A Short Stereoselective Synthesis of (±) Epiasarinin

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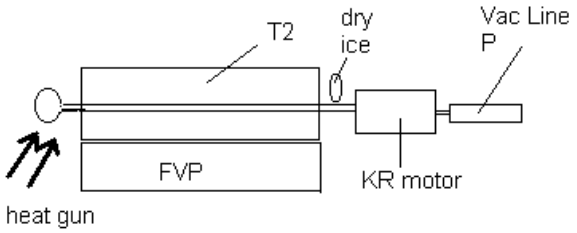
EXPERIMENTAL DATA

Methyl 4,5-epoxy-5-[3',4'-methylenedioxyphenyl]pent-2-enoate **13**

LDA (34mmol) {generated by the addition of nBuLi 1.6M (23.4 ml, 37.4 mmol) to a solution of diisopropylamine (4.75 ml, 34 mmol) in THF (40 ml) at –20°C under N_2} was added dropwise to stirred solution of piperonal (10.2g, 68 mmol) and methyl 4-bromocrotonate (2 ml, 17 mmol) in THF (60 ml) under N_2 at –20°C. Typically, the transfer lasted 1hr for 20 mmol of crotonate. The reaction was stirred for 2h at –20°C and then quenched with sat. aq. NH_4Cl (40ml). The layers were separated and the aqueous layer extracted with ether (3x20 ml). The combined organic layers were then washed with sat. aq. $NaHSO_3$ (40g of $NaHSO_3$ solid), sat. aq. $NaHCO_3$ (20 ml) and brine (3x30 ml), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (ether : petrol (1:3)) afforded the title ester **13** as (43:57) mixture of *syn* and *anti* epoxides (2.95g, 70%). ν_{max} 2992 (epoxide), 2781 (OCH_2O); 1719 (α,β unsaturated COOR); 1179 ($COOCH_3$); δ_H (300MHz) 6.82-6.77 (3.43H; m; Ar-*H* + 3-*H* isomer B); 6.46 (0.57H; dd; J=15.6, 8.1; 3-*H* A); 6.18 (0.57H; d; J=15.6; 2-*H* A); 6.16 (0.43H; d; J=15.6; 2-*H* B); 5.95 (2H; s; OCH_2O); 4.25 (0.57H; d; J=4.2; 5-*H* A); 3.76-3.67 (4H; m; $COOCH_3$ + 4-*H* A + 5-*H* B); 3.41 (0.43H; dd; J= 6.9, 1.8; 4-*H* B); δ_C (100MHz) isomer A: 165.6 (*C-1*); 148.1, 147.7, 141.4, 127.6, 126.2, 119.9 (aromatics); 108.2 (*C-2*); 106.7 (*C-3*); 101.1 (OCH_2O); 59.3 ($COOCH_3$); 57.9 (*C-5*); 51.6 (*C-4*); Isomer B: 166.0 (*C-1*); 147.9, 147.5, 143.8, 129.8, 123.4, 119.9 (aromatics); 108.3 (*C-2*); 105.3 (*C-3*); 101.2 (OCH_2O); 61.1 ($COOCH_3$); 60.3 (*C-5*); 51.7(*C-4*); *m/z* (EI) 248 (12%) (M^+); 135 (100%); *m/z* (CI, NH_3) 266 (20%) (MNH_4^+); 252 (80%); 233 (100%)

Cis 4-Methoxycarbonyl-5-[3',4'-methylenedioxyphenyl]-2,3-dihydrofuran **16c**



A sample of the vinylepoxide **13** (~500mg) was placed in a 25ml rb flask and attached to the fvp apparatus as indicated in the schematic above. The apparatus was then evacuated to ≤ 0.04mbar and the oven heated to 500˚C. When the apparatus had stabilised at these conditions the sample was heated directly with a heat gun. The crude material collected in the cold trap was then purified by flash chromatography (ether : petrol (3:7)) to afford the desired pure *cis* dihydrofuran **16c** (66%) and a small amount of the *trans* isomer **16t** (~8%). For **16c**: Found: C 62.80, H 4.85. $C_{13}H_{12}O_5$ requires C 62.90, H 4.87%. υ_{max} 1733 (COOR); 1250 cm^{-1}; δ_H (300 MHz): 6.82-6.76 (3H; m; aromatics); 6.68 (1H; t J=2.25; 2-*H*); 5.94 (2H; s; OCH_2O); 5.67 (1H; d J=11.1; 5-*H*); 5.04 (1H; t J=2.25; 3-*H*); 4.06 (1H; dt J=2.25, 11.1; 4-*H*); 3.30 (3H; s; OCH_3); δ_C (125 MHz): 171.5 (*C*OOMe); 148.8 (*C-2*); 147.4, 147.3, 131.0, 120.0, 107.8, 106.9 5 (aromatics); 101.0 (O*C*H_2O); 99.3 (*C-3*); 84.3 (*C-5*); 53.4 (*C-4*); 51.6 (O*C*H_3); R_t GC-MS=1130s; *m/z* (EI) 248 (28.6%) ($M^{+\cdot}$); 159 (100%); *m/z* (CI, NH_3) 266 (40%) (MNH_4^+); 249 (100%) (MH^+).

4-Hydroxymethyl-5-[3',4'-methylenedioxyphenyl]-2,3-dihydrofuran **17**

A solution of ester **16c** (400 mg, 1.61 mmol) in ether (10 ml) was introduced slowly to a suspension of $LiAlH_4$ (150 mg, 3.95 mmol, 2.45 eq) in ether (10 ml) at –40 °C under argon. The reaction mixture was stirred 3 h at –40 °C under argon and quenched with distilled water (150 µl), NaOH 3N (150 µl) and finally water (450 µl) before being filtered through a celite bed and concentrated (347 mg, y=98%). The title alcohol was unstable and was used without further purification (storage at -20 °C under argon for a couple of hours only). *Cis* alcohol: δ_H (300 MHz): 6.9-6.8 (3H; m; aromatics); 6.57 (1H; dd J=1.5, 2.7; 2-*H*); 5.97 (2H; s; OCH_2O); 5.54 (1H; d J=9.45; 5-*H*); 4.99 (1H; t J=2.7; 3-*H*); 3.40-3.18 (3H; m; 4-*H*+CH_2OH); δ_C (62.5 MHz): 147.9 (*C-2*); 147.2, 147.0, 131.1, 119.6, 108.2, 106.9 (aromatics); 101.5(*C-3*); 101.1 (O*C*H_2O); 84.6 (*C-5*); 62.6 (*C-4*), 48.7 (*C*H_2OH).

3,7-dioxa-4-methoxy-2,6-bis[3',4'-methylenedioxyphenyl]bicyclo[3.3.0]octane **21a**

A solution of alcohol **17** (347 mg, 1.58 mmol) in DCM (10 ml) was slowly added in a solution of acetal **18a** (800 mg, 4.08 mmol, 2.6 eq) and TMSOTf (42.5 µl, 2.38 mmol, 1.5 eq) in DCM (20 ml) at –40 °C under argon. The resulting solution (dark purple) was stirred for 17 hours at –40 °C, under argon, before being quenched with methanol (2 ml) and then sat. aq. $NaHCO_3$ (15ml). The aqueous layer was extracted with ether (3x15 ml). The combined organic layers were washed with aq. sat. $NaHSO_3$ (5x15 ml), to scavenge any piperonal, and with brine (3x15 ml), dried over $MgSO_4$ and concentrated. The pure *endo* methyl furofuran **21a** (333.7 mg, 55%) was obtained after flash chromatography (petrol:ether (7:3)). Found MNa^+, 407.1139. $C_{21}H_{20}O_7Na$ requires *M*, 407.1107). υ_{max} 2894, 1503, 1489, 1444, 1239, 1098, 1063, 1037cm^{-1}. δ_H (300 MHz): 6.91-6.82 (6H, m, aromatics); 5.98 (2H, s, OC*H*$_2$O); 5.97 (2H, s, OC*H*$_2$O); 5.25 (1H, d J=6, 2-*H*); 4.82 (1H, d J=5.7, 6-*H*); 4.53 (1H, s, 4-*H*); 3.71 (1H, d J=8.4, 8-H_{endo}); 3.50-3.44 (1H, m, 8-H_{exo}); 3.17 (3H, s, OC*H*$_3$), 3.15-3.09 (2H, m, 1-*H*, 5-*H*). δ_C (125 MHz): 147.7, 147.6, 146.8, 146.7, 132.7, 132.4, 120.0, 119.5, 108.5, 108.4, 107.6, 107.1 (aromatics); 105.5 (*C-4*); 101.2 (O*C*H$_2$O); 82.9 (*C-6*); 81.7 (*C-2*); 68.9 (*C-8*); 56.3 (*C-3*); 54.6 (O*C*H$_3$); 48.3 (*C-1*). *m/z* (EI) 384 (32%) (M^+); 203 (42%); 178 (99%); 84 (100%); *m/z* (CI, CH_4) 385 (MH^+); 353; 307; 135; 57 (100%)

3,7-dioxa-2,6-bis[3',4'-methylenedioxyphenyl]bicyclo[3.3.0]octane(Epiasarinin) **1**

Triethylsilane (220 µl, 2.6 mmol, 10 eq) was slowly added to a solution of acetal **21a** (100 mg, 0.26 mmol, 1 eq), in DCM (6 ml) at –40 °C under argon. BF_3•OEt_2 (50 µl, 0.275 mmol, 1.06 eq), was then added under the same conditions and the colour of the solution turned to dark red. The resulting solution was stirred for 15 hours at –40 °C under argon before being poured into a saturated solution of sodium bicarbonate. The aqueous layer was extracted with ether (3x5 ml and the combined organic layers were washed with brine (3x5 ml), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (ether:petrol:triethylamine 1:3:0.1) to afford Epiasarinin (25mg, 27%) and Asarinin (3mg, 3.3%) and a mixture of the two diastereoisomers and starting material (37mg, 40%) which could be recycled. *Epiasarinin* **1** mp = 140-142 °C; Found: C 67.60, H 5.13. $C_{20}H_{18}O_6$ requires C 67.79, H 5.12% υ_{max} 2922, 1460, 1376, 1253 cm^{-1}; δ_H (500 MHz): 6.89 (2H, s, Ar-*H*); 6.82 (4H, s, Ar-*H*); 5.97 (4H, s, OC*H*$_2$O); 4.87 (2H, d, J=5.04, 2-*H*, 6-*H*); 3.72 (2H, d J=9.7, 4-H_{endo}, 8-H_{endo}); 3.52 (2H, pseudo d J=9.45, 6.85, 4-H_{exo}, 8-H_{exo}); 3.13 (2H, m, 1-*H*, 5-*H*); δ_C (125 MHz): 147.6,146.7, 132.1, 119.5, 108.1, 107.1 (aromatics); 100.9 (O*C*H$_2$O); 84.1 (*C-2,C-6*); 68.7 (*C-4,C-8*); 49.5 (*C-1,C-5*); *m/z* (ES^+): 377.1 (MNa^+); 731 (M_2Na^+). *Asarinin* **2** υ_{max} 2922, 1460, 1376, 1253; δ_H (500 MHz): 6.86-6.78 (6H, m, Ar-*H*); 5.96 (2H, s, OC*H*$_2$O); 5.95 (2H, s, O*CH*$_2$O); 4.83 (1H, d J=5.15, 2-*H*); 4.39 (1H, d J=6.86, 6-*H*); 4.09 (1H, d, J=9.3 Hz, 4-

H$_{endo}$); 3.83-3.80 (2H, m, 4-*H*$_{exo}$, 8-*H*$_{endo}$); 3.31-3.29 (2H, m, 1-*H*, 8-*H*$_{exo}$); 2.88-2.83 (1H, m, *5-H*); δ_C (125 MHz):147.9, 147.6, 147.2, 146.5, 135.0, 132.2, 119.6, 118.7, 108.5, 106.5, 106.4 (aromatics); 101.0, 100.9 (O*C*H$_2$O); 87.6 (*C-6*); 82.0 (*C-2*); 70.9 (*C-4*); 69.7 (*C-8*); 54.6 (*C-5*); 50.1 (*C-1*).