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### The Preparation of Immunosuppressant SR-31747

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## THE PREPARATION OF IMMUNOSUPPRESSANT SR-31747

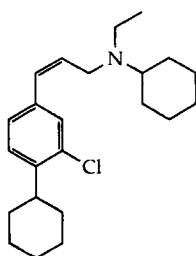
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**Abstract:** The preparation of immunosuppressant SR-31747 is described. Attempts to install the Z-allyl amine included Lindlar partial hydrogenation and vinyl stannane methodologies. Ultimately, the Wittig olefination of aldehyde **12** with the ylide derived from  $\beta$ -aminoethyl phosphonium salt **13** proved successful.

A recent patent from Sanofi disclosed the immunosuppressive activity of SR-31747 (**1**) in which this allylic amine was claimed to be a potent sigma receptor antagonist specific for human lymphocytes.<sup>2</sup> In vitro, SR-31747 was reported to inhibit the proliferation of activated T-cells and suppress the production of IL-1, IL-6 and TNF- $\alpha$ .<sup>3</sup> In addition, this compound is said to have a long duration of action and good bioavailability<sup>4</sup> with potency similar to cyclosporin A<sup>5</sup> and is in Phase I

clinical trials. Thus, as part of our ongoing discovery efforts in immune suppression, this compound was prepared for in-house profiling.



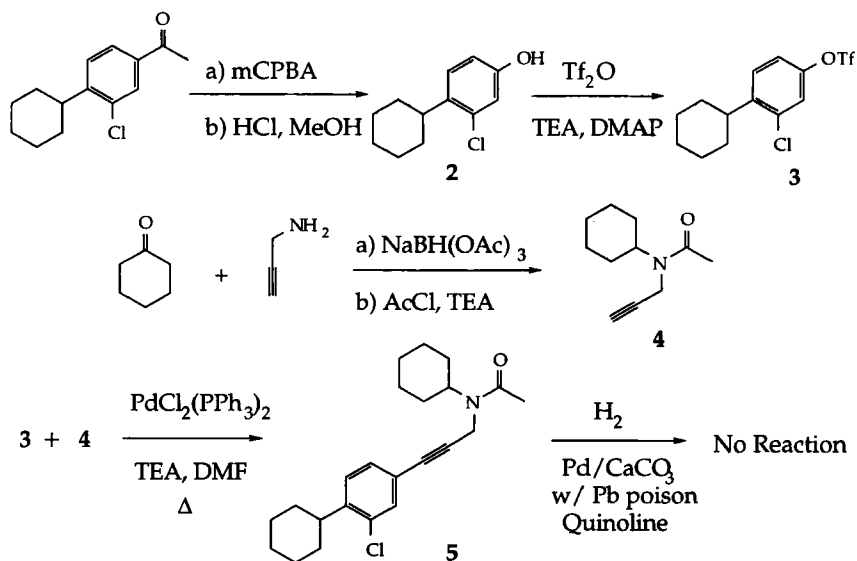
SR-31747 (1)

Our original synthetic strategy, based upon the Sanofi patent, relied on the partial hydrogenation of a suitable alkyne, under Lindlar conditions, to access the requisite Z-olefin (Scheme 1). In the event, alkyne **5** was prepared from triflate **3** (generated from a commercially available acetophenone<sup>6</sup> in 3 steps; 71% overall) and amide **4** (made in 2 steps; 43% overall) via palladium mediated coupling.<sup>7</sup> Unfortunately, the application of Lindlar hydrogenation conditions<sup>8</sup> to **5** returned only starting material or, upon using more forcing conditions, inseparable mixtures of Z- and E-olefins.

Another strategy that was briefly explored entailed the use of a hydrozirconation procedure to manufacture a Z-stannane for coupling to triflate **3** (Scheme 2). The necessary alkynyl stannane (**9**) was prepared by N-alkylation of **7** with the mesylate of propargyl alcohol (**6**)

to provide the tertiary amine **8** followed by C-stannylation. Unfortunately, exposure of stannane **9** to the Schwartz reagent,<sup>9</sup> bis(cyclopentadienyl)zirconocene chloride hydride (either commercial

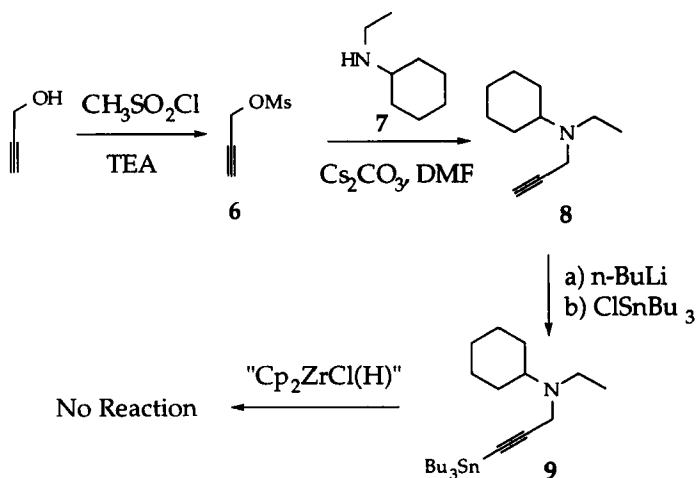
Scheme 1



material or freshly prepared), failed to provide the desired hydrozirconation product, Z-vinyl stannane. Only starting material or decomposition products resulted.

Ultimately, a more traditional synthetic route involving the construction of the crucial carbon-carbon Z double bond as the last step proved to be a successful and efficient. Based on the work of Marxer<sup>10</sup> and others,<sup>11</sup> a procedure involving the use of  $\beta$ -aminoethyl

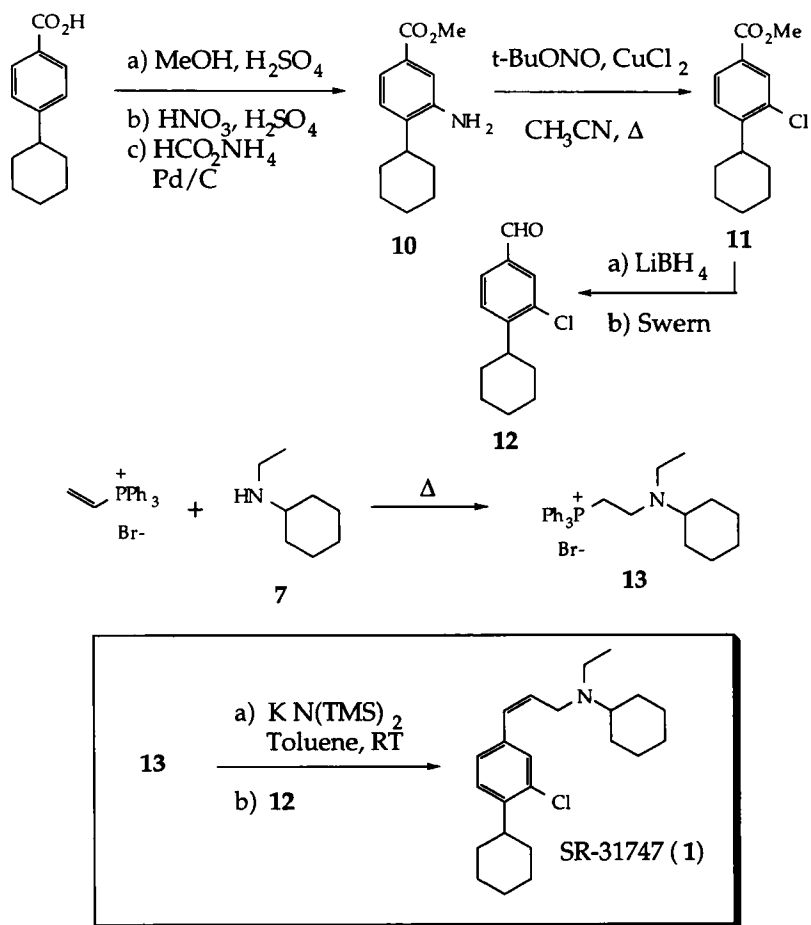
Scheme 2



phosphonium salts in Wittig olefinations emerged as ideally suited for the preparation of SR-31747 (see Scheme 3). Commercially available 4-cyclohexylbenzoic acid was efficiently esterified (97%), nitrated (97%), and reduced (91%) to the desired aniline **10**. Application of the Doyle modification of the Sandmeyer reaction,<sup>12</sup> converted **11** to the 3-chloro derivative **13** (99%). Subsequent reduction and oxidation of the ester generated aldehyde **12** (91% for two steps). Meanwhile, the requisite  $\beta$ -aminoethyl phosphonium salt (**13**) was readily prepared by gently heating a mixture of vinyl triphenylphosphonium bromide and commercially available amine **7** (95%).

Treatment of phosphonium salt **13** with potassium bis(trimethylsilyl)amide at room temperature to generate an ylide *in*

Scheme 3



*situ*, followed by addition of the aldehyde **12**, provided the desired *Z*-olefin, SR-31747 (**1**) in 55% yield (isolated), while no traces of the *E* isomer could be detected.<sup>13</sup> This excellent stereospecificity is typical of a non-stabilized ylide applied to the lithium salt-free Wittig protocol in

which "stereochemical drift" of the intermediate oxaphosphetane is suppressed.<sup>14</sup>

In-house profiling of SR-317474 demonstrated that it indeed possesses immunosuppressant activity ( $IC_{50} = 3.4 \mu M$  in the mixed lymphocyte reaction/T cell proliferation assay and  $ED_{50} = 23 \text{ mg/kg}$  in the 1-day murine delayed type hypersensitivity *in vivo* assay) and studies are continuing in an effort to understand its unusual mechanism of action.

## EXPERIMENTAL SECTION

### 4-Cyclohexyl-benzoic acid methyl ester

A stirred, cloudy solution of 4-cyclohexylbenzoic acid (5.0 g; 24.5 mmol; available from Lancaster) and concentrated sulfuric acid (0.5 mL) in methanol (50 mL) was heated to reflux for 15 h under nitrogen atmosphere. The resulting clear, light yellow solution was then allowed to cool to room temperature and was concentrated in vacuo. The residual yellow solid was dissolved in ether (75 mL) and washed with saturated, aqueous  $NaHCO_3$ , then dried ( $MgSO_4$ ), filtered and concentrated in vacuo to provide the methyl ester as a light yellow solid (5.20g; 97%). mp 46-47 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.95 (dd, 2H,  $J = 1.8, 6.6 \text{ Hz}$ ), 7.26 (dd, 2H,  $J = 1.6, 6.7 \text{ Hz}$ ), 3.89 (s, 3H), 2.55 (c, 1H), 1.87-1.74 (m, 5H), 1.49-1.23 (m, 5H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  167.2, 153.5, 129.7, 127.7, 126.9, 51.9, 44.7, 34.1, 26.7, 26.0. IR ( $CHCl_3$ ) 2930, 2854, 1717, 1610, 1437, 1282, 1115  $cm^{-1}$ . LRMS  $m/e$  219, 236. Microanalysis for  $C_{14}H_{18}O_2$  calculated C: 77.03, H: 8.31 (Found C: 76.83, H: 8.35).

### 4-Cyclohexyl-3-nitro-benzoic acid methyl ester

To a stirred cooled (0 °C) portion of concentrated sulfuric acid (5 mL) was added the methyl (4-cyclohexyl)benzoate (2.22g; 10.2 mmol), portionwise, over 5 min. To the resulting brown, vigorously stirred, cooled solution was added a solution of concentrated nitric acid (2 mL; 32 mmol) in concentrated sulfuric acid (2 mL) dropwise, via addition funnel over 20 min. The resulting clear, yellow solution was stirred at 0 °C for 30 min. The reaction was then poured over crushed ice (200 mL) and extracted with ethyl acetate (3 x 75 mL). Combined organic



layers were then washed with saturated aqueous  $\text{NaHCO}_3$  and brine then dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo to give the nitro benzoate as a viscous yellow oil (2.59 g; 97%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (d, 1H,  $J = 1.7$  Hz), 8.09 (dd, 1H,  $J = 1.7, 8.3$  Hz), 7.49 (d, 1H,  $J = 8.3$  Hz), 3.89 (s, 3H), 2.97 (c, 1H), 1.86-1.70 (m, 5H), 1.47-1.20 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  165.0, 149.8, 146.1, 132.8, 128.8, 128.5, 124.9, 52.5, 39.3, 33.7, 26.5, 25.8. IR ( $\text{CHCl}_3$ ) 2934, 2904, 1726, 1533, 1438, 1359, 1302, 1274, 1261, 1135  $\text{cm}^{-1}$ . LRMS  $m/e$  281. Microanalysis for  $\text{C}_{14}\text{H}_{17}\text{NO}_4$  calculated C: 63.87, H: 6.51, N: 5.32 (Found C: 63.58, H: 6.45, N: 5.36).

### 3-Amino-4-cyclohexyl-benzoic acid methyl ester (10)

To a stirred solution of methyl (3-nitro, 4-cyclohexyl)benzoate (1.72g; 6.1 mmol) in dry methanol (40 mL) was added 5% palladium on charcoal (0.085g) and anhydrous ammonium formate (3.8g; 60 mmol). The resulting dark solution was heated to reflux for 6 h under nitrogen atmosphere. The reaction mixture was then allowed to cool to room temperature and was concentrated in vacuo. The residue was dissolved in ethyl acetate (200 mL), filtered, dried ( $\text{MgSO}_4$ ), filtered again, and was then concentrated in vacuo to provide the aniline as a light yellow solid (1.39g; 91%). mp 108-109.5  $^\circ\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (dd, 1H,  $J = 1.8, 8.1$  Hz), 7.34 (d, 1H,  $J = 1.7$  Hz), 7.16 (d, 1H,  $J = 8.0$  Hz), 3.87 (s, 3H), 3.74 (br s, 2H), 2.48 (c, 1H), 1.89-1.76 (m, 5H), 1.48-1.23 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  167.3, 143.4, 137.0, 128.2, 126.0, 120.2, 116.5, 51.9, 38.6, 32.5, 27.0, 26.2. Microanalysis for  $\text{C}_{14}\text{H}_{19}\text{NO}_2$  calculated C: 72.07, H: 8.21, N: 6.00 (Found C: 71.95, H: 8.00, N: 6.09).

### 3-Chloro-4-cyclohexyl-benzoic acid methyl ester (11)

To a stirred yellow mixture of copper (II) chloride (0.087g; 0.64 mmol) in dry acetonitrile (2 mL) was added the *t*-butyl nitrite (0.10 mL; 0.80 mmol) via syringe at room temperature under nitrogen atmosphere. The resulting dark green suspension was then heated (65  $^\circ\text{C}$ ) with vigorous stirring. To the warm, stirred mixture was added a solution of methyl (3-amino, 4-cyclohexyl)benzoate (0.125g; 0.54 mmol) in dry acetonitrile (4 mL) via cannulae over a 5 min. period (bubbling). The resulting black solution was stirred at 65  $^\circ\text{C}$  for 30 min. then allowed to cool to room temperature. The reaction was diluted with ether (20 mL), washed with 1N aqueous HCl, washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo to provide the chloro benzoate as a light orange oil (0.135g; 99%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (d, 1H,  $J = 1.7$  Hz), 7.85 (dd, 1H,  $J = 1.7, 8.2$  Hz), 7.31 (d, 1H,  $J = 8.1$  Hz), 3.88 (s, 3H), 3.03 (c, 1H), 1.88-1.75 (m, 5H), 1.51-1.19 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0, 149.9, 133.7, 130.6, 128.9, 128.0, 127.1, 52.2, 40.8, 32.8, 26.7, 26.1. IR ( $\text{CHCl}_3$ ) 2932, 2855, 1721, 1437, 1294, 1272, 1255  $\text{cm}^{-1}$ . HRMS for  $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Cl}$  ( $M+1$ ) calculated 253.0995 (Found 253.1004).

Microanalysis for  $C_{14}H_{17}ClO_2$  calculated C: 66.53, H: 6.78 (Found C: 66.70, H: 6.54).

### (3-Chloro-4-cyclohexyl-phenyl)-methanol

To a cooled (0 °C), stirred solution of methyl (3-chloro, 4-cyclohexyl)benzoate (0.18g; 0.71 mmol) in dry tetrahydrofuran (3 mL) was added a lithium borohydride-tetrahydrofuran solution (1.1 mL; 2.0 M; 2.1 mmol), via syringe under nitrogen atmosphere. The resulting cloudy solution was stirred at 0 °C for 2 h. then allowed to warm to room temperature and then heated to reflux for 4 h. The resulting cloudy solution was then allowed to cool to room temperature and was carefully quenched with addition of 1N aqueous HCl (5 mL) via syringe (Caution! Vigorous hydrogen evolution!). The resulting mixture was then extracted with methylene chloride (3 x 20 mL) and the combined organic extracts were washed with brine, dried ( $MgSO_4$ ), filtered and concentrated in vacuo to give the benzyl alcohol as a light yellow oil (0.15g; 93%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.32 (d, 1H,  $J$  = 1.6 Hz), 7.23 (d, 1H,  $J$  = 8.0 Hz), 7.16 (dd, 1H,  $J$  = 1.5, 8.0 Hz), 4.55 (s, 2H), 3.00 (c, 1H), 2.55 (br s, 1H), 1.88-1.75 (m, 5H), 1.52-1.20 (m, 5H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  144.0, 139.7, 133.6, 127.9, 127.3, 125.5, 89.2, 64.3, 40.3, 33.1, 26.2, 26.2. IR ( $CHCl_3$ ) 2931, 2854  $cm^{-1}$ . Microanalysis for  $C_{13}H_{17}ClO$  calculated C: 69.48, H: 7.62 (Found C: 69.88, H: 7.72).

### 3-Chloro-4-cyclohexyl-benzaldehyde (12)

To a cooled (-78 °C), stirred solution of anhydrous dimethyl sulfoxide (0.11 mL; 1.5 mmol) in dry methylene chloride (2 mL) was added oxalyl chloride (0.13 mL; 1.5 mmol) via syringe under nitrogen atmosphere (bubbling). After stirring at -78 °C for 10 min., the resulting solution was allowed to warm briefly (cooling bath removed for 3 min) then re-cooled to -78 °C and treated with a solution of 3-chloro-4-cyclohexyl benzyl alcohol (0.14g; 0.62 mmol) in dry methylene chloride (4 mL) via cannulae. The resulting solution was stirred at -78 °C for 15 min. then triethylamine (0.43 mL; 3.1 mmol) was added via syringe. The resulting cloudy solution was stirred at -78 °C for 45 min. then warmed to room temperature over 10 min. The reaction mixture was diluted with ether (50 mL) and washed with water, saturated  $NH_4Cl$  aq., and brine then dried ( $MgSO_4$ ), filtered and concentrated in vacuo to provide the aldehyde as a light yellow oil (0.13g; 98%) which was used immediately in the preparation of 1 without further purification.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  9.90 (s, 1H), 7.82 (d, 1H,  $J$  = 1.7 Hz), 7.70 (dd, 1H,  $J$  = 1.7, 8.0 Hz), 7.41 (d, 1H,  $J$  = 8.0 Hz), 3.05 (c, 1H), 1.88-1.75 (m, 5H), 1.52-1.22 (m, 5H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  151.7, 135.3, 134.6, 130.5, 128.1, 127.8, 41.0, 32.8, 26.6, 26.0.

**Cyclohexyl-ethyl-[2-(triphenylphosphonium bromide)-ethyl]-amine (13)**

To a vigorously stirred portion of cyclohexyl(ethyl)amine (12 mL; 79 mmol) was added vinyltriphenyl phosphonium bromide (8.5g; 23 mmol) at room temperature under nitrogen atmosphere. After stirring for 2 h., the reaction became an unstirrable mixture which was then heated to 70 °C for another 1 h. After cooling to room temperature, the solid mass was diluted with ether (200 mL) and the solids trapped on a Buchner funnel with suction. This residue was washed with ether then dried in vacuo to generate the  $\beta$ -aminoethyl phosphonium salt as a tan solid (10.9g; 95%). mp 156-159 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84-7.61 (m, 15H), 3.82 (dt, 2H,  $J = 6.3, 12.6$  Hz), 2.94 (dt, 2H,  $J = 6.3, 20.0$  Hz), 2.46 (q, 2H,  $J = 7.1$  Hz), 2.31 (c, 1H), 1.60-1.44 (m, 4H), 1.13-0.93 (c, 2H), 0.89-0.76 (m, 7H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  134.9, 134.1, 134.0, 130.4, 130.2, 119.3, 118.2, 59.0, 43.7, 43.6, 43.2, 28.8, 26.1, 25.9, 13.4. Microanalysis for  $\text{C}_{28}\text{H}_{35}\text{BrNP}$  calculated C: 67.74, H: 7.11, N: 2.82 (Found C: 67.50, H: 7.09, N: 2.67).

**[(Z)-3-(3-Chloro-4-cyclohexyl-phenyl)-allyl]-cyclohexyl-ethyl-amine (1)**

To a stirred suspension of N-ethyl-N-cyclohexyl-2-(triphenylphosphonium bromide)ethylamine (0.79g; 1.6 mmol) in dry toluene (4 mL) was added a solution of potassium hexamethyldisilazide in toluene (3.3 mL; 0.5 M; 1.65 mmol) via syringe at room temperature under nitrogen atmosphere. The resulting orange solution was stirred for 15 min. then a solution of 3-chloro-4-cyclohexyl benzaldehyde (0.13g; 0.6 mmol) in dry toluene (1 mL) was added via cannulae. The reaction was then stirred at RT for 3 h., then concentrated at reduced pressure to remove all toluene. The residue was dissolved in ethyl acetate (30 mL) and washed with saturated, aqueous  $\text{NaHCO}_3$  and brine then dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo to give a yellow semi-solid (0.6g). Purification by flash chromatography (4% methanol in methylene chloride) on silica gel provided the Z olefin (0.11g; 55%) as a clear, light yellow oil (mp of HCl salt 189-191 °C (lit<sup>2</sup> 192 °C)).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.20 (m, 2H), 7.09 (d, 1H,  $J = 8.0$  Hz), 6.40 (d, 1H,  $J = 11.8$  Hz), 5.82 (dt, 1H,  $J = 6.3, 11.9$  Hz), 3.42 (d, 2H,  $J = 6.3$  Hz), 2.99 (c, 1H), 2.66-2.53 (m, 3 H), 1.90-1.00 (c, 20H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1, 136.2, 133.2, 132.6, 129.6, 128.8, 127.4, 126.8, 59.8, 47.8, 44.1, 40.3, 33.1, 29.2, 26.8, 26.3, 26.2, 26.1, 13.6. IR ( $\text{CHCl}_3$ ) 2932, 2855  $\text{cm}^{-1}$ . HRMS calculated for  $\text{C}_{23}\text{H}_{35}\text{NCl}$  (M+1) 360.2458; found 360.2465. Microanalysis for  $\text{C}_{23}\text{H}_{34}\text{ClN}$  calculated C: 76.74, H: 9.52, N: 3.89 (Found C: 76.79, H: 9.70, N: 3.90).

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