Tetrahedron 66 (2010) 1955–1962

Contents lists available at ScienceDirect

Tetrahedron

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

Tetrahedron report number 904

Chemistry of thyroxine: an historical perspective and recent progress on its synthesis

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ARTICLE INFO

Article history:
Received 22 November 2009
Available online 4 January 2010

Keywords:
Thyroxine
Sodium salt of levothyroxine
Hypothyroidism
Synthesis
Biomimetic

Contents

1. Introduction

Thyroxine [*O*-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosine, T_4, (**1**), Figure 1] is an essential hormone produced by the thyroid gland, which in humans, is located in the neck just below the larynx. The thyroid gland utilizes iodine, primarily from food (e.g., seafood, bread, and salt) to produce thyroxine (**1**) along with small amounts of 3,5,3′-triiodothyronine (T_3, **2**), in about 99.9:0.1 ratio, respectively. 3,5,3′-Triiodothyronine (**2**) exhibits most of the physiological activity and it is primarily produced by deiodination of thyroxine (**1**) in tissues other than the thyroid gland. T_3 (**2**) has a much shorter half-life, less than two days, when compared to T_4 (**1**).[1] The thyroid hormones (THs), thyroxine (**1**), and 3,5,3′-triiodothyronine (**2**), are the only two endogenous hormones containing iodine atoms. Thyroid hormones regulate a variety of metabolic processes and play a critical role in normal growth and development, carbohydrate metabolism, oxygen consumption, and maturation of the central nervous system and bone. Indeed, these hormones (**1**, **2**) are required for normal function of nearly all tissues.

Disorders related to the thyroid gland are common and remain a major public health issue. In normal humans, the biosynthesis, secretion and circulating level of thyroxine (**1**) is appropriately and maintained. However, if the thyroid gland produces an excessive amount of **1**, the condition is called hyperthyroidism and the symptoms include restlessness, intolerance to heat, sweating, trouble concentrating, rapid heart rate, frequent bowel movements, and weight loss. Lower-than-normal amounts of hormone (**1**) lead

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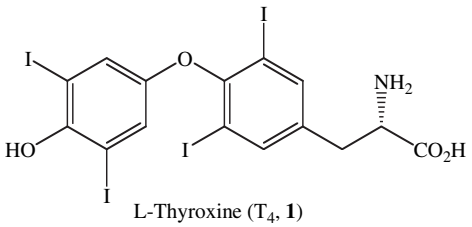
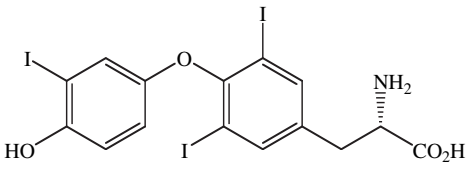
doi:10.1016/j.tet.2009.12.044



L-Thyroxine (T_4, **1**)



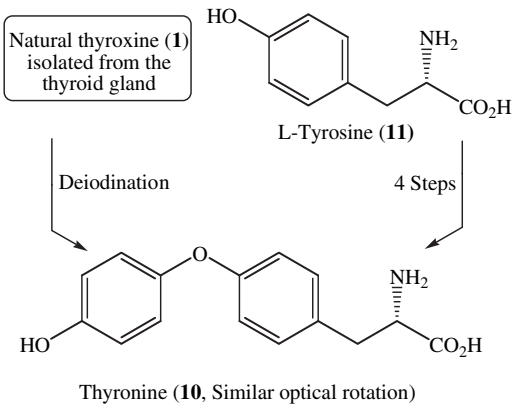
L-3,5,3'-Triiodothyronine (T_3, **2**)

Figure 1. Structure of L-thyroxine (**1**) and L-3,5,3′-triiodothyronine (**2**).

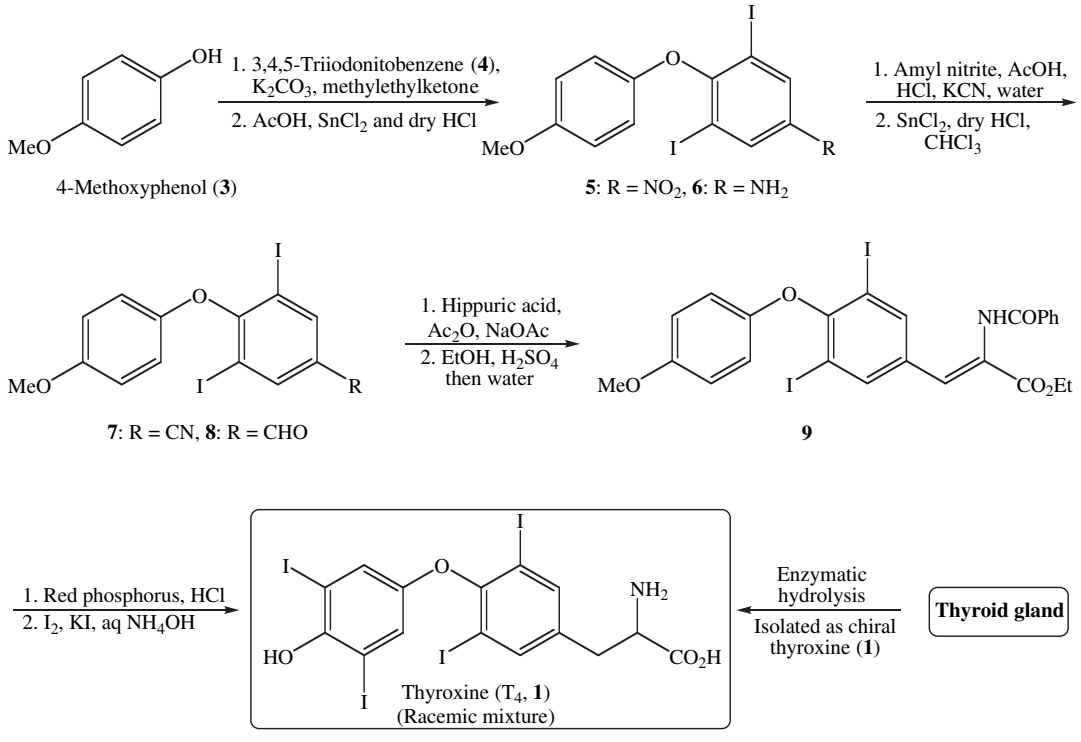
to hypothyroidism, whose common symptoms include fatigue, lethargy, feeling excessively cold, constipation, and weight gain. It is estimated that about 3–5% of the general population has some form of hypothyroidism and symptoms of both disorders vary depending on the level of thyroxine (**1**) present in the blood.[2] Synthetic hormone (Thyroxine, T_4, **1**) is prescribed as its sodium salt, which is commonly called 'levothyroxine sodium,' to supplement the deficiency of natural hormone and alleviate the symptoms in patients suffering from congenital or acquired hypothyroidism.[1,2] In this article, we review the various synthetic approaches developed for preparation of thyroxine (**1**), along with its biosynthesis and physicochemical properties.

2. Biosynthesis of thyroxine

Although existence of the thyroid gland has been known for hundreds of years, the first report linking cretinism and hypothyroidism to the destruction of this gland was published in 1888 by the Clinical Society of London.[3] The existence of hormone containing iodine as a normal constituent of the thyroid gland was foretold by Baumann in 1895,[4] but it was Kendall[5] in 1919, who first isolated the hormone via alkaline hydrolysis of hog thyroid glands and named the compound, 'Thyroxine'. Kendall successfully isolated 7 g of crystalline thyroxine and provided, incorrectly, the empirical formula $C_{11}H_{10}O_3NI_3$.[5c] Later, Harington and co-workers[6] employed an enzymatic hydrolysis to liberate the thyroxine from hog thyroid glands, and correctly reported its empirical formula to be $C_{15}H_{11}O_4NI_4$. They also reported the correct structure of the isolated thyroxine (**1**, Fig. 1) based on extensive analysis and subsequently an independent chemical synthesis [Scheme 1; see the 'Synthesis of thyroxine' section below for more details]. Similar structural elucidation results on thyroxine were also obtained by Foster et al.,[7] who employed an acid hydrolysis following a brief enzymatic digestion of the hog thyroid gland. The stereochemistry of this α-amino acid was designated to be L-series by Canzanelli et al.,[8] who found similar optical rotations for two L-thyronine (**10**) samples, which were prepared (Scheme 2) by conversion of natural



Scheme 2. Assignment of stereochemistry for L-thyroxine (**1**).



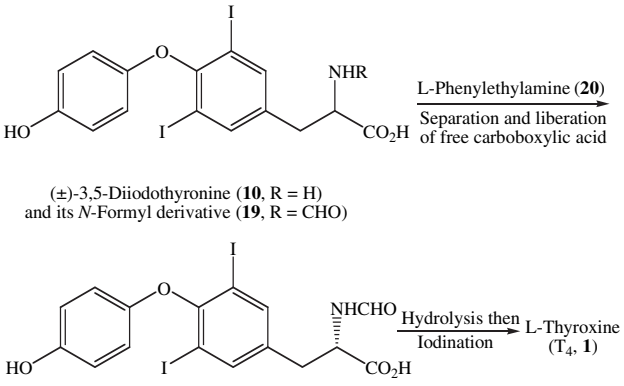
Scheme 1. Structural elucidation of thyroxine (**1**) via isolation from thyroid gland and comparison to the material (**1**) produced by total synthesis.

thyroxine (**1**) isolated from thyroid gland, and synthesized from L-tyrosine (**11**).

Biosynthesis of thyroxine has been the subject of continued investigation for decades, and the precise mechanism of this interesting biochemical process is not yet fully understood. The coupling of two 3,5-diodotyrosine (DIT, **12** in Scheme 3) molecules to form thyroxine (**1**) was first suggested as early as 1927 by Harington and Barger.[6b] Subsequently, von Mutzenbecher[9] in 1939 reported that the incubation of a basic solution of DIT (**12**) produced a small amount of thyroxine (**1**). Two possible mechanisms, intra- and intermolecular coupling processes, were subsequently proposed for the in vivo formation of thyroxine in the thyroid gland, which is catalyzed by the enzyme, thyroid peroxidase (TPO).[10,11] It was initially proposed that free DIT (**12**) was involved in this conversion,[12a] but, later studies indicated that peptide linked DIT within thyroglobulin (TGB) is more likely the precursor of thyroxine (**1**).[12] It is generally believed that thyroxine (**1**) is formed via oxidative free radical coupling[11] of the phenol groups from two units of DIT (**12**) with the loss of a three-carbon unit, which was later reported by Johnson and Tewkesbury,[11a] to be pyruvic acid (**13**, Scheme 3). Subsequently, other groups reported identification of the three-carbon unit, which is lost in the transformation of DIT into thyroxine as alanine (**14**),[18] serine (**15**),[13a] hydroxypyruvic acid (**16**),[13b] and dehydroalanine (**17**).[14] For some time, dehydroalanine (**17**) was favored as the lost three-carbon unit in the biosynthesis of thyroxine (**1**). However, Sih and co-workers[15] recently showed (Scheme 3) that the three-carbon unit lost in this coupling process is in fact aminomelonic acid semialdehyde (**18**) and further suggested that both intra and intermolecular mechanisms could be operating in the biosynthesis of thyroid hormones.

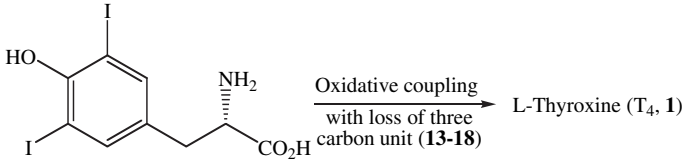
3. Synthesis of thyroxine

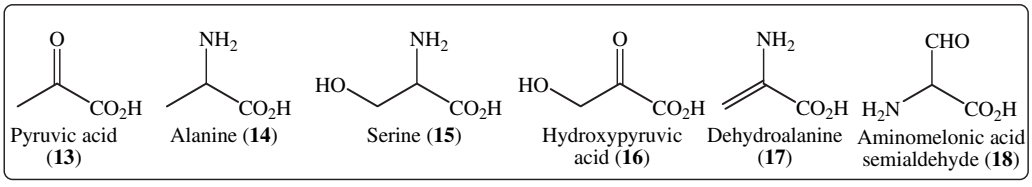
The first synthesis of (±)-thyroxine (**1**), was achieved by Harington and Barger[6b] in 1927 (Scheme 1) in eight steps starting from 4-methoxyphenol (**3**). The synthesis began from 4-methoxyphenol (**3**), which was coupled with 3,4,5-triiodonitrobenzene (**4**) and subsequently reduced the nitro group to give the corresponding aniline derivative (**6**). The amine group in **6** was then converted to a nitrile (**7**) via diazotization, which up on reduction with anhydrous stannous chloride gave 3,5-diiodo-4-(4′-methoxyphenoxy) benzaldehyde (**8**). The arylaldehyde derivative (**8**) was further reacted with hippuric acid in the presence of fused sodium acetate and further treated with sulfuric acid in ethanol to afford cinnamic ester derivative (**9**). The olefin in ester (**9**) was reduced using red phosphorous in hydrochloric acid, which also hydrolyzed the benzamide and ethyl ester groups. The resulting product was treated with iodine and potassium iodide in aqueous ammonium hydroxide solution to afford (±)-thyroxine (**1**). This synthesis, as discussed earlier, gave racemic hormone for comparison with the material isolated from thyroid gland and ultimately paved the way for confirmation of the structure of thyroxine. Harington[16] also prepared L-thyroxine (**1**) via optical resolution (Scheme 4) starting from (±)-3,5-diiodothyronine (**10**). The (±)-3,5-diiodothyronine (**10**), which was synthesized as shown in Scheme 1, was converted to the corresponding *N*-formyl derivative (**19**) by treating with formic acid and then resolved using L-1-phenylethylamine (**20**) to give the corresponding 3,5-diiodo-L-thyronine derivative (**21**). Hydrolysis of **21** and subsequent iodination afforded the L-thyroxine (**1**) in its natural form thus again confirming the stereochemistry of the lone chiral center.



Scheme 4. Preparation of L-thyroxine (**1**) via resolution.

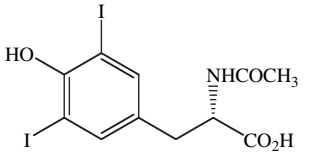
Biomimetic synthesis of L-thyroxine starting from 3,5-diiodo-L-tyrosine (DIT, **12**), as initially observed by von Mutzenbecher,[9] continued to attract much attention[17] in the subsequent period (Scheme 3). Harington and Pitt-Rivers[17b] achieved a 4% yield of L-thyroxine (**1**) via oxidation of DIT (**12**) using hydrogen peroxide. A variation of this biomimetic synthesis (Scheme 5) was later reported by Pitt-Rivers,[18] which involved aerobic incubation of *N*-acetyl derivative of 3,5-diiodo-L-tyrosine (*N*-Ac-DIT **22**) in 1 N sodium hydroxide solution followed by hydrolysis to afford L-thyroxine (**1**) in 4.7% yield. At about the same time, Turner and Reineke[19] reported that using manganese oxide (Mn_3O_4) catalyst and oxygen for the coupling process of DIT (**12**) produced L-thyroxine in





Scheme 3. Oxidative coupling of two molecules of 3,5-diiodotyrosine (**12**) to give thyroxine (**1**) with the loss of three-carbon-units (**13**–**18**).

2.8% yield. Later, it was found that the coupling of *N*-Ac-DIT (**22**) in borate buffer using manganese sulfate ($MnSO_4$) and oxygen, significantly improved the yield.[20] Efforts have continued with different variations in this interesting approach (Scheme 5) to further improve the purity and yield.[21]



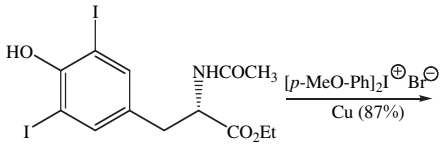
N-Acetyl-3,5-diiodo-L-tyrosine (**22**)

Biomimetic oxidative coupling reaction → L-Thyroxine (T_4, **1**)

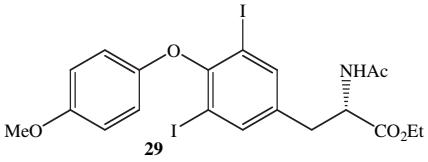
Scheme 5. An improved biomimetic synthesis of L-thyroxine (**1**) from *N*-acetyl-L-3,5-diiodotyrosine (**22**).

A different approach for the synthesis of L-thyroxine (**1**) was reported by Chalmers and co-workers[22a–c] who started from L-tyrosine (**11**, Scheme 6), and isolated 29 g of hormone in its natural 'L' form. In this synthesis, L-tyrosine (**11**) was first nitrated using a mixture of sulfuric acid and nitric acid to produce the corresponding 3,5-dinitrotyrosine (**23**) in 87% yield. The amine and carboxylic acid groups in **23** were protected and the product was tosylated and coupled with 4-methoxyphenol (**26**) to afford dinitro-thyronine derivative (**27**) in 82% yield. Reduction of both nitro groups followed by diazotization of the resulting aniline groups and further treatment with iodine gave L-diiodothyronine derivative (**29**) in 82% yield. Subsequent hydrolysis of **29** with hydroiodic acid followed by iodination using iodine and potassium iodide gave L-thyroxine (**1**) in 89% yield. Utilizing L-tyrosine (**11**), as a chiral starting material, Chalmers et al.,[22a] achieved about 25% overall yield of L-thyroxine (**1**) without any appreciable degree of racemization. This group also prepared the L-thyroxine (**1**) sodium salt and determined that it crystallizes as hydrate, and contains five molecules of water. As described, the sodium salt of L-thyroxine (**1**) pentahydrate is still used as an active pharmaceutical ingredient (API) for treatment of hypothyroidism. An improved version of the Chalmers method was recently described for the preparation of L-thyroxine (**1**) on a large scale.[22d]

Hillmann[23a,b] in 1956 and more recently others[23c,d] have reported a different approach (Scheme 7) for the assembly of the biphenyl–ether system present in L-thyroxine (**1**). *N*-Acetyl 3,5-diiodo-L-tyrosine ethyl ester (**31**) was coupled with bis-(4-



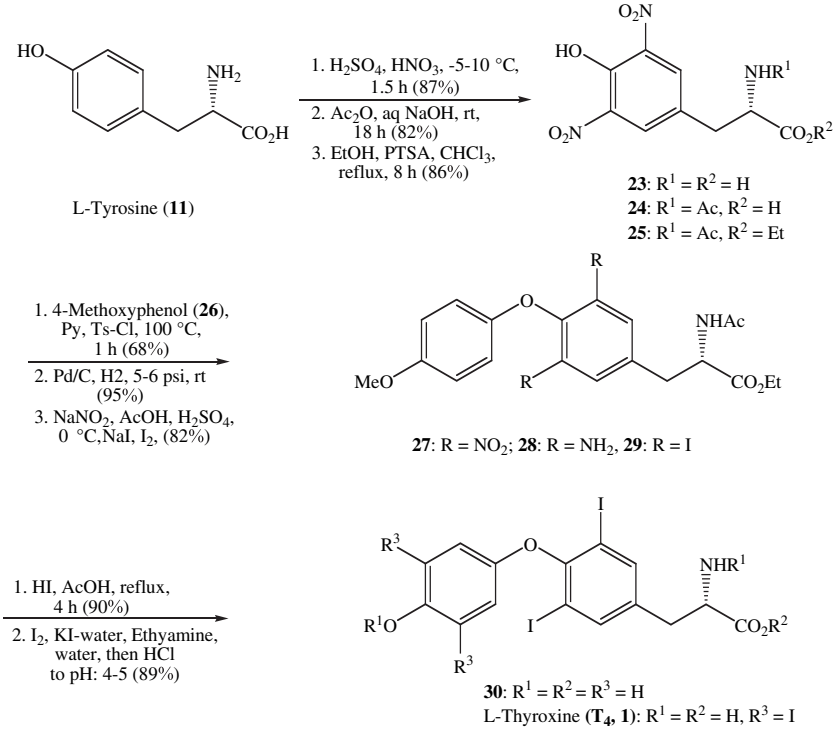
N-Acetyl-3,5-diiodo-L-tyrosine ethyl ester (**31**)



29

HI, HBr, AcOH (84%) then I_2 (92%) → L-Thyroxine (T_4, **1**)

Scheme 7. Synthesis of L-thyroxine via phenylation of *N*-acetyl-3,5-diiodo-L-Tyrosine ethyl ester (**31**).

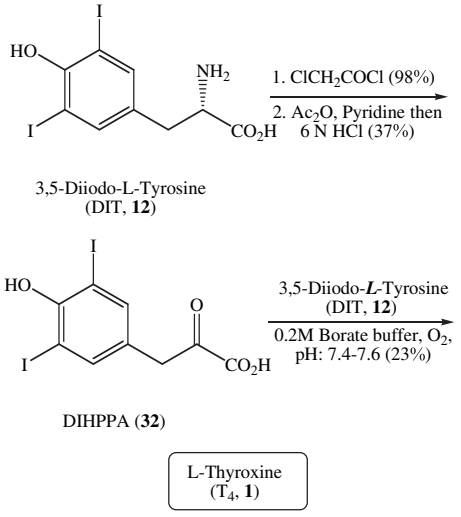


L-Tyrosine (**11**)

Scheme 6. Synthesis of L-thyroxine (**1**) from L-Tyrosine (**11**).

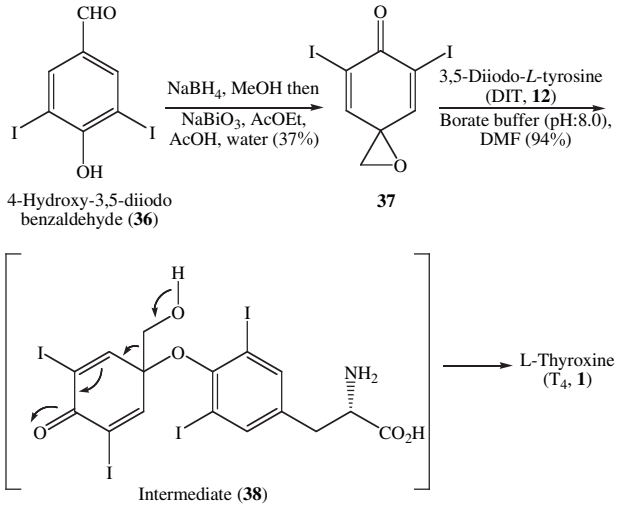
methoxyphenyl)iodonium bromide using copper catalyst to afford the phenyl ether derivative (**29**) in 87% yield. All three protective groups in **29** (acetamide, methyl ether, ethyl ester) were cleaved using a mixture of hydriodic acid and hydrobromic acid, and the subsequent iodination using iodine, as described in Scheme 6, gave L-thyroxine (**1**) in 92% yield.

A different version of the biomimetic synthesis of L-thyroxine (**1**, Scheme 8),[24] involves an oxidative coupling of 3,5-diiodo-4-hydroxyphenylpyruvic acid (DIHPPA, **32**) with 3,5-diodo-L-tyrosine (DIT, **12**). The crucial coupling reaction was carried out in borate buffer by bubbling oxygen and maintaining pH 7.4–7.6 to afford L-thyroxine (**1**) in 23% yield.[24a,12b,c] It was later reported that by irradiation of DIHPPA and DIT in borate buffer or in the presence of cupric acetate produced L-thyroxine (**1**).[24b,c] More recently, this approach has been further improved by using water–acetone mixture as a solvent during the coupling reaction to give a 47% yield.[24d]



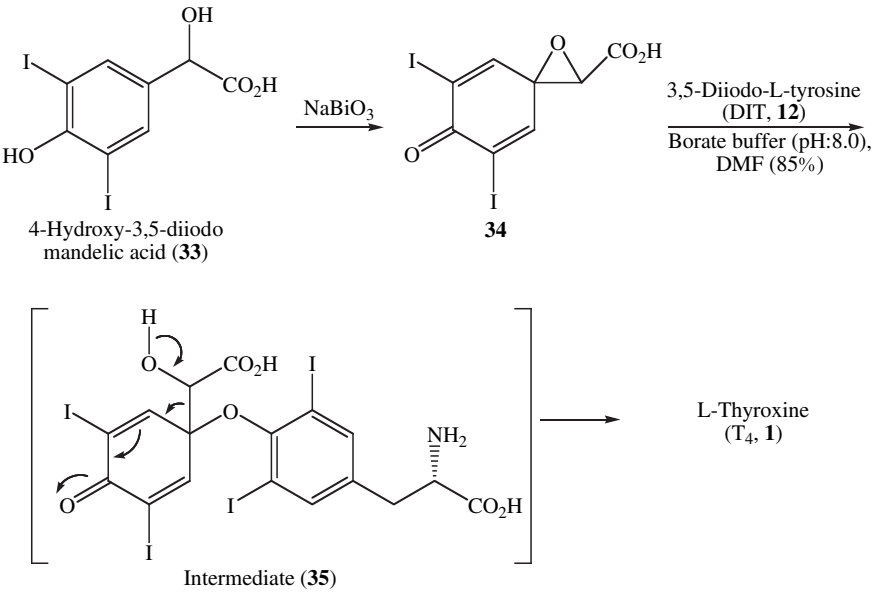
Scheme 8. A biomimetic synthesis of L-thyroxine (**1**) via intramolecular coupling.

Sih and co-workers[25] described the synthesis of L-thyroxine (**1**, Scheme 9) during their mechanistic studies to identify the key intermediate in the biomimetic coupling of DIHPPA (**32**) with DIT (**12**). In this study, they oxidized 4-hydroxy-3,5-diiodomandelic (**33**) with sodium bismuthate in an ethyl acetate–acetic acid–water medium to form the quinol-epoxide **34**, which was then treated with DIT (**12**) in borate buffer at pH 8.0 to afford L-thyroxine (**1**) in 85% yield via the intermediate (**35**). Based on these studies, the authors have concluded that quinol-epoxide **34** is one of the intermediates formed during the biomimetic synthesis of L-thyroxine (**1**) involving the coupling of DIHPPA (**32**) and DIT (**12**). Subsequently, Sih and co-workers[26] also described a concise synthesis of L-thyroxine (**1**, Scheme 10) starting from 4-hydroxy-3,5-diiodobenzaldehyde (**36**). This aldehyde **36** was first reduced with sodium borohydride to the corresponding alcohol followed by oxidation with sodium bismuthate in a mixture of ethyl acetate, acetic acid and water (10:8:1 ratio by volume) to afford the epoxide (**37**) in 37% yield. The epoxide (**37**) was then reacted with DIT (**12**) in borate buffer at pH 8.0 to afford L-thyroxine (**1**) in excellent yield (94%) via the intermediate (**38**) as describe in Scheme 10.

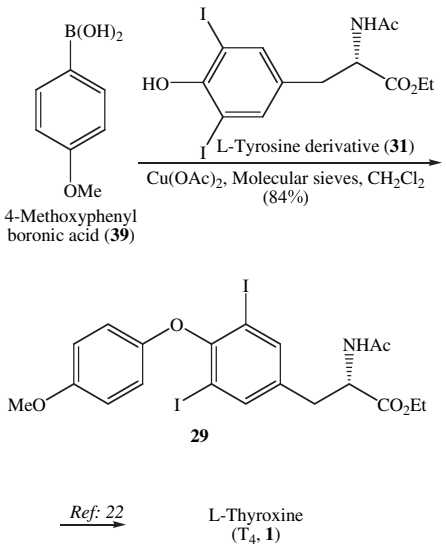


Scheme 10. Synthesis of L-thyroxine (**1**) from 4-hydroxy-3,5-diiodobenzaldehyde (**36**).

Evans and co-workers[27] later described an expedient formal synthesis of L-thyroxine (**1**, Scheme 11) via copper (II)-promoted coupling of an arylboronic acid derivative (**39**) with a phenol group in **31**. The reaction of 4-methoxy-phenylboronic acid (**39**) with *N*-acetyl-3,5-diiodo-L-tyrosine (**31**) in the presence of cupric



Scheme 9. Synthesis of L-thyroxine (**1**) from 4-hydroxy-3,5-diiodomandelic acid (**31**).



Scheme 11. Synthesis of L-thyroxine (**1**) from 4-methoxy-phenylboronic acid (**38**).

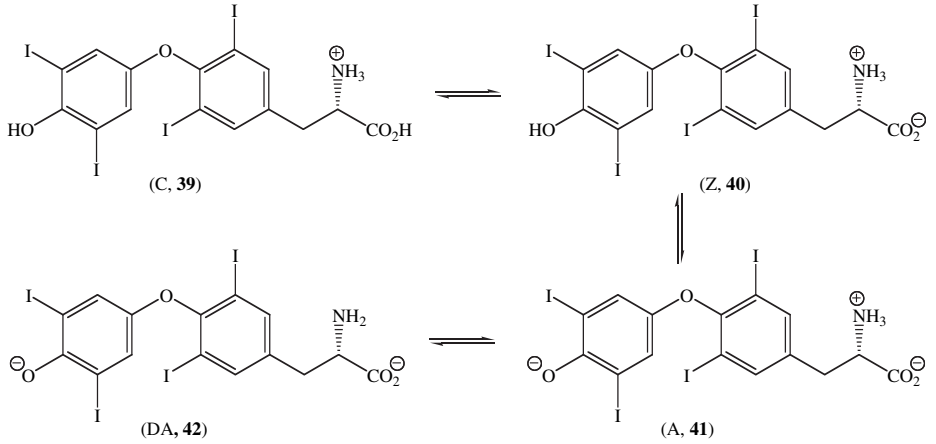
acetate in dichloromethane solvent afforded the key intermediate, L-diiodothyronine derivative (**29**) in 84% yield. The intermediate **29** was previously converted in the literature to L-thyroxine (**1**).[22]

Although, several approaches have been developed over the years for the preparation of synthetic hormone, L-thyroxine (T_4, **1**), two methods stands out for novelty, efficiency and their amenability for large scale adaptation: (1) Biomimetic approach, which was originally proposed by Harington and Barger.[6b] and first reported by von Mutzenbecher,[9] and (2) Chemical synthesis utilizing L-tyrosine (**11**) as a chiral template, which was reported by Chalmers and co-workers.[22a–c] One of the crucial transformations in the synthesis of this important hormone is the construction of biphenyl–ether linkage and with the advancement of newer methodologies, it is our belief that more elegant synthetic or enzymatic approaches can be expected in the future for synthesis of L-thyroxine (T_4, **1**).

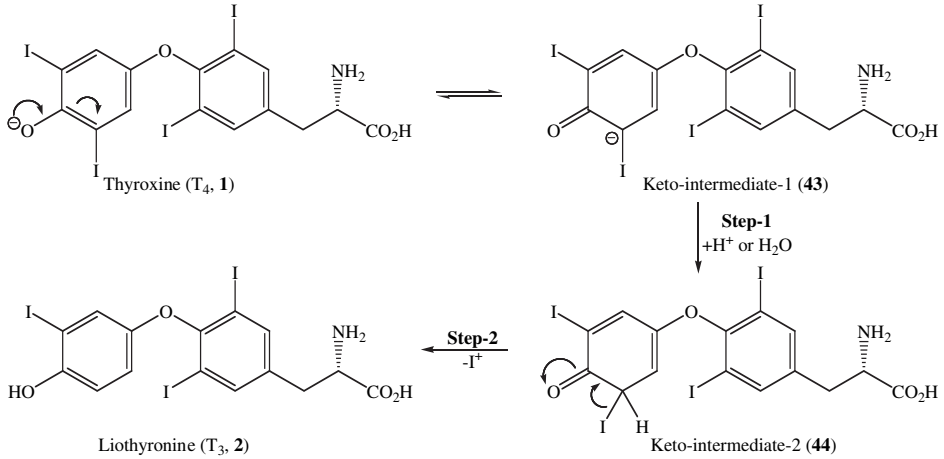
4. Deiodination of thyroxine

L-Thyroxine (**1**) has three ionizable moieties and can exist as the cation (C, **39**, Scheme 12), zwitterion (Z, **40**), anion (A, **41**), and/or dianion (DA, **42**) depending on the pH of the solution.[28] The pK_a values for the three functional groups are: 2.40 for the carboxyl group, 6.87 for the phenolic OH group and 10.1 for the amino group.[28b] The solubility and pH profile shows a break around pH 10, thus indicating a saturation point of the solubility of A, and as the pH increases, more DA is formed. The aqueous solubility of L-thyroxine sodium salt decreases as pH increases from pH 1 to 3, remains constant between 3–7 and significantly increases above pH ~7.

L-Thyroxine (**1**) under goes deiodination (Scheme 13) to produce 3,5,3′-triiodothyronine (T_3, **2**). Deiodination occurs mainly in



Scheme 12. Ionization of L-Thyroxine (**1**) in solution at different pH.



Scheme 13. Deiodination of L-thyroxine (**1**) and formation of 3,5,3′-triiodothyronine (T_3, **2**).

solution and the rate of the degradation increases as the medium becomes more acidic. Won studied the kinetics[28a] of the deiodination of L-thyroxine sodium (**1**) and the role of temperature in aqueous solutions over the pH range of 1–12. Among the four iodines, those at 3′ and 5′-positions in ring-B are more labile than those of 3 and 5-positions in ring-A. The phenoxide ion moiety gives 3′ and 5′-carbons cationic character by resonance, so that these carbons are favored for electrophilic attack by proton or other electrophiles, as shown in Scheme 13.

The secretion of L-thyroxine (**1**) is regulated by hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the release of thyrotropin-stimulating hormone (TSH) from the pituitary gland, which in turn stimulates the synthesis/secretion of L-thyroxine (T_4, **1**) along with small amounts of 3,5,3′-triiodothyronine (T_3, **2**). Circulating T_3 and T_4 levels exert a feed back effect on both TRH and TSH secretion, when the levels of hormones increase, the secretion of TRH and TSH decreases and when the hormones levels decrease, the secretion of TRH and TSH increases.[1] Liver is the major site of degradation for both T_4 and T_3 and they are metabolized via conjugation to glucuronides and sulfates, and eventually excreted in urine. A portion of the conjugated hormone also reaches the colon and is eliminated in the stool.[1]

5. Conclusion

We have reviewed the chemistry of thyroxine (**1**) and a variety of synthetic methods developed for the preparation of this important hormone. Understanding of the chemistry of thyroxine and its in vivo formation has evolved considerably since its initial discovery over a century ago. Today, this important hormone is commercially produced on a multi-kilo scale and marketed as levothyroxine sodium for the treatment of hypothyroidism. An increased awareness of the serious maladies associated with the deficiency of this hormone, coupled with rapid and advanced screening assays in the diagnosis and therapeutic monitoring of patients to manage the disease, will certainly help to address the public health issue of hypothyroidism.

Acknowledgements

We thank Dr. Martin Babcock, Director of API Chemistry for support, Dr. Liam Feely, Vice President, Manufacturing Science & Technology for suggestions, Dr. Tom Paulus for helpful discussion and Dr. Steven Springer-Wilson for critical proof reading and help in preparing the article.

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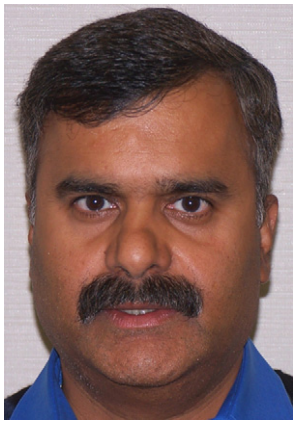
Biographical sketch



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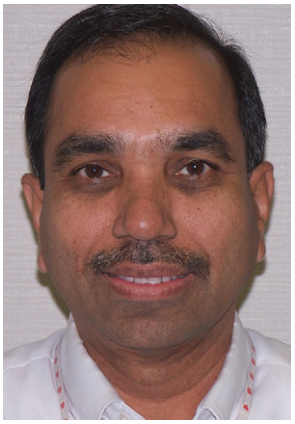

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