Supporting Information

for

A two step synthesis of a key unit B precursor of cryptophycins by asymmetric hydrogenation

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Full experimental procedures and detailed analytical data for the synthesis of 10 and 4 including chiral HPLC spectra.
General information

CH$_2$Cl$_2$ was dried over CaH$_2$. Dry methanol was obtained by carefully adding magnesium shavings and a few iodine crystals to an excess of methanol (Caution!) and subsequent heating to reflux. TLC plates were stained by dipping into ammonium heptamolybdate/cerium(IV) sulfate solution [10.0 g (NH$_4$)$_6$Mo$_7$O$_{24}$·4 H$_2$O, 0.4 g Ce(SO$_4$)$_2$, 5.4 mL conc. H$_2$SO$_4$, 180 mL H$_2$O], followed by subsequent heating. All NMR spectra were recorded at 298 K in CDCl$_3$. TMS was used for internal calibration (1H NMR and 13C NMR: 0.00 ppm). IR spectra were obtained on an instrument containing an ATR accessory. The enantiomeric excess (ee) of the asymmetric hydrogenation reaction utilizing [(COD)Rh-(R,R)-Et-DuPhos]BF$_4$ and its enantiomer for comparison was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 9:1, 1 mL/min, 254 nm).

Experimental

(Z)-Methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino)acrylate (10):

According to a slightly modified literature procedure [1] 3-chloro-4-methoxybenzaldehyde (0.449 g, 2.63 mmol) and rac-Boc-α-phosphonoglycine trimethyl ester (9) (1.00 g, 3.36 mmol) were dissolved in dry CH$_2$Cl$_2$ (26 mL) at 0 °C. 1,1,3,3-Tetramethylguanidine (0.496 mL, 0.455 g, 3.95 mmol) was added over a 15 min period. After 4 h at 0 °C the solution was stirred overnight at rt. CH$_2$Cl$_2$ (100
(R)-Methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino)propanoate (4):

According to a slightly modified literature procedure [1] dry and degassed methanol (16 mL) was added to olefin 10 (0.410 g, 1.20 mmol) and [(COD)Rh-(R,R)-Et-DuPhos]BF$_4$ (0.015 g, 0.023 mmol, 1.9 mol %) in a hydrogenation flask. After three purging cycles the initial suspension was stirred under a hydrogen atmosphere (3–6 bar) for 21.5 h in a hydrogenation apparatus. The solvent was removed in vacuo and the catalyst separated from the already highly pure product by column chromatography (hexane/EtOAc: 3:1) to yield ester 4 (0.399 g, 97%, 98% ee) as a
colorless oil. \( R_f \) (hexane/EtOAc: 7:3) = 0.63; HPLC (Chiralpak AD, hexane/2-propanol 9:1, 1 mL/min, 254 nm): \( t_R = 9.8 \) min (4), 11.2 min (ent-4). \([\alpha]_D^{24} = -49 \) (c = 0.78 in CHCl\(_3\); Lit. \([\alpha]_D^{24} = -45 \) [2]). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) [ppm] = 1.43 (s, 9H, NHCO\(_2\)C(CH\(_3\))\(_3\)), 2.96 (dd, \( J = 5.9, 14.1 \) Hz, 1H, CH\(_A^H\)B), 3.06 (dd, \( J = 5.6 \) Hz, 14.0 Hz, 1H, CH\(_A^H\)B), 3.73 (s, 3H, CO\(_2\)CH\(_3\)), 3.88 (s, 3H, C\(_ar\)OCH\(_3\)), 4.52 (m, 1H, C\(\alpha\)H), 4.99 (d, \( J = 7.5 \) Hz, 1H, NH), 6.85 (d, \( J = 8.4 \) Hz, 1H, C\(5\)H), 6.99 (dd, \( J = 2.1 \) Hz, 8.4 Hz, 1H, C\(6\)H), 7.13 (d, \( J = 1.6 \) Hz, 1H, C\(2\)H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) [ppm] = 28.3 (NHCO\(_2\)C(CH\(_3\))\(_3\)), 37.2 (CH\(_A^H\)B), 52.3 (CO\(_2\)CH\(_3\)), 54.4 (C\(\alpha\)H), 56.1 (C\(4\)OCH\(_3\)), 80.1 (C(CH\(_3\))\(_3\)), 112.1 (C\(5\)H), 122.3 (C\(3\)Cl), 128.5 (C\(6\)H), 129.1 (C\(1\)), 131.1 (C\(2\)H), 154.1 (C\(4\)OCH\(_3\)), 155.0 (NHCO\(_2\)C(CH\(_3\))\(_3\)), 172.1 (CO\(_2\)CH\(_3\)).

The \(^1\)H and \(^{13}\)C NMR data are in complete agreement with previously published data, where 4 was synthesized by the chlorination and methylation of D-tyrosine [3]. However, the \(^{13}\)C NMR shift value of the aromatic carbon C\(3\)Cl (122.3 ppm), where the chloro substituent is attached to, disagrees with specifications from two other references: 135.6 ppm [2] and 132.4 ppm [4]. As we have obtained compound 4 according to a completely different route, we are confident that our data is correct.
ESI–MS: \( m/z \) 366.0 \([\text{M+Na}]^+\); 708.6 \([2\text{M+Na}]^+\).

**Elemental analysis:** calculated (%) for \( \text{C}_{16}\text{H}_{22}\text{ClNO}_5 \): C 55.90, H 6.45, N 4.07; found: C 55.74, H 6.31, N 4.00.
$^1$H NMR: (Z)-Methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino) acrylate (10)
$^{13}$C NMR: (Z)-Methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino) acrylate (10)
$^1$H NMR: (R)-Methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino)propanoate (4)
$^{13}$C NMR: (R)-Methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino)propanoate (4)
Chiral HPLC Run: Synthesis of (R)-methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino)propanoate (4)

$t_R = \text{ca. } 9.8\text{ min (4)}$

$t_R = \text{ca. } 11.2\text{ min (ent-4)}$
Chiral HPLC Run: Synthesis of (S)-methyl 3-(3-chloro-4-methoxyphenyl)-2-(tert-butoxycarbonylamino)propanoate (ent-4)

$t_R = \text{ca. 9.8 min (4)}$

$t_R = \text{ca. 11.2 min (ent-4)}$
Chiral HPLC Run: Mixture of 4 and ent-4

$t_R = \text{ca. 9.8 min (4)}$

$t_R = \text{ca. 11.2 min (ent-4)}$
Literature


