3.1 Alternative Synthesis of (±)-SPF-32629A (1)

We report herein an efficient route for the synthesis of (±)-SPF-32629A through one-pot reduction and regioselective O-acylation strategy. This methodology enabled us to accomplish the synthesis of SPF-32629A in a straightforward way by circumventing previously reported undesired protection and deprotection strategy.

In Chapter-2 we described the first total synthesis of racemic SPF-32629A via two routes. Although, both the routes could be easily conducted they suffer from considerable drawbacks including the following limitations: (a) low conversion of N-oxide to amide; (b) formation of significant amount of byproduct; and (c) undesired protection and deprotection strategy. In light of these limitations, we sought to devise a simple and straightforward route to synthesize SPF-32629A. Toward this goal, we wish to report herein an improved and efficient synthesis of SPF-32629A through a one-pot reduction and regioselective O-acylation approach. Our straightforward approach is considerably more efficient than the previously reported methods; avoids undesired protection and deprotection strategy and affords pure SPF-32629A in a shorter way.

As shown in Scheme 4, the synthesis of SPF-32629A was achieved in four steps starting from 7, which was in turn readily prepared from
cheaply available pyridine by following previously reported procedures as illustrated in Chapter-2.\textsuperscript{31-32} the reaction of 7 with phosphorous oxychloride under reflux for 12h afforded 15.\textsuperscript{34} In subsequent experiments, step wise conversion of 15 to 17 was achieved in two steps. Thus, when a solution of 15 in aqueous acetic acid was heated in a sealed tube at 180~190 °C for a period of 6h afforded debenzylated product 16, which upon prolonged heating for further 7h, produced 17. Alternatively, compound 17 can be more conveniently prepared by effecting debenzylation and dechlorination in a single step. This involved the reaction of 15 with aqueous acetic acid under similar conditions for extended reaction time (12h) to obtain 17\textsuperscript{21} in much higher yields without the need for isolation of intermediate 16.

Reagents and conditions: (n) POCl₃, reflux, 12 h, 83%; (o) AcOH, H₂O, Sealed tube, 180~190 °C, 6 h, 83%; (p) AcOH, H₂O, Sealed tube, 180~190 °C, 7 h, 76%; (q) AcOH, H₂O, Sealed tube, 180~190 °C, 12 h, 91%; (r) NaBH₄, THF:MeOH (8:2), rt, 2 h, 100% (crude); (s) Isovaleric acid, EDC.HCl, DMAP (cat), THF:DCM (1:2), 0 °C to rt, 12 h, 79%.

With an efficient route to the key precursor 17 in hand, we turned our attention toward the introduction of isovaleryl ester moiety via a straightforward synthetic route; and our initial investigations centered upon the mild protecting groups for the OH and CONH groups of 17 with the aim to accomplish reduction, acylation and deprotection in one-pot. Consequently, we investigated protection with mild protecting groups such as tert-butoxycarbonyl and acetyl independently under standard experimental conditions. However, despite numerous exploratory experiments undertaken including variation of reaction conditions such as time, temperature and catalysts failed to give the desired protection for the OH and CONH groups. Given the poor selectivity of the acylation of OH and CONH groups of 17 we hypothesized that SPF-32629A could be regioselectively assembled in a one-pot procedure by a tandem reduction and acylation protocol in presence of free OH and CONH groups. Accordingly, reduction of 17 under standard sodium borohydride mediated reduction conditions furnished the requisite crude intermediate...
18 in quantitative yield, which upon extractive isolation was used in the next step without further purification. Gratifyingly, as expected the resulting crude alcohol 18 underwent coupling with isovaleric acid in a regioselective manner to produce SPF-32629A in good yield with high purity. The spectral data including IR, MASS, 1H NMR, 13C NMR and LCMS of our synthetic compound SPF-32629A were in consistent with the reported data. However, the melting point (127~130°C) is slightly higher than the reported value (108~112°C), probably due to the high purity of our compound; which is also reflected in the color of the compound (obtained colorless against reported yellow color).

In summary, we have developed a novel and efficient approach for the synthesis of pure SPF-32629A by employing direct reduction and regioslective acylation as the key step, wherein no protecting group was employed for the amide and phenol functional groups.

3.2 Experimental section.

3.2.1. Synthesis of (4-(Benzyloxy)-6-chloropyridin-2- yl) (phenyl) methanone (15).
A flame-dried flask was cooled under a stream of nitrogen and charged with phosphorous oxychloride (250 mL) at room temperature. Compound 7 (25 g, 81.87 mmol) was added portion wise at 40–50 °C over a period of 15 min and the resulting reaction mixture was slowly heated to reflux and stirred until the starting material was completely consumed as judged by TLC analysis (12 h). The mixture was then cooled and distilled out phosphorous (v) oxychloride under reduced pressure to obtain crude residue. Crude residue was cooled to 0 °C, added ice cold water and neutralized with aqueous sodium carbonate solution. Extracted with ethyl acetate and combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to obtain crude solid. Obtained crude solid was purified by flash column chromatography over silica gel 60 (230–400 mesh) using 25% EtOAc: Pet-ether as eluent to afford the title compound 15 as colorless solid (22 g, 83%).

\[ R_f = 0.6 \] (Etylacetate:N-Hexane, 25:75).

\[ \text{mp} = 106-108 \text{ °C}. \]

\[ \text{IR (KBr pellet): } \nu_{\text{max}} 1666, 1588, 1544 \text{ cm}^{-1}. \]
$^1$H NMR (400 MHz, CDCl$_3$): δ 8.10 (2H, d, J 7.2 Hz), 7.61-7.58 (1H, m), 7.55 (1H, d, J 2.4 Hz), 7.50-7.38 (7H, m), 7.08 (1H, d, J 1.6 Hz), 5.18 (2H, s).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 191.71 (C), 167.04 (C), 156.22 (C), 151.36 (C), 135.48 (C), 134.63 (C), 133.22 (CH), 131.08 (2CH), 128.83 (2CH), 128.69 (CH), 128.17 (2CH), 127.60 (2CH), 112.99 (CH), 110.68 (CH); 70.73 (CH$_2$).

MS (APCI) m/z 324.36 (M+H)$^+$.  

LCMS: (ES) m/z calcd for C$_{19}$H$_{15}$ClNO$_2$, [M+H]$^+$: 324.08, found: 324.36; Column used: Develosil ODS MG-3 (4.6x33 mm), Mobile Phase: A: 0.1% Aq.HCOOH, B: 0.1% HCOOH (Acetonitrile), T/%B: 0/30, 4/90, 8/90, 8.1/30; Flow Rate: 1.0 mL/min, Diluent: Acetonitrile; UV: 220 nm, RT = 4.79, Purity = 99.46%.

HPLC: Column used: Kromasil 100-5-C-18 (4.6x250 mm), 5 µ; Mobile Phase: A: 0.05% Aq.Trifluoroacetic acid; B: Acetonitrile; T/%B: 0/30, 2/30, 6/90, 16/90, 18/30, 20/30; Flow Rate: 1.0 mL/min, Diluent: Acetonitrile; UV: 217 nm; RT = 11.213; Purity = 97.7%.

### 3.2.2. Synthesis of (6-Chloro-4-hydroxypyrindin-2-yl) (phenyl) methanone (16).
A solution of compound 15 (20 g 61.77 mmol), acetic acid (300 mL) and water (10 mL) was heated in a sealed tube at 180~190 °C for 6 h. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and concentrated in vacuo to obtain crude solid. Obtained crude solid was purified by flash column chromatography over silica gel 60 (230–400 mesh) using 2% Methanol:Dichloromethane as eluent to give compound 16 as off white solid (12 g; 83%).

R_f = 0.5 (Methanol:Dichloromethane, 5:95).

mp = 142-146 °C.

IR (KBr pellet): ν_{max} 3349, 1651, 1594, 1576, 1430 cm^{-1}.

^{1}H NMR (400 MHz, d_6-DMSO): δ 11.73 (1H, s, D_2O exchangeable OH)), 7.93-7.91 (2H, m), 7.70-7.66 (1H, m), 7.57-7.53 (2H, m), 7.31 (1H, d, J 2 Hz), 7.08 (1H, d, J 2 Hz).

^{13}C NMR (100 MHz, d_6-DMSO): δ 191.84 (C), 166.95 (C), 155.67 (C), 150.23 (C), 135.51 (C), 133.23 (CH), 130.45 (2CH), 128.28 (2CH), 113.50 (CH), 111.69 (CH).

MS (APCI) m/z 234.37 (M+H)^{+}.

LCMS: (ES) m/z calcd for C_{12}H_{9}ClNO_2, [M+H]^+: 234.65, found: 234.37; Column used: Develosil ODS MG-3 (4.6x33 mm), Mobile Phase: A: 0.1%
Aq.HCOOH, B: 0.1% HCOOH (Acetonitrile), T/%B: 0/30, 4/90, 10/90, 10.1/30; Flow Rate: 1 mL/min, Diluent: Acetonitrile; UV: 257 nm, RT = 2.97, Purity = 98.96%.

**HPLC**: Column used: Kromasil 100-5-C-18 (4.6×250 mm), 5 µ; Mobile Phase: A: 0.1% Aq.HCOOH, B: Acetonitrile; T/%B: 0/30, 2/30, 6/90, 16/90, 18/30, 20/30; Flow Rate: 1.0 mL/min, Diluent: Acetonitrile; UV: 210 nm; RT = 8.360; Purity = 98.01%.

### 3.2.3. Synthesis of 6-Benzoyl-4-hydroxypyridin-2(1H)-one (17)

![Chemical Structure](image)

**Step-p**: Compound 16 (10 g; 42.79 mmol) was reacted with acetic acid (150 mL) and water (5 mL) for 7 h according to the method described for compound 16 to provide the title compound as pale greenish solid (7 g; 76%).

**Step-q**: Compound 15 (20 g; 61.9 mmol) was reacted with acetic acid (300 mL) and water (10 mL) for 12 h according to the method described for compound 16 to afford the title compound as pale greenish solid, (12 g 90%).

**R_f** = 0.4 (Methanol:Dichloromethane, 10:90).

**mp** = 258-262 °C.
**IR** (KBr pellet): $\nu_{\text{max}}$ 3438, 1669, 1639, 1596, 1446 cm$^{-1}$.

**$^1$H NMR** (400 MHz, d$_6$-DMSO): $\delta$ 11.0 (1H, brs, D$_2$O exchangeable OH), 10.85 (1H, s, D$_2$O exchangeable CONH), 7.82 (2H, d, $J$ 7.6 Hz), 7.72-7.69 (1H, m), 7.59-7.55 (2H, m), 6.28 (1H, s), 5.85 (1H, s).

**$^{13}$C NMR** (100 MHz, d$_6$-DMSO): $\delta$ 189.55 (C), 165.95 (C), 163.76 (C), 143.76 (C), 135.4 (C), 133.42 (CH), 129.70 (2CH), 128.63 (2CH), 105.82 (CH), 101.79 (CH).

**MS** (ESI) $m/z$ 216.42 (M+H)$^+$.  

**LCMS**: (ES) $m/z$ calcd for C$_{12}$H$_{10}$NO$_3$, [M+H]$^+$: 216.20, found: 216.4; Column used: Develosil ODS MG-3 (4.6x33 mm), Mobile Phase: A: 0.1% Aq.HCOOH, B: 0.1% HCOOH (Acetonitrile), T/%B: 0/30, 4/90, 8/90, 8.1/30; Flow Rate: 1 mL/min, Diluent: Methanol; UV: 215 nm, RT = 3.25, Purity = 99.05%.

**HPLC**: Column used: Eclipse-XDB-C8 (4.6×150 mm), 5 µ; Mobile Phase: A: 0.01 M Aq.Ammonium acetate; B: Acetonitrile; T/%B: 0/10, 2/10, 6/90, 16/90, 18/10, 20/10; Flow Rate: 1 mL/min, Diluent: Acetonitrile; UV: 215 nm; RT = 5.387; Purity = 98.44%.

**3.2.4. Synthesis of 4-hydroxy-6-(hydroxy (phenyl) methyl) pyridin-2(1H)-one (18).**
To a cooled solution of compound 17 (2 g, 9.29 mmol) in tetrahydrofuran (16 mL) and methanol (4 mL) was portion wise added sodium borohydride (0.36 g, 9.29 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 to 10 °C for 2 h and treated drop wise with concentrated hydrochloric acid until pH = 4 at 0 °C. The resulting reaction mixture was stirred for 15 minutes, filtered to remove borate salts and the filtrate was concentrated under *vacuo* at 50 °C to obtain crude solid. Obtained crude solid was purified by flash column chromatography over silica gel 60 (230–400 mesh) using 8% methanol: DCM as eluent to afford the title compound 18 as a cream colour solid (1.85 g, 91.67%).

**R<sub>f</sub>** = 0.3 (Methanol:Dichloromethane 10:90).

**mp** = 119-123°C.

**IR** (KBr pellet): ν<sub>max</sub> 3363, 1645, 1610, 1428 cm<sup>-1</sup>.

**H NMR** (400 MHz, d<sub>6</sub>-DMSO): δ 10.75 (1H, brs, D<sub>2</sub>O exchangeable Pyridine-<wbr/>OH), 10.41 (1H, s, D<sub>2</sub>O exchangeable CONH), 7.43-7.41 (2H, m), 7.35-7.32 (2H, m), 7.29-7.24 (H, m), 6.125 (1H, d, <i>J</i> 4 Hz, D<sub>2</sub>O exchangeable OH), 5.863 (1H, d <i>J</i> 1.2 Hz), 5.40 (1H, d <i>J</i> 4 Hz), 5.34 (1H, d <i>J</i> 2 Hz).
**13C NMR** (100 MHz, d$_6$-DMSO): δ 167.59 (C), 164.26 (C), 152.79 (C), 142.32 (C), 128.20 (2CH), 127.59 (CH), 126.41 (2CH), 96.63 (CH), 95.76 (CH), 70.82 (CH).

**MS** (ESI) $m/z$ 216.1 [M-H]$^-$.

**LCMS**: (ES) $m/z$ calcd for C$_{12}$H$_{10}$NO$_3$, [M-H]: 216.07, found: 216.1; Column used: Develosil ODS MG-3 (4.6x33 mm), Mobile Phase: A: 0.1% Aq.HCOOH, B: 0.1% HCOOH (Acetonitrile: MeOH (50:50)), T/%B: 0/10, 4/50, 6/90, 10/90, 10.1/10; Flow Rate: 1mL/min, Diluent: Acetonitrile; UV: 282 nm, RT = 3.30, Purity = 99.04%.

**HPLC**: Column used: Eclipse-XDB-C18 (4.6×150 mm), 5 µ; Mobile Phase: A: 0.1% Aq.HCOOH; B: methanol; T/%B: 0/30, 8/90, 15/90, 15.1/30; Flow Rate: 1.0 mL/min, Diluent: Acetonitrile; UV: 285 nm; RT = 4.801; Purity = 96.71%.

**Chiral HPLC**: racemic mixture; Column used: Chiral PAK-IA (4.6x250 mm), 5 µ, Mobile Phase: A: B: n-hexane: Ethanol (80:20), Isocratic; Flow Rate: 0.7 mL/min, Diluent: Ethanol, Run time: 30 min, UV: Max Plot nm, RT = 9.41 and 11.35.

**3.2.5. Synthesis of (4-Hydroxy-6-oxo-1, 6-dihydropyridin-2-yl) (phenyl) methyl-3-methylbutanoate [racemic SPF-32629A (1)].**
To a cooled solution of compound 18 (2 g, 9.29 mmol) in a mixture of tetrahydrofuran:dichloromethane (1:2, 30 mL) was sequentially added isovaleric acid (0.95 g, 9.31 mmol), EDC.HCl (2.13 g, 11.15 mmol) and 4-(dimethylamino)pyridine (20 mg) at 10 °C and stirred at room temperature for 12 h. Quenched with ice cold water, separated organic layer and again extracted aqueous layer with dichloromethane. Combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain crude solid. Obtained crude solid was purified by flash column chromatography over silica gel using 10% methanol: dichloromethane as eluent to afford 2.2 g (79%) of (±)-SPF-32629A as colorless solid.

Analytical data Described in 2.2.10 (Chapter-2)

Spectral data Described in 2.3.9 (Chapter-2)

3.3 Analytical Reports section.
3.3.1. Spectral data of (4-(benzyloxy)-6-chloropyridin-2-yl) (phenyl) methanone (15).
Expansion of $^1$H NMR

$^{13}$C NMR in CDCl$_3$
Expansion of $^{13}$C NMR

MS-SPECTRUM
HPLC

Chromatographic Conditions

Column: Kromasil 100-5-C18 (4.6x250mm)5.0 μm
Mobile Phase: A: 0.05% TFA (AQ)
Mobile Phase: B: ACN
T % B: 0/30, 2/30, 6/90, 15/50, 15/30, 20/30
Flow Rate: 1.0 mL/min UV: 217 nm
Temp: 25 °C
Diluent: ACN

Purity Chromatogram

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3.3.2. Spectral data of (6-chloro-4-hydroxypyridin-2-yl) (phenyl) methanone (16).
Expansion of $^1$H NMR

$^1$H NMR $\text{D}_2\text{O}$-Exchange

$^1$H NMR $\text{D}_2\text{O}$-Exchange
$^{13}$C NMR in $d_6$-DMSO

MS-SPECTRUM
**HPLC**

**Chromatographic Conditions**

Column: Kromasil 100-5-C-18 (4.6X250 mm) 5μ
Mobile Phase A: 0.1% FA (AQ)
Mobile Phase B: ACN
Time: 0/30, 2/30, 6/90, 16/90, 18/30, 20/30
Flow Rate: 1.0 mL/min  UV: 210 nm
Temp: 25 °C
Diluent: ACN

**Purity Chromatogram**

![Purity Chromatogram](image)

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3.3.3. Spectral data of 6-benzoyl-4-hydroxypyridin-2(1H)-one (17).

FT-IR

\[ \text{HO} \]
\[ \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \]

17

\[ 1669.73 \] \[ 1439.50 \] \[ 1445.92 \] \[ 1396.65 \]

\[ 342.80 \] \[ 330.45 \] \[ 536.69 \] \[ 489.81 \]

\[ 548.77 \] \[ 734.24 \] \[ 768.86 \] \[ 736.96 \]

\[ 1220.68 \] \[ 1360.06 \] \[ 1660.90 \] \[ 1133.92 \]

\[ 1596.69 \] \[ 1365.61 \] \[ 982.56 \] \[ 1622.73 \]

\[ 3115.62 \] \[ 3023.98 \] \[ 3483.05 \] \[ 3109.52 \]

\[^{1}H\] NMR in \( d_6\)-DMSO

\[ \text{HO} \]
\[ \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \]

17

\[ 8.84 \] \[ 5.84 \] \[ 7.84 \] \[ 7.54 \]

\[ 7.84 \] \[ 7.84 \] \[ 7.84 \] \[ 7.84 \]

\[ 7.84 \] \[ 7.84 \] \[ 7.84 \] \[ 7.84 \]

\[ 7.84 \] \[ 7.84 \] \[ 7.84 \] \[ 7.84 \]

\[ 7.84 \] \[ 7.84 \] \[ 7.84 \] \[ 7.84 \]

\[ 7.84 \] \[ 7.84 \] \[ 7.84 \] \[ 7.84 \]

\[ 7.84 \] \[ 7.84 \] \[ 7.84 \] \[ 7.84 \]
Expansion of $^1$H NMR

$^1$H NMR D$_2$O Exchange
$^{13}$C NMR in $d_6$-DMSO

MS - SPECTRUM
HPLC

Chromatographic Conditions

Column: Eclipse-XDB-C8 (4.6x150 mm) 5.0μ
Mobile Phase A: 0.01M Ammonium Acetate
Mobile Phase B: Acetonitrile
Time/Min: 0/10, 2/10, 5/20, 10/10, 18/10, 20/10
Flow Rate: 1.0 mL/Min
Temp: 25 °C
Diluent: ACN

Purity Chromatogram

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3.3.4. Spectral data of 4-Hydroxy-6-(hydroxy (phenyl) methyl) pyridin-2(1H)-one (18).
\[ ^1H \text{NMR in } d_6-\text{DMSO} \]

\[ ^1H \text{NMR } D_2O \text{ Exchange} \]
$^{13}$C NMR in $d_6$-DMSO

Expansion of $^{13}$C NMR
Chromatographic Conditions

Column: Eclipse XDB-C18 (4.6x150mm) 5.0 µ
Mobile Phase A: 0.1% Formic Acid (aq)
Mobile Phase B: Methanol
T%: 0/30/60/15/00/15/130
Flow Rate: 1.0 mL/min UV 285 nm
Temp: 25 °C
Diluent: ACN

Purity Chromatogram

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<td>11.26</td>
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Chiral HPLC

**Chromatographic Conditions**

- **Column**: ChiralPAK IA (4.6x250mm) 5u
- **Mobile Phase**: A: Hexane, B: EtOH
- **RATIO**: (80:20)
- **Flow Rate**: 0.7 ml/min
- **Temp**: N/A
- **Diluent**: Ethanol

![Purity Chromatogram](image)

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---End for Chapter-3---