Preparation of Pyrrolidine Based PDE4 Inhibitors via Enantioselective Conjugate Addition of α -Substituted Malonates to Aromatic Nitroalkenes.

Paul J. Nichols*, John A. DeMattei, Bradley R. Barnett, Nicole A. LeFur, Tsung-Hsun Chuang, Anthony D. Piscopio, and Kevin Koch

Department of Process Chemistry Research

Array BioPharma

3200 Walnut St.

Boulder, CO 80301

Supporting Information

General Experimental

^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz at 25 °C. LCMS data was acquired using APCI ionization. Enantiomeric excess was determined using either HPLC or SFC. The separation conditions and columns will be provided for each compound where applicable. Optical rotations were measured at room temperature (c 1.00, CHCl_3). Elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, New York. The X-ray crystal structure was solved at the University of Colorado at Boulder.

All starting materials were commercially available and used as received from the manufacturer unless stated otherwise. All solvents were used as received from the manufacturer without any additional manipulation. Chiral ligand **3** was prepared according to the procedure of Davies.¹

Procedures for the 1 Kg Preparation of Common Intermediate 1

(S)-dimethyl 2-(1-(3-(benzyloxy)-4-methoxyphenyl)-2-nitroethyl)-2-methylmalonate (4)

To a 50 L 5-neck flask equipped with an internal temperature probe and overhead stirring was added CHCl_3 (4320 mL), the chiral ligand **3** (54.8 g, 0.154 moles), and $\text{Mg}(\text{OTf})_2$ (45.2 g, 0.14 moles). Stir for a minimum of 20 minutes. Take a Karl Fischer (KF) titration measurement for a baseline reading. The typical baseline reading was between 60 and 140 ppm. Add water (10.4 mL) and stir a minimum of 1 h. The typical KF after water addition was between 300 to 450 ppm. Add CHCl_3 (11.48 L) and 4Å powdered molecular sieves (784 g). Stir for a minimum of 1 h and take a KF measurement. The reaction is considered dry if the KF is below 40 ppm. Continue stirring if not dry. More sieves may be added if necessary. When the reaction is dry bubble N_2 through the mixture to degas for a minimum of 0.5 h. Add the nitrosyrene **2** as a solid (4 Kg, 14.0 moles) over 20 minutes. Next, rinse the funnel with CHCl_3 (250 mL) and add the dimethylmethyl malonate (2.482 Kg, 16.96 moles, 2260.5 mL) over 1 minute to the reaction. Rinse the malonate container with CHCl_3 (250 mL) and add NMM (18.4 g, 0.182 moles, 20 mL) rapidly via syringe. Degas the yellow, heterogeneous mixture by bubbling N_2 through the reaction for a minimum of 1 h. Let the reaction stir for 18 h.

Prepare an HPLC standard sample that is approximately 0.5 mg/mL concentration which contains a molar ratio of 95:5 product:starting material. Use this as an HPLC standard to judge reaction completion. Take a 500 μL sample of the organic and dilute to 100 mL in a volumetric flask. This should provide an approximation of a 0.5 mg/mL soln. If the sample contains less starting material than the standard, judged by area count ratios, stir an additional hour and quench. The reaction has typically been complete in 18-24 h.

To quench the reaction, add water (1.6 L) to the reaction. This results in a mild exotherm (3 °C). Stir for a minimum of 1 h. This allows the sieves to swell and results in a better filtration. Filter the reaction through a bed of Celite (0.5-1 inch) in an extra-course funnel. Wash the organic filtrate with 1:1 brine: H_2O solution (8 L). Separate the organic layer and concentrate on a rotary evaporator to a solid

suspension. Solvent switch to EtOH using 200 proof EtOH (8 L) which also aides in drying the solid prior to isolation. Isolate the yellow solid by filtration and wash the cake with a minimal amount of 200 proof EtOH (500 mL). Air dry the cake for at least 0.5 h and take a sample for baseline ee determination. The initial ee was 86%.

Add the wet cake to a 50 L flask equipped with overhead stirring, internal temperature probe, and a heating mantle. Suspend the solid in 190 proof EtOH (9 gallons) and warm to 50 C. The suspension was stirred at 50 C for 2 hours and allowed to cool to rt over 15 h. Isolate product via filtration. Take a sample for ee ratio determination. Purification serves to remove any starting material, yellow color, and any salts which were carried through from the work-up. Isolated (*S*)-dimethyl 2-(1-(3-(benzyloxy)-4-methoxyphenyl)-2-nitroethyl)-2-methylmalonate **4** as an off-white crystalline solid (5.275 Kg, 12.23 moles, 87% yield, 87% ee). Mp 114-155 °C; R_f =0.34 (2:1 hexane:EtOAc); ^1H NMR (CDCl_3 /400 MHz) δ : 7.39 (br, d, 2H, Bn-H), 7.34 (br t, 2H, Bn-H), 6.78 (d, J =8.4 Hz, 1H, Ar-H), 6.68 (dd, J =2.0, 8.4 Hz, 1H, Ar-H), 6.66 (d, J =2.0 Hz, 1H, Ar-H), 5.13 (d, J =12.30, 1H, -OCH₂-Ar), 5.09 (d, J =12.30, 1H, -OCH₂-Ar), 4.91 (d, J =7.2 Hz, 2H, NO₂-CH₂), 4.00 (t, J =7.2 Hz, 1H, NO₂CH₂CHAr), 3.82 (s, 3H, Ar-OCH₃), 3.67 (s, 3H, -CO₂CH₃), 3.65 (s, 3H, -CO₂CH₃), 1.21 (s, 3H, q. CH₃). ^{13}C NMR (CDCl_3 /400 MHz) δ : 171.53, 170.89, 149.94, 147.99, 136.98, 128.69, 128.03, 127.47, 127.16, 122.02, 115.69, 111.83, 77.75, 71.33, 56.97, 55.97, 53.12, 52.90, 48.10, 20.34; MS (APCI/negative) m/z (rel intensity) 431 (M^+ , 30), 430 (M^+H , 100); Rotation: $[\alpha]^{24}$ =28.7 (c =1, chloroform). Anal. Calcd for C₂₂H₂₅NO₈: C, 61.25; H, 5.84; N, 3.25. Found: C, 61.11; H, 5.96; N, 3.15. Chiralcel OD-RH 4.6x150 mm column at 25 °C with solvents 70% H₂O: 30% ACN (45 min isocratic) at 1.5 mL/min, UV detection @220 nm. ee=87%.

(3*S*,4*S*)-methyl 4-(3-(benzyloxy)-4-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxylate (5)

To a 50 L 5-neck flask equipped with a reflux condenser, temperature probe, mechanical stirrer, and an addition funnel is added the nitroalkane **4** (1953 g, 4.531 moles, 1.00 eq.) followed by 190 proof

EtOH (11.4 L, 5.84 mL/g). Next, cautiously add conc. HCl (5.9 L, 70.8 moles, 15.6 eq.) via an addition funnel over 1h. The addition is very exothermic and the reaction temperature increased from 23 °C to 48 °C.

Begin adding the zinc dust (2069 g, 31.7 moles, 6.98 eq.) portionwise to maintain a temperature of 45 °C to 52 °C. Going above 52 °C causes the incompletely reduced hydroxyl amine to cyclize giving hydroxamic acid. This impurity is not reduced under these conditions. For this scale the zinc addition rate with no external heating is about 250 g/hour. After adding ~75% of the zinc begin monitoring the reaction by HPLC.

When the reaction is judged complete, hydroxylamine completely reduced to amine, the gray suspension is cooled to 0 °C. On this scale, with no external heating or cooling, the addition time is about 9 h. The suspension is diluted with MTBE (12 L) and cooled to 0 °C. Next add aqueous NaOAc (3 Kg diluted to 10 L with H₂O) keeping the temperature below 5 °C. The layers of the biphasic mixture are allowed to stand and separate, this requires ~30 min. (aqueous volume was ~15 L, pH~5). All subsequent washes are done below 5 °C.

The organic layer is washed with aqueous NaOAc (4.5 Kg. diluted to 16 L with H₂O) and the layers slowly separate, ~30 min. (Aqueous volume ~16 L, pH~6, HPLC shows a significant amount of amine in the aqueous). At this point, the HPLC of the opaque yellow organic layer shows >90 area % amine.

The organic layer is next washed with aqueous NaHCO₃ (1 Kg. diluted to 8 L with H₂O) and the layers slowly separate. The addition of NaHCO₃ causes the precipitation of a considerable amount of, presumably, zinc carbonate. This aqueous layer contains a significant amount of amine, pH~6. The organic layer still indicates >90 area % amine

The three aqueous layers are combined (aqueous volume is about 40 L) and extracted with CH₂Cl₂ (4 L). Even though CH₂Cl₂ was used the organic layer was still the upper layer with the aqueous on bottom. This aqueous layer contains very little amine. The organic layer is concentrated to remove the CH₂Cl₂ then this solution is added to the bulk organic solution.

The bulk organic solution is cooled to -10 °C then aqueous NaHCO₃ (1.5 Kg diluted to 12 L with H₂O) is added and the biphasic mixture is stirred overnight. The pH of the mixture should be pH > 9.

When the NaHCO_3 is added more zinc salts precipitate from the reaction. The cyclization is monitored by HPLC.

When the cyclization is complete the zinc salts, which complicate the extractions, are dissolved by adding 6 N HCl (~4 L) until the majority of the salts have dissolved. The layers are separated and the organic layer is dried over Na_2SO_4 (500 g). The aqueous layer, pH~6, did contain some product. HPLC of the organic layer indicates a ratio of 77:18:4 desired diastereomer:undesired diastereomer:hydroxamic acid. By weight % analysis compared with an pure standard the mass of the desired plus undesired diastereomers is 1304 g, 78%. This organic solution is filtered through celite (200 g) to give a clear light brown solution.

The solution was concentrated under reduced pressure to a low volume (~5 L) and then seeded for crystallization. The product is crystallized overnight with stirring at 23 °C. The product is isolated by filtration and the white cake is washed with MTBE (2 L). The product is air dried in the funnel for 3 h then dried in a vacuum oven at 40 °C for 12 h. Isolated 736 g, 44% of (3*S*,4*S*)-methyl 4-(3-(benzyloxy)-4-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxylate **5**, with an HPLC purity of 98% containing 1.5% hydroxamic acid and 0.5% undesired diastereomer. Mp 104-105 °C; ^1H NMR (CDCl_3 /400 MHz) δ : 7.42 – 7.26 (m, 5H, C_6H_5), 6.83 (d, J =8.2 Hz, 1H, Ar-H), 6.71 (dd, J =1.8, 8.2 Hz, 1H, Ar-H), 6.64 (d, J =1.8 Hz, 1H, Ar-H), 6.33 (s, 1H, NH), 5.14 (s, 2H, $-\text{OCH}_2\text{-Ar}$), 4.11 (t, J =7.7 Hz, 1H, NCH_2), 3.68 (dd, J =8.2, 9.0, 1H, NCH_2), 3.51 (dd, J =8.4, 9.4, 1H, NCH_2CHAr), 3.88 (s, 3H, Ar- OCH_3), 3.77 (s, 3H, $-\text{CO}_2\text{CH}_3$), 0.98 (s, 3H, $-\text{CH}_3$). ^{13}C NMR (CDCl_3 /400 MHz) δ : 177.33, 172.82, 149.41, 147.99, 137.10, 129.33, 128.82, 128.16, 127.51, 121.13, 114.66, 111.82, 71.34, 56.19, 56.06, 53.14, 48.05, 44.73, 15.21; MS (APCI/negative) m/z (rel intensity) 370 (M^+H , 100), 310 (20), 280 (25); Rotation: $[\alpha]^{24} = -14.39$ ($c=1$, chloroform). Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.08; H, 6.38; N, 3.82. HPLC conditions: Waters 4.6x50 mm YMC ODS-AQ S3 μm 120 Å; mobile phase H_2O containing 1.0% IPA and 0.1% TFA/ CH_3CN containing 1.0% IPA and 0.05% TFA; gradient: 95:5 to 5:95 over 5 min., flow rate 2 mL/min., monitoring at 220 nm and 254 nm. Retention times: nitroalkane 3.8 min., desired amine 2.5 min., hydroxylamine 2.6 min., hydroxamic acid 2.9 min., cyclized diastereomers 3.0 min. Chiral Separation Conditions: Chiralpak IA (4.6x250mm) column at 25 °C with solvents 10% ethanol: 90% hexanes (30 min isocratic) at 1.0 mL/min, UV detection @220 nm. ee=91%. Retention times: 20.6 minutes and 25.3 minutes for the two enantiomers.

1-((3*S*,4*S*)-4-(3-(benzyloxy)-4-methoxyphenyl)-3-methylpyrrolidin-3-yl)ethanone (6)

To a 50 L round-bottom flask equipped with overhead stirring and an internal temperature probe was added the methyl ester **5** (1.94 Kg, 5.26 moles), toluene (15 L), and *t*-butyl acetate (1.32 Kg, 11.6 moles, 1.53 L). The mixture was then cooled below 0 °C (–5 to –10 °C ideal). The LiHMDS in THF (1 M) was transferred from an 18 Kg cylinder to a 20 L carboy by weight (14.1 Kg, 15.8 moles). The LiHMDS solution was then added to the reaction in portions maintaining a temperature below 15 °C. The addition is exothermic and efficient cooling will shorten the addition time. The addition was done over 80 minutes but can be done in less time with more efficient cooling. Stir for 15 minutes at 10-15 °C and take an HPLC sample by quenching 1 mL of the reaction into 1 mL 1N HCl. Separate the organic layer and dilute 50 µL of the organic with 1 mL ACN. The reaction is considered complete when less than 6% starting material remains. The reaction can also be followed by TLC (4:1 EtOAc:Hexane, UV or PMA visualization, sm R_f =0.23, product R_f =0.39).

To quench the reaction, cool the reaction below 0 °C (–5 to –10 °C) and add 3 N HCl (10 L). The addition is exothermic with temperature increases of 25-30 °C. Following the addition check the pH. If the reaction is still basic, add concentrated HCl (350 mL) until acidic (~pH 4). Transfer mixture to a separatory funnel and separate layers. Wash the organic with brine (10 L) and separate layers. Start concentrating the organic layer by rotary evaporation. Add the acidic wash back to the separatory funnel and add toluene (12 L) to back extract the aqueous layer. Add NaCl (s) (~50 g) to saturate the aqueous layer and separate layers. An emulsion may result in this step. Wash the organic back extraction with brine (5 L) and separate the layers. Add the back extraction to the rotary evaporator after the initial organic layer has been concentrated to effect the removal of the THF and solvent switch into toluene. Concentrate the crude solution to a final volume of approximately 8 L. The final solution is typically a light yellow

color. The aqueous layers were checked by HPLC and no product was observed. The reaction is presumed quantitative and is taken directly into the hydrolysis/decarboxylation reaction.

The crude solution of the β -keto ester (~8 L, 2.386 Kg, 5.26 moles) was pumped into a 50 L round-bottom flask equipped with overhead stirring, an internal temperature probe, reflux condenser, and a heating mantle. Dilute the solution with toluene to ~20 L total. Add pTSA (300 g, 1.58 moles) and heat to 90 °C for a minimum of 5 h. Reactions are typically complete after 5 h heating with total disappearance of starting material. Reaction becomes dark over the course of the reaction. Note: Proper venting must be done to avoid pressure build up during the decarboxylation. The reaction can be monitored by HPLC or TLC (4:1 EtOAc:Hexane, UV or PMA visualization, sm R_f =0.39, product R_f =0.23). HPLC samples were prepared directly from the reaction mixture (50 μ L in 1 mL of ACN). Upon reaction completion, cool the reaction to room temperature.

To work up the reaction, add saturated sodium bicarbonate solution (10 L) to the reaction mixture at RT. Check to make sure aqueous layer is basic. If it is still acidic add more bicarbonate solution until basic. Transfer the mixture to a separatory funnel and separate the layers. Wash the organic layer with brine (10 L) and separate layers. Take a wt% assay sample for HPLC and compare the area count to a known standard to determine crude yield. In this case the wt% yield was 1.64 Kg, 4.6 moles, 88% for compound **6**. Concentrate the toluene solution by rotary evaporation to an oil. Add additional toluene (4 L) and concentrate to assist in drying the crude product. The following reduction steps are water sensitive. Add THF (4 L) and concentrate to approximately 2 L by volume. Finally, add THF (8 L) to make the final crude solution of 1-((3*S*,4*S*)-4-(3-(benzyloxy)-4-methoxyphenyl)-3-methylpyrrolidin-3-yl)ethanone **6** for the reduction (~ 0.5 M soln in THF). In-process HPLC method: YMC ODS-AQ 50x4.6 mm column at ambient temperature using a four minute gradient from 5:95 ACN:H₂O to 95:5 ACN:H₂O at 2 mL/min, UV detection at 220 nm and 254 nm.

(*R*)-1-((3*S*,4*S*)-4-(3-(benzyloxy)-4-methoxyphenyl)-3-methylpyrrolidin-3-yl)ethanol (1)

To a solution of 1-((3S,4S)-4-(3-(benzyloxy)-4-methoxyphenyl)-3-methylpyrrolidin-3-yl)ethanone **6** (0.5 M in 9 L of THF, 1.64 Kg, 4.6 mol,) in a 100 L flask equipped with an overhead stirrer and an internal temperature probe was added Li(t-BuO)₃AlH (1.0 M in THF, 12.06 Kg, 13.34 mol, 2.9 equiv.) slowly via cannula over 50 min at –43 °C (dry ice/acetonitrile) under N₂. The resulting mixture was stirred at –57 °C (dry ice/acetonitrile/acetone) for 1 h (HPLC showed 18% of methyl ketone remained) and then warmed to –4.4 °C (by removing dry ice/acetonitrile/acetone and adding ice when temperature was at –10 °C). The reaction was monitored at –7 °C by HPLC and found that 13 % of methyl ketone remained. LiAlH₄ (1.0 M in THF, 8.4 Kg , 9.2 mol, 2.0 equiv.) was added slowly at –4.4 °C (ice-bath) via cannula over 20 min (temperature changed from –4.4 °C to 13 °C, HPLC showed no methyl ketone remained at 13 °C). The ice bath was removed and the mixture was heated to gentle reflux (61 °C). After heating at 61 °C for 15 h, the reaction was cooled to room temperature and HPLC showed 6% of lactam remained.

The solution was diluted with THF (40 L) and quenched by addition of water (850 mL), 15% NaOH (850 mL), and water (2.5 L) in ice-bath (temperature changed from 6 °C to 13 °C). After quenching, the suspension was stirred for 1.5 h at room temperature and filtered through a table-top funnel equipped with filter paper (Diam. 61 cm). The cake was washed with THF (4 L x 3) and the filtrates were filtered through 3 L fritted Buchner funnel containing a 1 cm pad of Celite. The combined filtrates were assayed by HPLC and found to contain 1114 g, 70% of **1** as a 10:1 mixture of diastereomers.

The filtrates were concentrated on a rotary evaporator until 5 L of solution remained as a slurry. Add 6 L of isopropyl acetate (IPAc) to the slurry. The slurry was then concentrated to 5 L before addition of another 6 L of IPAc. The slurry was then concentrated to approximately 4 L. The suspension was filtered through a fritted Buchner funnel and washed with IPAc/Hexane (2/1, 1.4 L). The solids were dried in a vacuum oven (35 °C) for 2 days to give the common intermediate (*R*)-1-((3S,4S)-4-(3-(benzyloxy)-4-methoxyphenyl)-3-methylpyrrolidin-3-yl)ethanol **1** as a white solid (1011 g, yield 64% of a single diastereomer,). Mp 143-144 °C; MS (APCI/negative) *m/z* (rel intensity) 342 (M⁺H, 100), 252 (55);

Rotation: $[\alpha]^{24}_D = 1.46$ (c=1, chloroform). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.77; H, 8.10; N, 4.11. HPLC conditions: Column- Luna C18 reverse analytical column, 100x4.6 mm, 3 μ particle size; gradient eluent 95/5 to 5/95 water/MeCN containing 0.1% TFA and 0.1% IPA, 1.5 ml/min for 30 min, isocratic 5/95 water/MeCN containing 0.1% TFA and 0.1% IPA, 1.5 ml/min for 3 min, gradient eluent 5/95 to 95/5 water/MeCN containing 0.1% TFA and 0.1% IPA, 1.5 ml/min for 3 min. Total run time 36 min. Integration of absorption was at 206 nm.

Elucidation of Structure by NMR of Common Intermediate (1)

Proof of structure of compound **1** (designated as E11468_001_2 in the following spectra for internal identification purposes) was achieved by multi-dimensional nuclear magnetic resonance spectroscopy (NMR). All NMR spectra were acquired at 25 °C on a Varian Inova 400 MHz spectrometer equipped with a 5 mm Indirect-detection (ID) probe, incorporating pulse shaping and z-axis pulsed field gradient capabilities. The resonance assignments of the compound were obtained using two-dimensional (2D) homo- and hetero-nuclear gDQCOSY, TOCSY, ROESY, gHSQC, and gHMBC experiments. The spectral width in both dimensions was 4186 Hz for homonuclear experiments, and was 17090 Hz in ^{13}C dimension for 1H - ^{13}C gHSQC and 24125 Hz for 1H - ^{13}C gHMBC heteronuclear experiments. All 2D spectra were recorded in phase-sensitive mode (TPPI), or in absolute mode for gHMBC, using 200 (homo) or 128 (hetero) or 400 (hetero) and 1024 complex points in the F1 and F2 dimensions, respectively. TOCSY spectra were acquired with a clean-DIPS1-2 sequence with a mixing time of 80 ms. ROESY experiments were performed using mixing times of 80 ms, 200 ms and 500 ms. The compound was dissolved in $CDCl_3$ containing 0.05% v/v TMS, its chemical shifts were reported in parts per million (ppm, δ scale), relative to the singlet at 0 ppm of TMS for both 1H and ^{13}C .

NMR in the 1H domain exhibited, via integration, 25 non-exchangeable protons portrayed in chemically shifted non-equivalent resonances, consistent with expected ratios. Eight of these protons are in the aromatic region, seventeen are in the aliphatic region. TOCSY experiment classified these protons further into two aromatic groups, two separate aliphatic groups, two isolated aliphatic singlets.

NMR data obtained from the carbon domain revealed 19 separate carbon resonances, which were generated from carbon observed with a fully decoupled proton domain. These carbon signals were subdivided by

gHSQC and gHMBC experiments to reveal three methyls (CH₃), two methines (CH), three methylenes (CH₂), six aromatic methines (=CH), and five quaternary carbons (C), consistent with the proposed structure. NMR experiments gHMBC utilizing the long-range coupling (over 2-bonds) between ¹H-¹³C produced cross correlations consistent with the connections expected from the proposed structure.

The ¹H and ¹³C chemical shifts for compound **1** are given below:

¹H NMR (400 MHz, CDCl₃, 25 °C): δ 7.42 (d, *J*=7.3 Hz, 2H), 7.34 (t, *J*=7.1Hz, 2H), 7.27 (t, *J*=7.3 Hz, 1H), 6.82 (d, *J*=7.8 Hz, 1H), 6.75 (d, *J*=8.1 Hz, 1H), 6.70 (s, 1H), 5.19 (d, *J*=12.9 Hz, 1H), 5.16 (d, *J*=12.9 Hz, 1H), 3.88 (s, 3H), 3.47 (q, *J*=6.4 Hz, 1H), 3.38-3.20 (m, 3H), 3.08 (m, 1H), 2.55 (d, *J*=10.8 Hz, 1H), 1.07 (d, *J*=6.4Hz, 3H), 0.42 (s, 3H). ¹³C NMR (100 MHz): δ 148.3, 147.2, 137.5, 132.8, 128.4, 127.6, 127.1, 121.6, 116.1, 111.5, 72.5, 71.1, 56.0, 54.9, 52.0, 49.8, 49.5, 19.5, 19.0.

Determination of Stereochemistry: The stereochemical assignment of the compound was carried out by ROESY experiments. The strong cross peak between phenyl protons and the single methyl peak of the pyrrolindine ring (instead of between methyl and the methine of the pyrrolindine) suggest the phenyl and the methyl groups are on the same side of the pyrrolidine ring (see figure 4). The stereochemical position of the ethanol to the pyrrolindine was unclear by NOE experiments due to the rotation of the ethanol group.

Note:

TMS: tetramethylsilane

gDQCOSY: gradient-selected Double-quantum filtered Correlation Spectroscopy

TOCSY: Total Spin Correlation Spectroscopy

ROESY: Rotating-frame Nuclear Overhauser Effect Spectroscopy

gHSQC: gradient-selected Heteronuclear Single-Quantum Correlation

gHMBC: gradient-selected Heteronuclear Multiple-Bond Correlation

E11468_001_2

Pulse Sequence: s2pul

Figure 1: Proton spectrum of compound **1** at 400 MHz.

E11468_001_2

Pulse Sequence: gHSQC

Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

INOVA-400 "as400"

Figure 2: ¹H-¹³C gHSQC NMR spectrum of compound **1**. The resonance assignments are as annotated in the figure.

E11468_001_2
Pulse Sequence: gHMBC
Solvent: CDCl₃
Temp. 25.0 C / 298.1 K
INOVA-400 "as400"

Figure 3: ¹H-¹³C gHMBC spectrum of compound **1**.

E11468_001_2

Pulse Sequence: ROESY

No nOe between
8 and 11 protons

Figure 4: ^1H - ^1H ROESY spectrum (200ms) of compound **1**.

(3*S*,4*S*)-methyl 4-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-((*R*)-1-hydroxyethyl)-3-methylpyrrolidine-1-carboxylate (IC86518)

Take up the crude amide (0.585 g, 1.46 mmol) in 15 mL of MeOH and add 500 mg of 10% Pd/C degussa type. Degas and add hydrogen (balloon pressure). Stir for a minimum of 12 h.

Add 20 mL of DMF to the crude intermediate **7** (0.453 g, 1.46 mmol). Add Cs₂CO₃ (0.95 g, 2.93 mmol) and the bromocyclopentane (0.240 g, 1.46 mmol, 0.17 mL) dropwise. Heat the reaction to 50 °C and stir for 1 h. Sample at 1 h and evaluate by HPLC. The product was forming but very slowly. Added an additional 50 uL of bromocyclopentane and more Cs₂CO₃ (0.95 g, 2.93 mmol) and stirred an additional 14 h.

By HPLC the reaction was over 90% complete. The reaction was cooled to rt and filtered through a medium frit to remove any Cs_2CO_3 and salts. The filtrate was concentrated. The concentrate was washed

with water and extracted twice with EtOAc. The material was purified by flash chromatography using 2:1 EtOAc:hexane. After concentrating the appropriate fractions and drying on high vacuum, 409 mg, of IC86518 was isolated as a white foam. This corresponds to a 74% isolated yield over three steps. $R_f=0.48$ (2:1 EtOAc:Hexane); ^1H NMR ($\text{CDCl}_3/400$ MHz) δ : 6.86 – 6.74 (m, 3H, Ar-H), 4.76 (s, 1H, OH), 6.74 (dd, $J=1.8, 8.2$ Hz, 1H, Ar-H), 3.83 (s, 3H, OCH_3), 5.19 (m, 2H, $-\text{OCH}_2-\text{Ar}$), 3.83 – 3.50 (m, 5H, pyrrolidine CH_2), 3.71 (s, 3H, OCH_3), 3.35 – 3.20 (m, 1H, pyrrolidine CH_2), 1.98 – 1.77 (m, 7H, cyclopropyl), 1.60 (s, 2H, cyclopropyl), 1.15 (t, $J=6.8$ Hz, 3H, CHCH_3), 0.75 (s, 3H, CH_3). ^{13}C NMR ($\text{CDCl}_3/400$ MHz) (rotomers) δ : (156.21, 156.18), 149.21, 147.32, 129.47, (121.34, 121.23), (116.27, 116.13), 111.69, 80.61, 69.12, 56.22, (53.16, 52.84), (52.68, 52.64), (49.45, 49.04), (49.28, 48.54), (46.53, 45.87), (33.08, 33.03), 24.33, 19.78, (17.66, 17.60); MS (APCI/negative) m/z (rel intensity) 378 (M^+H , 100), 360 (58); 320 (20), 230 (90); Rotation: $[\alpha]^{24} = 37.30$ ($c=1$, chloroform). Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.68; H, 8.35; N, 3.69. In-process HPLC method: YMC ODS-AQ 50x4.6 mm column at ambient temperature using a four minute gradient from 5:95 ACN: H_2O to 95:5 ACN: H_2O at 2 mL/min, UV detection at 220 nm and 254 nm.

Preparation of Single Crystal X-ray Structure via Derivatization of Common Intermediate 1

1-((3*S*,4*S*)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-((*R*)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl)-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)ethanone

Add the common intermediate **1** (1.0 g, 2.93 mmol) to a 100 mL flask. Add 40 mL of DCM and triethylamine (0.296 g, 2.93 mmol, 0.41 mL). Cool to 0 °C and add (-) menthoxyacetyl chloride (0.716 g,

3.08 mmol). Monitor the reaction by HPLC. The reaction gives complete conversion to product in 30 minutes. The material was concentrated and purified by flash chromatography (1:1 hexanes:EtOAc Rf=0.25). Upon concentration of the appropriate fractions, isolated 1-((3*S*,4*S*)-3-((*R*)-1-hydroxyethyl)-4-(4-methoxy-3-phenoxyphenyl)-3-methylpyrrolidin-1-yl)-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)ethanone as a crude white foam, 0.9 g, 1.7 mmol, 57%. The NMR was clean. The foam was taken directly to a hydrogenation reaction.

Take up the crude 1-((3*S*,4*S*)-3-((*R*)-1-hydroxyethyl)-4-(4-methoxy-3-phenoxyphenyl)-3-methylpyrrolidin-1-yl)-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)ethanone (0.9 g, 1.7 mmol) in 20 mL of MeOH and add 534 mg of 10% Pd/C degussa type. Degas and add hydrogen (balloon pressure). Stir for a minimum of 12 h.

Filter a small amount and check by HPLC. By HPLC there was complete conversion to product. By TLC there was a single spot (EtOAc, Rf=0.75). Filter off the catalyst using filter aid under nitrogen. Concentrate the filtrate to isolate an off white foam. An LCMS showed the product peak. The ¹H NMR was consistent with the desired debenzylated structure. The isolated foam, 1-((3*S*,4*S*)-4-(3-hydroxy-4-methoxyphenyl)-3-((*R*)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl)-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)ethanone weighed 700 mg, 93% crude yield. A portion of the foam was taken crude to the alkylation.

Add 15 mL of DMF to the crude 1-((3*S*,4*S*)-4-(3-hydroxy-4-methoxyphenyl)-3-((*R*)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl)-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)ethanone (0.300 g, 0.670 mmol). Add Cs₂CO₃ (0.88 g, 2.68 mmol) and the bromocyclopentane (0.150 g, 1.01 mmol, 0.108 mL) dropwise. Heat the reaction to 50 °C for a minimum of 14 h.

By HPLC the reaction was complete. The reaction was cooled to rt and filtered through a medium frit to remove any Cs₂CO₃ and salts. The filtrate was concentrated. The concentrate was washed with water and extracted twice with EtOAc. The material was purified by flash chromatography using 2:1 EtOAc:hexane. After concentrating the appropriate fractions and drying on high vacuum, 305 mg, of 1-((3*S*,4*S*)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-((*R*)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl)-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)ethanone as an oil. This corresponds to an 88% yield. Over time the oil solidified. The solid was recrystallized using EtOAc:Heptane to give single X-ray quality crystals.

$R_f=0.51$ (2:1 EtOAc:Hexane); ^1H NMR (CDCl_3 / 400 MHz) (rotamers) δ 6.84-6.74 (m, 3H, Ar-H), 4.75 (m, 1H, CH-cyclopentane), (4.23, 4.21) (d, 13.4 Hz, 1H, CH_2 -carbamate), (4.07, 4.06) (d, 12.8 Hz, 1H, CH_2 -carbamate), 3.97-3.74 (m, 2H, CH_2 -pyrrolidine), 3.83 (s, 3H, OCH_3), (3.77, 3.35) (d, 10.3 Hz, 1H, CH_2 -pyrrolidine), (3.75, 3.58) (m, 1H, CH-pyrrolidine), 3.58 (m, 1H, CH-pyrrolidinyethanol), (3.63, 3.43) (d, 12.1 Hz, 1H, CH_2 -pyrrolidine), 3.23 (td, 10.6, 4.2 Hz, 1H, O-CH-cyclohexane), 2.29 (hepd, 7.0, 2.6 Hz, 1H, CH-isopropylcyclohexane), 2.16 (m, 1H, CH_2 -cyclohexane), 1.95-1.75 (m, 6H, CH_2 -cyclopentane), 1.72-1.58 (m, 4H, CH_2 -cyclopentane, CH_2 -cyclohexane), (1.58, 1.47) (d, 4.9 Hz, 1H, OH), 1.43-1.23 (m, 2H, CH-cyclohexane), 1.16 (t, 7.3 Hz, 3H, CH_3 -ethanol), 0.98 (qd, 13.0, 3.4 Hz, 1H, CH_2 -cyclohexane), 0.95-0.85, (7H, CH_3 -isopropylcyclohexane, CH_3 -cyclohexane, CH_2 -cyclohexane), 0.89-0.82 (m, 1H, CH_2 -cyclohexane), 0.80 (dd, 7.0, 1.0 Hz, 3H, CH_3 -isopropylcyclohexane), (0.76, 0.75) (s, 3H, CH_3 -pyrrolidine). ^{13}C NMR (CDCl_3 /400 MHz) (rotomers) δ : (169.03, 168.89), 149.13, 147.22, (129.32, 128.86), (121.16, 120.92), (116.14, 115.95), (111.65, 111.62), (80.50, 80.46), (68.96, 68.92), (68.54, 68.41), 56.02, (52.85, 52.55), (49.61, 47.33), (49.15, 49.05), (48.31, 48.27), (46.56, 45.01), (39.95, 39.92), 34.45, (32.88, 32.83), 31.49, (25.61, 25.42), (24.10, 24.07), (23.24, 23.13), 22.30, 21.06, (19.67, 19.54), (17.64, 16.87), (16.31, 16.15); MS (ESI/positive) m/z (rel intensity) 516 (M^+ , 100), 378 (55); Rotation: $[\alpha]^{24} = -12.29$ ($c=1$, chloroform). Anal. Calcd for $\text{C}_{31}\text{H}_{49}\text{NO}_5$: C, 72.20; H, 9.58; N, 2.72. Found: C, 72.29; H, 9.74; N, 2.73. In-process HPLC method: YMC ODS-AQ 50x4.6 mm column at ambient temperature using a four minute gradient from 5:95 ACN:H₂O to 95:5 ACN:H₂O at 2 mL/min, UV detection at 220 nm and 254 nm.

X-ray Crystallography. Crystal data and collection parameters and bond lengths and angles can be found in the crystallographic information file (cif).

General Procedure. A crystal of appropriate size was mounted on a glass fiber using Apiezon-T grease, transferred to a Siemens SMART diffractometer/CCD area detector, centered in the beam (Mo-K α ; $\lambda = 0.71073$ Å; graphite monochromator), and cooled to -123(2) °C by a nitrogen-flow low-temperature apparatus. Preliminary orientation matrix and cell constants were determined by collection of 60 10-second frames, followed by spot integration and least-squares refinement. A minimum of a hemisphere of data was collected using 0.3° ω scans. The raw data were integrated and the unit cell parameters refined using

SAINT. Data analysis was performed using XPREP. Absorption correction was applied using SADABS. The data were corrected for Lorentz and polarization effects, but no correction for crystal decay was applied. Structure solutions and refinements were performed on F^2 using the SHELXTL software package.²

Refinement. There is one molecule in the asymmetric unit. Since the molecule is a weak anomalous scatterer and the data is weak, the Flack parameter (-0.8(2.9)) did not refine to an acceptable value. Thus, the absolute structure could not be determined although it is known from earlier studies. Preliminary data indicated a primitive orthorhombic cell. Analysis of the systematic absences of the full data set suggested the space group $P2_12_12_1$ (#19). This choice was confirmed by the successful solution and refinement of the structure. The molecule has is disordered in both the cyclopentane ring and the cyclohexane ring. The cyclopentane ring is completely disordered over two positions with refined occupancies of 44% (C27-C31) and 56% (C27A-C31A). Bond lengths (1,2 and 1,3) within the 5-membered ring were constrained to be equal using the SADI command. The cyclohexane ring and the methyl group are disordered over two positions with occupancies of 54% (C4-C10) and 46% (C4A-C10A). Bond lengths (1,2 and 1,3) within the 6-membered ring were constrained to be equal using the SADI command. All disordered carbon atoms were refined isotropically. All other non-hydrogens were refined anisotropically. Hydrogens were put in idealized positions and were included in structure factor calculations, but were not refined. Bond lengths and angles associated with the disordered portions of the molecule should be considered somewhat unreliable.

Figure 5: X-Ray crystal structure of a menthol derivative of Compound **1**.

Typical Procedure for the Enantioselective Michael Addition of Substituted Malonates with Nitrostyrene. Preparation of **8e:**

Mg(OTf)₂ (28.25 mg, 0.088 mmol), the chiral ligand **3** (34.25 mg, 0.097 mmol), and chloroform (CHCl₃) (2.5 mL) were added to a 25 mL flask. The mixture was stirred for at least 20 minutes followed by the addition of water (6.5 μL). The resulting mixture was stirred for at least 1 hour. Chloroform (7.5 mL) and powdered 4Å molecular sieves (367.5 mg) were added to the reaction mixture, and stirring was continued for a minimum of 1 h. Water content was then determined by Karl Fischer titration. If the water content is ≥40 ppm, stirring was continued and additional molecular sieves were added. When the water content is ≤40 ppm, nitrogen gas is bubbled through the reaction mixture for a minimum of 2 minutes. Nitrostyrene (1.31 g, 8.77 mmol) was added as a solid over 1 minute. Chloroform (1 mL) was added as a rinse, followed by the addition of diethyl allylmalonate (2.13 g, 10.65 mmol, 2.09 mL) over 1 minute via syringe. *N*-methylmorpholine (11.5 mg, 0.114 mmol, 12.5 μL) was added rapidly via pipet. Nitrogen gas

is again bubbled through the reaction mixture for a minimum of 2 minutes. The reaction mixture was stirred under nitrogen for 45 hours at room temperature. The reaction was monitored for completion by HPLC. Water (1 mL) was added to quench the reaction. The mixture was allowed to stir at least 5 minutes to allow the sieves to swell. Next, the reaction mixture was filtered through a bed of Celite. The layers of the filtrate were separated, then the organic layer was washed with brine (15 mL). The organic layer was dried with 5 g of Na₂SO₄ solid. The organic layer was concentrated by rotary evaporation to provide a yellow oil. The oil was purified using flash chromatography by eluting with 9:1 hexanes:EtOAc. Chromatography is necessary to separate the starting material ($R_f=0.4$) and the product ($R_f=0.31$). After concentration under vacuum the desired product **8e** was obtained as a clear oil (2.2 g, 6.29 mmol, 72% yield). The purity by HPLC was >98area % and the ee was 82%.

(S)-diethyl 2-methyl-2-(2-nitro-1-phenylethyl)malonate (8a)

R_f = 0.21 (EtOAc:hexane = 1:9); MP = 69 – 71 °C. ¹H NMR (CDCl₃ / 400 MHz) δ 7.34 – 7.25 (m, 3H, C₆H₅), 7.21 – 7.15 (m, 2H, C₆H₅), 5.05 (d, J = 6.4 Hz, 2H, -CH₂NO₂), 4.25 (q, J = 7.2 Hz, 4H, -OCH₂CH₃), 4.22 – 4.12 (m, 1H, -CHCH₂NO₂), 1.34 (s, 3H, -CH₃), 1.29 (t, J = 7.0 Hz, 3H, -OCH₂CH₃), 1.25 (t, J = 7.0 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 171.2, 170.5, 135.4, 129.3, 129.0, 128.6, 77.9, 62.3, 62.1, 56.9, 48.5, 20.5, 14.2, 14.1; MS (APCI/positive) m/z (rel intensity) 323 (M⁺H, 10), 277 (80), 249 (100); [α]_D²³ = 29.94 (c 1.00, CHCl₃); Anal. Calcd for C₁₆H₂₁NO₆: C, 59.43; H, 6.55. Found: C, 59.28; H, 6.53. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.544 min.; Chiralcel OD 4.6x250 mm column at 35 °C with solvents 95% CO₂ : 5% IPA (10min isocratic) at 2 mL/min, 100 bar, UV detection @206 nm: ee= 93%

(R)-diethyl 2-(tert-butoxycarbonyl)-2-(2-nitro-1-phenylethyl)malonate (8b)

$R_f = 0.23$ (EtOAc:hexane = 1:1); MP = 138 – 140 °C. ^1H NMR (CDCl_3 / 400 MHz) δ 7.32 – 7.21 (m, 5H, C_6H_5), 5.93 (s, 1H, -NH-Boc), 5.50 (dd, $J = 12.7, 2.9$ Hz, 1H, $-\text{CH}_2\text{NO}_2$), 4.72 (t, $J = 12.5$ Hz, 1H, $-\text{CHCH}_2\text{NO}_2$), 4.63 (dd, $J = 12.1, 2.9$ Hz, 1H, $-\text{CHCH}_2\text{NO}_2$), 4.32 – 4.23 (m, 2H, $-\text{OCH}_2\text{CH}_3$), 4.19 – 4.09 (m, 1H, $-\text{OCH}_2\text{CH}_3$), 4.05 – 3.95 (m, 1H, $-\text{OCH}_2\text{CH}_3$), 1.57 – 1.44 (m, 9H, $-\text{OC}(\text{CH}_3)_3$), 1.27 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 1.21 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 / 100 MHz) δ 166.6, 166.5, 155.0, 134.3, 129.2, 128.9, 81.4, 67.8, 63.7, 62.9, 48.5, 28.4, 14.2, 14.0; MS (APCI/negative) m/z (rel intensity) 424 (M^+H , 5), 325 (100); $[\alpha]_D^{23} = 4.08$ (c 1.00, CHCl_3); Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_6$: C, 56.59; H, 6.65. Found: C, 56.81; H, 6.69. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H_2O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.892 min.; Chiralpak IA 4.6x250 mm column at 35 °C with solvents 95% CO_2 : 5% IPA (10 min isocratic) at 2 mL/min, 100 bar, UV detection @206 nm. ee= 65%.

(R)-dimethyl 2-methoxy-2-(2-nitro-1-phenylethyl)malonate (8c)

$R_f = 0.35$ (EtOAc:hexane = 1:4); MP = 67 – 69 °C. ^1H NMR (CDCl_3 / 400 MHz) δ 7.34 – 7.24 (m, 5H, C_6H_5), 5.25 (dd, $J = 13.9, 3.9$ Hz, 1H $-\text{CH}_2\text{NO}_2$), 4.84 (dd, $J = 13.9, 10.0$ Hz, 1H, $-\text{CH}_2\text{NO}_2$), 4.28 (dd, $J = 10.2, 3.9$ Hz, 1H, $-\text{CH}_2\text{NO}_2$), 3.85 (s, 3H, $-\text{CO}_2\text{Me}$), 3.59 (s, 3H, $-\text{CO}_2\text{Me}$), 3.48 (s, 3H, $-\text{OMe}$); ^{13}C NMR (CDCl_3 / 100 MHz) δ 168.2, 167.6, 135.4, 129.6, 128.7, 128.6, 86.3, 56.3, 53.2, 52.5, 49.1; MS (APCI/negative) m/z (rel intensity) 311 (M^+ , 10), 365 (60), 251 (100); $[\alpha]_D^{23} = -5.42$ (c 1.00, CHCl_3); Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_7$: C, 54.02; H, 5.50. Found: C, 53.89; H, 5.56. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50mm with solvents H_2O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.158 min.; Chiralcel OD-RH 4.6x150 mm column at 25 °C with solvents 70% H_2O : 30% ACN (45 min isocratic) at 1.5 mL/min, UV detection @220 nm. ee= 90%.

(R)-diethyl 2-acetamido-2-(2-nitro-1-phenylethyl)malonate (8d)

$R_f = 0.38$ (EtOAc:hexane = 1:5), MP = 108 – 110 °C. ^1H NMR (CDCl_3 / 400 MHz) δ 7.34 – 7.23 (m, 3H, C_6H_5), 7.23 – 7.14 (m, 2H, C_6H_5), 6.68 (s, 1H $-\text{NH}-$), 5.57 – 5.46 (m, 1H, $-\text{CHCH}_2\text{NO}_2$), 4.76 – 4.64 (m, 2H, $-\text{CH}_2\text{NO}_2$), 4.36 – 4.23 (m, 2H, $-\text{OCH}_2\text{CH}_3$), 4.23 – 4.12 (m, 1H, $-\text{OCH}_2\text{CH}_3$), 4.12 – 4.00 (m, 1H, $-\text{OCH}_2\text{CH}_3$), 2.12 (s, $-\text{COCH}_3$), 1.27 (t, $J = 7.6$ Hz, 3H $-\text{OCH}_2\text{CH}_3$), 1.25 (t, $J = 7.6$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 / 100 MHz) δ 170.3, 166.7, 166.0, 134.2, 129.1, 129.0, 128.9, 67.5, 63.9, 63.1, 48.6, 23.3, 14.2, 14.0; MS (APCI/negative) m/z (rel intensity) 366 (M^+ , 10), 289 (15), 193 (20), 141 (100), 102 (60); $[\alpha]_D^{22} = 20.50$ (c 1.00, CHCl_3); Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_7$: C, 55.73; H, 6.05. Found: C, 55.40; H, 6.30. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H_2O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.001 min.;

Chiralpak IA 4.6x250 mm column at 35 °C with solvents 95% CO₂ : 5% IPA (15 min isocratic) at 2 mL/min, 200 bar, UV detection @204 nm. ee= 44%.

(S)-diethyl 2-allyl-2-(2-nitro-1-phenylethyl)malonate (8e)

R_f = 0.13 (EtOAc: hexane = 1:1); oil; ¹H NMR (CDCl₃ / 400 MHz) δ 7.36 – 7.24 (m, 3H, C₆H₅), 7.18 – 7.08 (m, 2H, C₆H₅), 5.82 – 5.68 (m, 1H, -CH₂CHCH₂), 5.18 – 4.92 (m, 4H, -CH₂NO₂ and -CH₂CHCH₂), 4.36 – 4.14 (m, 5H, PhCHCH₂NO₂ and -OCH₂CH₃), 2.57 (dd, J = 14.6, 6.6 Hz, 1H, -CH₂CHCH₂), 2.27 (dd, J = 14.6, 8.0 Hz, 1H, -CH₂CHCH₂), 1.31 (t, J = 7.2 Hz, 3H, -OCH₂CH₃), 1.27 (t, J = 7.2 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 169.9, 169.7, 135.3, 132.1, 129.2, 129.0, 128.7, 120.1, 78.8, 62.2, 60.7, 46.9, 38.6, 14.3, 14.2; MS (APCI/positive) m/z (rel intensity) 350 (M⁺H, 70), 303 (100); [α]_D²³ = 31.96 (c 1.00, CHCl₃); Anal. Calcd for C₁₈H₂₃NO₆: C, 61.88; H, 6.64. Found: C, 61.56; H, 6.80. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.816 min., Chiralcel OD 4.6x250 mm column at 35 °C with solvents 95% CO₂ : 5% IPA (10 min isocratic) at 2 mL/min, 100 bar, UV detection @206 nm. ee= 82%.

(R)-diethyl 2-chloro-2-(2-nitro-1-phenylethyl)malonate (8f)

$R_f = 0.21$ (EtOAc:hexane = 1:8); MP = 96 – 98°C. ^1H NMR (CDCl_3 / 400 MHz) δ 7.41 – 7.25 (m, 5H, C_6H_5), 5.24 (dd, $J = 13.5, 3.3$ Hz, 1H $-\text{CH}_2\text{NO}_2$), 4.99 (dd, $J = 13.5, 10.4$ Hz, 1H, $-\text{CHCH}_2\text{NO}_2$), 4.64 (dd, $J = 10.4, 3.3$ Hz, 1H $-\text{CH}_2\text{NO}_2$), 4.38 – 4.24 (m, 2H, $-\text{OCH}_2\text{CH}_3$), 4.13 – 3.95 (m, 2H - OCH_2CH_3), 1.29 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 1.11 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 / 100 MHz) δ 166.3, 164.6, 133.7, 129.5, 129.3, 128.9, 76.9, 72.1, 63.9, 63.8, 48.4, 14.0, 13.9; MS (APCI/positive) m/z (rel intensity) 344 (M^+H , 5), 322 (100); $[\alpha]_D^{23} = -4.42$ (c 1.00, CHCl_3); Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{ClNO}_6$: C, 52.41; H, 5.28. Found: C, 52.34; H, 5.35. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H_2O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.553 min.; Chiralcel OD 4.6x250 mm column at 35 °C with solvents 95% CO_2 : 5% IPA (10 min isocratic) at 2 mL/min, 100 bar, UV detection @206 nm. ee= 99%.

(R)-diethyl 2-fluoro-2-(2-nitro-1-phenylethyl)malonate (8g)

$R_f = 0.16$ (EtOAc:Heptane = 2:8); MP = 49 – 51 °C. ^1H NMR (CDCl_3 / 400 MHz) δ 7.36 – 7.29 (m, 5H, C_6H_5), 4.92 (dd, $J = 13.3, 4.5$ Hz, 1H, $-\text{CH}_2\text{NO}_2$), 4.81 (dd, $J = 13.3, 10.0$ Hz, 1H, $-\text{CH}_2\text{NO}_2$), 4.57 (ddd, $J = 30.5, 10.0, 4.5$ Hz, 1H, $-\text{CHCH}_2\text{NO}_2$), 4.41 – 4.32 (m, 2H, $-\text{OCH}_2\text{CH}_3$), 4.09 – 3.94 (m, 2H, $-\text{OCH}_2\text{CH}_3$), 1.35 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 1.02 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 / 100 MHz) δ

164.6 (d, $J = 76.7$ Hz, -CO-), 164.3 (d, $J = 77.5$ Hz, -CO-), 133.2, 129.5, 129.2, 129.1, 95.5 (d, $J = 206.3$ Hz, -CF), 75.8, 63.9, 63.2, 47.6, 47.4, 14.1, 13.8; ^{19}F NMR (CDCl_3) δ -172.8 (d, $J = 30.3$ Hz, 1F); (MS (APCI/positive) m/z (rel intensity) 327 (M^+H , 10), 281 (50), 193 (55), 178 (20); $[\alpha]_{\text{D}}^{22} = 28.94$ (c 1.00, CHCl_3); Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{FNO}_6$: C, 55.04; H, 5.80. Found: C, 55.13; H, 5.52. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H_2O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_{R} : 3.332 min.; Chiralpak AD 4.6x250 mm column at 30 °C with solvents 92% CO_2 : 8% IPA (15 min isocratic) at 1 mL/min, 100 bar, UV detection @204 nm. ee= 94%.

(S)-Diethyl 2-(1-(furan-2-yl)-2-nitroethyl)-2-methylmalonate (9a)

$R_f = 0.18$ (EtOAc:hexane = 1:8); oil. ^1H NMR (CDCl_3 / 400 MHz) δ 7.30 (d, $J = 1.8$ Hz, 1H, $\text{C}_4\text{H}_3\text{O}$), 6.52 – 6.26 (m, 1H, $\text{C}_4\text{H}_3\text{O}$), 6.22 (d, $J = 3.3$ Hz, 1H, $\text{C}_4\text{H}_3\text{O}$), 4.98 – 4.93 (m, 2H, $-\text{CH}_2\text{NO}_2$), 4.37 (dd, $J = 8.6$, 5.5 Hz, 1H, $-\text{CHCH}_2\text{NO}_2$), 4.30 – 4.14 (m, 4H, $-\text{OCH}_2\text{CH}_3$), 1.42 (s, 3H, $-\text{CH}_3$), 1.29 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 1.26 (t, $J = 7.2$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 / 100 MHz) δ 170.6, 170.1, 149.3, 143.1, 110.7, 110.2, 76.0, 62.4, 62.2, 56.3, 42.3, 19.6, 14.2, 14.1; MS (APCI/negative) m/z (rel intensity) 314 (M^+H , 20), 298 (60), 267 (100), 239 (80); $[\alpha]_{\text{D}}^{23} = 19.20^\circ$ (c 1.00, CHCl_3); Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_7$: C, 53.67; H, 6.11. Found: C, 53.44; H, 6.23. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H_2O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_{R} : 3.352 min.; Chiralpak AD 4.6x250 mm column at 25 °C with solvents 95% Hexane : 5% EtOH (isocratic) at 0.3 mL/min, UV detection at 206 nm. ee= 92%.

(S)-diethyl 2-methyl-2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate (9b)

R_f = 0.18 (EtOAc:hexane = 1:8); MP = 57 – 58°C. ¹H NMR (CDCl₃ / 400 MHz) δ 7.24 (t, *J* = 3.7 Hz, 1H, C₄H₃S), 6.93 (d, *J* = 2.7 Hz, 2H, C₄H₃S), 4.99 – 4.96 (m, 2H, -CH₂NO₂), 4.54 – 4.49 (m, 1H, -CHCH₂NO₂), 4.28 – 4.18 (m, 4H, -OCH₂CH₃), 1.44 (s, 3H, -CH₃), 1.30 (t, *J* = 7.2 Hz, 3H, -OCH₂CH₃), 1.27 (t, *J* = 7.2 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 170.7, 137.6, 128.6, 127.0, 126.2, 79.2, 62.5, 62.3, 57.3, 44.4, 20.2, 12.1; MS (APCI/negative) *m/z* (rel intensity) 329 (M⁺H, 5), 283 (95), 255 (100); [α]_D²³ = 22.90° (c 1.00, CHCl₃); Anal. Calcd for C₁₄H₁₉NO₆S: C, 51.05; H, 5.81. Found: C, 50.91; H, 5.85. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R: 3.482 min.; Chiralpak AD 4.6x250 mm column at 25 °C with solvents 95% Hexane : 5% EtOH (isocratic) at 0.3 mL/min, UV detection at 206 nm. ee= 92%.

(S)-diethyl 2-(1-(4-bromophenyl)-2-nitroethyl)-2-methylmalonate (9c)

R_f = 0.27 (EtOAc:hexane = 1:7); oil; ¹H NMR (CDCl₃ / 400 MHz) δ 7.44 (d, *J* = 8.6 Hz, 2H, C₆H₅), 7.08 (d, *J* = 8.4 Hz, 2H, C₆H₅), 5.04 – 4.98 (m, 2H, -CH₂NO₂), 4.30 – 4.08 (m, 5H, -CHCH₂NO₂ and -OCH₂CH₃), 1.33 (s, 3H, -CH₃), 1.28 (t, *J* = 7.2 Hz, 3H,

-OCH₂CH₃), 1.26 (t, J = 7.2 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 170.9, 170.3, 134.5, 132.2, 131.0, 122.8, 77.6, 62.4, 62.3, 56.8, 48.0, 20.5, 14.2, 14.1; MS (APCI/negative) m/z (rel intensity) 402 (M⁺H, 12), 357 (100), 327 (98); $[\alpha]_D^{22}$ = 32.14° (c 1.00, CHCl₃); Anal. Calcd for C₁₆H₂₀BrNO₆: C, 47.78; H, 5.01. Found: C, 47.43; H, 4.84. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.821 min.; Chiralcel OD 4.6x250 mm column at 35 °C with solvents 95% CO₂ : 5% IPA (isocratic) at 2 mL/min, 100 bar, UV detection at 206 nm. ee= 94%.

(S)-diethyl 2-methyl-2-(2-nitro-1-(2-nitrophenyl)ethyl)malonate (9d)

R_f = 0.50 (EtOAc:hexane = 1:5), MP = 101 – 103°C. ¹H NMR (CDCl₃ / 400 MHz) δ 7.85 (d, J = 8.0 Hz, 1H, C₆H₅NO₂), 7.58 (t, J = 7.6 Hz, 1H, C₆H₅NO₂), 7.47 (t, J = 8.0 Hz, 1H, C₆H₅NO₂), 7.40 (d, J = 7.8 Hz, 1H, C₆H₅NO₂), 5.19 – 5.08 (m, 2H, -CH₂NO₂), 5.06 – 4.96 (m, 1H, -CHCH₂NO₂), 4.34 – 4.17 (m, 4H, -OCH₂CH₃), 1.39 (s, 3H, -CH₃), 1.31 (t, J = 7.2 Hz, 3H, -OCH₂CH₃), 1.28 (t, J = 7.2 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 170.9, 170.4, 151.8, 133.1, 131.0, 129.4, 128.7, 125.5, 78.1, 62.7, 62.5, 57.1, 40.6, 20.4, 14.2, 14.1; MS (APCI/negative) m/z (rel intensity) 369 (M⁺H, 15), 322 (100); $[\alpha]_D^{23}$ = -24.16° (c 1.00, CHCl₃); Anal. Calcd for C₁₆H₂₀N₂O₈: C, 52.17; H, 5.47. Found: C, 52.39; H, 5.58. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.443 min.; Chiralcel OD 4.6x250 mm column at 45 °C with solvents 95% CO₂ : 5% IPA with 0.01%TEA (isocratic) at 2 mL/min, 120 bar, UV detection at 206 nm. ee= >99%.

(S)-diethyl 2-methyl-2-(2-nitro-1-(4-(trifluoromethoxy)phenyl)ethyl)malonate (9e)

R_f = 0.32 (EtOAc:heptane = 1:9); oil. ¹H NMR (CDCl₃ / 400 MHz) δ 7.28 – 7.22 (m, 2H, C₆H₄), 7.19 – 7.14 (m, 2H, C₆H₄), 5.02 (d, *J* = 7.0 Hz, 2H, -CH₂NO₂), 4.24 (q, *J* = 7.0 Hz, 1H, -CHCH₂NO₂), 4.20 (q, *J* = 7.0 Hz, 2H, -OCH₂CH₃), 4.19 (q, *J* = 7.0 Hz, 2H, -OCH₂CH₃), 1.34 (s, 3H, -CH₃), 1.28 (t, *J* = 7.0 Hz, 3H, -OCH₂CH₃), 1.25 (t, *J* = 7.0 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 170.9, 170.3, 149.4, 134.2, 130.8, 121.2, 120.6 (q, *J* = 258 Hz, -OCF₃), 77.7, 62.4, 62.3, 56.9, 47.9, 20.5, 14.1; ¹⁹F NMR (CDCl₃) δ -58.3 (s, 3F); MS (APCI/positive) *m/z* (rel intensity) 408 (M⁺H, 10), 362 (20), 361 (100), 333 (90); [α]_D²² = -26.00° (c 1.00, CHCl₃); Anal. Calcd for C₁₇H₂₀F₃NO₇: C, 50.13; H, 4.95. Found: C, 50.20; H, 4.93. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R: 3.869 min.; Chiralcel OD 4.6x250 mm column at 35 °C with solvents 95% CO₂ : 5% IPA (isocratic) at 2 mL/min, 100 bar, UV detection at 206 nm. ee = 93 %.

(S)-diethyl 2-methyl-2-(2-nitro-1-(3-(trifluoromethyl)phenyl)ethyl)malonate (9f)

R_f = 0.29 (EtOAc:heptane = 1:9); MP= 47 - 50°C. ¹H NMR (CDCl₃ / 400 MHz) δ 7.60 – 7.54 (m, 1H, C₆H₄), 7.50 – 7.38 (m, 3H, C₆H₄), 5.08 (s, 1H, -CH₂NO₂), 5.06 (d, *J* = 2.3 Hz, 1H, -CH₂NO₂), 4.32 – 4.12 (m, 5H, -CHCH₂NO₂ and -OCH₂CH₃), 1.34 (s, 3H, -CH₃), 1.28 (t, *J* = 7.0 Hz, 3H, -OCH₂CH₃), 1.26 (t, *J* = 7.0 Hz, 3H, -OCH₂CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 170.8, 170.3, 136.7, 132.8, 129.5, 125.8 (dq, *J* = 3.8, 44.5 Hz, 1C, -CF₃), 122.6, 76.9, 62.5, 62.4, 56.9, 48.3, 20.3, 14.1; ¹⁹F NMR (CDCl₃) δ -63.2 (s, 3F); MS (APCI/negative) *m/z* (rel intensity) 392 (M⁺H, 15), 350 (35), 345 (100); [α]_D²³ = -17.80° (c 1.00, CHCl₃); Anal. Calcd for C₁₇H₂₀F₃NO₆: C, 52.18; H, 5.15. Found: C, 52.37; H, 5.25. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA, 0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R: 3.773 min.; Chiralcel OD 4.6x250 mm column at 30 °C with solvents 96% CO₂ : 4% IPA (isocratic) at 2 mL/min, 100 bar, UV detection at 206 nm. ee= 90%.

(S)-diethyl 2-methyl-2-(2-nitro-1-(2-(trifluoromethyl)phenyl)ethyl)malonate (9g)

R_f = 0.18 (EtOAc:heptane = 1:9); MP = 72 – 74 °C; IR (KBr) cm⁻¹ 2995, 1728, 1555; ¹H NMR (CDCl₃ / 400 MHz) δ 7.70 (d, *J* = 7.4 Hz, 1H, C₆H₄), 7.55 (t, *J* = 7.6 Hz, 1H, C₆H₄), 7.47 – 7.37 (m, 2H, 2-CF₃(C₆H₄)), 5.16 (dd, *J* = 12.1, 3.3 Hz, 1H, -CH₂NO₂), 5.02 – 4.94 (m, 1H, -CHCH₂NO₂), 4.65 (dd, *J* = 10.2, 3.3 Hz, 1H, -CH₂NO₂), 4.35 – 4.23 (m, 4H, -OCH₂CH₃), 1.31 (t, *J* = 7.2 Hz, 3H, -OCH₂CH₃), 1.30 (t, *J* = 7.2 Hz, 3H, -OCH₂CH₃), 1.24 (s, 3H, -CH₃); ¹³C NMR (CDCl₃ / 100 MHz) δ 171.3, 170.6, 135.4, 132.6, 130.7 (q, *J* = 29.9 Hz), 128.7, 128.6, 127.2 (q, *J* = 6.1 Hz, -CF₃), 125.5, 122.7, 79.7, 62.6, 62.4, 57.5, 43.6, 20.9, 14.1; ¹⁹F NMR (CDCl₃) δ -56.9 (s, 3F); MS (APCI/negative) *m/z* (rel intensity) 391 (M⁺H, 10), 345 (100); [α]_D²² = -65.62° (c 1.00, CHCl₃); Anal. Calcd for C₁₇H₂₀F₃NO₆: C, 52.18; H, 5.15. Found: C, 52.11; H, 5.19. HPLC conditions: Zorbax-XDB-C18 RX column 4.6x50 mm with solvents H₂O (1%IPA,

0.01%HFBA)/ACN (from v.95:5 to 5:90) at 2.0 mL/min., UV detection @220 nm. t_R : 3.751 min.; Chiralcel OD 4.6x250 mm column at 30 °C with solvents 96% CO₂ : 4% IPA (isocratic) at 2 mL/min, 100 bar, UV detection at 206 nm. ee= 98%.

References:

1. Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753-1754.
2. Sheldrick, G. M. *A Program for Crystal Structure Determination*: Version 5.1, Bruker AXS: Madison, WI, 1998.