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# A straightforward route to obtain $^{13}C_1$-labeled clenbuterol

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ABSTRACT

Singly-labeled $^{13}C_1$-clenbuterol has been synthesized employing a straightforward pathway starting from easily available acetanilide. The critical step was the Friedel–Crafts acylation of this compound with marked acetyl chloride, being the first example of the use of this methodology applied to the synthesis of a clenbuterol derivative. Subsequent chemical reactions afforded the desired product with good yields.


## 1. Introduction

Clenbuterol (**1**, Fig. 1a), as a member of the $\beta_2$-agonists family, has extensively been (and is still) prescribed as bronchodilatator in asthmatic patients.[1] In fact, this compound is licensed in the EU for therapeutic use in food producing species and approved by the US Food and Drug Administration (FDA) for use in horses.[2] Its therapeutical role to combat skeletal muscle atrophy secondary to disuse, injury and denervation has intensively been investigated and is not completely clear its relevance in this point.[3]

The main problem of this type of compounds is that they are illegally employed because of their anabolic effects on skeletal muscle and their lipolytic effect, on the one hand, by sportsmen for doping purposes, and on in the other hand, by farmers to feed cattle due to financial profit reasons. This has raised public health concern and highlights the relevance for developing efficient analytical methods to detect clenbuterol and similar growth promoting substances in low levels.[4] For this reason, identification and quantification of these compounds is difficult and requires reliable methodologies. Immunological,[5] electrochemical,[5] spectrophotometric,[6] and mass spectrometric approaches have been described but those based on chromatography coupled to mass spectrometric detection, such as GC–MS[7] or LC–MS[8] provide an easier

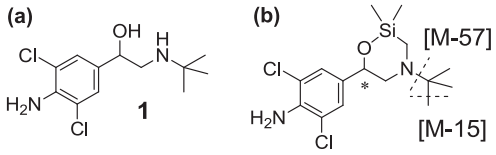


**Fig. 1.** (a) Clenbuterol. (b) $^{13}C_1$-Labeled DMS-clenbuterol derivative and two of the characteristic breaks in its MS spectrum. The symbol * refers to the enriched $^{13}C$ position in the molecule.

implementation for a routine basis. The accuracy and precision in the results is an important handicap due to matrix effects and the required time-consuming sample preparation steps. Isotope Dilution Mass Spectrometry (IDMS)[9] is regarded as an absolute measurement method directly traceable to the International System of units as it provides results with the highest metrological quality. Most of the procedures use deuterated[10] compounds as internal standards, however, labeling with 1 mass unit ('minimal labeling') with $^{13}C$ is more efficient to avoid differences in the physicochemical properties between the unlabeled and labeled compounds.[11]

The EU regulations require the confirmation of the presence of clenbuterol by gas chromatography–mass spectrometry. When a full scan spectrum is recorded, a minimum of four ions shall be present with a relative intensity of ≥10% of the base peak.[12] In the analysis of clenbuterol by GC–MS, several reagents have been employed to derivatize it into a volatile and thermally stable

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molecule. Among them, chloro(chloromethyl)dimethylsilane[13] produces a dimethylsilamorpholine (DMS) derivative with five ions [i.e., 331 ($M-CH_3$) and 289 ($M-{}^tBu$) *m*/*z*, Fig. 1b] with a relative intensity of ≥10% of the base peak that confirms the presence of clenbuterol.[14]

Due to this, it was envisaged the synthesis of a singly-labeled clenbuterol analogue at the carbon linked to the hydroxyl group, since both breaks will contain the isotopic label and therefore will be suitable for IDMS quantification. There are few routes described to obtain clenbuterol,[15] labeled analogues, such as $D_9$- and $D_3$-clenbuterol,[16] or a radiolabeled monotritiated derivative.[17] In these protocols, the starting material was usually 4-aminoacetophenone or similar compounds, that obviously cannot be employed as precursors of our target molecule since we need to introduce the mark at the carbonyl position. In our case, due to its easy accessibility, aniline (**2**) or acetanilide (**3**) was chosen as the starting material, and therefore the key-step to introduce the labeled carbon was the employment of a Friedel–Crafts acylation protocol.

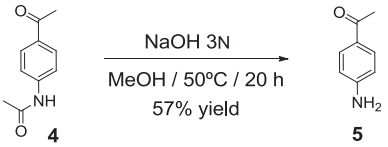
## 2. Results and discussion

Friedel–Crafts acylation[18] provides a useful methodology to achieve aromatic ketones. The usual way to perform it makes use of Lewis acids such as $AlCl_3$. While with *ortho*- and *para*-directing groups like alkyl, alkoxy, or halogen present in the benzene moiety, the *p*-acylated product is usually obtained with high yields, when highly deactivating or amino groups are present at the molecule, this reaction is more difficult to achieve. In fact, there are only few examples employing aniline or acetanilide as substrates in order to obtain the corresponding acetophenone derivatives. Thus, $ZrO_2$ and acetyl chloride at 60 °C,[19] aluminum metal powder[20] or zinc[21] with acetyl chloride under microwave conditions, and $Ga(OTf)_3$ with acetic anhydride at 50 °C[22] have been used to perform this specific transformation. Unfortunately, in our hands most of these procedures did not work although several conditions were tried (see Supporting data).

Due to this, we decided to achieve this transformation under the more usual conditions with $AlCl_3$ or $FeCl_3$ (Table S1, Supporting data). When aniline was used as substrate with acetyl chloride or acetic anhydride as acylating agent, *N*-acylation was always achieved, therefore we tried this reaction with acetanilide directly. Microwave or thermal conditions were employed with $AlCl_3$ and acetyl chloride[23] in dichloromethane, but no or very low conversion (8%) was observed. The use of $FeCl_3$ as catalyst was not efficient as well. Finally, we were glad to obtain a good conversion of 70% of **3** into **4** when 3.2 equiv of $AlCl_3$ and 2 equiv of acetyl chloride were employed in 1,2-dichloroethane at 60 °C for 24 h. When this reaction was repeated employing marked $CH_3{}^{13}COCl$ to obtain **4a**, the reaction yield was comparable.

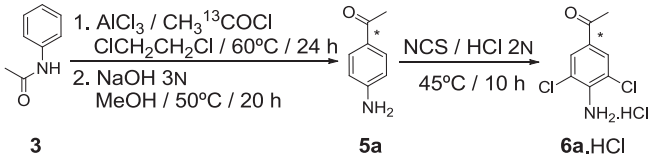
Once compound **4** was achieved with good yield, the next step was to find the suitable reaction conditions to hydrolyze the acetamido into the corresponding amine affording **5**, since the following chlorination step would need the free amino group to activate positions 3 and 5 in order to achieve derivative **6**. Among the different methodologies to obtain aniline derivatives from their acetylated counterparts,[24] we chose the basic hydrolysis employing NaOH 3 N in MeOH at 50 °C (Scheme 1). Thus, after 20 h the desired compound was obtained as the only product with good yield. In a subsequent experiment, the two first reactions were done without purification of **4**, synthesizing **5** from **3** with a combined yield of 40% after flash chromatography.

The next step is the chlorination of the phenyl ring at positions 3 and 5. Among all methods described in the bibliography to perform this transformation, it can be highlighted the use of NaOCl,[15a,25] chlorine,[26] and *N*-chlorosuccinimide (NCS). Due to its easy handling, we chose this last reagent trying to find the optima



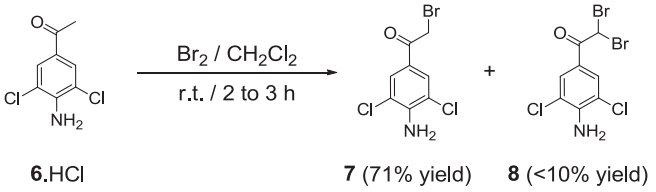

**Scheme 1.** Synthesis of compound **5** starting from **4**.

conditions (Table S2, Supporting data). Thus, we started employing an excess of NCS with *p*-toluenesulfonic acid (*p*-TsOH) at different temperatures, but in all cases a mixture of different compounds was obtained. When employing a lower excess of both NCS and acid, the desired product was isolated with 25% yield after flash chromatography. Finally, we followed a procedure using NCS in HCl 2 N at 45 °C.[15b] Under these conditions, hydrochloride **6**·HCl was obtained as a precipitate in the reaction medium, and therefore a simple filtration afforded the desired product with 75% yield. When repeating this sequence starting from **3** and using $CH_3{}^{13}COCl$, labeled compound **6a**·HCl was achieved with similar yields (Scheme 2).




**Scheme 2.** Obtaining of derivative **6a**·HCl from acetanilide **3**.

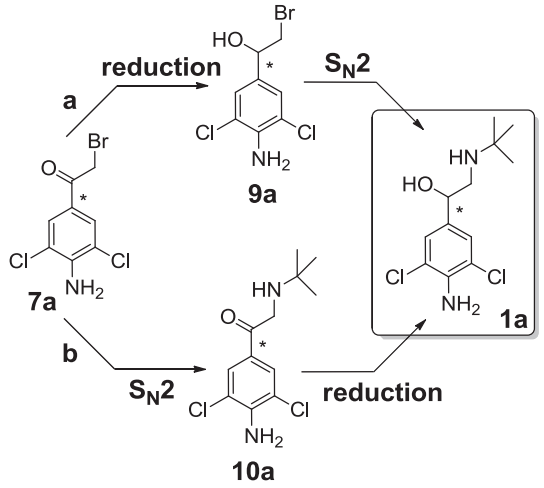
The next step was the α-bromination of **6**·HCl to obtain derivative **7** employing the typical conditions with $Br_2$ in $CH_2Cl_2$. The same transformation was previously reported in chloroform.[27] This reaction was very dependent concerning the bromine equivalents and the addition procedure. Thus, it was found that the best conditions were observed when adding at the beginning 0.6 equiv of $Br_2$ and later several portions of 0.2 equiv of bromine until the α,α-dibrominated derivative **8** was detected by TLC. At this point, we were able to isolate compound **7** with a yield of 71%, as previously shown in chloroform (Scheme 3).[27] Again, this reaction afforded a comparable yield when marked substrate **6a**·HCl was used as substrate.



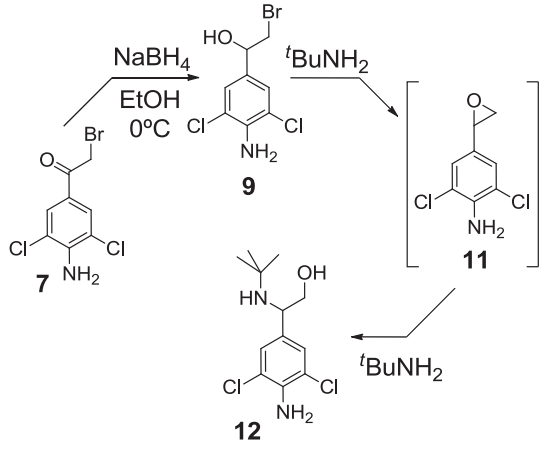

**Scheme 3.** Bromination of derivative **6**·HCl to afford **7** and **8**.

To synthesize labeled clenbuterol **1a** from intermediate **7a**, two different approaches can be done (Scheme 4). This is: (a) reduction of the ketone into the corresponding bromohydrin **9a** and subsequent $S_N2$ reaction with *tert*-butylamine; or (b) nucleophilic substitution with ${}^tBuNH_2$ to afford ketone **10a** and subsequent reduction of this intermediate.

Firstly, pathway 'a' (Scheme 4) was tried employing substrate **7**. Thus, reduction with $NaBH_4$ in EtOH at 0 °C quantitatively afforded the desired alcohol **9** with traces of epoxide **11**, but this should not be a problem since the $S_N2$ reaction over both substrates should afford clenbuterol. Surprisingly, when this substitution reaction was done with ${}^tBuNH_2$ in different solvents and temperatures (Table S3, Supporting data), the reaction proceeded forming one product, although by $^1H$ NMR and MS it was discovered that this compound was not **1** but its regioisomer **12** (Scheme 5). This fact can be explained taking into account the formation of epoxide **11** as




**Scheme 4.** Pathways to obtain labeled clenbuterol **1a** from derivative **7a**.




**Scheme 5.** Formation of derivative **12** through epoxide **11**.

intermediate of this process catalyzed by the amine. The synthesis of similar derivatives through the corresponding epoxides has already been described.[28]

Due to this, we chose pathway 'b' (Scheme 4) to obtain clenbuterol. Thus, reaction of **7** with *tert*-butylamine in $CHCl_3$ at 50 °C afforded derivative **10** after 24 h. Due to its low stability, the reduction process was performed in situ, after evaporation of the solvent and the remaining $^tBuNH_2$, using $NaBH_4$ in MeOH or $LiAlH_4$ in THF at room temperature, but in both cases the final product could not be isolated. However, when the reduction with $NaBH_4$ was kept at pH 7, the final product could be obtained as chlorhydrate with a combined yield of 25% for both processes. When these reactions were done over labeled **7a**, $^{13}C_1$-clenbuterol **1a**·HCl was achieved with comparable yield.

## 3. Conclusions

Recent analytical findings[11] have demonstrated the utility of labeled compounds with a minimum number of $^{13}C$-atoms to develop new methodologies based on IDMS for the analysis of organic compounds. Thus, we strongly believe that demand of further single $^{13}C$-enriched compounds will significantly increase in the near future. Herein, we have described the first synthesis of the singly-labeled $^{13}C_1$-clenbuterol derivative. The crucial step was the Friedel–Crafts reaction with marked acetyl chloride over acetanilide, and the following reactions were done under typical conditions with good yields. This is the first time where a Friedel–Crafts protocol has been applied to the synthesis of a clenbuterol derivative. Special mention must be done in the formation of the regioisomer of clenbuterol when the substitution reaction occurs over the epoxide and not over the bromohydrin, being a nice example of how although epoxides and halohydrins are considered as similar chemical functionalities, they can offer different features that can be exploited chemoselectively.[29]

## 4. Experimental section

### 4.1. General

All employed reagents were purchased from commercial sources. Reagents and solvents were of the highest quality available. 4-Acetamidoacetophenone was purchased from Sigma–Aldrich (St. Louis, MO, USA). Labeled compound $^{13}C_1$-acetyl chloride (99% nominal enrichment) was obtained from Sigma–Aldrich (St. Louis, MO, USA) in pure liquid form. Aluminum chloride, *N*-chlorosuccinimide, bromine, *tert*-butylamine, sodium borohydride and sodium hydroxide of pure grade were commercially supplied by Sigma–Aldrich. All solvents (hexane, methanol, dichloroethane, dichloromethane and chloroform) were obtained from Merck.

Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on an Infrared Fourier Transform spectrophotometer using KBr or NaCl pellets. Flash chromatography was performed using silica gel 60 (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were measured on DPX-300 ($^1H$, 300.13 MHz and $^{13}C$, 75.5 MHz). Chemical shifts are given in delta ($\delta$) values, the coupling constants ($J$) in hertz (Hz), and tetramethylsilane was used as the internal standard. $ESI^+$ or $EI^+$ was used to record mass spectra (MS) and high-resolution mass spectra (HRMS). Microwave employed was purchased from CEM Corporation, Mathews, N.C., USA.

*4.1.1. $^{13}C_1$-4′-Acetamidoacetophenone (**4a**).* To a solution of acetanilide (0.8 mmol, 108 mg) in 1,2-dichloroethane (2 mL), $AlCl_3$ (2.55 mmol, 341 mg) and $^{13}C_1$-acetyl chloride (1.6 mmol, 117 μL) were added under nitrogen atmosphere. The resulting mixture was stirred and heated at 60 °C during 24 h. The progress of the reaction was followed by TLC (60% ethyl acetate/hexane), and it was stopped when the starting material had been totally consumed. After cooling at room temperature, the crude was firstly extracted with dichloromethane (5×10 mL). The aqueous phase was treated with NaOH pellets until pH 5–6 was reached, and then it was extracted with dichloromethane (2×10 mL). The organic layers were combined, washed with brine (2×10 mL), and dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford a crude that was purified by flash chromatography using mixtures of ethyl acetate/hexanes as eluent, affording **4a** with 70% isolated yield. Solid; mp 165–169 °C; IR (NaCl) $\nu$ 744, 896, 1179, 1265, 1422, 1601, 1642, 2306, 2987, 3055; $^1H$ NMR (300 MHz, MeOD-$d_4$) $\delta$ 2.33 (*s*, 3H, $H_a$), 2.74 (d, 3H, $H_2$, $^2J_{CH}$ 5.7 Hz), 7.88 (d, 2H, $H_m$, $^3J_{HH}$ 8.5 Hz), 8.13 (dd, 2H, $H_o$, $^3J_{HH}$ 8.3, $^3J_{CH}$ 3.3 Hz); $^{13}C$ NMR (75 MHz, MeOD-$d_4$) $\delta$ 22.6 ($C_a$), 25.0 (d, $C_2$, $^1J_{CC}$ 42.4 Hz), 118.6 (d, $C_m$, $^3J_{CC}$ 3.8 Hz), 129.3 (d, $C_o$, $^2J_{CC}$ 2.8 Hz), 132.2 (d, $C_i$, $^1J_{CC}$ 53.2 Hz), 142.1 ($C_p$), 170.5 ($C_c$), 198.0 ($C_1$); MS [$EI^+$, $m/z$ (%)] 179 (6), 178 (32), 163 (10), 136 (20), 121 (100); HRMS ($ESI^+$) calcd for $^{13}CC_9H_{11}NNaO_2$ [$(M+Na)^+$] 201.0715, found 201.0715.

*4.1.2. $^{13}C_1$-4′-Aminoacetophenone (**5a**).* To a solution of $^{13}C_1$-4′-acetamidoacetophenone (5.75 mmol, 1019.2 mg) in methanol (10 mL), NaOH 3 N (45 mmol, 15 mL) was added under stirring. The mixture was heated at 50 °C for 20 h. The progress of the reaction was followed by TLC (60% ethyl acetate/hexane). After cooling at room temperature, the solvent was removed by evaporation under

reduced pressure. The crude material was extracted with dichloromethane (3×20 mL), the organic layers were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (silica gel) using ethyl acetate/hexane mixtures as eluent, affording **5a** in 61% isolated yield. Solid, mp 103–107 °C; IR (NaCl) $\nu$ 740, 896, 1266, 1422, 1596, 2306, 2987, 3055, 3405; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.50 (d, 3H, $H_2$, $^2J_{CH}$ 5.8 Hz), 6.64 (d, 2H, $H_m$, $^3J_{HH}$ 8.6 Hz), 7.80 (dd, 2H, $H_o$, $^3J_{HH}$, 8.4 $^3J_{CH}$ 3.5 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4 (d, $C_2$, $^1J_{CC}$ 42.3 Hz), 114.1 (d, $C_m$, $^3J_{CC}$ 3.9 Hz), 128.3 (d, $C_i$, $^1J_{CC}$ 55.8 Hz), 131.1 (d, $C_o$, $^2J_{CC}$ 2.6 Hz), 151.4 ($C_p$), 196.8 ($C_1$); MS [EI$^+$, *m*/*z* (%)] 137 (4), 136 (48), 121 (100), 92 (42); HRMS calcd for $^{13}CC_7H_9NNaO$ [(M+Na)$^+$] 159.0615, found 159.0609.

*4.1.3. $^{13}C_1$-4′-Amino-3′,5′-dichloroacetophenone·HCl (**6a**·HCl).* *N*-Chlorosuccinimide (3.14 mmol, 420 mg) was added into a solution of **5a** (1.26 mmol, 170 mg) in HCl 2 N (2 mL). The reaction was heated at 50 °C and stirred during 10 h. The progress of the reaction was followed by TLC (60% ethyl acetate/hexane), until the starting material was totally consumed. The formed solid was filtered, washed with water at 0 °C (2×20 mL), and dried under reduced pressure to give the corresponding product in 75% isolated yield. Solid, mp 163–168 °C; IR (NaCl) $\nu$ 740, 896, 1266, 1422, 1610, 2307, 2987, 3055, 3399; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.50 (d, 3H, $H_2$, $^2J_{CH}$ 5.9 Hz), 4.93 (*s*, 2H, NH), 7.82 (d, 2H, $H_o$, $^3J_{CH}$ 3.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 25.9 (d, $C_2$, $^1J_{CC}$ 42.9 Hz), 118.7 (d, $C_m$, $^3J_{CC}$ 5.7 Hz), 127.5 (d, $C_i$, $^1J_{CC}$ 54.6 Hz), 128.5 (d, $C_o$, $^2J_{CC}$ 3.0 Hz), 144.1 ($C_p$), 194.4 ($C_1$); MS [EI$^+$, *m*/*z* (%)] 208 (8), 206 (30), 204 (48), 193 (16), 191 (64), 189 (100), 164(2), 162 (10), 160 (14), 124 (22); HRMS (ESI$^+$) calcd for $^{13}CC_7H_7Cl_2NNaO$ [(M+Na)$^+$] 226.983, found 226.9832.

*4.1.4. $^{13}C_1$-4′-Amino-2-bromo-3′,5′-dichloroacetophenone (**7a**).* To a solution of **6a**·HCl (1.70 mmol, 350 mg) in dichloromethane (8 mL), a bromine solution [(1.02 mmol, 52 μL) in dichloromethane (2 mL)] was added dropwise under strong agitation. The progress of the reaction was followed by TLC every few minutes (60% hexane/dichloromethane), and when no progress was observed, other 0.2 equiv of $Br_2$ in 0.5 mL of $CH_2Cl_2$ was added until the formation of 2,2-dibrominated derivative was detected by TLC. The reaction was kept at room temperature and the total time was usually 2 h. The solvent was removed by evaporation at reduced pressure and the residue was subjected to flash chromatography (silica gel) using dichloromethane/hexane mixtures as eluent, affording **7a** in 70% isolated yield. Solid, mp 153–158 °C; IR (NaCl) $\nu$ 739, 896, 1076, 1265, 1421, 1488, 1583, 1619, 2306, 2987, 3054, 3394, 3492; $^1$H NMR (300 MHz, MeOD-$d_4$) $\delta$ 4.55 (d, 2H, $H_2$, $^2J_{CH}$ 3.4 Hz), 7.92 (d, 2H, $H_o$, $^3J_{CH}$ 3.8 Hz); $^{13}$C NMR (75 MHz, MeOD-$d_4$) $\delta$ 31.9 (d, $C_2$, $^1J_{CC}$ 44.3 Hz), 119.8 (d, $C_m$, $^3J_{CC}$ 6.0 Hz), 124.7 (d, $C_i$, $^1J_{CC}$ 59.2 Hz), 131.0 (d, $C_o$, $^2J_{CC}$ 3.0 Hz), 148.0 ($C_p$), 190.8 ($C_1$); MS [ESI$^+$, *m*/*z* (%)] 208 (M−Br, 9), 206 (M−Br, 29), 204 (M−Br, 46), 193 (14),;191 (64), 189 (100).

As byproduct, $^{13}C_1$-4′-amino-2,2-dibromo-3′,5′-dichloroacetophenone **8a** was also obtained. Solid, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.13 (*s*, 2H, $NH_2$), 6.53 (d, 1H, $H_2$, $^2J_{CH}$ 0.7 Hz), 7.98 (d, 2H, $H_o$, $^3J_{CH}$ 3.8 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 38.9 (d, $C_2$, $^1J_{CC}$ 44.1 Hz), 118.6 (d, $C_m$, $^3J_{CC}$ 6.2 Hz), 120.1 (d, $C_i$, $^1J_{CC}$ 62.6 Hz), 129.9 (d, $C_o$, $^2J_{CC}$ 2.8 Hz), 145.2 ($C_p$), 182.8 ($C_1$); HRMS (ESI$^+$) calcd for $^{13}CC_7H_5Br_2Cl_2NNaO$ [(M+Na)$^+$] 382.804, found 382.8044.

*4.1.5. $^{13}C_1$-1-(4′-Amino-3′,5′-dichlorophenyl)-2-(tert-butylamino) ethanone·HCl (**10a**·HCl).* In a sealed tube **7a** (0.52 mmol, 150 mg) was dissolved in anhydrous chloroform (3 mL) and then *tert*-butylamine (8.20 mmol, 860 μL) was added. The solution was heated at 50 °C with agitation for 24 h. After this time, the solution had an intense orange color. After cooling to room temperature, the solvent and the excess of *tert*-butylamine were removed by evaporation under reduced pressure and the residue was extracted with chloroform (5×2 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The solid was diluted in 3 mL of anhydrous chloroforme and HCl/diethylether was added dropwise to afford the chlorhydrate. Some drops of diethylether were added to improve the precipitation. The resulting solid was filtered, washed with diethylether (2×3 mL), and dried under reduced pressure obtaining **10a**·HCl. Due to its instability, we subsequently proceeded with the reduction.

*4.1.6. $^{13}C_1$-1-(4′-Amino-3′,5′-dichlorophenyl)-2-(tert-butylamine) ethanol·HCl or $^{13}C_1$-clenbuterol·HCl (**1a**·HCl).* To a solution of **10a**·HCl (0.25 mmol, 80 mg) in water (1.5 mL) and methanol (2 mL), NaOH 1 N was added until pH 7, and afterwards a $NaBH_4$ solution in water (0.05 mmol, 2 mg of $NaBH_4$ in 0.5 mL of water) was added in portions. The mixture was stirred at room temperature and after 1 h, the mixture was basified with NaOH 2 N until pH 10. The progress of the reaction was followed by TLC (50% dichloromethane/methanol) until the starting material was totally consumed. Methanol was removed by evaporation at reduced pressure. The aqueous phase was extracted with dichloromethane (3×10 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The solid was dissolved with dichloromethane (1 mL) and drops of HCl/diethylether (pH 3–4) were added to afford the chlorhydrate. Then, 1 mL of diethylether was added and the product was left at −20 °C to allow the precipitation of the final product **1a**·HCl (25% yield from **7a**). The resulting solid was filtered, washed with diethylether (2×5 mL) and dried under reduced pressure. Solid, mp decompose. IR (NaCl) $\nu$ 740, 896, 1265, 1421, 1626, 2306, 2987, 3055, 3402; $^1$H NMR (300 MHz, MeOD-$d_4$) $\delta$ 1.42 (*s*, 9H, $^t$Bu), 2.99–3.18 (*m*, 2H, $H_2$), 4.81 (ddd, 1H, $H_1$, $^1J_{CH}$ 157.6, $^3J_{HH}$ 13.1, $^3J_{HH}$ 3.2 Hz), 7.37 (d, 2H, $H_o$, $^3J_{CH}$ 4.2 Hz); $^{13}$C NMR (75 MHz, MeOD-$d_4$) $\delta$ 26.4 ($C_4$), 58.9 (d, $C_2$, $^1J_{CC}$ 7.4 Hz), 70.2 ($C_1$), 80.0 ($C_3$), 121.3 (d, $C_m$, $^3J_{CC}$ 5.6 Hz), 127.5 (d, $C_o$, $^2J_{CC}$ 3.4 Hz), 133.1 (d, $C_i$, $^1J_{CC}$ 48.8 Hz), and 142.4 ($C_p$); MS [ESI$^+$, *m*/*z* (%)] 282 (10), 280 (63), 278 (100), 262 (15), 260 (24), 206 (19), 204 (30); HRMS (ESI$^+$) calcd for $^{13}CC_{11}H_{18}Cl_2N_2O$ [M$^+$] 278.0902, found 278.0900.

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## Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.05.118.

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