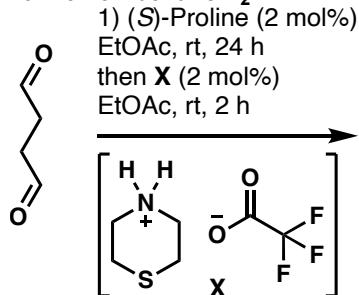


# Synthesis, Stability, and Biological Studies of Fluorinated Analogues of Thromboxane A<sub>2</sub>

21.02.24

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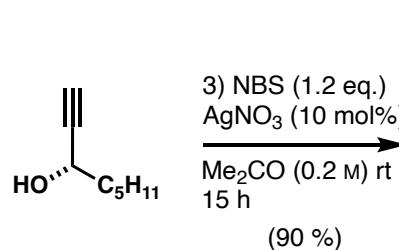
## 10-F-thromboxane A<sub>2</sub>



A

2) PMBOH (2 eq.)  
 Amberlyst 15 (cat.)  
 MgSO<sub>4</sub> (2.5 eq.)  
 DCM, 0 °C → rt, 24 h,  
 then MnO<sub>2</sub>, rt, 8 h  
 (81 %, 1.7:1 dr)

B



C

4) LiAlH<sub>4</sub> (2 eq.)  
 AlCl<sub>3</sub> (1.5 eq.)  
 Et<sub>2</sub>O, rt, 1 h  
 (90 %)

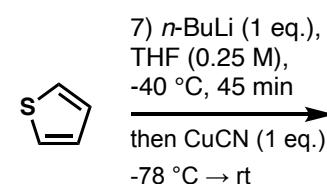
D

5) Imid (2.0 eq.)  
 TBSCl (1.5 eq.)  
 DCM, 0 °C → rt  
 16 h (94 %)

E

6) t-BuLi (2.4 eq.)  
 Et<sub>2</sub>O, -78 °C →  
 -40 °C, 4 h

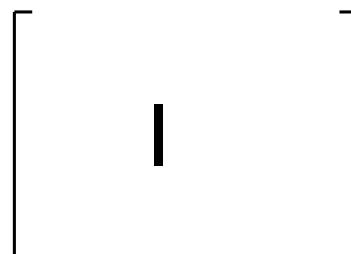
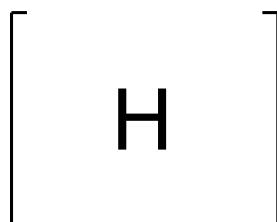
F



G

-78 °C → -20 °C, 1 h

10) m-CPBPA (2.5 eq.)  
 NHCO<sub>3</sub> (2.7 eq.)  
 DCM, 0 °C → rt, 3 h  
 (64 %, o3s)



I

9) O<sub>3</sub>-O<sub>2</sub>, -78 °C  
 ~5 min, then  
 PPh<sub>3</sub> (0.6 eq.)  
 -78 °C, 1 h  
 DCM/MeOH (3:1)

J

15) Ph<sub>3</sub>P(C<sub>4</sub>H<sub>8</sub>COOH)Br (4 eq.)  
 LiHMDS (8 eq.), THF 0 °C, 2 h  
 16) TMSCHN<sub>2</sub> (3 eq.)  
 Et<sub>2</sub>O/MeOH (9:1), 0 °C → rt, 1 h  
 (82 %, Z/E = 5:1 o2s)

K

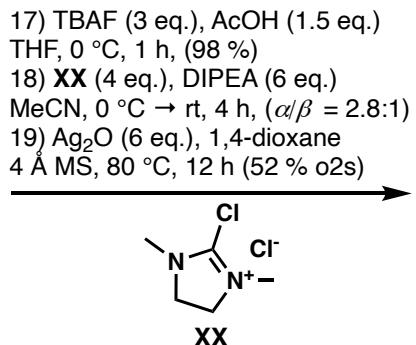
11) NFSI (2.5 eq.)  
 KHMDs (1.2 eq.)  
 Et<sub>2</sub>O (0.033 M)  
 -78 °C, 4 h  
 (51 %, 10:1 dr)

L

12) DIBAL-H (10 eq.)  
 THF, -78 °C, 3 h (quant.)  
 13) TIPSOTf (2 eq.)  
 2,6-lutidine (4 eq.)  
 DCM, 0 °C → rt, 3 h  
 14) DDQ (1.5 eq.)  
 DCM/H<sub>2</sub>O (9:1)  
 0 °C → rt, 6 h, (82 %, o2s)

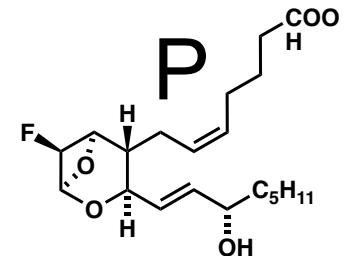
M

N



O

- 20) NaOH<sub>aq.</sub> (1 M, 250 eq.)  
1,4-dioxane, 0 °C → rt, 1 h
- 21) TBAF (3 eq.), THF,  
0 °C → rt, 12 h, (78 % o2s)

**10-F<sub>2</sub>-thromboxane A<sub>2</sub>**

K

- 22) NFSI (4 eq.)  
KHMDs (2.4 eq.)
- $\xrightarrow{\quad}$
- E<sub>t</sub>2O (0.1 M)  
-78 °C, 4 h, (40 %)

Q

- 23) DIBAL-H (10 eq.)  
THF, -78 °C, 3 h (quant.)
- 24) TIPSOTf (2 eq.)  
2,6-lutidine (4 eq.)  
DCM, 0 °C → rt, 4 h
- $\xrightarrow{\quad}$
- 25) DDQ (1.5 eq.)  
DCM/H<sub>2</sub>O (9:1)  
0 °C → rt, 6 h, (84 %, o2s)

R

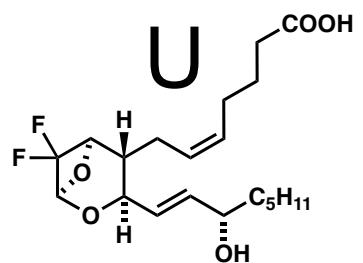
- 26) Ph<sub>3</sub>P(C<sub>4</sub>H<sub>8</sub>COOH)Br (4 eq.)  
LiHMDS (8 eq.), THF 0 °C, 2 h
- 27) TMSCHN<sub>2</sub> (3 eq.)  
Et<sub>2</sub>O/MeOH (9:1), 0 °C → rt, 1 h
- $\xrightarrow{\quad}$
- (73 %, Z/E = 5:1 o2s)

S

- 28) Ac<sub>2</sub>O (2 eq.), py (4 eq.), DMAP  
(0.5 eq.), DCM, 0 °C → rt, 3 h (97 %)
- 29) TBAF (3 eq.), AcOH (1.5 eq.)  
THF, 0 °C, 1 h (94 %)
- 30) MsCl (1.5 eq.), Et<sub>3</sub>N (10 eq.), DCM  
0 °C → rt, 1.5 h (96 %,  $\alpha/\beta = 1:2$ )
- $\xrightarrow{\quad}$
- 31) <sup>t</sup>BuOK (2 eq.), THF/PrOH, 4 Å MS  
0 °C → rt, 3 h (67 %)
- 32) TBAF (3 eq.), THF, 0 °C → rt 12 h  
(94 %)

T

- 32) NaOH<sub>aq.</sub> (1 M, 300 eq.)  
1,4-dioxane, 0 °C → rt, 24 h



Unexpected reaction:

M

- 33) Ph<sub>3</sub>P(C<sub>4</sub>H<sub>8</sub>COOH)Br (4 eq.)  
<sup>t</sup>BuOK (8 eq.), THF 40 °C, 1 h  
(67 %)
- $\xrightarrow{\quad}$

V

