

Supplementary material 1: chemical synthesis of analytical standards

α -PHP, α -PHPP, α -PHP-M1, α -PHPP-M1, α -PHP-M2, and α -PHPP-M2 were synthesized in our laboratory based on our previously published methods [11–13], as follows:

α -PHP

To a methylene chloride (CH_2Cl_2) solution of hexanophenone (500 mg), one drop of bromine was added, and this was stirred for 5 min to initiate the reaction. An equivalent of bromine in CH_2Cl_2 solution was added and stirred over 10 min. The solvent was then removed under vacuum to yield 2-bromo-hexanophenone.

To a solution of 2-bromo-hexanophenone (200 mg) in tetrahydrofuran (THF) was added dropwise pyrrolidine in THF, and the mixture was stirred at room temperature overnight. The reaction mixture was treated with 10 % HCl to make it acidic and was then washed with diethyl ether. The aqueous layer was then made basic with 10 % Na_2CO_3 and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 , and evaporated to give crude α -PHP as pale yellow oil. Finally, 10 % HCl MeOH solution was added dropwise to the oil. After removal of the solvent, the crude hydrochloride salt was purified by recrystallization from diethyl ether/2-propanol.

1-Phenyl-2-(pyrrolidin-1-yl)hexane-1-ol (α -PHP-M1)

To a solution of α -PHP (150 mg) in ethanol at 60 °C was added sodium tetrahydroborate, and the mixture was stirred at 60 °C for 1 h. The reaction mixture was evaporated under vacuum, and the residue was treated with 10 % HCl aqueous solution to make it acidic and was then washed with diethyl ether. The aqueous layer was then made basic with 10 % Na_2CO_3 and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 , and evaporated to give diastereomic α -PHP-M1 (referred to α -PHP-M1-D1 and α -PHP-M1-D2 as defined below) as pale yellow oil. The product ratio of the diastereomers was determined by NMR spectroscopy.

Proton NMR

Proton NMR data is presented in the following order: (multiplicity, integration, coupling constants in Hz, assignment).

^1H NMR (400 MHz, CDCl_3 ; compound exists as a mixture of diastereomers, α -PHP-M1-D1 is denoted by \S , α -PHP-M1-D2 denoted by *): δ 7.38–7.29 (m, 4H^\S and 4H^* , ArH), 7.29–7.20 (m, 1H^\S and 1H^* , ArH), 5.00 (d, $J = 3.6$ Hz, 1H^* , $-\text{CH}(\text{OH})-$), 4.18 (d, $J = 9.2$ Hz, 1H^\S , $-\text{CH}(\text{OH})-$), 2.83–2.63 (m, 5H^\S and 4H^* , $-\text{CH}_2\text{-N-CH}_2-$ and $-\text{CH}(\text{OH})\text{CH}_2^\S$), 2.54 (dd, $J = 8.8, 3.6$ Hz, 1H^* , $-\text{CH}(\text{OH})\text{CH}_2-$), 1.85–1.75 (m, 4H^* and 4H^\S , $-\text{NCH}_2\text{CH}_2\text{CH}_2-$), 1.54–1.36 (m, 1H^* and 1H^\S , $-\text{C}(\text{OH})\text{CHCH}_2-$), 1.33–0.92 (m, 5H^* and 5H^\S , $-\text{C}(\text{OH})\text{CHCH}_2-$ and $-(\text{CH}_2)_2\text{CH}_3$), 0.74 (t, $J = 7.2$ Hz, 3H^* , $-\text{CH}_2\text{CH}_3$), 0.70 (t, $J = 7.2$ Hz, 3H^\S , $-\text{CH}_2\text{CH}_3$). The ratios of diastereomers is 1.0 (D1/D2).

High-resolution mass spectrometry (HRMS): calculated for $[\text{M}+\text{H}]^+$ 248.2009, found 248.2007.

α -(2''-Oxo-pyrrolidino)hexanophenone (α -PHP-M2)

To a solution of 2-bromo-hexanophenone (200 mg) in THF at 0 °C was added, dropwise, suspension of 2-pyrrolidinone and NaH (60 %, dispersion in paraffin, Tokyo Chemical Industry, Tokyo, Japan) in THF. The mixture was stirred at 0 °C for 1 h. The reaction mixture was added water and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 , and evaporated under vacuum. The resultant residue was subjected to column chromatography using a silica gel column and an ethyl acetate/*n*-hexane mixture (2:3, v/v) as an eluent to isolate α -PHP-M2. Finally, the solution was concentrated under vacuum to give α -PHP-M2 as pale yellow oil.

Proton NMR

^1H NMR (400 MHz, CD_3OD): δ 8.07–8.02 (m, 2H, ArH), 7.60–7.55 (m, 1H, ArH), 7.49–7.44 (m, 2H, ArH), 5.64 (dd, $J = 9.4, 5.8$ Hz, 1H, $-\text{COCHCH}_2-$), 3.36 (ddd, $J = 9.6, 8.4, 6.4$ Hz, 1H, $-\text{CH}_2\text{NCO-}$), 3.26 (ddd, $J = 9.6, 8.4, 5.6$ Hz, 1H, $-\text{CH}_2\text{NCO-}$), 2.43 (ddd, $J = 17, 9.6, 7.2$ Hz, 1H, $-\text{NCOCH}_2-$), 2.33 (ddd, $J = 17, 9.2, 6.4$ Hz, 1H, $-\text{NCOCH}_2-$), 2.04–1.84 (m, 3H, $-\text{NCOCH}_2\text{CH}_2-$ and $-\text{COCHCH}_2-$), 1.80–1.69 (m, 1H, $-\text{COCHCH}_2-$), 1.49–1.15 (m, 4H, $-\text{CH}_2\text{CH}_2\text{CH}_3$), 0.90 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). HRMS: calculated for $[\text{M}+\text{H}]^+$ 260.1645, found 260.1649.

α -PHPP and α -(2''-oxo-pyrrolidino)heptanophenone (α -PHPP-M2)

α -PHPP and α -PHPP-M2 were synthesized via α -PHP 2-bromo-heptanophenone, according to the method described above for α -PHP and α -PHP-M2, respectively.

Proton NMR of α -PHPP-M2

^1H NMR (400 MHz, CD_3OD): δ 8.07–8.02 (m, 2H, ArH), 7.60–7.54 (m, 1H, ArH), 7.50–7.44 (m, 2H, ArH), 5.64 (dd, $J = 9.2, 5.6$ Hz, 1H, $-\text{COCH}_2\text{CH}_2-$), 3.36 (ddd, $J = 9.6, 8.4, 6.0$ Hz, 1H, $-\text{CH}_2\text{NCO}-$), 3.26 (ddd, $J = 9.6, 8.4, 5.4$ Hz, 1H, $-\text{CH}_2\text{NCO}-$), 2.43 (ddd, $J = 17, 9.4, 7.2$ Hz, 1H, $-\text{NCOCH}_2-$), 2.33 (ddd, $J = 17, 9.4, 6.4$ Hz, 1H, $-\text{NCOCH}_2-$), 2.04–1.84 (m, 3H $-\text{NCOCH}_2\text{CH}_2-$ and $-\text{COCHCH}_2-$), 1.79–1.68 (m, 1H, $-\text{COCHCH}_2-$), 1.41–1.21 (m, 6H, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.88 (t, $J = 6.6$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). HRMS: calculated for $[\text{M}+\text{H}]^+$ 274.1802, found 274.1801.

1-Phenyl-2-(pyrrolidin-1-yl)heptan-1-ol (α -PHPP-M1)

α -PHPP-M1 was synthesized from α -PHPP according to the above mentioned method for α -PHP-M1.

Proton NMR

^1H NMR (400 MHz, CDCl_3 ; compound exists as a mixture of diastereomers, α -PHPP-M1-D1 is denoted by \S , α -PHPP-M1-D2 denoted by *): δ 7.39–7.29 (m, 4H § and 4H*, ArH), 7.28–7.20 (m, 1H § and 1H*, ArH), 5.00 (d, $J = 4.0$ Hz, 1H*, $-\text{CH}(\text{OH})-$), 4.18 (d, $J = 9.2$ Hz, 1H § , $-\text{CH}(\text{OH})-$), 2.82–2.62 (m, 5H § and 4H*, $-\text{CH}_2\text{-N-CH}_2-$ and $-\text{CH}(\text{OH})\text{CH}_2-$), 2.54 (dd, $J = 8.8, 4.0$ Hz, 1H*, $-\text{CH}(\text{OH})\text{CH}_2-$), 1.88–1.75 (m, 4H* and 4H § , $-\text{NCH}_2\text{CH}_2\text{CH}_2-$), 1.53–1.36 (m, 1H § and 1H*, $-\text{C}(\text{OH})\text{CHCH}_2-$), 1.35–0.90 (m, 7H § and 7H*, $-\text{C}(\text{OH})\text{CHCH}_2-$ and $-(\text{CH}_2)_2\text{CH}_3$), 0.77 (t, $J = 7.2$ Hz, 3H*, $-\text{CH}_2\text{CH}_3$), 0.74 (t, $J = 7.2$ Hz, 3H § , $-\text{CH}_2\text{CH}_3$). The ratios of diastereomers is 1.2 (D1/D2). HRMS: calculated for $[\text{M}+\text{H}]^+$ 262.2165, found 262.2163.