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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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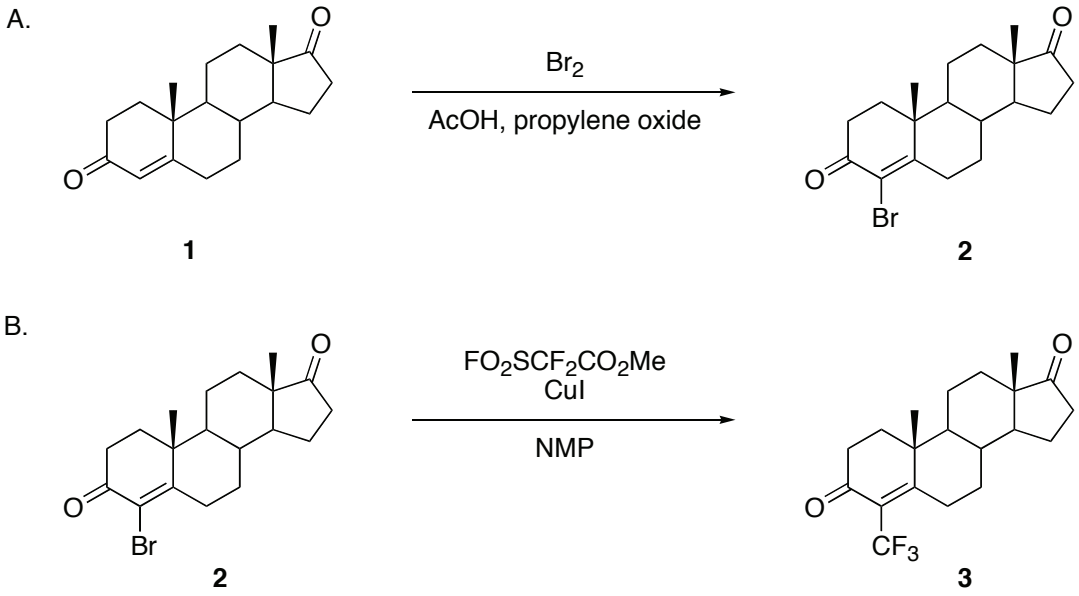
NEW, CONVENIENT ROUTE FOR TRIFLUOROMETHYLATION OF STEROIDAL MOLECULES



Submitted by Xiang-Shu Fei, Wei-Sheng Tian, Kai Ding, Yun Wang and Qing-Yun Chen.[1]
Checked by Takayuki Yamakawa and Tohru Fukuyama.

1. Procedure

Caution! Br_2 develops harmful vapors and should be handled only in an efficient fumehood.

A. *4-Bromoandrost-4-ene-3,17-dione*. A modification of Kirk's procedure was employed (Note 1). A 250-mL, single-necked, round-bottomed flask is well wrapped with aluminum foil and fitted with a 3.0-cm octagon-shaped stir bar and a 100-mL pressure-equalizing dropping funnel connected to an oil bubbler (Note 2). The flask is charged with androst-4-en-3,17-dione **1** (11.4 g, 40 mmol) (Note 3) and propylene oxide (120 mL) and cooled to 0 °C (Note 3). A solution of bromine (12 g, 75 mmol) (Notes 3 and 4) in acetic acid (60 mL) (Note 3) is added over 30 min via the dropping funnel. After completion of the addition, the mixture is allowed to stir for 2 h in the dark at 0 °C. After complete consumption of the starting material (as

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monitored by TLC, Note 4), the reaction is quenched with the addition of saturated aq. Na_2SO_3 solution until the red color disappears. This mixture is diluted with EtOAc (300 mL) and washed with H_2O (200 mL × 2). The aqueous layer is re-extracted with EtOAc (150 mL) and the combined organic phases are washed successively with saturated aq. sodium hydrogen carbonate (200 mL) and brine (200 mL). The organic phase is dried over Na_2SO_4, filtered through a glass funnel with a cotton wool plug into a 2-L round-bottomed flask and concentrated under reduced pressure with a rotary evaporator (Note 5). A 300-mL single-necked round-bottomed flask fitted with a 3.0-cm octagon-shaped stir bar is charged with the residue, CH_2Cl_2 (100 mL) and Et_3N (5 mL). (Notes 3 and 6). After stirring for 5 h, the mixture is diluted with 200 mL of EtOAc and washed successively with saturated aq. sodium hydrogen carbonate (100 mL), 2 M hydrochloric acid (100 mL) and brine (100 mL), and dried with anhydrous Na_2SO_4. The organic phase is concentrated by rotary evaporation to a thick slurry, which was added to a 100-mL single-necked round-bottomed flask fitted with a 2.0-cm octagon shaped stir bar. The slurry is diluted through the addition of ethyl acetate (15 mL) and hexanes (30 mL). After a few minutes of stirring, the resulting solid is collected by filtration, then washed with hexanes and dried under high-vacuum (0.2 mmHg) to afford compound **2** (8.0 g) as yellow solid. The mother liquor is concentrated under reduced pressure, and the yellow residue is purified by chromatography on SiO_2 to afford an additional 1.7 g of compound **2** (Note 7). The combined crystals are dissolved in boiling methanol (50 mL) and allowed to cool to 0 °C. Colorless needles are collected by suction filtration to afford the pure compound **2** as colorless needles (7.7 g, 52%). The mother liquor is concentrated to 10 mL and cooled to 0 °C to give additional product (1.6 g, 11%) (Note 8).

B. *4-(Trifluoromethyl)androst-4-ene-3,17-dione*. A flame-dried, 50-mL single-necked round-bottomed flask, containing a 2.0-cm octagon-shaped stir bar and equipped with a rubber septum and nitrogen inlet, is charged with compound **2 (**3.65 g, 10 mmol), CuI (2.3 g, 12 mmol) (Note 3) and methyl fluorosulfonyldifluoroacetate (8.0 mL, 63 mmol) (MFSDA, Note 3) in dry NMP (10 mL) (Notes 3 and 9). After stirring for 5 h at 80 °C (Note 10), the dark red solution is allowed to cool to room temperature. Additional MFSDA (2 mL, 16 mmol) is added *via* syringe (Note 11). The solution is stirred at 80 °C for an additional 10 h. After complete consumption of the starting material (as monitored by ^{1}H NMR, Note 12), the mixture is filtered

through a Celite pad and washed with ethyl acetate (300 mL). The solution is washed with H_2O (100 mL × 3) and the aqueous layer is re-extracted with EtOAc (50 mL). The combined organic layer is washed with brine (50 mL) and dried over Na_2SO_4. After the Na_2SO_4 is removed by filtration through a glass funnel with a cotton wool plug, the solution is concentrated. The residue is eluted through a short silica gel column to remove the colored impurities (Note 13). The eluent is concentrated to afford the crude product as yellow solid. Recrystallization with ethyl acetate and hexanes provides compound **3** as a white powder (2.8 g, 79%) (Note 14). The mother liquor is concentrated under reduced pressure, and the pink residue is eluted through a short silica gel column to afford additional **3** (0.12 g, 3.4%) (Notes 15 and 16).

2. Notes

1. Kirk provided two methods for the 4-bromination of androst-4-en-3,17-dione.[2] The submitters performed the procedure with an excess of Br_2/collidine for 48 h to obtain compound **2**.[3] Because of the unpleasant odor of collidine and the laborious purification by chromatography, an alternative method[2,4] with propylene oxide as an acid scavenger was used to prepare compound **2** on large scale.

2. The use of an oil bubbler prevents the leakage of harmful vapors.

3. (Submitter) Androst-4-en-3,17-dione **1** was obtained from Xinchang Pharmaceutical Company and was used after recrystallization from ethyl acetate (>95% purity of **1**). Compound **1** can also be purchased from Acros Organics or Aldrich Chemical Company. Acetic acid (99.5+%), propylene oxide (99.5+%), Et_3N (99+%), CH_2Cl_2 (99.5+%), Br_2 (99.5+%, freshly opened bottle), CuI (99.5+%, freshly opened bottle) were purchased from Sinopharm Chemical Reagent Co., Ltd and were used as received. DMF, HMPA, NMP (99.5+%) were purchased from Shanghai Chemical Reagent Co., Ltd and were distilled from CaH_2 prior to use. Methyl fluorosulfonyldifluoroacetate (MFSDA), purchased from Acros Organics or Aldrich Chemical Company, was distilled prior to use (66 °C/85 mmHg).

(Checker) Androst-4-en-3,17-dione **1** was purchased from Tokyo Chemical Industry Co., Ltd and was used after recrystallization from ethyl acetate. Acetic acid (>99.7%), propylene oxide (>99.5%), and Et_3N (>98.0%) were purchased from Kanto Chemical Co. Inc., and CH_2Cl_2 (>99.0%), Br_2 (>99.0%, freshly opened bottle), CuI (>99.5%) were

purchased from Wako Pure Chemical Industried, Ltd and were used as received. NMP (>99.0%) was purchased from Kanto Chemical Co., Inc. and was distilled prior to use. Methylfluorosulfonyldifluoroacetate (MFSDA) was purchased from Tokyo Chemical Industry Co. Ltd and used as received. Instead of hexanes, *n*-hexane was used during the checking process.

4. TLC: starting material **1**, R_f= 0.40; compound **2**, R_f= 0.45 (SiO_2, GF254, hexane/ethyl acetate, 3:1). Spots are visualized with UV light or by staining with aqueous ceric ammonium molybdate solution followed by heating

5. Concentration at high temperature (60 °C) results in a significant formation of a more polar by-product.

6. The additional step promotes the elimination of bromide, which improves the yield and purity of product.

7. The concentrated mother liquid, a mixture of compound **2** and a polymer of propylene oxide, is mixed with SiO_2 (30 g, 100-200 mesh) and washed with hexane through a plug of SiO_2 (10 g, 100-200 mesh). After the non-polar polymer is eluted, the column is eluted with CH_2Cl_2/ethyl acetate/hexane (1:1:5). The fractions containing the product are combined and evaporated under reduced pressure to give an additional 1.6 g of compound **2**. Checkers used the procedure as follows; the residue is purified on SiO_2 (120 g) and eluted with EtOAc/*n*-hexane (10% to 15%). After concentration on a rotary evaporator, a magnetic stir bar is added to the flask and the slurry is diluted with ethyl acetate (15 mL) and *n*-hexane (30 mL). After a few minutes of stirring, the resulting solid is collected by filtration, washed with hexanes, and dried under high-vacuum (0.2 mmHg) to afford compound **2** (1.7 g) as a yellow solid.

8. An alternative workup procedure was less laborious but gave a lower yield on a 40 mmol-scale preparation: The crude product was dissolved in ethyl acetate (10 mL). Petroleum ether was added until the resulting solid became sticky. The semi-solid (14 g) was crystallized from ethyl acetate and petroleum ether twice to afford a yellow solid (7.3 g, 50%), which was pure enough for further use. Compound **2** has the following physical and spectroscopic properties: mp 164.0–165.0 °C (The submitter reported a mp of 149.0–149.3 °C); $[\alpha]_D^{25}$ = +203.3 (c 1.16, $CHCl_3$); IR (KBr): 2944, 2857, 1738, 1685, 1574, 1053, 1011, 915, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (s, 3 H), 1.04 (ddd, J = 11.9, 11.0, 4.1 Hz, 1H), 1.15 (dddd, J = 14.0, 12.5, 12.5, 4.1 Hz, 1H), 1.25 (s, 3 H), 1.23-1.33 (m, 2H),

1.46 (dddd, J = 13.7, 13.7, 11.9, 3.7 Hz, 1H), 1.58 (dddd, J = 12.5, 12.5, 9.2, 8.9 Hz, 1H), 1.65-1.82 (m, 3H), 1.86 (ddd, J = 12.8, 3.7, 2.7 Hz, 1H), 1.93-2.06 (m, 3H), 2.10 (ddd, J = 19.5, 9.2, 9.2 Hz, 1H), 2.29 (ddd, J = 15.1, 14.0, 5.3 Hz, 1H), 2.47 (dd, J = 19.5, 8.9 Hz, 1H), 2.54-2.68 (m, 2H), 3.32 (ddd, J = 15.1, 4.1, 2.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 13.7, 17.8, 20.4, 21.6, 30.0, 31.2, 32.5, 33.9, 34.5, 34.8, 35.7, 42.4, 47.4, 50.7, 53.9, 122.2, 167.1, 190.4, 220.0; LRMS (EI) *m/z* 364 (M^+, 11), 285 (M-Br, 100); Anal. calcd. for $C_{19}H_{25}BrO_2$: C, 62.47; H, 6.90; found: C, 62.52; H, 6.96.

9. Submitters used DMF as the reaction solvent. MFSDA reacts with DMF to produce a byproduct $CF_3SO_2CH{=}CHNMe_2$,[5] which was removed by sublimation. The checkers changed the solvent from DMF to NMP in order to avoid the need for the sublimation. Removal of the byproduct by chromatography would necessitate a laborious purification for a large-scale preparation due to the similar R_f value of compound **3** and the byproduct. When HMPA is used as the solvent, the formation of byproduct $CF_3SO_2CH{=}CHNMe_2$ is avoided; however, the use of toxic HMPA is undesirable. The reaction could not be carried out in DMSO or DMA.

10. The submitters used a Schlenk tube for the transformation. The stopcock of the Schlenk tube must be closed to prevent traces of solvent and reagents from entering the nitrogen system while heating the reaction. The reaction is carried out under sealed conditions.

11. Addition of MFSDA in one batch results in incomplete conversion (about 10–20% starting material after 20 h).

12. The reaction process cannot be monitored by TLC because compounds **2** and **3** have identical R_f values.

13. The residue is eluted with CH_2Cl_2/petroleum ether/ethyl acetate (1:4:2) through a plug of 20 g of SiO_2 (200-300 mesh). The Checkers used a different eluent with the same amount of SiO_2 (EtOAc/*n*-hexane, 10% to 20%)

14. The crude material is dissolved in as little ethyl acetate as possible (~3 mL, 80 °C). 20 mL of hexane is added with stirring. The suspension is stirred at 80 °C for 30 min, and then cooled to room temperature. The resulting solid is collected by filtration and dried in vacuo to afford 2.8 g of compound **3** as a white powder.

15. Washing with petroleum ether through a plug of 5 g of SiO_2 (200-300 mesh) removes low polar impurities to prevent aggregation. Then finely powdered product is obtained after eluting with CH_2Cl_2/petroleum

ether/ethyl acetate (1:6:2). The Checkers used *n*-hexane instead of petroleum ether.

16. Purification by chromatography provides a higher yield (85%) on a 5 mmol scale preparation with HMPA as solvent. Compound **3** has the following characteristics: mp 148.1–148.9 °C; $[\alpha]_D^{25}$ 201.1 (*c* 1.06, $CHCl_3$); IR (KBr): 2944, 2857, 1738, 1685, 1574, 1053, 1011, 915, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (s, 3 H), 1.12 (ddd, *J* = 11.9, 11.0, 4.1 Hz, 1 H), 1.14-1.26 (m, 1 H), 1.28 (s, 3 H), 1.25-1.34 (m, 2 H), 1.47 (dddd, *J* = 14.3, 14.3, 11.0, 3.6 Hz, 1 H), 1.58 (dddd, *J* = 12.5, 12.5, 9.2, 8.9 Hz, 1 H), 1.67-1.84 (m, 3 H), 1.87 (ddd, *J* = 14.2, 3.6, 3.6 Hz, 1 H), 1.92-2.06 (m, 3 H), 2.10 (ddd, *J* = 19.5, 9.2, 9.2 Hz, 1 H), 2.19-2.30 (m, 1 H), 2.41-2.52 (m, 3 H), 3.09 (ddd, *J* = 14.7, 3.2, 3.2 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 13.7, 18.0, 20.5, 21.6, 28.2, 30.9, 31.2, 33.9, 33.9, 34.9, 35.7, 41.1, 47.4, 50.6, 54.3, 123.0 (q, *J* = 279.3 Hz), 125.3 (q, *J* = 25.9 Hz), 174.7, 193.0, 219.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –56.4 (s); LRMS (EI) *m/z* 354 (M^+, 70), 192(100); Anal. calcd. for $C_{20}H_{25}F_3O_2$: C, 67.78; H, 7.11; found: C, 67.53; H, 7.13.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

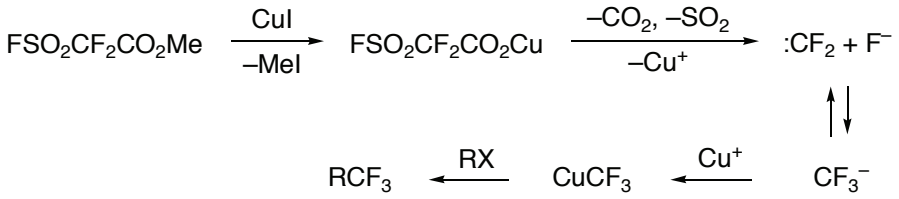
3. Discussion

The unique properties of the trifluoromethyl group, e.g. its high electronegativity, stability and lipophilicity, have ensured that trifluoromethylated compounds play an increasingly important role in bioorganic and medicinal chemistry.[6] With respect to the synthesis of structurally simple molecules, the selection of a trifluoromethylated building block followed by several necessary synthetic steps seems to be straightforward and convenient.[7] However, for the synthesis of complicated trifluoromethylated natural products, such as steroids, terpenes and alkaloids, the building block strategy is very difficult, if not impossible, to apply. Trifluoromethylation of halides offers a direct approach to introduce the trifluoromethyl group into complex molecules. Although numerous methods have been employed for the trifluoromethylation of aryl halides,[8]

these methods often suffer from (1) low reactivity and yield, (2) expensive and unstable reagents, (3) harsh conditions, and (4) poor generality.

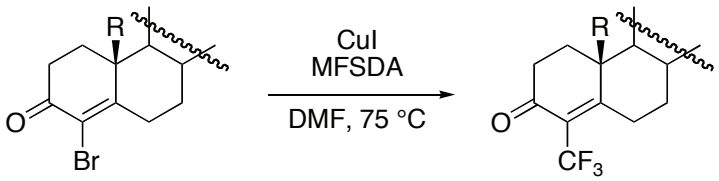
We previously found that $FO_2SCF_2CO_2Me$ (MFSDA), an inexpensive, stable and low-toxicity trifluoromethylating agent, can successfully replace a halogen in allyl, aryl and alkenyl halides under mild conditions.[9] The method is also efficient for the trifluoromethylation of some complex steroidal molecules and can be used to provide a series of trifluoromethylated natural products (Table 1).[3] The preparation on a 15 mmol-scale, as described in this procedure, provides the desired trifluoromethylated product with no drop in yield.

The mechanism of this trifluoromethylation is suggested to involve a difluorocarbene intermediate and proceed as shown in Scheme 1. Methyl difluoro(fluorosulfonyl)acetate reacts with copper(I) iodide. After elimination of SO_2 and CO_2, difluorocarbene and fluoride ion furnish $[CF_3Cu]$ in the presence of CuI. Nucleophilic trifluoromethylation of aryl or alkenyl halide leads to RCF_3.



Scheme 1

Table 1 Trifluoromethylation of 4-Bromo-3-oxo-Δ^4-steroids.[a]



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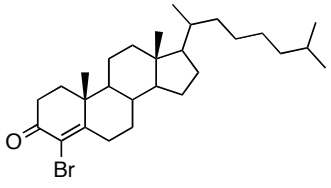
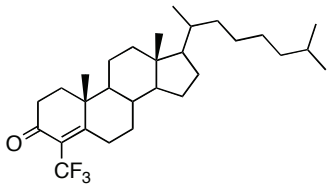
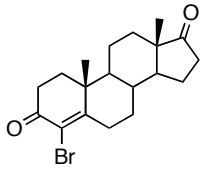
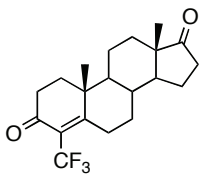
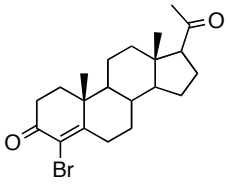
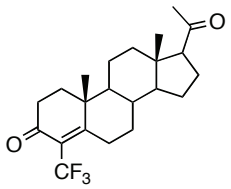
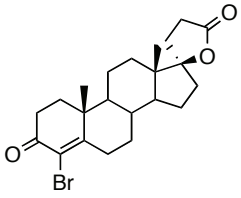
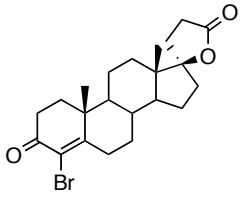
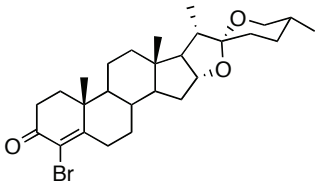
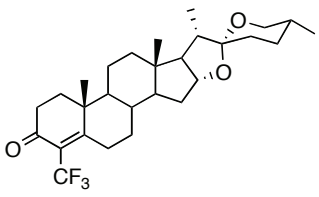
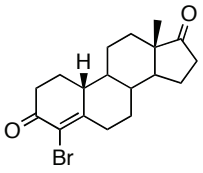
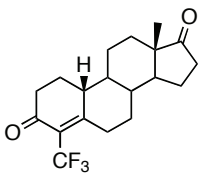
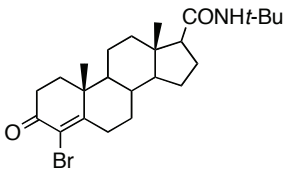
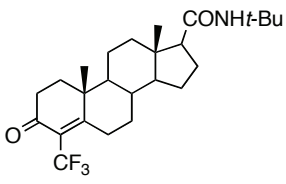
1			90
2			81
3			74
4			70
5			71
6			82
7			91

[a] Reactions performed on 100 mg scale. [b] Isolated yield.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

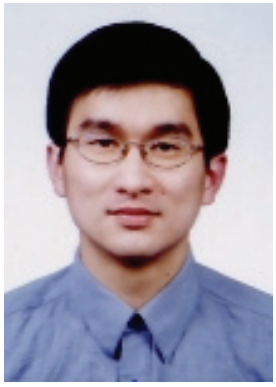
Androst-4-ene-3,17-dione; (63-05-8)
Oxirane, 2-methyl-; (75-56-9)
Bromine; (7726-95-6)
Androst-4-ene-3,17-dione, 4-bromo-; (19793-14-7)
Acetic acid, 2,2-difluoro-2-(fluorosulfonyl)-, methyl ester; (680-15-9)

Copper iodide; (7681-65-4)
Phosphoric triamide, *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethyl- ; (680-31-9)
Androst-4-ene-3,17-dione, 4-(trifluoromethyl)-; (201664-30-4)
2-Pyrrolidinone, 1-methyl-; (872-50-4)

Qing-Yun Chen graduated from Peking University in 1952. He was a graduate student in 1956-1960 at Institute of Elementoorganic Compounds USSR and received candidate Ph.D. in 1960. He joined the faculty team of Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences in 1963 and was elected the academician of Chinese Academy of Sciences in 1993. His research interests focus on perfluoroalkanesulfonic acids and their derivatives, difluorocarbene, trifluoromethylation, single electron transfer reactions and fluorinated porphyrins.

Xiang-Shu Fei received his B.S. degree and M.S. degree from Xiamen University in 1991 and 1994, respectively. During 1994-1997 he pursued his Ph.D. at the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences with Professor Qing-Yun Chen and Wei-Sheng Tian. He did postdoctoral research at Texas A&M University with Professor Sir Derek H. R. Barton from 1997-1998. He also served as a post-doctoral researcher at Wayne State University with Professor Aloke K. Dutta from 1999-2001.

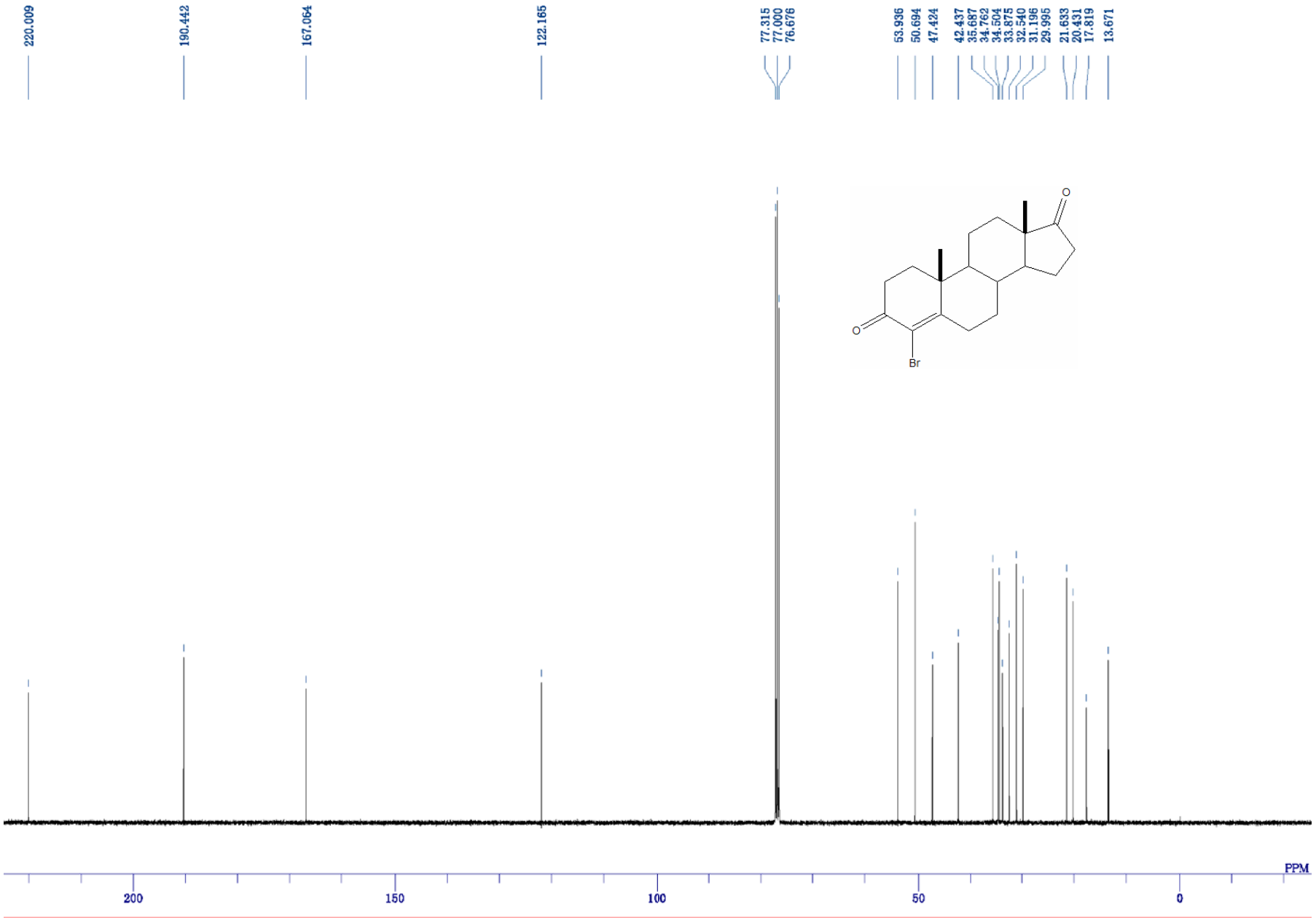
Wei-Sheng Tian received his Ph.D. degree from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences in 1985 under the supervision of Professor Weishan Zhou. He worked as a postdoctoral fellow for two years (1986-1988) with Professor T. Livinghouse at University of Minnesota and Montana State University. He was appointed as an Associate Professor at SIOC In 1990 and promoted to Full Professor in 1995. His research interests focus on the synthetic of natural and/or artificial resource molecules (Resource Chemistry).



Kai Ding was born in 1976 in Hubei, China. He obtained his B.S. degree in 1996 and M.S. degree in 1999 from East China University of Science and Technology. He joined the Shanghai Institute of Organic Chemistry to obtain his doctorate in 2003 studying natural products total synthesis. After being a research assistant for two years, he joined the group of Professor Albert, S.C. Chan at the Hong Kong Polytechnic University as a postdoctoral research associate. In 2008, he moved back to Shanghai and became associate professor at Shanghai Institute of Organic Chemistry. His research focused on natural product total synthesis.

Yun Wang was born in 1978 in Shanghai, China. She received her M.S. degree in 2003 from the Shanghai University. Then she moved to Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, where she is now a research assistant of organic chemistry. Her current interest is in the synthesis and application of steroid drugs.

Takayuki Yamakawa was born in 1983 in Hiroshima, Japan. He graduated in 2007 and received his M.S. degree in 2009 from University of Tokyo under the direction of Professor Tohru Fukuyama. The same year he started his Ph.D. study under the supervision of Professor Fukuyama. His research interest is total synthesis of natural products.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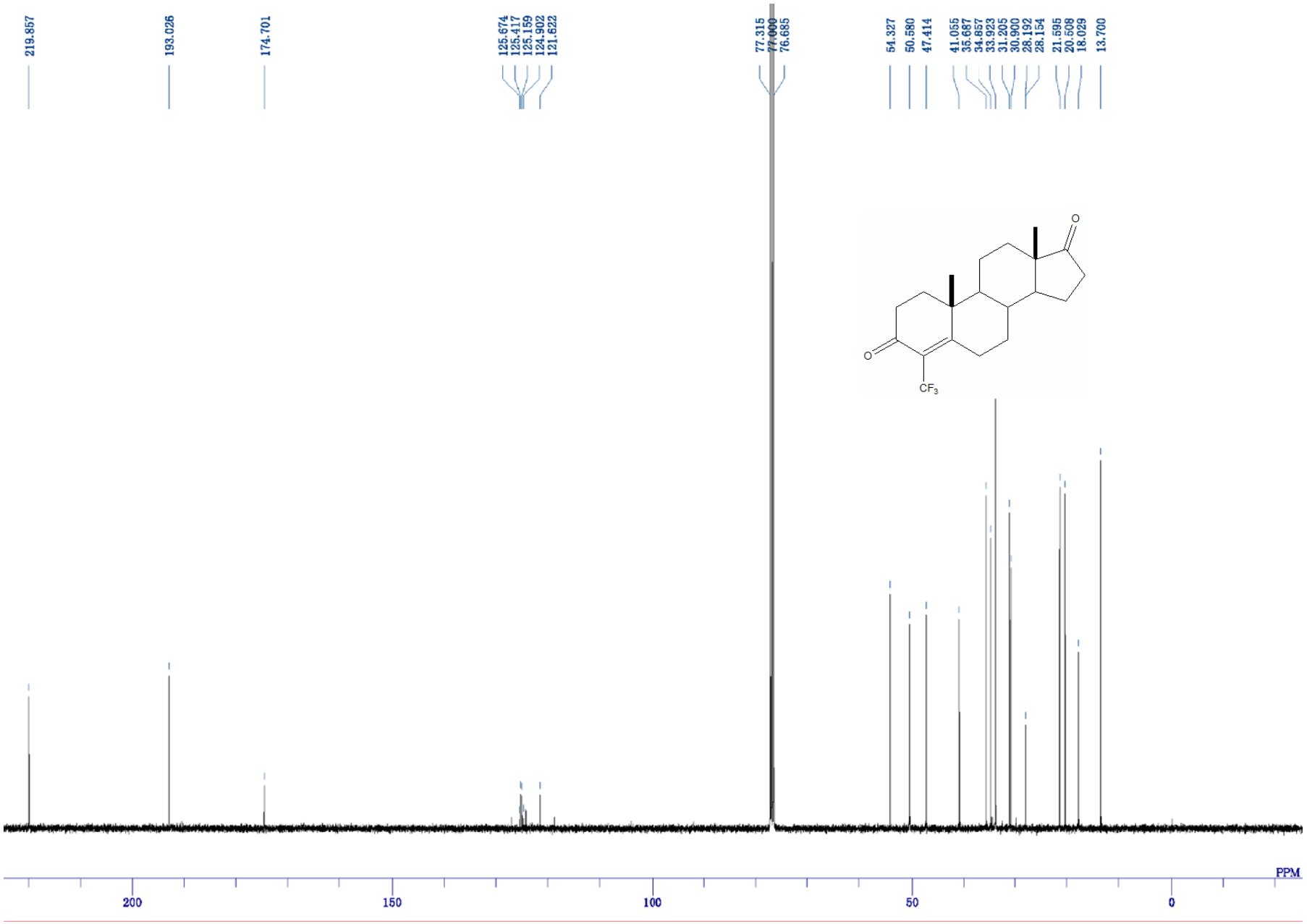
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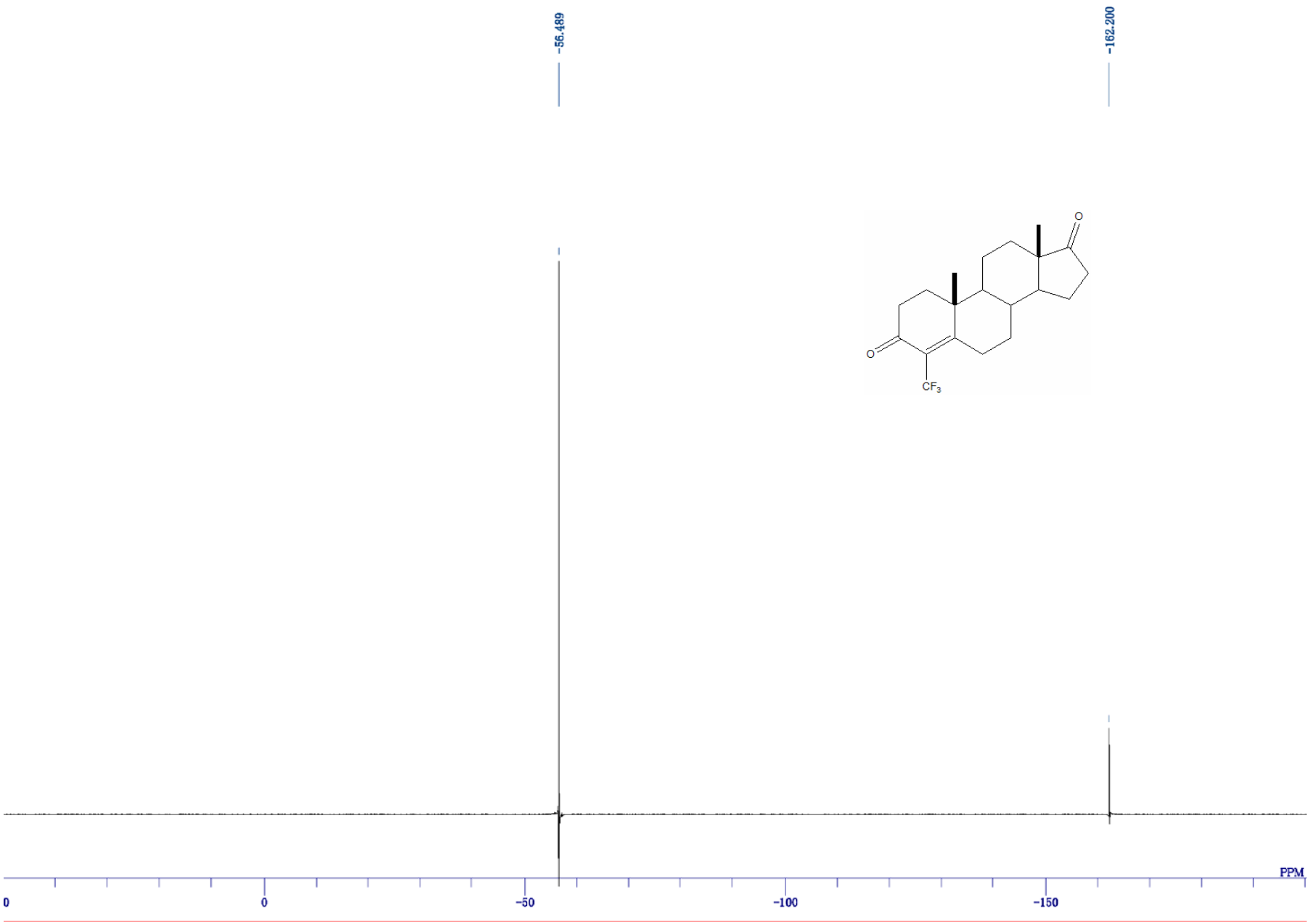
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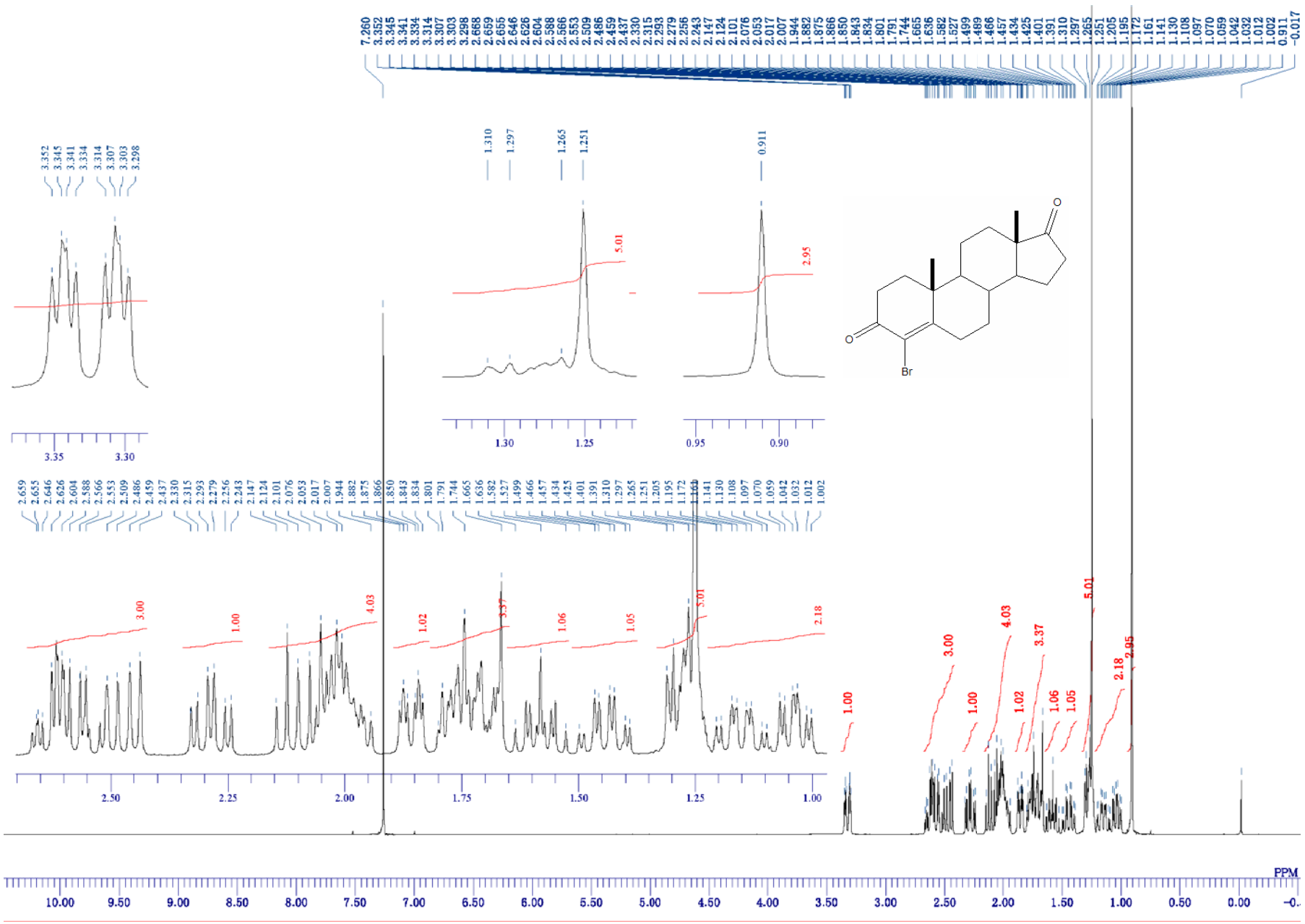
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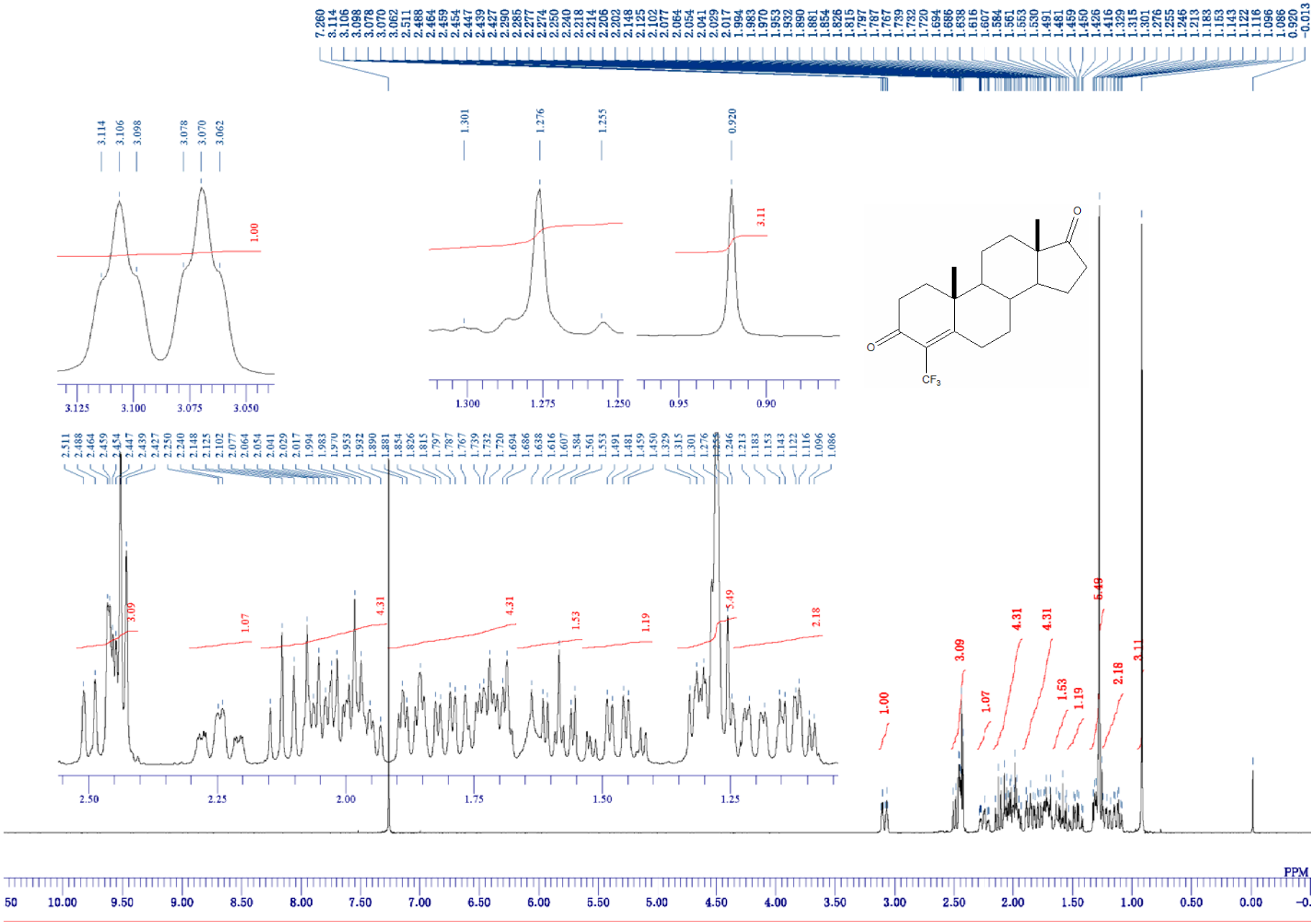
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