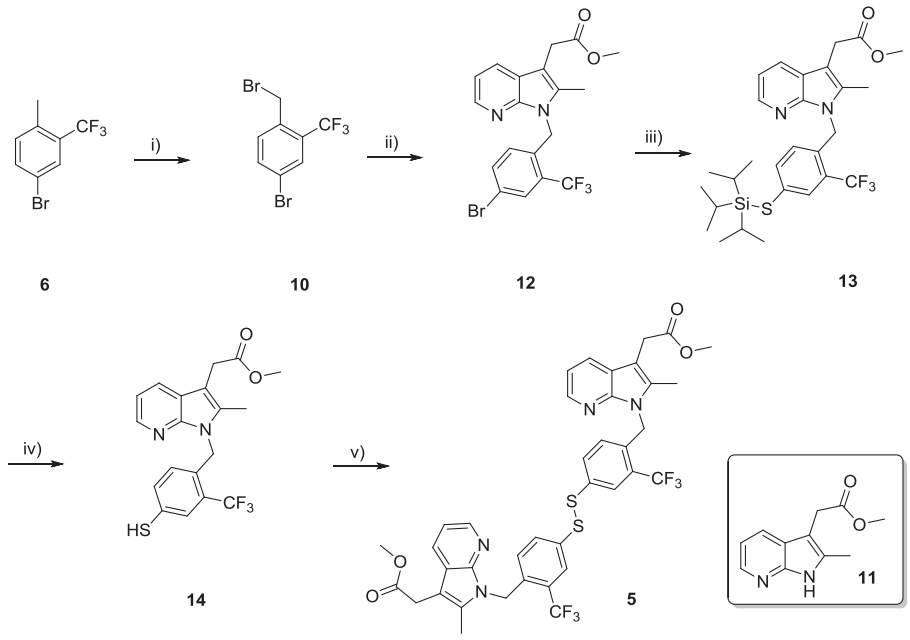


Figure 2. Four-step high specific activity retro-synthesis for the tritium isotopologue of the 3-(2-methyl-7-aza-indolyl) acetic acid derivative **4b** from its bench-stable precursor **5**. Steps 1–4 are mentioned in the text and are shown in Schemes 1–3.



Scheme 1. Route A for the synthesis of the disulfide **5**. (i) TIPSSH, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, toluene, 110 °C, 30 min, n.y.d.; (ii) Bu_4NF, THF, 25 °C, 2 h, n.y.d.; (iii) NaBr, $NaBrO_3$, aqueous HCl, 0 °C, 10 min, 25%; NBS, $(PhCO_2)_2$, CCl_4, 25 °C, 16 h, decomposition (n.y.d = no yield determined).



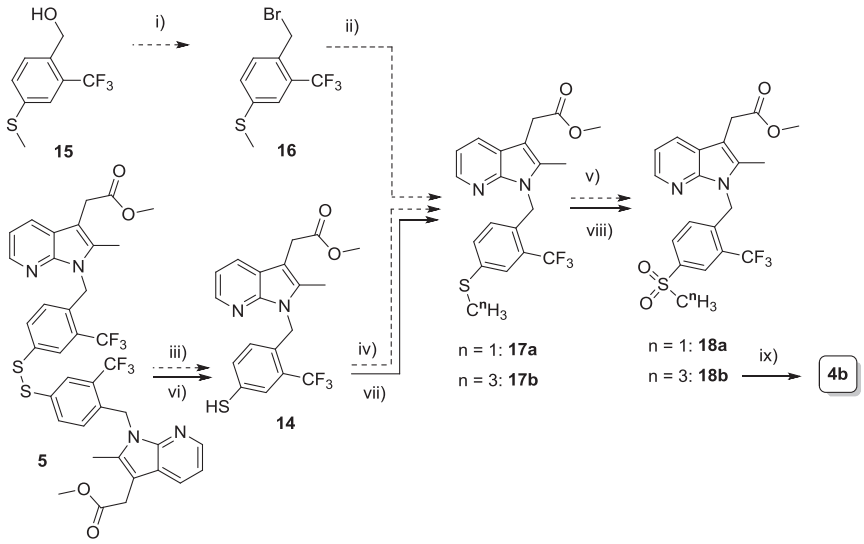
Scheme 2. Route B. (i) NBS, AIBN, CCl_4, 5 h, reflux, 55%; (ii) **11**, BEMP, DMF, 24 h, 25 °C, 71%; (iii) TIPSSH, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, toluene, 30 min, 110 °C, 80%; (iv) Bu_4NF, THF, 2 h, 25 °C, 44%; v) NaBr, $NaOBr_3$, H_2O, 10 min, 4 °C, 40%.

spectroscopy unambiguously showed the existence of a sulfide-bridged constitution of **5** by a weak but characteristic stretch absorption at 499 cm^{-1}.

Synthesis of reference compounds and radiosynthesis

Prior to the radiosynthesis of **4b** (Scheme 3), access to unlabeled products **17a** and **18a** needed to be prepared to serve as reference compounds. These reference compounds served for the characterization of their tritium isotopologues **17b** and **18b** by means of HPLC-retention times comparison during radiosynthesis. The synthesis of **17a** and **18a** is shown in Scheme 3 and is illustrated using dashed arrows, while the synthesis of **17b** and **18b** starting from the Cleland reduction product **14** is shown in the same scheme but using through-drawn arrows. It was important for us to synthesize reference compounds **17a** and **18a** by two different ways (upper and lower parts of Scheme 3). The reason for this was that we desired to synthesize the reference compounds on a millimolar scale, where all the intermediates could be well characterized spectroscopically (sequence **15** → **16** → **17a** → **18a**) in order to use them as reference compounds in the micromolar-scale tritium synthesis (sequence **5** → **14** → **17a** → **18a**) where characterization of the unlabeled, relatively unstable intermediate **14** and the tritium intermediates **17b** and **18b** exclusively depends on the comparison of their HPLC retention times.

Substitution of the primary hydroxyl group in compound **15** using PBr_3 yielded bromide **16** in a good yield. Subsequent pyrrolo-N alkylation using bromide **16** as discussed for route B (Scheme 2) resulted in **17a**. The radiochemical route to generate **17b**, that is, the chemical cross-linking with MeONos during the reduction of the homogenous disulfide **5** in a solution of around 0.1 M of DTT also required more investigation. In fact, clean cross-linking formation of **17a** was observed overnight, when the aforementioned solution of **5** was treated with 4 eq of the methylating agent. The same was observed when in a different experiment, two portions each of 1 eq of the MeONos/Cs_2CO_3 reaction pair were added once the spontaneous DTT reduction was completed. Lowering the excess of methylating agent of course was an advantage during work-up. In both cases, **17a** synthesized from **5** was characterized by means of co-injection with **17a** synthesized from **16**. Nevertheless, the sulfur oxidation in **17** was problematic, mostly because of the presence of the *bis*-aza-heterocyle moiety. First, the oxidation of **17a** was attempted with 0.8 eq of acidic potassium permanganate, and the reaction was followed by liquid chromatography (LC)–MS. Theoretically, this ratio of the oxidizing agent relative to **17a** should give clean



Scheme 3. Tritium and natural abundance isotopologues differ by notation 'a' for natural abundance and 'b' for the tritium case. Synthesis steps with unlabeled material are denoted by a dashed arrow, and synthesis steps with labeled material are denoted by a solid line. Upper part, dashed arrow: synthesis of the unlabeled reference compounds **17a** and **18b** from **15** via **16**. (i) PBr_3, Et_2O, 0 → 25 °C, 16 h, 81%; (ii) 11 (see Scheme 2 for structure), BEMP, DMF, 16 h, 33%. Lower part, dashed arrow: Unlabeled optimizations for the radiochemical case were tested in the sequence **5** to **14** and further micromolar downscaling to **17a** and **18a**. (iii) DTT, NEt_3, ACN/THF, 30 min, 25 °C, n.y.d.; (iv) Cs_2CO_3, MeONos, ACN/THF, 16 h, 25 °C, n.y.d.; (v) OsO_4, NMO, acetone/water/*tert*-butanol, 16 h, 25 °C, n.y.d. Lower part, solid arrow: Radiosynthesis of **4b** from **5** via **14**, **17b**, and **18b**. (vi) DTT, NEt_3, ACN/THF, 30 min, 25 °C, n.y.d; (vii) Cs_2CO_3, [$^3H_3$]MeONos, ACN/THF, 3 h, 25 °C, 61% radiochemical yield SA = 2.6 TBq/mmol (determined by HPLC); (vii) OsO_4, NMO, acetone/water/*tert*-butanol, 16 h, 25 °C, RA-HPLC 78%; (vii) a. 6-M HCl, b. semi-preparative HPLC, 20% radiochemical yield referred to **17b** (n.y.d. = no yield determined; see experimental part for UV purities of post extraction products).

formation of the sulfone **18a**. However, when this stoichiometry was used, the oxidation stopped at the level of the sulfoxide. When the reaction was forced to completion using a 3.2-fold excess of permanganate, about 10–15% of the sulfone-N-oxide by-product was detected in the LC–MS trace. Faced with these results, osmium tetroxide-catalyzed, NMO-mediated oxidation,[26] which in other hands was shown to successfully transform quinolinyl residue bearing tetrahydrothiophenes to their corresponding sulfones[27] using an excess of oxidant, was tested. Indeed, when these conditions were applied in a micromolar scale, the reaction was clean, and **18a** was the only product formed.

The optimized conditions described earlier were applied to the radiosynthesis. However, because it was shown that complete methylation with stoichiometric amounts of [$^3H_3$]MeONos would be hard to achieve, an inverted stoichiometry was used in the tritiation step where 6 eq of **14** were treated with 1 eq of [$^3H_3$]MeONos. This procedure gave crude **17b** with 87% radiochemical purity and 61% radiochemical yield (relative to [$^3H_3$]MeONos) after final purification. Oxidation to **17b** occurred smoothly as developed for the unlabeled case. As shown by Sandham and coworker[15], the ester hydrolysis of **18b** would not have been possible without a significant loss of tritium label, which is why **4b** was generated from **18b** under strongly acidic conditions with a radiochemical yield of 20% after final HPLC purification. The specific activity of **4b** was determined to be 3.11 TBq/mmol. Thus, it was possible to use a material with 97% tritium labelling per tritiated position for occupancy studies on cell membranes with low receptor density and also to reach sufficient counting efficiency with a low-energy β-particle radioligand (E_{max} of ^3H = 18.6 keV).

Discussion

In the context of the maximal specific activity achieved for **4b**, it must be noted that direct hydrogen-isotope exchange (HIE) techniques[28] would not have produced the specific activity needed as shown by Sandham and coworker.[15] Indeed, during the preparation of this manuscript, two publications emerged describing transition metal-catalyzed HIE with deuterium gas on very relevant model substrates in a safer manner, thus opening a way to circumvent the radioprotection risks that one would have to face if THO was used as tritium source. Muri *et al.*[29] for instance applied an iridium(I) complex with an electron-rich N,P – 'NeoPHOX' – ligand[30] in order to achieve HIE in position ortho–ortho' of (methylsulfonyl)benzene, 1-(3,5-dimethoxyphenyl)ethanone, and 2-phenylpyridin. Using D_2, a 2 × 95% degree of deuteration was achieved in the ortho–ortho' positions of (methylsulfonyl)benzene and 1-(3,5-dimethoxyphenyl)ethanone, while – probably because of Ir coordination to the N-heterocycle – only 2 × 50% degree of deuteration was obtained in the case of 2-phenylpyridin. Facing the functional group complexity of NVP-QAW039 (**4a**, Figure 1) having not only an electron-withdrawing trifluoromethyl group in the meta position of its methyl sulfone moiety but also a pyrrolo-pyridine moiety capable of trapping the Ir catalyst by coordination, it only can be speculated that the exposure of esterified NVP-QAW039 to this particular complex in a tritium gas atmosphere would yield maximum specific activity of what is maximally possible based on the given structure of fevipiprant, that is, for this catalyst 2 TBq/mmol.

A similar lesson can be learned from the regioselective deuteration of simple indole and pyridine substrates using ruthenium nanoparticles dispersed in polyvinylpyrrolidone ('RuNp@PVP').[31] In this publication, Chaudret *et al.* reported HIE on the QAW039-model substrates quinoline, 3-methylpyridine, and 3-methyl-1*H*-indole. For quinoline, 2 × 97% deuteration was observed on C(2) and C(8), and for 3-methylpyridine deuteration was observed on C(2) and C(6) (80% and 90%, respectively). For 3-methyl-1*H*-indole, deuteration was observed on C(2) (94%), and for the methyl-group on C(3) (17%) and on C(7) (42%). Translating these values to the hypothetical outcome of HIE

on esterified NVP-QAW039 using Ru nanoparticles as catalyst, a high degree of tritiation only would be expected on C(6) of the pyrrolo-pyridine moiety, while only traces of tritium would be found on the β-C of the acetic acid side chain. Overall, it is unlikely to obtain a tritium isotopologue of fevipiprant with a specific activity higher than 1.25 TBq/mmol if this catalyst would have been used.

To summarize for the synthesis of [$^3H_3$]fevipiprant, we still conclude that high specific activity of the targeted isotopologue only can be achieved by a multistep build-up approach of a suitable bench-stable precursor and its methylation with a high specific activity, commercially available reagent such as [$^3H_3$]MeONos in the later steps of this multistep process.

Experimental part

General

Solvents, reagents, and registered reference compounds

Commercially available absolute solvents were purchased over molsieve (4 Å) and stored under argon. Reagents and compound **6** used for the experimental work were purchased from commercial sources in the highest available quality. Compound **15** was synthesized as described elsewhere.[32] Compounds **11**, **18**, and **4a** were obtained from the compound archive of Novartis Pharma AG, Basel, Switzerland. [$^3H_3$] MeONos (radiochemical purity (RCP) > 99% (TLC); specific activity (SA) > 2.96 TBq/mmol; 185 MBq/mL in toluene) was prepared at RC Tritec AG, Teufen CH-9053, Switzerland, following a method described by Pounds, where SA = 3.03 TBq/mmol was reported.[19]

Special equipment and glassware

All air and moisture sensitive reactions were carried out in dried glassware under inert gas atmosphere. Microwave assistant synthesis was performed using CEM Microwave Discover apparatus ramping with 200 W at 110 °C.

Flash chromatography, TLC, and solid-phase extraction

Analytical TLC was run on Merck TLC Silica 60 plates with fluorescence indicator (merckmilipore.com) and was visualized at 254 nm or with iodine vapors. Column chromatography was performed using silica gel 60 (Merck, 70–230 mesh) or on high-purity grade silica (Fluka, 230–400 mesh). Solid-phase extraction cartridges were purchased either at Agilent (ChemElut) or at Phenomenex (StrataX).

HPLC and RA-HPLC

HPLC for in-process control of compounds **15**, **16**, **17ab**, **18ab**, and **4b** were run on Agilent 1200 Series HPLC system with ChemStation Plus spectra software (v9) using a Sunfire C_{18}-RP column (4.6 × 250 mm). The HPLC release analysis of [3H3]MeONos and of compound **18b** was performed on a modular Gilson HPLC system equipped with a Macherey & Nagel Nucleodur C_{18}-Gravity column (5 μm, 4.6 × 150 mm). For all compounds, solvent systems A (water plus 0.05–0.1% TFA) and solvent systems B (Acetonitrile (ACN) plus 0.1–0.05% TFA) were used. For HPLC release analysis of compound **4b**, a 0.30 mg/mL sample (H_2O/EtOH 1 : 1, v/v) was prepared and analyzed on Agilent 1290 Infinity using a Waters XBridge RP18 column (3.5 μm, 2.1 × 100 mm) (flow 1.0 mL/min). For RA-HPLC, a Berthold LB509 radio detector with a 100-μL Z-cell was used in all cases. Scintillation cocktails were either Perkin Elmer's Flow-Scint A at 3.0 mL/min or Zinser's Quickzint Flow 302 at 2.8mL/min. In most cases, ultraviolet (UV) detection was done at 215–220 nm, except [$^3H_3$]MeONos, which was analyzed at 254 nm.

LC–MS

LC–MS analysis of purified unlabeled compounds was acquired on a Waters ZQ2000 single-stage quadrupole mass spectrometer equipped with an Ascentis Express C_{18} column (2.7 μm, 2.1 × 30 mm) using water/0.05% HCO_2H/3.75 mM $(NH_4)OAc$ and ACN/0.04% HCO_2H as eluent or on Waters Acquity UPLC–MS H Class with PDA SQD2 detector equipped with a Waters CSH C_{18} column 1.7 μm (2.1 × 50 mm) using water/0.1% HCO_2H and ACN/0.1% HCO_2H as eluent. The LC–MS release analysis of compound **4b** was performed on a Finnigan LCQ-Advantage MAX equipped with Waters Sunfire C_{18} (30 × 2.1 mm) using water/ACN/HCO_2H 99:1:0.1 (system A) and water/ACN/HCO_2H 5:95:0.1 (system B) an injection volume of 5–10 mL and a sample concentration of around 3 mg/mL in H_2O/EtOH. The specific activity of **4b** was calculated from the distribution of the monotritiated, bitritiated and tritritiated isotopologues after correction of the molecular ion by the natural abundance of the (X + 1) element carbon using the commonly accepted approach.[33]

NMR-spectroscopy

Chemical shifts (δ) are given in ppm referenced to the residual solvent peak.[34] ^{1}H-NMR spectra were recorded on Bruker AVANCE 400 and on Bruker DRX600 with 1.7-mm-cryoprobe TCI-C/N probehead. ^{3}H-NMR spectra of compound **4b** were acquired on Bruker DPX400 with SXI-3H probehead using **4a** as external reference for NMR difference spectroscopy. ^{13}C-NMR shifts of **5** were extracted from the HSQC data set as much as this was possible. The processing software in all cases was XWin-NMR. Proton assignments of the disulfide **5** were based on HSQC, COSY and ROESY data sets. Coupling constants (*J*) are given in Hz and were determined using the multiplet analysis mode of the MNova software (v8.1.).

Optical spectroscopy

FT-IR spectra were acquired on Bruker Vertex 70 FT-IR coupled with a Hyperion 2000 FT-IT microscope. Raman spectra were acquired on Bruker MultiRam FT-Rama spectrometer (laser power 300 mW).

*(4-(Bromomethyl)-3-(trifluoromethyl)phenyl)(methyl)sulfane (**16**).* At 0 °C, PBr_3 (385 μmol, 106 mg) was added to a solution of the benzylalcohol **15** (95 mg, 38.5 mmol) in Et_2O (500 μL), and the reaction mixture was stirred overnight at room temperature. Then, 0.2-M NaOH (1 mL) was added, the biphasic system was passed over a liquid/liquid extraction cartridge (ChemElut, 3 mL) and the cartridge was washed with Et_2O. The combined organic phases were evaporated under reduced pressure, and the residue was purified on silica (eluent hexane/EtOAc 10:1). After evaporation of the product fractions, 90 mg (81%) of pure **16** (R_f = 0.70 (hexane/EtOAc 10:1)) was obtained. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 4.76 (s, 2H), 2.55 (s, 3H). ESI-MS (cation mode) *m/z* 205 [$C_9H_8F_3S^+$].

*Methyl 2-(2-methyl-1-(4-(methylthio)-2-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**17a**) by N-alkylation of azaindole **11** with benzylbromide **16**.* Under Ar, BEMP (52 μL, 176 μmol) was added to a solution of **16** (51 mg, 0.176 mmol) and **11** (40 mg, 176 μmol) in dimethylformamide (DMF) (3.0 mL). The reaction was stirred for 16 h, then adjusted with HCl (5%) to pH 7.5, diluted with water and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The crude material was purified on silica (10 g, eluent hexane/EtOAc 4:1). After evaporation of the product fractions, 24 mg of colorless oil was obtained. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.14 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.11 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.10 (d, *J* = 8.3 Hz, 1H), 5.62 (s, 2H), 3.62 (s, 3H), 3.30 (d, *J* = 9.5 Hz, 2H), 2.47 (s, 3H), 2.24 (s, 3H). ESI-MS (cation mode) *m/z* 409.0 [MH^+].

*Compound **17a** by alkylation of the in situ generated thiol **14** with an excess of MeONos.* A mixture of disulfide **5** (10 mg, 12.7 μmol), DTT (19.6 mg, 127.1 μmol) and NEt_3 (0.88 μL, 6.3 μmol) in ACN/Tetrahydrofurane (THF) (5 : 2, v/v, 1.40 mL) was stirred under Ar for 30 min until a yellow solution was obtained. Subsequently, Cs_2CO_3 (16.6 mg, 50.8 μmol) and MeONos (11.4 mg, 50.8 μmol) were added to the reaction and stirring was maintained for a total time of 16 h. Subsequently, the reaction

mixture was diluted with water (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness in order to yield 11 mg of product (64% UV purity), which was characterized by HPLC using the reference product **17a** prepared as described in the previous section.

*Methyl 2-(2-methyl-1-(4-(methylsulfonyl)-2-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetate (**18a**).* Compound **17a** (0.41 mg, 1 μmol) synthesized by alkylation of azaindole **11** with benzylbromide **16** was dissolved in a solution of NMO (1.3 mg, 9 μmol) in acetone/water (2 : 1 v/v, 300 μL). Then, an aliquot (30 μL, 0.6 μmol) of a solution of 5% OsO_4 *tert*-butanol was added and the reaction mixture (c (**17a**) = 3 mM) was incubated at room temperature overnight. Afterwards, the reaction mixture was diluted with EtOAc (3 mL) and washed with brine (2 × 1 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated to yield **18a** (90% UV purity), which was characterized by co-injection with an authentic reference sample.

*Triisopropyl((4-methyl-3-(trifluoromethyl)phenyl)thio)silane (**7**) and 4-methyl-3-(trifluoromethyl)-benzenethiol (**8**).* A microwave tube was charged with $Pd(OAc)_2$ (24 mg, 10 μmol), PPh_3 (140 mg, 530 μmol), Cs_2CO_3 (902 mg, 2.77 mmol, 1.3 eq.) and **6** (500 mg, 2.13 mmol). Then, the reaction mixture was suspended in dry toluene (10 mL) and the mixture was degassed. TIPSSH (527 mg, 2.77 mmol) was added, the tube was sealed via a septum and the reaction mixture was heated for 30 min under microwave irradiation (T = 110 °C, P_{max} = 200 W). After cooling at room temperature, aqueous NH_4Cl (1%, 5 mL) was added and the reaction mixture was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100/0 to 90/10) to yield 380 mg of impure **7** as a colorless oil (R_f = 0.6 (cyclohexane 100%)). Then, about 300 mg of this oil was dissolved in THF (10 mL), Bu_4NF (480 mg, 1.63 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. Subsequently, aqueous NH_4Cl (1%, 5 mL) was added and the reaction mixture was extracted with Et_2O (2 × 15 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to obtain a pale-yellow oil. According to LC–MS analysis, this product consisted out of **7** and **8** in a 7:3 ratio. R_f = 0.2 (cyclohexane 100%). ESI-MS (anion mode) *m/z* 191.0 $[C_8H_6F_3S]^-$, 381 $[C_{16}H_{11}F_6S_2]$.

*1,2-Bis(4-methyl-3-(trifluoromethyl)-phenyl)disulfane (**9**).* At 0 °C, the total amount of the crude product obtained in the previous step was suspended in water (2.5 mL). NaBr (5 mg, 0.05 mmol.) and $NaBrO_3$ (25 mg, 0.16 mmol) were added, followed by the dropwise addition of 1 N HCl (0.2 mL). Then, the reaction mixture was stirred for 10–12 min and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100/0 to 95/5) to yield compound **9** (90 mg) as a colorless oil. R_f = 0.44 (cyclohexane 100%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 2.26 (s, 6H).

*4-Bromo-1-(bromomethyl)-2-(trifluoromethyl)benzene (**10**).* Under Ar, 4-bromo-1-methyl-2-(trifluoromethyl)benzene (**6**, 1.5 g, 6.3 mmol) was dissolved in CCl_4 (20 mL). NBS (1.35 g, 7.6 mmol) and AIBN (0.3 mmol, 50 mg) were added and the suspension was refluxed for 5 h in the dark. After cooling, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (eluent cyclohexane 100%). Evaporation of the product fractions yielded 1.1 g (55%) of pure **10**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 4.60 (s, 2H).

*Methyl 2-(1-(4-bromo-2-(trifluoromethyl)benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**12**).* Under Ar, azaindole **11** (300 mg, 1.37 mmol) and compound **10** (525 mg, 1.65 mmol) were dissolved in dry DMF (6 mL). BEMP (450 mg, 1.65 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. Subsequently, water (10 mL) was added and the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc 90:10) in order to yield 430 mg (71%) of compound **12**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.85 (d, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.13 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 5.68 (s, 2H), 3.76 (2, 3H), 3.71 (s, 3H), 2.25 (s, 3H). ESI-MS (cation mode) *m/z* 441.03 [MH+].

*Methyl 2-(2-methyl-1-(2-(trifluoromethyl)-4-((triisopropylsilyl)thio)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**13**).* A sealable tube was charged with $Pd(OAc)_2$ (10 mg, 0.02 mmol), PPh_3 (30 mg, 0.11 mmol), Cs_2CO_3 (195 mg, 0.59 mmol), compound **12** (200 mg, 0.45 mmol) and dry toluene (4 mL). After degassing the suspension, TIPSSH (115 mg, 0.59 mmol) was added and the sealed reaction mixture was exposed to microwave irradiation (t = 30 min; T = 110 °C, P_{max} = 200 W). After cooling at room temperature, aqueous NH_4Cl (1%, 5 mL) was added the suspension was extracted with EtOAc (2 × 10 mL); the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent cyclohexane/EtOAc 95:5) to yield 210 mg (80%) of oily compound **13** (81% UV). ESI-MS (cation mode) *m/z* 551.23 [MH+].

*Methyl 2-(1-(4-mercapto-2-(trifluoromethyl)benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**14**).* Bu_4NF (370 mg, 1.26 mmol) and compound **13** (370 mg, 0.67 mmol) were dissolved in THF (12 mL) and the solution was stirred at room temperature for 2 h. Subsequently, aqueous NH_4Cl (1%, 12 mL) was added and the reaction mixture was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure and the residue was purified by chromatography on silica gel (gradient cyclohexane/EtOAc 95:5 to 60:40). After evaporation of the product fractions (R_f = 0.4 (cyclohexane/EtOAc = 75:25)), compound **14** (91% UV) was obtained as a pale-yellow solid in moderate yields (100 mg, 44%) together with a small amount of disulfide **5** (40 mg, 15%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.17 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.10 (ddd, *J* = 7.8, 4.7, 3.1 Hz, 1H), 6.25 (dd, *J* = 8.3, 5.7 Hz, 1H), 5.66 (s, 2H), 3.73 (s, 2H), 3.69 (s, 3H), 3.50 (s, 1H), 2.22 (s, 3H).

*Dimethyl 2,2'-(1,1'-((disulfanediylbis(2-(trifluoromethyl)-4,1-phenylene))bis-(methylene))bis(2-methyl-1H-pyrrolo[2,3-b]pyridine-3,1-diyl))diacetate (**5**).* Compound **14** (120 mg, 0.30 mmol) was suspended in ice-cold water (3 mL). Sodium bromide (3 mg, 0.03 mmol) and sodium bromate (15 mg, 0.09 mmol) were added, followed by the dropwise addition of 1-N HCl (0.12 mL). The reaction mixture was stirred for 10 min and then extracted with EtOAc (2 × 20 mL). The combined organic were washed with saturated $Na_2S_2O_3$ (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by chromatography on silica (gradient cyclohexane/EtOAc 95:5 to 70:30). After evaporation of the product fractions (R_f = 0.45 (cyclohexane/EtOAc = 75:25)), compound **5** (48 mg, 40%) was obtained, which crystallized upon standing at room temperature. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.12 (dd, *J* = 4.7, 1.6 Hz, 2H), 7.91 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.86 (d, *J* = 2.1 Hz, 2H), 7.62 (dd, *J* = 8.3, 2.1 Hz, 2H), 7.10 (dd, *J* = 7.8, 4.7 Hz, 2H), 6.21 (d, *J* = 8.4 Hz, 2H), 5.63 (s, 4H), 3.82 (s, 4H), 3.60 (s, 6H), 2.21 (s, 6H). ^{13}C-NMR {HSQC} (DMSO-d_6) δ 142.9, 133.8, 129.0, 128.1, 126.5, 117.2, 53.1, 29.8, 11.2. IR (neat, 1/cm): 3048, 3011 (ν(C_{ar}–H)), 2958, 2927 (ν(C–H), 1737 (ν(C=O)), 1309 (ν(C_{ar}–CF_3)),1160, 1117 (ν(CF_3). Raman (neat, 1/cm): 3075 (ν(C_{ar}–H), 2949 (ν(C–H)), 1734 (ν(C=O), 1605, 1560 (ν(C_{ar}–C_{ar}), 499 (ν(S–S)). ESI-MS (cation mode) *m/z* 787.4 [MH+].

*Methyl 2-(2-methyl-1-(2-(trifluoromethyl)-4-(([$^3H_3$]methyl)thio)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetate (**17b**).* In vial A, disulfide **5** (5.3 mg, 6.7 μmol) and DTT (10.1 mg, 66 μmol) were solubilized in ACN/THF (7:3, 1.1 mL). Then, NEt_3 (0.5 μL, 4 μmol) in THF (300 μL) was added. The solution was quickly stirred and kept about 30 min at room temperature. In parallel, an aliquot of a stock solution of [$^3H_3$]MeONos (about 2.4 μmol,

6.95 GBq, SA = 3.0 TBq/mmol) was evaporated to dryness in vial B. The residue in vial B was mixed with Cs_2CO_3 (2.66 mg, 8.2 μmol). An aliquot of the thiolate solution from vial A (0.75 mL) was added and the mixture was incubated for 3 h at room temperature. Afterwards, the reaction solvent was removed, the crude product was dissolved in THF (400 μL) and TFA (10 μL) was added. This product solution (6.95 GBq, 87% RA-HPLC) was injected in portions (11 × 35 μL) on a reversed-phase HPLC column and the product was eluted with ACN/water. Pure product fractions were combined. The pH was set to 9.5 using $NaHCO_3$ and the product was adsorbed on a StrataX cartridge (100 mg). After washing the cartridge with water (2 × 2 mL), the free base of the product was eluted with EtOH (30 mL) and characterized as such by comparison of the HPLC retention times with those of unlabeled **17a**. The product solution contained 4.22 GBq of **4b** (61% radiochemical yield, 96% RA-HPLC, SA = 2.6 TBq/mmol).

*Methyl 2-(2-methyl-1-(4-([$^3H_3$]methylsulfonyl)-2-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetate (**18b**).* Compound **17b** (0.31 mg, 0.75 μmol, 1.0 GBq) was dissolved in a solution of NMO (0.45 mg, 3.4 μmol) in acetone/water (2:1 v/v, 90 μL). Then, an aliquot (8 μL, 0.15 μmol) of a solution of 5% OsO_4 in *tert*-butanol was added and the reaction mixture (c (**17b**) = 7.5 mM) was incubated at room temperature overnight. The reaction mixture was evaporated, and the product (78% purity RA-HPLC) was characterized by comparison of the HPLC retention times with those of unlabeled **18a**. Crude **18b** was used in the next step without further purification.

*2-(2-Methyl-1-(4-([$^3H_3$]methylsulfonyl)-2-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid (**4b**).* Crude active material **18b** obtained in the previous step was dissolved in 6-M HCl (300 μL) and kept at room temperature for 2 h. Then, the solution was lyophilized and the residue was purified by semi-preparative HPLC in order to yield 199 MBq of pure **4b** (20% radiochemical yield referred to **18b**, 98.2% purity RA-HPLC, SA = 3.1121 TBq/mmol) stored in EtOH (14 mL). The purified product was characterized by comparison of the HPLC retention times with those of unlabeled **4a**. ESI-MS (cation mode) *m/z* 427.2 [MH^+, [$^3H_0$]$C_{19}H_{14}T_3F_3N_2O_4S$]] (0.83%), 429.3 [$MH^+$, [$^3H_1$]$C_{19}H_{14}T_3F_3N_2O_4S$]] (0.90%), 431.2 [$MH^+$, [$^3H_2$]$C_{19}H_{14}T_3F_3N_2O_4S$]] (3.79%), 433.2 [$MH^+$, [$^3H_2$]$C_{19}H_{14}T_3F_3N_2O_4S$]] (100%). ^{3}H-NMR (400 MHz, DMSO-d_6): δ 3.27.

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Conflict of Interest

Synthesis of [$^3H_3$]MeONos will not be disclosed.

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