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Flexible Synthesis of Polyfunctionalised 3-Fluoropyrroles.

Thomas J. Cogswell, Craig S. Donald, and Rodolfo Marquez

An efficient and selective approach for the synthesis of polyfunctionalised 3-fluoropyrroles has been developed starting from commercial aldehydes. The methodology is concise, efficient and allows for the modular and systematic assembly of polysubstituted 3-fluoropyrroles. This synthesis provides an alternative and highly convergent strategy for the generation of these chemically and biologically important units.

Introduction

Polyfunctionalised pyrroles are an integral part of medicinal chemistry, forming the core unit of a number of biologically active compounds. Fluorinated polyfunctionalised pyrroles are particularly interesting due to their useful biological, metabolic, physical and pharmacokinetic properties. Key fluorinated pyrroles include compounds such as 1 and 2 which have been developed as anti-inflammatory and anti-hypertension agents respectively (Figure 1).

Thus, it is not surprising the significant amount of interest that has been devoted to the synthesis of fluorinated pyrroles in recent years. As such, new flexible and efficient methods for their syntheses are desired.

Fluorinated α,β-unsaturated lactams were first synthesised via a ring-closing metathesis approach by Haufe and co-workers. The work was extended by the groups of Rutjes and Marquez to produce a number of novel fluorinated compounds (Scheme 1). We feel fluorinated α,β-unsaturated γ-lactams would be the ideal building block to provide access to polyfunctionalised fluorinated pyrroles.

Herein, we would like to report a quick, flexible and modular synthesis of polyfunctionalised fluorinated pyrroles. The methodology allows for the systematic introduction of substituents to produce novel polyfunctionalised fluorinated building blocks (Scheme 1).

Results and Discussion

Scheme 2. Synthesis of fluorinated α,β-unsaturated lactam 8.
Our initial approach to the synthesis of the pyrrole core began with the condensation of benzaldehyde 3 with tert-butylsulfinamide to generate the corresponding imine, which upon vinylation with vinylmagnesium bromide afforded the desired allylic amine 4 in excellent yield. Reductive amination of amine 4 with p-anisaldehyde then produced the PMB protected amine 5 in high yield (Scheme 2).

Coupling of amine 5 with 2-fluoroacrylic acid 6 then proceeded to produce the desired amide unit 7 in reasonable yield. Subsequent treatment of diene 7 with Grubbs 2nd gen. catalyst then afforded the expected α,β-unsaturated lactam 8 in good yield.

Rewardingly, alkylation of fluorolactam 8 with methyllithium proceeded cleanly to generate the desired pyrrole unit 9 in excellent yield (Scheme 3).

Mechanistically, we believe that this aromatisation process takes place through hemiaminal formation followed by elimination of water and double bond isomerisation.

<table>
<thead>
<tr>
<th>Table 1. Introduction of different nucleophiles (RM) in the synthesis of tetrasubstituted pyroles (9-13).</th>
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<tbody>
<tr>
<td>RM</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>DIBAL-H</td>
</tr>
<tr>
<td>PhLi</td>
</tr>
<tr>
<td>rBuLi</td>
</tr>
<tr>
<td>AllyMgBr</td>
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The alkylation-aromatisation methodology was then expanded by including an array of nucleophiles as to allow for the selective introduction of substituents at the C2 position of the C3 fluorinated-pyrrole ring. Thus, a collection of organometallic reagents including DiBAL-H, n-butyllithium, phenyllithium and allylmagnesium bromide were used to generate the desired substituted pyroles 10-13 in high yields (Table 1).

Having demonstrated the ability to incorporate substituents at the pyrrole C2 position through an alkylation-aromatisation process, it was decided to explore the ability of our methodology to incorporate substituents in the other pyrrole positions.

Thus, it was decided to showcase the methodology by generating a number of C3 fluorinated pyrrole analogues with different N-substituents. Synthetically, the generation of the new analogues was envisioned as originating through the incorporation of different aldehyde units during the reductive amination step.

Following this approach, different aromatic substitution patterns were initially explored with the benzyl and 4-bromobenzyl derivatives 14a and 14b being cleanly converted to the RCM precursors 15a and 15b in high yields (Table 2).

The non-aromatic derivative 15c, bearing a cyclohexylmethyl group, worked well with yields upwards of 80% for both steps. N-Methylpyrrole-2-carboxaldehyde was also cleanly incorporated, yielding the desired diene 15d in good yield over the sequence.

Ring-closing metathesis was then successfully carried out in all cases, with isolated yields higher than 80%. Gratifyingly, treatment of pyrrolidone compounds 16a-d with methyllithium under our alkylation-aromatisation methodology afforded the desired N-substituted pyrrole derivatives 17a-d in excellent isolated yields (Table 3).
At this point, it was decided to now focus on exploring the nature and effect of the starting aldehyde on our pyrrole forming sequence. By changing the identity of the starting aldehyde, a range of functional groups could be efficiently installed at the C5 position (Table 4).

Electron donating and withdrawing aromatic analogues were investigated, resulting in good yields of the allylic amine intermediates 18a-c. Aliphatic aldehydes could also be converted to the corresponding primary amines 18d-e in reasonable yields. Treatment of the crude allylic amines 18a-e under reductive amination conditions afforded the secondary amines 19a-e which upon coupling with 2-fluorocrotonic acid 6 generated the desired fluorinated amides 20a-20e in good yields.

Ring-closing metathesis in all cases proceeded in high yields (Table 5). However, examples with electron withdrawing substituents required extended reaction times and higher catalyst loadings (15% mol) to achieve high yields. Gratifyingly, treatment of all the pyrrolidone intermediates (21a-21e) under the methyllithium promoted alkylation-aromatisation conditions yielded the desired fluorinated tetrasubstituted pyrroles 22a-e in good to excellent yield.

Conclusion

In conclusion, we have developed an efficient and selective approach for the synthesis of polyfunctionalised 3-fluorinated pyrroles. The methodology is concise and allows for the modular synthesis of chemically and biologically important units.

Acknowledgments

We would like to thank the EPSRC and AstraZeneca for postgraduate support (T.C.) and for a Leadership Fellowship (R.M.). The authors also thank Dr. Ian Sword and the EPSRC (grant EP/H005692/1) for funding.

Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, toluene and dichloromethane (DCM) were purified through a solvent purification system. Petroleum ether refers to the fraction boiling between 40-60 °C. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C unless otherwise stated. IR spectra were recorded as thin films on NaCl plates using a Fourier Transform spectrometer. Only significant absorptions (ν_max) are reported in wavenumbers (cm⁻¹). Proton magnetic resonance spectra (¹H NMR) were recorded at either 400 or 500 MHz. Fluorine magnetic resonance spectra (¹⁹F NMR) were recorded at either 377 or 470 MHz. Carbon magnetic resonance spectra (¹³C NMR) were recorded at either 100 or 125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The
order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad), (3) and coupling constant (J) quoted in Hertz to the nearest 0.1 Hz. High resolution mass spectra were obtained by electrospray (EI) chemical ionisation (CI) mass spectrometry operating at a resolution of 15000 full widths at half height. Flash chromatography was performed using silica gel (40-63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Silica Gel 60 F254) unless otherwise stated. The plates were visualised by the quenching of UV fluorescence (λmax 254nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

**General procedure I.** A solution of the diene (1 eq) in toluene (0.005 g ml⁻¹) and was heated to 100 °C. Grubbs 2nd generation catalyst was added in portions and the reaction was stirred until completion as indicated by TLC analysis. The reaction was cooled down to room temperature, the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography.

**General procedure II.** α, β-Unsaturated lactam (1 eq) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Methyl lithium (1.1 eq) was added dropwise and the mixture was stirred for 1 h. Following this, the reaction was quenched with H2O (10 mL), extracted with diethyl ether (3 x 10 mL), dried (Na2SO4) and evaporated in vacuo. The crude residue was purified by flash column chromatography.

3-Fluoro-1-[(4’-methoxyphenyl)methyl]-2,5-diphenyl-1H-pyrrole, 8. Dialkene 7 (270 mg, 0.84 mmol) was treated with 7.5 mol % Grubbs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0-15% EtOAc in petroleum ether) to yield the desired α, β-un saturated lactam 8 (210 mg, 0.71 mmol, 83%) as a pale yellow oil. 1H NMR (CDCl3, 400 MHz) δ: 5.68-6.51 (4H, m), 5.96 (1H, s), 4.93 (2H, s), 3.72 (3H, s), 1.98 (3H, d, JF = 1.6 Hz). 13C NMR (CDCl3, 400 MHz) δ: -169.4. 13C NMR (CDCl3, 125 MHz) δ: 158.7, 149.2 (d, JF = 235.6 Hz), 132.9, 130.6, 130.1 (d, JF = 6.9 Hz), 128.8 (2C), 128.5 (2C), 127.1, 126.7 (2C), 114.2 (1C), 121.5 (2d, JF = 234.3 Hz), 96.4 (d, JF = 16.4 Hz), 55.3, 47.3, 8.2. m/z [EL (+ve)] 295.2 [M]+, HRMS found [M]+ 295.1373 C23H23FNO requires 295.1372. IR (thin film) νmax = 2928, 2359, 1614, 1599, 1512, 1324, 1174 cm⁻¹, m.p. 73-75 °C.

4-Fluoro-1-[(4’-methoxyphenyl)methyl]-2-phenyl-1H-pyrrole, 10. α, δ-Unsaturated lactam 8 (40 mg, 0.13 mmol) was dissolved in CH2Cl2 (4 mL) and cooled to -78 °C. Disobutylaluminium hydride (0.41 mL, 0.41 mmol, 1 M in ether) was added dropwise and the mixture was stirred for 16 h. Following this time, the reaction was quenched with H2O (10 mL), extracted with diethyl ether (3 x 10 mL), dried (Na2SO4) and evaporated in vacuo. The crude residue was purified by flash column chromatography (0-2.5% diethyl ether in petroleum ether) to yield the pyrrole 10 (30 mg, 0.11 mmol, 85%) as a yellow oil. 1H NMR (CDCl3, 400 MHz) δ: 7.40-7.32 (5H, m), 6.98 (2H, d, JF = 8.7 Hz), 6.86 (2H, d, JF = 8.7 Hz), 6.46 (1H, d, JF = 3.2 Hz, JF = 2.0 Hz), 6.04 (1H, d, JF = 2.4 Hz), 4.99 (2H, s), 3.82 (3H, s). 13C NMR (CDCl3, 75 MHz) δ: -165.4. 13C NMR (CDCl3, 125 MHz) δ: 159.0, 152.0 (d, JF = 239.1 Hz), 132.5 (d, JF = 1.6 Hz), 131.8 (d, JF = 6.4 Hz), 130.2, 129.0 (2C), 128.5 (2C), 127.9 (2C), 127.5, 114.1 (2C) 105.5 (d, JF = 27.3 Hz), 97.1 (d, JF = 16.4 Hz), 55.3, 50.2. m/z [EL (+ve)] 281.1 [M]+, HRMS found [M]+ 281.1215, C19H18FNO requires 281.1216. IR (thin film) νmax = 2956, 2837, 1701, 1612, 1512, 1247, 1176 cm⁻¹.

3-Fluoro-1-[(4’-methoxyphenyl)methyl]-2-phenyl-1H-pyrrole, 11. α, δ-Unsaturated lactam 8 (45 mg, 0.15 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Phenyllithium (87 µL, 0.13 mmol, 1.6 M in pentane) was treated with 7.5 mol % Grubbs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0-2.5% diethyl ether in petroleum ether) to yield the pyrrole 11 (50 mg, 0.14 mmol, 93%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.39-7.36 (7H, m), 7.35-7.37 (3H, m), 6.66 (2H, d, JF = 8.8 Hz), 6.55 (2H, d, JF = 8.8 Hz), 6.17 (1H, br s), 5.10 (2H, s), 3.74 (3H, s). 13C NMR (CDCl3, 400 MHz) δ: -165.3. 13C NMR (CDCl3, 125 MHz) δ: 158.5, 149.6 (d, JF = 242.5 Hz), 133.0 (d, JF = 7.1 Hz), 132.9 (d, JF = 1.8 Hz), 130.8, 129.9 (d, JF = 3.3 Hz), 129.5, 129.1 (2C), 128.5 (2C), 128.5 (2C), 127.5, 127.3 (2C), 127.2, 119.1 (d, JF = 21.0 Hz), 113.7 (2C), 98.4 (d, JF = 16.6 Hz), 55.2, 48.3. m/z [EL (+ve)] 357.0 [M]+, HRMS found [M]+ 357.1531, C19H18FNO requires 357.1529. IR (thin film) νmax = 3063, 2955, 2835, 1610, 1512, 1492, 1435, 1247, 1176 cm⁻¹. m.p. 84-86 °C.

2-Butyl-3-fluoro-1-[(4’-methoxyphenyl)methyl]-5-phenyl-1H-pyrrole, 12. α, δ-Unsaturated lactam 8 (38 mg, 0.13 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. n-
Butyllithium (54 µL, 0.13 mmol, 2.5 M in hexanes) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H₂O (10 mL), extracted with diethyl ether (3 x 10 mL), dried (Na₂SO₄) and evaporated in vacuo. The crude residue was purified by flash column chromatography (0-2.5% diethyl ether in petroleum ether) to yield the pyrrole 12 (34 mg, 0.10 mmol, 78%) as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ: 7.22-7.14 (5H, m), 6.74 (4H, m), 5.95 (1H, s), 4.94 (2H, s), 3.71 (3H, s), 2.37 (2H, t, J= 7.6 Hz), 1.43-1.34 (2H, m), 1.25-1.18 (2H, m). 0.78 (3H, t, J= 7.3 Hz). ¹³C NMR (CDCl₃, 470 MHz) δ: -168.0. ¹⁹F NMR (CDCl₃, 470 MHz) δ: -151.2, 1464, 1249 cm⁻¹.

Dialkene (thin film) IR (thin film) vₙ = 337.1842.  IR (thin film) vₙ = 163.0 (s), 152.4 (d, J= 16.1 Hz), 114.1 (2C), 96.7 (d, J= 16.6 Hz), 55.3, 47.1, 31.3 (J= 2.0 Hz), 23.1 (d, Jₚ= 2.6 Hz), 22.4. 3.8. m/z [EI (⁺ve)] 337.2 [M⁺]¹, HRMS found [M⁺]¹ 337.1840, C₈₂H₂₄FNO requires 337.1842.

3-Fluoro-1-[(4'-bromophenyl)methyl]-5-phenyl-2,5-dihydro-1H-pyrrole-2-one, 16a. Diene 15a (110 mg, 0.36 mmol) was treated with 7.5 mol % Grubbs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0-10% EtOAc in petroleum ether) to yield the desired 3-Fluoro-1-[(4'-bromophenyl)methyl]-5-phenyl-2,5-dihydro-1H-pyrrole-2-one, 16a (104 mg, 0.24 mmol, 68%) as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ: 7.31-7.23 (5H, m), 7.09-7.07 (2H, m), 6.20 (1H, d, J = 1.5 Hz), 4.90 (1H, dd, J = 5.5 Hz, J = 2.0 Hz), 3.48 (1H, dd, J = 14.0, 8.7 Hz), 2.46 (1H, dd, J = 14.0, 6.0 Hz), 1.63-1.58 (2H, m), 1.40-1.43 (3H, m), 1.09-1.04 (3H, m), 0.87-0.79 (3H, m). ¹³C NMR (CDCl₃, 470 MHz) δ: -138.4. ¹⁹F NMR (CDCl₃, 470 MHz) δ: -151.2. ¹⁳C NMR (CDCl₃, 125 MHz) δ: 163.3 (d, J = 31.0 Hz), 152.6 (d, J = 279.3 Hz), 134.2, 129.3 (2C), 129.1, 127.4 (2C), 117.9 (d, J = 4.4 Hz), 60.7 (d, J = 5.9 Hz), 46.6, 47.0, 30.9, 30.4, 26.3, 25.7, 25.6. m/z [EI (⁺ve)] 273.2 [M⁺]¹, HRMS found [M⁺]¹ 273.1528, C₁₇H₁₉FNO requires 273.1529.

IR (thin film) vmax = 2922, 2852, 1703, 1666, 1448, 1220, 1116 cm⁻¹.

3-Fluoro-1-(cyclohexylmethyl)-5-phenyl-2,5-dihydro-1H-pyrrole-2-one, 16c. Diene 15c (150 mg, 0.5 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0-7.5% EtOAc in petroleum ether) to yield the desired 3-Fluoro-1-(cyclohexylmethyl)-5-phenyl-2,5-dihydro-1H-pyrrole-2-one, 16c (130 mg, 0.46 mmol, 92%) as a pale yellow oil. ¹H NMR (CDCl₃, 500 MHz) δ: 7.37-7.22 (3H, m), 7.09-7.07 (2H, m), 6.20 (1H, d, J = 1.5 Hz), 4.90 (1H, dd, J = 5.5 Hz, J = 2.0 Hz), 3.48 (1H, dd, J = 14.0, 8.7 Hz), 2.46 (1H, dd, J = 14.0, 6.0 Hz), 1.63-1.58 (2H, m), 1.40-1.43 (3H, m), 1.09-1.04 (3H, m), 0.87-0.79 (3H, m). ¹³C NMR (CDCl₃, 470 MHz) δ: -138.4. ¹⁹F NMR (CDCl₃, 470 MHz) δ: -151.2.

IR (thin film) vmax = 3063, 1710, 1666, 1456, 1220, 1186 cm⁻¹. m.p. 92-94°C.
1-Benzyl-3-fluoro-2-methyl-5-phenyl-1H-pyrrole, 17a. α, β-Unsaturated lactam 16a (33 mg, 0.13 mmol) was reacted with methyllithium (100 µL, 0.14 mmol, 1.4 M in diethyl ether) following General Procedure II. The product was purified by flash column chromatography (0.2-5% diethyl ether in petroleum ether) to yield the pyrrole 17a (29 mg, 0.11 mmol, 86%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.30-7.09 (8H, m), 6.87-6.84 (2H, m), 5.98 (1H, s), 4.99 (2H, s), 1.97 (3H, d, J = 1.6 Hz). 13C NMR (CDCl3, 100 MHz) δ: -127.1, 125.6 (2C), 112.6 (d, J = 10.1 Hz, phenyl-1). 19F NMR (CDCl3, 470 MHz) δ: -169.3. IR (thin film) v_max [EF (+ve)] 343.1 (M+), HRMS found [M+Br] 265.1 (M+) requires 265.1267. IR (thin film) ν_max = 2924, 1662, 1599, 1118 cm⁻¹. m.p. 44-46 °C.

1-Benzyl-3-fluoro-5-(4'-bromophenyl)-2,5-dihydro-1H-pyrrole-2-one, 21a. Diakene 20a (100 mg, 0.31 mmol) was treated with 7.5 mol % Grubs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0.1-10% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam 21a (70 mg, 0.22 mmol, 71%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.35-7.29 (3H, m), 7.14-7.13 (2H, m), 7.03 (2H, d, J = 8.7 Hz), 6.93 (2H, d, J = 8.7 Hz), 6.25 (1H, d, J = 1.6 Hz), 5.15 (1H, d, J = 15.0 Hz), 4.75 (1H, dd, d, J = 5.8 Hz, J = 2.1 Hz), 3.85 (3H, s), 3.61 (1H, d, J = 15.0 Hz). 13C NMR (CDCl3, 100 MHz) δ: 149.3 (d, J = 136.5 Hz), 137.7, 132.6, 131.9 (2C), 130.2 (d, J = 6.8 Hz), 128.8 (2C), 128.6 (2C), 127.3 (2C), 127.3, 121.0, 113.7 (d, J = 22.9 Hz), 96.8 (d, J = 16.5 Hz), 47.2, 8.1 (d, J = 2.1 Hz). m/z [EI (+ve)] 43.4 (M+) requires 43.3072. IR (thin film) ν_max = 2992, 2924, 2680, 1500, 1489, 1367, 1362, 1017, 1010 cm⁻¹. m.p. 98-100 °C.

1-Benzyl-3-fluoro-5-(4'-trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole-2-one, 21b. Diakene 20b (80 mg, 0.22 mmol) was treated with 15 mol % Grubs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0.1-10% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam 21b (70 mg, 0.20 mmol, 88%) as a pale yellow oil. 1H NMR (CDCl3, 400 MHz) δ: 7.58 (2H, d, J = 8.1 Hz), 7.26-7.21 (3H, m), 7.16 (2H, d, J = 8.1 Hz), 7.03-7.01 (2H, m), 6.19 (1H, d, J = 1.2 Hz), 5.09 (1H, d, J = 15.0 Hz), 4.77 (1H, dd, d, J = 4.8 Hz, J = 2.0 Hz), 3.57 (1H, d, J = 15.0 Hz). 19F NMR (CDCl3, 470 MHz) δ: -62.9, -137.2. 13C NMR (CDCl3, 125 MHz) δ: 162.9 (d, J = 31.2 Hz), 152.7 (d, J = 280.9 Hz), 138.1, 136.1, 131.7, 131.4, 129.0 (2C), 128.4 (2C), 128.1, 128.0 (2C), 126.3 (2C, q, J = 3.7 Hz), 118.0 (d, J = 5.0 Hz), 58.7 (d, J = 5.7 Hz), 44.4. m/z [EI (+ve)] 335.0 (M+) requires 335.0932. IR (thin film) ν_max = 2362, 2332, 1718, 1670, 1421, 1325, 1166, 1126, 1066 cm⁻¹.
mmol, 94%) as a pale yellow oil. 1H NMR (CDCl₃, 400 MHz): δ: 7.54 (2H, d, J₉ = 8.4 Hz), 7.36-7.30 (3H, m), 7.13-7.10 (2H, m), 7.00 (2H, d, J₉ = 8.4 Hz), 6.26 (1H, d, J₉ = 1.6 Hz), 5.17 (1H, d, J₉ = 15.0 Hz), 4.76 (1H, d, J₉ = 5.8 Hz), J₉ = 2.2 Hz), 3.62 (1H, d, J₉ = 15.0 Hz). 15F NMR (CDCl₃, 470 MHz): δ: -137.7. 13C NMR (CDCl₃, 125 MHz): δ: 163.2 (d, J₂ = 8.7 Hz), 152.8 (d, J₂ = 15.2 Hz), 7.32-7.30 (1H, m), 1.83-1.69 (2H, m), 1.66-1.54 (3H, m), 1.31-1.18 (2H, m), 1.05-0.97 (3H, m), 0.87-0.77 (1H, m). 19F NMR (CDCl₃, 470 MHz): δ: -136.3, 132.9 (d, J₁ = 15.2 Hz), 136.3, 133.9 (d, J₁ = 2.2 Hz), 132.5 (2C), 129.2 (2C), 128.9 (2C), 128.4 (2C), 128.0, 123.2, 118.1 (d, J₁ = 4.7 Hz), 58.6 (d, J₁ = 5.7 Hz), 44.2. m/z [El (+ve)] 345.1 [M⁺], HRMS found [M⁺] 345.0165. C₂₇H₃₈BrFNO requires 345.0165.

1-Benzyl-3-fluoro-5-cyclohexyl-2,5-dihydro-1H-pyrrole, 22a. Dialkene 20d (100 mg, 0.34 mmol) was treated with 7.5 mol % Grubbs 2nd generation catalyst as described in General Procedure I. The crude product was purified by flash column chromatography (0-5% EtOAc in petroleum ether) to yield the desired 2a,6-unSATurated lactam 21d (90 mg, 0.32 mmol, 95%) as a white solid. 1H NMR (CDCl₃, 400 MHz): δ: 7.28-7.16 (5H, m), 7.10 (2H, d, J₉ = 8.9 Hz), 6.86-6.84 (2H, m), 6.76 (2H, d, J₉ = 8.9 Hz), 5.91 (1H, s), 4.95 (2H, s), 3.71 (3H, s), 1.97 (3H, d, J₁ = 1.6 Hz). 19F NMR (CDCl₃, 470 MHz): δ: -169.6. 13C NMR (CDCl₃, 125 MHz): δ: 158.9, 149.1 (d, J₂ = 235.4 Hz), 138.7, 130.2 (2C), 129.9 (d, J₂ = 3.3 Hz), 128.8 (2C), 127.1, 126.5 (2C), 127.3 (2C), 113.9 (2C), 111.8 (d, J₂ = 24.4 Hz), 96.0 (d, J₂ = 16.4 Hz), 53.5, 47.6, 8.1 (d, J₂ = 2.0 Hz). m/z [El (+ve)] 295.2 [M⁺], HRMS found [M⁺] 295.1372. IR (thin film) νmax = 2929, 1653, 1603, 1454, 1249, 1176 cm⁻¹. m.p. 75-77 °C.

1-Benzyl-3-fluoro-2-methyl-5-[(4'-trifluoromethyl)phenyl]-1H-pyrrole, 22b. α,β-UnSATurated lactam 21b (22 mg, 0.06 mmol) was reacted with methyl lithium (51 µL, 0.07 mmol, 1.4 M in diethyl ether) following general procedure II. The product was purified by flash column chromatography (0-2.5% diethyl ether in petroleum ether) to yield the pyrrole 22b (16 mg, 0.05 mmol, 73%) as a yellow solid. 1H NMR (CDCl₃, 400 MHz): δ: 7.46 (2H, d, J₉ = 8.7 Hz), 7.32-7.17 (5H, m), 6.87-6.85 (2H, m), 6.05 (1H, s), 5.01 (2H, s), 2.00 (3H, d, J₁ = 1.6 Hz). 19F NMR (CDCl₃, 470 MHz): δ: -62.5, -168.5. IR (thin film) νmax = 2922, 1606, 1325, 1166, 1124 cm⁻¹. m.p. 75-77 °C.
2922, 1614, 1496, 1454, 1417, 1363, 1114 cm⁻¹. m.p. 55-57 °C.

1-Benzyl-3-fluoro-2-methyl-5-(2'-phenylethyl)-1H-pyrrole, 22e. α, β-Unsaturated lactam 21e (34 mg, 0.11 mmol) was reacted with methyllithium (91 μL, 0.12 mmol, 1.4 M in diethyl ether) following general procedure II. The product was purified by flash column chromatography (0-2.5% diethyl ether in petroleum ether) to yield the pyrrole 22e (24 mg, 0.08 mmol, 74%) as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ: 7.24-7.08 (6H, m), 7.04-7.00 (2H, m), 6.80-6.76 (2H, m), 5.71 (1H, s), 4.83 (2H, s), 2.76-2.71 (2H, m), 2.64-2.60 (2H, m), 1.97 (3H, br s).

19F NMR (CDCl₃, 470 MHz) δ: -170.5. ¹³C NMR (CDCl₃, 125 MHz) δ: 148.3 (d, JF = 234.1 Hz), 141.4, 138.2 (2C), 128.4 (2C), 128.3 (2C), 127.9 (d, JF = 6.3 Hz), 127.2, 126.1, 125.5 (2C), 110.0 (d, JF = 24.6 Hz), 94.1 (d, JF = 16.8 Hz), 46.5, 35.4, 28.4, 7.9 (d, JF = 2.1 Hz). m/z [M⁺] requires 293.1580. IR (thin film) v_max = 2292, 1614, 1496, 1454, 1417, 1363, 1114 cm⁻¹.

References