Supporting Information

Optimization of Two Steps in Scale-up Synthesis of Nannocystin A

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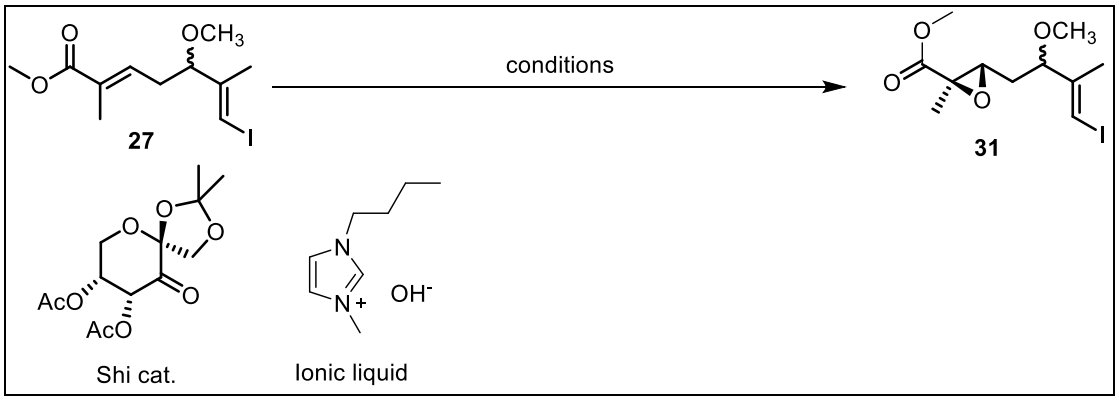
S1. Conditions of direct epoxidation of compound 27



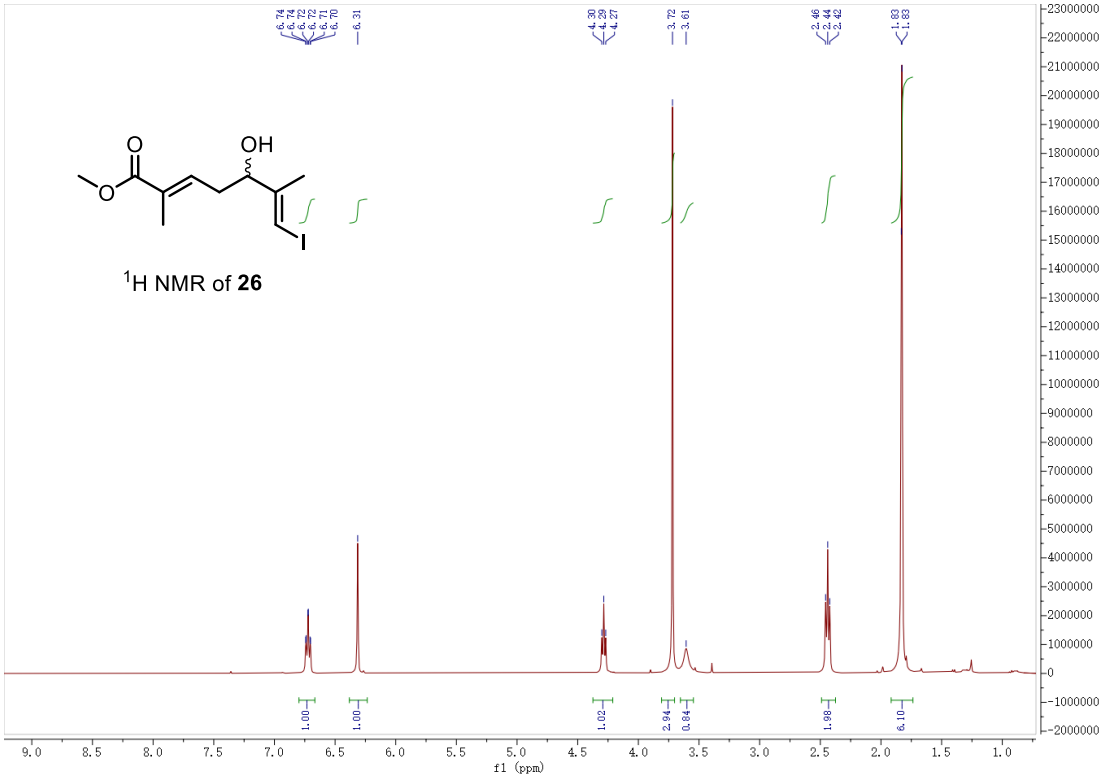
All the entries were excuted at room temperature unless extra notes.

entry	oxygen source	equivalent	Addition and equivalent	result
1	*m*-CPBA	1.5	DCM (25 V eq)[a]	messy
2	Oxone	1.1	DCM (25 V eq)	no reaction
3	*t*-BuOOH[b]	1.2	*S*-BINOL (0.08 eq), TPPO (0.1 eq), 4A MS (5 m), Y(O*i*Pr)$_3$ (0.08 eq), MeCN (100 V eq)	no reaction
4	*t*-BuOOH[b]	1.2	*S*-BINOL (0.08 eq), TPPO (0.1 eq), 4A MS (5 m), Y(O*i*Pr)$_3$ (0.08 eq), THF(100 V eq)	no reaction
5	Oxone	1	Shi cat. (0.15 eq), buffer (pH=7.4, 2 V), Na_2EDTA (2 eq), MeCN (5 V eq)	no reaction
6	Oxone	1	Shi cat. (0.15 eq), ionic acid (2 V eq), MeCN (1.5 V eq)	no reaction
7	H_2O_2 (30% in H_2O)	1.1	Shi cat. (0.15 eq), ionic acid (1.5V eq), MeCN(1.5V eq)	trace
8	Oxone	3	Shi cat. (0.15 eq), ionic acid (2 V eq), MeCN (1.5 V eq)	no reaction
9	H_2O_2 (30% in H_2O)	3.3	Shi cat. (0.15 eq), ionic acid (1.5 V eq), MeCN (1.5 V eq)	trace

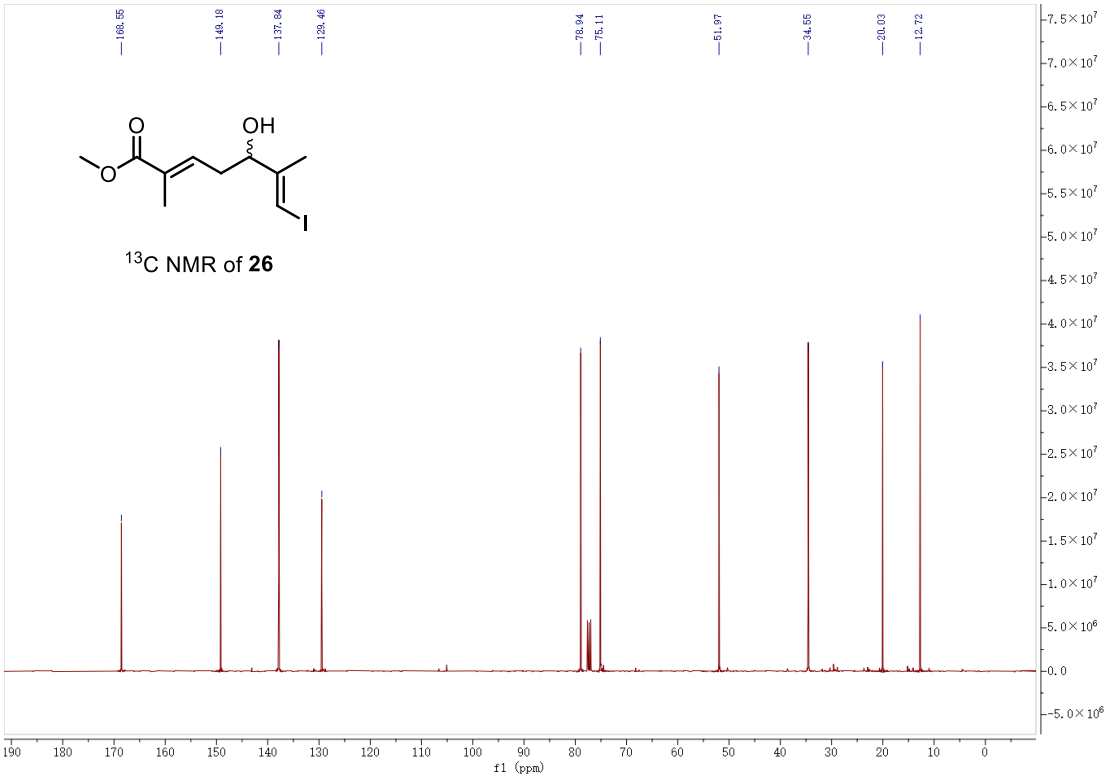
a Excuted under ice bath.

b *t*-BuOOH was prepared from 40% solution in water and excessive Na_2SO_4.

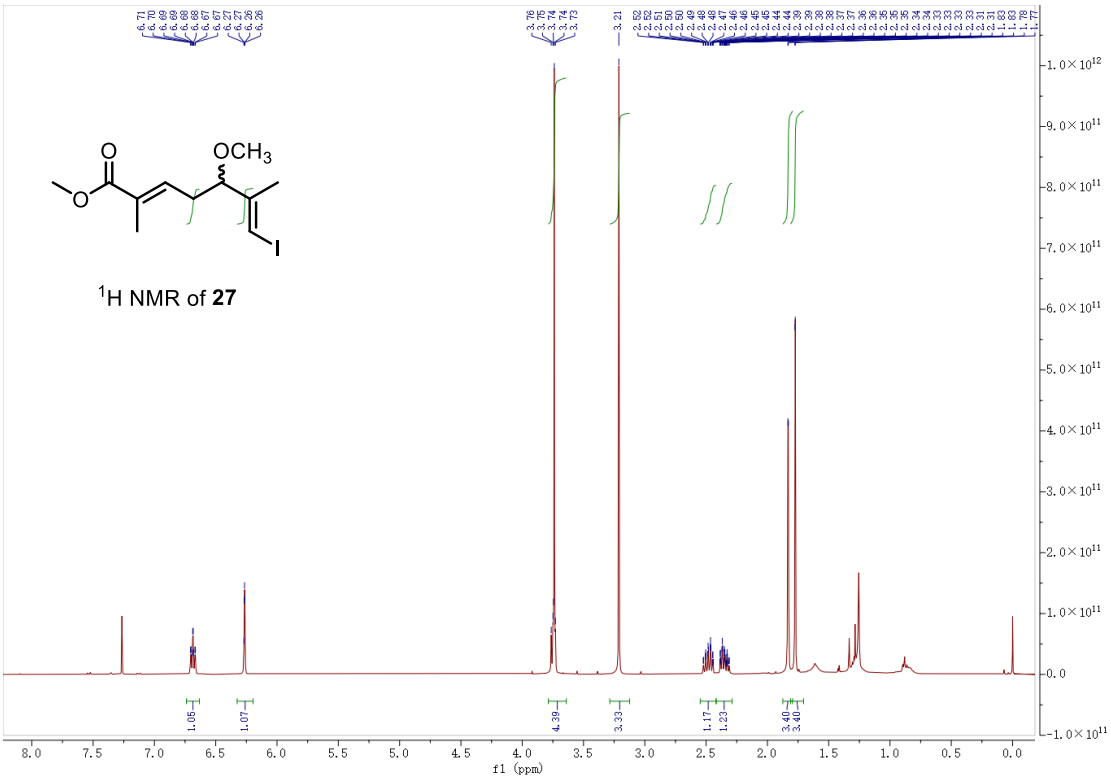
S2. NMR Spectra of new compounds



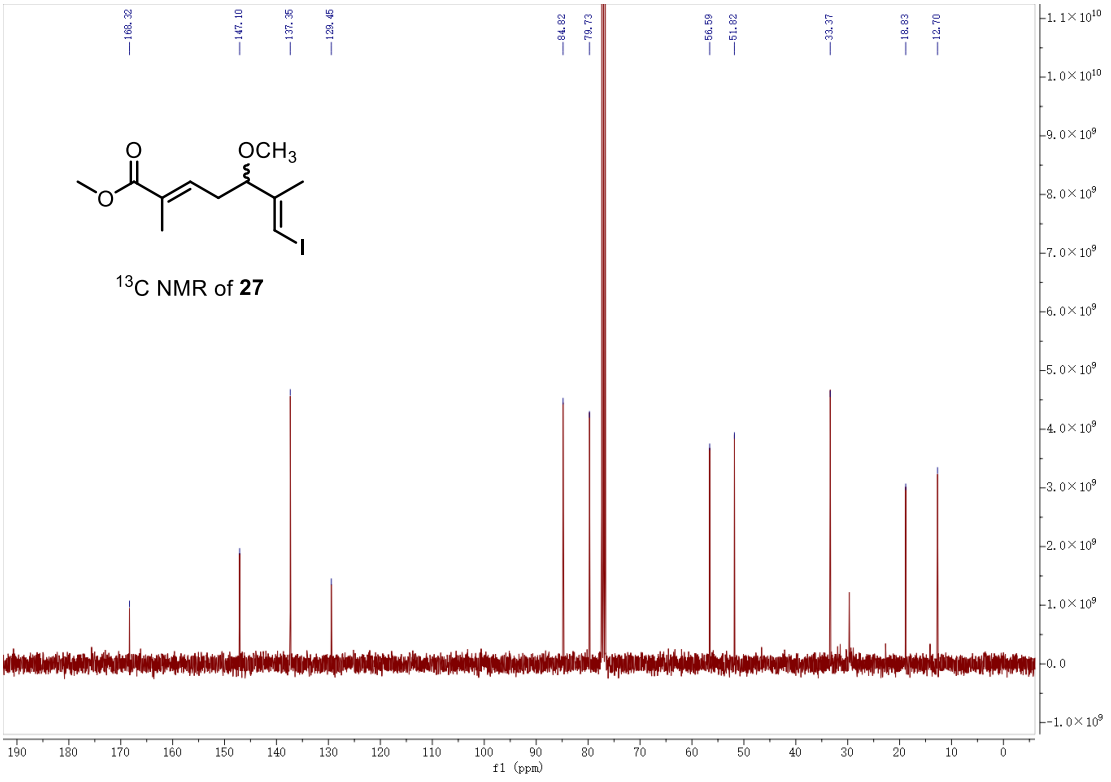
^{1}H NMR of **26**



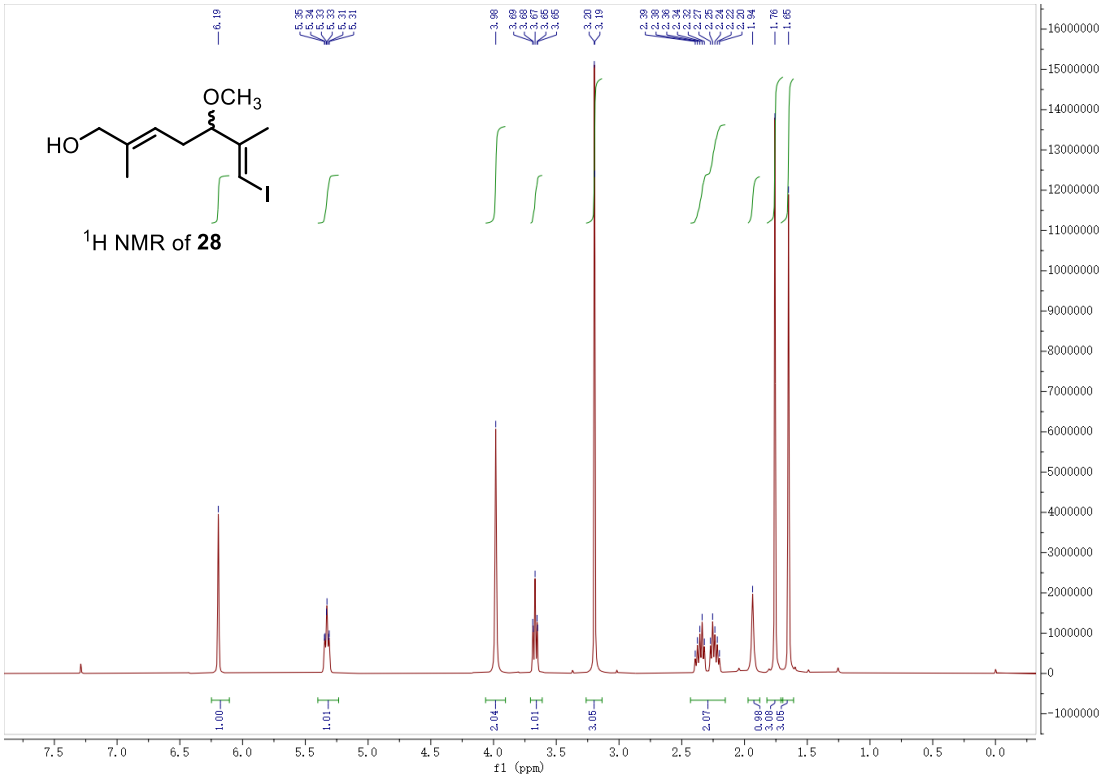
^{13}C NMR of **26**

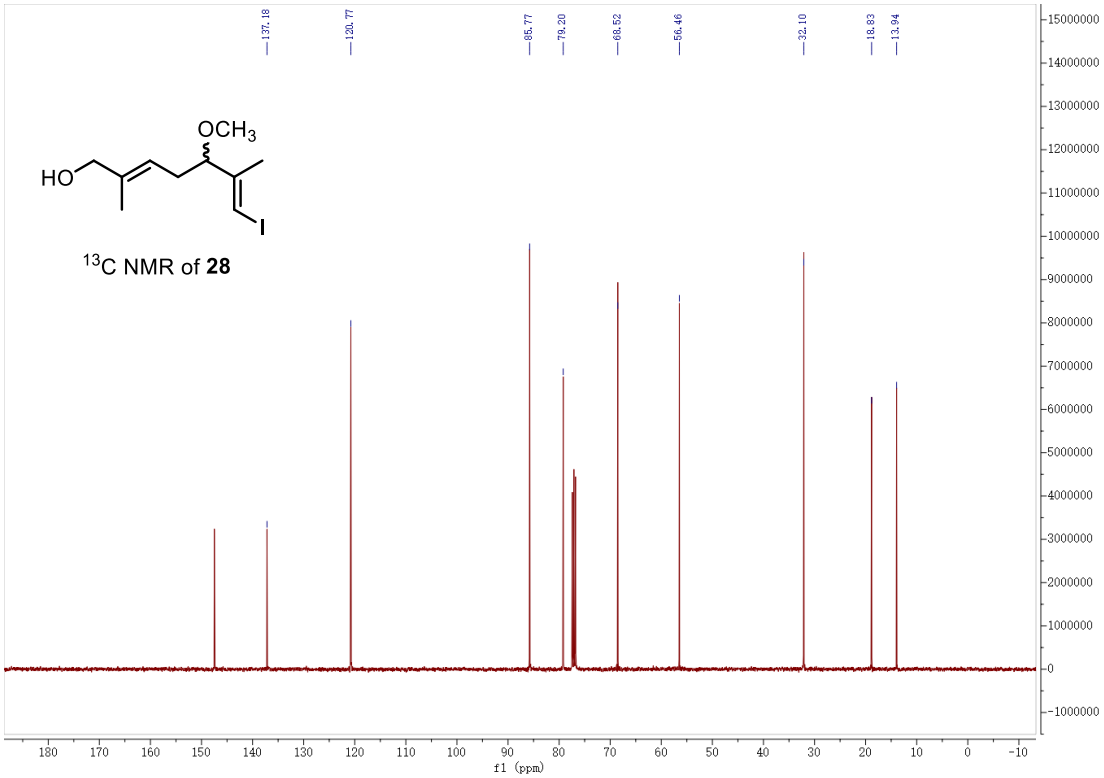


^{1}H NMR of **27**

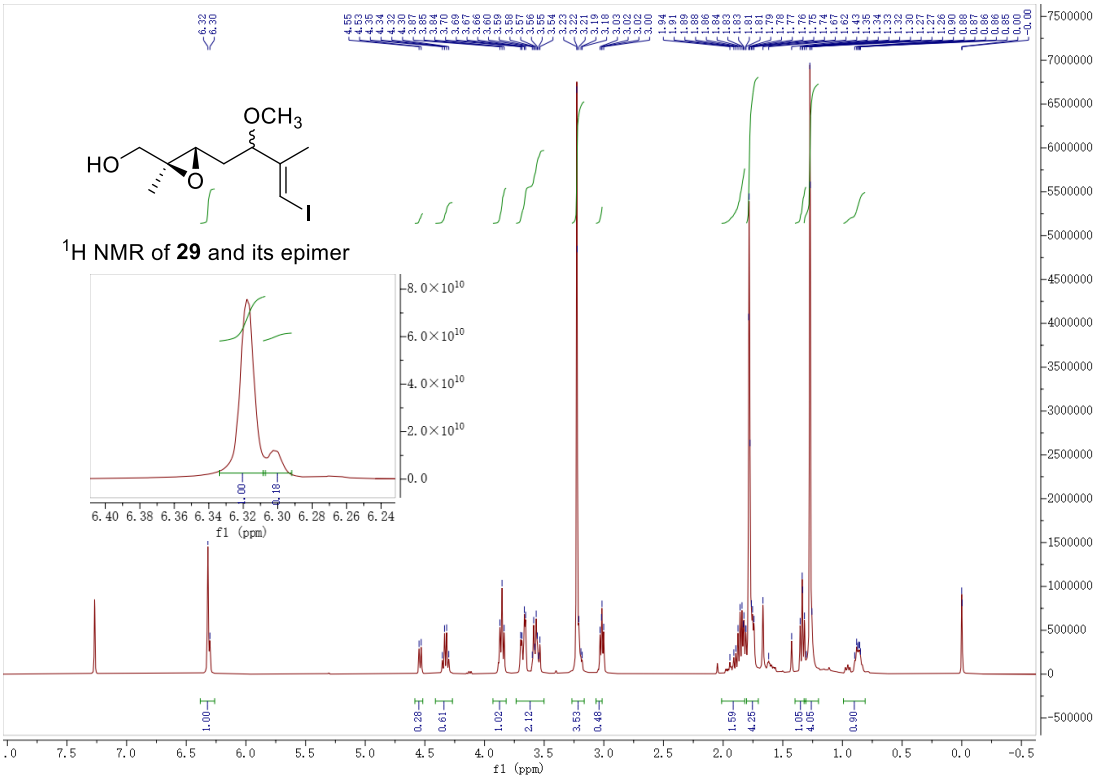


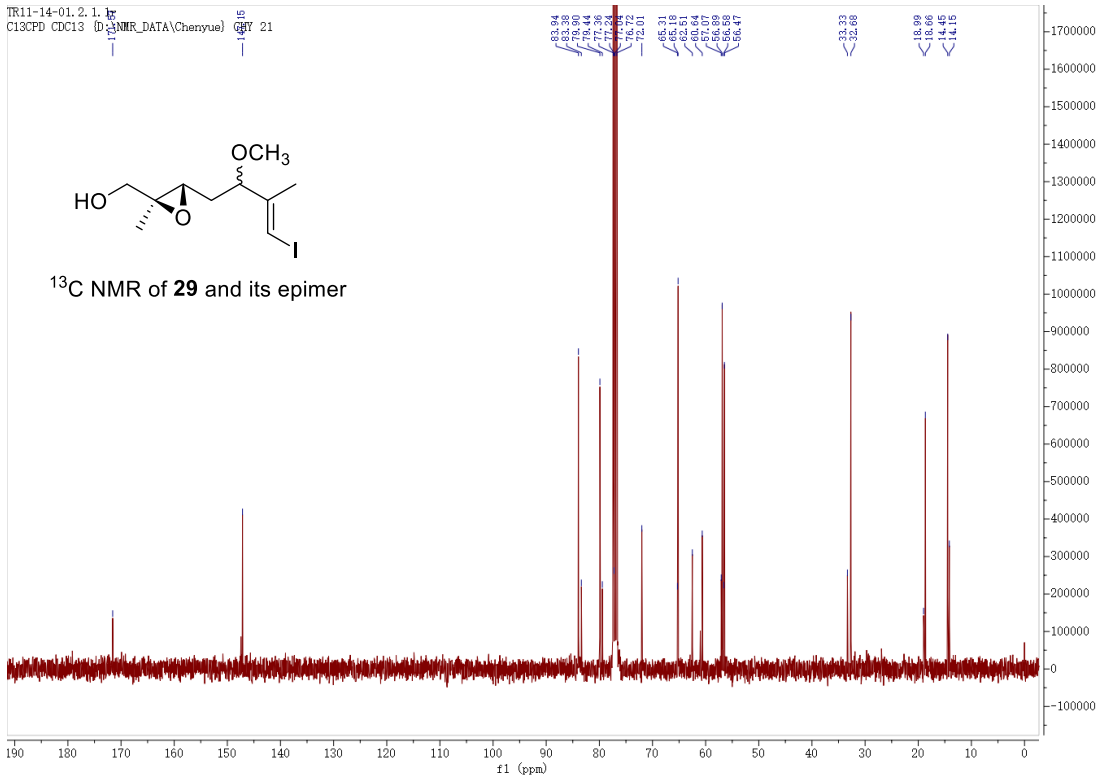
^{13}C NMR of **27**


OCH3
HO
I
1H NMR of 28
f1 (ppm)


OCH3
HO
I
13C NMR of 28
f1 (ppm)

S3. The e.e. value of Mukaiyama aldol reaction is > 66% shown in ^{1}H NMR of compound 29 and chiral HPLC data of compound 26.

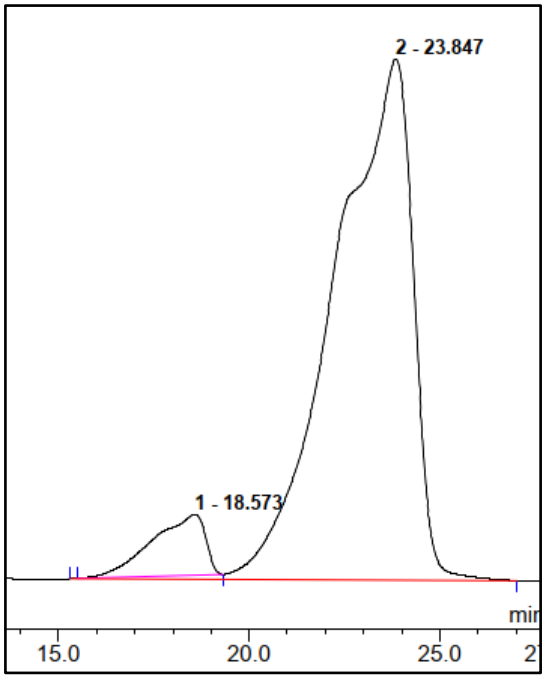




The ee value was determined by chiral HPLC (Chiralpak AD-H, 25° C, flow rate: 1 mL/min);

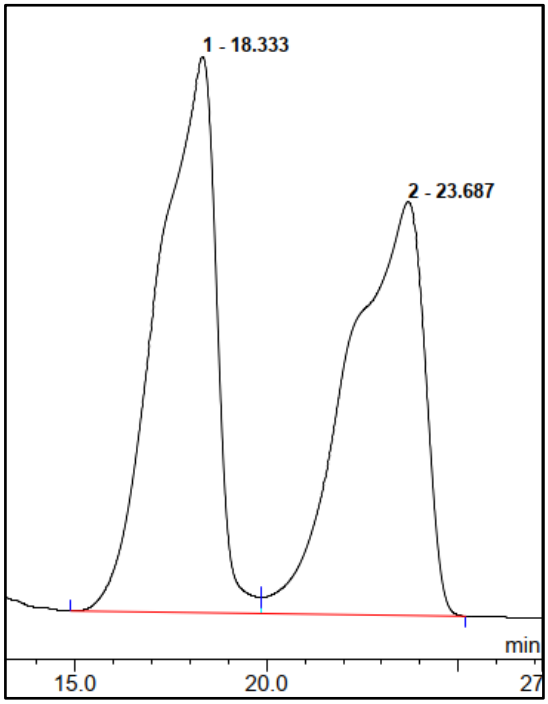
HPLC: 4 % isopropanol in hexane, (R)-enantiomer: retention time = 23.69 minutes, (S)-enantiomer: retention time = 18.33 minutes. The ee value of this reaction was determined as 85% (er value as 12.7:1).

HPLC for our product compound **26**:



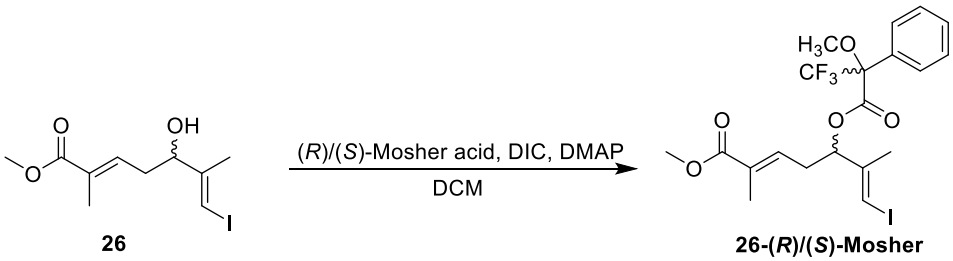
Serial Number	Retention Time	Peak Name	Peak Height /mAU	Peak Area /mAU*min	Relative Peak area/%	Sample volume	Type
1	18.57	n.a.	14.066	22.703	7.29	n.a.	Ru
2	23.85	n.a.	120.363	288.513	92.71	n.a.	BMB
Total:			134.429	311.216	100.00		

HPLC for racemates:



Serial Number	Retention Time	Peak Name	Peak Height /mAU	Peak Area /mAU*min	Relative Peak area/%	Sample volume	Type
1	18.33	n.a.	147.085	260.238	50.82	n.a.	BM
2	23.69	n.a.	109.367	251.866	49.18	n.a.	MB
Total:			256.452	512.105	100.00		

S4. The determination of the absolute configuration by Mosher esters of Compound 26



26 **26-(*R*)/(*S*)-Mosher**

To a solution of **26** (70.0 mg, 0.226 mmol, 1.2 equiv) in dry DCM (2 mL) at room temperature

was added DMAP (2.3 mg, 0.019 mmol, 0.1 equiv), (*R*) or (*S*)-Mosher acid (44 mg, 0.188 mmol, 1.0 equiv) and DIC (47 mg, 0.376 mmol, 2.0 equiv). After being stirred for 1 hour at room temperature, the reaction mixture filtered and concentrated in vacuo. The resultant was purified by silica gel column chromatography (5% EtOAc in Hexanes) to provide **26**-(*R*) and (*S*)-Mosher (89 mg, 75%) as colourless oils.

26-(*R*)-Mosher

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.33 (m, 5H), 6.52 (d, *J* = 6.1 Hz, 2H), 5.63 (dd, *J* = 8.0, 5.7 Hz, 1H), 3.73 (d, *J* = 1.4 Hz, 3H), 3.49 (s, 3H), 2.62 (m, 1H), 2.55 – 2.42 (m, 1H), 1.85 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.78, 165.66, 143.80, 134.40, 131.93, 131.07, 129.71, 128.49, 127.30, 83.23, 77.93, 55.36, 51.90, 31.99, 23.51, 20.07, 12.58.

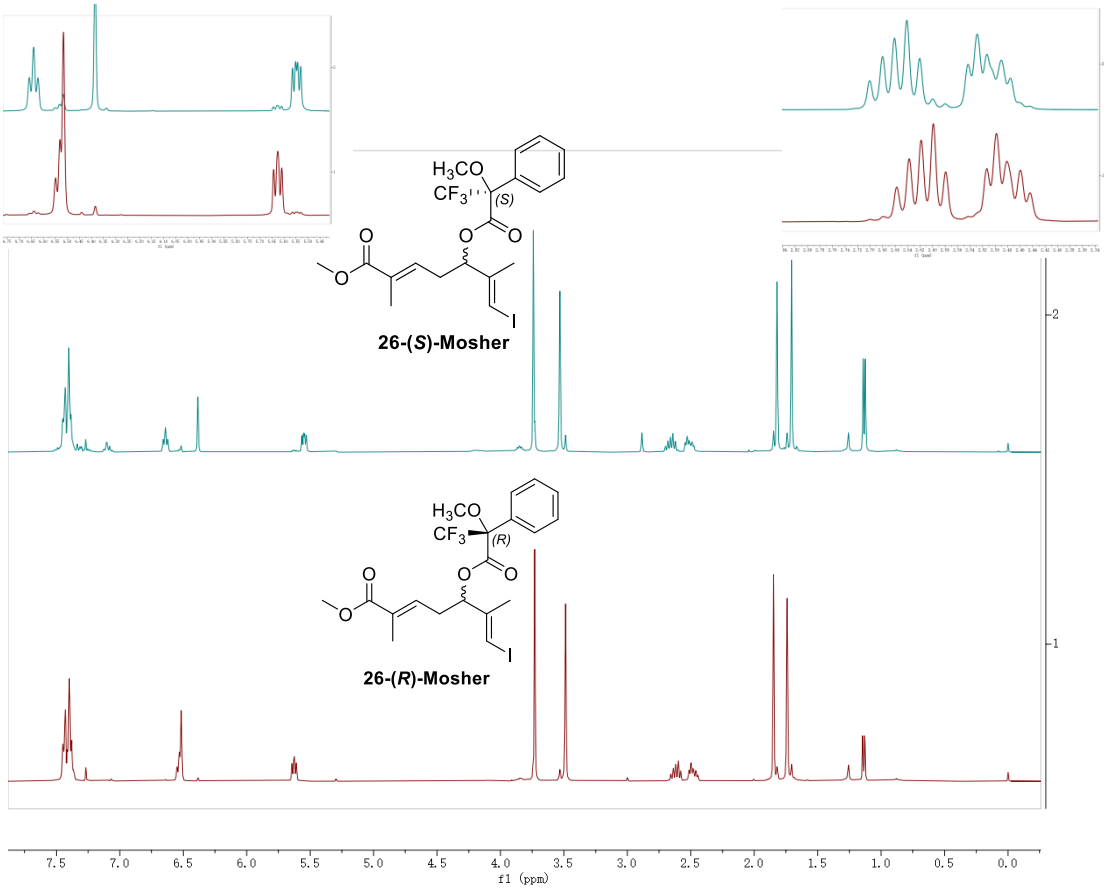
^{19}F NMR (376 MHz, $CDCl_3$) δ -71.16.

26-(*S*)-Mosher

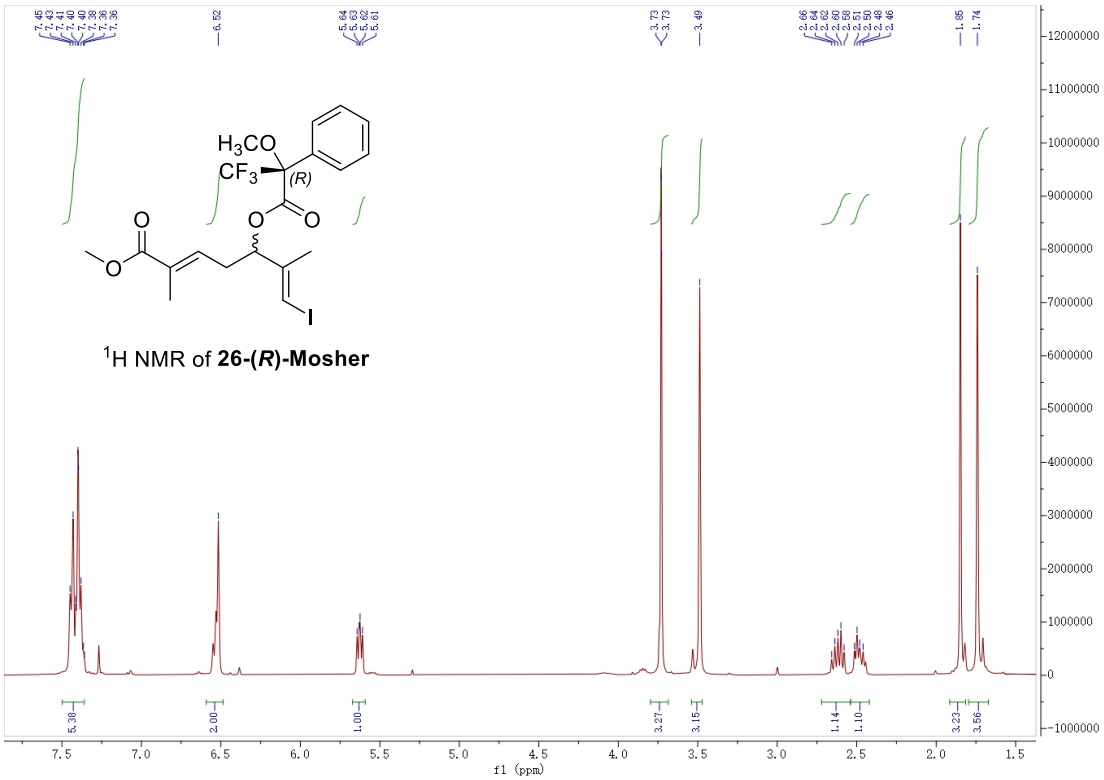
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (q, *J* = 7.3, 6.8 Hz, 6H), 6.64 (t, *J* = 7.4 Hz, 1H), 6.39 (s, 1H), 5.55 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.74 (s, 3H), 3.53 (s, 3H), 2.72 – 2.58 (m, 1H), 2.58 – 2.45 (m, 1H), 1.82 (s, 3H), 1.71 (s, 3H).

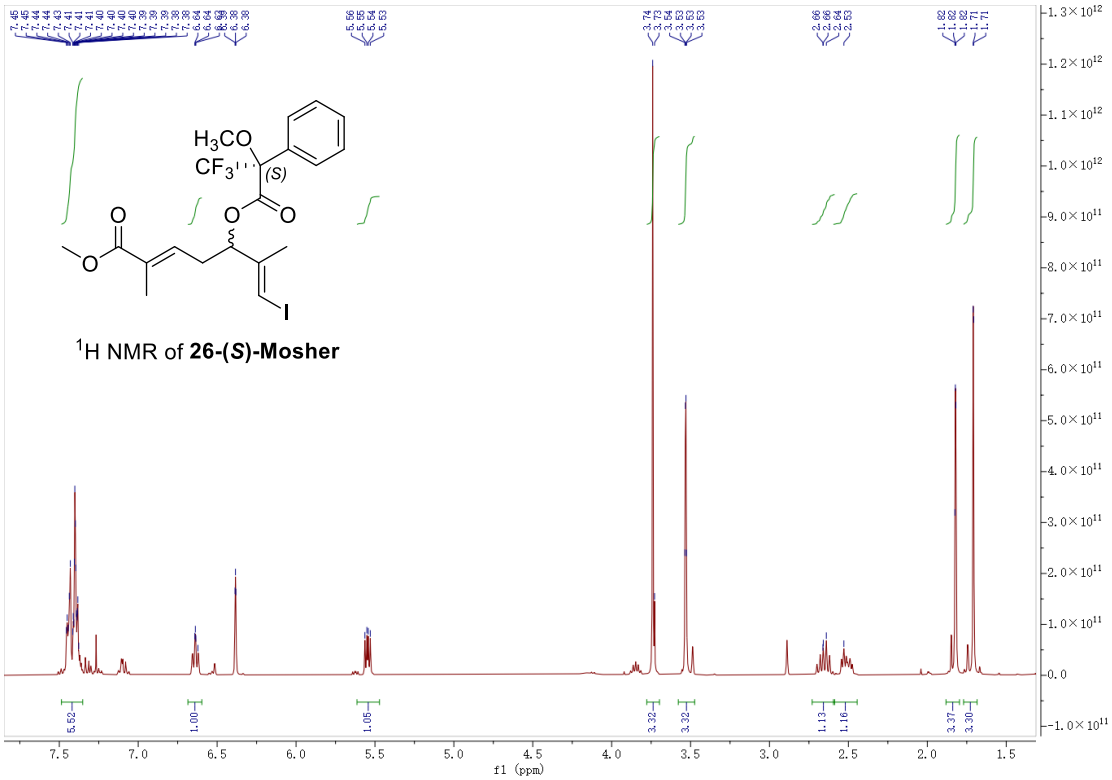
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.83, 165.57, 143.75, 134.85, 131.98, 131.13, 129.72, 128.47, 127.10, 82.94, 78.21, 55.65, 51.95, 32.00, 23.51, 19.89, 12.67.

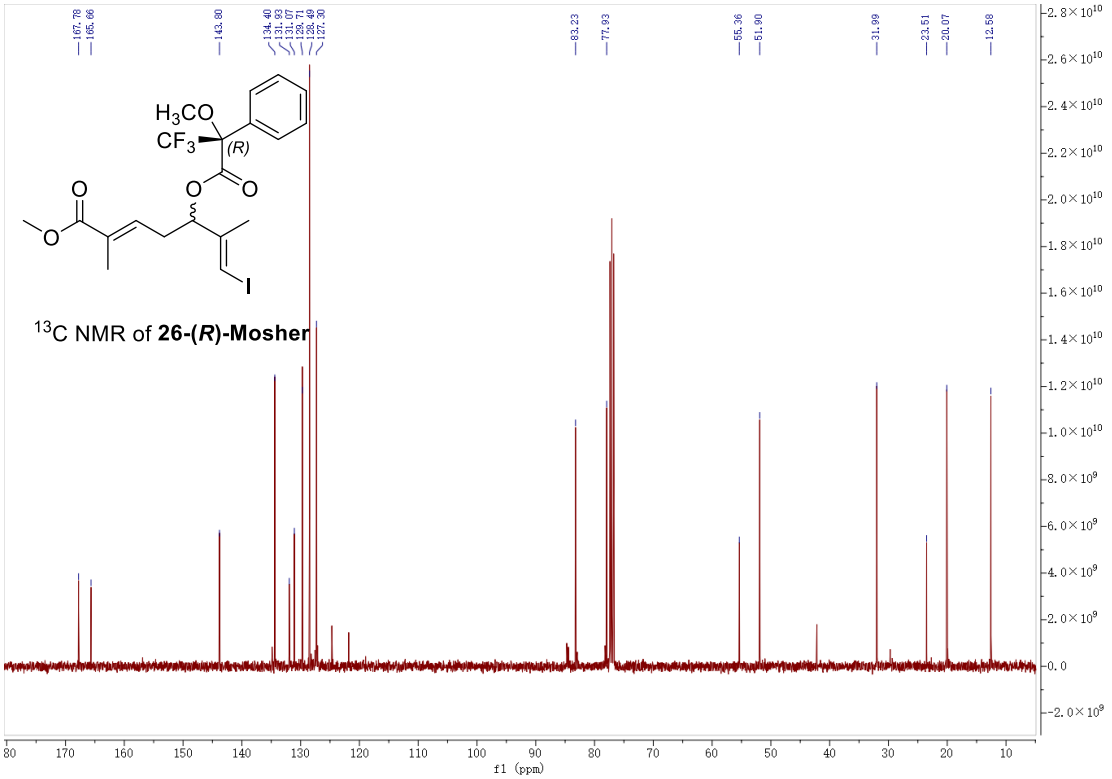
^{19}F NMR (376 MHz, $CDCl_3$) δ -71.30.

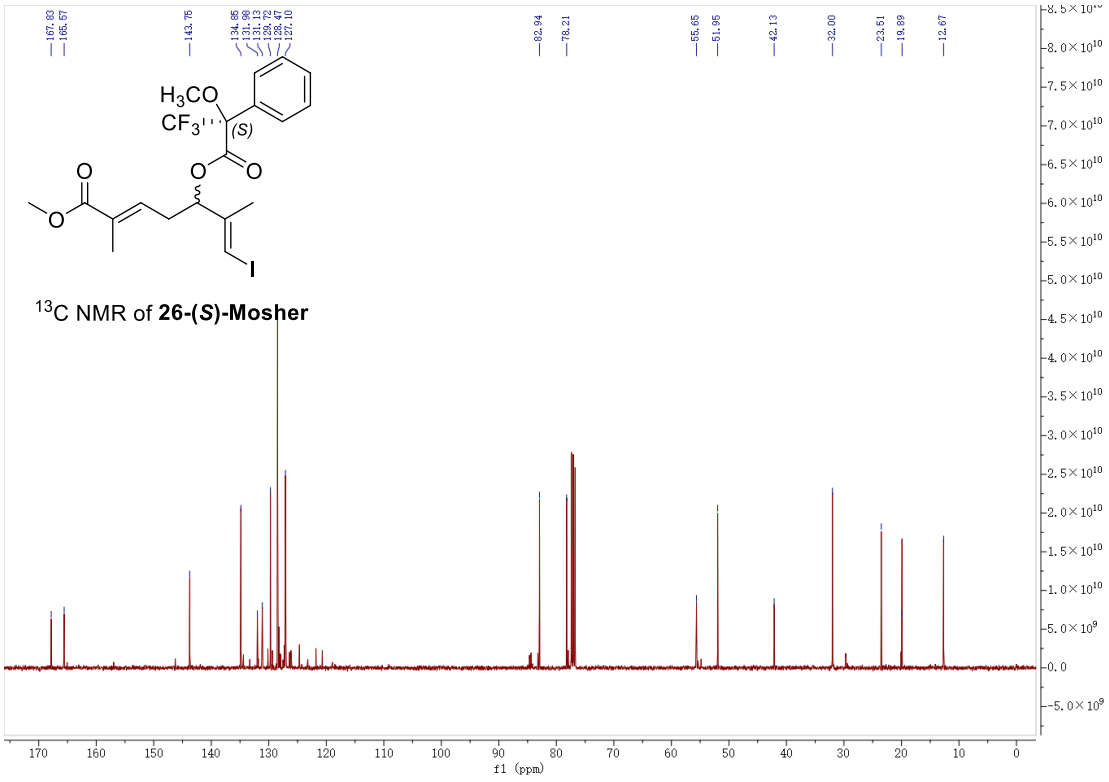


$\Delta\delta\ ^{SR}$C4-H > 0, so the most of the absolute stereochemistry of C5 is R.

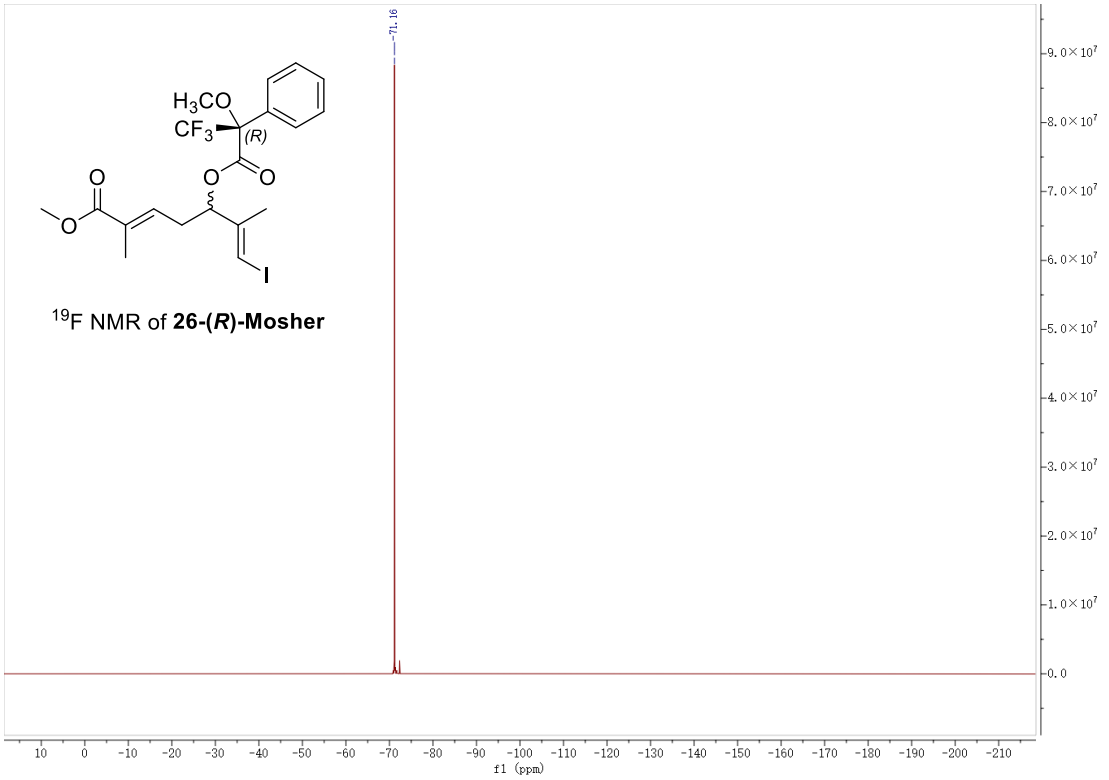



H3CO
CF3
(S)
O
O
O
O
I
1H NMR of 26-(S)-Mosher
f1 (ppm)

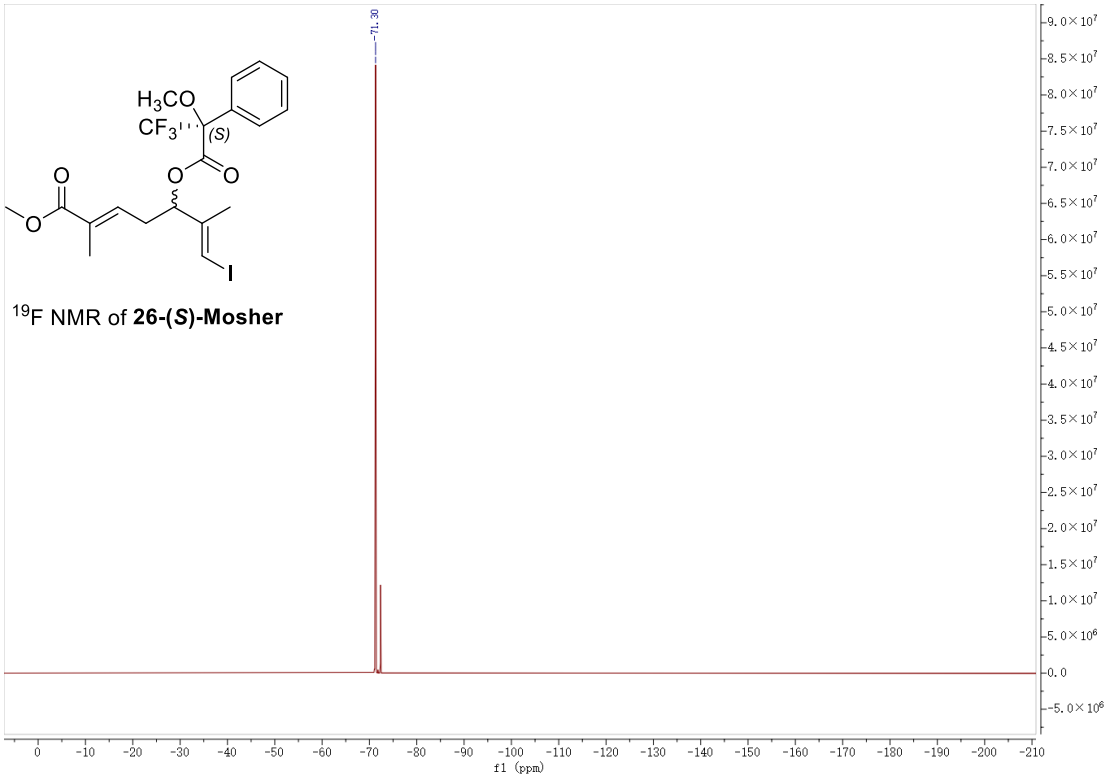

H3CO
CF3
(R)
O
O
O
O
I
13C NMR of 26-(R)-Mosher
f1 (ppm)



^{13}C NMR of **26-(*S*)-Mosher**

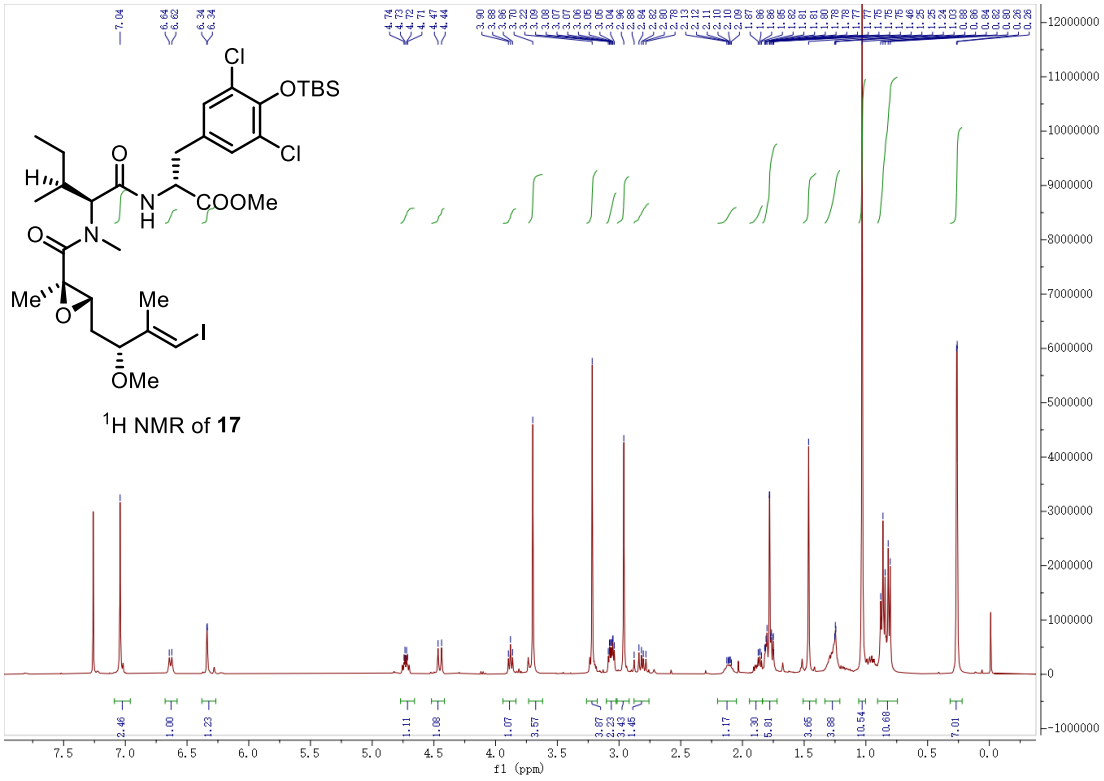


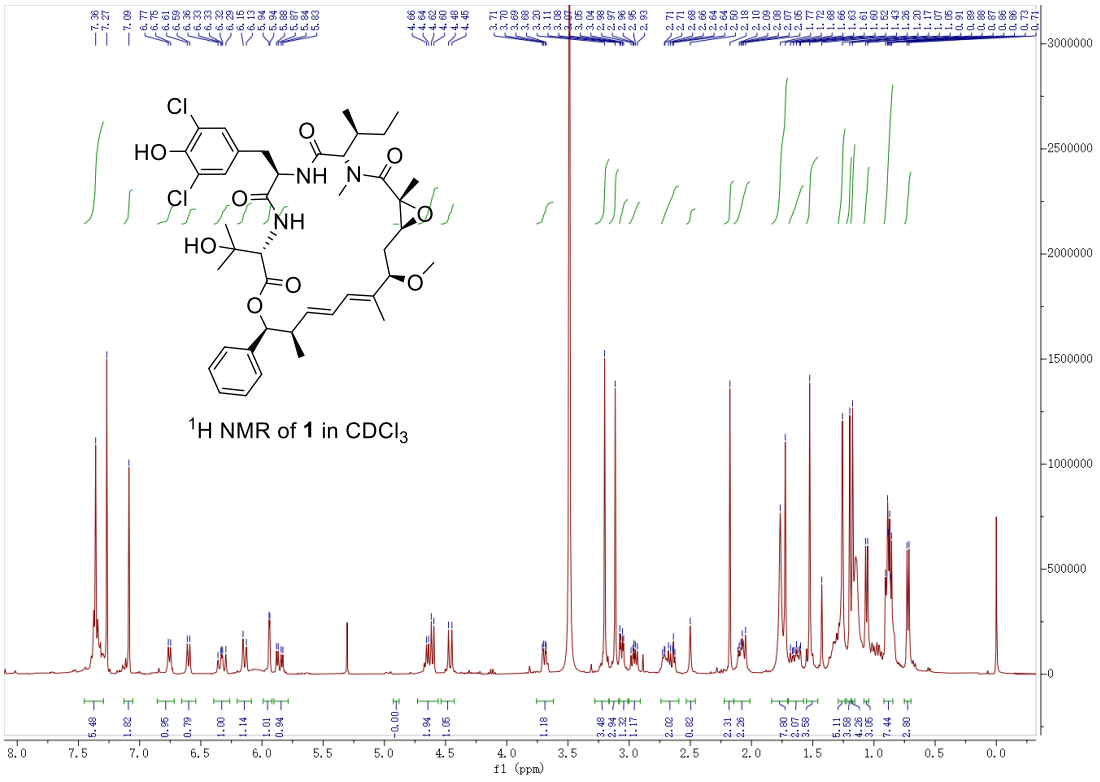
^{19}F NMR of **26-(*R*)-Mosher**



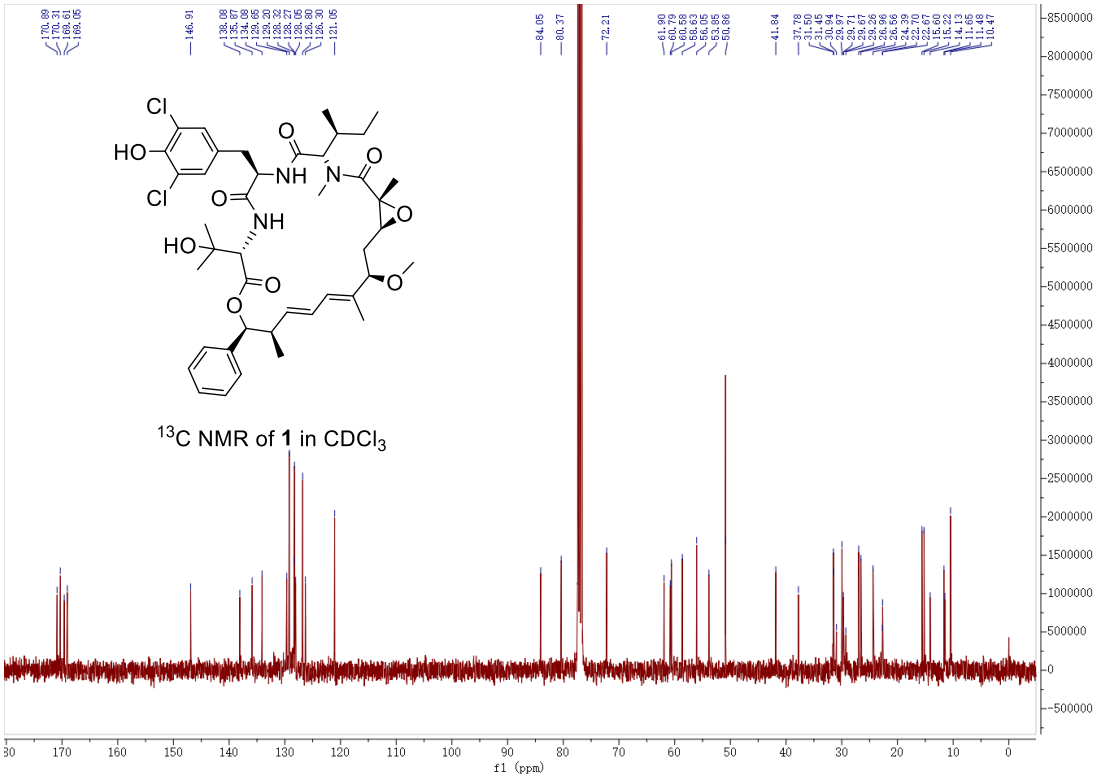
^{19}F NMR of **26-(*S*)-Mosher**

S5. ^{1}H NMR for compound 17; 1H NMR and ^{13}C NMR for nannocystin A





^{1}H NMR of **1** in $CDCl_3$



^{13}C NMR of **1** in $CDCl_3$