Effective and Diastereoselective Preparation of Dispiro[cyclopent-3′-ene]bisoxindoles via Novel [3 + 2] Annulation of Isoindigos and MBH Carbonates

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Supporting Information

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1. General Information

Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance (300 MHz for $^1$H NMR, 75 MHz for $^{13}$C NMR) instrument. Data for $^1$H NMR are reported as chemical shift (ppm, tetramethylsilane as the internal standard), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet), coupling constant (Hz). Data for $^{13}$C NMR are reported as chemical shift. High resolution mass spectra were obtained with the Q-TOF-Premier mass spectrometer. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light.

2. General Procedures for the preparations of Isoindigos 1 and Morita–Baylis–Hillman Carbonates 2

All isoindigos 1 were synthesized according to our previous report. [1]

Morita–Baylis–Hillman carbonates 2 were synthesized as reported method: [2]

Benzaldehyde (1.06 g, 10 mmol), methyl acrylate (1.72 g, 20 mmol) and DABCO (1.25 g, 10 mmol) were stirred for 3-7 days in a round-bottom flask. The reaction was detected by TLC. When completed, 20 mL water was added, and the aqueous phase was extracted with CH$_2$Cl$_2$ (20 mL × 2). The combined organic phase was washed with brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the crude product was further purified by flash column chromatography (petroleum ether : ethyl acetate = 10:1) to obtain the MBH alcohol.

To the solution of MBH alcohol (1 g, 5.4 mmol) and Boc$_2$O (1.62 g, 5.73 mmol) in 10 mL CH$_2$Cl$_2$ was added DMAP (0.12 g, 1.04 mmol) in 2 mL CH$_2$Cl$_2$ dropwise. The mixture was stirred at room temperature for 90 mins and washed with water (20 mL×2). The CH$_2$Cl$_2$ phase was washed with brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the crude product was further purified by flash column chromatography (petroleum ether : ethyl acetate = 15:1) to obtain the MBH carbonates 2.

Other MBH carbonates were synthesized with the same procedures.

Methyl 2-((tert-butoxycarbonyloxy)(phenyl)methyl)acrylate (2a). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.34 (m, 5H), 6.48 (s, 1H), 6.40 (s, 1H), 5.91 (s, 1H), 3.71 (s, 3H), 1.46 (s, 9H)

Methyl 2-((tert-butoxycarbonyloxy)(2-fluorophenyl)methyl)acrylate (2b). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.32 (m, 2H), 7.08 (m, 1H), 7.05 (m, 1H), 6.77 (s, 1H), 6.46 (s, 1H), 5.86 (d, $J = 0.6$ Hz, 1H), 3.71 (s, 3H), 1.46 (s, 9H)
Methyl 2-((tert-butoxycarbonyloxy)(4-fluorophenyl)methyl)acrylate (2c). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.45–7.31 (m, 2H), 7.09–6.92 (m, 2H), 6.44 (s, 1H), 6.40 (d, $J = 0.9$ Hz, 1H), 5.94 (dd, $J = 1.5$, 0.8 Hz, 1H), 3.70 (s, 3H), 1.45 (s, 9H).

Methyl 2-((tert-butoxycarbonyloxy)(2-chlorophenyl)methyl)acrylate (2d). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.57–7.32 (m, 2H), 7.32–7.04 (m, 2H), 6.89 (d, $J = 1.0$ Hz, 1H), 6.48 (t, $J = 0.8$ Hz, 1H), 5.66 (dd, $J = 1.5$, 0.8 Hz, 1H), 3.75 (s, 3H), 1.47 (s, 9H).

Methyl 2-((tert-butoxycarbonyloxy)(3-chlorophenyl)methyl)acrylate (2e). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.39 (s, 1H), 7.33–7.20 (m, 3H), 6.43 (dq, $J = 1.5$, 0.9 Hz, 2H), 5.95 (dd, $J = 1.4$, 0.6 Hz, 1H), 3.72 (s, 3H), 1.47 (s, 9H).

Methyl 2-((tert-butoxycarbonyloxy)(4-chlorophenyl)methyl)acrylate (2f). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.36–7.29 (m, 4H), 6.42 (d, $J = 6.2$ Hz, 2H), 5.94 (d, $J = 1.4$ Hz, 1H), 3.71 (s, 3H), 1.46 (s, 9H).
Methyl 2-((tert-butoxycarbonyloxy)(4-nitrophenyl)methyl)acrylate (2m). \(^1\)H NMR (300 MHz, Chloroform-d) \(\delta\) 8.21 (d, \(J = 6.8\) Hz, 2H), 7.60 (d, \(J = 6.8\) Hz, 2H), 6.53 (s, 1H), 6.47 (s, 1H), 6.03 (s, 1H), 3.73 (s, 3H), 1.47 (s, 9H).

Methyl 2-((tert-butoxycarbonyloxy)(furan-2-yl)methyl)acrylate (2n). \(^1\)H NMR (300 MHz, Chloroform-d) \(\delta\) 7.39 (dd, \(J = 1.7, 1.0\) Hz, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 6.37–6.28 (m, 2H), 6.06 (dd, \(J = 1.4, 0.7\) Hz, 1H), 3.73 (s, 3H), 1.50 (s, 9H).

Butyl 2-((tert-butoxycarbonyloxy)(phenyl)methyl)acrylate (2o). \(^1\)H NMR (300 MHz, Chloroform-d) \(\delta\) 7.44–7.29 (m, 5H), 6.48 (s, 1H), 6.41 (s, 1H), 5.89 (s, 1H), 4.10 (td, \(J = 6.6, 4.8\) Hz, 2H), 1.63–1.50 (m, 2H), 1.46 (s, 9H), 1.37–1.21 (m, 2H), 0.88 (t, \(J = 7.4\) Hz, 3H).

3. Procedure for Gram-Scale [3 + 2] Annulation and the deprotection of [3 + 2] product 3a

The Gram-Scale [3 + 2] Annulation: 3 mmol 1a (1.38 g), 3.6 mmol 2a (1.05 g) and 20 mol% Bu3P was stirred in 25 mL toluene at room temperature under N2 atmosphere, detected by TLC. After the reaction was complete (about 0.17 h), the crude product was directly purified by silica gel chromatography to give the desired [3 + 2] product 3a (1.87 g, 98% yield, HPLC 99.5%).

To a solution of 3a (63.6 mg, 0.1 mmol) in CH2Cl2 (5 mL) was added CF3COOH (1.4 mL, 20 mmol) at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred for 2h. Saturated Na2CO3 aqueous solution (10 mL) was added to quench the reaction, and the resulting mixture was extracted with CH2Cl2 (10 mL×3) and the combined organic layer was washed with brine (20 mL) and dried by anhydrous Na2SO4. After removal of solvent, the crude product was purified by flash column chromatography (PE:EA = 2:1) to afford the product 8 (41.9 mg, 96% yield, HPLC 99.3%).

Anti-1′-ethyl-spiro[4.3′]oxindole-spiro[5.3′]1′′-H-oxindole-cyclopent-2-methoxy carbonyl-3-benzene-1-ene 8: 96% yield, white solid, m.p. 218.6–219.3 °C; \(^1\)H NMR (300 MHz, Chloroform-d) \(\delta\) 9.88 (s, 1H), 9.19 (s, 1H), 7.27–6.37 (m, 1H), 7.16 (d, \(J = 6\) Hz, 1H), 6.66 (m, 6H), 6.47 (m, 3H), 6.36 (m, 1H), 6.31 (m, 1H), 6.07 (m, 1H), 4.98 (d, \(J = 2.5\) Hz, 1H), 3.28 (s, 3H); \(^{13}\)C NMR (75 MHz, Chloroform-d) \(\delta\) 175.2, 174.0, 163.6, 142.4, 141.7, 141.6, 140.2, 135.5, 128.2, 127.9, 127.8, 126.3, 126.2, 126.0, 125.7, 125.0, 124.1, 121.1, 120.9, 108.8, 108.2, 66.8, 64.3, 56.0, 50.5, 39.5, 39.3, 39.0, 38.7, 38.4. HRMS-ESI (m/z): Calcd for C27H30N2O4 (M + H): 437.14958, found: 437.14978.
4. Crystal Information for 3f

Crystal data for 3f (CCDC 1550592):

View of a molecule of 3f with the atom-labelling scheme.
Displacement ellipsoids are drawn at the 30% probability level.

View of the pack drawing of 3f.
Hydrogen-bonds are shown as dashed lines.

Table 1. Crystal data and structure refinement for mo_wlx_rhx1_0m.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>mo_wlx_rhx1_0m</th>
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<tbody>
<tr>
<td>Empirical formula</td>
<td>C37 H35 Cl N2 O8</td>
</tr>
<tr>
<td>Formula weight</td>
<td>671.12</td>
</tr>
</tbody>
</table>
Temperature 100(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group \( \text{P2}_1/c \)
Unit cell dimensions 
\( a = 15.0500(15) \ \text{Å} = 90^\circ. \)
\( b = 15.9438(16) \ \text{Å} = 113.382(2)^\circ. \)
\( c = 15.0274(15) \ \text{Å} = 90^\circ. \)

Volume 3309.8(6) Å\(^3\)
Z 4
Density (calculated) 1.347 Mg/m\(^3\)
Absorption coefficient 0.172 mm\(^{-1}\)
\( F(000) \) 1408
Crystal size 1.080 x 0.510 x 0.310 mm\(^3\)
Theta range for data collection 1.474 to 31.087°.
Index ranges \(-21 \leq h \leq 20, -21 \leq k \leq 22, -21 \leq l \leq 21\)
Reflections collected 36531
Independent reflections 9809 [R(int) = 0.0271]
Completeness to theta = 25.242° 99.8 %
Absorption correction Semi-empirical from equivalents
Refinement method Full-matrix least-squares on \( F^2 \)
Data / restraints / parameters 9809 / 0 / 440
Goodness-of-fit on \( F^2 \) 1.026
Final R indices [I>2sigma(I)] R1 = 0.0410, wR2 = 0.1064
R indices (all data) R1 = 0.0506, wR2 = 0.1126
Extinction coefficient n/a
Largest diff. peak and hole 1.296 and -0.507 e.Å\(^{-3}\)
5. $^1$H and $^{13}$C NMR spectra for related reactants and products

Reactant 2a

Reactant 2b
Reactant $2c$

Reactant $2d$
Reactant 2g

[Chemical structure image]

Reactant 2h

[Chemical structure image]
Reactant 2o

Product 3a
Product 3a' (the diastereomer of 3a)
Product 3c
Product 3d
Product 3i
Product 3j
Product 3k
Product 3l
Product 3n
Product 3o
Product 3p
Product 3q
Product 3r
Product 3t
Product 3w