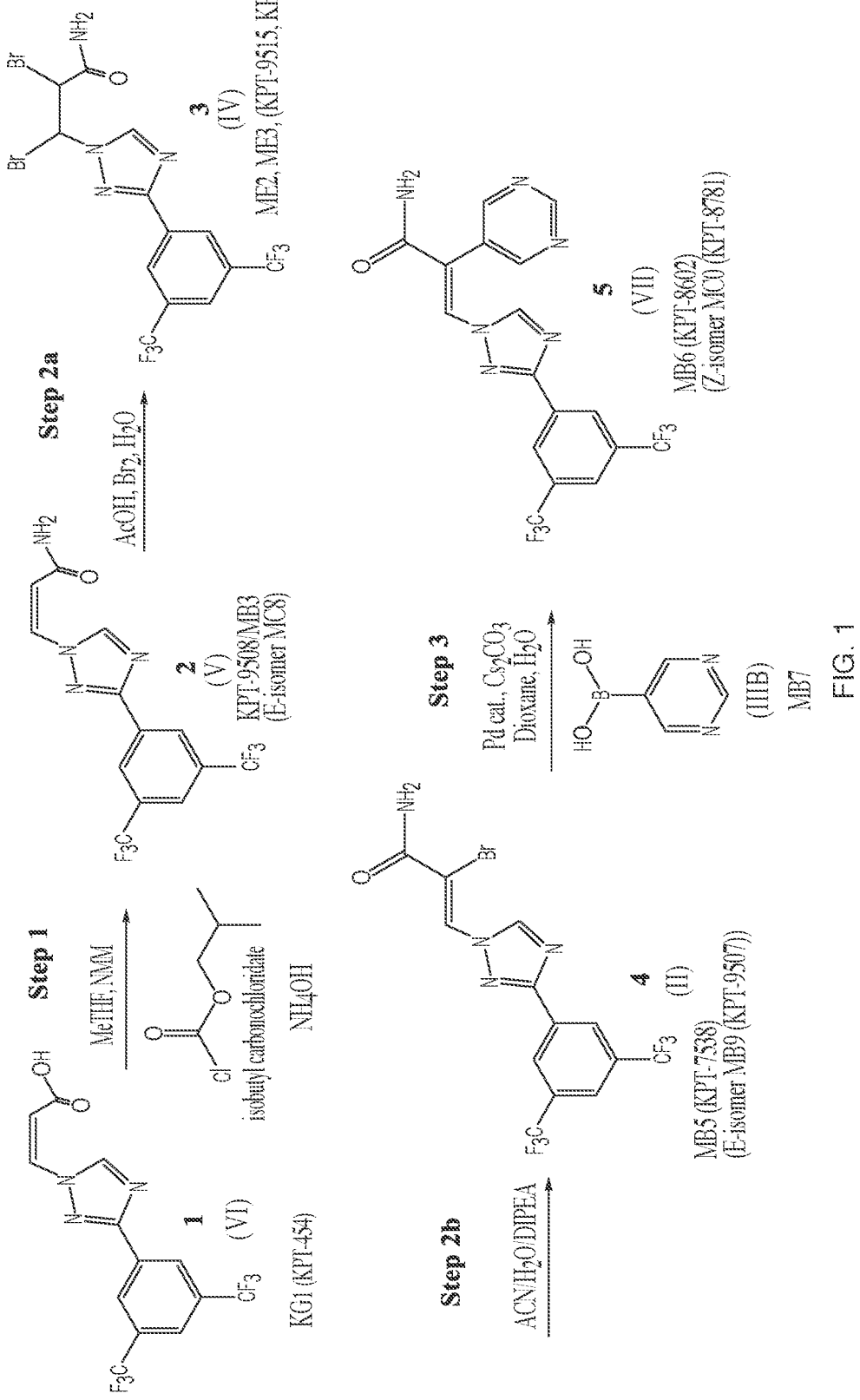

Step 1
MeTHF, NMM
isobutyl carbonochloridate
NH4OH
KG1 (KPT-454)
1
(VI)
Step 2a
AcOH, Br2, H2O
2
(V)
KPT-9508/MB3
(E-isomer MC8)
3
(IV)
ME2, ME3, (KPT-9515, KPT-9506)
Step 3
Pd cat., Cs2CO3
Dioxane, H2O
(IIIB)
MB7
5
(VII)
MB6 (KPT-8602)
(Z-isomer MC0 (KPT-8781)
Step 2b
ACN/H2O/DIPEA
4
(II)
MB5 (KPT-7538)
(E-isomer MB9 (KPT-9507))

FIG. 1

| | | | | 4 h IPC (%a/a) | | | | | | | | 24 h IPC (%a/a) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TC | MC0 | MB6 | MB3/ MC8 | MB9 | MB8 | PF9 | | | MC0 | MB6 | MB3/ MC8 | MB9 | MB8 | PF9 | | | |
| | | | KPT# | 8781 | 8602 | 9508 | | 7838 | | | | 8781 | 8602 | 9508 | | 7838 | | | | |
| | | | m/z | 429 | 429 | 351 | 429/ 431 | 429/431 | 699 | | 630 | 429 | 429 | 351 | 429/ 431 | 429/431 | 699 | | 630 | |
| Entry | Exp (1457-PK-) | Catalyst | RT | 2.9 | 3.0 | 3.2 | 3.3 | 3.5 | 3.9 | 4.1 | 4.2 | 2.9 | 3.0 | 3.2 | 3.3 | 3.5 | 3.9 | 4.1 | 4.2 | Conversion |
| 1 | 134-R1 | PdDPPFCl2DCM (control) | | 5.2 | 34.2 | 15.8 | 2.3 | 28.9 | 2.3 | 0.0 | 0.0 | 71.1 | 5.4 | 38.6 | 18.1 | 2.3 | 28.3 | 3.7 | 0.0 | 0.0 | 71.7 | |
| 2 | 134-R2 | QPhosPd(Crotyl)Cl | | 0.0 | 7.1 | 6.0 | 2.2 | 77.0 | 2.4 | 0.0 | 0.0 | 23.0 | 0.0 | 11.0 | 16.0 | 7.5 | 54.0 | 0.0 | 2.6 | 7.6 | 46.0 | |
| 3 | 134-R3 | AmPhos Pd(crotyl)Cl | | 0.0 | 73.6 | 1.5 | 0.0 | 22.0 | 2.9 | 0.0 | 0.0 | 78.0 | 0.0 | 68.9 | 1.8 | 0.0 | 18.7 | 3.6 | 6.8 | 0.0 | 81.3 | |
| 4 | 134-R4 | [P(tBu)3] Pd(crotyl)Cl | | 0.3 | 83.0 | 2.9 | 0.0 | 7.9 | 2.3 | 0.0 | 0.0 | 92.1 | 0.0 | 84.1 | 3.8 | 0.0 | 6.5 | 2.6 | 0.0 | 0.0 | 93.5 | |
| 5 | 134-R5 | XPhos Pd(crotyl)Cl | | 2.7 | 17.0 | 5.8 | 0.0 | 61.9 | 6.2 | 0.0 | 0.0 | 38.1 | 3.3 | 22.7 | 10.6 | 0.0 | 36.7 | 6.7 | 0.0 | 0.0 | 43.3 | |
| 6 | 134-R6 | RuPhos Pd(crotyl)Cl | | 0.0 | 12.9 | 15.9 | 10.7 | 47.6 | 0.0 | 0.0 | 2.0 | 52.4 | 1.8 | 15.1 | 22.3 | 12.7 | 28.2 | 1.0 | 1.7 | 7.0 | 71.8 | |
| 7 | 134-R7 | SPhos Pd(crotyl)Cl | | 2.5 | 29.5 | 12.0 | 3.9 | 43.9 | 1.1 | 0.0 | 0.0 | 56.1 | 3.6 | 47.8 | 18.4 | 3.5 | 19.6 | 2.3 | 0.0 | 0.0 | 80.4 | |
| 8 | 134-R8 | BrettPhos Pd(crotyl)OTf | | 0.6 | 4.2 | 6.1 | 2.5 | 86.0 | 0.0 | 0.0 | 0.0 | 14.0 | 0.0 | 7.0 | 13.9 | 5.7 | 62.9 | 0.0 | 0.0 | 9.0 | 37.1 | |
| 9 | 134-R9 | [(R)-BINAP Pd(allyl)]Cl | | 0.0 | 0.0 | 3.6 | 3.4 | 83.8 | 8.2 | 0.0 | 0.0 | 16.2 | 0.0 | 0.0 | 7.8 | 7.9 | 67.5 | 9.0 | 0.0 | 4.0 | 32.5 | |
| 10 | 134-R10 | [XantPhos Pd(allyl)]Cl | | 0.3 | 4.0 | 3.4 | 3.1 | 83.5 | 0.0 | 0.0 | 0.0 | 16.5 | 0.0 | 9.0 | 12.2 | 6.4 | 38.1 | 0.0 | 0.0 | 9.4 | 41.9 | |
| 11 | 136-R1 | [P(tBu)3] Pd(crotyl)Cl | | 0.0 | 87.0 | 4.8 | 0.0 | 4.7 | 3.3 | 0.0 | 0.0 | 95.3 | 0.0 | 87.0 | 3.7 | 0.0 | 2.8 | 3.1 | 0.0 | 0.0 | 97.2 | |
| 12 | 136-R2 | [P(Cy)3] Pd(crotyl)Cl | | 0.0 | 41.0 | 6.5 | 0.0 | 46.0 | 2.1 | 0.0 | 0.0 | 54.0 | 0.7 | 67.9 | 11.2 | 0.0 | 5.0 | 5.3 | 0.0 | 0.0 | 95.0 | |

FIG. 2

| | | | | 4 h IPC (%a/a) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TC | MC0 | MB6 | MB3/ MC8 | MB9 | MB5 | PF9 | | | |
| | | | KPT# | 8781 | 8602 | 9508 | | 7538 | | | | |
| | | | m/z | 429 | 429 | 351 | 429/ 431 | 429/431 | 699 | 630 | | |
| Entry | Exp (1457-PK-) | Org A (pts.) | Solvent B (pts.) | RT | 2.9 | 3.0 | 3.2 | 3.3 | 3.5 | 3.9 | 4.1 | 4.2 | Conversion |
| 1 | 138-R1 | Dioxane (30) | $H_2O$ (6) | | 5.2 | 83.0 | 9.6 | 0.0 | 0.0 | 1.9 | 0.0 | 0.0 | 100.0 |
| 2 | 138-R2 | THF (30) | $H_2O$ (6) | | 0.0 | 85.0 | 9.9 | 0.0 | 0.0 | 3.6 | 0.0 | 0.0 | 100.0 |
| 3 | 138-R3 | MeTHF (30) | $H_2O$ (6) | | 0.0 | 72.0 | 8.7 | 0.0 | 0.0 | 6.3 | 0.0 | 0.0 | 90.3 |
| 4 | 138-R4 | EtOH/MeTHF (45) | $H_2O$ (6) | | 1.6 | 75.0 | 17.0 | 0.0 | 0.0 | 1.8 | 0.0 | 0.0 | 100.0 |
| 5 | 138-R5 | Tol/MeTHF (45) | $H_2O$ (6) | | 0.0 | 31.8 | 11.4 | 0.0 | 51.5 | 1.5 | 0.0 | 0.0 | 48.5 |

Notes:

1. All experiments were carried out using 3 mol% catalyst [P(tBu)3] Pd(croty)Cl loading and 0.5 eq. of $Cs_2CO_3$ at 70 °C (except THF – reflux).
2. Data was only collected at the 4 hour time point.
3. The impurity with m/z = 351 was initially identified as MB3 based on mass, but was likely MC8 based on retention time and expected stereochemistry of the debromination side reaction. MC8 was identified as the major debromination product by authentic spiking in later experiments.

FIG. 3

| | | | | | | 24 h IPC (%a/a) | | | | | | | | | 24 h IPC (%a/a) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TC | MC 0 | MB 6 | MB3 / MC8 | MB 9 | MB5 | PF 9 | | | | MC 0 | MB 6 | MB3 / MC8 | MB 9 | MB5 | PF 9 | | | |
| | | | | | KPT # | 8781 | 8602 | 9508 | | 7538 | | | | | 8781 | 8602 | 9508 | | 7538 | | | | |
| | | | | | m/z | 429 | 429 | 351 | 429/431 | 429/431 | 699 | | 630 | | 429 | 429 | 351 | 429/431 | 429/431 | 699 | | 630 | |
| Entry | Exp (1457-PK-) | Catalyst | Org A (pts.) | Base (eq.) | RT | 2.9 | 3.0 | 3.2 | 3.3 | 3.5 | 3.9 | 4.1 | 4.2 | Conversion | 2.9 | 3.0 | 3.2 | 3.3 | 3.5 | 3.9 | 4.1 | 4.2 | Conversion |
| 1 | 140-R1 | AmPhos Pd(crotyl)Cl | Dioxane (30) | $Cs_2CO_3$ (0.5) | | 0.0 | 70.5 | 6.6 | 0.0 | 19.5 | 3.3 | 0 | 0.0 | 80.5 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| 2 | 140-R2 | AmPhos Pd(crotyl)Cl | Dioxane (30) | $Cs_2CO_3$ (1) | | 0.9 | 47.9 | 15.9 | 3.0 | 30.1 | 1.5 | 0 | 0.0 | 69.9 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| 3 | 144-R1 | [P(tBu)3] Pd(crotyl)Cl | MeTHF (30) | $Cs_2CO_3$ (1) | | 1.0 | 63.9 | 15.0 | 3.0 | 15.9 | 0.0 | 0.0 | 0.0 | 84.1 | 1.4 | 69.0 | 19.8 | 3.3 | 3.1 | 2.3 | 0.0 | 0.0 | 96.9 |
| 4 | 144-R2 | [P(tBu)3] Pd(crotyl)Cl | MeTHF (30) | $NaHCO_3$ (2) | | 0.8 | 46.9 | 12.4 | 3.1 | 35.5 | 0.0 | 0.0 | 0.0 | 64.5 | 1.5 | 51.6 | 16.2 | 3.6 | 20.1 | 1.9 | 0.0 | 0.0 | 79.9 |
| 5 | 144-R3 | [P(tBu)3] Pd(crotyl)Cl | MeTHF (30) | $K_2CO_3$ (1) | | 0.7 | 55.6 | 12.1 | 2.8 | 25.2 | 0.0 | 0.0 | 1.9 | 74.8 | 1.1 | 68.8 | 17.9 | 3.3 | 5.8 | 2.2 | 0.0 | 0.0 | 94.2 |
| 6 | 144-R4 | [P(tBu)3] Pd(crotyl)Cl | MeTHF (30) | $K_3PO_4$ (2) | | 0.7 | 55.6 | 12.1 | 2.8 | 25.3 | 0.0 | 0.0 | 1.8 | 74.7 | 7.1 | 55.7 | 21.8 | 3.4 | 12.5 | 1.6 | 0.0 | 0.0 | 87.5 |

Notes:

1. All experiments were carried out using 3 mol% catalyst loading in 30 pts of solvent A (dioxane or MeTHF) and 6 pts of solvent B (water) at 70 °C.
2. ND = not determined.
3. The impurity with m/z = 351 was initially identified as MB3 based on mass, (LCMS), but was likely MC8 based on retention time and expected stereochemistry of the debromination side reaction. MC8 was identified as the major debromination product by authentic spiking in later experiments.

FIG. 4

| No | Reaction Conditions (MB5: 1.0 eq; MB7: 2.0 eq; $Cs_2CO_3$: 0.5 eq; 5g) | Pd Catalyst | IPC Result (MB5 wrt MB6 % a/a) | MB6 Purity in Reaction Mixture (% a/a) | Major By-products wrt MB6 (% a/a) | Conclusions | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | Degassed THF:$H_2O$ 7:1 (16 parts); at reflux (65 °C); 4 hrs | $^tBu_3PPd(crotyl)Cl$, 3% | 115 | 37 | MC8: 21.3<br>PF9: 1.5 | 1.Reaction stalled<br>2.High levels of by-products | 1473-JZ-001 |
| 2 | Degassed THF:$H_2O$ 15:2 (34 parts); at reflux (63 °C); 6 hrs | $^tBu_3PPd(crotyl)Cl$, 3% | 1.1 | 80 | MC8: 7.9<br>PF9: 3.7 | High levels of by-products | 1473-JZ-004 |
| 3 | Degassed THF:$H_2O$ 15:2 (34 parts); at reflux (63 °C); 8 hrs | $^tBu_3PPd(crotyl)Cl$, 3% | 86 | 43 | MC8: 22<br>PF9: 3.2 | High levels of by-products | 1473-JZ-009 |
| 4 | Repeated the above trial using a new lot Pd catalyst | $^tBu_3PPd(crotyl)Cl$, 3% | Almost no reaction | - | - | No reaction | 1473-JZ-018 |
| 5 | Degassed dioxane:$H_2O$ 15:2 (34 parts); 70-76 °C, 4 hrs | $^tBu_3PPd(crotyl)Cl$, 3% | 86 | 37 | MC8: 29<br>PF9: 9.0 | 1.Reaction stalled<br>2.High levels of by-products | 1473-JZ-007 |

FIG. 5

| No | Reaction Conditions (MB5: 1.0 eq; MB7: 2.0 eq; $Cs_2CO_3$: 0.5 eq) | Pd Catalyst | IPC Result (MB5 wrt MB6 % a/a) | MB6 Purity in Reaction Mixture (% a/a) | Major By-products wrt MB6 (% a/a) | Conclusions | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | Degassed THF:$H_2O$ 15:2 (17 parts); at reflux (64 °C); 7 hrs | Strem Pd 46-0232, 2% | Almost no reaction | - | - | No reaction | 1473-JZ-013 |
| 2 | Degassed THF:$H_2O$ 15:2 (17 parts); at reflux (64 °C); 7 hrs | Strem SPhos Palladacycle Gen. 2 (Cat #46-0283), 2% | Almost no reaction | - | - | No reaction | 1473-JZ-015 |
| 3 | Degassed THF:$H_2O$ 15:2 (17 parts); at reflux (63 °C); 8 hrs | Strem Amphos Palladacycle Gen. 2 (Cat #46-0342), 2% | 10.9 | 76.1 | MC8: 3.1<br>PF9: 13.7 | 1.Reaction stalled<br>2.High levels of by-products | 1473-JZ-011 |
| 4 | Degassed THF:$H_2O$ 15:2 (22 parts); at reflux (63 °C); 7 hrs | Strem Amphos Palladacycle Gen. 2 (Cat #46-0342), 3% | 4.8 | 77.6 | MC8: 13.9<br>PF9: 9.7 | 1.Reaction stalled<br>2.High levels of by-products | 1473-JZ-016 |
| 5 | Degassed dioxane:$H_2O$ 15:2 (34 parts); 70-76 °C; 4 hrs | Strem Amphos Palladacycle Gen. 2 (Cat #46-0342), 3% | No MB5 detected | 89.2 | MC8: 1.6<br>PF9: 3.1 | Good reaction | 1473-JZ-019 |
| 6 | Repeated the above trial at 11g scale | Strem Amphos Palladacycle Gen. 2 (Cat #46-0342), 3% | 0.1 | 86.5 | MC8: 0.6<br>PF9: 3.0 | Good reaction | 1473-JZ-028 |
| 7 | Degassed dioxane:$H_2O$ 15:2 (34 parts); 60-65 °C; 4 hrs | JM Amphos Pd(crotyl)Cl (Pd-161), 3% | No MB5 detected | 88.3 | MC8: 1.7<br>PF9: 3.8 | Good reaction | 1473-JZ-021 |

FIG. 6

| No | Reaction Conditions (MB7: 2.0 eq; $Cs_2CO_3$; 0.5 eq; 5g scale) | Amount of Strem Amphos Paladacycle Gen. 2 | IPC Result (% a/aMB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PF9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 60-65 °C; 4 hrs | 3 mol % | 0.1 | 87.7 | 0.5 | 2.2 | 2.6 | Good result | 1473-JZ-153 |
| 2 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 60-65 °C; 4 hrs | 2 mol % | 0.2 | 85.5 | 0.3 | 2.6 | 3.9 | Good result | 1473-JZ-155 |
| 3 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 60-65 °C; 4 hrs | 1 mol % | 19.0 | 70.1 | 0.3 | 4.5 | 2.0 | Reaction stalled | 1473-JZ-157 |

FIG. 7

| No | Reaction Conditions (MB7: 2.0 eq; $Cs_2CO_3$: 0.5 eq; 5g scale) | Amount of MB7 (Eq) | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PF9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3% Strem Pd 46-0342, 24 parts of degassed dioxane: $H_2O$ 7:1, 60-65 °C, 4 hrs | 1.5 | 9.0<br>8.4 after 7 hours | 80.8 | 0.2 | 2.0 | 5.1 | Reaction stalled even extending the reaction time | 1473-JZ-141 |
| 2 | 3% Strem Pd 46-0342, 34 parts of degassed dioxane: $H_2O$ 7:1, 60-65 °C, 4 hrs | 1.5 | 9.6<br>8.8 after 9 hours | 81.3 | 0.2 | 1.9 | 4.6 | Reaction stalled even extending the reaction time | 1473-JZ-151 |
| 3 | 2% Strem Pd 46-0342, 24 parts of degassed | 1.8 | 0.6 | 88.2 | 0.1 | 1.7 | 2.9 | Good result, but the residual MB5 | 1499-JZ-001 |

FIG. 8

| No | Reaction Conditions (2.0 eq MB7; 0.5 eq $Cs_2CO_3$; 2% Strem Pd 46-0342; 5g scale) | Degassed Solvents | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PF9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3% Strem Pd 46-0342; 60-65 °C; 4 hrs | Degassed dioxane:$H_2O$ 7:1 24 parts | 0.1 | 87.7 | 0.5 | 2.2 | 2.6 | Good result | 1473-JZ-153 |
| 2 | 60-65 °C; 4 hrs | Degassed THF:$H_2O$ 3:1 24 parts | 3.6 | 75.6 | 0.2 | 11.0 | 2.9 | Reaction stalled and higher level Impurities | 1473-JZ-161 |
| 3 | 60-65 °C; 4 hrs | Degassed THF:$H_2O$ 1:1 24 parts | 0.03 | 79.5 | 1.6 | 9.2 | 2.0 | Higher level Impurities | 1473-JZ-163 |
| 4 | 60-65 °C; 4 hrs | Degassed MeOH:$H_2O$ 5:1 24 parts | 0.6 | 58.5 | 4.6 | 32.1 | 3.0 | Higher level Impurities | 1473-JZ-162 |
| 5 | 60-65 °C; 4 hrs<br><br>8 hours more | Degassed MeTHF:$H_2O$ 7:1, 24 parts | 36.8<br><br>14.8 | 66.4<br><br>72.5 | 0.1<br><br>0.1 | 2.1<br><br>2.7 | 5.5<br><br>10.8 | Reaction stalled<br><br>Reaction stalled again and higher level PF9 | 1473-JZ-169 |

FIG. 9

| No | Reaction Conditions (MB7: 2.0 eq; $Cs_2CO_3$: 0.5 eq; 2% Strem Pd 46-0342); 5g scale | Degassed Dioxane:$H_2O$ Ratio (v/v) | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PI9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 24 parts solvents; 60-65 °C; 8 hrs | 14:1 | 6.6 | 83.5 | 0.2 | 1.9 | 3.4 | Reaction stalled even extending the reaction time | 1473-JZ-174 |
| | | | 3.9 after 13 hours | 84.2 after 13 hours | 0.2 | 2.0 | 4.4 | | |
| 2 | 24 parts solvents; 60-65 °C; 4 hrs | 7:1 | 0.2 | 85.5 | 0.3 | 2.6 | 3.9 | Good reaction | 1473-JZ-155 |
| 3 | 24 parts solvents; 60-65 °C; 4 hrs | 2:1 | 0.1 | 80.9 | 3.5 | 6.4 | 0.9 | Higher level Impurities than the above one | 1473-JZ-165 |

FIG. 10

| No | Reaction Conditions (2.0 eq MB7; 0.5 eq $Cs_2CO_3$; 5g scale) | Degassed Dioxane:$H_2O$ 7:1 v/v Parts | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PP9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3% Strem Pd 46-0342; 60-65 °C; 4 hrs | 34 | No MB5 detected | 89.2 | 0.7 | 1.6 | 3.1 | Good reaction | 1473-JZ-019 |
| 2 | 3% Strem Pd 46-0342; 60-65 °C; 4 hrs | 24 | 0.1 | 87.2 | 0.5 | 2.2 | 3.4 | Good reaction | 1473-JZ-153 |
| 3 | 2% Strem Pd 46-0342; 60-65 °C; 4 hrs | 24 | 0.2 | 85.5 | 0.3 | 2.6 | 3.9 | Good reaction too, comparing with above one | 1473-JZ-155 |
| 4 | 2% Strem Pd 46-0342; 55-60 °C; 5.5 hrs | 24 | 0.1 | 87.9 | 0.3 | 2.1 | 3.9 | Good reaction too, comparing with above one | 1473-JZ-180 |
| 5 | 2% Strem Pd 46-0342; 60-65 °C; 6 hrs | 18 | 0.9 | 86.3 | 0.1 | 2.4 | 4.8 | Good reaction, but the residual MB5 close to the limit (<1%) | 1473-JZ-172 |
| 6 | Reducing top volume to 12 parts, | 12 | 9.6 | 79.0 | 0.1 | 2.7 | 3.5 | Reaction stalled. A biphasic mixture | 1473-JZ-167 |

FIG. 11

| No | Reaction Conditions (MB7; 2.0 eq; $Cs_2CO_3$; 0.5 eq; 24 parts of degassed dioxane:$H_2O$ 7:1; 2% Strem Pd 46-0342); 5g scale | Reaction Time Needed | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PF9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 50-55 °C | 14 hrs | 1.3 | 86.8 | 0.1 | 2.1 | 3.1 | Cleaner reaction, but required longer time | 1473-JZ-177 |
| 2 | 55-60 °C | 5.5 hrs | 0.1 | 87.9 | 0.3 | 2.1 | 3.9 | Best one | 1473-JZ-180 |
| 3 | 60-65 °C | 4 hrs | 0.2 | 85.5 | 0.3 | 2.6 | 3.9 | Good one | 1473-JZ-155 |
| 4 | Reflux (71-72 °C) | 4 hrs | 0.1 | 79.4 | 5.8 | 3.0 | 4.8 | Much higher level of MC0 | 1473-JZ-176 |

FIG. 12

| No | Reaction Conditions | Time for Reaction Mixture Degassing After Reagents Combined | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PF9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | MB7: 2.0 eq; $Cs_2CO_3$: 0.5 eq; 24 parts of degassed dioxane:$H_2O$ 7:1; 2% Strem Pd 46-0342; 55-60 °C; 8.5 hrs; 5g scale | 55 min. | N/D | 85.9 | 0.1 | 2.4 | 3.9 | Good reaction | 1473-IZ-180 |
| 2 | MB7: 2.0 eq; $Cs_2CO_3$: 0.5 eq; 24 parts of degassed dioxane:$H_2O$ 7:1; 2% Strem Pd 46-0342; 55-60 °C; 7 hrs; 5g scale | 0 min. | 0.08 | 89.2 | 0.1 | 2.0 | 2.9 | Comparable one, even though no degassing of the reaction mixture before heating | 1473-IZ-203 |

FIG. 13

| No | Reaction Conditions (2.0 eq MB7; 2% Strem Pd 46-0342; 5g scale) | Base | IPC Result (% a/a MB5 wrt MB6) | MB6 Purity in Reaction Mixture (% a/a) | MC0 wrt MB6 (% a/a) | MC8 wrt MB6 (% a/a) | PP9 wrt MB6 (% a/a) | Note | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 60-65 °C; 4 hrs | $Cs_2CO_3$ 0.5 eq | 0.1 | 87.7 | 0.5 | 2.2 | 2.6 | Good reaction | 1473-JZ-180 |
| 2 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 60-65 °C; 4 hrs | $K_3PO_4$ 0.5 eq | 29.4 | 67.0 | 0.1 | 2.9 | 5.2 | Reaction stalled | 1473-JZ-159 |
| 3 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 60-65 °C; 7.5 hrs | $Cs_2CO_3$/CsH$CO_3$ 0.25 eq each | 34.0 | 65.3 | 0.1 | 2.9 | 3.7 | Reaction stalled | 1499-JZ-026 |
| | Charged more $CsHCO_3$ and heated for 5 more hrs | 0.25 eq more $CsCO_3$ | N/D after 5 hrs | 84.5 after 5 hrs | 0.1 | 2.7 | 5.7 | Good reaction after charging more base | |
| 4 | Degassed dioxane:$H_2O$ (7:1, 24 parts); 55-60 °C; 7.5 hrs | $Cs_2CO_3$/CsOH 0.25 eq/0.50 eq | N/D | 86.8 | 0.1 | 2.4 | 3.8 | As good as $Cs_2CO_3$. Similar impurity profile | 1499-JZ-034 |

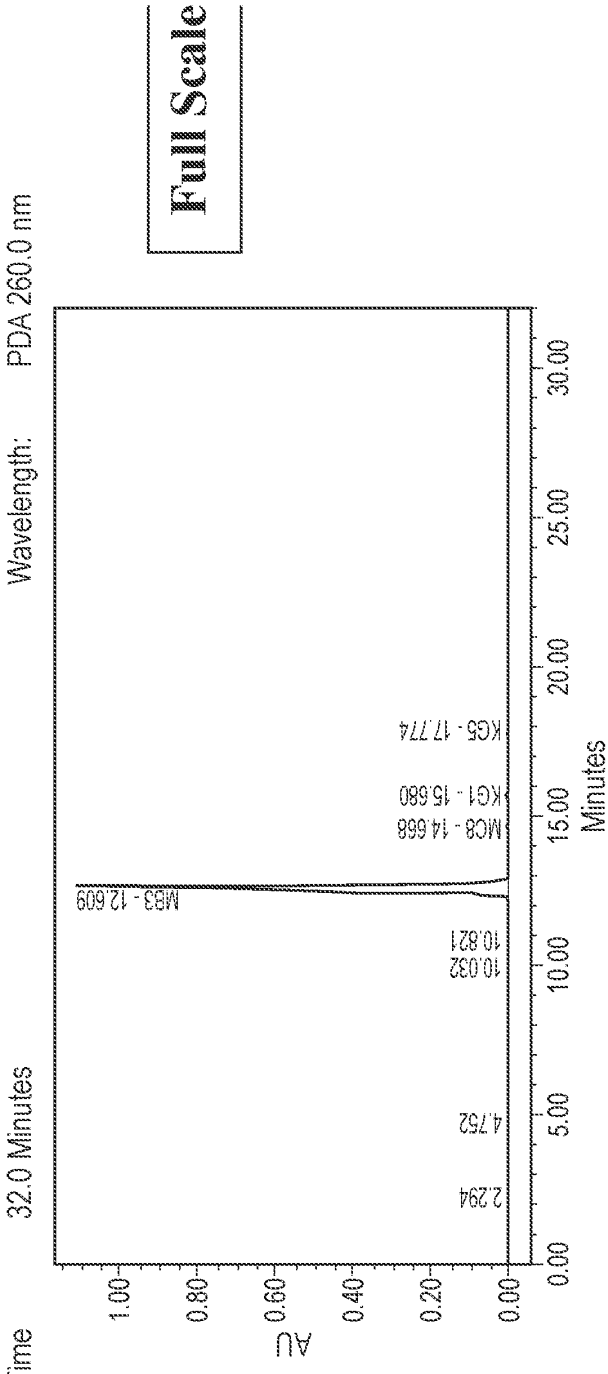
FIG. 14

| Entry | Parameter | Change | Comment |
|---|---|---|---|
| 1 | Catalyst Type | Catalyst changed from tetrakis(triphenylphosphine)palladium to Strem Amphos Palladacycle Gen. 2, cat. #46-0342 | High conversion, less side reactions |
| 2 | Catalyst loading | Loading Reduced from 10 mol% to 2 mol% | Potential reduce in cost and lower burden on Pd removal |
| 3 | MB7 eq. | Increased form 1.5 eq. to 2.0 eq. | Increased cost and burden on isolation purging<br><br>Offset by significant increase in performance and yield. Purging studies indicate that MB7 can be effectively purged |
| 4 | $Cs_2Co_3$ eq. | Decreased from 0.75 eq. to 0.50 eq. | Reduced cost and lower side reactions |
| 5 | Dioxane volume | Increased from 16 pts to 21 pts. | Ensures single phase reaction to improve robustness |
| 6 | Water Volume | Increased from 2 pts to 3 pts | Ensures single phase |

FIG. 15A

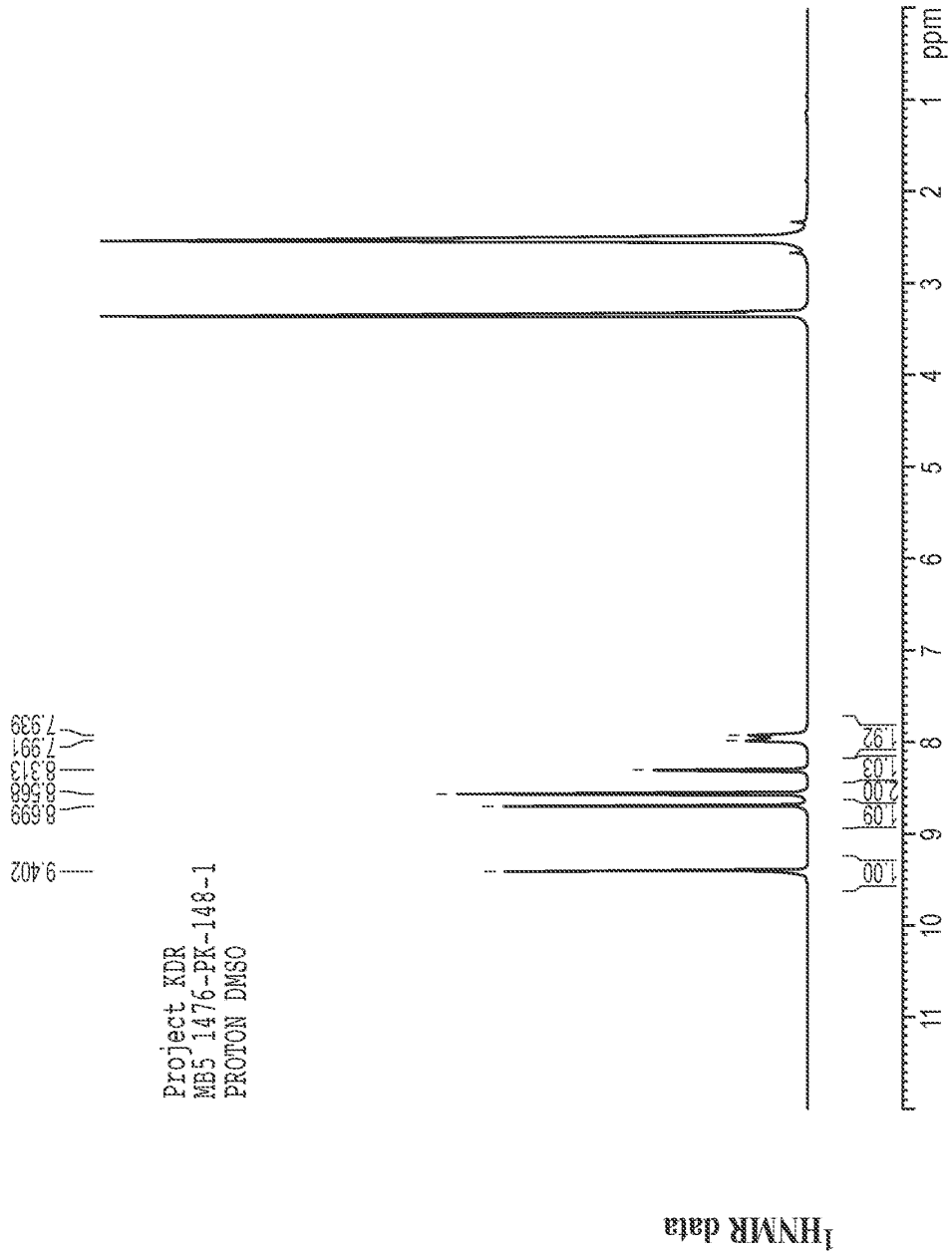
| Entry | Parameter | Change | Comment |
|---|---|---|---|
| | | | reaction to improve robustness |
| 7 | Reaction Temperature | Reduced from 70-75°C to 55-60 °C | Less energy intensive and lower side reactions |
| 8 | Reaction Time | Reduced from 24 hours to ~7 hours | Reduced cycle times. |

FIG. 15B




| | Name | RT | Area | % Area | In: Type | USP Plate Count | USP Tailing | USP Resolution |
|---|---|---|---|---|---|---|---|---|
| 1 | | 2.294 | 168.44 | 0.00 | bb | 3224 | 0.867 | |
| 2 | | 4.752 | 1488.90 | 0.01 | bb | 11843 | 0.812 | 16.677 |
| 3 | | 10.032 | 534.76 | 0.00 | bb | 38200 | 0.821 | 21.444 |
| 4 | | 10.821 | 459.18 | 0.00 | bb | 34997 | 0.661 | 2.742 |
| 5 | MB3 | 12.609 | 13898415.37 | 98.27 | bv | 23056 | 0.794 | 5.719 |
| 6 | MC8 | 14.668 | 62154.46 | 0.44 | vb | 36375 | 0.906 | 6.595 |
| 7 | KG1 | 15.680 | 140789.13 | 1.00 | bb | 50950 | 0.971 | 3.521 |
| 8 | KG5 | 17.774 | 38882.03 | 0.27 | bb | 70027 | 0.937 | 7.719 |
| Sum | | | 14142892.3 | | | | | |

FIG. 16


$^1$HNMR data
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0.046
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0.016
0.014
0.012
0.010
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0.006
0.004
0.002
0.000
ppm
1
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6
7
8
9
10
11
1.00
1.09
2.00
1.03
1.92

FIG. 17

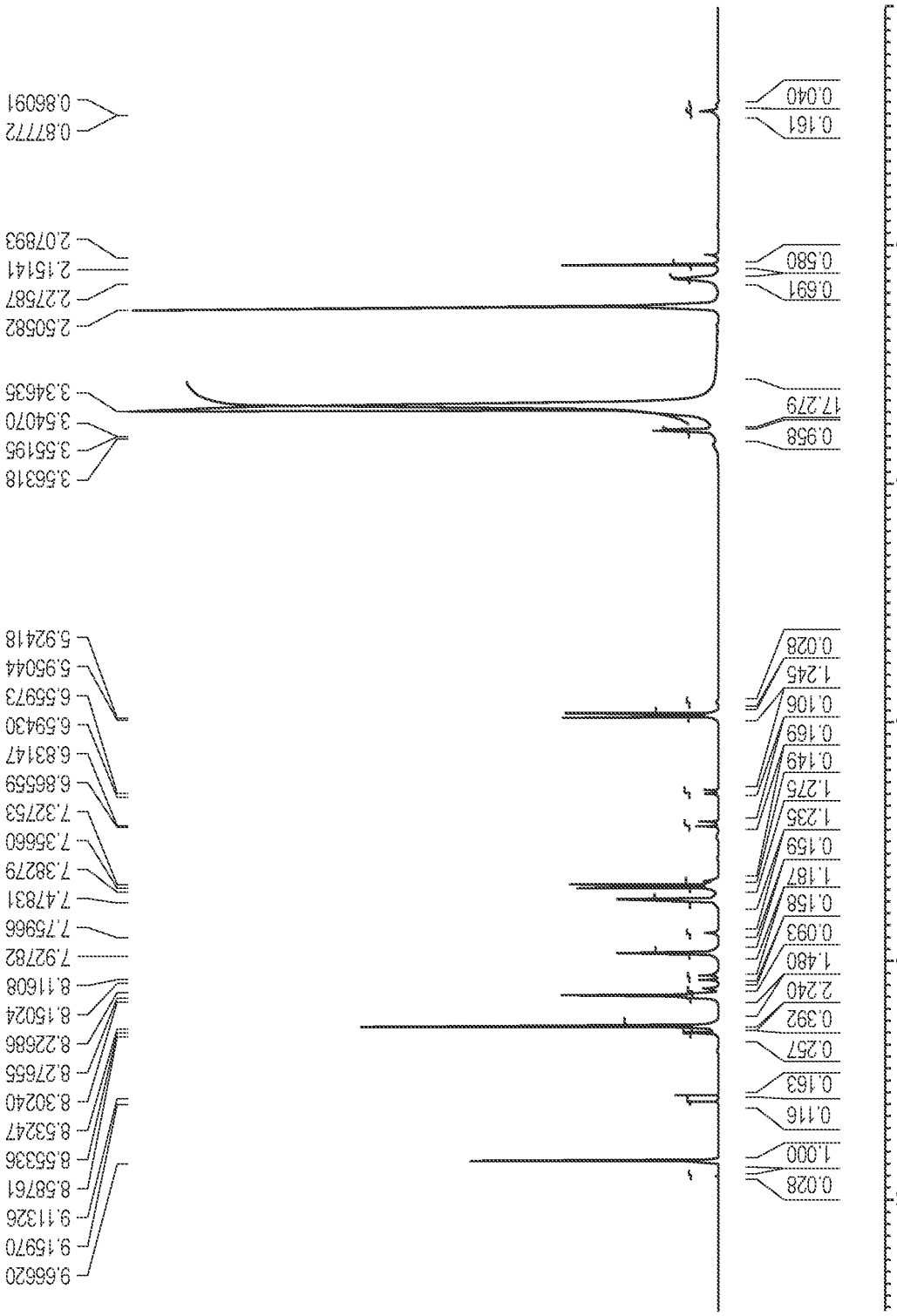
0.86091
0.87772
2.07893
2.15141
2.27587
2.50582
3.34635
3.54070
3.55195
3.56318
5.92418
5.95044
6.55973
6.59430
6.83147
6.86559
7.32753
7.35660
7.38279
7.47831
7.75966
7.92782
8.11608
8.15024
8.22686
8.27655
8.30240
8.53247
8.55336
8.58761
9.11326
9.15970
9.56620
0.040
0.161
0.580
0.691
17.279
0.958
0.028
1.245
0.106
0.169
0.149
1.275
1.235
0.159
1.187
0.158
0.093
1.480
2.240
0.392
0.257
0.163
0.116
1.000
0.028
2
4
6
8
10

FIG. 18

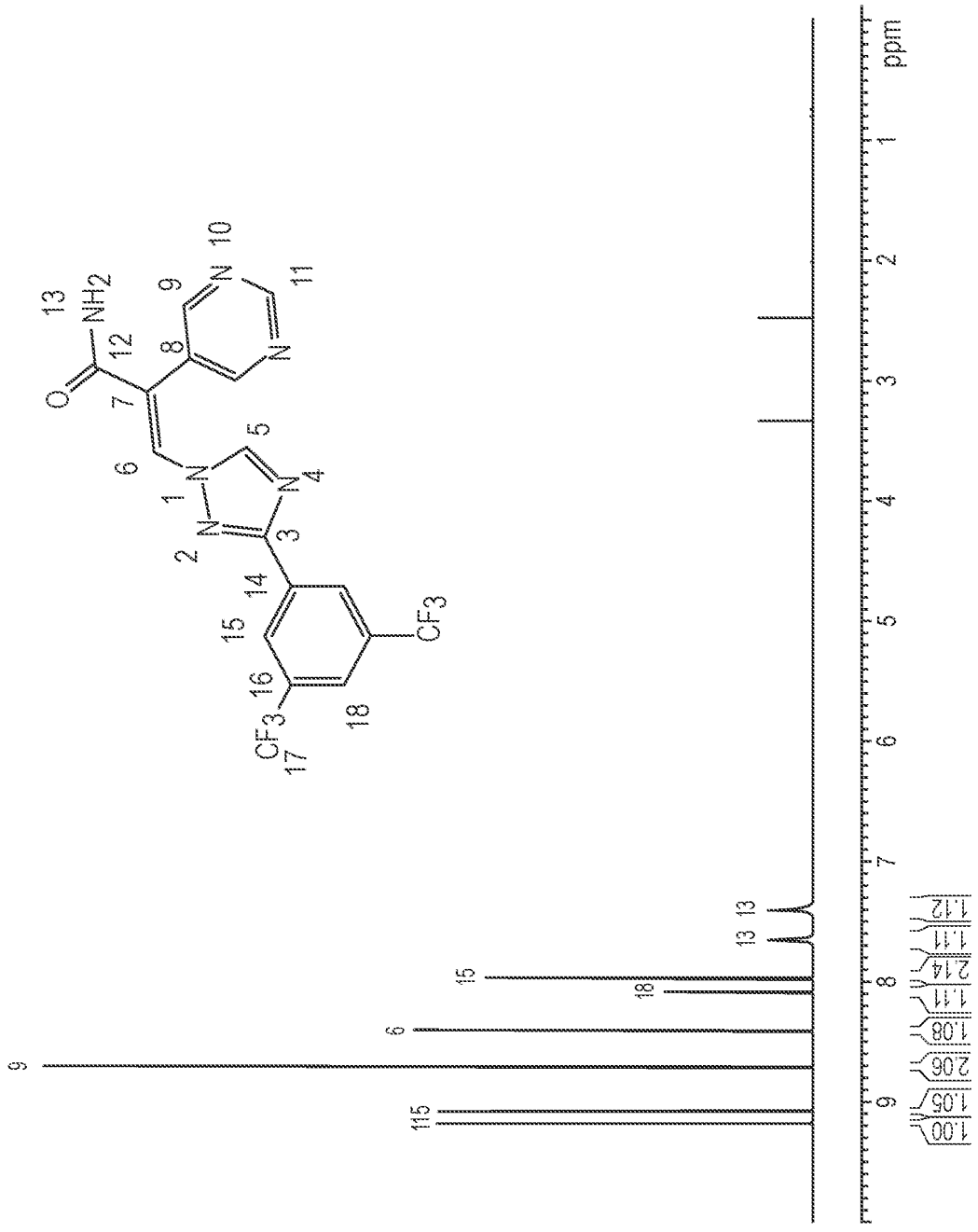


FIG. 19

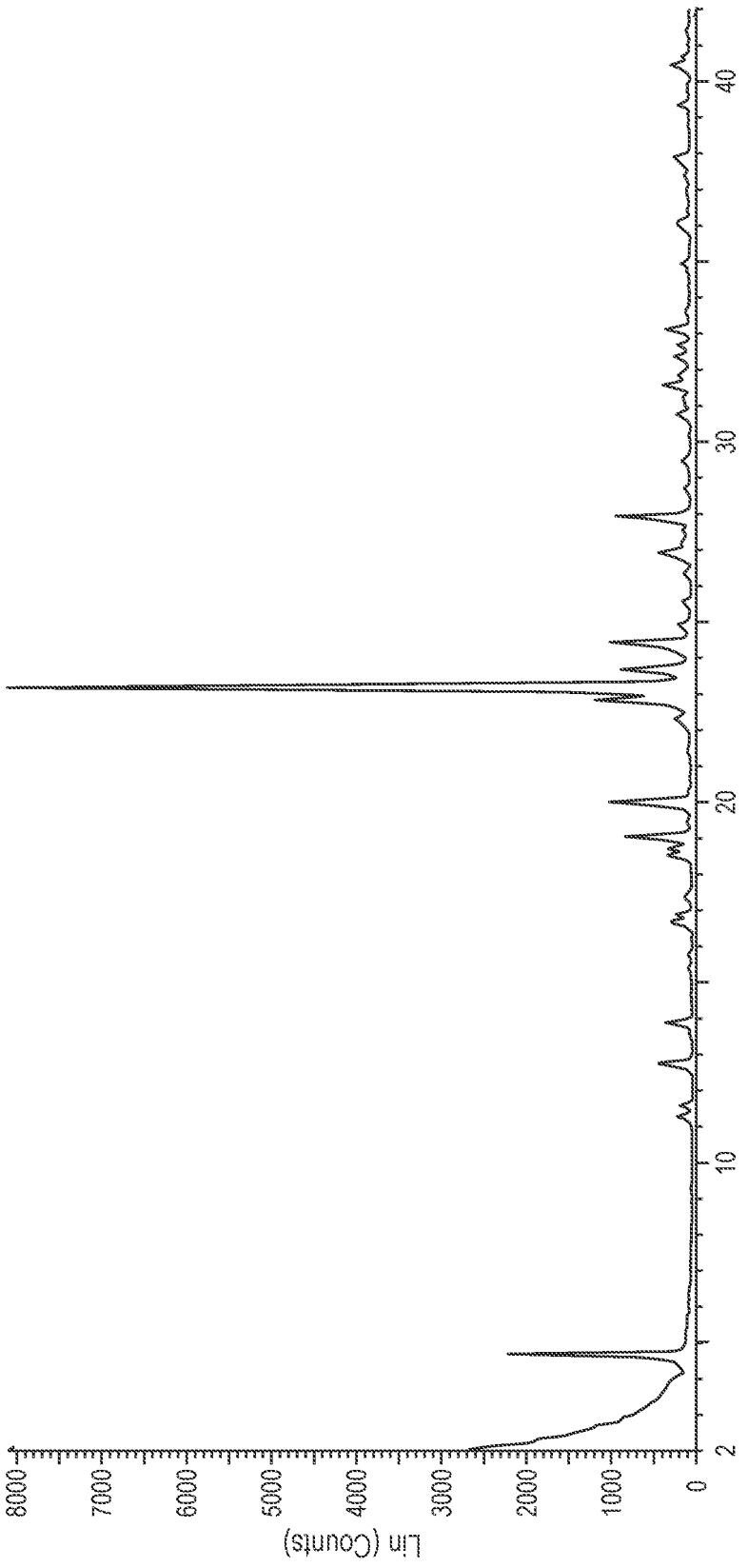
Lin (Counts)
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
40
2-Theta - Scale

FIG. 20

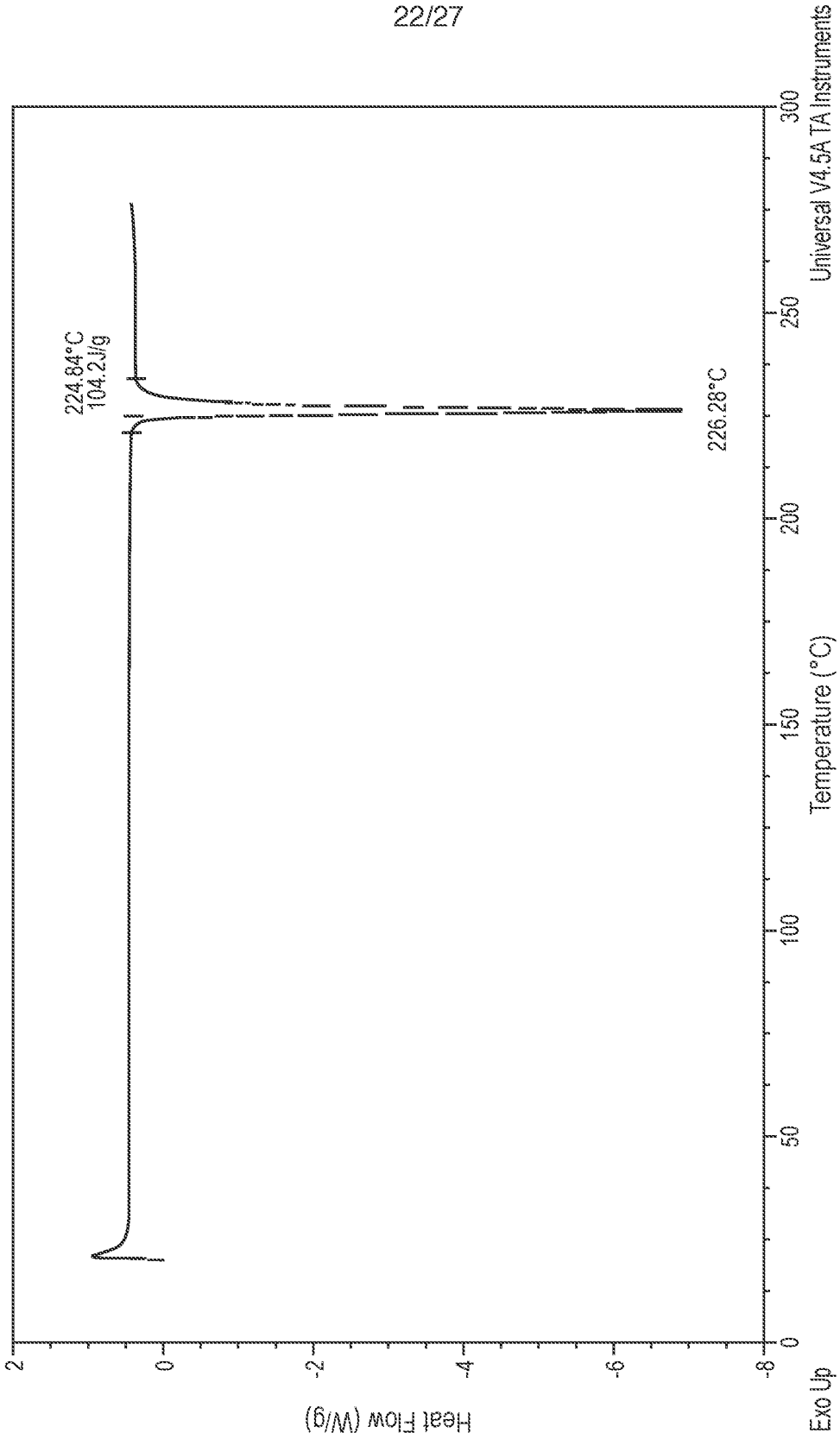
224.84°C
104.2J/g
226.28°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments

FIG. 21

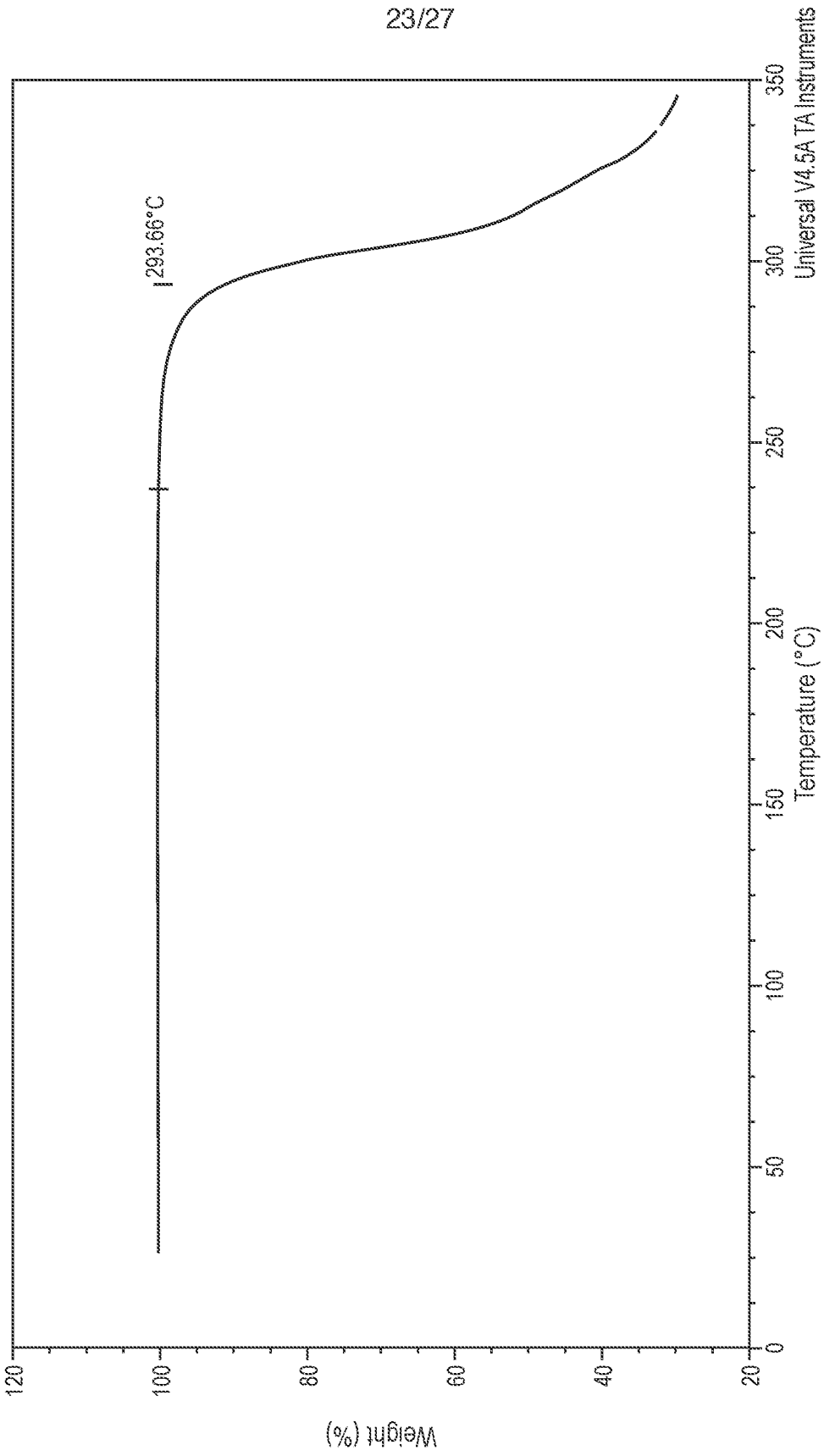
293.66°C
Weight (%)
120
100
80
60
40
20
0
50
100
150
200
250
300
350
Temperature (°C)
Universal V4.5A TA Instruments

FIG. 22

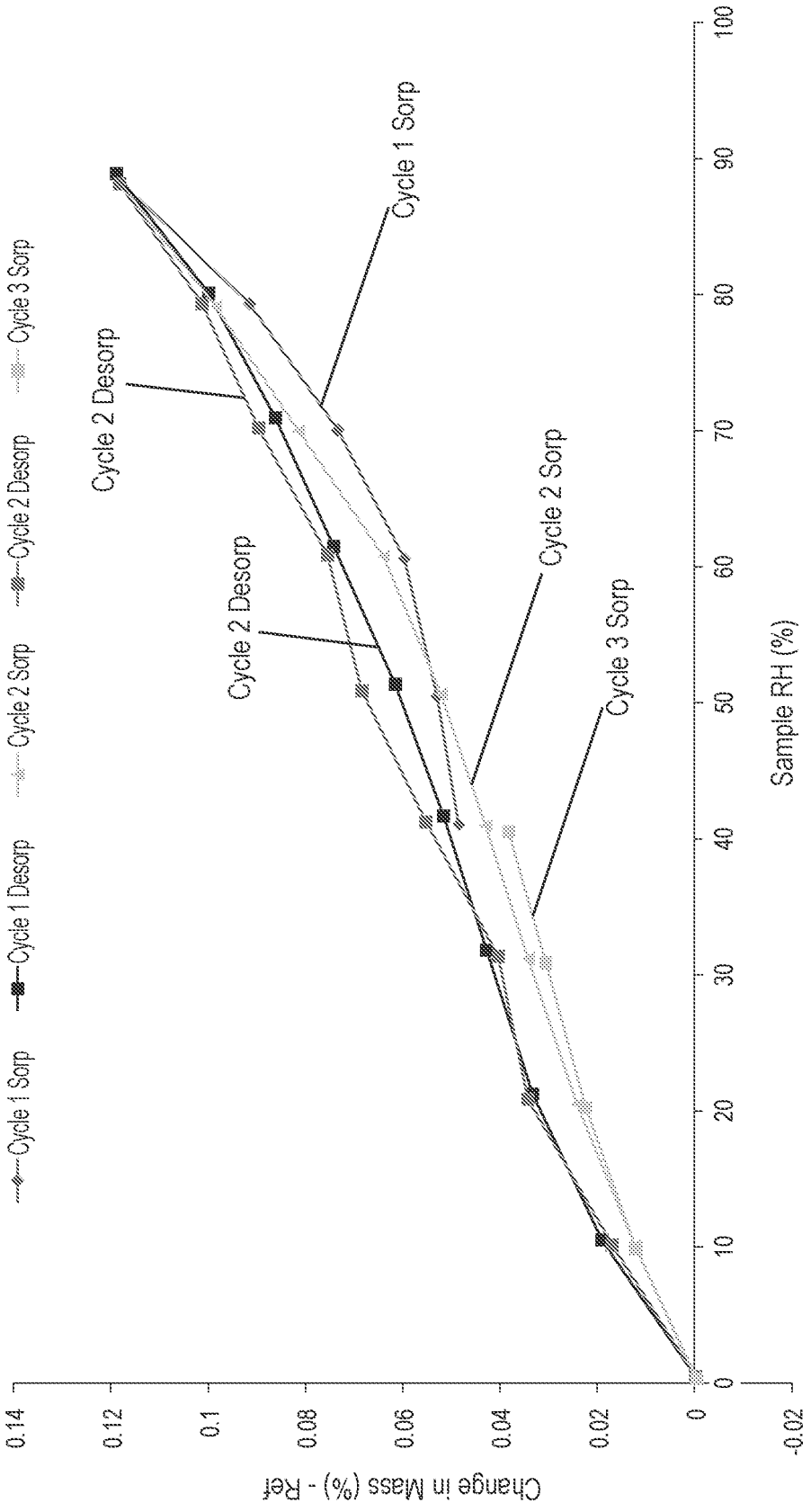
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Cycle 3 Sorp
Cycle 1 Sorp
Cycle 2 Desorp
Cycle 2 Desorp
Cycle 2 Sorp
Cycle 3 Sorp
Change in Mass (%) - Ref
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
0
10
20
30
40
50
60
70
80
90
100
Sample RH (%)

FIG. 23

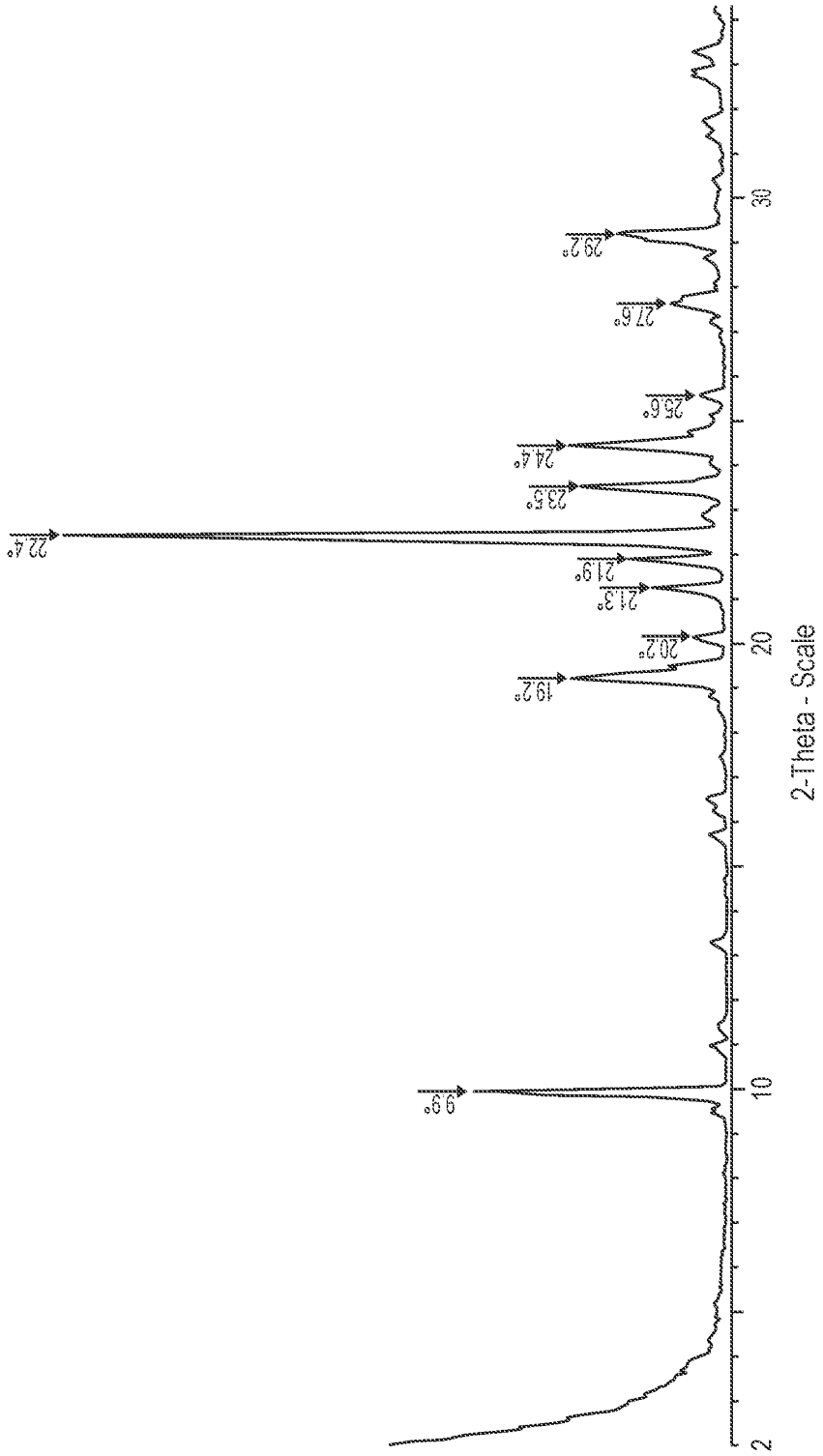
9.9°
19.2°
20.2°
21.3°
21.9°
22.4°
23.5°
24.4°
25.6°
27.6°
29.2°
2
10
20
30
2-Theta - Scale

FIG. 24

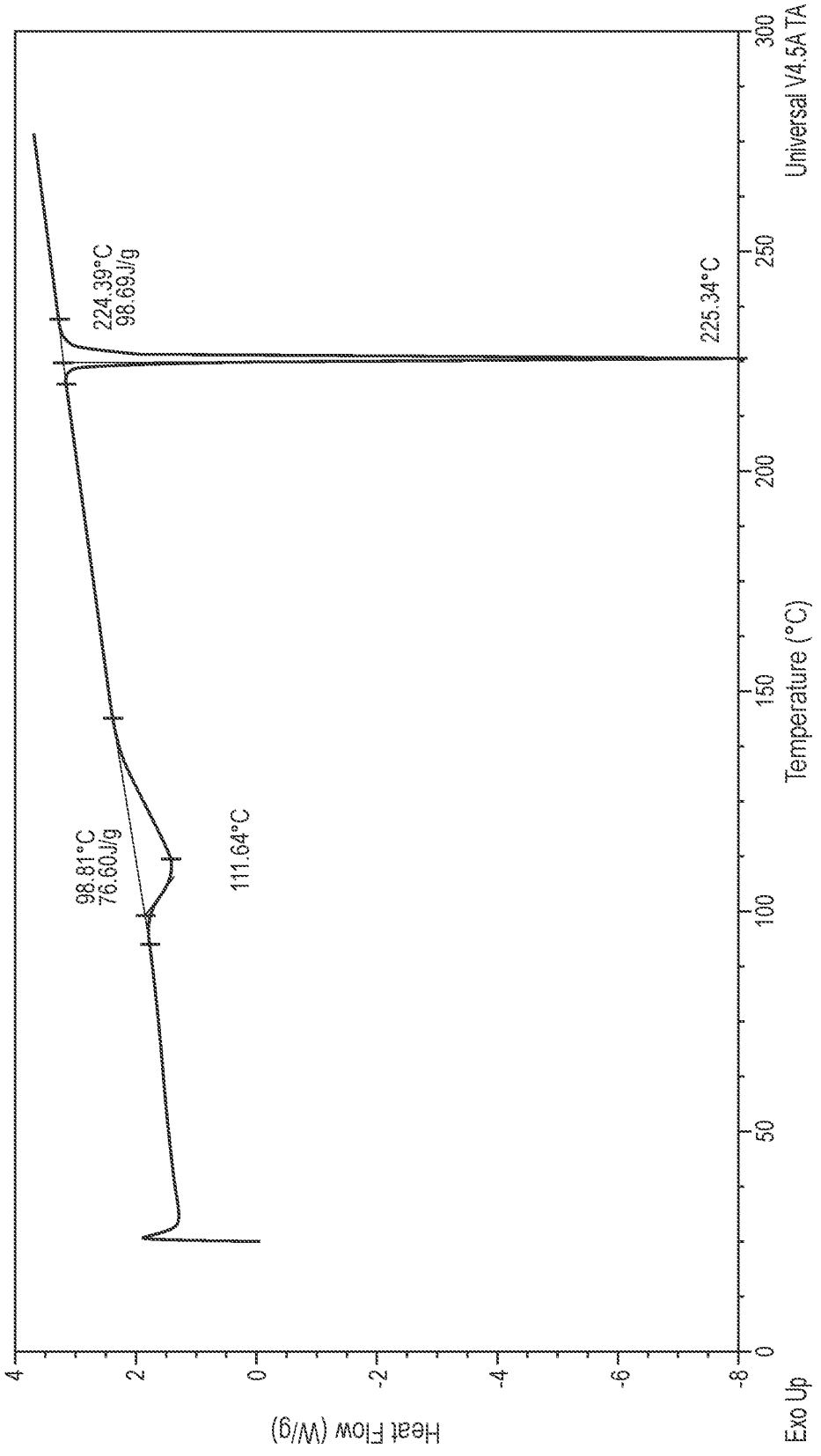
224.39°C
98.69J/g
225.34°C
98.81°C
76.60J/g
111.64°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.5A TA

FIG. 25

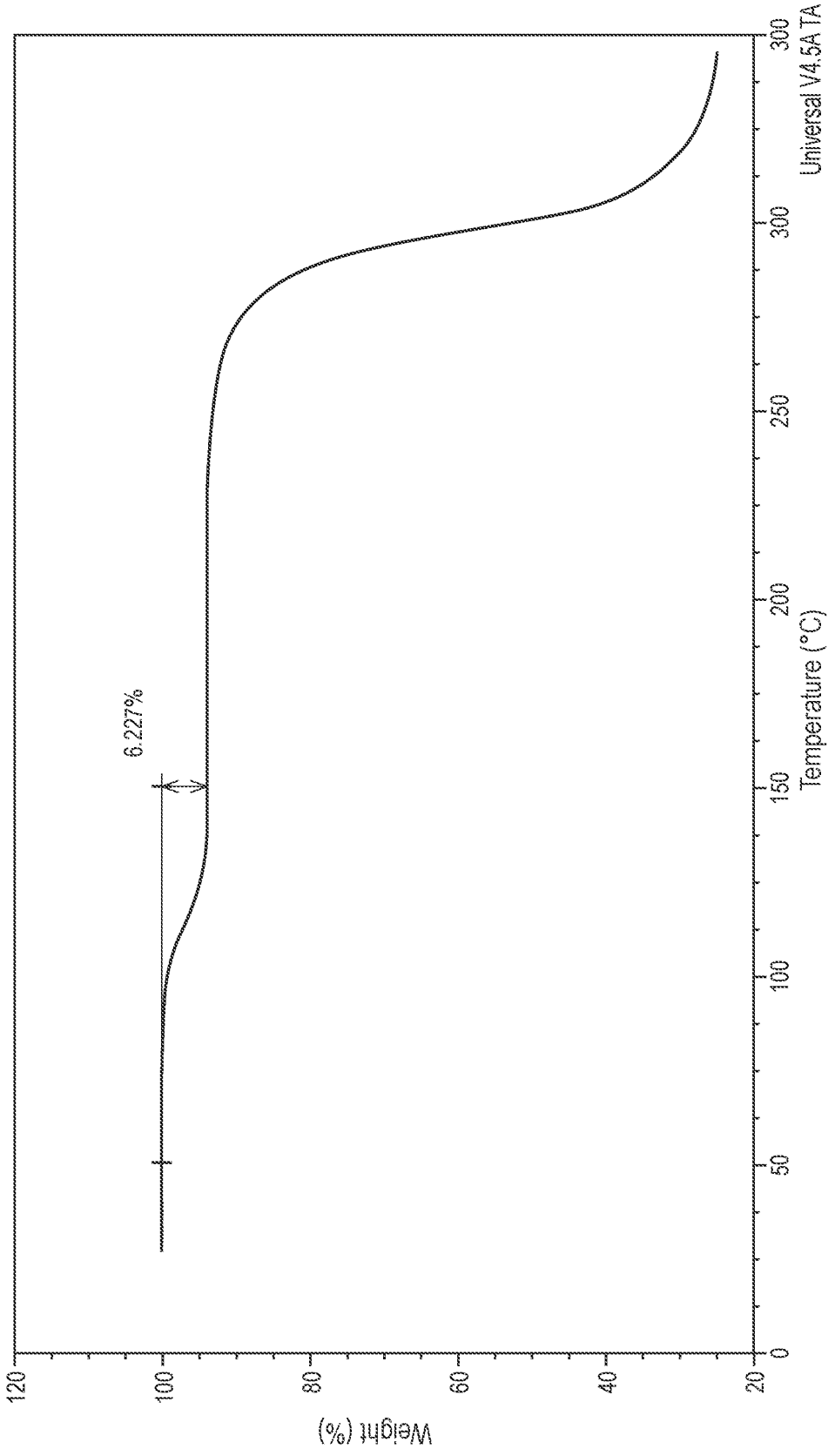
Weight (%)
120
100
80
60
40
20
0
50
100
150
200
250
300
Temperature (°C)
Universal V4.5A TA
6.227%

FIG. 26