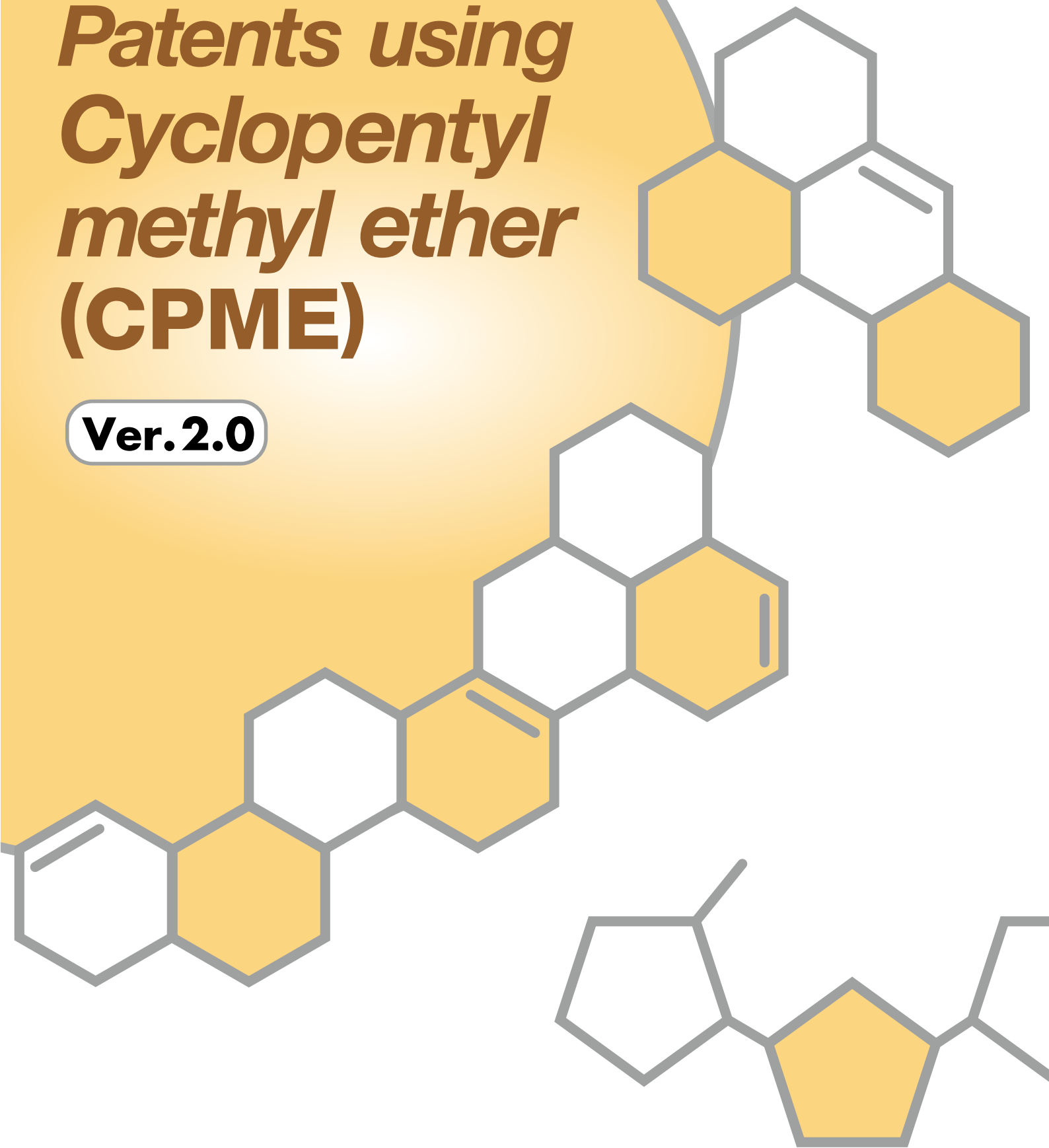


ZEON

*Patents using
Cyclopentyl
methyl ether
(CPME)*

Ver.2.0



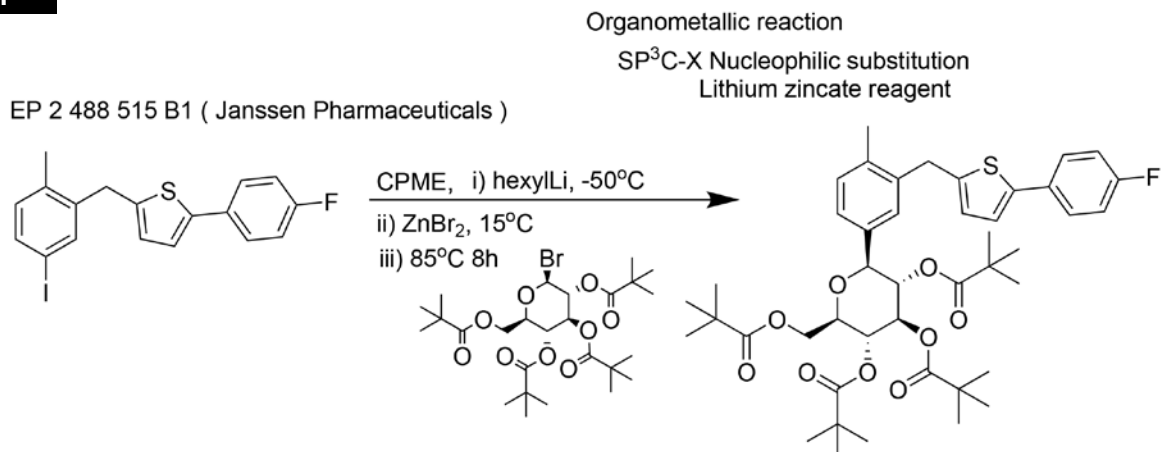
ZEON CORPORATION

C O N T E N T S

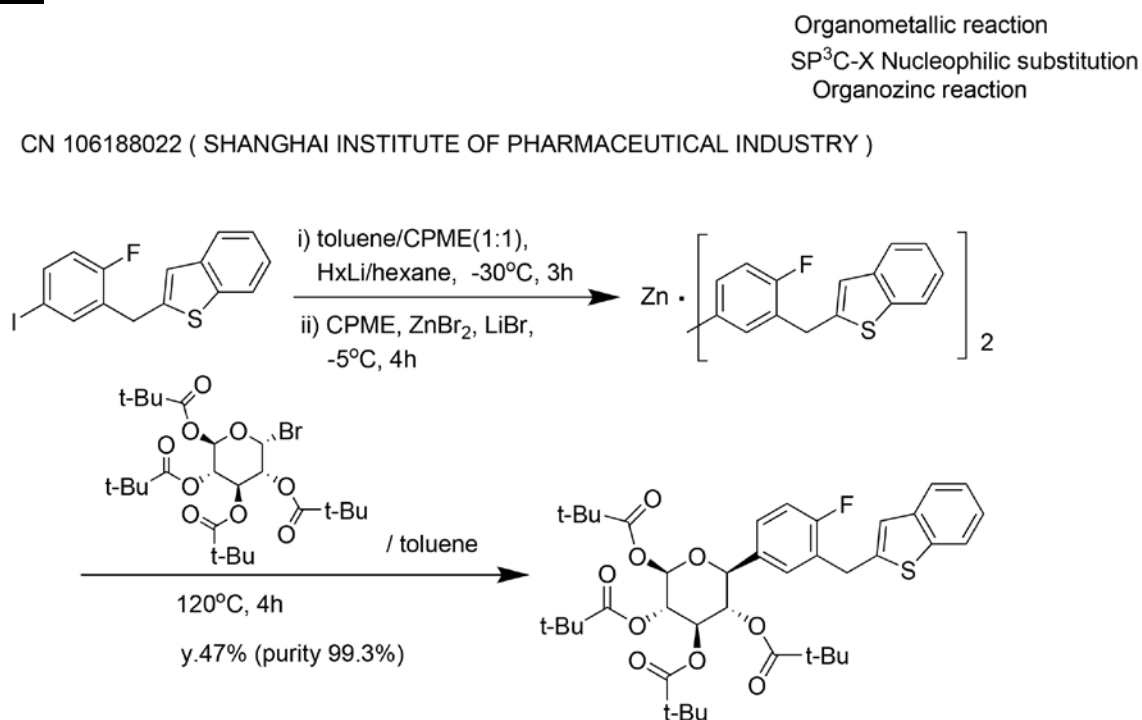
1. Nucleophilic substitution reaction (Alkylation, Amination, Hydrogenolysis etc.)	3
2. Addition reaction to carbonyl(C=O), imino(C=NH) and nitrile(CN)	6
2-1. Addition of organometallic compound	6
2-2. Addition of Enolates	9
2-3. Hydrogenation	10
3. Addition reaction to alkene	11
4. Esterification, Amidation and Deprotection reaction	12
5. Transition Metal Catalytic Coupling Reaction.....	16
6. Borylation reaction	18
7. Silylation reaction	20
8. Indole synthesis, Fluorination and Oxidation reactions	22
9. Extraction	23
10. Crystallization	24
10-1. Creation of new crystal form.....	24
10-2. Optical resolution	27
10-3. Purification Isolation	30

1 Nucleophilic substitution reaction (Alkylation, Amination, Hydrogenolysis etc.)

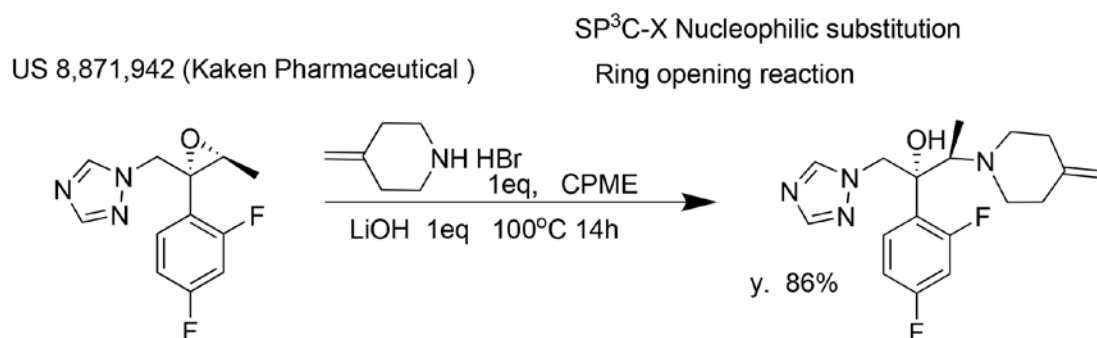
No.1



No.2

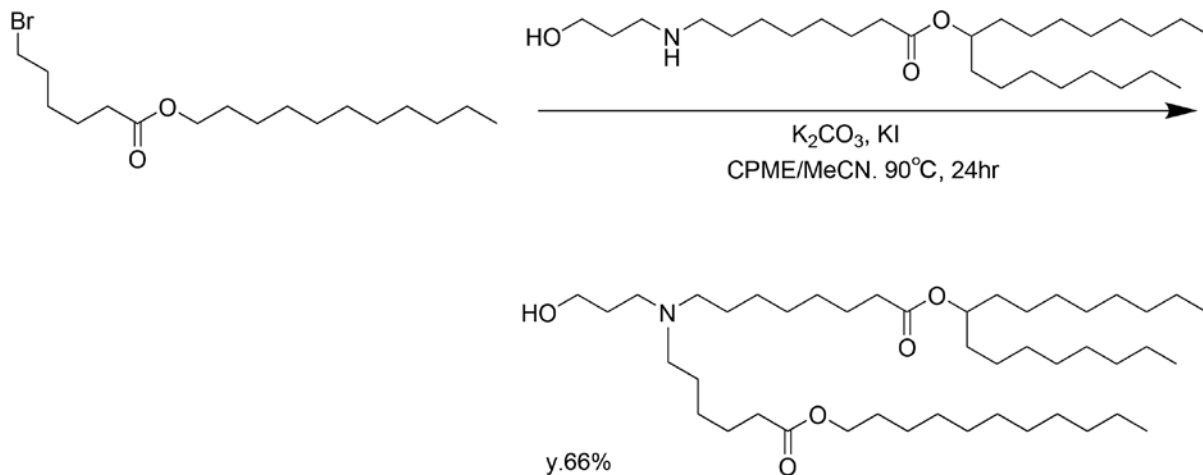


No.3

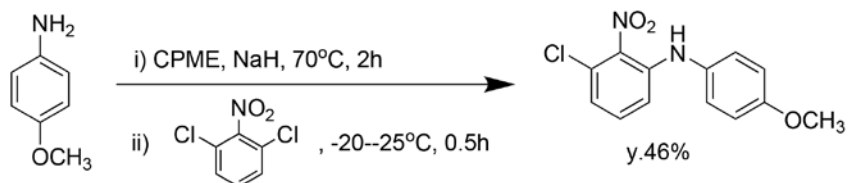


No.4

WO 2018/170306 (MODERNATX, INC.)

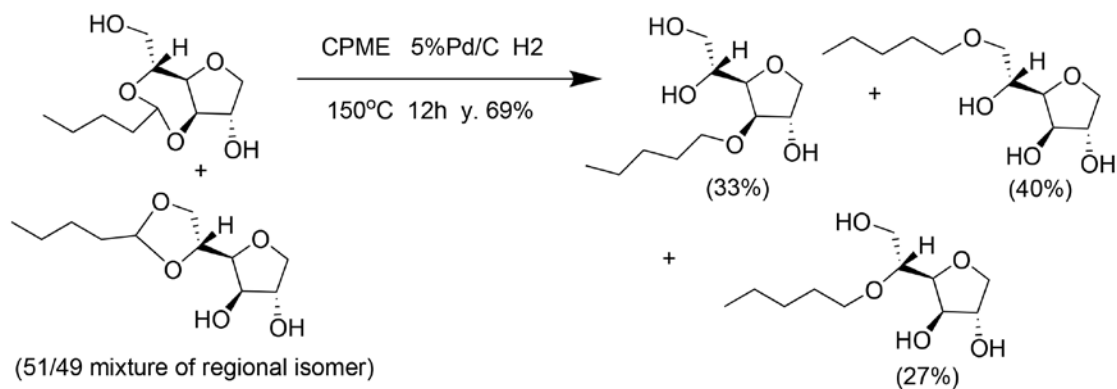
SP³C-X Nucleophilic substitution**No.5**

EP 2792667 (Kumiai Chemical)

Nucleophilic substitution
SP²C-X**No.6**

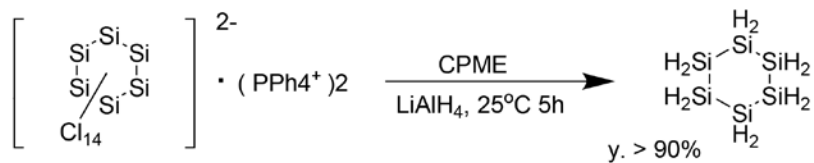
CN 106687206 (SYRAL BELGIUM NV)

Hydrogenation



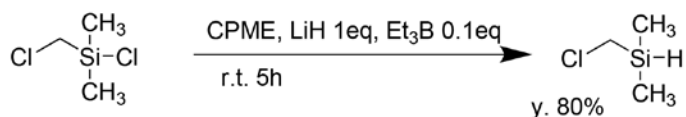
No.7

US 2014/0012029 (Nippon Shokubai)

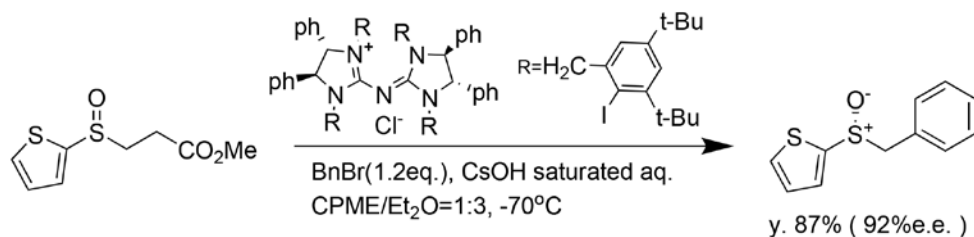
Hydrogenation
LAH**No.8**

Nucleophilic substitution

CN 108129510 (INSTITUTE OF CHEMISTRY CHINESE ACADEMY OF SCIENCES)

**No.9**SP³C-X Nucleophilic substitutionasymmetric alkylation
of Sulfonate anion

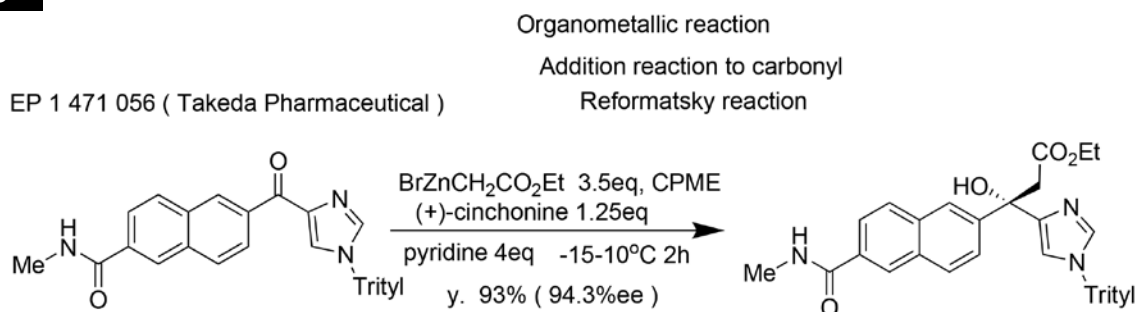
WO 2016/039691 (NANYANG TECHNOLOGICAL UNIVERSITY)



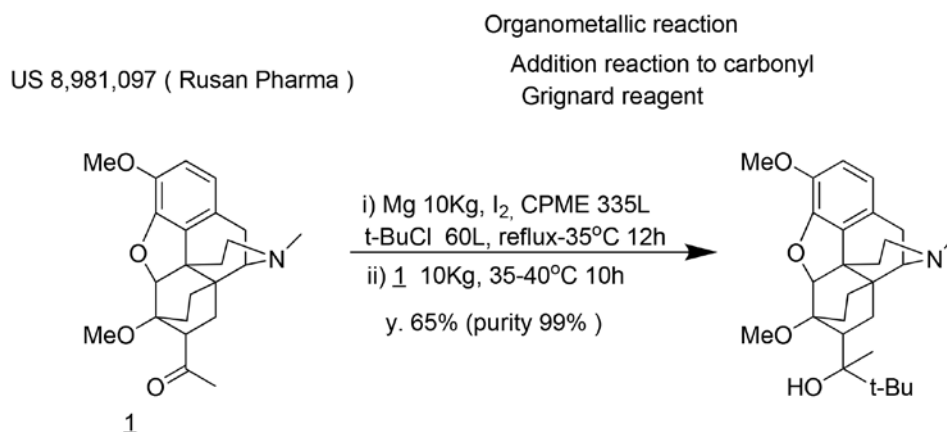
2 Addition reaction to carbonyl(C=O), imino(C=NH) and nitrile(CN)

2-1 Addition of organometallic compound

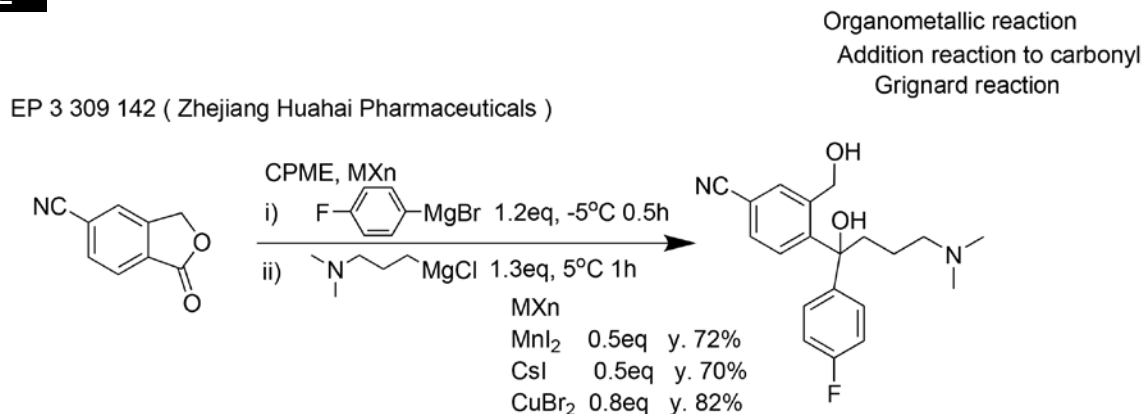
No.10



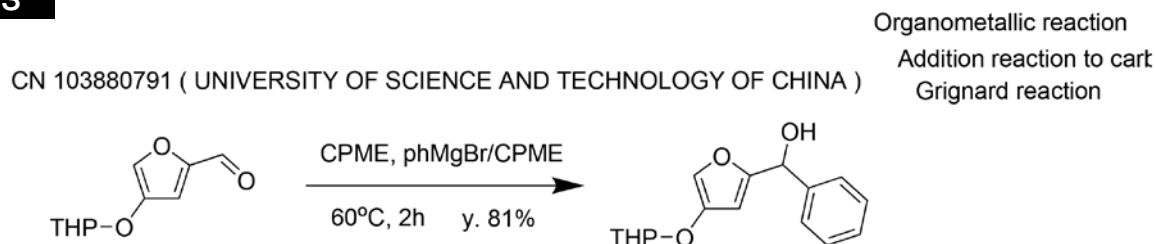
No.11



No.12

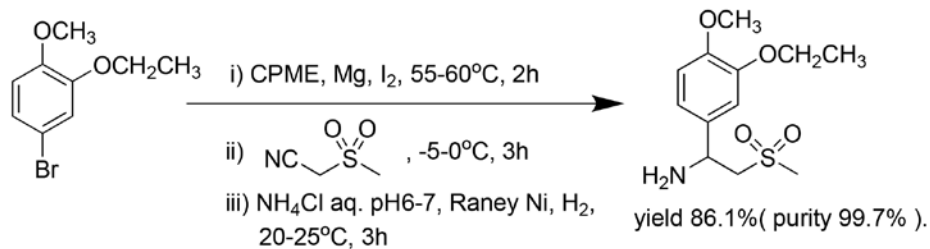


No.13



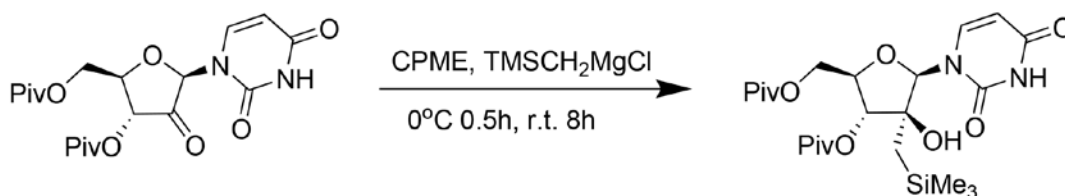
No.14

CN 105348172 (XINFA PHARMACEUTICAL)

Organometallic reaction
Addition reaction to nitrile
Grignard reaction**No.15**

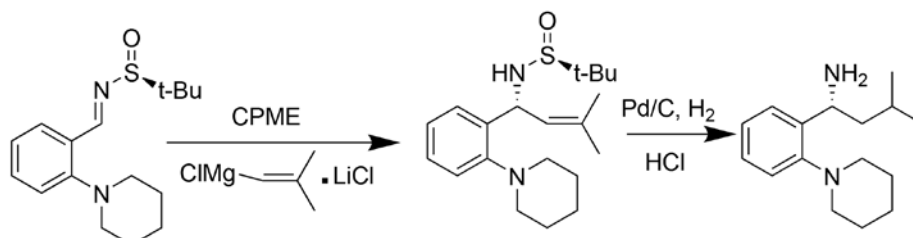
US 10,214,554 (Merck Sharp & Dohme)

Grignard reaction

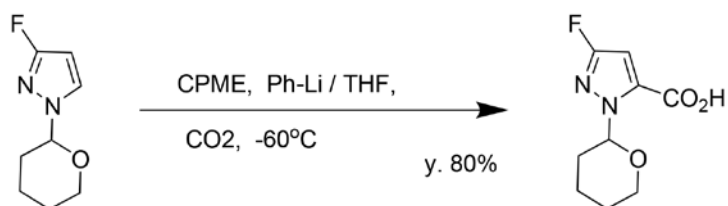
**No.16**

CN 109970681 (ANHUI HAIKANG PHARMACEUTICAL)

Grignard reaction

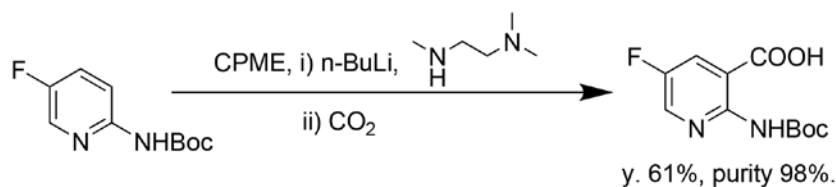
**No.17**

CN 107759574 (PHARMABLOCK SCIENCES)

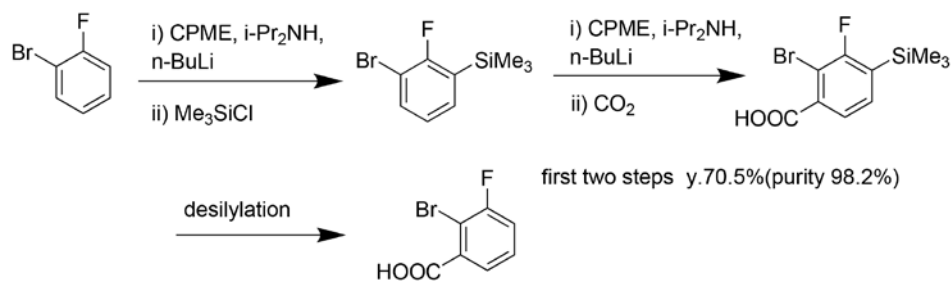
Organometallic reaction
Addition reaction to carbonyl

No.18

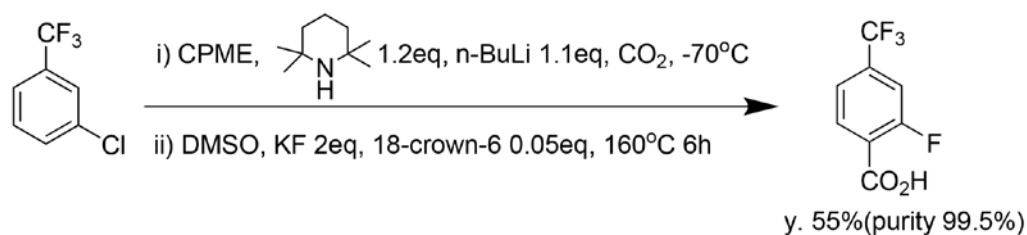
CN 107903209 (SHANGHAI TBBMED)

Organometallic reaction
Addition reaction to carbonyl**No.19**

CN 108003016 (SHANGHAI TBBMED)

Organometallic reaction
Silylation**No.20**

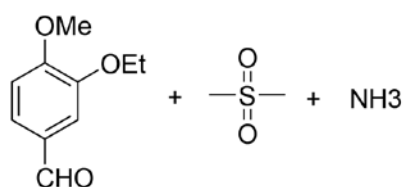
CN 106083563 (CANGZHOU PURUI DONGFANG SCIENCE & TECHNOLOGY)

Organometallic reaction
Addition reaction to carbonyl

2-2 Addition of Enolates

No.21

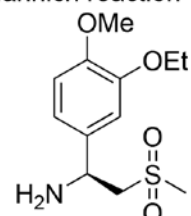
CN 104447443 (XINFA PHARMACEUTICAL)



L-PROLINES
D-tartaric acid
CPME
20-25°C 6h
y. 80.6% (98.8ee%)

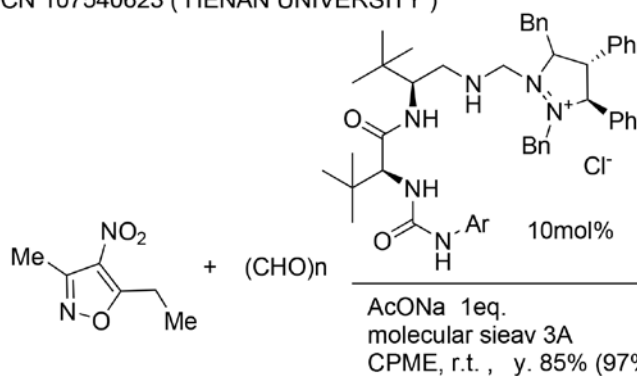
Addition reaction

Mannich reaction

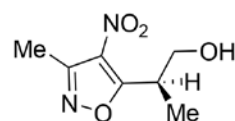


No.22

CN 107540623 (HENAN UNIVERSITY)

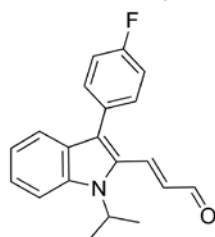


Addition reaction to carbonyl
Aldol reaction

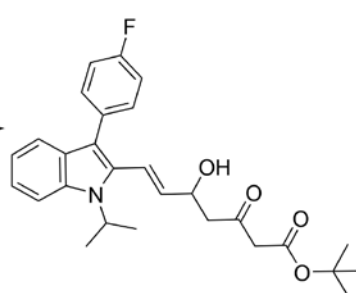


No.23

CN 107663164 (SHANGHAI PUYI CHEMICAL TECHNOLOGY)



Addition reaction to carbonyl
Aldol reaction

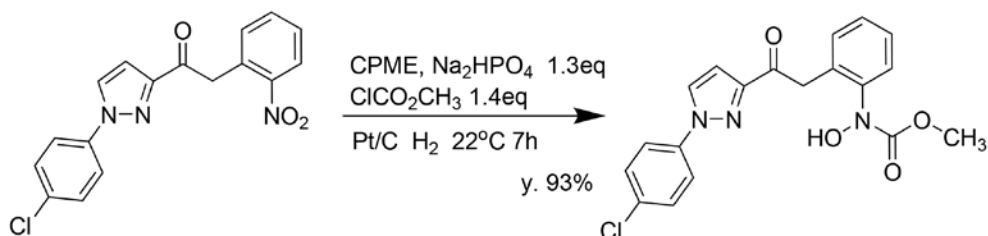


2-3 Hydrogenation

No.24

EP 3 357 905 (Solvias AG)

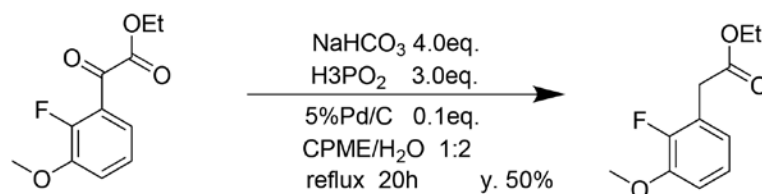
Hydrogenation



No.25

Hydrogenation

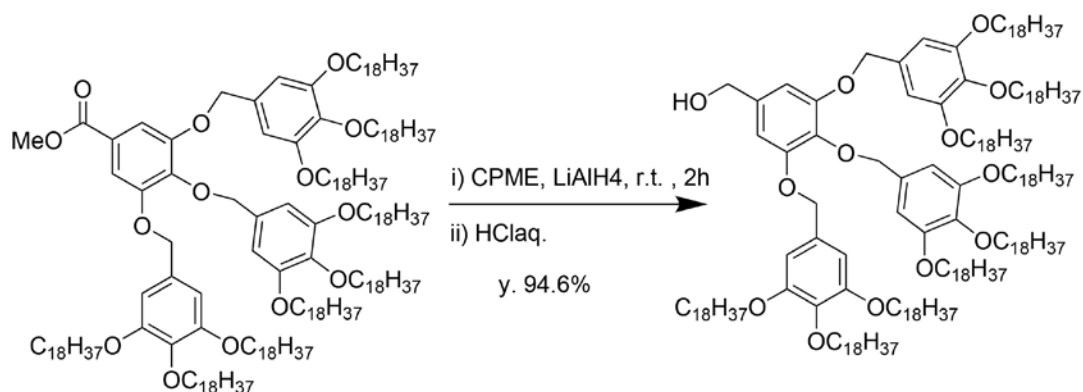
CN109761809 (ANHUI HUASHENG PHARMACEUTICAL TECHNOLOGY)



No.26

Hydrogenation
LAH

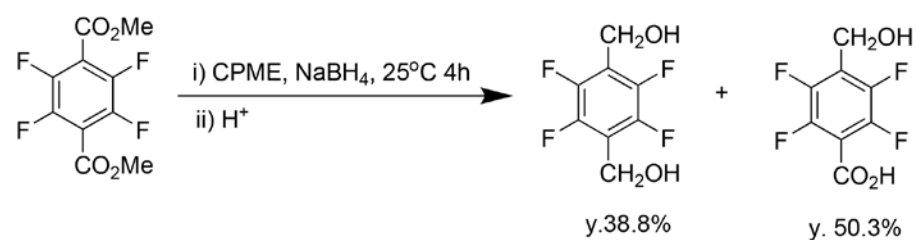
US 9,029,528 (Ajinomoto)



No.27

Hydrogenation
NaBH₄

CN 109704916 (JIANGSU YANGNONG CHEMICAL)

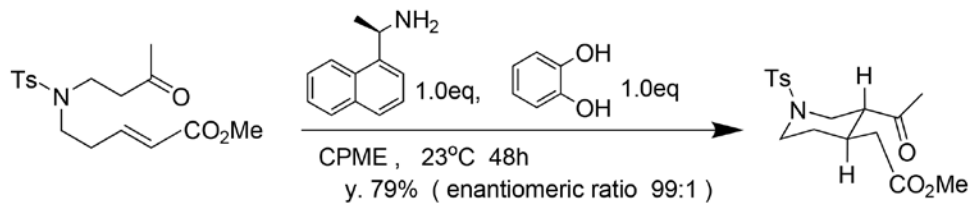


3 Addition reaction to alkene

No.28

WO 2016/179184 (NORTHWESTERN UNIVERSITY)

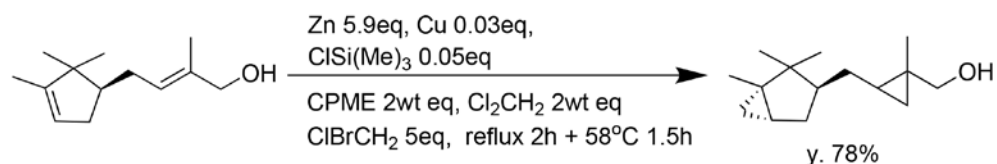
Addition reaction to SP²C
Michael addition



No.29

WO 2017/024126 (INTERNATIONAL FLAVORS & FRAGRANCES)

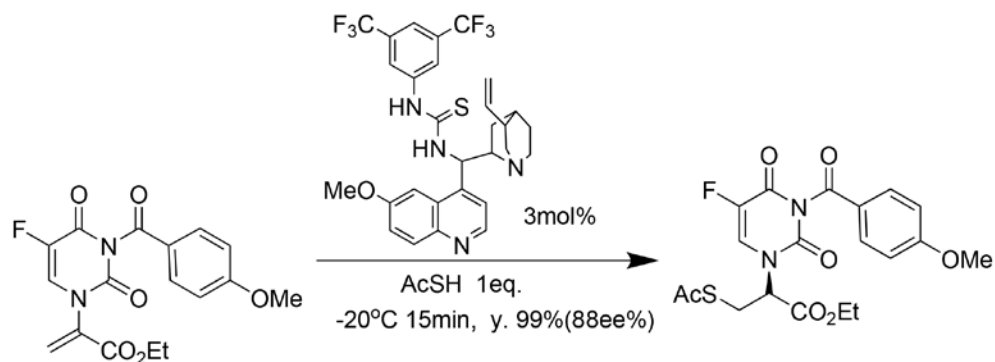
Addition reaction to SP²C
Simmons-Smith reaction



No.30

CN 107759429 (HENAN NORMAL UNIVERSITY)

Addition reaction to SP²C
Michael addition

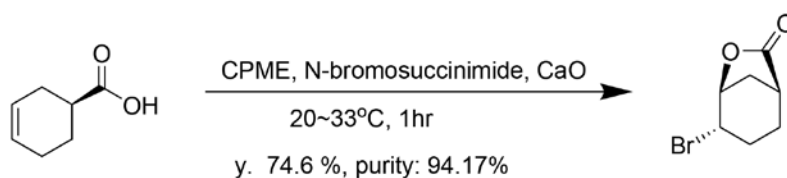


No.31

WO 2014/081047 (DAIICHI SANKYO)

preparation of key intermediate for edoxaban

Addition reaction to SP²C
Halogenation

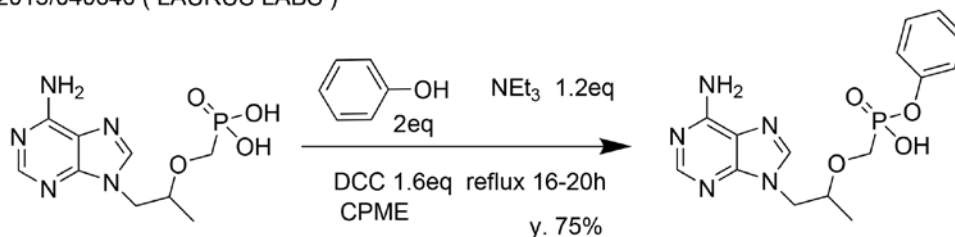


4 Esterification, Amidation and Deprotection reaction

No.32

WO 2015/040640 (LAURUS LABS)

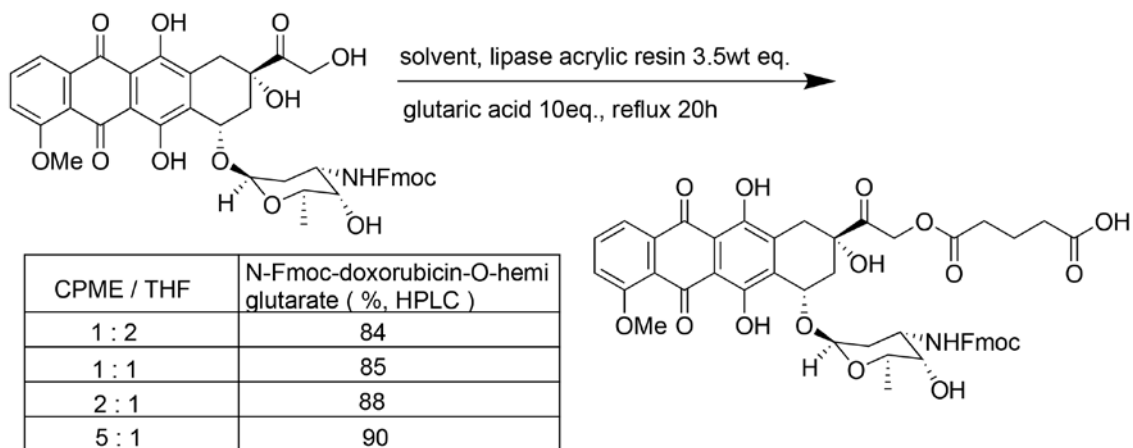
Esterification



No.33

WO 2016/116335 (Aeterna Zentaris GmbH)

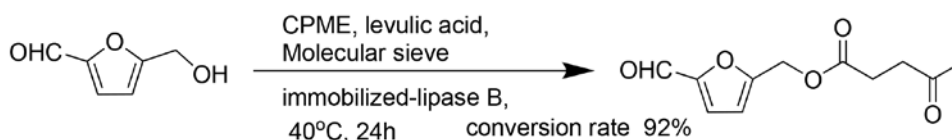
Esterification
Lipase



No.34

CN 105838748 (South China University of Technology)

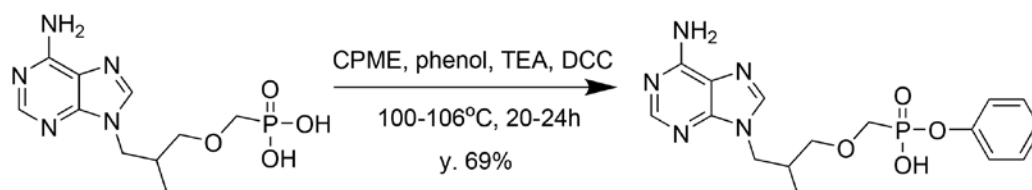
Esterification
Lipase



No.35

WO 2017/221189 (LAURUS LABS)

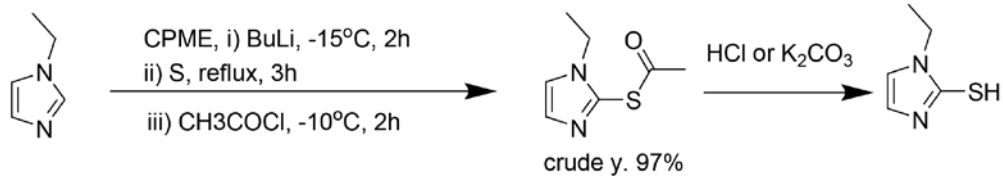
Esterification



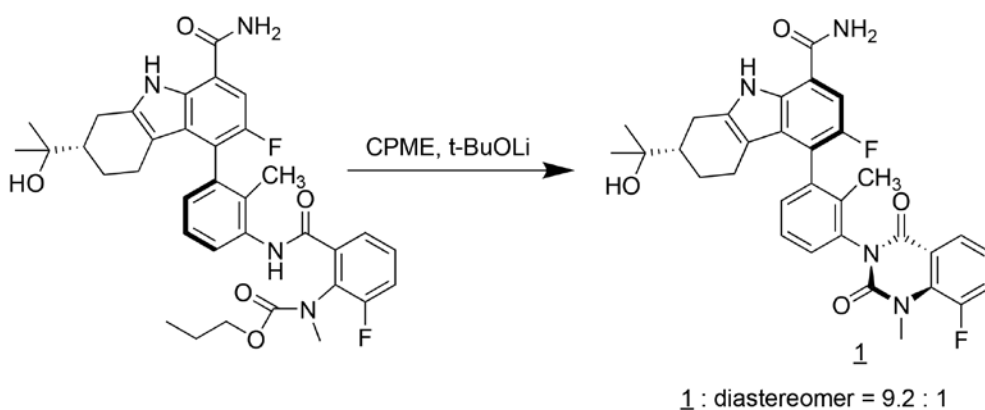
No.36

CN 107522661 (PLUS SCIENCE & TECHNOLOGY)

Organometallic reaction

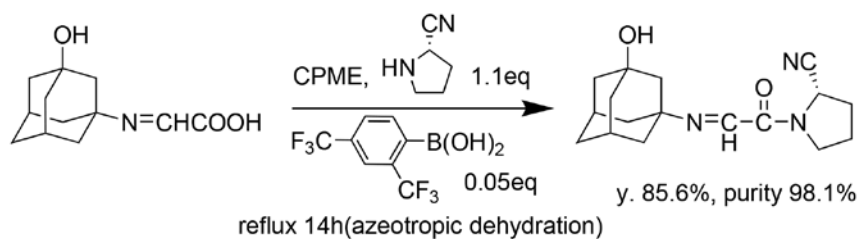
**No.37**

WO 2018/118830 (BRISTOL-MYERS SQUIBB)

Nucleophilic substitution
Amidation**No.38**

CN 108503571 (DALIAN ZHENGBANG INFORMATION CONSULTING)

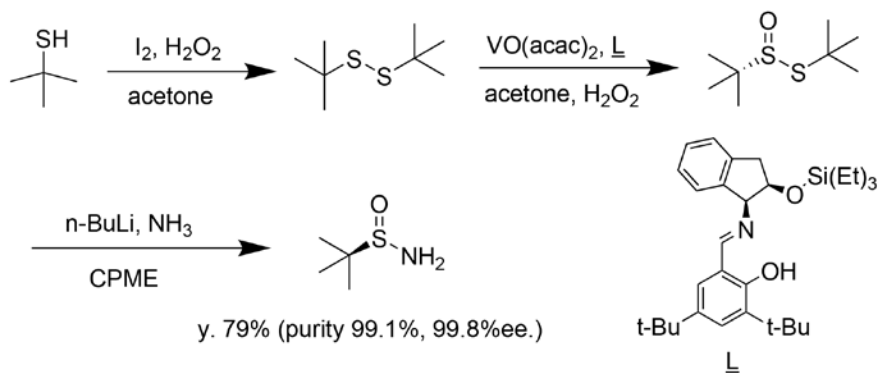
Amidation



No.39

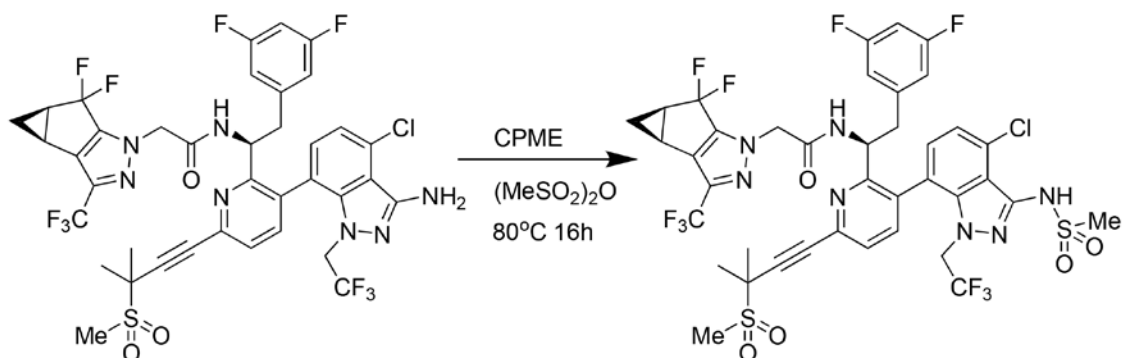
Nucleophilic substitution
Amidation

CN 106478471 (SHANGHAI HANHONG TECHNOLOGY)

**No.40**

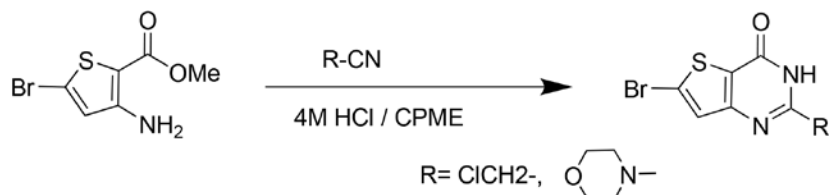
Amidation

WO 2019/161280 (GILEAD SCIENCES)

**No.41**

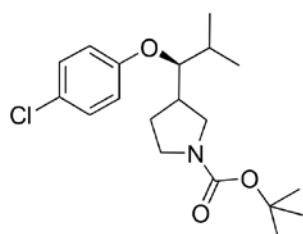
Amidation

EP 3 533 797 (Takeda Pharmaceutical Company)

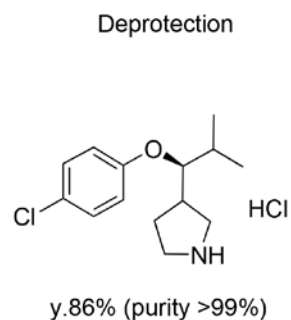


No.42

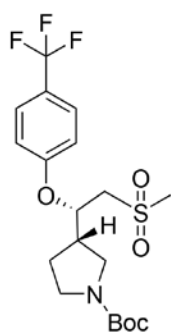
WO 2012/006205 (THERAVANCE INC)



i) 3M HCl / CPME 8eq. r.t. 1nt
ii) solvent removed by distillation
iii) recrystallized from diisopropyl ether and EtOAc

**No.43**

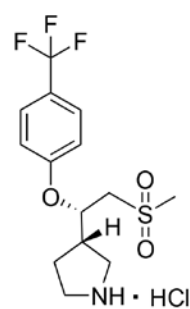
WO 2013/049617 (Theravance Biopharma)



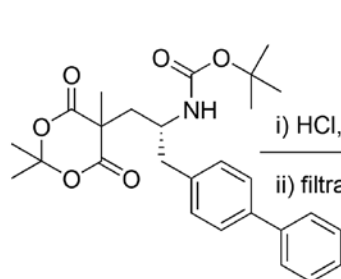
crude oil

i) CPME / heptane 20°C
ii) filtration and dry
iii) 3M HCl / CPME 20°C
(process iii) y. 87.8% purity 99%

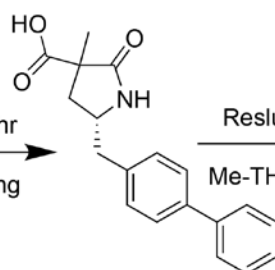
Crystallization
Deprotection

**No.44**

WO 2013/123222 (Theravance Biopharma)

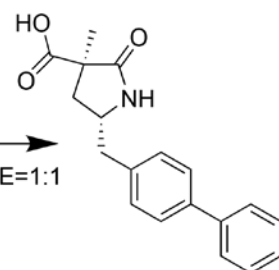


i) HCl, CPME, r.t., 24hr
ii) filtration and drying



y. 78% (86% d.e.)

Reslurrying
Me-THF/CPME=1:1

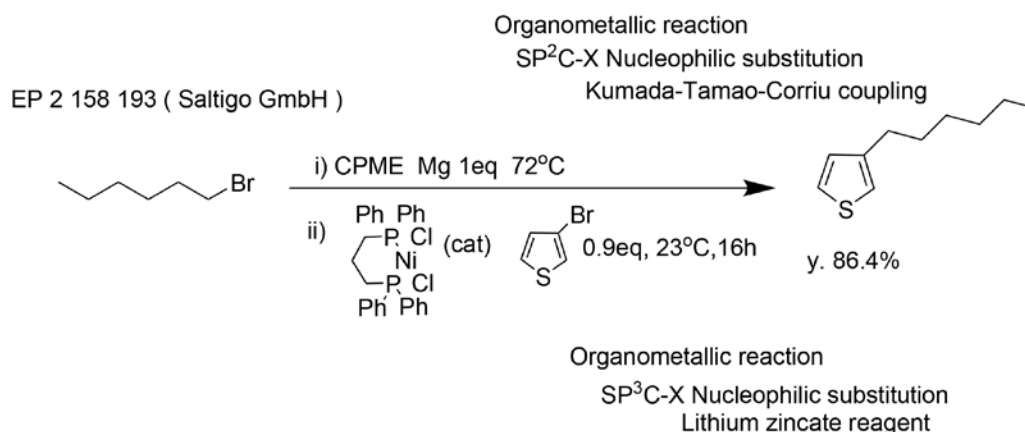


y. 83% (98% d.e.)

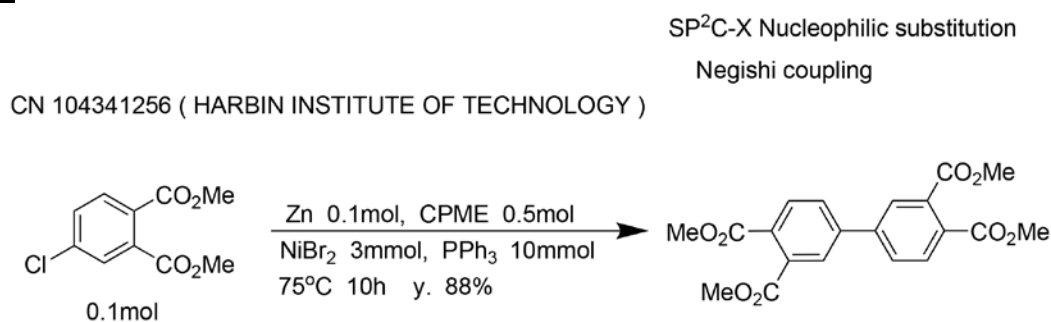
Deprotection
Optical resolution

5 Transition Metal Catalytic Coupling Reaction

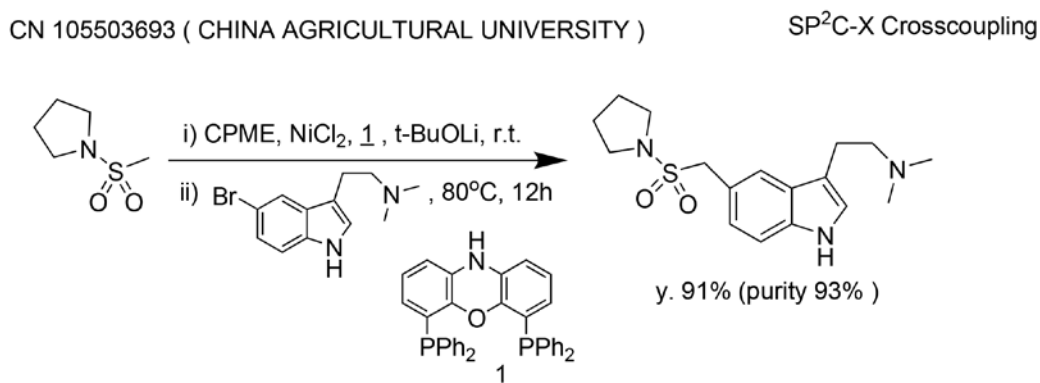
No.45



No.46



No.47

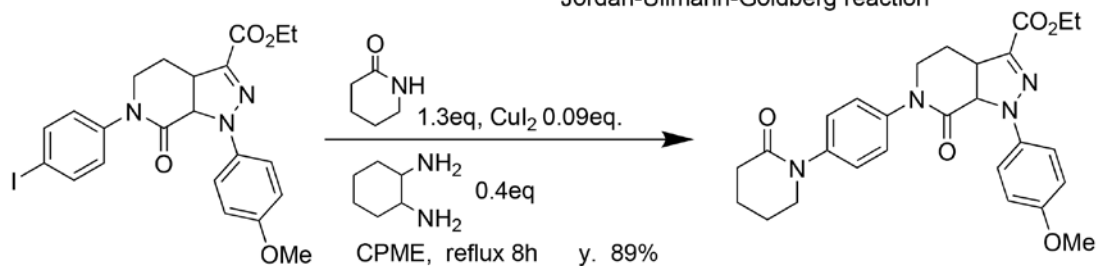


No.48

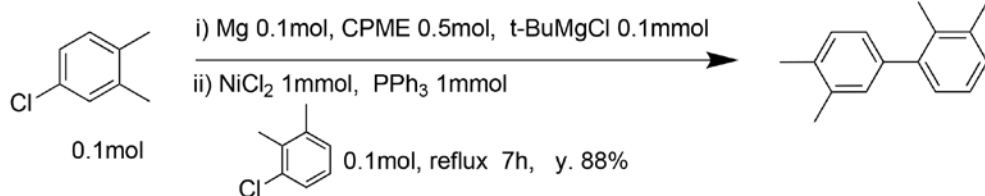
WO 2014/075648 (ZENTIVA K.S.)

SP²C-X Nucleophilic substitution

Jordan-Ullmann-Goldberg reaction

**No.49**

CN 104370685 (HARBIN INSTITUTE OF TECHNOLOGY)

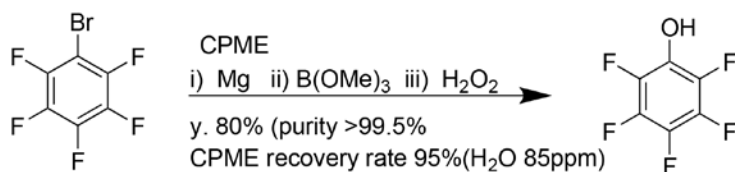
SP²C-X Nucleophilic substitution
Kumada-Tamao-Corriu coupling

6 Borylation reaction

No.50

CN 106966871 (DALIAN QIKAI MEDICAL TECHNOLOGY)

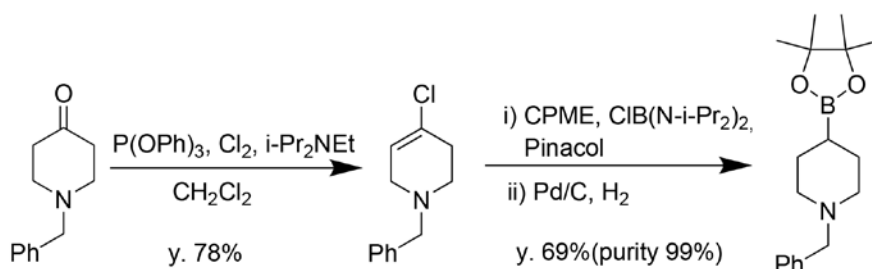
Organometallic reaction
Grignard reagent Borylation



No.51

CN 105566368 (CANGZHOU PURUI DONGFANG SCIENCE & TECHNOLOGY)

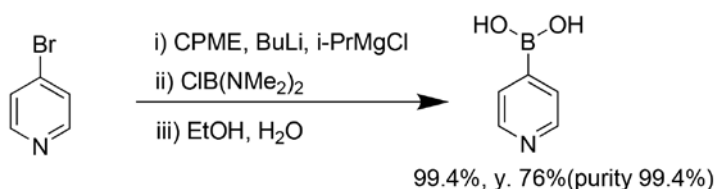
SP²C-X Borylation



No.52

CN 107892699 (CANGZHOU PURUI DONGFANG SCIENCE & TECHNOLOGY)

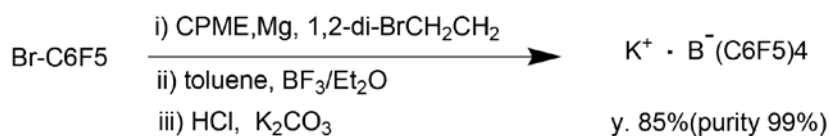
Organometallic reaction
Borylation

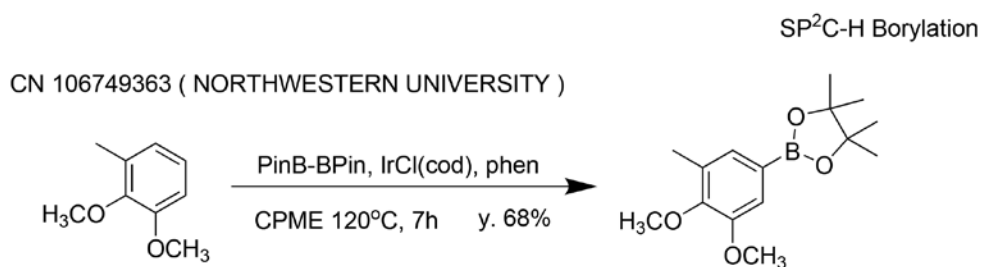
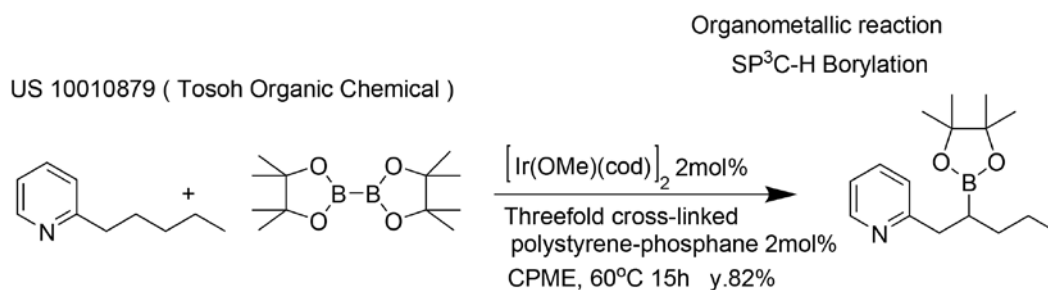
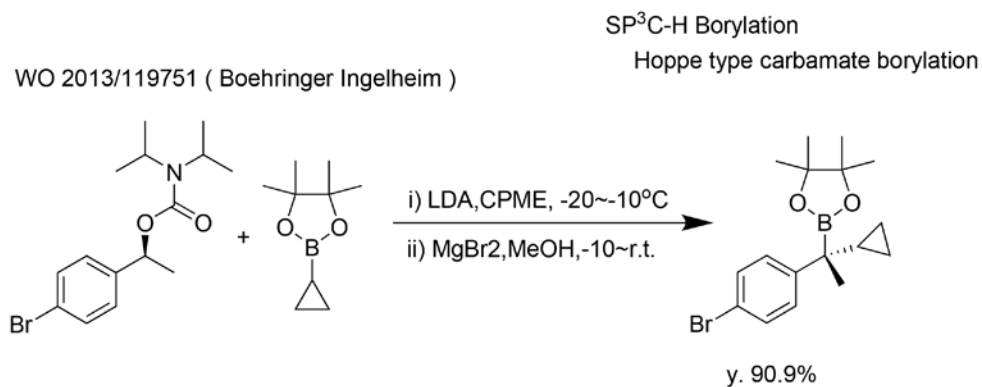


No.53

CN 110041354 (ZHENJIANG JUJIE NEW MATERIAL TECHNOLOGY DEVELOPMENT CENTER)

Grignard reaction
Borylation



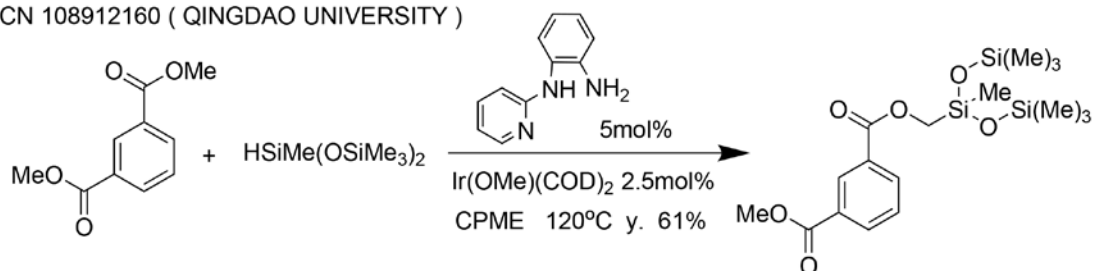
No.54**No.55****No.56**

7 Silylation reaction

No.57

SP³C-H Silylation

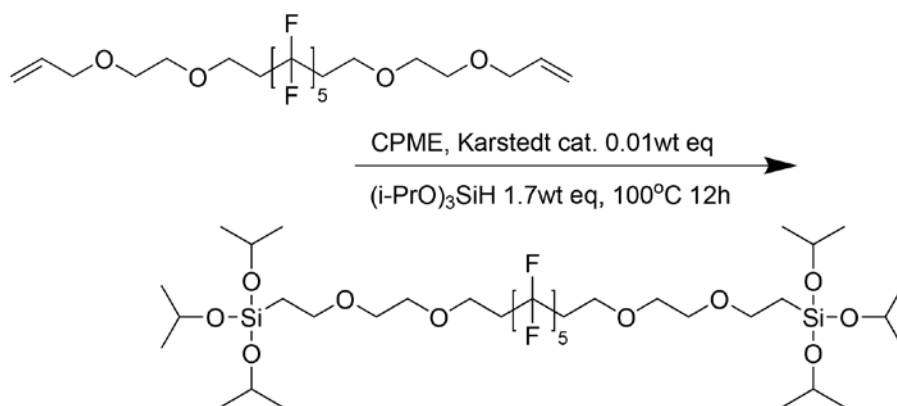
CN 108912160 (QINGDAO UNIVERSITY)



No.58

Silylation

CN 108587456 (SHENZHEN ETSUCH TECHNOLOGY)

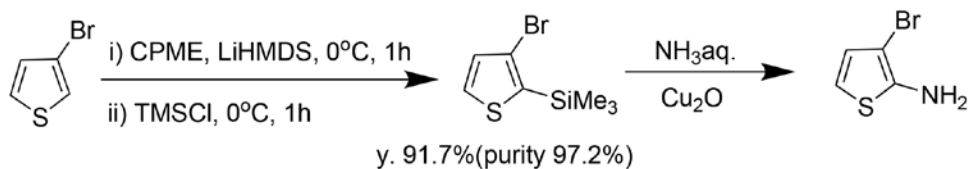


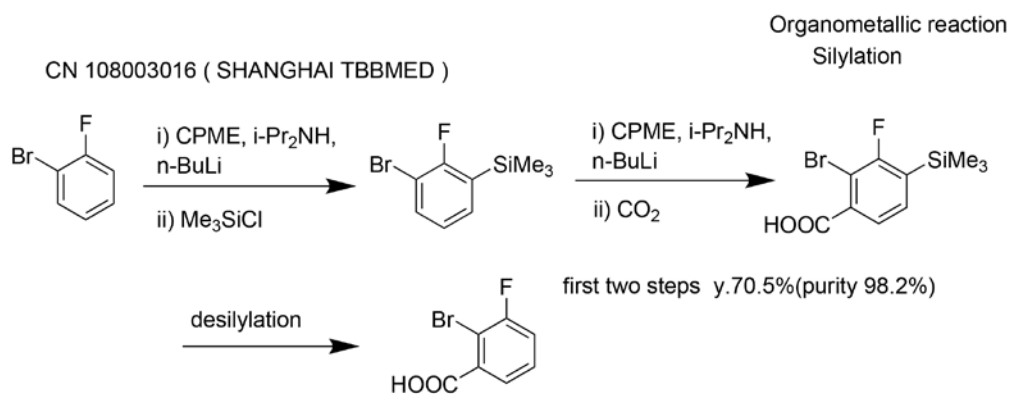
No.59

Nucleophilic substitution

Silylation

CN 107880015 (SHANGHAI TBBMED)



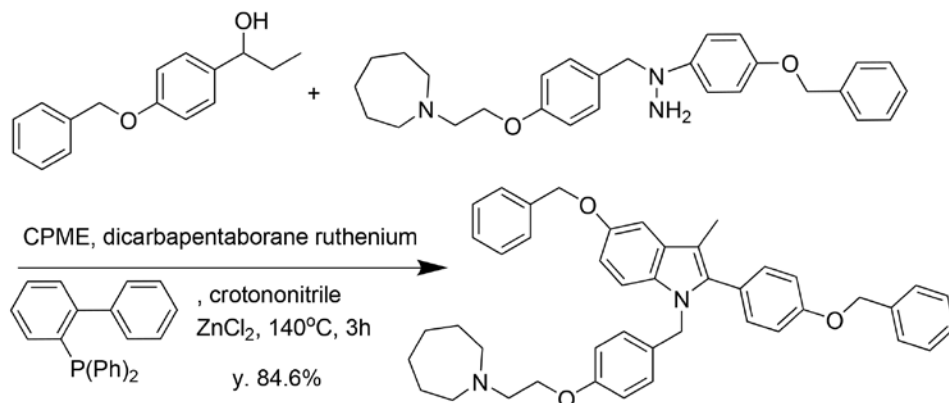
No.60

8 Indole synthesis, Fluorination and Oxidation reactions

No.61

Indole synthesis

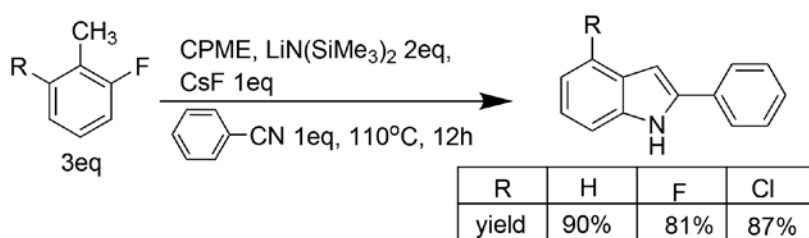
CN 103864665 (SUZHOU TERUI PHARMACEUTICAL)



No.62

Indole synthesis

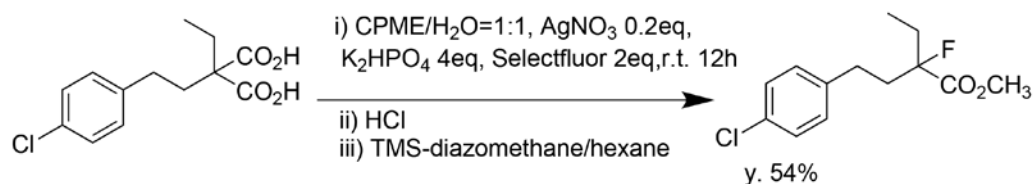
CN 109665984 (NANJING TECH UNIVERSITY)



No.63

Substitution reaction
Fluorination

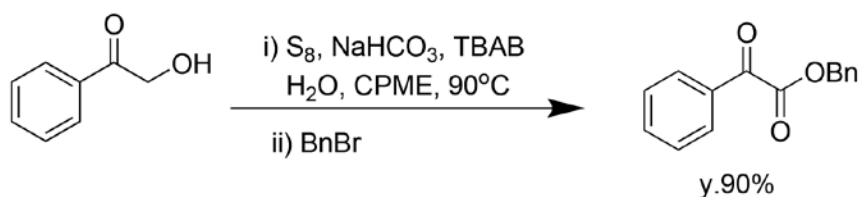
CN 109824472 (NANJING TECH UNIVERSITY)



No.64

Oxidation

CN 110015983 (EAST CHINA NORMAL UNIVERSITY)

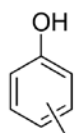


9 Extraction

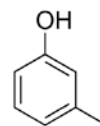
No.65

Purification

CN 104230669 (SUZHOU FEIXIANG NEW MATERIAL RESEARCH INSTITUTE)



i) NH_2CONH_2 , toluen, hexane
 85°C 2h, 50°C 1h, 7°C 1.5h, filtration
 ii) filter cake, CPME, 25°C , 1h, filtration
 iii) distillation the filtrate



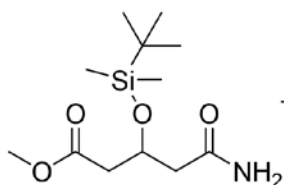
p:m:2,6-di=16.5%:81.6%:1.9%

y. 86%(purity 99.6%)

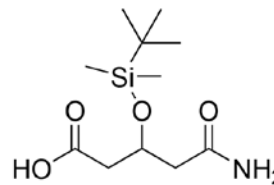
No.66

Purification

CN 104356155 (ZHEJIANG NEO-DANKONG PHARMACEUTICAL)



i) $\text{CH}_3\text{OH}/\text{H}_2\text{O}$, LiOH, $40-45^\circ\text{C}$
 ii) CPME extraction
 iii) aqueous phase
 HCl aq, CPME extraction

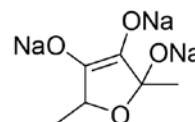
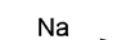
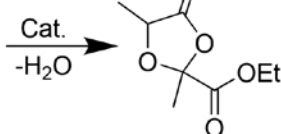
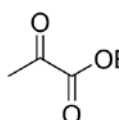
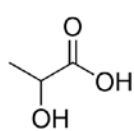


y. 86.5%

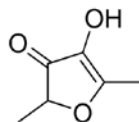
No.67

Purification

CN 106588837 (ADVANBIOCHEM)



i) 6N HCl aq., rt 1h
 ii) extraction with CPME
 iii) crystallization



y.90%

10 Crystallization

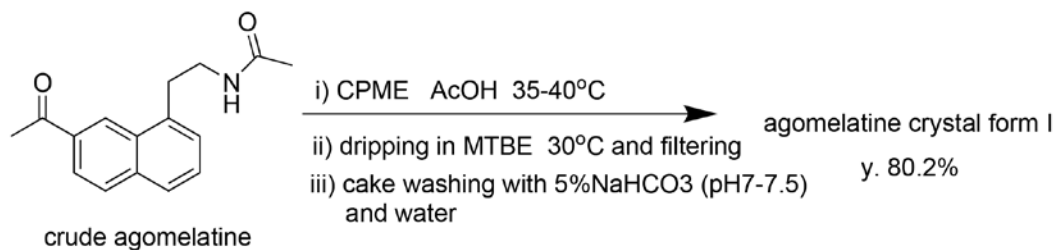
10-1 Creation of new crystal form

No.68

CN 104341315 (SHANGHAI SYNCORES TECHNOLOGIES)

Crystallization

preparation of agomelatine crystal form I (brand name Valdoxan)

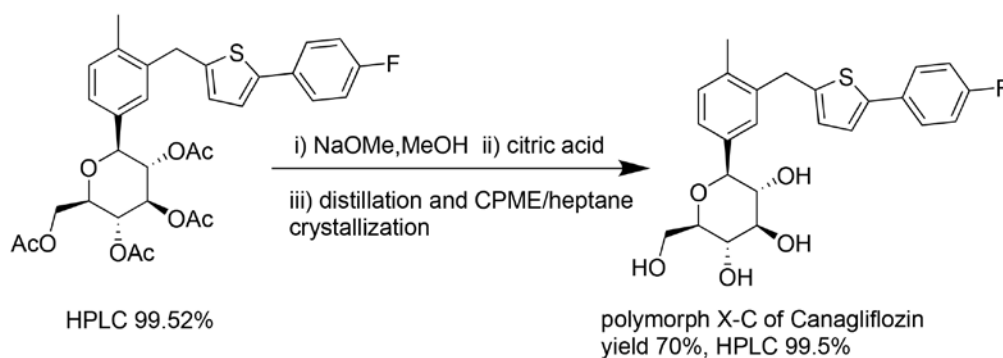


No.69

WO 2017/084644 (Zentiva K.S.)

Crystallization

new crystalline form of Canagliflozin

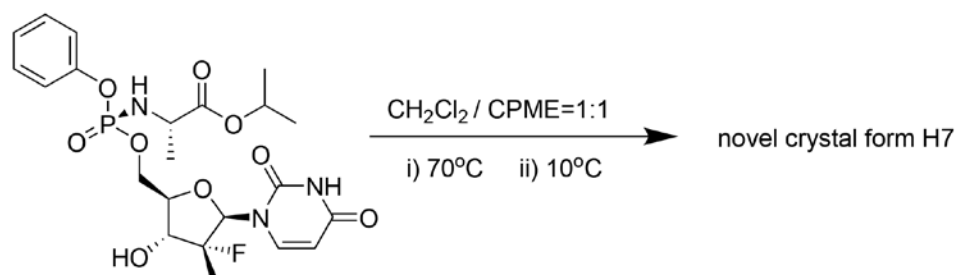


No.70

CN 104804054 (CHARM PHARMATECH)

Crystallization

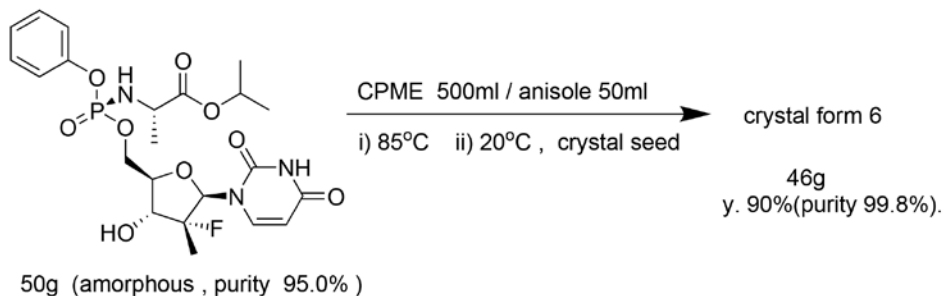
novel Sofosbuvir crystal form H7



No.71

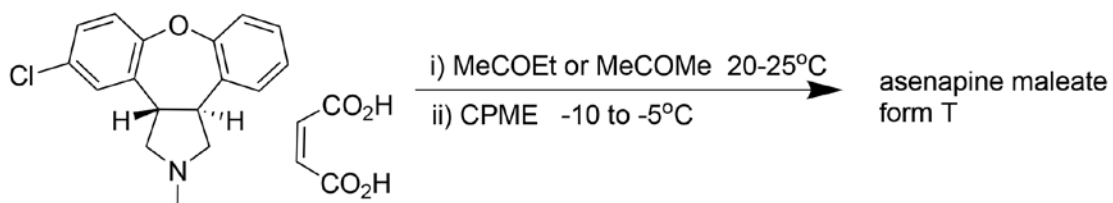
CN 104829673 (NANJING QICHANG PHARMACEUTICAL TECHNOLOGY)
novel crystallization method for preparing a sofosbuvir crystal form 6

Crystallization

**No.72**

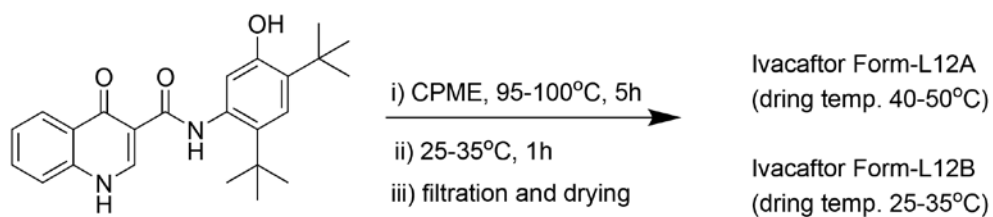
WO 2012/123325 (MEDICHEM)
new crystal forms of asenapine maleate

Crystallization

**No.73**

WO 2016/092561 (LAURUS LABS)
new polymorphic forms of ivacaftor

Crystallization

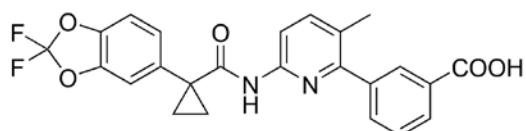


No.74

WO 2018/037350 (LAURUS LABS)

Crystallization

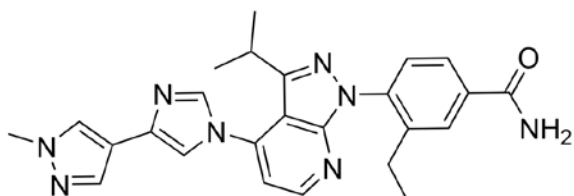
Use for new amorphous form of lumacaftor

**No.75**

EP 3 296 299 (Taiho Pharmaceutical)

Crystallization

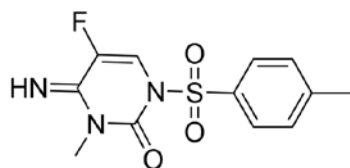
Use for new crystal form of an antitumor agent

**No.76**

WO 2019/038583 (ADAMA MAKHTESHIM)

Crystallization

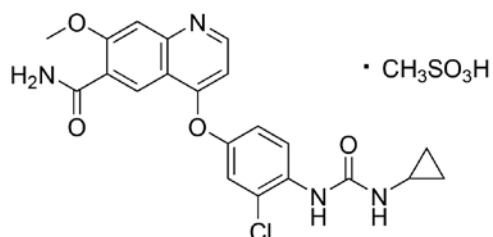
Use for preparation of polymorph, hydrate or solvate crystals

**No.77**

CN 109988112 (SICHUAN KELUN PHARMACEUTICAL RESEARCH INSTITUTE)

Crystallization

Use for crystallization of lenvatinib mesylate

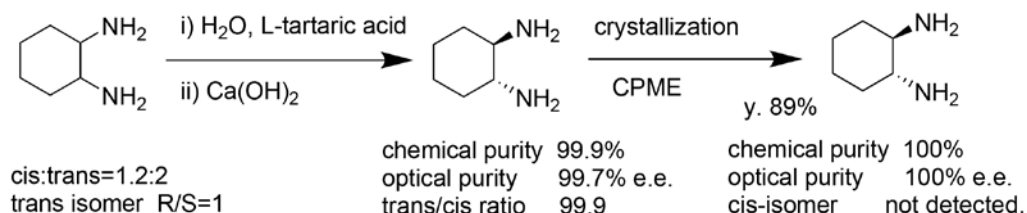


10-2 Optical resolution

No.78

US 2016/0016885 (TORAY FINE CHEMICALS)

Crystallization
Optical resolution

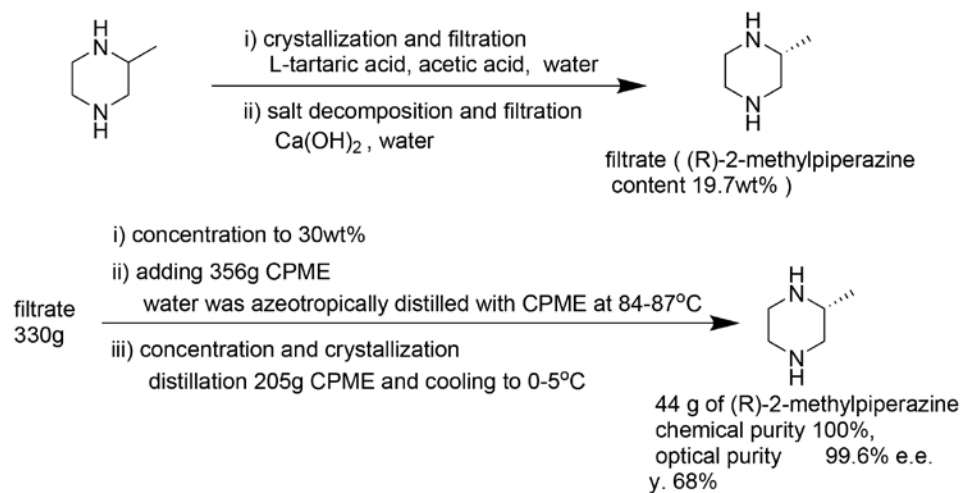


No.79

US 9,994,530 (TORAY FINE CHEMICALS)

a method of producing an optically active 2-methylpiperazine

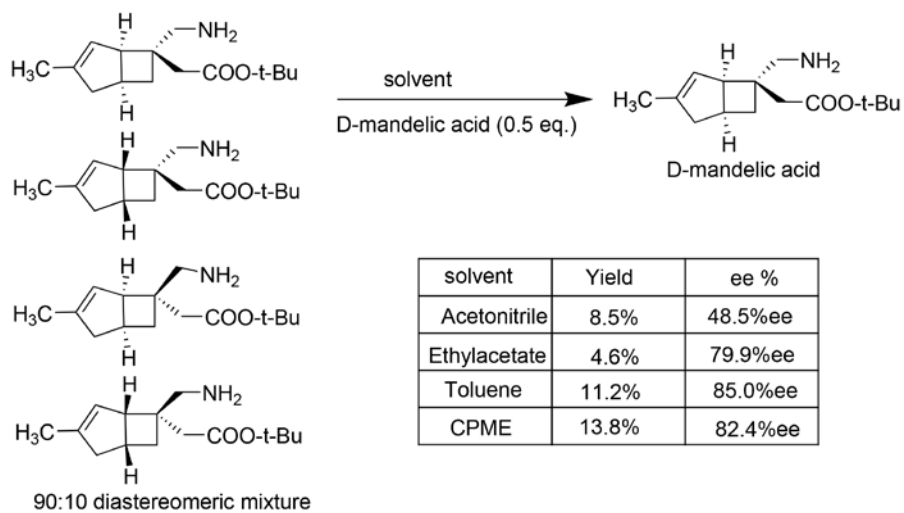
Crystallization



No.80

US 8,324,425 (DAIICHI SANKYO)

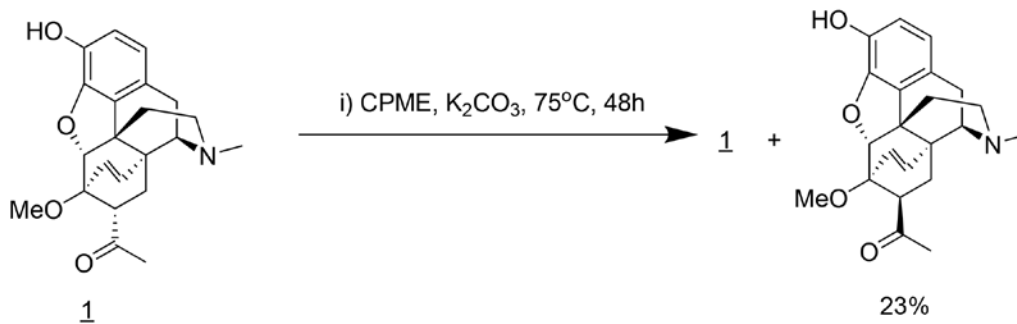
Use for optical resolution of a bicyclic amino acid derivatives

Crystallization
Optical resolution**No.81**

WO 2014/102591 (RHODES TECHNOLOGIES)

Epimerization of compound 1 with K_2CO_3

Epimerization

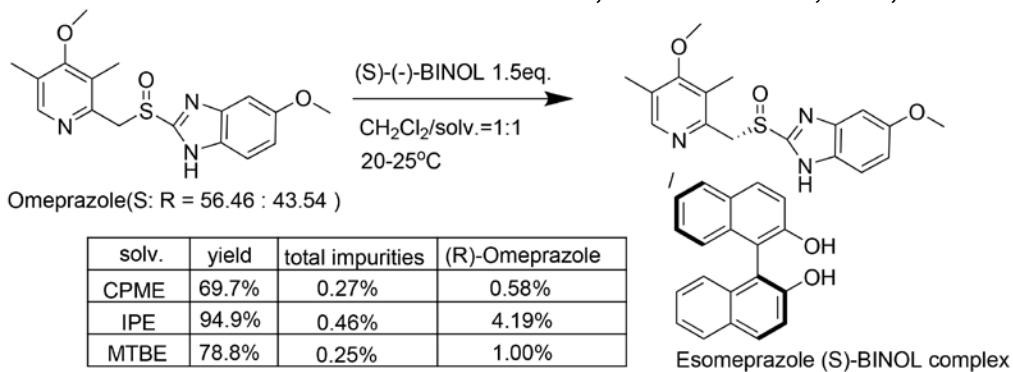


No.82

EP 2 980 086 (Fabbrica Italiana Sintetici)

Crystallization
Optical resolution

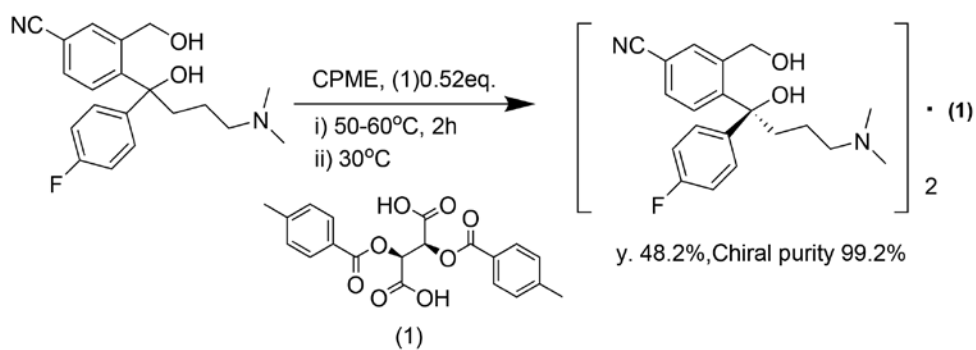
Mori, *Chem. Commun.*, 2008, 3882



No.83

EP 3 219 702 (Zhejiang Huahai Pharmaceuticals)

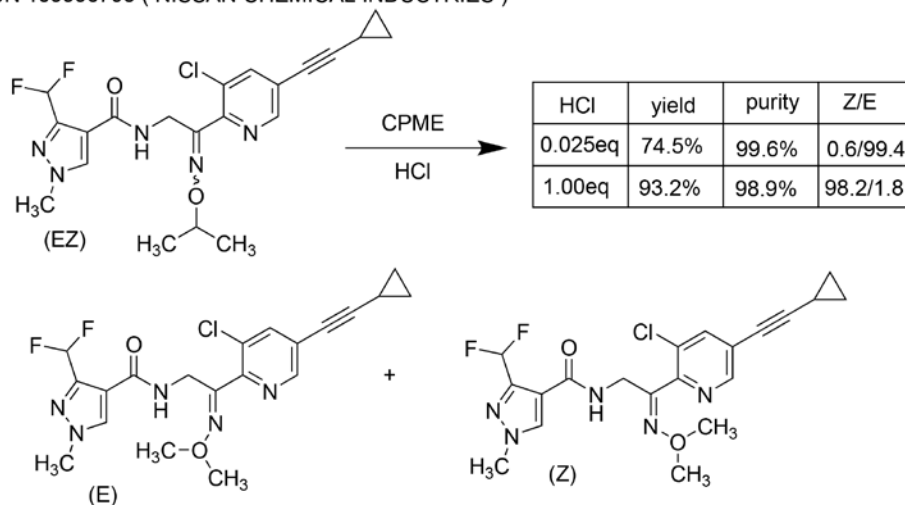
Crystallization
Optical resolution



No.84

CN 109996793 (NISSAN CHEMICAL INDUSTRIES)

Crystallization



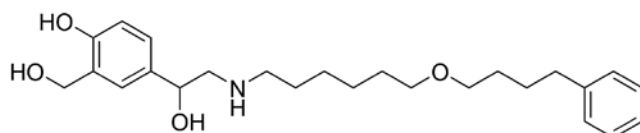
10-3 Purification Isolation

No.85

WO 2016/142582 (FERMION OY)

PREPARATION OF CRYSTALLINE SALMETEROL

Crystallization



crude (purity 94 area%)

i) CPME : heptane=7:3(v/v) 65°C

ii) cooling to r.t. and filterig

SALMETEROL

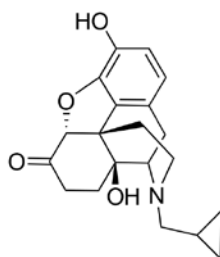
y.75% purity 98.8 area%

No.86

WO 2018/070943 (SANECA PHARMACEUTICALS)

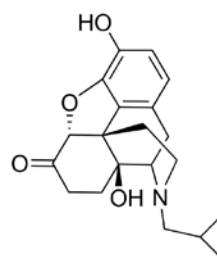
method for purification of naltrexone

Crystallization



naltrexone 10.0g
(weight content 90%)

CPME 40ml
10°C , trituration and filtration



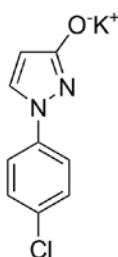
8.05 g (87% yield)
(purity 99% , weight content 98%)

No.87

WO 2018/091338 (BASF SE)

Process for the purification of 1-(4-chlorophenyl)pyrazol-3-ol

Crystallization



600.3 g (13.5% aqueous solution, pH13.3)
0.348 mol

A) Protonation and pH adjustment

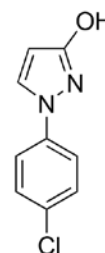
10%HCl , 20-25°C , pH 6

B) Extraction

CPME 300g , 85°C , phases separation

C) Crystallization, Filtration, Washing, Drying

the organic phase is cooled down
from 85°C to -10°C over 8 h.

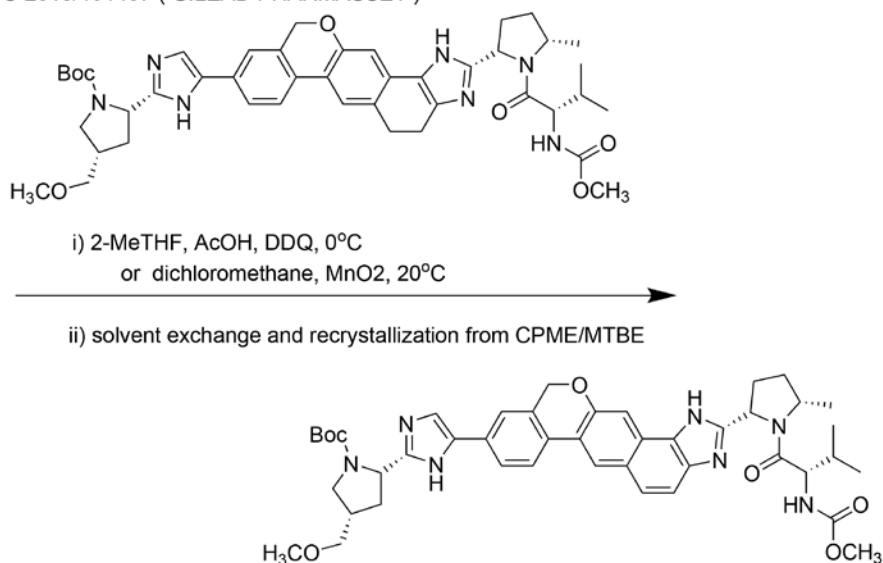


59.1 g (content 99.4% , y. 86.7%)

No.88

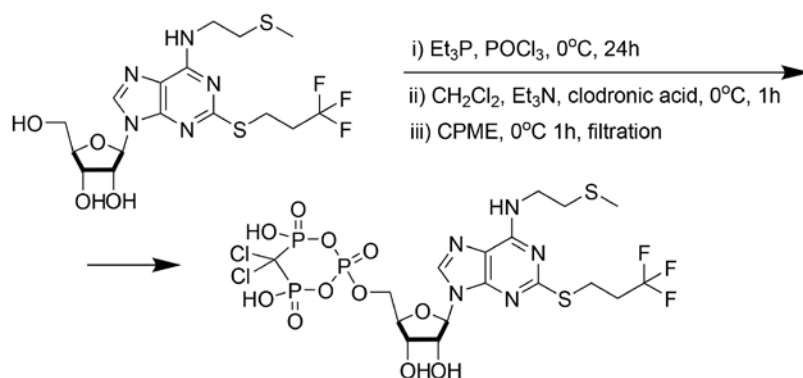
WO 2015/191437 (GILEAD PHARMASSET)

Crystallization

**No.89**

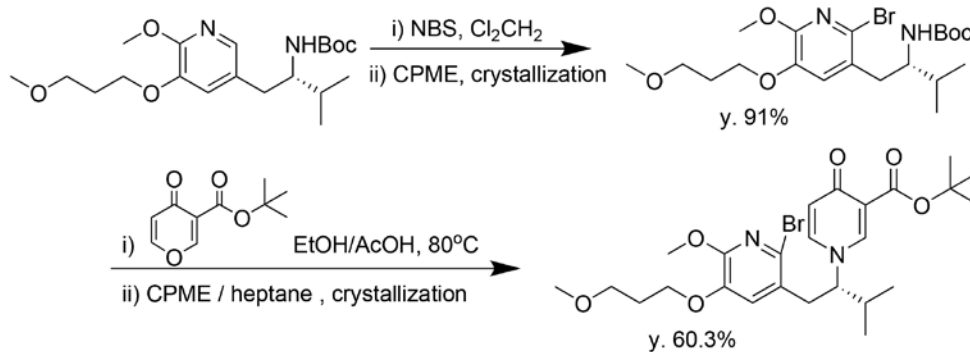
WO 2019/092546 (OLON S.P.A.)

Crystallization

**No.90**

WO 2019/200109 (ARBUTUS BIOPHARMA)

Crystallization



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<https://www.zeon.co.jp>

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