Tetrahedron 71 (2015) 5946–5951

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# New synthetic routes to thyroid hormone analogs: $d_6$-sobetirome, $^3$H-sobetirome, and the antagonist NH-3

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ARTICLE INFO

*Article history:*
Received 23 March 2015
Received in revised form 13 May 2015
Accepted 14 May 2015
Available online 20 May 2015

*Keywords:*
Sobetirome
Thyroid hormone
NH-3
Thyromimetics

ABSTRACT

New synthetic routes for the preparation of isotopically labeled versions of thyroid hormone agonist sobetirome were developed using Knochel's iodine–magnesium exchange. A more efficient synthesis of the thyroid hormone antagonist NH-3 was developed from a common intermediate in the sobetirome route. Using the new synthetic routes, $d_6$-and $^3$H-sobetirome were prepared for their use in studying biodistribution and the cellular uptake of sobetirome. The new route to NH-3 allows for a more rapid and efficient synthesis and provides access to an advanced intermediate to facilitate antagonist analog production in the final bond-forming synthetic step.



## 1. Introduction

Sobetirome (also known as GC-1, Fig. 1) is a selective thyroid hormone agonist, a class of experimental therapeutics often referred to as thyromimetics. Sobetirome was first synthesized and its action at the thyroid hormone receptors (TR) characterized in 1998 by Chiellini and colleagues.[1] Sobetirome was found to be a potent thyromimetic with a 10-fold increase in binding affinity and agonist potency at the thyroid hormone receptor β-form (TR$\beta_1$) as compared to the TR$\alpha_1$. Sobetirome has been studied in a wide range of cellular and animal models where it has proven useful as a tool to probe the effects of tissue and TR isoform selective activation.[2] These studies eventually led to clinical studies of sobetirome as a cholesterol-lowering agent where it was found to be effective at lowering cholesterol in human subjects.[2] The sobetirome agonist scaffold can also be modified at the 5′-position of the outer ring to produce antagonists and NH-3 (Fig. 1) is one of the few examples of a potent TR antagonist.[3]

There has been considerable recent interest in the use of thyromimetics for the treatment of demyelinating neurological disorders such as x-linked adrenoleukodystrophy[4] and multiple sclerosis.[5] The use of thyromimetics for these indications would seem to require efficient distribution of the agent from circulation to the central nervous system. Stable and radioactive isotope labeled derivatives of sobetirome would be useful reagents for distribution studies. The original synthetic route to sobetirome[1] as well as and improved method[6] are not readily amenable to incorporation of isotopic labels. We report here a new synthetic route to sobetirome and sobetirome analogs such as the antagonist NH-3 that is more efficient than any of the previous syntheses and allows for the incorporation of isotopic labels.

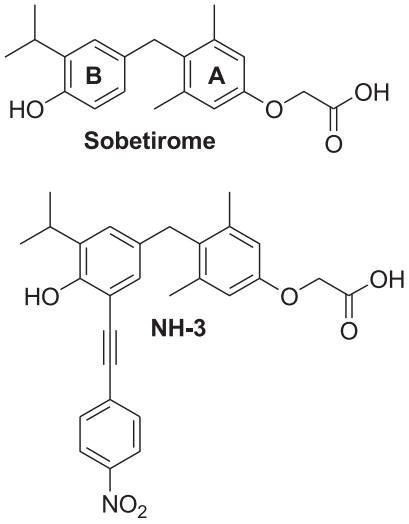


**Fig. 1.** Chemical structures of TR agonist Sobetirome and the TR antagonist NH-3.

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http://dx.doi.org/10.1016/j.tet.2015.05.049
0040-4020/

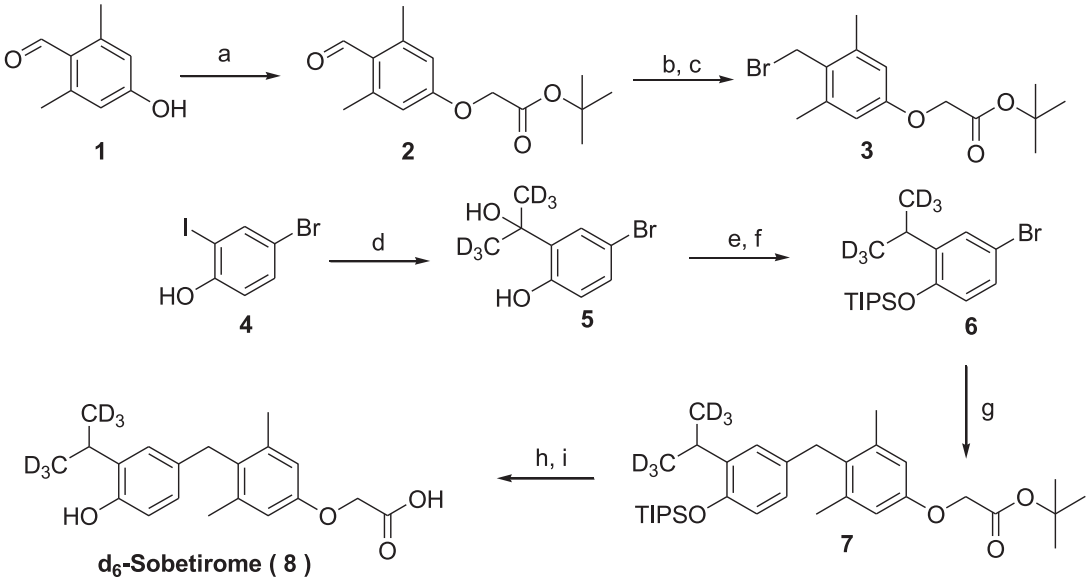
## 2. Results

The new sobetirome and NH-3 synthetic routes all utilized the iodine–magnesium exchange developed by Knochel and colleagues.[9] This iodine–magnesium exchange, accomplished with iPrMgCl, enabled us to install the $d_6$-isopropyl moiety of $d_6$-sobetirome and generate the carbon bridge between the two aryl rings of $^3$H-sobetirome and NH-3. This method in conjunction with the two triethylsilane-mediated carbinol reduction methods[10,11] allows for the preparation of the key common intermediates for the syntheses of $d_6$-sobetirome, $^3$H-sobetirome, and NH-3.

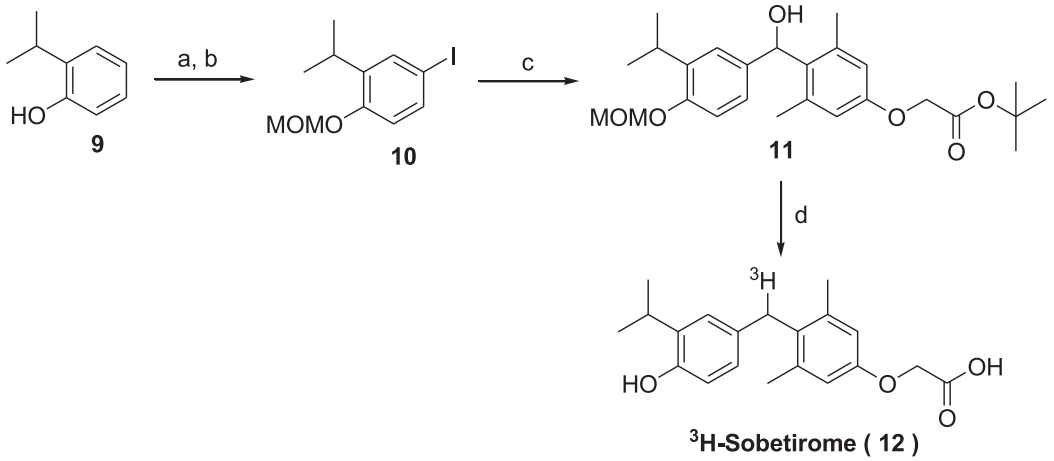
The $d_6$-sobetirome synthetic route is outlined in Scheme 1. The original 8-step sobetirome synthesis described by Chiellini and colleagues[5] was altered to allow for the installation of the $d_6$-outer ring (B) later in the synthesis. For the A-aryl ring, 4-hydroxy-2,6-dimethylbenzaldehyde **1** was first alkylated with t-butyl chloroacetate to provide the desired product **2** in an 89% yield. The aldehyde of **2** was then converted into the benzyl bromide via reduction to the benzyl alcohol using $NaBH_4$ followed by applying the Corey-Kim bromination procedure[12] to yield the desired benzyl bromide **3** in a 57% yield over the two steps. The outer *B*-aryl ring containing the $d_6$-labeled isopropyl, was synthesized by performing the Knochel iodine–magnesium exchange[9] on 4-bromo-2-iodophenol **4** with iPrMgCl. This procedure allowed for the selective iodine–magnesium exchange while leaving the aryl bromide intact. The corresponding aryl magnesium species was then quenched with $d_6$-Acetone to yield the carbinol **5**. The carbinol was then reduced using TFA and $Et_3SiH$[11] in DCM to yield the desired 4-bromo-2-($d_6$-isopropyl)phenol in an 80% overall yield from **4**. Following protection of the phenol with TIPS, **6** was converted into the Gilman reagent by generation of the corresponding aryl lithium species with nBuLi, followed by the addition of CuI. With the Gilman reagent generated, a solution of the benzyl bromide **3** in THF was added and the diarylmethane **7** was produced in a 75% yield. To complete the synthesis of the $d_6$-sobetirome **8**, the TIPS group was deprotected with TBAF, followed by saponification of the ester with NaOH. The total synthetic sequence was completed in 6 linear steps with a 21% overall yield from **1**, which compares favorably in terms of efficiency with the previously published synthesis.[1,6]

With the A-ring intermediate **2** already in hand from the $d_6$-sobetirome synthesis, the outer B-ring **10** was prepared by first iodinating the para position of 2-isopropylphenol using NaI and NaOCl[13] and then protecting the phenol using MOM-Cl (Scheme 2). The Knochel iodine–magnesium exchange[9] was performed with iPrMgCl, which when added to **10** provided the aryl Grignard reagent of **10**. The aryl magnesium reagent was then cooled to −78 °C and a solution of **2** in THF was added. The coupling was kept at −78 °C to ensure the aldehyde of **2** was the only functional group affected by the aryl Grignard reagent. This coupling produced carbinol **11** in a 71% yield and allowed for the generation of a protected-sobetirome intermediate containing a site (carbinol) for radiolabeling with $NaB^3H_4$. After optimization of a procedure developed by Gribble and colleagues[14] for reducing carbinols to diarylmethanes using TFA and $NaBH_4$ for **11**, $^3$H-sobetirome **12** was prepared from **11** with $NaB^3H_4$ and TFA in DCM. Although the tritium-labeling/deprotection procedure proceeded in only 11% yield from **11**, the fast reaction time (10 min) and high specific activity (6.90 mBq) obtained made the labeling procedure a satisfactory final step in the synthesis of $^3$H-sobetirome. In addition to the 4 step synthesis of $^3$H-sobetirome **12**, this synthetic route has also been used to prepare large quantities (>10 g) of sobetirome by substituting the $NaBH_4$/TFA step for the triethylsilane/TFA reduction (Scheme 1).

The new route to NH-3 (**18**) begins with the protection of the phenol moiety of 4-iodo-2-isopropylphenol as a benzyl ether (**13**) (Scheme 3). The aryl Grignard reagent of **13** was generated using the Knochel procedure and then coupled with aldehyde **2**. The resulting carbinol **14** was then subjected to catalytic hydrogenation conditions, using triethylsilane as the hydrogen donor,[10] yielding the t-butyl ester protected sobetirome **15** in a 70% overall yield from **13**. Several iodination procedures were attempted on **15** with $I_2$ and aq $NH_3$ proving to be the superior conditions for generation of the 5′-aryliodide **16a**. Following protection of the phenol with MOM-Cl (**16b**), the Sonogashira coupling procedure to install the 4-nitrophenylacetylene moiety was attempted between **16b** and 4-nitrophenylacetylene. The best conditions were found to require THF as a solvent, $Pd(PPh_3)_4$ as the catalyst, and 50 °C as the reaction temperature, providing the protected NH-3 intermediate **17** in an 87% yield.




**Scheme 1.** Synthesis of $d_6$-Sobetirome **8**. Reagents and Conditions: (a) DMF, $Cs_2CO_3$, *t*-butyl chloroacetate, 89%; (b) $NaBH_4$, MeOH, 0 °C to rt, 76%; (c) DMS, NBS, DCM, 0 °C to rt, 60% 2 steps; (d) (i) iPrMgCl, THF, rt; (ii) Acetone-$D_6$, −78 °C to rt; (e) $Et_3SiH$, TFA, DCM, rt; (f) TIPS-Cl, Imidazole, DCM, rt, 51% (3 steps); (g) (i) nBuLi, THF, 4 Å MS, −78 °C; (ii) CuI, THF, **3**, −78 °C to rt 75%; (h) TBAF, THF, rt; (i) MeOH, 5 M NaOH, rt 72% (two steps).




**Scheme 2.** Synthesis of $^3$H-Sobetirome **12**. Reagents and Conditions: (a) NaI, NaOCl, NaOH, MeOH, $H_2O$, 75%; (b) MOM-Cl, DCM, TBAI, 10 M NaOH, 81%; (c) iPrMgCl, THF, 4 Å MS, (ii) **2**, THF, −78 °C, 64%; (d) DCM, $NaB^3H_4$, TFA, 14%.

Intermediate **17** was first subjected to TFA conditions for removing both the MOM-ether and t-butyl ester moieties simultaneously. However, TFA resulted in the formation of significant amounts of a benzofuran side product (**17a**) (25%), resulting from the cyclization of the phenol and acetylene motifs. The benzofuran could not be separated from NH-3 (**18**) so the deprotection strategy developed by Gopinathan and Rehder[15] for NH-3 was utilized instead. Following the hydrolysis of the ester with NaOH, the crude product was then subjected to aqueous HCl providing the antagonist NH-3 (**18**), in a 61% overall yield without any benzofuran side product (**17a**) contamination.

## 3. Discussion

In summary, using the Knochel iodine–magnesium exchange protocol three new syntheses were developed for producing the isotopically labeled $d_6$-sobetirome, $^3$H-sobetirome, and the TR antagonist NH-3. The 4 step synthetic sequence for producing $^3$H-sobetirome was also adaptable for producing large quantities of unlabeled sobetirome, which is in our hands, the most efficient process currently known for preparing this thyromimetic agent. Lastly, the improved synthetic procedure for NH-3 includes a shorter overall route than the previously published syntheses,[3,15] and also allows access to a late stage 5′-iodinated intermediate that will allow for the incorporation of a variety of 5′-antagonist extensions thus facilitating the preparation of new antagonist analogs. The improved efficiency of this synthetic approach should facilitate the development of these TR ligands as biological probes and experimental therapeutics.

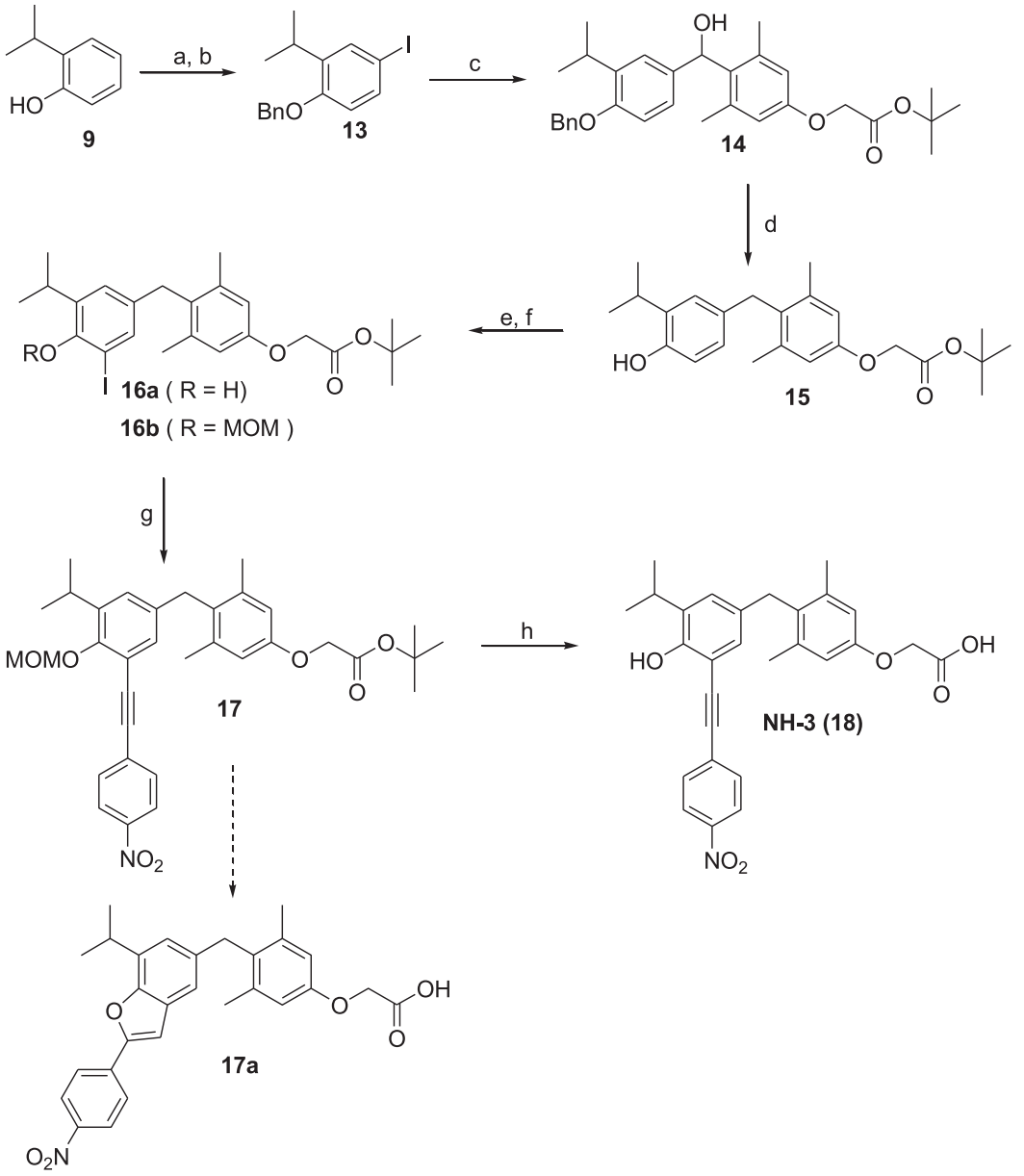
## 4. Experimental

$^1$H NMR were taken on a Bruker 400. All $^1$H NMR were calibrated to the NMR solvent reference peak ($d_6$-DMSO, $CDCl_3$, $CD_3OD$). High resolution mass spectrometry (HRMS) with electrospray ionization was performed by the Bioanalytical MS Facility at Portland State University. Inert atmosphere reactions were performed under argon gas passed through a small column of drierite and were conducted in flame-dried rbfs. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), and dimethylformamide (DMF) were obtained from a Seca Solvent System. All other solvents used were purchased from Sigma–Aldrich or Fisher.

*tert*-Butyl 2-(4-formyl-3,5-dimethylphenoxy)acetate (**2**). To a solution of 4-hydroxy-2,6-dimethylphenol (**1**) (15.02 g, 100 mmol) and DMF (400 mL) was added $Cs_2CO_3$ (65.2 g, 200 mmol). The resulting mixture was cooled to 0 °C and t-butylchloroacetate (17.9 mL, 125 mmol) was slowly added. The reaction mixture was then stirred at rt for 3 h and subsequently slowly poured into 800 mL $H_2O$. The resulting solution was stirred for 15 min at rt and then extracted with diethyl ether (3×500 mL). The combined organic fractions were washed with water (3×1 L), brine, dried with $MgSO_4$ and concentrated. Recrystallization of the residue with hexanes gave **2** (23.6 g, 89%). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 10.43 (s, 1H), 6.65 (s, 2H), 4.65 (s, 2H), 2.58 (s, 6H), 1.49 (s, 9H). HRMS exact mass calcd for $C_{15}H_{21}O_4$ $[M+H]^+$: 265.14344. Found 265.14445.

*tert*-Butyl 2-(4-(bromomethyl)-3,5-dimethylphenoxy)acetate (**3**). A solution of **2** (26.3 g, 99.5 mmol) in MeOH (400 mL) was cooled to 0 °C and $NaBH_4$ (3.76 g, 99.5 mmol) was slowly added over 5 min. The solution was stirred at room temperature for 1 h and the reaction was quenched by pouring the solution into 800 mL of 0.5 N HCl. The aqueous layer was then extracted three times with ethyl acetate and the combined organic layers were then washed with brine, dried with $MgSO_4$ and concentrated. Purification of the residue with flash chromatography (silica, 10%–30% ethyl acetate/hexanes) yielded the benzyl alcohol (20.2 g, 76%). To a cooled solution of NBS (26.7 g, 150 mmol) and DCM (300 mL) was added dimethylsulfide (11.09 mL, 150 mmol). This solution was stirred at 0 °C for 5 min where then a solution of the benzyl alcohol (20 g, 75 mmol) and DCM (75 mL) was added. The reaction mixture was stirred at 0 °C for 1 h and then 30 min at room temperature. The reaction was quenched with brine and the organic layer was isolated. The aqueous layer was extracted two more time with dcm and the combined organic layers were washed with brine, dried, and concentrated. The resulting solid was collected with cold hexanes to yield the desired benzyl bromide **3** (18.63 g, 75% (57% overall yield)). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.57 (s, 2H), 4.55 (s, 2H), 4.48 (s, 2H), 2.39 (s, 6H), 1.49 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.03, 157.79, 139.49, 127.32, 114.55, 82.48, 65.56, 30.06, 28.14, 19.72.

4-Bromo-2-iodophenol (**4**). 2-Iodophenol (11 g, 50 mmol) was dissolved in DCM (200 mL) and MeOH (100 mL). Tetrabutylammonium tribromide (TBATB) (25.31 g, 52.5 mmol) was then added portionwise over 10 min. The solution was stirred at room temperature for 2 h and then quenched with 1 N HCl (200 mL). The DCM layer was extracted and the aqueous layer was extracted another two times with DCM. The organic layers were then combined, washed with brine, dried, and concentrated. Purification of the residue with flash chromatography (silica, 50%–100% DCM/Hexanes) yielded 4-bromo-2-iodophenol (10.2 g, 68%). H NMR




**Scheme 3.** Synthesis of NH-3. Reagents and Conditions: (a) NaI, NaOCl, NaOH, MeOH, $H_2O$, 75%; (b) $K_2CO_3$, benzyl bromide, DMF, 75 °C, 77%; (c) (i) iPrMgCl, THF, 4 °A MS, (ii) **3**, THF, −78 °C; (d) MeOH, 10% Pd/C, $Et_3SiH$, 55%(two steps); (e) Aq NH3, THF, $I_2$,, 80%; (f) DMF, $Cs_2SO_3$, MOM-Cl, 78%; (g) $NEt_3$, $Pd(PPh_3)_4$, CuI, THF, 4-nitrophenyl acetylene, 50 °C, 87%; (h) (i) MeOH, 2 N NaOH; (ii) THF, $H_2O$, HCl, 61%.

matched the reported spectrum for 4-bromo-2-iodophenol as in Marton Csekei et al. *Tetrahedron* **2008**, 62, 8992–8996.

4-Bromo-2-(2-hydroxy-($D_6$-propan-2-yl)phenol (**5**). A solution of **4** (10.2 g, 34 mmol), THF (140 mL), and 4 Å molecular sieves (2 g) was placed under reduced pressure for 1 min and then placed under argon for 1 min. This process was repeated three times to ensure a deoxygenated solution. The solution was then cooled to 0 °C and an iPrMgCl solution (2 M THF, 42.6 mL, 85.3 mmol) was added. The reaction mixture was then stirred at rt for 2.5 h where it was then cooled to −78 °C. Acetone-$D_6$ (170.5 mmol, 12.54 mL) was added to the chilled solution and the reaction was allowed to warm to room temperature over 6 h. The reaction was then quenched with 0.5 M HCl and extracted with ethyl acetate three times. The combined organic fractions were washed with brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure.

4-Bromo-2-[(1,1,1,3,3,3-$^2H_6$)propan-2-yl]-phenoxytriisopropy lsilane (**6**). The crude residue was then dissolved in DCM (75 mL) and $Et_3SIH$ (27.2 mL, 170 mmol) was added, followed by trifluoroacetic acid (25 mL). The solution was stirred at room temperature for 22 h and then concentrated. Purification of the residue with flash chromatography (silica, 0%–60% DCM/Hexanes) yielded 4-bromo-2-($D_6$-propan-2-yl)phenol (6.0 g, 80%). To a solution of 4-bromo-2-($D_6$-propan-2-yl)phenol (6 g, 27 mmol) and DCM (90 mL) was added TIPS-Cl (11.44 mL, 54 mmol) followed by Imidazole (5.51 mL, 81 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched with 0.5 M HCl. The DCM layer was extracted and the aqueous layer was further extracted two more times with DCM. The combined organic layers were washed with brine, dried, and concentrated. Purification of the residue with flash chromatography (silica, Hexanes) yielded 4-bromo-2-[(1,1,1,3,3,3-$^2H_6$)propan-2-yl]-phenoxytriisopropylsilane (**6**) (6.60 g, 65%). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.29 (d, 1H, $J$=2.5 Hz), 7.15 (dd, 1H, 8.6 Hz, $J$=2.5 Hz), 6.66 (d, 1H, $J$=8.6 Hz), 3.30 (s, 1H), 1.34 (sept, 3H, $J$=7.2 Hz), 1.34 (d, 18H, $J$=7.2 Hz). $^{13}C$

NMR (100 MHz, $CDCl_3$): $\delta$ 152.5, 141.1, 129.4, 129.1, 119.5, 113.3, 26.6, 18.1, 13.3.

*tert*-Butyl 2-[3,5-dimethyl-4-({3-[(1,1,1,3,3,3-$^2H_6$)propan-2-yl]-4-{[tris(propan-2-yl)silyl]oxy}phenyl}methyl)phenoxy]acetate (**7**). A solution of **6** (1.66 g, 4.4 mmol), THF (20 mL), and 4 Å molecular sieves (1 g) was placed under reduced pressure for 1 min and then placed under argon for 1 min. This process was repeated three times to ensure a deoxygenated solution. The solution was then stirred at −78 °C and a nBuLi solution (2.5 M hexanes, 2 mL, 5 mmol) was added. The reaction mixture was stirred at −78 °C for 1.5 h and CuI (419 mg, 2.2 mmol) was then added. The reaction mixture was stirred for 5 min at −78 °C and 20 min at 0 °C. The solution was cooled back to −78 °C and a solution of **3** (658 mg, 2.0 mmol) and THF (5 mL) was added. The reaction mixture was then allowed to slowly warm to room temperature over 16 h. The reaction was quenched with 10% $NH_4Cl$ and the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine, dried, and concentrated. Purification of the residue with flash chromatography (silica, 0%–7.5% ethyl acetate/hexanes) yielded *tert*-butyl 2-[3,5-dimethyl-4-({3-[(1,1,1,3,3,3-$^2H_6$)propan-2-yl]-4-{[tris(propan-2-yl)silyl]oxy}phenyl}methyl)phenoxy]acetate (**7**) (818 mg, 75%).

$D_6$-Sobetirome (**8**). To a 0 °C solution of **7** (818 mg, 1.50 mmol) and THF (10 mL) was added TBAF (7 mL, 7 mmol). The solution was stirred at room temperature for 1 h and then the reaction was quenched with 0.5 M HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. Purification of the residue with flash chromatography (silica, 0%–20% ethyl acetate/hexanes) yielded the desired product as a yellow residue. The residue was then dissolved in methanol (20 mL) and 5 M NaOH (3 mL, 15 mmol) was slowly added. The reaction mixture was stirred at room temperature for 1 h and then acidified with 1 M HCl. The aqueous mixture was then extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried, and concentrated. Purification of the residue with flash chromatography (silica, 0%–5% MeOH/(DCM+2% AcOH)) yielded $D_6$-Sobetirome (**8**) (361 mg, 54%). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 6.76 (d, 1H, $J$=2 Hz), 6.58 (s, 2H), 6.52 (d, 1H, $J$=8.2 Hz), 6.44 (dd, 1H, $J$=8.2 Hz, 2 Hz), 4.55 (s, 2H), 3.82 (s, 2H), 3.10 (s, 1H), 2.14 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 174.0, 155.4, 150.9, 138.9, 134.3, 132.1, 131.4, 126.3, 125.4, 115.3, 114.2, 64.9, 33.9, 26.8, 20.6. LRMS (ESI-): 333.32. HRMS exact mass calcd for $C_{20}H_{18}D_6O_4$ $[M-H]^-$: 333.19675. Found 333.19710.

4-Iodo-2-isopropyl-1-(methoxymethoxy)benzene (**10**). To a stirring solution of 2-isopropylphenol (**9**) (13.62 g, 100 mmol), sodium iodide (14.98 g, 100 mmol) and methanol (300 mL), was added 10 mL of a 10 M NaOH solution. The reaction mixture was then cooled to 4 °C and a solution of NaOCl (6% aq, 129 mL, 115 mmol) was slowly added dropwise over 18 h. The reaction mixture was then allowed to stir at room temperature for 2 h. A 10% $Na_2S_2O_3$ solution (300 mL) was added followed by acidificiation of the solution to neutral pH with conc. HCl. The solution was then extracted with diethyl ether (3×300 mL). The combined organic fractions were washed with brine, dried with $MgSO_4$ and concentrated. Purification of the residue with flash chromatography (silica, 0%–75% dichloromethane/hexanes) gave 4-iodo-isopropylphenol (19.6 g, 75%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.45 (1H, d, $j$=2 Hz), 7.35 (1H, dd, $J$=8.4 Hz, 2 Hz), 6.52 (1H, d, $J$=8.4 Hz), 3.14 (1H, septet, $J$=7.2 Hz), 1.23 (6H, d, $J$=7.2 Hz). To a solution of 4-iodo-isopropylphenol (12.6 g, 48 mmol) in DCM (200 mL) was added TBAI (1.77 g, 4.8 mmol) and 10 M NaOH (48 mL, 480 mmol). This solution was stirred at room temperature for 10 min and MOM-Cl (6 M in methyl acetate, 192 mmol, 32 mL) was then added. The reaction mixture was then stirred at room temperature for 3 h. The mixture was next diluted with 200 mL of $H_2O$ and subsequently extracted with dichloromethane (3×200 mL). The combined organic fractions were washed with brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure. Purification of the residue with flash chromatography (silica, 25%–50% dcm/hexanes) yielded **10** (10.21 g, 82%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.5 (d, 1H, $J$=2.2 Hz), 7.44 (dd, 1H, $J$=8.7 Hz, 2.2 Hz), 6.85 (d, 1H, $J$=8.7 Hz), 5.20 (s, 2H), 3.49 (s, 3H), 3.29 (sept, 1H, $J$=7 Hz), 1.22 (d, 6H, $J$=7 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 154.38, 140.44, 135.49, 135.33, 116.24, 94.44, 85.01, 56.18, 27.01, 22.78.

*tert*-Butyl 2-(4-(hydroxy(3-isopropyl-4-(methoxymethoxy)phenyl)methyl)-3,5-dimethylphenoxy)acetate (**11**). A solution of **10** (10.21 g, 33.33 mmol), THF (140 mL), and 4 Å molecular sieves (3 g) was placed under reduced pressure for 1 min and then placed under argon for 1 min. This process was repeated three times to ensure a deoxygenated solution. The solution was then cooled to 0 °C and an iPrMgCl solution (2 M THF, 25 mL, 50 mmol) was added. The reaction mixture was then stirred at rt for 2.5 h where it was then cooled to −78 °C. A solution of **2** (5.87 g, 22.22 mmol) and THF (11 mL) was then added and the reaction mixture was stirred at −78 °C for 2 h and at room temperature for 0.5 h. The reaction was quenched with a 10% $NH_4Cl$(aq) solution (200 mL) and extracted with ethyl acetate (3×200 mL). The combined organic fractions were washed with brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure. Purification of the residue with flash chromatography (silica, 5%–20% ethyl acetate/hexanes) yielded **11** (7.0 g, 71%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.23 (d, 1H, $J$=2 Hz), 6.94 (d, 1H, $J$=8 Hz), 6.88 (dd, 1H, $J$=8.5 Hz, 2 Hz), 6.23 (d, 1H, $J$=3.5 Hz), 5.17 (s, 2H), 4.49 (s, 2H), 3.48 (s, 3H), 3.30 (sept, 1H, $J$=7 Hz), 2.23 (s, 6H), 1.49 (s, 9H), 1.19 (t, 6H, $J$=7 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168, 156.8, 153.2, 138.8, 137.3, 136.2, 132.9, 123.9, 123.8, 115.1, 113.7, 94.7, 82.4, 70.8, 56.1, 28.1, 27.2, 22.9, 21.1. HRMS exact mass calcd for $C_{26}H_{36}O_6$ $[M+Na]^+$: 467.24041. Found 467.24053.

$^3$H-Sobetirome (**12**). To a vial containing Sodium Borohydride [$^3$H] (American Radiolabeled Chemicals Inc., ART 0121, 250 mCi/mmol, 25 mCi, 0.10 mmol) was added TFA (153 uL, 2.0 mmol). This solution was stirred at rt for 10 min or until all of the solid $NaB^3H_4$ dissolved. A solution of **11**(14.8 mg, 0.033 mmol) and 500 uL of DCM was then added to the reaction vial and the contents were stirred at room temperature for 10 min. The reaction was quenched by adding 1.5 mL of water and the solution was stirred for 5 min at room temperature. DCM (1 mL) was next added and the organic layer was separated. The aqueous layer was further extracted two more times with DCM and the combined organic layers were washed with brine, dried, and concentrated with air. The crude mixture was purified via preparatory TLC (silica, 5% Methanol/DCM+1% AcOH) to yield **12** (1.5 mg, 14%). A cold standard of Sobetirome was spotted on the prep TLC plate and the band corresponding to Sobetirome was scraped off the plate and isolated from the silica gel with ethyl acetate. The specific activity of the $^3$H-Sobetirome (**12**) was determined to be 6.90 mBq.

1-(Benzyloxy)-4-iodo-2-isopropylbenzene (**13**). To a solution of 4-iodo-isopropylphenol (16.18 g, 61.73 mmol) in DMF (200 mL) was added $K_2CO_3$ (25.6 g, 185.2 mmol) and benzyl bromide (11 mL, 92.6 mmol). The reaction mixture was then stirred at 75 °C for 16 h. After cooling the solution the room temperature, the mixture was then slowly poured into 600 mL of $H_2O$ and subsequently stirred at rt for 15 min. The mixture was then extracted with hexanes (3×500 mL). The combined organic fractions were washed with water (3×500 mL), brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure. Purification of the residue with flash chromatography (silica, 0%–2% ethyl acetate/hexanes) yielded **5** (16.7 g, 77%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.41–7.24 (m, 5H), 6.91 (d, 1H, $J$=2 Hz), 6.76 (d, 1H, $J$=8.4 Hz), 6.63 (m, 3H), 4.97 (s, 2H), 4.58 (s, 2H), 3.89 (s, 2H), 3.30 (sept, 1H, $J$=7.1 Hz), 2.17 (s, 6H), 1.14 (d, 6H, $J$=7.1 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 155.8, 140.3, 137.1, 134.5, 135.3, 128.7, 128.0, 127.2, 114.1, 83.9, 70.1, 27.0, 22.6.

*tert*-Butyl 2-(4-((4-(benzyloxy)-3-isopropylphenyl)(hydroxy) methyl)-3,5-dimethylphenoxy)acetate (**15**). The procedure to synthesize **11** was used to synthesize **14**. The partially purified solution was then subjected to catalytic hydrogenation conditions. A solution of **14** (12.06 g, 25 mmol), 95% EtOH (150 mL) was placed under reduced pressure for 1 min and then placed under argon for 1 min. This process was repeated three times to ensure a deoxygenated solution. With argon flowing into the rbf, 10% Pd/C (3 g) was added. Lastly, $Et_3SiH$ (60 mL, 375 mmol) was added dropwise. The solution was allowed to stir at room temperature for 24 h. The reaction mixture was then filtered over Celite and concentrated. Purification of the residue with flash chromatography (silica, 0%–20% ethyl acetate/hexanes) yielded **15** (6.72 g, 70% overall yield (2 steps)). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.93 (d, 1H, $J$=2 Hz), 6.63 (s, 2H), 6.58 (m, 2H), 4.70 (s, 1H), 4.52 (s, 2H), 3.91 (s, 2H), 3.17 (sept, 1H, $J$=7 Hz), 2.24 (s, 6H), 1.5 (s, 9H), 1.27 (d, 6H, $J$=7 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.5, 156.0, 150.9, 138.5, 134.3, 132.3, 130.6, 126.2, 125.5, 115.2, 114.2, 82.3, 65.8, 33.8, 28.2, 27.2, 22.7, 20.6. HRMS exact mass calcd for $C_{24}H_{32}O_4$ $[M+Na]^+$: 407.21928. Found 407.21974.

*tert*-Butyl 2-(4-{[4-hydroxy-3-iodo-5-isopropylphenyl]methyl}-3,5-dimethylphenoxy)acetate (**16a**). To a solution of **14**(2.37 g, 6.16 mmol) and THF (45 mL) was added conc. NH3 (aq) (45 mL), followed by $I_2$ (1.88 g, 7.39 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with water. The aqueous mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried, and concentrated. Purification of the residue with flash chromatography (silica, 5%–10% ethyl acetate/hexanes) yielded **16a** (2.51 g, 80%). %). $^1$H NMR (400 MHz, $CDCl_3$): 6.99 (d, 1H, $J$=2 Hz), 6.88 (d, 1H, $J$=2 Hz), 6.65 (s, 2H), 5.18 (s, 1H), 4.54 (s, 2H), 3.88 (s, 2H), 3.26 (sept, 1H, $J$=7 Hz), 2.22 (s, 6H), 1.52 (s, 9H), 1.19 (d, 6H, $J$=7 Hz). HRMS exact mass calcd for $C_{24}H_{31}IO_4$ $[M+Na]^+$: 533.11592 Found 533.11615. *tert*-Butyl 2-(4-(3-iodo-5-isopropyl-4-(methoxymethoxy)benzyl)-3,5-dimethylphenoxy)acetate (**16b**). To a solution of **16b** (1.54 g, 3.39 mmol) in DMF (20 mL) was added $Cs_2CO_3$ (3.31 g, 10.17 mmol). This solution was then cooled to 0 °C and then MOM-Cl (6.5 M Methyl Acetate, 0.783 mL, 5.09 mmol) was added. The solution was allowed to slowly warm to room temperature over two hours. The reaction mixture was then diluted with 100 mL of $H_2O$ and subsequently extracted with diethyl ether (3×200 mL). The combined organic fractions were washed with brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure. Purification of the residue with flash chromatography (silica, 10% ethyl acetate/hexanes) yielded **10** (1.47 g, 78%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.18 (d, H, $J$=2 Hz), 6.91 (d, 1H, $J$=2 Hz), 6.64 (s, 2H), 5.03 (s, 2H), 4.53 (s, 2H), 3.90 (s, 2H), 3.66 (s, 3H), 3.38 (sept, 1H, $J$=7 Hz), 2.21 (s, 6H), 1.53 (s, 9H), 1.15 (d, 6H, $J$=7 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.43, 156.2, 152.5, 143.3, 138.6, 138.5, 135.9, 129.4, 126.6, 114.4, 100.4, 92.99, 82.23, 65.8, 57.9, 33.6, 28.2, 27.4, 23.7, 20.7. HRMS exact mass calcd for $C_{26}H_{35}IO_5$ $[M+Na]^+$: 577.14214 Found 577.14347.

*tert*-Butyl 2-(4-(3-isopropyl-4-(methoxymethoxy)-5-(2-(4-nitrophenyl)ethynyl)benzyl)-3,5-dimethylphenoxy)acetate (**17**). A solution of **16b** (1.24 g, 2.24 mmol), THF (20 mL), and 4-nitrophenylacetylene (824 mg, 5.6 mmol) was placed under reduced pressure for 1 min and then placed under argon for 1 min. This process was repeated three times to ensure a deoxygenated solution. $Pd(PPh_3)_4$ (259 mg, 0.224 mmol) and CuI (85 mg, 0.448 mmol) were added followed by $NEt_3$ (3.12 mL, 22.4 mmol) and the solution was stirred at 50 °C overnight under an argon atmosphere. The following day the solution was filtered over Celite and concentrated. Purification of the residue with flash chromatography (silica, 5%–20% ethyl acetate/hexanes) yielded **17** (1.12 g, 87%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.19 (d, 2H, $J$=8.66 Hz), 7.62 (d, 2H, $J$=8.72 Hz), 7.05 (d, 1H, $J$=2.2 Hz), 6.85 (d, 1H, $J$=2.2 Hz), 6.64 (s, 2H), 5.23 (s, 2H), 4.52 (s, 2H), 3.92 (s, 2H), 3.62 (s, 3H), 3.40 (sept, 1H, $J$=7.26 Hz), 2.23 (s, 6H), 1.52 (s, 9H), 1.21 (d, 6H, $J$=7.26 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.5, 156.3, 154.4, 147.0, 142.4, 138.6, 136.3, 132.2, 130.49, 129.8, 129.54, 128.1, 123.8, 115.7, 114.4, 100.2, 92.6, 91.0, 82.4, 65.8, 57.8, 33.9, 28.2, 26.63, 23.5, 20.7. HRMS exact mass calcd for $C_{34}H_{39}NO_7$ $[M+NH_4]^+$: 591.30648 found 591.30738.

{4-[4-Hydroxy-3-isopropyl-5-(4-nitrophenylethynyl)-benzyl]-3,5-dimethylphenoxy}acetic acid (NH-3, **18**). To a solution of **17** (201 mg, 0.351 mmol) and MeOH (5 mL) was added 2 M NaOH (4.06 mL, 8.11 mmol). The reaction mixture was allowed to stir at room temperature for 2 h and then concentrated to remove the methanol. The mixture was then acidified with 20 mL of 1 M HCl and the resulting aqueous layer was extracted three times with DCM. The combined organic fractions were washed with brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure. The crude mixture was then dissolved in 20 mL of THF and 6 mL of $H_2O$. Conc. HCl (2.0 mL) was added and the solution was stirred at room temperature for 48 h. The reaction mixture was then diluted with $H_2O$ and the resulting aqueous layer was extracted three times with DCM. The combined organic fractions were washed with brine, dried with $Mg_2SO_4$, and concentrated under reduced pressure. Purification of the residue with flash chromatography (silica, 0%–4% MeOH/DCM+1% AcOH) yielded (NH-3, **18**) (102 mg, 61%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.20 (d, 2H, $J$=8.7 Hz), 7.64 (d, 2H, $J$=8.7 Hz), 7.02 (d, 1H, $J$=2 Hz), 6.70 (d, 1H, $J$=2 Hz), 6.66 (s, 2H), 5.30 (br, 1H), 4.69 (s, 2H), 3.90 (s, 2H), 3.26 (sept, 1H, $J$=6.8 Hz), 2.21 (s, 6H), 1.20 (d, 6H, $J$=6.8 Hz). Matches the reported spectrum of Nguyen, N–H., et al. J Med Chem. 2002, 45, 3310–3320.

## Acknowledgements

This work was supported by a grant from the National Institutes of Health (DK-52798, T.S.S.)

## Supplementary data

Supplementary data ($^1$H NMR spectra of the following compounds (**2**, **3**, **6**, **8**, **10**, **11**, **13**, **15**, **16a**, **16b**, **17**, **18**). ) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.049.

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