Supplementary Material (ESI) for Chemical Communications

Supplementary information for:

"A Ramberg-Bäcklund route to the stilbenoid anti-cancer agents combretastatin A-4 and DMU-212"

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Experimental procedures and selected data for the synthesis of DMU-212

Experimental details

All reagents were purchased from commercial sources and used without further purification. All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere using standard syringe and septum techniques unless otherwise stated. Diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone. Thin layer chromatography was performed on precoated 0.2 mm Merck Kieselgel 60 F_{254} silica plates and compounds were visualized under 245 nm ultraviolet irradiation followed by staining in either alkaline potassium permanganate or ethanolic vanillin solution. Flash column chromatography was performed using Fluka Kieselgel 60 F (220-440 mesh) with the indicated solvents.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded with a ThermoNicolet IR100 spectrophotometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}).

^{1}H and ^{13}C NMR spectra were obtained using either a JEOL 400 MHz spectrophotometer operating at either 400 MHz or 100 MHz or a Bruker AMX 500 spectrometer operating at 500 MHz or 125 MHz, respectively. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard or relative to $CDCl_3$. All *J* values are given in Hz. Assignments are made with the aid of DEPT 135, COSY, HSQC and HMBC experiments.

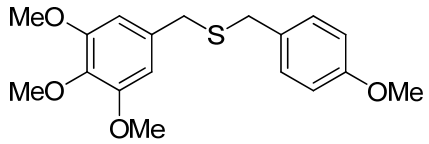
High resolution mass spectra were recorded using a Fisons Analytical VG-Autospec spectrometer operating in chemical ionization (CI), electron ionisation (EI) or fast atom bombardment (FAB) mode, or a Bruker micrOTOF spectrometer operating in electrospray ionization (ESI) mode.

Experimental data

General procedure for the preparation of sulfides

Powdered potassium hydroxide (8.55 mmol) was added to a degassed solution of thiol (7.78 mmol) in ethanol (60 mL) at 0 °C. After stirring for 0.5 h a degassed solution of bromide (7.78 mmol) in ethanol (20 mL) was added and the mixture allowed to warm to room temperature over 12 h. The solvent was removed and the resultant residue purified by flash column chromatography using the eluent specified to give the *title compounds* (41-56%).

3,4,5-Trihydroxy-1-(4'-methoxybenzylsulfanylmethyl)-benzene



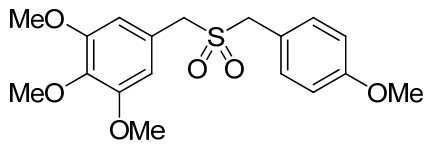
Purification by flash column chromatography using petroleum ether-ethyl acetate (8:2-1:99) as the eluent gave the *title compound* (0.53 g, 73%) as a colourless solid; m.p. 74-76 °C; ν_{max}(film)/cm^{-1} 2937, 1589, 1509, 1459, 1331, 1243, 1177, 1126, 1034 and 832; δ_H (400 MHz, $CDCl_3$) 3.53 (2 H, s, CH_2S), 3.59 (2 H, s, CH_2S), 3.78 (3 H, s, OMe), 3.83 (9 H, s, OMe), 6.48 (2 H, s, H2), 6.84 (2 H, d, *J* 8.6, H3') and 7.20 (2 H, d, *J* 8.6, H2'); δ_C (100 MHz, $CDCl_3$) 35.0 (CH_2, *C*H_2S), 35.8 (CH_2, *C*H_2S), 55.1 (CH_3, OMe), 55.9 (CH_3, OMe), 60.6 (CH_3, OMe), 105.6 (CH, C2), 113.6 (CH, C3'), 129.8 (quat., C1), 129.9 (CH, C2'), 133.6 (quat., C1'), 136.6 (quat., C4), 152.9 (quat., C3) and 158.4 (quat., C4'); *m/z*

(ESI): 352 ($M+NH_4^+$, 100); HRMS (ESI): Found $M+NH_4^+$, 352.1579. $C_{18}H_{26}NO_4S$ requires, 352.1577.

General procedure for the preparation of sulfones 12, 19, 23, 25 and 29

To a stirred solution of sulfide (0.79 mmol) in dichloromethane (30 mL) at 0 °C under an atmosphere of nitrogen was added sodium bicarbonate (0.20 g, 2.37 mmol) and *m*-chloroperoxybenzoic acid (0.55 g, 1.58 mmol). The mixture was allowed to warm to room temperature and was stirred for 12 h before removal of the solvent and purification of the resultant residue by flash column chromatography using the eluent specified to give the *title compounds* (67-94%).

3,4,5-Trihydroxy-1-(4'-methoxybenzylsulfonylmethyl)-benzene 29



Purification by flash column chromatography using dichloromethane-ethyl acetate (9:1-6:4) as the eluent gave the *title compound* **29** (0.42 g, 78%) as a yellow solid; m. p. 130-133 °C; ν_{max}(film)/cm^{-1} 2939, 2839, 1593, 1511, 1465, 1310 (SO_2), 1251, 1123 (SO_2), 1033, 912, 837 and 731; δ_H (400 MHz, $CDCl_3$) 3.72 (3 H, s, OMe), 3.76 (6 H, s, OMe), 3.77 (3 H, s, OMe), 3.99 (2 H, s, CH_2S), 4.06 (2 H, s, CH_2S), 6.50 (2 H, s, H2), 6.83 (2 H, d, *J* 8.6, H3') and 7.22 (2 H, d, *J* 8.6, H2'); δ_C (100 MHz, $CDCl_3$) 55.2 (CH_3, OMe), 56.0 (CH_3, OMe), 57.5 (CH_2, *C*H_2S), 57.7 (CH_2, *C*H_2S), 60.7 (CH_3, OMe), 107.8 (CH, C2), 114.2 (CH, C3'), 119.1 (quat., C1), 122.6 (quat., C1'), 131.9 (CH, C2'), 138.2 (quat., C4), 153.2 (quat., C3) and 160.0 (quat., C4'); *m/z* (ESI): 384 ($M+NH_4^+$, 100); HRMS (ESI): Found $M+NH_4^+$, 384.1463. $C_{18}H_{26}NO_6S$ requires, 384.1475.

General procedure for the Ramberg-Bäcklund reaction of sulfones 12, 19, 23, 25 and 29

Method 1: Meyers conditions

Sulfone (0.55 mmol) was dissolved in carbon tetrachloride (3.66 mL), *tert*-butyl alcohol (3.66 mL) and water (0.66 mL), and powdered potassium hydroxide (34 mg, 60 mmol) added. The mixture was heated under reflux for 12 h and diluted with ethyl acetate (10 mL). Hydrochloric acid (10%, 10 mL) was added and the aqueous layer extracted with ethyl acetate (4 x 15 mL). The combined organic extracts were dried over magnesium sulphate, filtered and the solvent removed. The resultant residue was purified by flash column chromatography using the eluent specified to give the *title compounds* (38-70%).

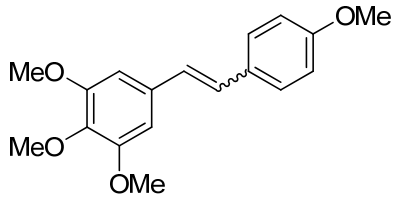
Method 2: Chan conditions

To a stirred suspension of sulfone (0.52 mmol), *tert*-butyl alcohol (2.08 mL) and potassium hydroxide on alumina (1.04 g) in dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen, was added dropwise dibromodifluoromethane (0.19 mL, 2.08 mmol). The mixture was allowed to slowly warm to room temperature over 12 h before removal of the solvent and purification of the resultant residue by flash column chromatography using the eluent specified to give the *title compounds* (24-81%).

Method 3: Franck conditions

To a stirred suspension of sulfone (0.24 mmol), *tert*-butyl alcohol (0.98 mL) and potassium hydroxide on alumina (0.49 g) under an atmosphere of nitrogen was added 1,2-dibromo-1,1,2,2-tetrafluoroethane (0.12 mL, 0.98 mmol). The mixture was, heated at reflux for 12 h before removal of the solvent and purification of the resultant residue by flash column chromatography using the eluent specified to give the *title compounds* (53-89%).

(*E*)- and (*Z*)-1-[2'-(4''-methoxyphenyl)vinyl]-3,4,5-trimethoxybenzene 27 and 30



Purification by flash column chromatography using dichloromethane-ethyl acetate (9:1) as the eluent gave an inseparable mixture of (*E*)- and (*Z*)-isomers of the title compounds **27** and **30** (***Meyers conditions***: 62 mg, 38%, (*E*):(*Z*) 42:58; ***Chan conditions***: 74 mg, 47%, (*E*):(*Z*) 91:9; ***Franck conditions***: 65 mg, 89%, (*E*):(*Z*) 97:3) as a colourless solid; **(*E*)-isomer 27**: recyrstallisation from ethanol gave colourless crystals (87%) of pure **(*E*)-27** m.p. 157-158 °C (lit.[1] m.p. 160-161 °C); δ_H (400 MHz, $CDCl_3$) 3.82 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.91 (6 H, s, OMe), 6.71 (2 H, s, H2), 6.89 (1 H, *J* 16.1, H1' or H2'), 6.89 (2 H, d, *J* 8.8, H3''), 6.97 (1 H, d, *J* 16.1, H1' or H2') and 7.44 (2 H, d, *J* 8.8, H2''); δ_C (100 MHz, $CDCl_3$) 55.3 (CH_3, OMe), 56.0 (CH_3, OMe), 60.9 (CH_3, OMe), 103.1 (CH, C2), 114.1 (CH, C3''), 126.5 (CH, C1' or C2'), 127.6 (CH, C3''), 127.7 (CH, C1' or C2'), 129.9 (quat., C1''), 133.4 (quat., C1), 137.5 (quat., C4), 153.3 (quat., C3) and 159.2 (quat., C4''); **(*Z*)-isomer 30**: δ_H (400 MHz, $CDCl_3$) 3.68 (6 H, s, OMe), 3.77 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.41 (1 H, d, *J* 12.7, H1' or H2'), 6.49 (2 H, s, H2), 6.53 (1 H, d, *J* 12.7, H1' or H2'), 6.78 (2 H, d, *J* 8.8, H3'') and 7.23 (2 H, d, *J* 8.8, H2''); δ_C (100 MHz, $CDCl_3$) 55.2 (CH_3, Me), 55.8 (CH_3, OMe), 60.9 (CH_3, OMe), 105.8 (CH, C2), 113.5 (CH, C3''), 128.6 (CH, C1' or C2'), 129.4 (CH, C1' or C2'), 129.6 (quat., C1''), 130.2 (CH, C2''), 132.9 (quat., C1''), 137.0 (quat., C4), 152.8 (quat., C3) and 158.6 (quat., C4''). This data was in agreement with that reported in the literature.[2]

References

1. J. W. Cook and L. L. Engel, *J. Chem. Soc.*, **1940**, 198.
2. M. Cushman, D. Nagarathnam, D. Gopal, A. K. Chakraborti, C. M. Lin and E. Hamel, *J. Med. Chem.*, **1991**, *34*, 2579.