Supporting Information

Improved Synthesis of Fluticasone Propionate

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Context

Safety assessment for the NaClO oxidation and fluorodecarboxylation

In our improved process for the synthesis of fluticasone propionate (**1**), it's the first time to apply haloform reaction and fluorodecarboxylation with $AgNO_3$ and selectfluor. The rest four steps could be conduct under a commercial scale according to the literature. Here we mainly calculate the safety of the haloform reaction and fluorodecarboxylation. For the haloform reaction: the NaClO oxidation system was environmentally friendly and suitable for industrialization.

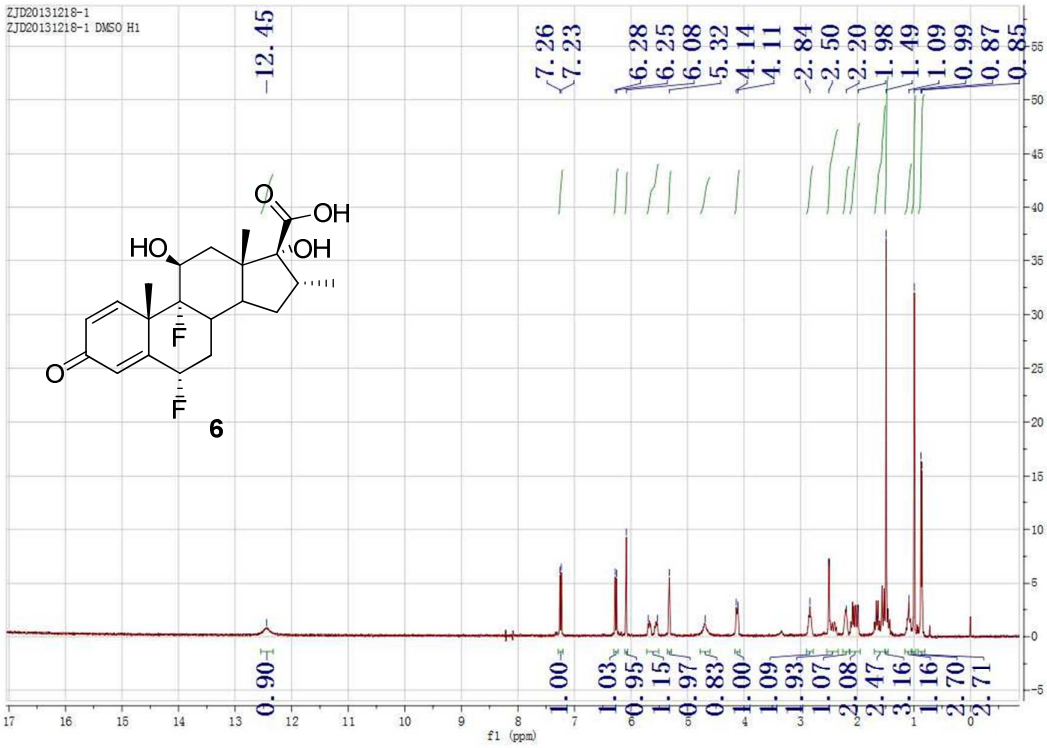
Safety assessment for the NaClO oxidation: NaOH (25.0 g, 0.625 mol) was dissolved in H_2O (0.040 L), the mixture was diluted with 0.500 L of THF and 0.500L of EtOH. Into the solution, **2** (50.0 g, 0.126 mol) was added, then 10% NaClO (0.500 L) was added gradually in 20 minutes at 25 °C. The reaction temperature was kept at 25−30 °C for 6 hours (table 1). Futhermore the reaction system was homogeneous, and NaClO was safe to use. So it is safe and possible to carry out at large-scale.

Table 1 The reaction temperatures at different time

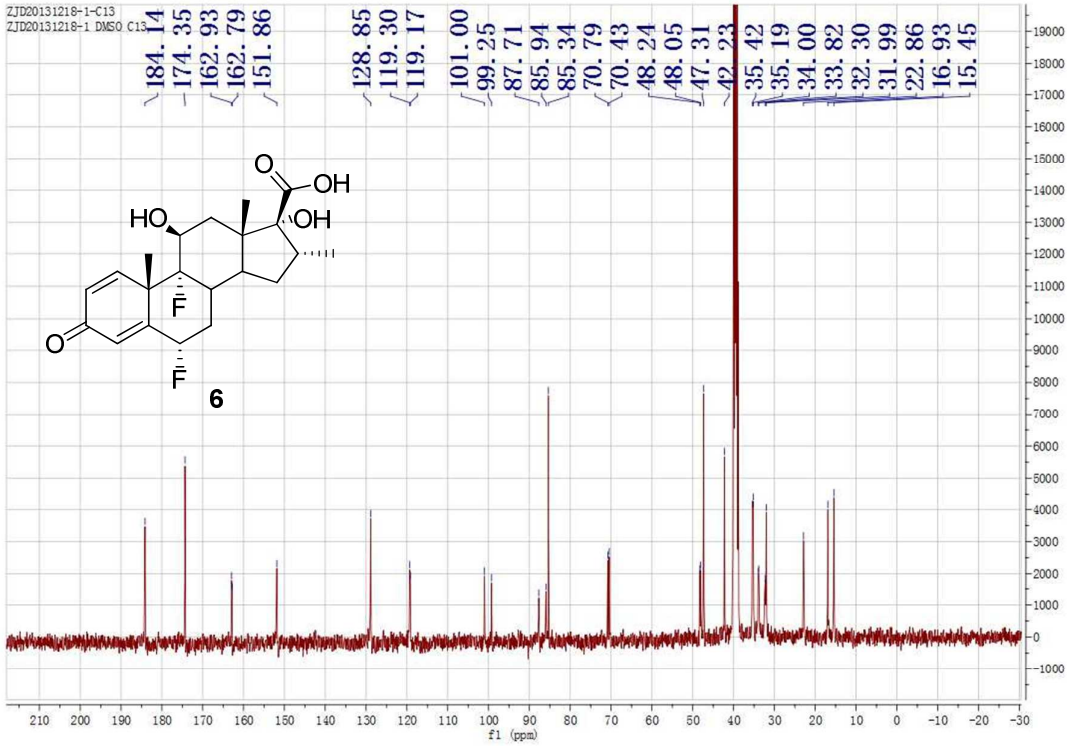
Reaction time	Reaction temperature	Reaction time	Reaction temperature
9:00 am	25 °C	10:00 am	26 °C
9:05 am	26 °C	11:00 am	25 °C
9:10 am	28 °C	12:00 am	25 °C
9:15 am	29 °C	13:00 am	25 °C
9:20 am	30 °C	14:00 am	25 °C
9:25 am	29 °C	15:00 am	25 °C
9:30 am	28 °C		

Safety assessment for the fluorodecarboxylation: the selectfluor is stable, easy to use, and commercially available. The reaction system was homogeneous, and the reaction temperature was kept at 45−47 °C during fluorodecarboxylation process. So it is safe to carry out at large-scale.

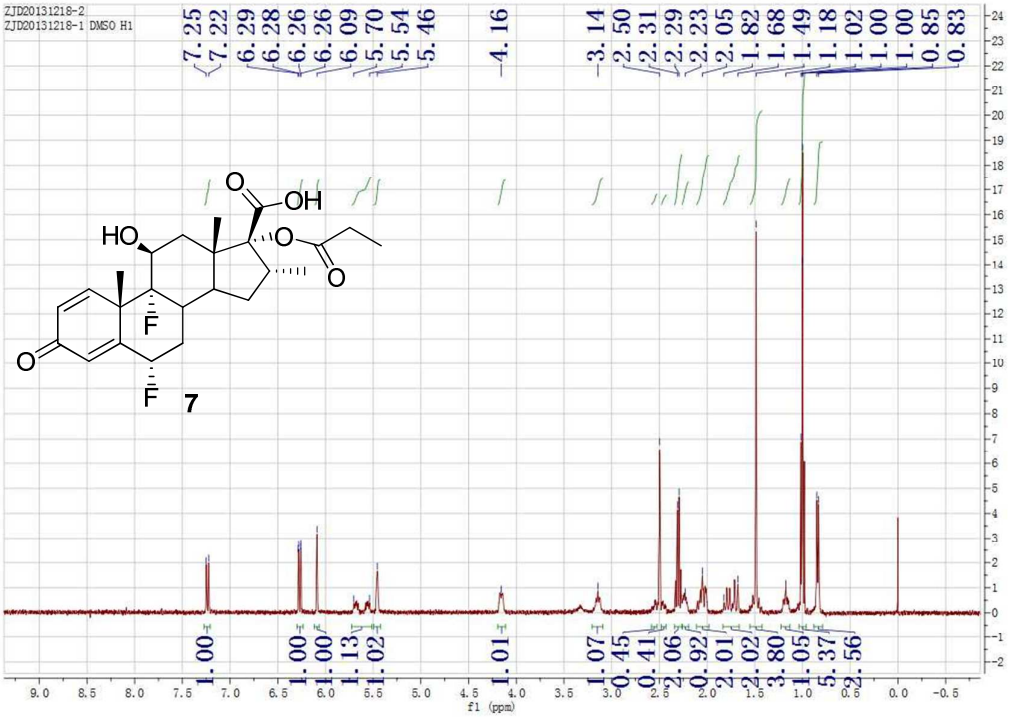
^{1}H NMR for compound 6



^{13}C NMR for compound 6



^{1}H NMR for compound 7



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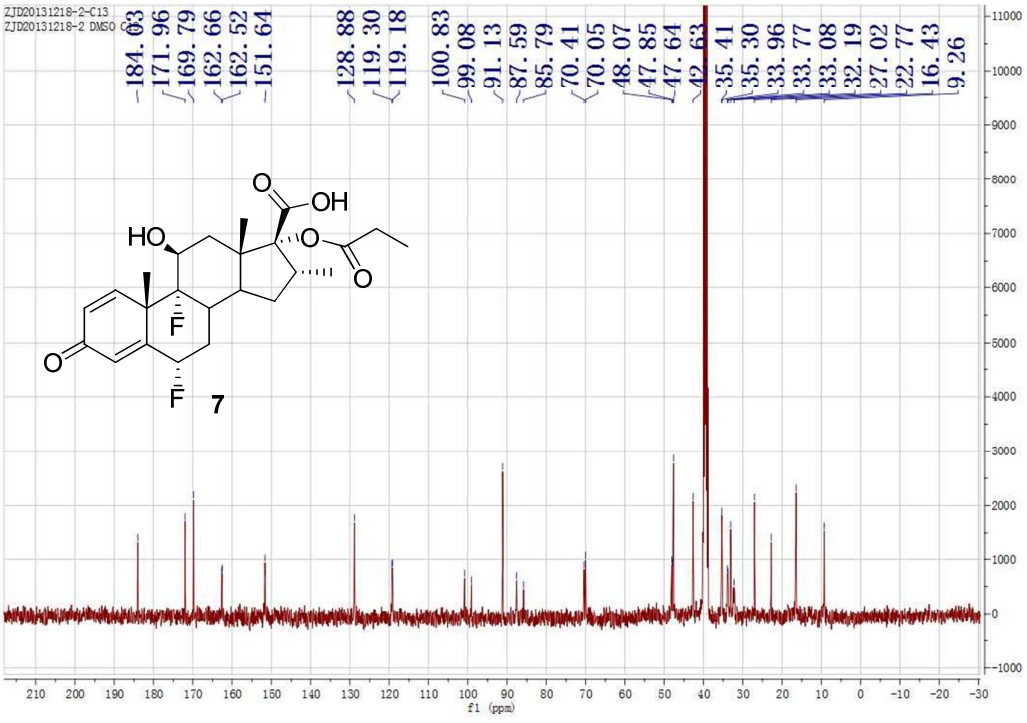
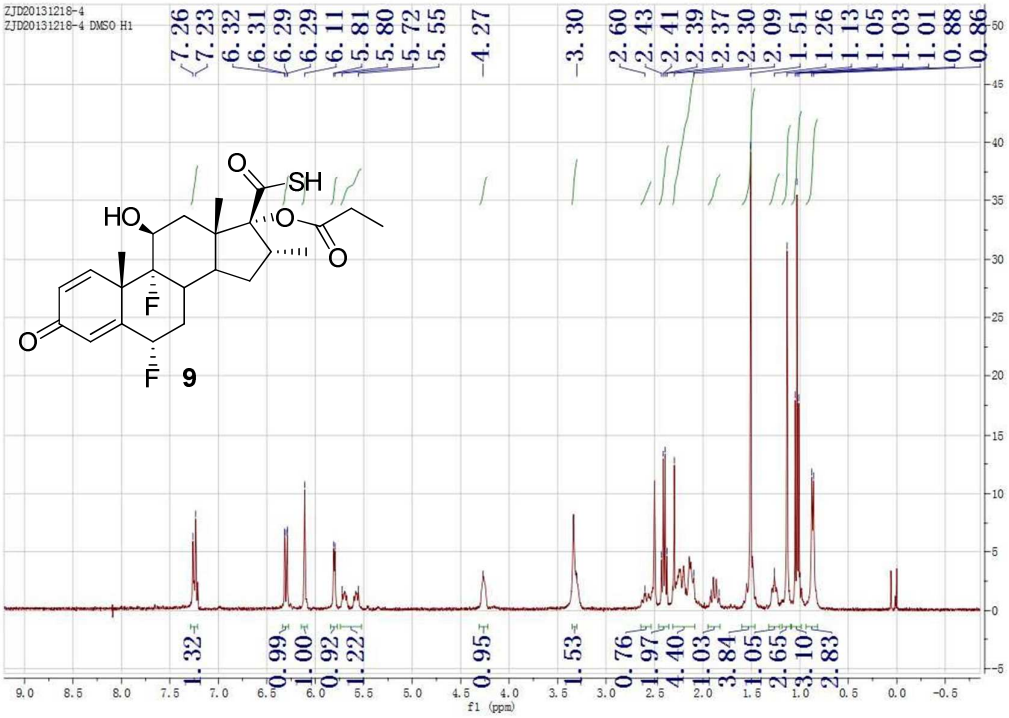


^{1}H NMR for compound 9



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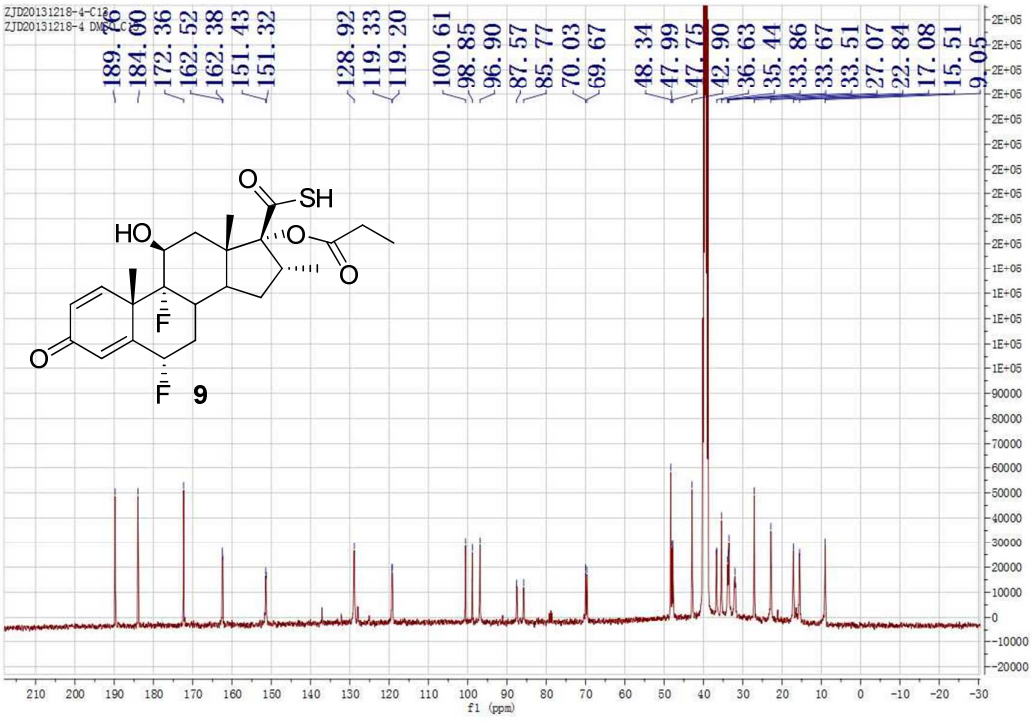
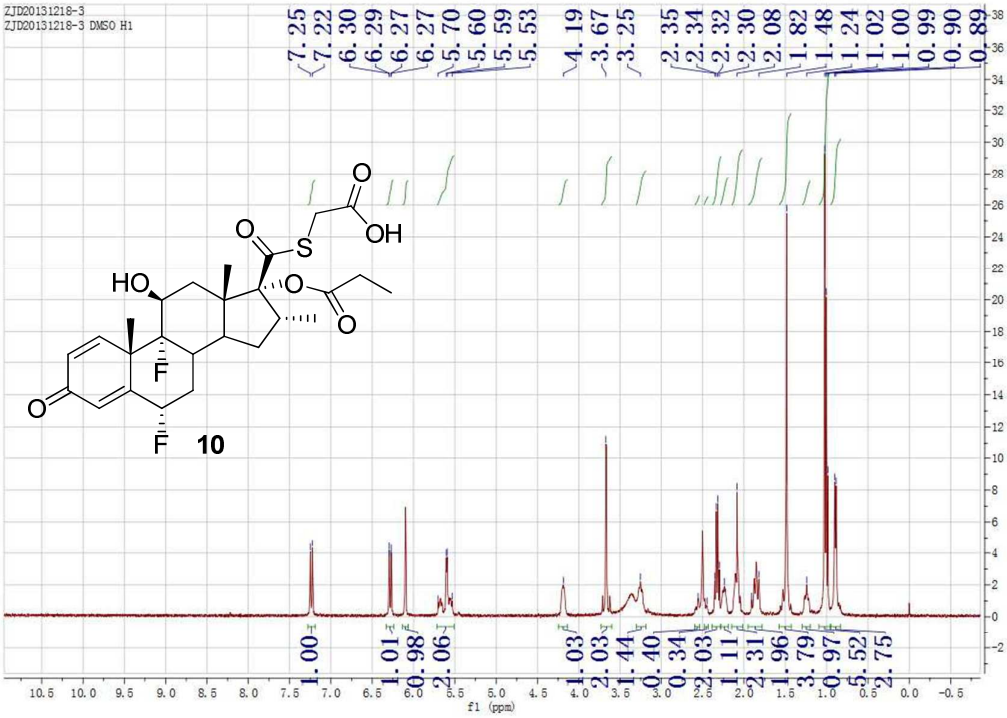


^{1}H NMR for compound 10



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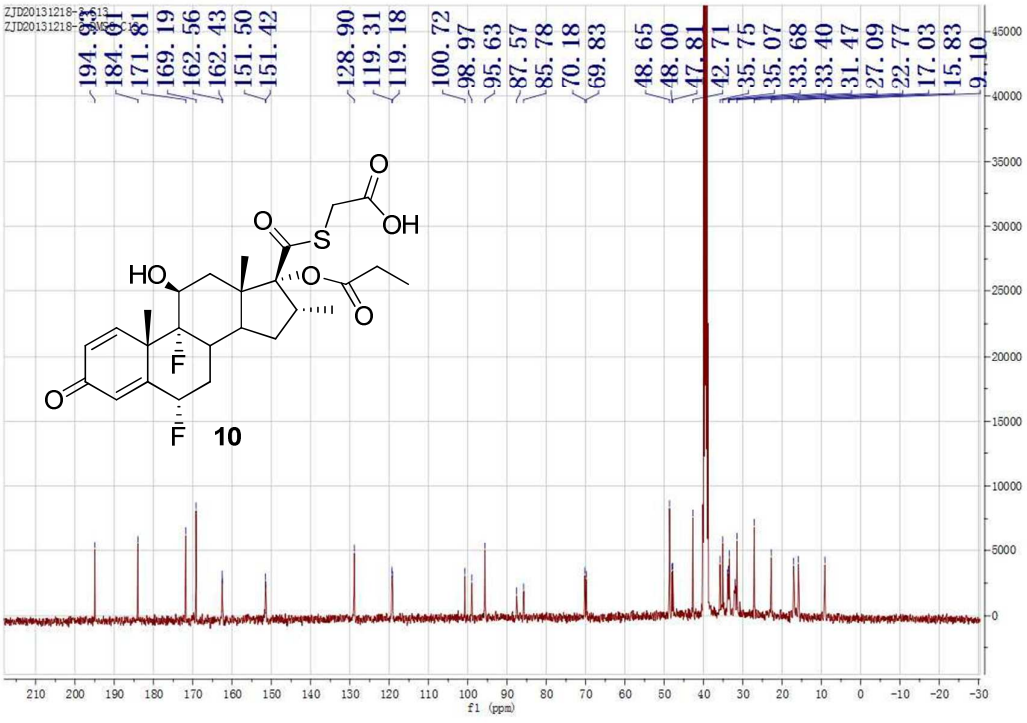
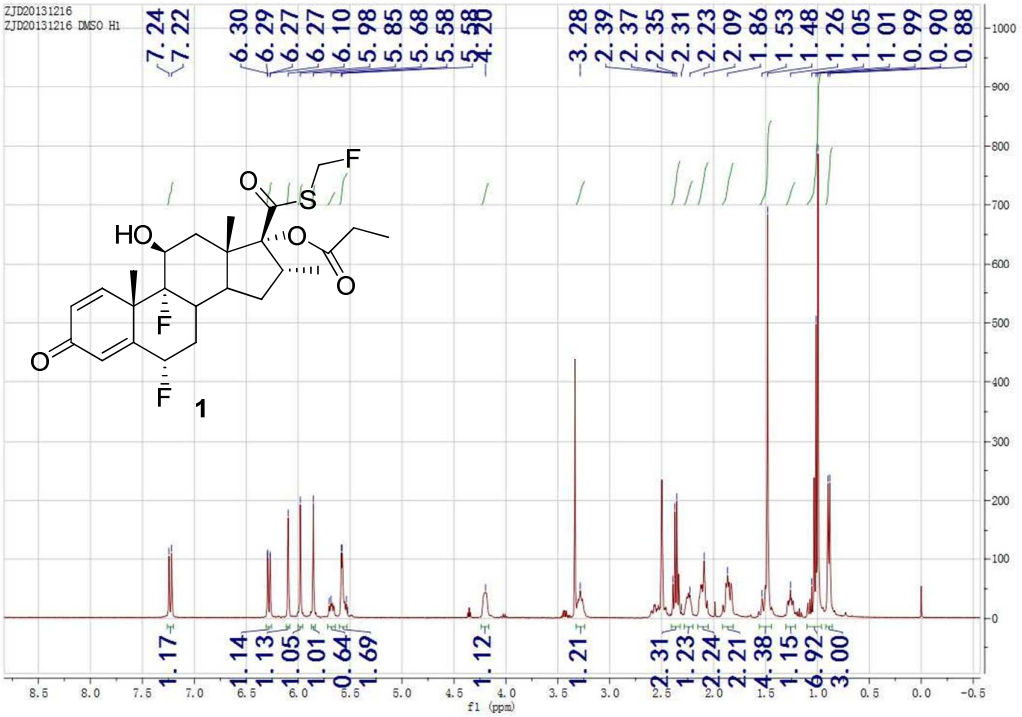


^{1}H NMR for compound 1



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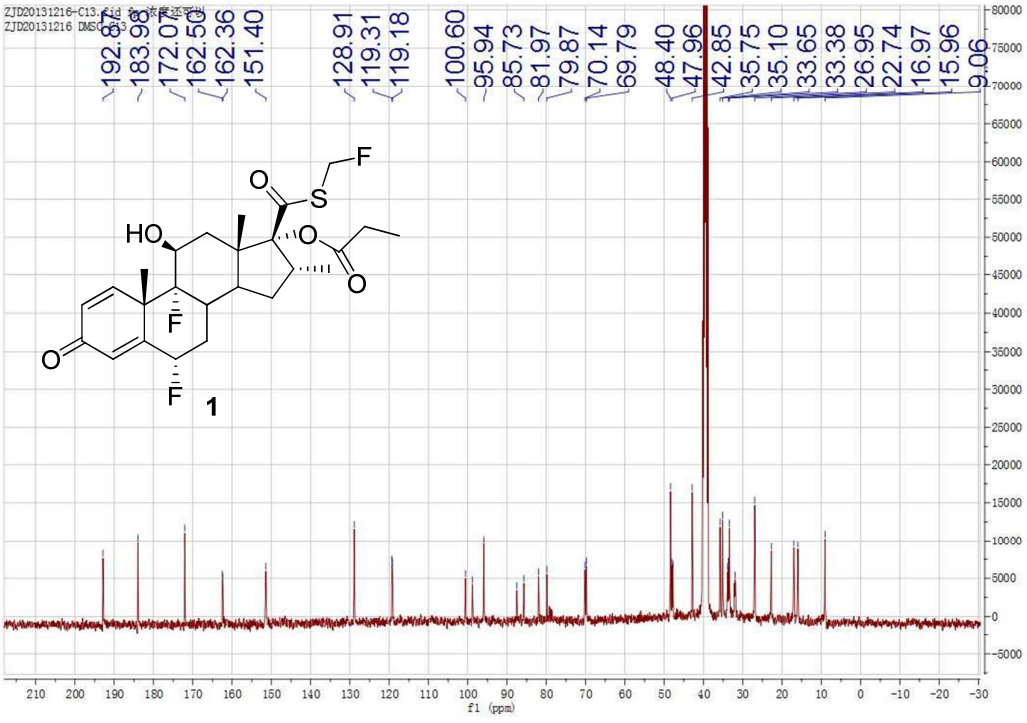
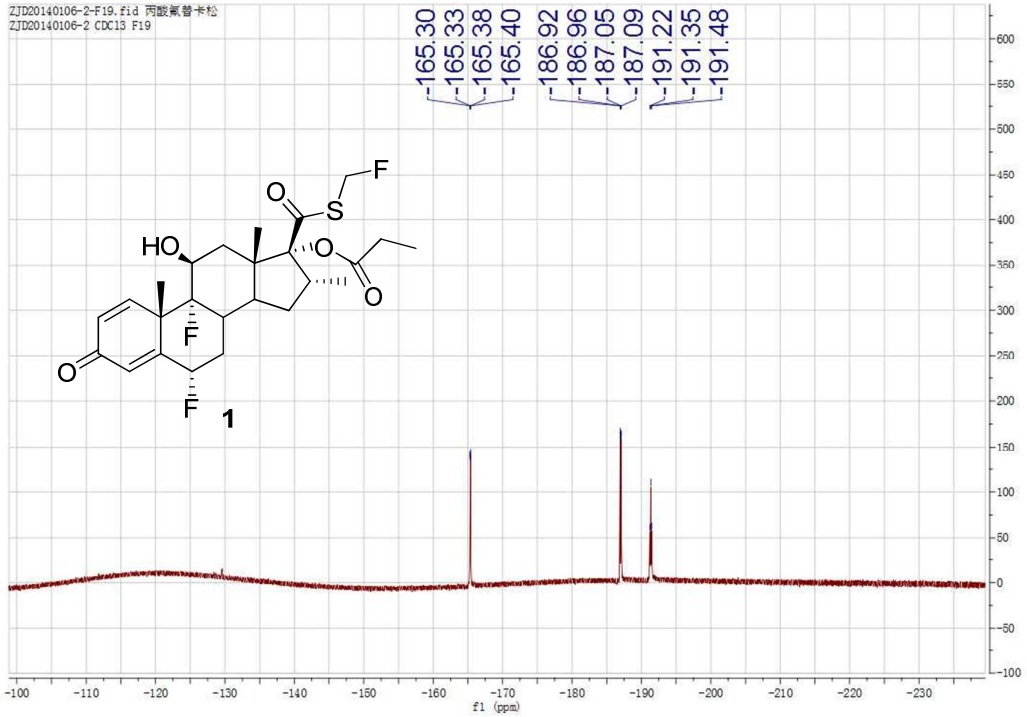
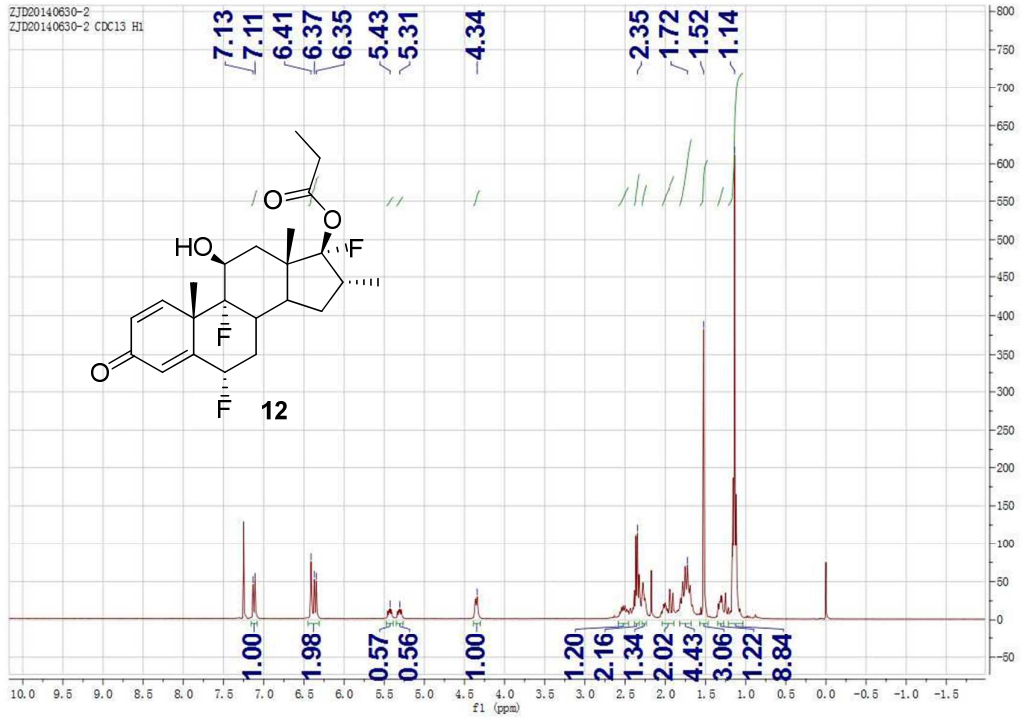


^{19}F NMR for compound 1



^{1}H NMR for compound 12



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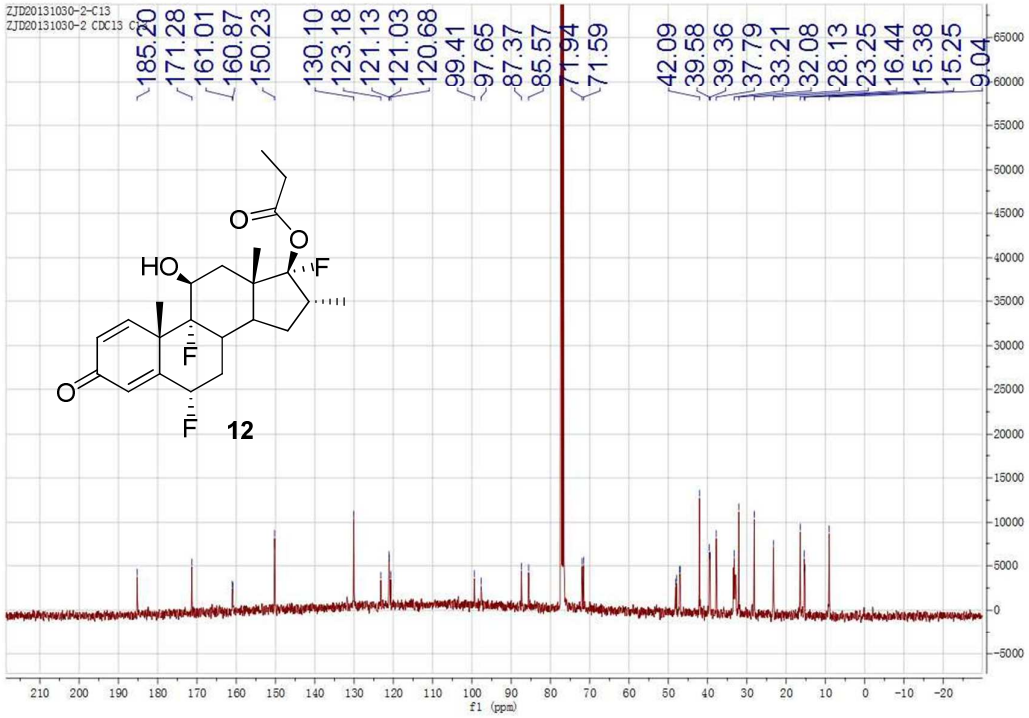
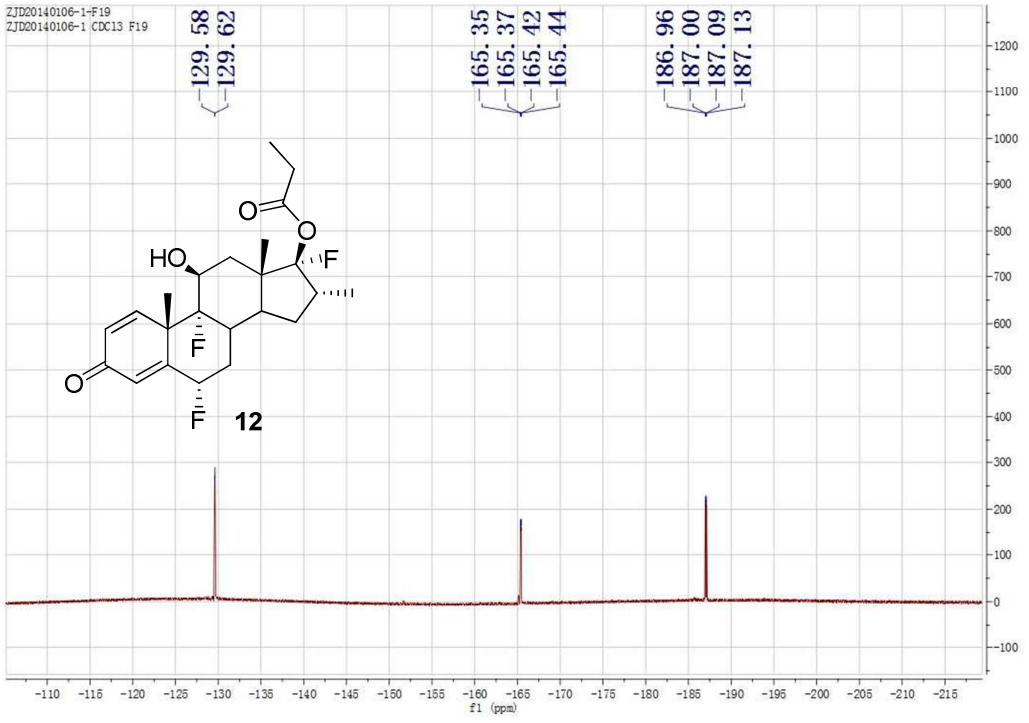


^{19}F NMR for compound 12



checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: p

Bond precision: C-C = 0.0031 A Wavelength=0.71073

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	alpha=90	beta=113.478(6)	gamma=90
Temperature:	303 K		

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Hall group	P 2yb	?
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Sum formula	C23 H29 F3 O4	C23 H29 F3 O4
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Dx,g cm-3	1.321	1.321
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Correction method= MULTI-SCAN

Data completeness= 1.76/0.91 Theta(max)= 25.990

R(reflections)= 0.0353(3378) wR2(reflections)= 0.0905(3825)

S = 1.030 Npar= Npar = 272

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT035_ALERT_1_B No _chemical_absolute_configuration info given . Please Do !

Alert level C

ABSTY02_ALERT_1_C An _exptl_absorpt_correction_type has been given without
a literature citation. This should be contained in the
_exptl_absorpt_process_details field.
Absorption correction given as multi-scan
STRVA01_ALERT_4_C Flack test results are meaningless.
From the CIF: _refine_ls_abs_structure_Flack -0.200
From the CIF: _refine_ls_abs_structure_Flack_su 0.600
PLAT230_ALERT_2_C Hirshfeld Test Diff for C14 -- C15 .. 6.2 su
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd. # 1 Note
C23 H29 F3 O4

Alert level G

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PLAT032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High . 0.600 Why ?
PLAT066_ALERT_1_G Predicted and Reported Tmin&Tmax Range Identical ? Check
PLAT093_ALERT_1_G No su's on H-positions, refinement reported as . mixed
PLAT791_ALERT_4_G The Model has Chirality at C4 ..... S Verify
PLAT791_ALERT_4_G The Model has Chirality at C8 ..... S Verify
PLAT791_ALERT_4_G The Model has Chirality at C10 ..... S Verify
PLAT791_ALERT_4_G The Model has Chirality at C11 ..... R Verify
PLAT791_ALERT_4_G The Model has Chirality at C12 ..... S Verify
PLAT791_ALERT_4_G The Model has Chirality at C15 ..... S Verify
PLAT791_ALERT_4_G The Model has Chirality at C16 ..... S Verify
PLAT791_ALERT_4_G The Model has Chirality at C19 ..... R Verify
PLAT791_ALERT_4_G The Model has Chirality at C20 ..... R Verify

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0 **ALERT level A** = Most likely a serious problem - resolve or explain
1 **ALERT level B** = A potentially serious problem, consider carefully
4 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
14 **ALERT level G** = General information/check it is not something unexpected

4 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
0 ALERT type 3 Indicator that the structure quality may be low
12 ALERT type 4 Improvement, methodology, query or suggestion
2 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

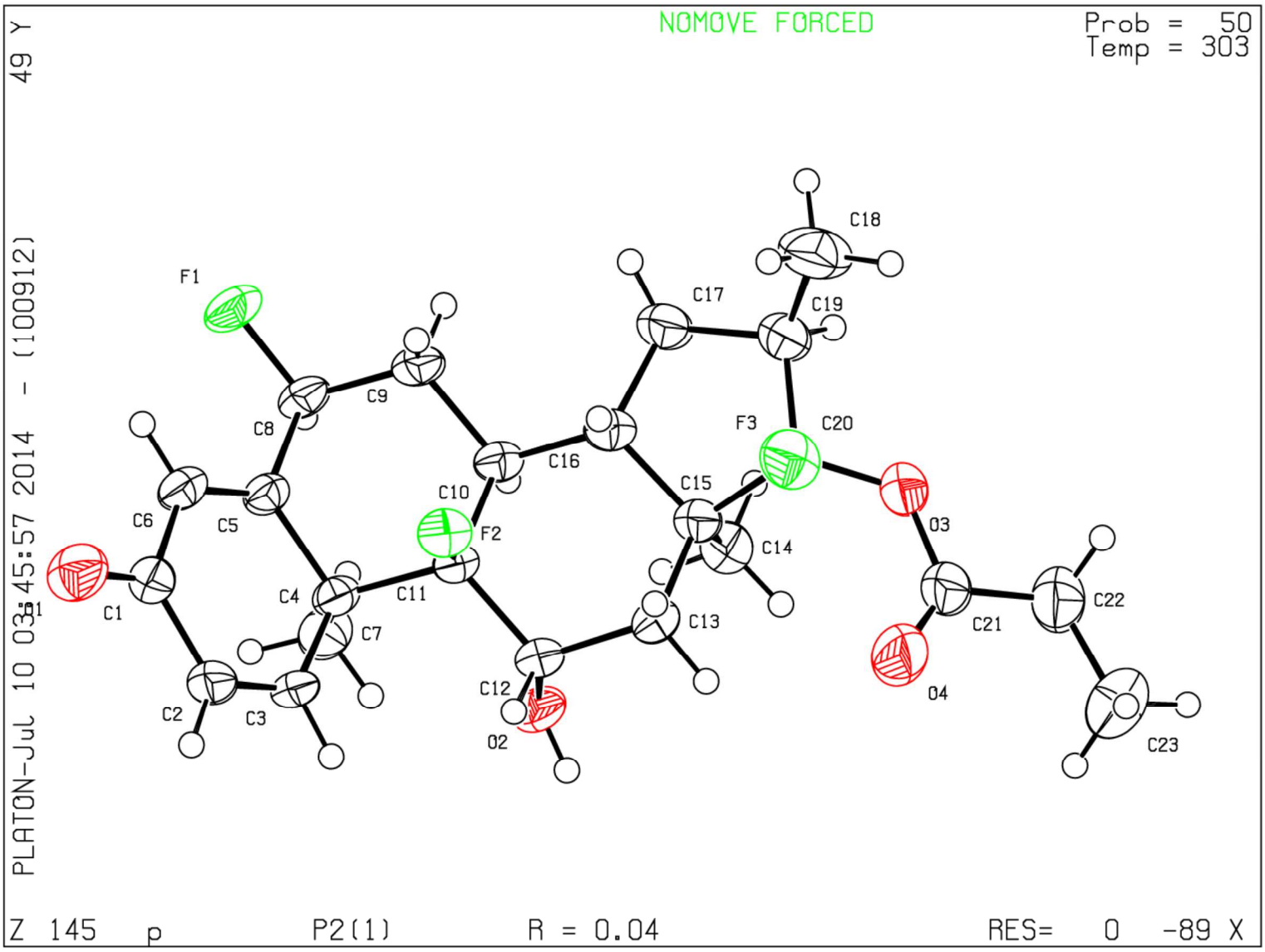
Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 05/02/2014; check.def file version of 05/02/2014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