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Improved Synthesis of the Iodine-Free Thyromimetic GC-1

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Abstract—Synthesis of the TRβ-selective thyromimetic **GC-1** has been improved using methoxymethyl (MOM) and triisopropylsilyl (TiPS) substituents as phenolic protecting groups. The new synthetic route is adaptable to analogue design.

Introduction

Thyroid hormones, of which 3,5,3′-triiodo-L-thyronine (T3) is the major active form, regulate many different physiological processes in different tissues in mammals.[1,2] A deficiency of these hormones or hypothyroidism results in severe impairment of mental development and growth in childhood. In the adult, hypothyroidism leads to a slow metabolism, decreased body temperature and heart rate, increased accumulation of glycosaminoglycans in subcutaneous tissues (mixedema), weight gain, and elevated cholesterol levels. By contrast, an elevated level of thyroid hormones or hyperthyroidism provokes tachycardia, increased metabolism and body temperature, weight loss, and decreased serum cholesterol levels. In current medical practice, thyroid hormones are used mostly as replacement therapy for patients with hypothyroidism, and to suppress the pituitary gland stimulation of the thyroid gland in patients with thyroid nodules or cancer. However, these hormones cannot be administered in high doses because of significant side effects, mainly on the heart.

Most of the physiological actions of T3 result from transcriptional regulation T3-responsive genes that is mediated through thyroid hormone receptors (TRs). The TR belongs to the nuclear receptor superfamily of ligand-activated transcription regulators that includes steroid receptors such as the estrogen receptor (ER) and glucocorticoid receptor (GR), as well as receptors that, like TR, are activated by non-steroidal ligands such as the retinoic acid receptor (RAR) and retinoid X receptor (RXR).[3–5] There are two major subtypes of the thyroid hormone receptor, TRα and TRβ, that are coexpressed in different ratios in different tissues.[6] Most thyroid hormones do not discriminate between the two TRs and bind both with similar affinity.

Observations suggest that the α-form of the receptors contribute in a substantial way to cardiac stimulating side effects,[7,8] and that a β-selective agonist would be less likely to have this side effect. A few attempts have been made to develop thyroid hormone analogues, which induce a differential thyroid hormone response and, for example, preferentially lower lipid levels but do not increase heart rate.[9,10] Such compounds might have medical utility.

We have recently designed and synthesized a halogen-free high-affinity TRβ-selective ligand, **GC-1** (Fig. 1), which is a member of a new class of thyromimetic compounds that are more synthetically accessible than traditional thyromimetics and have potentially useful receptor-binding and ligand-activation properties.[11] **GC-1** was initially synthesized in our laboratory by a convergent synthetic route wherein the key step is an efficient aldehyde addition reaction that forms the diarylmethane structure.[11] A major problem encountered in the process was the final mono-alkylation procedure of bis-phenol **2**, which unfortunately did not proceed with the expected selectivity,[12] leading to a mixture of both 1- and 4′-alkylated product **3**, as well as the bis-alkylated product **4**. This problem of over-alkylation could not be controlled and resulted in a 28% isolated yield for the final chemical step in the synthetic route (Scheme 1).

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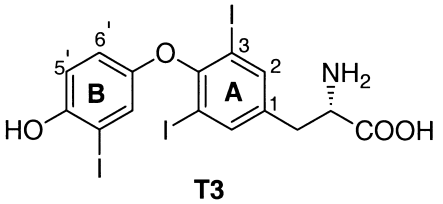
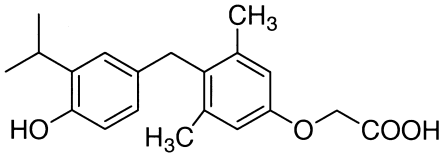
Based on the encouraging in vitro results with **GC-1**, we have begun to pursue in vivo experiments to ascertain the physiological effects of **GC-1** in different animal models. In order to perform these experiments, it was necessary to optimize the synthesis of **GC-1** such that multigram quantities of the compound could be prepared.

Chemistry

The new chemical synthesis of **GC-1** is outlined in Scheme 2. The two aryl halves of **GC-1** are constructed first and the phenols are differentiated at this stage with different protecting groups. For the B-aryl ring half 4-bromo-2-isopropylphenol[13] is converted to the corresponding methoxymethyl ether **5** by treatment of the phenoxide with chloromethyl methyl ether.[14] For the A-aryl ring half the 4-bromo-3,5-dimethylphenol is treated with triisopropylsilylchloride to provide the triisopropylsilyl ether **6**,[15] which is subsequently formylated via lithium–halogen exchange followed by treatment with dimethylformamide to provide the aldehyde **7**.[16] Bromide **5** and aldehyde **7** are then coupled via the addition of lithiated **5** to aldehyde **7** to give the biaryl alcohol **8**.[17] Hydrogenolysis of alcohol **8** provides the biarylmethane compound **9**.[18] Subsequent treatment of **9** with tetrabutylammonium fluoride allows selective removal of the phenolic silyl ether protecting group, providing the free phenol **10**.[19] Phenol **10** is then mono-alkylated using α-chloro-*t*-butylacetate, which successfully solves the main problem with the original route, providing the desired mono-ester **11**.[20] The target compound **GC-1** is then obtained from **11** by removal of the methoxymethyl phenolic protecting group under acidic conditions, followed by basic saponification of the *tert*-butyl ester.[21] Although *tert*-butyl esters are usually hydrolyzed under acidic conditions, we found that hydrolysis with base resulted in less decomposition and higher chemical yields for this step.



T3

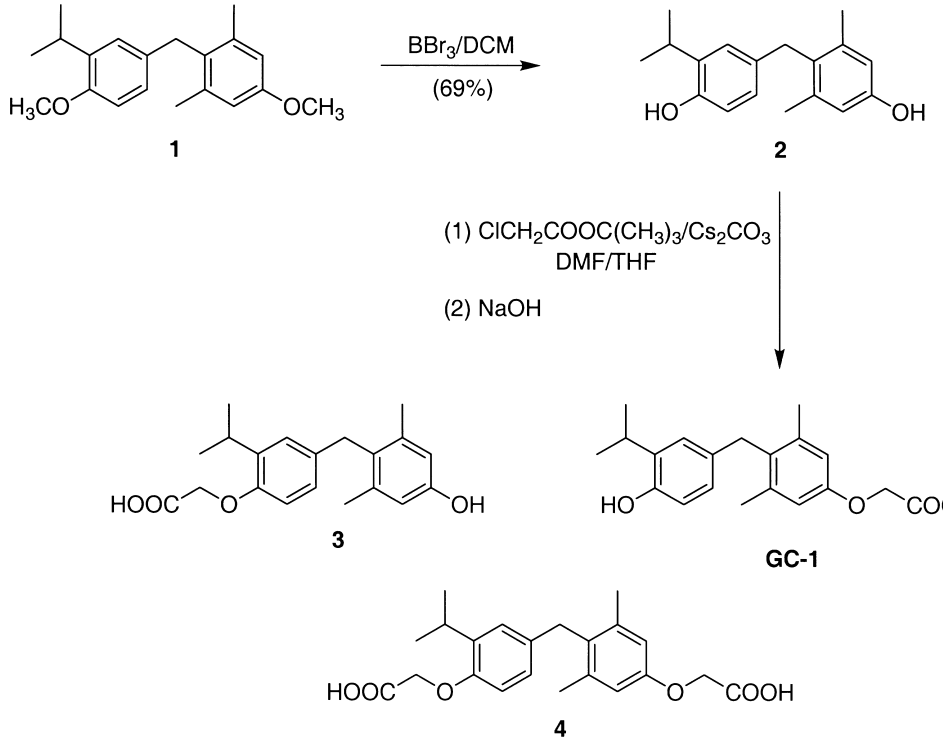


GC-1

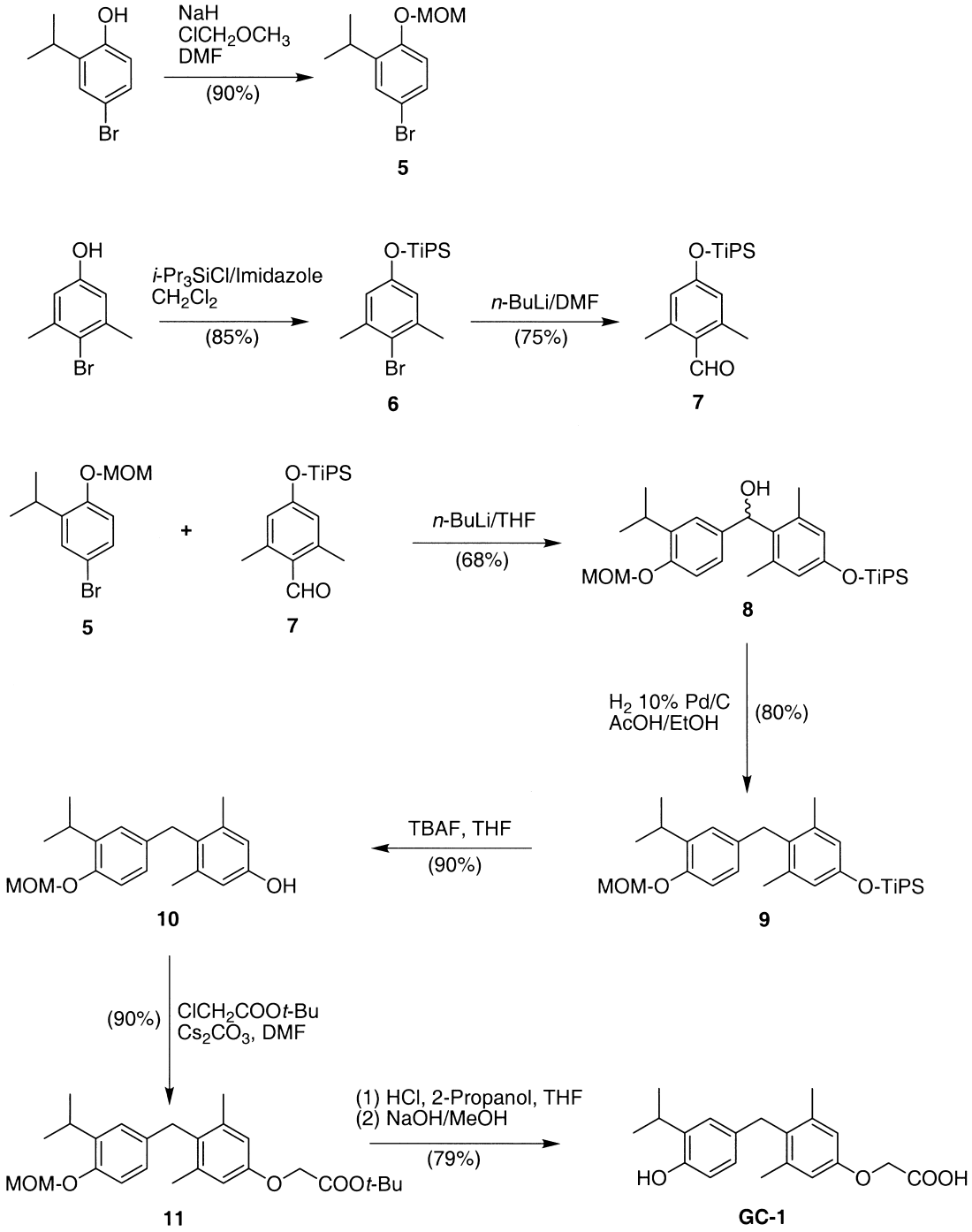
Figure 1. Chemical structure of thyroid hormone (T3) and the synthetic thyromimetic compound **GC-1**.

Results and Discussion

The new synthetic route described here allows one to prepare multigram quantities of **GC-1** and is more adaptable to analogue design than our original synthesis. Differentiating the two phenols early in the route with the appropriate protecting groups remedies the problem of overalkylation in the final step resulting in a



Scheme 1. Steps 6 and 7 of the original synthesis of **GC-1**. For the complete synthesis see ref 11.



Scheme 2. Synthetic route used for the preparation of **GC-1**.

substantial improvement in the overall yield of **GC-1**. This improved route provides **GC-1** in 22% overall yield from 4-bromo-3,5-dimethylphenol, whereas our original route resulted in a 7% yield of **GC-1** from this same starting material. We have used the new route to prepare multigram quantities of **GC-1** for use in animal studies. In addition to this improvement in efficiency, the differentiated phenol protecting groups offer a chemical handle for selective modification of the thyronine skeleton to produce new derivatives. The methoxymethyl protecting group can be used to direct orthometalation chemistry leading to new derivatives substituted at the 5′-position.[22] We are currently investigating this chemistry to produce a series of these new 5′-substituted thyronine analogues.

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14. **4-Bromo-2-isopropyl phenyl methoxymethyl ether (5).** 4-Bromo-2-isopropylphenol (22.0 g, 0.120 mol) was added dropwise to a slurry of sodium hydride pellets (3.70 g, 0.128 mol) in dimethylformamide (100 mL) at room temperature. Stirring at this temperature was continued until the evolution of hydrogen ceased (20 min). Monochloromethylether (9.47 g, 0.117 mol) was then added during 30 min and stirring was continued for an additional 30 min after which excess sodium hydride was destroyed by cautious addition of methanol (30 mL). The reaction mixture was diluted with 200 mL of ether and washed with 3×100 mL of water and 5×100 mL of brine. The organic portion was dried ($MgSO_4$), filtered, and evaportated to give an oil, which was purified by flash column chromatography (silica gel, 95:5 hexane:ethyl acetate) to give the pure product **5** (24.0 g, 0.093 mol, 90%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.2 (d, 6H, J=6.9 Hz), 3.29 (heptet, 1H, J=6.9 Hz), 3.47 (s, 3H), 5.17 (s, 2H), 6.94 (d, 1H, J=8.7 Hz), 7.22 (dd, 1H, J=8.7, 2.7 Hz), 7.30 (d, 1H, J=2.7 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 22.6, 26.9, 56.03, 94.5, 114.4, 115.7, 129.2, 139.9, 153.4. HR-MS calcd for $C_{11}H_{15}O_2Br$: 258.0255, found: 258.0253.

15. ***O*-Triisopropylsilyl-4-bromo-3,5-dimethylphenol (6).** A solution of 4-bromo-3,5-dimethylphenol (30 g, 0.149 mol) imidazole (25.3 g, 0.327 mol) and triisopropylsilyl chloride (27.3 g, 0.142 mol) in CH_2Cl_2 (300 mL) was stirred for 1 h. The reaction mixture was diluted with 600 mL of CH_2Cl_2, washed with water (500 mL), brine (500 mL), dried ($MgSO_4$), filtered and evaporated to give an oil, which was purified by flash column chromatography (silica gel, 90:10 hexane:ethyl acetate) to give 43.4 g (0.121 mol, 81%) of **6** as an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, 18H, J=6.9 Hz), 1.26 (m, 3H), 2.34 (s, 6H), 6.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.7, 17.7, 23.9, 117.5, 119.6, 138.9, 155.9. HR-MS calcd for $C_{17}H_{29}OBrSi$: 358.1150, found: 358.1144.

16. **2,6-Dimethyl-4-*O*-triisopropylsilylbenzaldehyde (7).** To **6** (30 g, 0.084 mol) in 200 mL of tetrahydrofuran at −78 °C was added 92.0 mL of *n*-butyllithium (2.0 M in pentane). The reaction mixture was stirred for 30 min at −78 °C and then DMF (12.3 g, 0.168 mol) was added. The reaction mixture was stirred for 1 h at −78 °C and for 1.5 h at room temperature, diluted with 200 mL of ether, and washed with 100 mL of water, acidified with 1 N HCl, and 5×50 mL of brine. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product, which was purified by flash column chromatography (silica gel, 90:10 hexane:ethyl acetate) to yield **7** (18 g, 0.059 mol, 70%) as a clear oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.1 (d, 18H, J=6.9 Hz), 1.26 (m, 3H), 2.57 (s, 6H), 6.56 (s, 2H), 10.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.6, 17.8, 20.9, 119.5, 120.8, 144.4, 159.8, 191.8. HR-MS calcd for $C_{18}H_{30}O_2Si$: 306.2015, found: 306.2014.

17. **3,5-Dimethyl-4-(3′-isopropyl-4′-*O*-methoxymethylbenzylhydroxy)-*O*-triisopropylsilylphenol (8).** To **5** (10 g, 0.038 mol) in 100 mL of tetrahydrofuran at −78 °C was added 29.0 mL of *n*-butyllithium (2.0 M in pentane) and the reaction mixture was stirred for 30 min at −78 °C under argon. The aldehyde **7** (11.8 g, 0.039 mol) in THF anhydrous (100 mL) was added and the mixture was stirred for 1 h at −78 °C and for 6 h at room temperature. Then, the reaction mixture was diluted with 150 mL of ether, washed with 200 mL of water and 5×50 mL of brine. The combined extracts were dried over $MgSO_4$, filtered, and evaporated to give the crude product, which was purified by flash chromatography (silica gel, 90:10 hexane:ethyl acetate) to yield **8** (12 g, 0.024 mol, 68%) as an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.1 (d, 18H, J=6.9 Hz), 1.2 (dd, 6H, J=6.6, 6.9 Hz), 1.26 (m, 3H), 2.20 (s, 6H), 3.3 (heptet, 1H, J=6.9 Hz), 3.48 (s, 3H), 5.17 (s, 2H), 6.22 (s, 1H), 6.55 (s, 2H), 6.93 (m, 2H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.7, 17.7, 20.8, 22.7, 27.0, 31.6, 56.03, 70.9, 94.63, 113.6, 120.4, 123.7, 132.2, 136.4, 137.2, 138.4, 153.1, 154.9. HR-MS calcd for $C_{29}H_{46}O_4Si$: 486.3165, found: 486.3159.

18. **3,5-Dimethyl-4-(3′-isopropyl-4′-*O*-methoxymethylbenzyl)-*O*-triisopropylsilyl phenol (9).** A solution of **8** (7.3 g, 0.015 mol) in 50 mL of 9% (v/v) AcOH in EtOH containing 10% Pd/C (500 mg) was hydrogenated at 1 atm at room temperature. When hydrogen uptake was complete (12 h), the catalyst was filtered off and the filtrate was diluted with 250 mL of ether, washed with sat. $NaHCO_3$ solution (3×50 mL). The solvent was evaporated to yield 5.65 g (0.012 mol, 80%) of **9** as an oil. This material was used in the next step without further purification; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.1 (d, 18H, J=6.9 Hz), 1.16 (d, 6H, J=6.9 Hz), 1.23 (m, 3H), 2.16 (s, 6H), 3.27 (heptet, 1H, J=6.9 Hz), 3.48 (s, 3H), 3.91 (s, 2H), 5.15 (s, 2H), 6.59 (s, 2H), 6.67 (dd, 1H, J=2.4, 8.4 Hz), 6.9 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 12.7, 17.0, 20.32, 22.78, 26.9, 33.73, 55.97, 94.71, 113.9, 119.4, 125.5, 129.8, 133.4, 137.3, 138.1, 152.4, 153.8. HR-MS calcd for $C_{29}H_{46}O_3Si$: 470.3216, found 470.3194.

19. **3,5-Dimethyl-4-(3′-isopropyl-4′-*O*-methoxymethylbenzyl) phenol (10).** Compound **9** (4 g, 8.5 mmol) and tetra-*n*-butylammonium fluoride (10.6 mmol, 1.0 M in THF) were combined in a round-bottom flask. Deprotection was determined to be nearly instantaneous by TLC. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2×75 mL) and brine (100 mL), dried and concentrated. The crude product was purified by flash column chromatography (80:20 hexane:ethyl acetate) to yield **10** (2.40 g, 7.60 mmol, 90%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 6H, J=6.9 Hz), 2.18 (s, 6H), 3.28 (heptet, 1H, J=6.9 Hz), 3.47 (s, 3H), 3.89 (s, 2H), 5.15 (s, 2H), 6.55 (s, 2H), 6.65 (dd, 1H, J=2.4, 8.4 Hz), 6.88 (d, 1H, J=8.4 Hz), 6.94 (d, 1H, J=2.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.52, 23.01, 27.18, 33.9, 56.2, 94.88, 114.2, 114.9, 125.5, 126.1, 129.8, 133.5, 137.6, 138.8, 153.6. HR-MS calcd for $C_{20}H_{26}O_3$: 314.1882, found 314.1869.

20. **[3,5-Dimethyl-4-(3′-isopropyl-4′-*O*-methoxymethylbenzyl) phenoxy] *tert*-butylacetate (11).** To cesium carbonate (10.4 g, 0.032 mol) and **10** (2 g, 0.0064 mol) in 50 mL of DMF was added *tert*-butylchloroacetate (1.2 g, 0.008 mol). The reaction

mixture was stirred for 30 min at room temperature, poured into 100 mL of cold 1 N HCl, and extracted with ethyl acetate (3×100 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 3.0 g of crude, which was purified using flash column chromatography (silica gel, 90:10 hexane:ethyl acetate) to yield **11** (2.50 g, 0.0058 mol 90%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (d, 6H, J = 6.9 Hz), 1.50 (s, 9H), 2.2 (s, 6H), 3.27 (heptet, 1H, J = 6.9 Hz), 3.47 (s, 3H), 3.90 (s, 2H), 4.49 (s, 2H), 5.14 (s, 2H), 6.61 (s, 2H), 6.67 (s, 1H), 6.9 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.73, 23.01, 27.18, 28.28, 29.92, 34.01, 56.2, 82.35, 94.89, 114.2, 125.6, 126.1, 120.64, 133.37, 137.6, 138.61, 152.7, 156.09, 168.57. HR-MS calcd for $C_{26}H_{36}O_5$: 428.2563, found 428.2567.

21. **[3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl) phenoxy] acetic acid (GC-1).** To the ester **11** (2.0 g, 0.00470 mol) in 40 mL of a 50% (v/v) mixture of *i*-PrOH and THF was added 2.0 mL of 1 N HCl. The reaction mixture was stirred for 2 h at room temperature, diluted with 50 mL of water and extracted with ethyl acetate (2×75 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 1.70 g of the corresponding *O*-methoxymethyl deprotected phenol, which was used directly in the following step. To the above phenol (1.50 g, 0.0039 mol) in 40 mL of methanol was added 26 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at room temperature, acidified with 30 mL of 2 N HCl, and extracted with ethyl acetate (2×100 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give **GC-1** (1.20 g, 0.0037 mol, 79%); ^{1}H NMR (CD_3OD, 300 MHz) δ 1.15 (d, 6H, J = 6.6 Hz), 2.18 (s, 6H), 3.21 (heptet, 1H, J = 6.6 Hz), 3.86 (s, 2H), 4.40 (s, 2H), 6.49–6.62 (m, 2H), 6.65 (s, 2H), 6.84 (s, 1H); ^{13}C NMR (CD_3OD, 300 MHz): δ 20.8, 23.0, 27.6, 34.4, 68.3, 115.2, 115.6, 126.0, 126.4, 126.5, 131.6, 135.6, 139.1, 152.8, 157.0, 177.9. HR-MS calcd for $C_{20}H_{24}O_4$: 328.1675, found: 328.1679.

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