Iodothyronine Deiodinase Mimics. Deiodination of *o,o′*-Diiodophenols by Selenium and Tellurium Reagents

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To better understand, and in the extension mimic, the action of the three selenium-containing iodothyronine deiodinases, *o,o′*-diiodophenols were reacted under acidic conditions with sodium hydrogen telluride, benzenetellurol, sodium hydrogen selenide, or benzeneselenol and under basic conditions with the corresponding deprotonated reagents. Sodium hydrogen telluride was found to selectively remove one iodine from a variety of 4-substituted *o,o′*-diiodophenols, including a protected form of thyroxine (**T_4**). Thus, it mimics the D1 variety of the iodothyronine deiodinases. Sodium telluride was a more reactive deiodinating agent toward *o,o′*-diiodophenols, often causing removal of both halogens. Benzenetellurol and sodium benzenetellurolate sometimes showed useful selectivity for monodeiodination. However, the products were often contaminated by small amounts of organotellurium compounds. Sodium hydrogen selenide, sodium selenide, benzeneselenol, and sodium benzeneselenolate were essentially unreactive toward *o,o′*-diiodophenols. To gain more insight into thyroxine inner-ring deiodination, substituted 2,6-diiodophenyl methyl ethers were treated with some of the chalcogen reagents. Reactivity and selectivity for monodeiodination varied considerably depending on the substituents attached to the aromatic nucleus. In general, it was possible to find reagents that could bring about the selective mono- or dideiodination of these substrates.

Introduction

Since the discovery that selenium is an essential microelement to man, the family of selenoenzymes has grown slowly but steadily.[1] The number of selenoproteins present in mammalian cells has been estimated to something between 20 and 100.[2] However, to date, the structure and function of less than a dozen of these are known with some certainty. Glutathione peroxidases (GPx)[3]—the best characterized subclass of selenoproteins—play an important role in the antioxidant defense of the organism, serving to reduce hydrogen peroxide and organic hydroperoxides using glutathione as the stoichiometric reducing agent. The four varieties of the enzyme known at present serve their protective function in cells (GSHPx-1),[4] plasma (GSHPx-P),[5] membranes (PHGPX),[6] and the gastrointestinal tract (GSHPx-GI).[7]

Thioredoxin reductase is a selenium-containing flavoprotein that catalyses the NADPH-dependent reduction of thioredoxin and other protein disulfides.[8] Thioredoxin has recently been found to exert specific control of a number of transcription factors,[9] to modulate their DNA-binding, and thus to regulate gene transcription.

In 1990 it was shown that one variety of the iodothyronine deiodinase enzymes contains a selenocysteine residue at the active site.[10] Recent molecular cloning studies have indicated that the other two varieties also contain selenocysteine.[11] These enzymes catalyze the interconversion of active and inactive forms of thyroid hormones.[12] Thyroid hormones are essential for the normal differentiation, growth, and integration of metabolic functions in most cells of higher vertebrates—including man. The follicular cells of the thyroid provide the sole source of thyroxin (**T_4**). However, this is only thought to be a prohormone requiring outer-ring (5′) deiodination to provide the active hormone **T_3** (Scheme 1). This transformation is brought about by the D1 and D2 varieties of the iodothyronine deiodinases. The D3 variety is known to cause inner-ring (5) deiodination of **T_4** to give reverse **T_3** (**r-T_3**), an inactive form of the hormone. Both **T_3** and **r-T_3** then undergo further monodeiodination, the former in the inner ring and the latter in the outer one. These processes (leading to **T_2**; Scheme 1) are also catalyzed by the three iodothyronine deiodinases.

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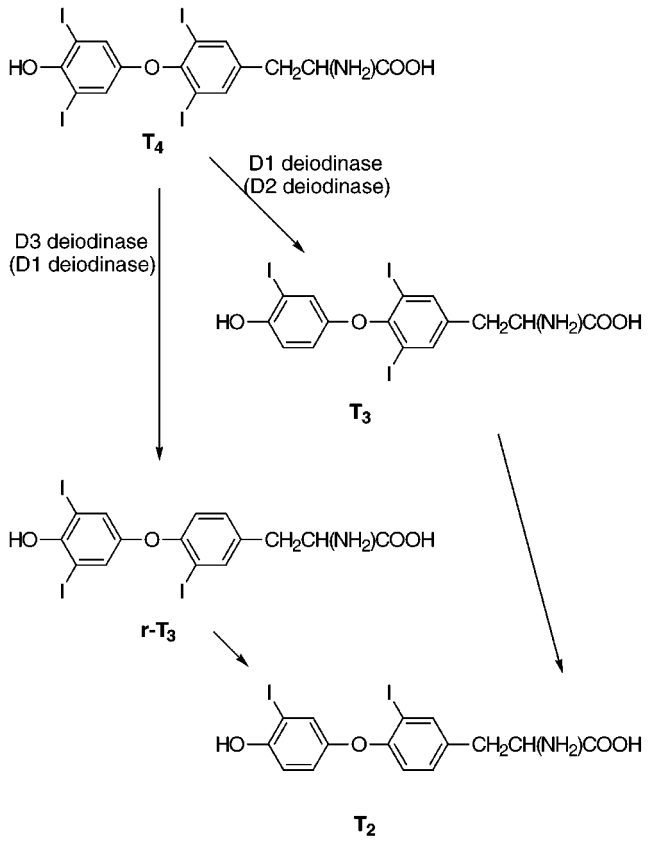
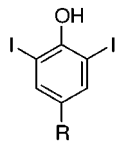
Scheme 1



A few years ago Reglinski and co-workers reported limited success in their attempts to mimic the action of the iodothyronine deiodinases.[13] These investigators treated 3,5-diiodotyrosine (**1a**), 4-amino-2,6-diiodophenol

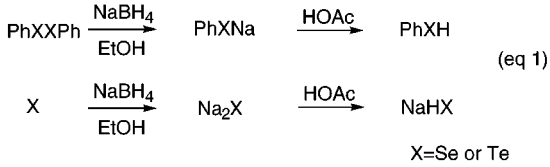


1a R=$CH_2CH(NH_2)COOH$
1b R=NH_2
1c R=NO_2

(**1b**), and 4-nitro-2,6-diiodophenol (**1c**) with benzeneselenol and potassium carbonate in refluxing ethanol for 12 h. However, only for the 4-nitro derivative (**1c**) did they report successful monodeiodination. Some time ago we tried to repeat this experiment. In our hands, compound **1c** resisted deiodination under the conditions given and only starting material was recovered. We therefore decided to evaluate the deiodinating capacity of a series of even more strongly nucleophilic selenium and tellurium reagents.

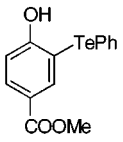
Results

Diphenyl diselenide and diphenyl ditelluride are readily reduced by sodium borohydride at ambient temperature in ethanol to give sodium benzeneselenolate (PhSeNa) and sodium benzenetellurolate (PhTeNa), respectively, complexed to triethylborate. Upon acidification the corresponding acids—benzeneselenol (PhSeH) and benzenetellurol (PhTeH)—are formed. Similarly, elemental selenium and elemental tellurium are reduced in ethanol to give sodium selenide (Na_2Se) and sodium telluride (Na_2Te), respectively, and, following addition of acetic acid, sodium hydrogen selenide (NaHSe) and sodium hydrogen telluride (NaHTe) (eq 1). The synthetic utility



of reagents of this type has previously been demonstrated in reductions of α,β-unsaturated carbonyl compounds, α,β-epoxy ketones, imines, *N*-oxides, and nitrones, in debromination of *vic*- and *gem*-dibromides, and in removal of α-substituents of carbonyl compounds.[14] Depending on the conditions, aromatic nitro compounds were reduced to azo or azoxy compounds, *N*-arylhydroxylamines, or anilines. This reactivity toward the nitro group made us select compounds other than **1c** for the initial deiodination experiments. The chalcogen reagents used in this study are extremely sensitive to air oxidation. Also, during acidification with acetic acid, small amounts of oxidized product (selenium/tellurium or diphenyldichalcogenides) were always formed. To compensate for these losses of reagent, the various diiodophenols and derivatives thereof were routinely treated with a 5-fold excess of reducing agent.

When refluxed in ethanol for 4 h with a 5-fold excess of NaHTe, methyl 3,5-diiodo-4-hydroxybenzoate (**2a**) was selectively monodeiodinated to give compound **3a** in high yield (99%) as shown in Table 1. Under similar conditions, Na_2Te caused only a 44% conversion of starting material. PhTeH (5 equiv) converted diiodophenol **2a** completely to products immediately at ambient temperature. In addition to monoiodophenol **3a** (41%), the corresponding organotellurium compound **5** was also isolated in 7% yield. Trace amounts of the iodo(phenyltelluro)phenol **6** and the corresponding bis(phenyltelluro)-substituted compound were also formed. However, neither of them could be isolated in pure form. Compound **2a** was essentially unreactive toward PhSeH, PhSeNa, PhTeNa, NaHSe, and Na_2Se.



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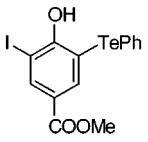

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Diiodophenol **2b**, carrying a strongly electron withdrawing cyano group in the 4-position, was also deiodinated by treatment with NaHTe. To improve the selectivity for monodeiodination, only a 3-fold excess of

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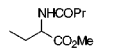
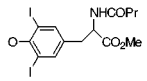
Table 1. Deiodination of Diiodophenols 2 by Tellurium Reagents

Diiodophenol	R	Reagent[a]	Total isolated yield of products (%)	Product composition (%)		
						unreacted **2**
2a	CO_2Me	NaHTe	99	**3a** (100)	-	-
		Na_2Te	90	**3a** (39)	**4a** (5)	**2a** (56)
2b	CN	NaHTe[b]	70	**3b** (90)	**4b** (10)	-
2c	Me	NaHTe	74	**3c** (52)	-	**2c** (48)
		Na_2Te	83	**3c** (74)	**4c** (16)	**2c** (10)
2d	Br	NaHTe	89	**3d** (97)	**4d** (3)	-
		Na_2Te[c]	76	-	**4d** (100)	-
2e	OPh[d]	NaHTe	83	**3e** (88)	-	**2e** (12)
		Na_2Te	92	**3e** (11)	**4e** (89)	-
2f		NaHTe	98	**3f** (73)	-	**2f** (27)
2g		NaHTe[e]	89	**3g** (60)	(14)[g]	**2g** (26)
		NaHTe[f]	90	**3g** (45)	(5)[g]	**2g** (50)
		Na_2Te	81	-	**4g** (95)[h]	-

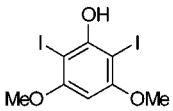
[a] NaHTe or Na_2Te (5 equiv), EtOH, reflux 4 h; see Experimental Section. [b] NaHTe (3 equiv). [c] Reaction time 6 h. [d] Containing 12% of the corresponding monoiodophenol. [e] 5 h at 60 °C using 5 equiv of NaHTe. [f] 4 h at 50 °C using 4 equiv of NaHTe. [g] Iodothyronine derivatives of unknown structure. [h] Completely deiodinated and transesterified material (*N*-butyrylthyronine ethyl ester). The remaining 5% is a monoiodo derivative of unknown structure.

reducing agent was used (62% isolated yield of compound **3b**). However, despite prolonged heating with a 10-fold excess of reagent, the conversion to monoiodophenol was only ca. 50% with the corresponding 4-methyl derivative **2c**. Since much elemental tellurium was deposited in the reflux condenser, the tellurium reagent was probably slowly driven out of solution as H_2Te. Na_2Te turned out to be a better reagent for the monodeiodination of compound **2c**. 2,6-Diiodo-4-bromophenol (**2d**) was selectively monodeiodinated using NaHTe (80% isolated yield) and converted to iodine-free phenol **4d** by Na_2Te (76% isolated yield) (Table 1). The corresponding selenium reagents were unreactive under similar conditions.

Due to its resemblance to thyroxine (**T_4**), 2,6-diiodo-4-phenoxyphenol (**2e**) was considered as an interesting model compound. This material was prepared by iodination of 4-phenoxyphenol (**4e**) in methanol containing potassium carbonate. According to NMR analysis, the crude product was a mixture of the desired diiodo compound **2e** (88%) and the corresponding monoiodophenol **3e**. However, all attempts to purify the major product on the column led to decomposition with release of iodine. The crude material was therefore used for the deiodination experiments. NaHTe caused selective monodeiodination whereas Na_2Te afforded the iodine-free phenol as the major product (Table 1).

Due to their poor solubility, 3,5-diiodotyrosine (**1a**) and thyroxine (**T_4**) were unsuitable for the usual deiodination conditions. They were therefore converted to the corresponding *N*-butyryl methyl ester derivatives **2f** and **2g** in 67% and 87% yields, respectively, by treatment with 2,2-dimethoxypropane and then with butyric anhydride. *N*-Butyryl-3,5-diiodotyrosine methyl ester (**2f**) was cleanly monodeiodinated by NaHTe with fair (73%) conversion (Table 1) and isolated yield (61%). Thyroxine derivative **2g** was more troublesome. By using 5 equiv of NaHTe at 60 °C, the target **T_3**-derivative **3g** was obtained as the main product contaminated by the starting material and some other further deiodinated products (the same components were also formed in ca. 20% yield by treatment of the authentic **T_3** derivative **3g** with NaHTe). The selectivity toward 5′-monodeiodination was slightly improved by running the reaction at lower temperature (50 °C) using 4 equiv of the tellurium reagent (50% conversion). The completely deiodinated and transesterified (ethyl ester) compound **4g** was formed by treatment of compound **2g** with Na_2Te in ethanol.

2,6-Diiodo-3,5-dimethoxyphenol (**7**) turned out to be one of the most reactive compounds investigated. NaHTe, Na_2Te, NaHSe, Na_2Se, and, surprisingly, Na_2S caused complete deiodination of this material, affording phenol **8** in essentially quantitative yield. PhTeH was the



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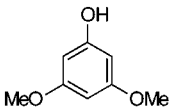

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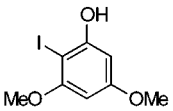

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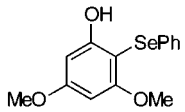
reagent of choice for the preparation of the monoiodo compound **9** (53% isolated yield). Interestingly, when treated with PhSeH, diiodophenol **7** afforded deiodination/substitution product **10** together with the fully deiodinated material **8** (2/1 ratio). Trace amounts of another substitution product **11** were also isolated.



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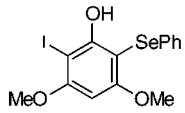

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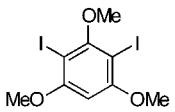
As mentioned above, thyroxine (**T_4**) can also undergo inner-ring deiodination (Scheme 1). We therefore investigated the deiodination of methyl ethers of diiodophenols **2a**, **2c**, and **7** as a simple model for this process. 2,4-Diiodo-1,3,5-trimethoxybenzene (**12**) was fully deiodinated by NaHTe and Na_2Te, affording 1,3,5-trimethoxybenzene **13** whereas PhTeH, PhTeNa, and Na_2Se afforded mainly monoiodo derivative **14** (81% isolated yield with PhTeNa). Less active diiodocresol ether **15** was mono-



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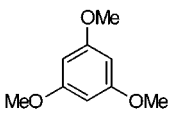

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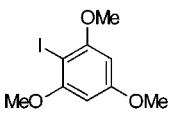

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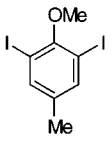

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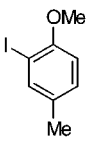

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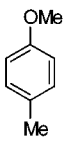

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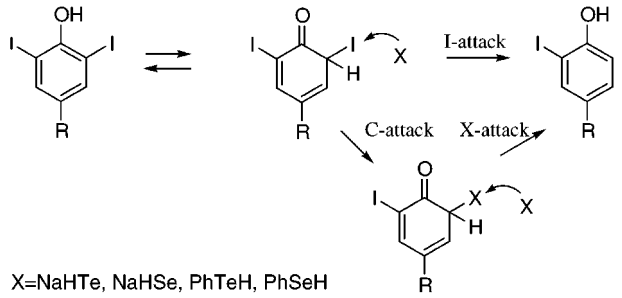
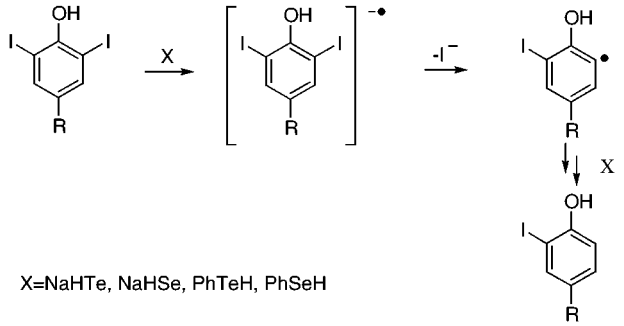
deiodinated with low conversion (18%) by NaHTe. The more powerful reducing agent Na_2Te afforded monoiodo derivative **16** as the major product together with a small amount of the iodine free ether **17**. In the case of methyl

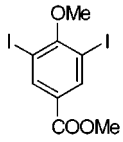
Scheme 2



Scheme 3



3,5-diiodo-4-methoxybenzoate (**18**), Na_2Te caused complete deiodination and essentially complete (90%) transesterification to give compound **19** as the major product. NaHTe and Na_2Se showed 100% selectivity for monodeiodination, the former reagent providing the methyl ester **20** (76% isolated yield), the latter affording the ethyl ester **21** as the major product (81% isolated yield of a 9/1 mixture of ethyl and methyl esters).



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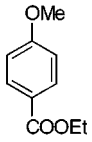

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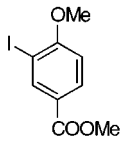

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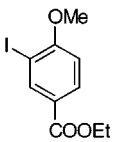

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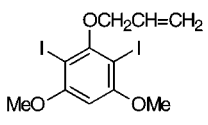
Discussion

In the late 1960s, Hartmann and co-workers had already suggested that deiodination of *o,o′*-diiodophenols could involve nucleophilic attack on iodine of the keto form of the aromatic compound (Scheme 2; I attack).[15] These investigators even showed that simple thiols (X = cysteine), at physiological pH, could effect incomplete monodeiodination of diiodotyrosine and thyroxine.[16] We feel that tellurium and selenium reagents under acidic conditions (NaHTe, NaHSe, PhTeH, PhSeH) could operate by a similar mechanism (Scheme 2). In some cases, small amounts of side products arising from substitution of aromatic iodine by benzenetellurolate or benzeneselenolate were isolated (compounds **5**, **6**, **10**, and **11**). This suggests an alternative pathway to product, involving substitution of iodine by the chalcogen reagent, followed by another nucleophilic attack on the chalcogen with release of the monoiodo phenol (Scheme 2). Related processes were observed in the removal of electronegative α-substituents from carbonyl compounds by nucleophilic tellurium reagents.[17] 2-Iodophenols are more than 2 pK_a units less acidic than their corresponding 2,6-diiodophenols.[18] Since the keto−enol tautomerism in Scheme 2 probably occurs via formation of phenolate ion, the concentration of the keto tautomer is probably much lower for monoiodides than for diiodides. This may explain the high selectivity for monodeiodination seen with NaHTe. Under basic conditions the phenols are present essentially in their deprotonated form, but deiodination could still occur via nucleophilic attack on the keto tautomer as shown in Scheme 2. The tendency for removal of both iodines under these conditions could be accounted for by the higher nucleophilicity of Na_2Te as compared to NaHTe.

In line with the above reasoning, 2,6-diiodophenols carrying electron-withdrawing substituents in the 4-position are more reactive toward NaHTe than those carrying electron-donating ones. In contrast, Na_2Te seems to be more reactive toward diiodophenols carrying electron-donating substituents. This result could be rationalized assuming that deprotonated phenols would not react with negatively charged chalcogenide ions. The high reactivity of 2,6-diiodo-3,5-dimethoxyphenol (**7**) may be explained by the extra resonance stabilization of the keto form provided by the two methoxy groups.

Alternative mechanisms involving single electron transfer (SET) could certainly not be excluded (Scheme 3). The radical anion formed in this process could lose iodide ion and then pick up a hydrogen atom or an electron/proton to form the observed product. In fact, such a process would seem plausible in the deiodination of methyl ethers of diiodophenols where enolization according to Scheme 2 is less likely to occur. To probe the SET mechanism, 2,6-diiodo-3,5-dimethoxyphenol was O-allylated and the resulting ether **22** subjected to the usual basic deiodination conditions using Na_2Te as a reducing agent. It was our hope here (cf. ref 19) to trap intermediate aryl radicals in a cyclization reaction before they were reduced (e.g., compound **23**). However, the iodine-free ether **24** (68% isolated yield) was the only product formed in the reaction. Since reduction of the purported radical intermediate could occur much more rapidly than carbocyclization, this result does not exclude a SET mechanism for the deiodination reaction.



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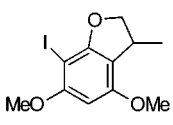

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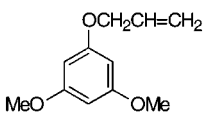

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Few other reagents have been used for the dehalogenation of *o,o′*-dihalophenols. Ethyl mercaptan in the presence of aluminum trichloride was found to reduc-

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tively remove both bromines from 2,6-dibromocresol.[20] 2,4,6-Tribromophenol was monodebrominated in the 2-position by zinc under acidic conditions and 2,4-didebrominated by the metal in an alkaline milieu.[21]

In conclusion, we have shown that NaHTe and Na_2Te are useful for the selective mono- or dideiodination of a variety of functionalized 2,6-diiodophenols and 2,6-diiodophenyl methyl ethers. Although our study does not provide much information as to the deiodination brought about by the selenium-containing iodothyronine deiodinases, the successful NaHTe reduction of **T_4** to **T_3** shows that the two outer iodines of **T_4** are intrinsically more reactive than the two inner ones. Furthermore, the facile Na_2Te-induced removal of iodine from 2,6-diiodophenyl methyl ethers does suggest that enzyme-bound selenocysteine could operate in a similar way to remove inner iodines from **T_4** and **T_3**. Finally, we feel confident that our findings will be helpful in the design and development of physiologically more relevant mimics of the iodothyronine deiodinases.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 spectrometer operating at 299.903 MHz (^{1}H NMR) and 75.419 MHz (^{13}C NMR). EI mass spectra were recorded at 70 eV using a Finnigan INCOS 50 instrument. M^+ ions are given for ^{130}Te and ^{80}Se. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. 3,5-Diiodo-4-hydroxybenzonitrile, 3,5-diiodotyrosine, 3,3′,5-triiodothyronine, and thyroxine were commercially available. Methyl 3,5-diiodo-4-hydroxybenzoate,[22] 2,6-diiodo-4-methylphenol,[23] and 2,6-diiodo-3,5-dimethoxyphenol[24] were prepared according to literature methods.

4-Bromo-2,6-diiodophenol (2d). To a stirred mixture of 4-bromophenol (1.73 g, 10.0 mmol) and K_2CO_3 (8.28 g, 60 mmol) in MeOH (40 mL) was added a solution of I_2 (5.58 g, 22.0 mmol) in MeOH (40 mL) during 2 h, and stirring was continued overnight. Since NMR analysis indicated incomplete iodination, more I_2 (3 g) and K_2CO_3 (4 g) were added and stirring was continued for 4 h. MeOH was then removed in vacuo, and the remaining slurry was treated with aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, the solvents were evaporated, and the residue was recrystallized from hexane affording 3.06 g (72%) of the title compound, mp 127 °C (lit.[25] mp 128 °C).

2,6-Diiodo-4-phenoxyphenol (2e). To a stirred mixture of 4-phenoxyphenol (0.186 g, 1.0 mmol) and K_2CO_3 (1.04 g) in MeOH (4 mL) was added a solution of I_2 (0.558 g, 2.2 mmol) in MeOH (10 mL) during 2 h. The reaction mixture was then stirred for an additional 6 h and evaporated. The residue was treated with water, and the organic components were extracted into ether. The combined extracts were washed with $Na_2S_2O_3$ and $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in ether (1 mL) and treated with hexane to precipitate some polymeric impurities. The filtrate was evaporated affording 0.378 g (78%) of a mixture of the title compound (88%) and 2-iodo-4-phenoxyphenol (12%). All attempts to further purify the material led to decomposition. For example, during chromatography on silica, iodine release was observed and several new compounds were formed. Therefore, the crude material was used for the deiodination experiments. ^{1}H NMR δ 5.55 (br s, 1H), 6.95 (dm, J = 7.5 Hz, 2H), 7.11 (tt, J = 7.4, 1.3 Hz, 1H), 7.34 (tm, J = 8.5 Hz, 2H), 7.38 (s, 2H). ^{13}C NMR δ 81.3, 118.2, 123.5, 129.8, 129.9, 150.1, 151.0, 157.2.

***N*-Butyryl-3,5-diiodotyrosine Methyl Ester (2f).** A suspension of 3,5-diiodotyrosine dihydrate (0.108 g, 0.23 mmol) in 2,2-dimethoxypropane (3 mL) was treated with concentrated HCl (0.115 mL) and stirred at rt for 1.5 days according to a literature procedure.[26] The volatile residue was evaporated, and excess HCl was coevaporated with some MeOH. The residue was suspended in a mixture of MeCN (2 mL), MeOH (1 mL), and Et_3N (0.024 g, 0.24 mmol), and finally butyric anhydride (0.040 g, 0.25 mmol) was added during 20 min. The mixture was stirred for 2−3 h, and the progress of the reaction was monitored by TLC. The solvents were removed in vacuo, the residue was treated with HCl (5% aqueous) and the organic components were extracted into CH_2Cl_2. The combined extracts were washed with brine, dried, and evaporated to a volume of ca. 0.5 mL. Addition of hexane caused precipitation of the title compound as a white solid 0.087 g (67%), mp 128 °C. ^{1}H NMR δ 0.96 (t, J = 7.4 Hz, 3H), 1.67 (m, 2H), 2.20 (t, J = 8.0 Hz, 2H), 2.95 (dd, J = 14.1, 5.2 Hz, 1H), 3.05 (dd, J = 14.0, 5.9 Hz, 1H), 3.76 (s, 3H), 4.81 (m, 1H), 5.79 (br s, 1H), 5.99 (br d, J = 7.0 Hz, 1H), 7.41 (s, 2H). ^{13}C NMR δ 13.8, 19.1, 35.9, 38.5, 52.5, 53.0, 82.2, 132.0, 139.9, 152.6, 171.7, 172.6. Anal. Calcd for $C_{14}H_{17}I_2NO_4$: C, 32.52; H, 3.31. Found: C, 32.50; H, 3.21.

***N*-Butyrylthyroxine Methyl Ester (2g)** was prepared using the procedure for compound **2f**. Yield 87%, mp 168 °C (dec). ^{1}H NMR δ 0.97 (t, J = 7.4 Hz, 3H), 1.67 (m, 2H), 2.22 (t, J = 8.0 Hz, 2H), 3.01 (dd, J = 13.7, 5.9 Hz, 1H), 3.13 (dd, J = 13.7, 5.8 Hz, 1H), 3.78 (s, 3H), 4.85 (m, 1H), 5.52 (br s, 1H), 6.01 (br d, J = 7.1 Hz, 1H), 7.10 (s, 2H), 7.61 (s, 2H). ^{13}C NMR δ 13.8, 19.2, 36.4, 38.5, 52.6, 52.9, 81.6, 90.7, 125.9, 137.6, 141.1, 149.4, 150.0, 152.5, 171.6, 172.6. Anal. Calcd for $C_{20}H_{19}I_4NO_5$: C, 27.90; H, 2.22. Found: C, 27.79; H, 2.15.

***N*-Butyryl-3,3′,5-triiodothyronine Methyl Ester (3g)** was prepared from authentic 3,3′,5-triiodothyronine using the procedure for compound **2f** and purified by column chromatography (30% EtOAc in pentane). Yield 48%, mp 161 °C. ^{1}H NMR δ 0.96 (t, J = 7.3 Hz, 3H), 1.67 (m, 2H), 2.22 (t, J = 7.4 Hz, 2H), 3.00 (dd, J = 13.7, 5.9 Hz, 1H), 3.14 (dd, J = 13.7, 5.8 Hz, 1H), 3.78 (s, 3H), 4.86 (m, 1H), 5.01 (br s, 1H), 5.99 (br d, J = 7.9 Hz, 1H), 6.65 (dd, J = 8.9, 2.9 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 2.9 Hz, 1H), 7.60 (s, 2H). ^{13}C NMR δ 13.8, 19.2, 36.3, 38.5, 52.6, 52.9, 85.3, 90.9, 115.1, 117.0, 124.7, 137.2, 141.0, 150.0, 150.5, 153.0, 171.6, 172.8. Anal. Calcd for $C_{20}H_{20}I_3NO_5$: C, 32.68; H, 2.74. Found: C, 32.86; H, 4.65.

2,4-Diiodo-1,3,5-trimethoxybenzene (12). Sodium metal (0.028 g, 1.2 mmol) was dissolved in MeOH (0.6 mL), and 2,4-diiodo-3,5-dimethoxyphenol (0.406 g, 1.0 mmol) in DMF (2.5 mL) was added. After 10 min MeI (0.284 g, 2.0 mmol) was added and the mixture was stirred at ambient temperature overnight. The solvents were then evaporated in vacuo, the residue was treated with water, and the product was extracted into CH_2Cl_2. The combined extracts were dried and concentrated, and the residue was crystallized from ethanol to afford 0.302 g (72%) of the title compound, mp 133 °C (lit.[27] mp 133.5 °C).

2,6-Diiodo-1-methoxy-4-methylbenzene (15) was prepared in 71% yield from compound **2c** by using the procedure for the preparation of compound **12**. The material was obtained as an oil (lit.[28] mp 25 °C). ^{1}H NMR δ 2.22 (t, J = 0.8 Hz, 3H), 3.81 (s, 3H), 7.56 (q, J = 0.8 Hz, 2H). ^{13}C NMR δ 19.6, 60.6, 90.1, 137.7, 140.1, 156.5.

Methyl 3,5-Diiodo-4-methoxybenzoate (18), mp 95 °C (lit.[22] mp 95 °C), was prepared in 64% yield from compound **2a** by using the procedure for the preparation of compound **12**.

2,6-Diiodo-3,5-dimethoxy-1-allyloxybenzene (22), mp 108 °C, was prepared in 74% yield from compound **7** by using

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the procedure for the preparation of compound **12** (allyl bromide instead of MeI). ^{1}H NMR δ 3.90 (s, 6H), 4.50 (dt, J = 5.8, 1.4 Hz, 2H), 5.32 (dq, J = 10.4, 1.7 Hz, 1H), 5.53 (dq, J = 17.1, 1.6 Hz, 1H), 6.21 (m, 1H), 6.25 (s, 1H). ^{13}C NMR δ 56.8, 73.1, 73.6, 91.8, 118.6, 133.0, 160.4, 160.4. Anal. Calcd for $C_{11}H_{12}I_2O_3$: C, 29.62; H, 2.71. Found: C, 29.69; H, 2.56.

Typical Procedure. Deiodination of Methyl 3,5-Diiodo-4-hydroxybenzoate (2a) with NaHTe. A stirred mixture of freshly finely powdered tellurium (0.16 g, 1.25 mmol) and $NaBH_4$ (0.113 g, 3.0 mmol) in EtOH (12 mL) was heated at reflux under nitrogen for ca. 20 min to give a pale purple solution of Na_2Te (see ref 29). To the cooled solution was added HOAc (0.5 mL), followed by methyl 3,5-diiodo-4-hydroxybenzoate (0.102 g, 0.25 mmol), while a brisk stream of nitrogen was passed through the open system. The reaction mixture was heated at reflux for 4 h, cooled, and stirred in the open air for about 10 min to complete precipitation of elemental tellurium. After filtration the solvents were evaporated in vacuo, the residue was treated with $NaHCO_3$ (5% aqueous), and the organic products were extracted into CH_2Cl_2. The combined extracts were dried over Na_2SO_4, and the solvent was evaporated to afford 0.069 g (99%) of methyl 4-hydroxy-3-iodobenzoate (**3a**), mp 158 °C (lit.[30] mp 155−156 °C), from hexane/benzene = 4/1.

Except for the omission of the HOAc addition, Na_2Te was prepared as described in the typical procedure. By replacing tellurium for selenium or sulfur, NaHSe, Na_2Se, and Na_2S were similarly prepared. Selenium and sulfur were reduced by $NaBH_4$ already at ambient temperature. Product compositions in NaHTe- and Na_2Te-induced deiodinations of diiodophenols **2** are shown in Table 1.

4-Hydroxy-3-iodobenzonitrile (3b). To the black reaction mixture obtained in the reduction of 3,5-diiodo-4-hydroxybensonitrile (typical procedure) was added silica gel (3 mL), and the solvent evaporated in vacuo. The solid material thus obtained was loaded on top of an SiO_2 column and eluted first with CH_2Cl_2/pentane = 1/1 and then with CH_2Cl_2 to afford the pure title compound, mp 142 °C (lit.[31] mp 144 °C), in 62% yield.

2-Iodo-4-methylphenol (3c). By using NaHTe as a reducing agent, the pure title compound, mp 34.5 °C (lit.[32] mp 35 °C), was isolated in 37% yield by column chromatography (5% EtOAc in pentane).

4-Bromo-2-iodophenol (3d), mp 70 °C (lit.[33] mp 71 °C), was isolated in 80% yield from the crude reaction product by column chromatography (50% CH_2Cl_2 in pentane).

2-Iodo-4-phenoxyphenol (3e) could not be isolated in pure form from the crude mixture of deiodination products (Table 1). An authentic sample of the material, mp 41 °C, was isolated in 37% yield by treatment of 4-phenoxyphenol (**4e**) with 1 equiv of I_2 (see ref 23), column chromatography (0.2% EtOH in CH_2Cl_2), and crystallization from hexane. ^{1}H NMR δ 5.14 (br s, 1H), 6.95 (m, 4H), 7.07 (t, J = 9.0 Hz, 1H), 7.31 (m, 3H). ^{13}C NMR δ 85.0, 115.2, 117.9, 121.5, 123.0, 128.8, 129.8, 150.5, 151.3, 157.8. Anal. Calcd for $C_{12}H_9IO_2$: C, 46.18; H, 2.91. Found: C, 46.08; H, 2.84.

***N*-Butyryl-3-iodotyrosine Methyl Ester (3f)**, mp 140 °C, was isolated in 61% yield from the crude product by column chromatography (25−40% EtOAc in pentane). ^{1}H NMR δ 0.93 (t, J = 7.3 Hz, 3H), 1.64 (m, 2H), 2.19 (t, J = 7.7 Hz, 2H), 2.96 (dd, J = 14.0, 5.9 Hz, 1H), 3.07 (dd, J = 14.0, 5.7 Hz, 1H), 3.76 (s, 3H), 4.86 (m, 1H), 5.58 (br s, 1H), 6.04 (br d, J = 7.9 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.96 (dd, J = 8.3, 2.2 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H). ^{13}C NMR δ 13.7, 19.1, 36.6, 38.4, 52.5, 53.0, 85.0, 115.1, 129.4, 130.5, 139.17, 154.6, 172.1, 173.1. Anal. Calcd for $C_{14}H_{18}INO_4$: C, 42.98; H, 4.64. Found: C, 43.14; H, 4.65.

***N*-Butyryl-3,3′,5-triiodothyronine Methyl Ester (3g)** obtained by deiodination of the corresponding thyroxine derivative was identical to authentic material prepared from 3,3′,5-triiodothyronine as described above. An inseparable 9/1 mixture (38% yield) of the title compound and an unknown iodothyronine derivative were isolated by column chromatography.

4-Bromophenol (4d). 4-Bromo-2,6-diiodophenol was refluxed with Na_2Te for 6 h according to the typical procedure. After filtration and evaporation, the residue was taken up into KOH (5 mL of 5% aqueous), and the aqueous phase washed with ether. Acidification, ether extraction, drying, and evaporation afforded the pure title compound, identical to an authentic sample, in 76% yield.

***N*-Butyrylthyronine Ethyl Ester (4g)** was isolated as an oil by column chromatography (1−2% MeOH in CH_2Cl_2). ^{1}H NMR δ 0.91 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.3 Hz, 3H), 1.63 (m, 2H), 2.18 (t, J = 7.2 Hz, 2H), 3.07 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.85 (m, 1H), 5.90 (br s, 1H), 6.03 (br d, J = 8.8 Hz, 1H), 6.70−6.95 (several peaks, 6H), 7.01 (dm, J = 8.7 Hz, 2H). ^{13}C NMR δ 13.7, 14.1, 19.0, 37.2, 38.4, 53.1, 61.7, 116.3, 117.3, 121.0, 129.5, 130.4, 149.3, 152.7, 157.8, 171.8, 173.1. MS m/z 371 (M^+).

During the purification of this material a product with a higher R_f value was isolated, supposedly a *N*-butyrylmonoiodothyronine ethyl ester of unknown structure. ^{1}H NMR δ 0.92 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.3 Hz, 3H), 1.63 (m, 2H), 2.17 (t, J = 7.2 Hz, 2H), 3.08 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.86 (m, 1H), 5.37 (br s, 1H), 5.91 (br d, J = 8.0 Hz, 1H), 6.85 (dm, J = 8.8 Hz, 2H), 6.95 (m, 2H), 7.05 (dm, J = 8.8 Hz, 2H), 7.33 (dd, J = 2.2, 0.9 Hz, 1H); irradiation at 7.33 ppm resulted in the collapse of the multiplet at 6.95 ppm.

Methyl 4-hydroxybenzoate (**4a**), 4-hydroxybenzonitrile (**4b**), 4-methylphenol (**4c**), and 4-phenoxyphenol (**4e**) obtained during deiodination experiments were identical to authentic samples.

Deiodination of Methyl 3,5-Diiodo-4-hydroxybenzoate (2a) with PhTeH. A degassed suspension of Ph_2Te_2 (0.307 g, 0.75 mmol) in EtOH (25 mL) was treated under nitrogen with $NaBH_4$ (0.076 g, 2.0 mmol). To the colorless solution was injected HOAc (1 mL) followed by methyl 3,5-diiodo-4-hydroxybenzoate (0.202 g, 0.50 mmol) while nitrogen was flushed through the open system. The mixture was stirred overnight and evaporated to dryness, $NaHCO_3$ (5% aqueous) was added to the residue, and the organic components were extracted into CH_2Cl_2. The combined extracts were dried and evaporated and some residual EtOH coevaporated with added toluene. Column chromatography (pentane then CH_2Cl_2) afforded the following products:

Methyl 4-Hydroxy-3-iodobenzoate (3a). Yield 0.057 g (41%). This material was identical to an authentic sample.[30] **Methyl 4-Hydroxy-3-(phenyltelluro)benzoate (5).** Yield 0.013 g (7.0%), mp 156 °C. ^{1}H NMR δ 3.88 (s, 3H), 6.64 (br s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.20 (m, 3H), 7.51 (dm, J = 8.1 Hz, 2H), 8.03 (dd, J = 8.6, 2.2 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H). ^{13}C NMR δ 52.0, 103.7, 113.3, 113.6, 123.7, 128.1, 129.8, 136.1, 134.3, 143.9, 161.4, 166.0. Anal. Calcd for $C_{14}H_{12}O_3Te$: C, 47.25; H, 3.40. Found: C, 47.08; H, 3.30. **Methyl 4-Hydroxy-5-iodo-3-(phenyltelluro)benzoate (6).** Less than 1 mg of the title compound, contaminated with compound **2a**, and presumably [^{1}H NMR δ 3.77 (s, 3H), 7.10 (br s, 1H), 8.13 (s, 2H)] methyl 3,5-bis(phenyltelluro)-4-hydroxybenzoate was obtained. ^{1}H NMR δ 3.84 (s, 3H), 6.65 (br s, 1H), 7.30 (m, 3H), 7.70 (dm, J = 8.1 Hz, 2H), 8.16 (d, J = 1.8 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H). ^{13}C NMR δ 52.2, 81.2, 103.2, 112.6, 125.5, 128.8, 130.0, 138.4, 140.7, 141.4, 158.5, 164.7. MS m/z 484 (M^+).

3,5-Dimethoxyphenol (8) was obtained as the only product in essentially quantitative yield by deiodination of 2,6-diiodo-3,5-dimethoxyphenol (**7**) by any of the reagents NaHTe, Na_2Te, NaHSe, Na_2Se, or Na_2S following the typical procedure. The product was identical to an authentic sample.

3,5-Dimethoxy-2-iodophenol (9). To a stirred degassed suspension of Ph_2Te_2 (0.307 g, 0.75 mmol) in EtOH (20 mL) was added $NaBH_4$ (0.070 g, 1.85 mmol) under nitrogen until the red color of ditelluride had disappeared (20 min). The solution was then acidified by injection of HOAc (0.4 mL) and 2,6-diiodo-3,5-dimethoxyphenol (**7**) (0.203 g, 0.50 mmol) was

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added. The mixture was stirred at 0 °C for 4 h, during which time the solution turned increasingly red due to reformation of Ph_2Te_2. The reaction flask was then opened to the air, and the solvent was evaporated. The residue was stirred with NaOH (5% aqueous) for 30 min followed by extraction of nonacidic components into ether. The aqueous phase was then acidified with HCl (0.1 M aqueous), and the phenolic products were extracted into CH_2Cl_2. The combined extracts were dried and evaporated to afford a mixture of compounds **7**, **8**, and **9** (ratio 74:20:6 according to ^{1}H NMR). The pure title compound (0.074 g, 53%), mp 73 °C, was obtained after column chromatography (0.1% EtOH in CH_2Cl_2). ^{1}H NMR δ 3.79 (s, 3H), 3.84 (s, 3H), 5.48 (s, 1H), 6.06 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 55.5, 56.4, 67.1, 92.0, 92.6, 156.5, 159.0, 162.3. Anal. Calcd for $C_8H_9IO_3$: C, 34.31; H, 3.24. Found: C, 34.52; H, 3.14.

3,5-Dimethoxy-2-(phenylseleno)phenol (10). A degassed suspension of diphenyl diselenide (0.195 g, 0.625 mmol) in EtOH (15 mL) was treated under nitrogen with $NaBH_4$ (0.057 g, 1.5 mmol). To the colorless solution was added HOAc (0.5 mL) by syringe followed by 2,6-diiodo-3,5-dimethoxyphenol (0.102 g, 0.25 mmol) while nitrogen was flushed through the open system. After the solution was stirred at ambient temperature for 4 h, EtOH was evaporated in vacuo, the residue was stirred with NaOH (20 mL 5% aqueous) during 30 min, and diphenyl diselenide was extracted with ether. The aqueous phase was acidified with HCl (10% aqueous) and the product was extracted with methylene chloride. Drying (Na_2SO_4) and evaporation afforded a crude product as a 2/1 mixture of the title compound and 3,5-dimethoxyphenol (**8**). Column chromatography (2% EtOAc in pentane) afforded 0.030 g (39%) of compound **10**, mp 68 °C. ^{1}H NMR δ 3.80 (s, 3H), 3.82 (s, 3H), 6.13 (d, J = 2.5 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 6.84 (s, 1H), 7.18 (br s, 5H). ^{13}C NMR δ 55.5, 56.2, 91.8, 92.0, 95.4, 126.3, 128.8, 129.2, 131.3, 159.0, 161.5, 163.7. Anal. Calcd for $C_{14}H_{14}O_3Se$: C, 54.38; H, 4.56. Found: C, 54.46; H, 4.60. MS m/z 310 (M^+).

3,5-Dimethoxy-6-iodo-2-(phenylseleno)phenol (11) in trace amounts was also eluted from the column, contaminated with some 2,6-diiodo-3,5-dimethoxyphenol. ^{1}H NMR δ 3.86 (s, 3H), 3.95 (s, 3H), 6.16 (s, 1H), 7.20 (br s, 5H), 7.36 (s, 1H). ^{13}C NMR δ 56.5, 56.5, 63.0, 88.1, 95.9, 126.7, 129.3, 129.3, 130.8, 157.7, 161.7, 162.1. MS m/z 436 (M^+).

1,3,5-Trimethoxybenzene (13) was obtained as the only product in 85% and 89% isolated yields, respectively, by treatment of 2,4-diiodo-1,3,5-trimethoxybenzene with NaHTe and Na_2Te (typical procedure). The product was identical to an authentic sample.

2-Iodo-1,3,5-trimethoxybenzene (14) was obtained as the only deiodination product by treatment of 2,4-diiodo-1,3,5-trimethoxybenzene with PhTeNa, following the procedure for the preparation of compound **9** (HOAc addition omitted). After column chromatography (10% EtOAc in pentane), the title compond, mp 120 °C (lit.[34] mp 121 °C), was isolated in 81% yield.

2-Iodo-1-methoxy-4-methylbenzene (16) was obtained by treatment of 2,6-diiodo-1-methoxy-4-methylbenzene with Na_2Te (typical procedure, HOAc addition omitted). According to ^{1}H NMR, the crude material (68% isolated yield) contained the title compound and 4-methylanisole as a 97/3 mixture. ^{13}C NMR data for compound **16** were in close agreement with the literature.[35] ^{13}C NMR δ 19.9, 56.4, 85.7, 110.7, 129.9, 132.0, 139.8, 156.0.

Ethyl 4-Methoxybenzoate (19) was obtained by treatment of methyl 3,5-diiodo-4-methoxybenzoate (**18**) with Na_2Te (typical procedure, HOAc addition omitted). The crude material (90% yield) contained 10% of the corresponding methyl ester. Both components were identical to authentic samples.

Methyl 3-Iodo-4-methoxybenzoate (20) was obtained by treatment of methyl 3,5-diiodo-4-methoxybenzoate with NaHTe (typical procedure). The crude product was a 9/1 mixture of the title compound and methyl 4-hydroxy-3-iodobenzoate (**3a**). After column chromatography (5% EtOAc in pentane), compound **20**, mp 94 °C (lit.[36] mp 94−95 °C), was isolated in 76% yield.

Ethyl 3-Iodo-4-methoxybenzoate (21), mp 62 °C (lit.[36] mp 64.75 °C), was obtained by treatment of methyl 3,5-diiodo-4-methoxybenzoate with Na_2Se (typical procedure; Se instead of Te; HOAc addition omitted). The crude product (81% yield) contained 10% of the corresponding methyl ester **20** which could be removed by crystallization from hexane.

3,5-Dimethoxyallyloxybenzene (24) was obtained as the only product in 68% isolated yield by treatment of 2,6-diiodo-3,5-dimethoxyallyloxybenzene with Na_2Te (typical procedure, HOAc addition omitted). The product was identical to an authentic sample prepared according to the literature.[37]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compound **4g** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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