Supplementary Information:

Unexpected Epimerization at C_2 in the Horner–Wadsworth–Emmons Reaction of Chiral 2-Substituted-4-oxopiperidines

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General Information

General procedures. Melting points were determined in open capillary tubes using a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 360 FT-IR spectrophotometer, spectra of oils were recorded as thin films on NaCl plates and spectra of solids were recorded as KBr pellets. FT-IR ν_{max} values expressed in cm^{-1} are given for the main absorption bands and prominent peaks. Optical rotations were measured in a cell with a 10 cm path length at 25 ºC using a JASCO P-1020 polarimeter, concentrations are given in g/100 mL. NMR spectra were acquired at 25 ºC in $CDCl_3$ on a Bruker AV-400 spectrometer (^1H, 400 MHz, ^{13}C, 100 MHz). The chemical shifts (δ) are reported in parts per million relative to $CHCl_3$ (δ = 7.26 ppm) for ^1H NMR spectra and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectra. Selective ge-1D NOESY experiments were performed with gradient pulses in the mixing time. Spectra were acquired at 300 K with mixing times of 750 ms and 128 transients per spectrum using the Bruker standard selnogp pulse program. Special precautions such as degassing of the sample were not taken. High resolution mass spectra were obtained using the FAB^+ ionization mode with a 3-NBA matrix.

Reagents and materials. Materials: All reagents for reactions were of analytical grade and were used as obtained from commercial sources with the exception of anhydrous lithium chloride, which was dried under vacuum at 140 ºC overnight before use. Reactions were carried out using anhydrous solvents. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualized using UV light (254 nm) and ethanolic phosphomolybdic acid solution followed by heating. Column chromatography was performed using silica gel (Kiesegel 60, 230–400 Mesh). (*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]-4-piperidone (**2**) was prepared as previously described in the literature[1] but with slight modifications.

(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-*N*-[(*S*)-1-phenylethyl]-5,6-didehydro-4-piperidone (1). To a suspension of 98% zinc (II) iodide (6.1 g, 19.2 mmol) in anhydrous CH_3CN (175 mL) at –20 ºC

under argon was added [(*S*)-*N*-(2,3-dibenzyloxypropylidene)]-[(*S*)-1-phenylethyl]amine (6.5 g, 17.4 mmol) in anhydrous CH_3CN (20 mL). The mixture was stirred for 10 min at –20 ºC. Then 98% Danishefsky's diene (4.5 g, 26.1 mmol) was added and the resulting mixture stirred at –20 ºC for 24 h. The reaction was treated with saturated aqueous $NaHCO_3$ (80 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure and subsequently chromatographed (1st eluent: Et_2O, 2nd eluent: AcOEt) to yield 6.6 g (86%) of compound **1** in diastereomerically pure form. This compound showed identical physical and spectroscopic data to those previously reported.[1]

(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-*N*-[(*S*)-1-phenylethyl]-4-piperidone (2). To a solution of compound **1** (6.6 g, 15 mmol) in anhydrous THF (150 mL) at –78 ºC under argon was added dropwise a 1.0 M solution of L-selectride® in THF (17.2 mL, 17.2 mmol). The mixture was stirred for 48 h at –78 ºC. The reaction mixture was allowed to warm up to 0 ºC and then water (3.5 mL), EtOH (13.8 mL), 2N aqueous NaOH (8.6 mL) and 35% H_2O_2 (13.8 mL) were added sequentially to the reaction mixture. **CAUTION** addition of H_2O_2 must be performed slowly since this oxidative treatment is very exothermic. The aqueous solution was saturated with K_2CO_3 and extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure and subsequently chromatographed (eluent: Et_2O/hexanes 1:1) to yield 5.6 g (85%) of compound **2** in diastereomerically pure form as a white solid (m.p. = 65–66 ºC). This compound showed identical spectroscopic data to those previously reported.[1]

(*E*/*Z*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylene-*N*-[(*S*)-1-phenylethyl]piperidine (3*E*/3*Z*). To a solution of triethyl phosphonoacetate (672 mg, 3 mmol) in anhydrous THF (10 mL) at room temperature under argon was added a 2.0 M solution of LDA in heptane/THF/ethylbenzene (1.75 mL, 3.5 mmol). The mixture was stirred for 10 min at room temperature. A solution of compound **2** (443 mg, 1 mmol) in anhydrous THF (20 mL) was added and the resulting mixture was stirred at room temperature for 14 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure and subsequently chromatographed using Et_2O/hexanes (eluent: Et_2O/hexanes 1:1) to yield a 97/3 mixture of **3*E*/3*Z*** in 97% isolated yield.

(*E*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylene-*N*-[(*S*)-1-phenylethyl]piperidine (3*E*).

From the 97/3 *E*/*Z* mixture. Oil; IR absorptions (pure) ν_{max} 1711, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, ^3J (H,H) = 7.0 Hz, 3H), 1.22 (d, ^3J (H,H) = 6.8 Hz, 3H), 2.12 (dd, ^2J (H,H) = 12.6, ^3J (H,H) = 7.4 Hz, 1H), 2.38–2.62 (m, 4H), 2.90–2.98 (m, 1H), 2.99–3.05 (m, 1H), 3.60 (dd, ^2J (H,H) = 10.9, ^3J (H,H) = 6.9 Hz, 1H), 3.84–3.88 (m, 2H), 4.02 (q, ^3J (H,H) = 6.8 Hz, 1H), 4.07

(q, ^3J (H,H) = 7.0 Hz, 2H), 4.47 (d, ^2J (H,H) = 12.1 Hz, 1H), 4.52 (d, ^2J (H,H) = 12.1 Hz, 1H), 4.58 (d, ^2J (H,H) = 11.8 Hz, 1H), 4.71 (d, ^2J (H,H) = 11.8 Hz, 1H), 5.57 (bs, 1H), 7.14–7.36 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 14.5 (CH_3), 29.4 (CH_2), 36.3 (CH_2), 43.8 (CH_2), 57.3 (CH), 59.2 (CH), 59.5 (CH_2), 71.1 (CH_2), 72.8 (CH_2), 73.5 (CH_2), 79.1 (CH), 114.3 (CH), 126.7 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 138.4 (C), 138.9 (C), 144.8 (C), 160.2 (C), 166.5 (C); HRMS (FAB^+) calcd for $C_{33}H_{40}NO_4$ (MH^+) 514.2957. Found 514.2942.

(*E*/*Z*)-(*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylene-*N*-[(*S*)-1-phenylethyl]piperidine (4*E*/4*Z*).

Epimerization procedure A (HWE-reaction): To a suspension of anhydrous lithium chloride (148 mg, 3.5 mmol) in anhydrous CH_3CN (10 mL) at room temperature under argon was added triethyl phosphonoacetate (784 mg, 3.5 mmol) and DBU (1.52 g, 10 mmol). The mixture was stirred for 10 min at room temperature. A solution of compound **2** (443 mg, 1 mmol) in anhydrous CH_3CN (20 mL) was added and the resulting mixture was stirred at room temperature for 7 d. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure and subsequently chromatographed (1st eluent: Et_2O/hexanes 1:2, 2nd eluent: Et_2O/hexanes 1:1) to yield a 88/12 mixture of **4*E*/4*Z*** in 78% isolated yield.

Epimerization procedure B (From olefines of 2*R* configuration): To a suspension of anhydrous lithium chloride (148 mg, 3.5 mmol) in anhydrous CH_3CN (10 mL) at room temperature under argon were added successively DBU (1.52 g, 10 mmol) and a solution of the compound **3** (513 mg, 1 mmol) in anhydrous CH_3CN (20 mL). The mixture was stirred at room temperature for 7 d. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated under reduced pressure and subsequently chromatographed (1st eluent: Et_2O/hexanes 1:2, 2nd eluent: Et_2O/hexanes 1:1) to yield a 81/19 mixture of **4*E*/4*Z*** in 51% isolated yield.

(*E*)-(*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylene-*N*-[(*S*)-1-phenylethyl]piperidine (4*E*). An analytically pure sample of **4*E*** was isolated by column chromatography (eluent: Et_2O/hexanes 1:2) from the 88/12 mixture of **4*E*/4*Z*** obtained according to method A. Oil; $[\alpha]^{25}_D$ = +38.8 (*c* = 0.68 in $CHCl_3$); IR absorptions (pure) ν_{max} 1734, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, ^3J (H,H) = 7.0 Hz, 3H), 1.25 (d, ^3J (H,H) = 6.7 Hz, 3H), 1.84–1.92 (m, 2H), 2.61–2.74 (m, 2H), 2.94–2.97 (m, 2H), 3.40 (bs, 1H), 3.55 (dd, ^2J (H,H) = 10.7, ^3J (H,H) = 7.5 Hz, 1H), 3.73 (dd, ^2J (H,H) = 10.7, ^3J (H,H) = 2.1 Hz, 1H), 3.78–3.83 (m, 1H), 3.91 (q, ^3J (H,H) = 6.7 Hz, 1H), 4.08 (q, ^3J (H,H) = 7.0 Hz, 2H), 4.42 (d, ^2J (H,H) = 12.1 Hz, 1H), 4.48 (d, ^2J (H,H) = 12.1 Hz, 1H), 4.60 (d, ^2J (H,H) = 12.0 Hz, 1H), 4.69 (d, ^2J (H,H) = 12.0 Hz, 1H), 5.60 (bs, 1H), 7.13–7.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 14.6

(CH_3), 26.9 (CH_2), 41.0 (CH_2), 43.1 (CH_2), 57.1 (CH), 57.9 (CH), 60.5 (CH_2), 72.4 (CH_2), 73.0 (CH_2), 73.3 (CH_2), 79.8 (CH), 124.5 (CH), 126.6 (CH), 127.4 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 131.8 (C), 138.7 (C), 139.1 (C), 144.98 (C), 171.5 (C); HRMS (FAB^+) calcd for $C_{33}H_{40}NO_4$ (MH^+) 514.2957. Found 514.2963.

(*Z*)-(*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylene-*N*-[(*S*)-1-phenylethyl]piperidine (4*Z*). An analytically pure sample of **4*Z*** was isolated by column chromatography (eluent: Et_2O/hexanes 1:2) from the 88/12 mixture of **4*E*/4*Z*** obtained according to method A. Oil; $[\alpha]^{25}_D$ = –20.1 (*c* = 0.69 in $CHCl_3$); IR absorptions (pure) ν_{max} 1733, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, ^3J (H,H) = 7.1 Hz, 3H), 1.27 (d, ^3J (H,H) = 6.6 Hz, 3H), 1.89 (1H, ^2J (H,H) = 16.9 Hz, 1H), 2.38–2.46 (m, 1H), 2.84–3.02 (m, 4H), 3.43–3.49 (m, 1H), 3.54 (dd, ^2J (H,H) = 10.9, ^3J (H,H) = 5.1 Hz, 1H), 3.73 (dd, ^2J (H,H) = 10.9, ^3J (H,H) = 2.3 Hz, 1H), 3.82–3.87 (m, 1H), 3.93 (q, ^3J (H,H) = 6.6 Hz, 1H), 4.04 (q, ^3J (H,H) = 7.1 Hz, 2H), 4.47 (d, ^2J (H,H) = 12.3 Hz, 1H), 4.51 (d, ^2J (H,H) = 12.3 Hz, 1H), 4.52 (d, ^2J (H,H) = 11.7 Hz, 1H), 4.71 (d, ^2J (H,H) = 11.7 Hz, 1H), 5.35 (bs, 1H), 7.08–7.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 19.6 (CH_3), 30.7 (CH_2), 42.6 (CH_2), 45.4 (CH_2), 52.7 (CH), 60.4 (CH), 60.5 (CH_2), 71.6 (CH_2), 72.4 (CH_2), 73.5 (CH_2), 78.8 (CH), 124.1 (CH), 126.5 (CH), 127.3 (CH), 127.3 (CH), 127.3 (CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), 128.2 (CH), 128.3 (C), 128.4 (CH), 138.5 (C), 139.2 (C), 146.7 (C), 171.6 (C); HRMS (FAB^+) calcd for $C_{33}H_{40}NO_4$ (MH^+) 514.2957. Found 514.2971.

References

1. R. Badorrey, C. Cativiela, M. D. Díaz-de-Villegas, J. A. Gálvez, *Tetrahedron*, 1999, **55**, 7601–7612.