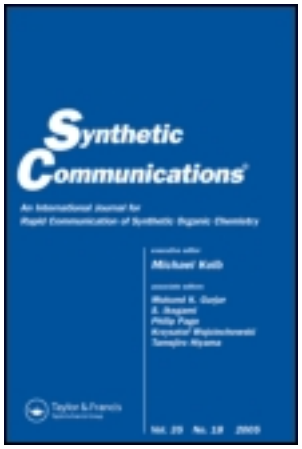


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

The Synthesis of $^{13}C_9$-^{15}N-Labeled The 3,5-Diiodothyronine and Thyroxine

Sarah A. Hackenmueller [a] & Thomas S. Scanlan [a]

[a] Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, Oregon, USA

Accepted author version posted online: 05 Jun 2012.Version of record first published: 05 Mar 2013.

To cite this article: Sarah A. Hackenmueller & Thomas S. Scanlan (2013): The Synthesis of $^{13}C_9$-^{15}N-Labeled The 3,5-Diiodothyronine and Thyroxine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:10, 1439-1446

To link to this article: http://dx.doi.org/10.1080/00397911.2011.639005

Synthetic Communications®, 43: 1439–1446, 2013

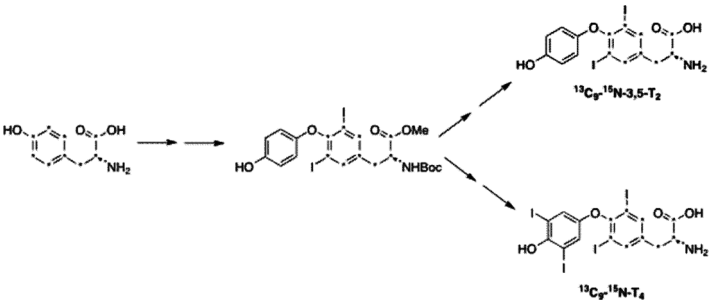
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.639005

Taylor & Francis
Taylor & Francis Group

THE SYNTHESIS OF $^{13}C_9$-^{15}N-LABELED THE 3,5-DIIODOTHYRONINE AND THYROXINE

Sarah A. Hackenmueller and Thomas S. Scanlan
Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, Oregon, USA

GRAPHICAL ABSTRACT



Abstract *Thyroid hormones undergo extensive metabolism to regulate hormone activity. A labeled thyroid hormone would be useful to track hormone metabolism through various pathways. While radiolabeled thyroid hormones have been synthesized and used for in vivo studies, a stable isotope labeled form of thyroid hormone is required for studying thyroid hormone metabolism by LC-MS/MS, an analytical technique that has certain advantages without the complications of radioactivity. Here we report the synthesis of $^{13}C_9$-^{15}N-T_2 and $^{13}C_9$-^{15}N-T_4, two labeled thyroid hormone derivatives suitable for in vivo LC-MS/MS studies.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords $^{13}C_9$-^{15}N-T_2; $^{13}C_9$-^{15}N-T_4; thyroid hormone; thyroxine

INTRODUCTION

Thyroid hormones (THs) are important endocrine signaling molecules that regulate a variety of physiological functions, including body temperature, cardiac function, metabolism, and mental status. THs are synthesized and secreted by the thyroid gland predominantly as 3,3′,5,5′-tetraiodothyronine (T_4, thyroxine), which

Received September 15, 2011.
Address correspondence to Thomas S. Scanlan, Department of Physiology and Pharmacology, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd., L334, Portland, OR 97239-3098 USA. E-mail: scanlant@ohsu.edu

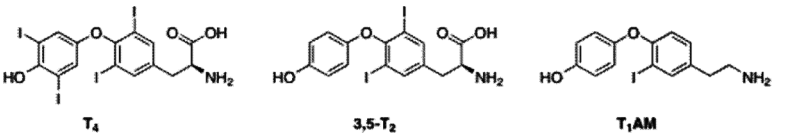


Figure 1. Structures of T_4, 3,5-T_2, and T_1AM.

undergoes extrathyroidal deiodination to 3,3′,5-triiodothyronine (T_3). T_3 is largely considered to be the active form of the hormone and exerts its effects by binding to TH nuclear receptors and regulating transcription of TH-responsive genes. In addition to the commonly known transcriptional actions of TH, there are rapid, nontranscriptionally mediated effects of TH that remain less well understood, suggesting the existence of additional biologically active TH metabolites.[1,2]

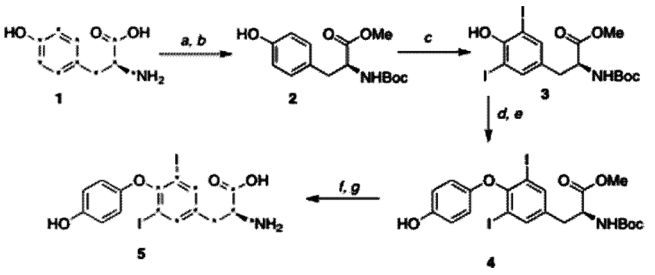
T_1AM is an endogenous compound present in serum and various tissues of rats, hamsters, and humans.[3–6] Acute administration of T_1AM *in vivo* results in induction of a torpor-like state characterized by hypothermia, bradycardia, a shift in respiratory quotient from carbohydrate to lipid utilization, hyperglycemia, and hypoinsulinemia.[3,5,7] In an *ex vivo* perfused rat heart, T_1AM decreases cardiac output.[3,8] These effects tend to be oppose those normally attributed to T_3 and suggest that T_1AM may also play a role in TH signaling by modulating the effects of T_3.

Structural similarities between T_4 and T_1AM (Fig. 1) have led to speculation that T_1AM is a deiodinated and decarboxylated derivative of TH, but this relationship has not been directly investigated. To test this metabolic question, it is necessary to definitively trace the fate of a suspected precursor, which can be accomplished through incorporation of a label in T_4. Several methods for analyzing T_1AM by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) have been reported.[4,9,10] This technique is ideal for analysis of isotopically labeled compounds, because any metabolites arising from a labeled precursor would contain a mass signature distinct from endogenous compounds. T_4, as the predominant form of TH produced endogenously, is the first candidate to test as a suspected precursor to T_1AM. Based on *in vitro* data showing that T_3 is not a substrate for outer ring deiodination, it remains unclear if 3,5-diiodothyroinine (3,5-T_2), another endogenous TH, arises from extrathyroidal metabolism of T_4 or some alternate biosynthetic pathway.[10] This indicates a second potential candidate for a biosynthetic precursor to T_1AM. Herein we describe the novel syntheses of $^{13}C_9$-^{15}N-3,5-T_2 and $^{13}C_9$-^{15}N-L-thyroxine ($^{13}C_9$-^{15}N-T_4) that can be used to study TH metabolism by liquid chromatography–tandem mass spectroscopy (LC-MS/MS).

RESULTS AND DISCUSSION

Synthesis of $^{13}C_9$-^{15}N-3,5-T_2

The synthesis of $^{13}C_9$-^{15}N-L-T_2 was carried out in parallel with unlabeled T_2 according to the route shown in Scheme 1. Commercially available $^{13}C_9$-^{15}N-L-tyrosine **1** was N-Boc and O-methyl ester protected and bis-iodinated with N-iodosuccinimide in dichloromethane (DCM), a modification of the method of Bovonsombat et al., to give $^{13}C_9$-^{15}N-3,5-diiodo-L-tyrosine **3** in 59% yield over the



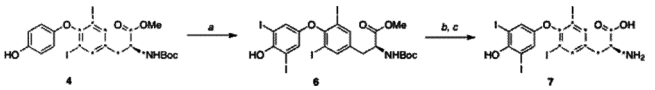
Scheme 1. Reagents and conditions: (*a*), HCl, 2,2-dimethoxypropane; (*b*), BOC_2O, $NaHCO_3$, THF/H_2O; (*c*), NIS, DCM; (*d*), 4-(triisopropyl)silyloxyphenyl boronic acid, $Cu(OAc)_2$, DIPEA, pyridine, DCM; (*e*), TBAF, THF; (*f*), LiOH, $MeOH/H_2O$; and (*g*), HCl, dioxane. An asterisk (*) indicates ^{13}C or ^{15}N.

three steps.[11,12] 4-(Triisopropyl)silyloxyphenyl boronic acid was synthesized as previously described and coupled to **3** via a copper(II)-mediated biaryl ether formation.[13,14] Deprotection with tetrabutylammonium flurodie (TBAF) gave N-boc-3,5-diiodo-$^{13}C_9$-^{15}N-L-thyronine-OMe **4** in 30% yield over two steps. Sequential deprotection with lithium hydroxide to cleave the methyl ester and hydrochloric acid to cleave the t-Boc gave $^{13}C_9$-^{15}N-3,5-T_2 **5**, in 28% yield as the trifluoroacetic acid (TFA) salt after purification by preparative high-performance liquid chromatography (HPLC).[15] Because of the difficulty in interpreting ^1H NMR spectra as a result of ^{13}C coupling effects, labeled intermediates and $^{13}C_9$-^{15}N-3,5-T_2 were characterized by high-resulution mass spectrometry (HRMS) and chromatographic comparison to unlabeled standards, which were synthesized in parallel to $^{13}C_9$-^{15}N-labeled compounds.

Synthesis of $^{13}C_9$-^{15}N-L-T_4

The synthesis of $^{13}C_9$-^{15}N-L-T_4 was carried out in parallel with unlabeled T_4 according to the route shown in Scheme 2. Biaryl ether **4** was bis-iodinated on the outer ring with iodine monochloride and butylamine to give N-Boc-$^{13}C_9$-^{15}N-T_4-OMe **6** in 37% yield.[13] Sequential deprotection of **6** as described previously produced $^{13}C_9$-^{15}N-T_4 **7**, which was purified by preparative HPLC as the TFA salt in 23% yield from **6**. As described for $^{13}C_9$-^{15}N-3,5-T_2, synthetic intermediates and $^{13}C_9$-^{15}N-L-T_4 were characterized by HRMS and chromatographic comparison to unlabeled standards, which were synthesized in parallel.

^{125}I, ^{131}I, and ^{14}C labeled THs have been used to study TH metabolism and pharmacokinetics but the use of radiolabels in metabolism studies is limited to tracing the fate of the radioactivity and does not provide information on metabolic pathways that do not involve radiolabeled portions of the hormones.[16–25] In addition, the use of outer ring labeled ^{125}I-T_4, the most commonly employed labeled



Scheme 2. Reagents and conditions: (*a*), ICl, $BuNH_2$, 4:1 DCM/DMF; (*b*), LiOH, $MeOH/H_2O$; and (*c*), HCl, dioxane. An asterisk (*) indicates ^{13}C or ^{15}N.

form of T_4, could not be used to follow T_4 metabolites that are extrathyroidally deiodinated in the outer ring, such as 3,5-T_2 and T_1AM. The incorporation of nonradioactive isotopes such as ^{13}C or ^{15}N into T_4 and other THs allows for more in-depth investigations of alternate pathways of TH metabolism by LC-MS/MS. The syntheses of unlabeled and of ^{13}C-labeled T4 and T3 have been reported, but here we report an alternate synthetic route to produce a novel labeled T_4 containing ^{15}N and ^{13}C.[14,26–29] Although the synthesis of ^{125}I-3,5-T_2 has been reported, to our knowledge this is the first reported synthesis of a stable isotope labeled T_2.[30]

EXPERIMENTAL

All chemicals used for synthesis were purchased from Aldrich, Sigma-Aldrich, Fluka, Acros or TCI. Anhydrous solvents were obtained from an in-house solvent distillation system. Intermediates were purified by flash chromatography (HPFC) on a Biotage SP1 purification system with a fixed wavelength ultraviolet detector (Biotage, Charlotte, NC). Syntheses of unlabeled and ^{13}C-^{15}N labeled compounds were carried out in parallel. The synthetic scheme was prospected using unlabeled material, which also served as standards to match ^{13}C-^{15}N-labeled compounds by thin-layer chromatography (TLC). NMR spectra for ^{13}C -labeled compounds were difficult to interpret due to ^{13}C J-couplings. For this reason, ^{13}C labeled compounds were characterized by high-resolution mass spectrometry (HRMS) only. ^1H NMR were taken for unlabeled compounds only. ^1H NMR spectra were taken on a Bruker 400 (400 MHz), and spectra were processed using ACD/NMR Processor Academic Edition software. HRMS and MS/MS fragmentation (contained in the Supplemental Figures, available online) using electrospray ionization (ESI) in positive polarity was performed at the Mass Spectrometry Laboratory at the University of Illinois at Urbana–Champaign. HRMS are reported for all novel compounds, and MS/MS fragmentation for $^{13}C_9$-^{15}N-labeled compounds are available in the Supplementary Material, available online.

Boc-OMe-L-tyrosine

Concentrated hydrochloric acid (2.7 ml) was added dropwise to a stirring solution of L-tyrosine (0.500 g, 2.76 mmol) in 2,2-dimethyoxypropane (33 ml). The reaction was stirred at room temperature for 24 h, and the crude reaction mixture was used in the next step.

$NaHCO_3$ (7.5 ml, 1.1 M in water) was added to crude OMe-L-tyrosine and Boc_2O (0.620 g, 2.85 mmol) in THF (12 ml). The reaction was stirred at room temperature for 24 h. The reaction was diluted with ether (20 ml), and the aqueous layer was extracted twice with ether. The combined organic layers were washed with 0.5 M HCl and brine and dried over $MgSO_4$. The crude material was purified by HPFC (10–80% ethyl acetate / hexanes over 10 column volumes) to give Boc-OMe-L-tyrosine (0.787 g, 2.66 mmol, 96.5% yield). ^1H NMR (400 MHz, chloroform-d)δ ppm 1.41 (s, 9 H) 2.86–3.21 (m, 2 H), 3.75 (s, 3 H), 4.47–4.63 (m, 1 H), 5.13 (br. s., 1 H), 5.48 (br. s., 1 H), 7.10 (s, 2 H), 7.64 (s, 2 H).

Boc-OMe-$^{13}C_9$-^{15}N-L-tyrosine **2** was synthesized using the same procedure with $^{13}C_9$-^{15}N-l-tyrosine (0.500 g, 2.62 mmol) as starting material, in 87.2% yield

(0.702 g, 2.30 mmol). HRMS (ESI+) for $C_6{}^{13}C_9H_{22}{}^{15}NO_5$ [M + H] calculated 306.1770, found 306.1776. MS/MS fragmentation spectrum is available in Supplemental Fig. S1, available online.

3,5-Diiodo-Boc-OMe-L-tyrosine

N-Iodosuccinimide (1.2 g, 5.32 mmol) was added to a stirring solution of Boc-OMe-L-tyrosine (0.787 g, 2.66 mmol) in DCM (17.7 ml) at 0 °C. The reaction was monitored by TLC (40% ethyl acetate / hexanes) for consumption of starting material, which occurred in ~40 min. A solution of 10% $Na_2S_2O_3$ was added dropwise, and the reaction mixture was diluted with water and extracted three times with ethyl acetate. The ethyl acetate layers were combined and dried over $MgSO_4$. The crude material was purified by HPFC (10–80% ethyl acetate / hexanes over 10 column volumes) to give 3,5-diiodo-Boc-OMe-L-tyrosine as a white solid (0.908 g, 1.66 mmol, 67.5% yield). ^{1}H NMR (400 MHz, chloroform-d)δ ppm 1.45 (s, 9 H), 2.96 (s, 2 H), 3.68–3.79 (m, 3 H), 4.49 (d, J = 7.07 Hz, 1 H), 5.03 (d, J = 7.58 Hz, 1 H), 5.70 (s, 1 H), 7.44 (s, 2 H).

3,5-Diiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-tyrosine **3** was synthesized following the same procedure from Boc-OMe-$^{13}C_9$-^{15}N-L-tyrosine (0.702 g, 2.30 mmol) starting material, in 67.5% yield (0.864 g, 1.55 mmol). HRMS (ESI+) for $C_6{}^{13}C_9H_{19}I_2{}^{15}NNaO_5$ [M + Na] calculated 579.9523, found 579.9528. MS/MS fragmentation spectrum is available in Supplemental Fig. S2, available online.

3,5-Diiodo-Boc-OMe-L-thyronine

Molecular sieves 4 Å were added to a round-bottom flask that was then flame dried and flushed with dry air. 4-(Triisopropyl)silyloxyphenyl boronic acid (0.612 g, 2.08 mmol), DCM (6.3 ml), diisopropylethylamine (4.15 mmol), and pyridine (4.15 mmol) were added under argon. Dry copper(II) acetate (0.151 g, 0.83 mmol) was added, and the reaction mixture was stirred under argon for 10 min. 3,5-Diiodo-Boc-OMe-L-tyrosine (0.452 g, 0.83 mmol) was added in DCM (2 ml) over 5 min. The reaction was stirred at room temperature under dry air for 48 h. The reaction was diluted with ether; filtered through silica/celite; sequentially washed with HCl, H_2O, and brine, and dried over $MgSO_4$. The crude reaction material was taken into the next reaction.

Crude biaryl ether was dissolved in THF and cooled to 0 °C. Tetra-N-butylammonium fluoride (3.15 mmol) was added dropwise over 5 min. The reaction was stirred at room temperature for 15 min. The reaction was diluted with ethyl acetate and washed with HCl. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed sequentially with H_2O and brine and dried over $MgSO_4$. The crude product was purified by HPFC (10–80% ethyl acetate / hexanes over 10 column volumes) to yield 3,5-diiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-thyronine as a solid (0.196 g, 0.31 mmol, 37.0% yield over two steps). ^{1}H NMR (400 MHz, chloroform-d)δ ppm 1.45 (s, 9 H), 2.83–3.19 (m, 2 H), 3.66–3.88 (m, 3 H), 4.54 (br. s., 1 H), 4.69 (br. s., 1 H), 5.10 (br. s., 1 H), 6.62–6.92 (m, 4 H), 7.63 (s, 2 H). HRMS (ESI+) for $C_{21}H_{23}I_2NNaO_6$ [M + Na] calculated 661.9512; found 661.9512.

3,5-Diiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-thyronine **4** was synthesized following the same procedure from 3,5-diiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-tyrosine (0.547 g, 0.98 mmol) starting material, in 29.9% yield (0.190 g, 0.29 mmol). HRMS (ESI+) for $C_{12}{}^{13}C_9H_{24}I_2{}^{15}NO_6$ [M + H] calculated 649.9965; found 649.9966. MS/MS fragmentation spectrum is available in Supplemental Fig. S3, available online.

3,5-Diiodo-$^{13}C_9$-^{15}N-L-thyronine ($^{13}C_9$-^{15}N-T_2) 5

To cleave the methyl ester, lithium hydroxide (0.39 mmol, 100 µl of 3.9 M in H_2O) was added to a stirred solution of 3,5-diiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-thyronine (0.051 g, 0.078 mmol) in methanol (300 µl) at 4 °C. The reaction was stirred at 4 °C for 90 min. Solvent was removed under argon, and the crude reaction product was dried in a modified Abderhalden drying apparatus for use in the next step.

The dried crude reaction product from the methyl ester deprotection was dissolved in 4 M HCl in dioxane (300 µl). The reaction was stirred under argon at room temperature overnight. The reaction mixture was diluted with 500 µl of 1:1 water/acetonitrile and purified by preparatory HPLC using a Rainin HPXL solvent delivery system and a Prostar PDA detector (Varian Inc., Paolo Alto, CA). Reaction product was injected onto a Varian Dynamax Microsorb C18 21.4 × 250 mm column and monitored at wavelength 254 nm. Mobile phases were A (water + 0.1% TFA) and B (acetonitrile + 0.1% TFA) with gradient conditions as follows: 5% B 0–5 min, 5–95% B 5–50 min, 95% B 50–65 min, 95–5% B 65–75 min, and 5% B 75–90 min. Commercially available 3,5-T_2 was used to determine the retention time of the product, 31.5 min. HRMS (ESI+) for $C_6{}^{13}C_9H_{14}I_2{}^{15}NO_4$ [M + H] calculated 535.9284; found 535.9291. MS/MS fragmentation spectrum is available in Supplemental Fig. S4, available online.

3,3′,5,5′-Tetraiodo-N-Boc-OMe-L-thyronine

Iodine monochloride in DCM (0.26 mmol, 260 µl) was added dropwise to a stirring solution of 3,5-diiodo-Boc-OMe-L-thyronine (0.072 g, 0.11 mmol) and butylamine (0.64 mmol, 64 µl) in 4:1 DCM/DMF (3.7 ml) at 0 °C. The reaction was stirred at 0 °C for 20 min. The reaction was diluted with ethyl acetate; washed sequentially with HCl, 10% sodium thiosulfate, H_2O, and brine; and dried over $MgSO_4$. The crude product was purified by HPFC (10–80% ethyl acetate / hexanes over 10 column volumes) to yield 3,3′,5,5′-tetraiodo-N-Boc-OMe-L-thyronine as a brown solid (0.022 g, 0.025 mmol, 22.9% yield). ^{1}H NMR (400 MHz, chloroform-d)δ ppm 1.41 (s, 9 H), 2.86–3.21 (m, 2 H), 3.75 (s, 3 H), 4.47–4.63 (m, 1 H), 5.13 (br. s., 1 H), 5.48 (br. s., 1 H), 7.10 (s, 2 H), 7.64 (s, 2 H). HRMS (ESI+) for $C_{21}H_{21}I_4NNaO_6$ [M + Na] calculated 913.7445; found 913.7437.

3,3′,5,5′-Tetraiodo-N-Boc-OMe-$^{13}C_9$-^{15}N-L-thyronine **6** was synthesized following the same procedure using 3,5-diiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-thyronine (0.150 g, 0.23 mmol) as starting material, in 36.9% yield (0.076 g, 0.085 mmol). HRMS (ESI+) for $C_{12}{}^{13}C_9H_{21}I_4{}^{15}NNaO_6$ [M + Na] calculated 923.7718; found 923.7715. MS/MS fragmentation spectrum is available in Supplemental Fig. S5, available online.

3,3′,5,5′-Tetraiodo-$^{13}C_9$-^{15}N-L-thyronine ($^{13}C_9$-^{15}N-T_4) 7

To cleave the methyl ester, lithium hydroxide (0.43 mmol, 110 µl of 3.9 M in H_2O) was added to a stirred solution of 3,3′,5,5′-tetraiodo-Boc-OMe-$^{13}C_9$-^{15}N-L-thyronine (0.076 g, 0.085 mmol) in methanol (330 µl) at 4 °C. The reaction was stirred at 4 °C for 90 min. Solvent was removed under argon and the crude reaction product was dried in a modified Abderhalden drying apparatus for use in the next step.

The dried crude reaction product from the methyl ester deprotection was dissolved in 4 M HCl in dioxane (320 µl). The reaction was stirred under argon at room temperature overnight. To the reaction mixture, 500 µl of 1:1 water/acetonitrile was added, and the solution was filtered through a 0.22-µm filter prior to purification by preparatory HPLC as described previously. Commercially available T_4 was used to determine the retention time of the product, 37.7 min. HRMS (ESI+) for $C_6{}^{13}C_9H_{11}I_4{}^{15}NO_4$ [M + H] calculated 787.7217; found 787.7218. MS/MS fragmentation spectrum is available in Supplemental Fig. S6, available online.

ACKNOWLEDGMENT

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

REFERENCES

1. Yen, P. M. *Physiol Rev.* **2001**, *81*(3), 1097–1142.
2. Davis, P. J.; Leonard, J. L.; Davis, F. B. *Front Neuroendocrinol.* **2008**, *29*(2), 211–218.
3. Scanlan, T. S.; Suchland, K. L.; Hart, M. E.; Chiellini, G.; Huang, Y.; Kruzich, P. J.; Frascarelli, S.; Crossley, D. A.; Bunzow, J. R.; Ronca-Testoni, S.; Lin, E. T.; Hatton, D.; Zucchi, R.; Grandy, D. K. *Nat Med.* **2004**, *10*(6), 638–642.
4. Saba, A.; Chiellini, G.; Frascarelli, S.; Marchini, M.; Ghelardoni, S.; Raffaelli, A.; Tonacchera, M.; Vitti, P.; Scanlan, T. S.; Zucchi, R. *Endocrinology* **2010**, *151*(10), 5063–5073.
5. Braulke, L. J.; Klingenspor, M.; DeBarber, A.; Tobias, S. C.; Grandy, D. K.; Scanlan, T. S.; Heldmaier, G. *J. Comp. Physiol. [B].* **2008**, *178*(2), 167–177.
6. Hoefig, C. S.; Kohrle, J.; Brabant, G.; Dixit, K.; Yap, B.; Strasburger, C. J.; Wu, Z. *J. Clin. Endocrinol. Metab.* **2011**, *96*(6), 1864–1872.
7. Regard, J. B.; Kataoka, H.; Cano, D. A.; Camerer, E.; Yin, L.; Zheng, Y. W.; Scanlan, T. S.; Hebrok, M.; Coughlin, S. R. *J. Clin. Invest.* **2007**, *117*(12), 4034–4043.
8. Chiellini, G.; Frascarelli, S.; Ghelardoni, S.; Carnicelli, V.; Tobias, S. C.; DeBarber, A.; Brogioni, S.; Ronca-Testoni, S.; Cerbai, E.; Grandy, D. K.; Scanlan, T. S.; Zucchi, R. *Faseb. J.* **2007**, *21*(7), 1597–1608.
9. DeBarber, A. E.; Geraci, T.; Colasurdo, V. P.; Hackenmueller, S. A.; Scanlan, T. S. *J. Chromatogr. A.* **2008**, *1210*(1), 55–59.
10. Piehl, S.; Heberer, T.; Balizs, G.; Scanlan, T. S.; Kohrle, J. *Rapid Commun. Mass Spectrom.* **2008**, *22*(20), 3286–3296.
11. Gennari, C.; Longari, C.; Ressel, S.; Salom, B.; Mielgo, A. *Eur. J. Org. Chem.* **1998**, 945–959.
12. Bovonsombat, P.; Khanthapura, P.; Krause, M. M.; Leykajarakul, J. *Tetrahedron Lett.* **2008**, *49*, 7008–7011

13. Hart, M. E.; Suchland, K. L.; Miyakawa, M.; Bunzow, J. R.; Grandy, D. K.; Scanlan, T. S. *J. Med. Chem.* **2006**, *49*(3), 1101–1112.
14. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*(19), 2937–2940.
15. Corey, E. J.; Szekely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, *40*, 3529–3532
16. Sterling, K.; Lashof, J. C.; Man, E. B. *J. Clin. Invest.* **1954**, *33*(7), 1031–1035.
17. Braverman, L. E.; Ingbar, S. H.; Sterling, K. *J. Clin. Invest.* **1970**, *49*(5), 855–864.
18. McConnon, J.; Row, V. V.; Volpe, R. *J. Endocrinol.* **1971**, *51*(1), 17–30.
19. Pittman, C. S.; Chambers Jr., J. B.; Read, V. H. *J. Clin. Invest.* **1971**, *50*(6), 1187–1196.
20. Surks, M. I.; Oppenheimer, J. H. *J.. Clin. Endocrinol. Metab.* **1971**, *33*(4), 612–618.
21. Nicoloff, J. T.; Low, J. C.; Dussault, J. H.; Fisher, D. A. *J. Clin. Invest.* **1972**, *51*(3), 473–483.
22. Surks, M. I.; Schadlow, A. R.; Stock, J. M.; Oppenheimer, J. H. *J. Clin. Invest.* **1973**, *52*(4), 805–811.
23. Inada, M.; Kasagi, K.; Kurata, S.; Kazama, Y.; Takayama, H.; Torizuka, K.; Fukase, M.; Soma, T. *J. Clin. Invest.* **1975**, *55*(6), 1337–1348.
24. Demeneix, B. A.; Henderson, N. E. *Gen. Comp. Endocrinol.* **1978**, *35*(1), 86–92.
25. DiStefano III, J. J.; Feng, D. *Endocrinology* **1988**, *123*(5), 2514–2525.
26. Chalmers, J.; Dickson, G.; Elks, J.; Hems, B. *J. Chem. Soc.* **1949**, 3424–2433.
27. Salamonczyk, G. M.; Oza, V. B.; Sih, C. J. *Tetrahedron Lett.* **1997**, *38*(40), 6965–6968.
28. De Meyer, M.; Guerit, N.; Hantson, A. L. Synthesis of thyroid hormones labelled with carbon-13. In *Synthesis and Application of Isotopically Labelled Compounds*; D. C. Dean, C. N. Filer, and K. E. McCarthy (Eds.); Wiley: New York, 2004; Vol. 8.
29. Nagao, H.; Imazu, T.; Hayashi, H.; Takahashi, K.; Minato, K. *J. Endocrinol.* **2011**, *210*(1), 117–123.
30. Sorimachi, K.; Cahnmann, H. J. *Endocrinology* **1977**, *101*(4), 1276–1280.