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An Efficient Substitution Reaction for the Preparation of Thyroid Hormone Analogues

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Abstract—The substitution of the sterically hindered carbon of the potent thyroid hormone agonist, GC-1, was effected by a reaction based on the solvolysis of the benzylic hydroxyl group. The reaction was found to proceed in high yield with a variety of nucleophiles including alcohols, thiols, allyl silanes and electron-rich aromatic compounds, providing a convenient route to the synthesis of new thyroid hormone analogues.

Introduction

3,5,3′-Triiodo-L-thyronine (T_3) (**2**, Figure 1) is the major active form of thyroid hormone, which is an important endocrine signaling molecule in vertebrates.[1] Most of the physiological actions of T_3 result from transcriptional regulation T_3-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 nonsteroid ligands such as the retinoic acid receptor (RAR) and retinoid X receptor (RXR).[2–4] There are two different TRs in vertebrates designated TRα and TRβ that are coexpressed in different ratios in different tissues.[5] The hypothesis that the different TRs are linked to the different tissue-specific effects of T_3 guides our efforts in TR ligand design.

Although antagonist ligands have been developed for a number of nuclear receptors, there is currently no reported high-affinity antagonist for the TR. Examination of known nuclear receptor antagonist ligands reveals that these compounds structurally resemble their agonist counterparts but contain a large (>8 carbon atom) extension group attached to the middle of the molecule.[6] This has led us to undertake synthetic studies of thyroid hormone analogues in an effort to prepare a high-affinity antagonist that contains an extension group attached to the middle of a TR agonist. We have recently prepared and characterized a high affinity TRβ-selective agonist ligand (**1**, Fig. 1) that contains several structural differences from T_3.[7] In particular, the methylene unit bridging the two phenyl rings introduces a new derivatizable position in the middle of the molecule which is unavailable in the natural ligand where an ether oxygen joins the rings.

It was toward this bridging carbon that we first directed our efforts in synthesizing derivatives of **1**. Initial attempts at adding extensions to the benzophenone **4** failed using alkyl lithium and Grignard reagents. Organocerium reagents were more successful but yields were generally too low to be useful. Using an S_N1 reaction inspired by one used in the preparation of semi-synthetic rapamycin derivatives,[8,9] we have found a route to the efficient derivatization of the bridging carbon with a panel of nucleophiles. The resulting derivatives can be converted to thyromimetics using the same chemistry that was established for the synthesis of **1**.[7]

Key words: Thyroid hormone; thyromimetic; S_N1.
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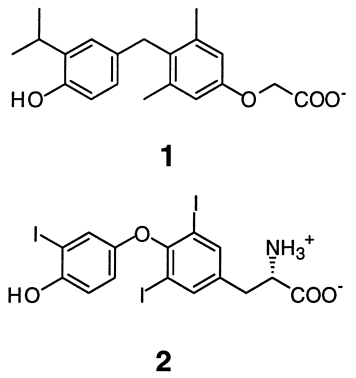


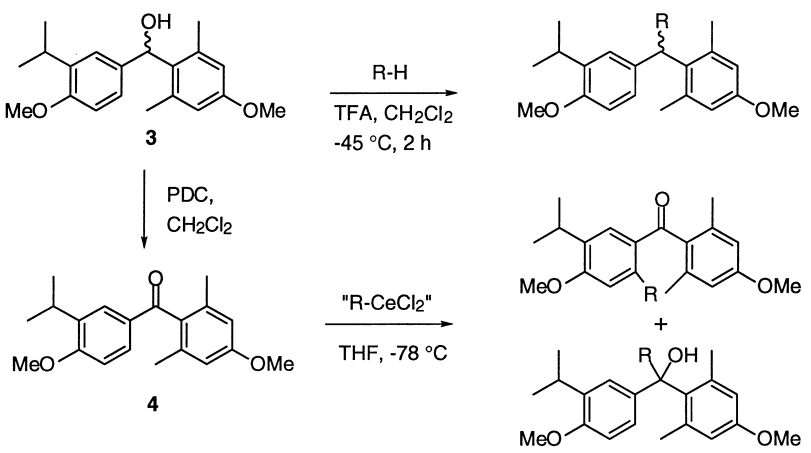
Figure 1.

Results and Discussion

The benzyl alcohol **3** produced by the coupling of the two rings was oxidized with PDC to the benzophenone **4** (Scheme 1). It was our plan to add extensions to the carbonyl function of **4** using organolithium nucleophiles. Attempts with *n*-butyllithium, *sec*-butyllithium, phenyllithium and lithium phenylacetylide resulted in poor yields and recovery of starting material. Grignard reagents also fared poorly, with *sec*-butylmagnesium chloride and octylmagnesium bromide both failing to react. Rationalizing the low reactivity of the carbonyl to its sterically congested environment, we then tried the organocerium(III) analogues, which had been previously shown to react with similarly sterically hindered phenyl ketones.[10] Butylcerium(III) reagents were prepared in situ via transmetalation from the corresponding butyllithiums and $CeCl_3$. *n*-Butylcerium(III) chloride (1.3 equiv) reacted with **4** to yield an approximate equimolar mix of the 1,4- and 1,2-addition products **5** and **6**, respectively; whereas a 10-fold excess of cerium reagent yielded **5** only (Table 1). The apparent 1,4-addition to the phenyl ring seen in **5** was also observed when *sec*-butylcerium(III) chloride was used. It is notable that this side reaction should occur given that organocerium reagents were previously observed to add exclusively in a 1,2 fashion to α,β-unsaturated ketones and furfural.[11] Methylcerium(III) chloride reacted with **4** to produce the 1,2-addition product **9** in 42% yield, which was the only product obtained in sufficient quantities to allow conversion into a thyroid hormone analogue.

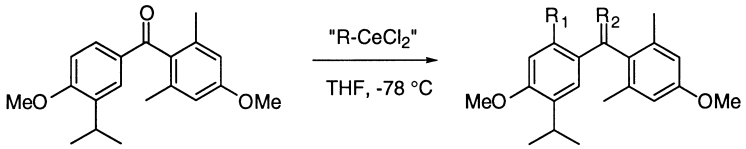
This route clearly was not efficient or versatile enough for our purposes and a new scheme was devised based on the solvolysis of the benzylhydroxyl group of **3**. We reasoned that a carbonium ion would be formed easily from **3** in acidic conditions. This carbonium ion would be stabilized by the two electron-rich aromatic rings leaving it vulnerable to attack by acid-stable nucleophilic species at the desired bridging carbon (Scheme 1). Following the conditions used for rapamycin[8,9] (TFA, CH_2Cl_2, −45 °C), we found ethanol to substitute in high yield with no detectable starting material or side products. Subsequent attempts with allyltrimethylsilane, 1,3-dimethoxybenzene, ethanethiol and thiophenol all proceeded in high yield (Table 2). Furan also seemed to work as a nucleophile, but the product decomposed during subsequent handling steps. Acetamide failed to react, and 1-phenyl-1-(trimethylsilyloxy)ethylene gave a series of decomposition products, probably owing to the strong acidic conditions.

While these results are very encouraging and the wide scope of these reactions promise to make easy the creation of many derivatives at this site, some problems remain. Most significantly, the acidic conditions that



Scheme 1.

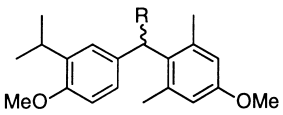
Table 1. Alkyl cerium(III) chloride additions to the benzophenone **4**

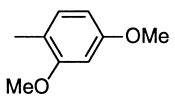


Organocerium reagent	Ratio (equiv)	Product	R_1	R_2	Yield[a] (%)
n-$BuCeCl_2$	10	**5**	*n*-Bu	O	38
n-$BuCeCl_2$	1.3	**5**	*n*-Bu	O	27
		6	H	OH, *n*-Bu	22
sec-$BuCeCl_2$	1.3	**7**	*sec*-Bu	O	22
		8	H	OH, *sec*-Bu	17
$MeCeCl_2$	1.5	**9**	H	OH, Me	42

[a]Isolated yield.

Table 2. Carbon bridge extensions via solvolysis of **3**



R	Compd	Yield[a] (%)
-OEt	**10**	73
-SEt	**11**	89
-SPh	**12**	66
$-CH_2CH=CH_2$	**13**	93
	**14**	90

[a]Isolated yield.

allows the easy formation of these derivatives is also a route to their decomposition. The substituents with nucleophilic heteroatoms, in this case the ethers and thioethers, require all subsequent steps in the synthesis of their corresponding thyroid hormone analogues to avoid both acidic and hydrogenating conditions or the extensions will lost to solvolysis or hydrogenolysis. Consequently, the phenolic methyl protecting groups, which are removed by BBr_3, will have to be replaced with silyl protecting groups, which can be removed by milder fluoride treatment.

The substitution reaction yields racemic product from racemic starting material (**3**) as a result of the extension attached to the bridging carbon. This site of asymmetry will be preserved in the conversion of these intermediates to thyroid hormone analogues. This affords the opportunity to probe stereochemical issues related to receptor binding and activation with these analogues. The thyroid hormone analogues easily accessible by this chemistry should provide valuable probes for studying the nature of the receptor–ligand interaction. Moreover, any high-affinity antagonists that result from this approach may be useful as biological probes of thyroid hormone signaling.

Experimental

General methods

Proton and carbon-13 nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were obtained on a General Electric QE–300 (300 MHz) spectrometer, with tetramethylsilane used as the reference. High resolution mass spectrometry was performed by the National Bio-Organic, Biomedical Mass Spectrometry Resource at UCSF. Flash chromatography on crude products was performed using 230–400 mesh silica gel (Aldrich Chemical Co.). Purity of compounds was determined by TLC using commercial silica gel plates (Alltech, Alugram® Sil G/UV 254) and by ^{1}H NMR and HRMS.

Glassware was oven- or flame-dried prior to use. Methylene chloride (anhydrous), tetrahydrofuran (anhydrous) and reagents were purchased from Aldrich Chemical Co. and used without further purification. Reactions were performed under Argon inert atmosphere.

4,4′-Dimethoxy-3′-(1-methylethyl)-2,6-dimethylbenzophenone (4). To alcohol **3** (10 g, 31.80 mmol) in 150 mL of methylene chloride at 0°C was added pyridinium

dichromate (23.93 g, 63.60 mmol). The reaction mixture was stirred for 4 h at 0 °C and then filtered through Celite. The filtrate was evaporated, and the residue was purified by flash column chromatography (silica gel, 95:5 hexane:ethyl acetate) to give **4** (6 g, 19.23 mmol, 60%); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 6H), 2.02 (s, 6H), 3.22 (heptet, J = 6.9 Hz, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 6.53 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 199.5, 161.5, 159.5, 137.7, 136.2, 133.1, 130.6, 130.4, 127.2, 113.0, 109.7, 55.7, 55.3, 27.0, 22.5, 19.9. HRMS exact mass calcd for $C_{20}H_{24}O_3$: 312.1725, found: 312.1724.

4,4′-Dimethoxy-6′-butyl-3′-(1-methylethyl)-2,6-dimethylbenzophenone (5). To a suspension of cerous chloride anhydrous ($CeCl_3$) (1.580 g, 6.41 mmol) in 20 mL of dry tetrahydrofuran at −78 °C was added 3.2 mL of butyllithium (2.0 M in pentane). The reaction mixture was stirred for 30 min at −78 °C and then ketone **4** (0.2 g, 0.641 mmol) in 5 mL of tetrahydrofuran was added and the mixture was stirred for 3–4 h. Then, the reaction mixture was treated with satd NH_4Cl solution, filtered through silica, and extracted with ethyl acetate. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product, which was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 98:2) to yield 90 mg (0.24 mmol, 38%) of addition product **5** as an oil. ^{1}H NMR ($CDCl_3$) δ 7.22 (s, 1H), 6.73 (s, 1H), 6.58 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.18 (heptet, J = 6.9 Hz, 1H), 3.05 (t, J = 7.8 Hz, 2H), 2.09 (s, 6H), 1.62 (quintet, J = 7.5, 7.8 Hz, 1H), 1.44 (sextet, J = 7.2, 7.5 Hz, 2H), 1.03 (d, J = 6.9 Hz, 6H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 201.1, 159.8, 159.4, 145.5, 136.4, 134.9, 134.2, 131.6, 129.5, 113.4, 113.0, 55.6, 55.3, 34.8, 33.8, 26.7, 23.3, 22.6, 20.2, 14.2. HRMS exact mass calcd for $C_{24}H_{32}O_3$: 368.2351, found: 368.2347.

4,4′-Dimethoxy-6′-butyl-3′-(1-methylethyl)-2,6-dimethylbenzophenone (5) and 1-(4-methoxy-2,6-dimethylphenyl)-1-[4-methoxy-3-(1-methylethyl)phenyl] pentanol (6). To a suspension of $CeCl_3$ (0.205 g, 0.832 mmol) in 3 mL of dry tetrahydrofuran at −78 °C was added 0.420 mL of butyllithium (2.0 M in pentane). After stirring for 30 min at −78 °C ketone **4** (0.2 g, 0.641 mmol) in 5 mL of tetrahydrofuran was added and the mixture was stirred for 3–4 h. Then, the reaction mixture was treated with sat. NH_4Cl solution, filtered through silica, and extracted with ethyl acetate. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product, which was purified by flash column chromatography (silica gel, hexane/ethyl acetate, 98:2) to give **5** (64 mg, 0.173 mmol, 27%) and **6** (52 mg, 0.141 mmol, 22%). (**6**): ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 2.1 Hz, 1H), 7.08 (dd, J = 2.1, 9 Hz, 1H), 6.76 (d, J = 9 Hz, 1H), 6.54 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.27 (heptet, J = 6.9 Hz, 1H), 2.31 (m, 2H), 2.21 (s, 6H), 1.57 (m, 2H), 1.35 (m, 2H), 1.18 (dd, J = 6.9 Hz, 6H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 157.1, 155.9, 142.1, 138.8, 136.9, 135.2, 124.2, 123.9, 115.9, 110.3, 81.9, 55.4, 55.1, 40.7, 27.3, 26.7, 25.1, 23.6, 22.9, 14.4.

4,4′-Dimethoxy-6′-(1-methylpropyl)-3′-(1-methylethyl)-2,6-dimethylbenzophenone (7) and 1-(4-methoxy-2,6-dimethylphenyl)-1-[4-methoxy-3-(1-methylethyl)phenyl]-2-methylbutanol (8). To a suspension of $CeCl_3$ (0.515 g, 2.1 mmol) in 7 mL of dry tetrahydrofuran at −78 °C was added 1.6 mL of *sec*-butyllithium (1.3 M in cyclohexane). After stirring for 30 min at −78 °C ketone **4** (0.5 g, 1.6 mmol) in 12 mL of tetrahydrofuran was added and the mixture was stirred for 3–4 h. Then, the reaction mixture was treated with satd NH_4Cl solution, filtered through silica, and extracted with ethyl acetate. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate, 98:2) to give **7** (130 mg, 0.35 mmol, 22%) and **8** (100 mg, 0.27 mmol, 17%). (**7**) ^{1}H NMR ($CDCl_3$), δ 7.18 (s, 1H), 6.85 (s, 1H), 6.57 (s, 2H), 3.88 (s, 3H), 3.83 (m, 1H), 3.82 (s, 3H), 3.15 (heptet, J = 6.9, 1H), 2.10 (s, 6H), 1.78 (m, 1H), 1.57 (m, 1H), 1.26 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.9 Hz, 6H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (C_6D_6) δ 201.1, 160.5, 160.3, 150.6, 137.1, 136.1, 134.5, 131.6, 131.1, 113.9, 109.2, 55.2, 55.0, 36.3, 31.9, 27.4, 23.0, 22.7, 20.7, 13.1. HRMS exact mass calcd for $C_{24}H_{32}O_3$: 368.2351, found: 368.2345. (**8**) ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 1.8 Hz, 1H), 7.46 (dd, J = 1.8, 8.1 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 6.61 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.26 (heptet, J = 6.9, 1H), 3.04 (m, 1H), 2.11 (s, 6H), 1.61 (m, 2H), 1.23 (m, 9H), 0.86 (t, J = 7.2 Hz, 3H).

α-Methyl-[4,4′-dimethoxy-3′-(1-methylethyl)-2,6-dimethyl] benzhydrol (9). To a suspension of $CeCl_3$ (0.592 g, 2.4 mmol) in 7 mL of dry tetrahydrofuran at −78 °C was added 1.71 mL of methyllithium (1.4 M in diethylether). After stirring for 30 min at −78 °C ketone **4** (0.5 g, 1.6 mmol) in 10 mL of tetrahydrofuran was added and the mixture was stirred for 3–4 h. Then, the reaction mixture was treated with sat. NH_4Cl solution, filtered through silica, and extracted with ethyl acetate. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product, which was purified by flash column chromatography (silica gel, 95:5 hexane/ethyl acetate) to yield the alcohol **9** (221 mg, 0.67 mmol, 42%). ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 2.1, 1H), 7.20 (dd, J = 2.1, 7.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.64 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.35 (heptet, J = 6.9 Hz, 1H), 2.22 (s, 6H), 2.00 (s, 3H), 1.20 (dd, J = 6.9 Hz, 6H).

General procedure for substitution of the bridging carbon. A solution of benzyl alcohol **3** (40 mg, 0.13 mmol) and nucleophile (5.1 mmol) in methylene chloride (8 mL) was cooled to −45 °C (dry ice/acetonitrile bath). Trifluoroacetic acid (167 μL, 2.2 mmol) was added and the reaction stirred 2 h at −45 °C. The reaction was quenched by adding satd $NaHCO_3$ (5 mL) and water (5 mL). Layers were separated and the aqueous phase extracted twice with Et_2O (7 mL). Combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and evaporated. Purification by flash chromatography (Et_2O-hexanes, 1:20) was performed. Note: in reactions involving thiols, the reaction was quenched with 0.5 M NaOH (10 mL), and the extracted aqueous phase treated with bleach to reduce the stench.

Spectral and analytical data of the prepared carbon-bridge derivatives.

Ethoxy-4,4′-dimethoxy-2,6-dimethyl-3′-(1-methylethyl)diphenylmethane (10). ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 1.6 Hz, 1H), 6.90 (dd, J = 1.5, 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.57 (s, 2H), 5.80 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.47 (br q, J = 7.0 Hz, 2H), 3.26 (heptet, J = 6.9 Hz, 1H), 2.24 (s, 6H), 1.26 (t, J = 7.0 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.15 (d, J = 6.7 Hz, 3H); HRMS exact mass calcd for $C_{22}H_{30}O_3$ 342.2195, found 342.2189.

Ethylthio-4,4′-dimethoxy-2,6-dimethyl-3′-(1-methylethyl) diphenylmethane (11). ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 1.6, 8.4 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 6.56 (s, 2H), 5.58 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.27 (heptet, J = 6.9 Hz, 1H), 2.67–2.48 (M, 2H), 2.23 (br s, 6H), 1.28 (t, J = 7.4 Hz, 3H), 1.17 (app t, J = 7.0 Hz, 6H); HRMS exact mass calcd for $C_{22}H_{30}O_2S$ 358.1966, found 358.1953.

4,4′-Dimethoxy-2,6-dimethyl-3′-(1-methylethyl)diphenylphenylthiomethane (12). ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.32 (s, 1H), 7.25–7.17 (m, 3H), 7.08 (dd, J = 1.7, 8.4 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.55 (s, 2H), 5.89 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.26 (heptet, J = 6.9 Hz, 1H), 2.13 (br s, 6H), 1.15 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H); HRMS exact mass calcd for $C_{26}H_{29}O_2S$ (M-H$^+$) 405.1888, found 405.1894.

4,4-[4′,4″-Dimethoxy-2′,6′-dimethyl-3′-(1-methylethyl)diphenyl]butan-1-ene (13). ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 1.7 Hz, 1H), 6.87 (dd, J = 1.6, 8.4 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.54 (s, 2H), 5.78–5.67 (m, 1H), 5.09 (dd, J = 1.0, 17.1 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 4.50 (t, J = 7.9 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.26 (heptet, J = 6.9 Hz, 1H), 3.09–3.00 (m, 1H), 2.80–2.70 (m, 1H), 2.15 (br s, 6H), 1.16 (d, J = 7.1 Hz, 3H), 1.14 (d, J = 7.1 Hz, 3H); HRMS exact mass calcd for $C_{23}H_{30}O_2$ 338.2246, found 338.2247.

4,4′,2″,4″-Tetramethoxy-2,6-dimethyl-3′-(1-methylethyl) triphenylmethane (14). ^{1}H NMR ($CDCl_3$) δ 6.85 (s, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.68 (s, 1H), 6.54 (s, 2H), 6.47 (d, J = 2.2 Hz, 1H), 6.36 (dd, J = 2.3, 8.5 Hz, 1H), 5.93 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.24 (heptet, J = 6.9 Hz, 1H), 1.99 (s, 6H), 1.09 (d, J = 6.9 Hz, 6H); HRMS exact mass calcd for $C_{28}H_{34}O_4$ 434.2457, found 434.2458.

Acknowledgements

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