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Enantioselective Synthesis of Natural Combretastatin

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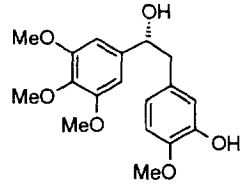
Abstract: In a process which appears to be general for the enantioselective synthesis of oxysubstituted 1,2-diarylethanols, a 4-methoxy-3-silyloxyphenyllithium, obtained by bromine-lithium exchange from the corresponding aryl bromide and *t*-butyllithium, added selectively at the b-carbon of (*S*)-2,3,4-trimethoxyphenyloxirane, elaborated from the corresponding styrene *via* Sharpless asymmetric dihydroxylation, to afford an adduct from which natural (-)-combretastatin was obtained by desilylation. Copyright © 1996 Elsevier Science Ltd

Combretastatin **1** is among the first and biologically most active compounds isolated from *Combretrum Caffrum*, a plant used in the traditional medicine of a wide area of South Africa. Because of its high anti mitotic and anti leukaemic activity and the relatively simple structure, combretastatin **1** has become the lead compound in a number of extensive studies of structure-activity relationship aimed at the discovery of new anti cancer drugs.[1] As a result of this interest, many oxysubstituted 1,2-diarylethanols have been prepared mobilising the whole armamentary of synthetic methods applicable to this class of compounds. Nevertheless, most of 1,2-diphenylethanol derivatives studied as combretastatine analogues have been tested as their racemates and the relationship between activity and absolute configuration is largely unknown. Enantiomerically pure (-)-combretastatin **1** has been obtained synthetically only on a small scale from the racemate by chromatographic separation on a chiral stationary phase.[2]



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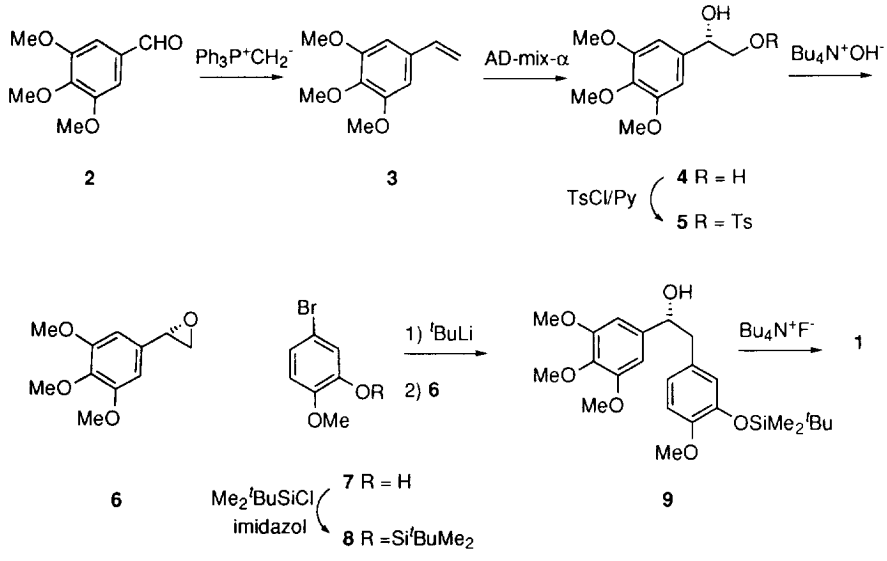
We wish to here report the first enantioselective synthesis of **1** which, in our opinion, should be of wide scope in the preparation of enantiomerically pure combretastatin analogues and, more generally, of enantiomerically pure 1,2-diarylethanols. Our approach adopts the very popular and effective Sharpless asymmetric *cis*-dihydroxylation[3] to introduce the absolute configurations and the regioselective opening of an aryloxirane by an aryllithium for the construction of the carbon framework.[4]

The trimethoxybenzaldehyde **2** was almost quantitatively converted to the styrene derivative **3** by Wittig olefination with triphenylmethylenephosphorane. *cis*-Dihydroxylation of **3** according to the Sharpless procedure using AD-mix-a[3] gave the diol **4** (97% yield) which afforded the aryloxirane **6** in 94% yield by monotosylation

followed by base induced β-elimination of *p*-toluenesulfonic acid from the intermediate hydroxytosylate **5**. The bromophenol **7**[5] was in turn protected as its ^{t}butyldimethylsilylether **8**, which was then subjected to bromine-lithium exchange with two equivalents of ^{t}BuLi; lithiated **8** added cleanly to **6** affording the adduct **9** in 75 % yield as the sole addition product, not contaminated by any of the other possible isomers arising from the attack of the organometallic derivative to the benzyl carbon of **6** or to the phenyacetaldehyde derived by rearrangement of **6** (which are typical competing mode of addition of organometallic compounds to aryloxiranes).[6] The e. e. of **9** (97%, as determined by HPLC on a chiral stationary phase) matches closely the typical values of enantiomeric purity obtained in the Sharpless asymmetric dihydroxylation of styrene derivatives, thus demonstrating the stereospecificity of the reaction between the aryllithium reagent and **6**. Removal of silyl protecting group from **9** by treatment with tetrabutylammonium fluoride afforded (-)-combretastatin **1**, whose ^{1}H-NMR and specific rotation are in perfect agreement with those reported for the natural compound **1**.[7] If the stereochemistry of the hydroxylation of styrene **3** is no exception to the general enantioselectivity rule observed with Sharpless AD reagents,[3] the above synthesis constitutes a confirmation of the absolute stereochemistry of natural **1** whose attribution was based thus far on circular dichroism studies.[7]

In conclusion, a novel entry to 1,2-diarylethanols enabling the control of their absoute stereochemistry has been established, which is exemplified with the enantioselective synthesis of natural combretastatin **1**.

Scheme



Experimental. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) specta were run on a Bruker AC 200 spectrometer, samples being dissolved in $CDCl_3$. Melting points were taken with a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. For chromatographies, the flash technique was applied,[8] eluting with mixtures of hexane (H) and ethyl acetate (EA). Dry solvents were obtained by distillation from sodium powder under nitrogen.

3,4,5-Trimethoxystyrene 3. To a stirred suspension of methyltriphenylphosphonium bromide (6.4 g, 17.9 mmol) in dry tetrahydrofuran (40 mL) butyllithium (17.9 mmol, 11.18 mL of a 1.6 M hexane solution) was added dropwise followed, after 15 min, by 3,4,5-trimethoxybenzaldehyde **2** (3 g, 15.3 mmol). The progress of the reaction was monitored by TLC (H/EA 4:1); after 1 h strring at room temperature the reaction was complete. The reaction mixture was partitioned between ether and water; the upper organic phase was washed with brine, dried and evaporated to affors a residue from which **3** (2.97 g, 100 % yield) was obtained by chromatography (H/EA 4:1) as an oil; ^{1}H NMR δ: 3.85 (s, 3H), 3.87 (s, 6H), 5.20 (dd, *J* = 0.6 and 10.8 Hz, 1H), 5.66 (dd, *J* = 0.6 and 17.5 Hz, 1H), 6.63 (dd, *J* = 10.8 and 17.5 Hz, 1H), 6.63 (s, 2H); ^{13}C NMR δ: 56.60, 61.45, 103.81, 113.80, 133.88, 137.33, 138.54, 153.86. Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.32; H, 6.97.

***(S)*-1-(3,4,5-Trimethoxyphenyl)-1,2-ethanediol 4.** A mixture containing ADmix-α[3] (Aldrich, 15 g) and the styrene **3** (2.3 g, 11.8 mmol) in a 1:1 ^{t}butanol/water (10 mL) was stirred in an ice-water bath for 18 h. Solid sodium sulfite (15 g) was then added and the mixture, after 30 min stirring at the room temperature, was partitioned between ether and brine; the upper organic phase was dried and evaporated to leave a residue from which pure **4** (2.58 g, 96% yield) was obtained by chromatography (3% MeOH in 2:3 H/EA) as an oil wich solidified on standing: mp 75-78 °C; ^{1}H NMR δ: 3.62-3.70 (m, 2H), 3.80 (s, 3H), 3.82 (s, 6H), 4.71 (dd, *J* = 3.4 and 7.8 Hz, 1H), 6.56 (s, 2H); ^{13}C NMR δ: 56.61, 61.38, 68.71, 75.31, 103.49, 137.13, 137.76, 153.74; $[\alpha]_D$+36.92 (c= 2.13, $CHCl_3$). Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.9; H, 7.1. Found: C, 57.7; H, 7.3.

***(S)*-1-(3,4,5-Trimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)ethanol 5.** *p*-Toluenesulfonyl chloride (1.9 g, 10 mmol) was added to a ice-cold solution of the diol **4** (2.3 g, 10 mmol) in pyridin (3 mL). After 2 h, a few drops of water were added to dissolve the precipiate formed and after 15 min the mixture was partitioned between ether and ice-water containing 3 mL of concentrated hydrogen chloride. The organic phase was washed with water and then with brine, dried, and evaporated to afford a residue from which pure **5** (3.64 g, 95 %) was obtained by chromatography (H/EA 2:3) as an oil which solidified on standing: mp 83-84 °C; ^{1}H NMR δ: 2.44 (s, 3H), 3.81 (s, 9H), 3.99-4.17 (m, 2H), 4.91 (m, 1H), 6.52 (s, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR δ: 22.22, 56.65, 61.36, 72.54, 74.83, 103.60, 128.48, 130.49, 133.11, 134.70, 138.31, 145.69, 153.90; $[\alpha]_D$ +39.36 (c= 1.77, $CHCl_3$); Anal. Calcd. for $C_{18}H_{22}O_7S$: C, 56.5; H, 5.8. Found: C, 56.3; H, 6.0.

***(S)*-3,4,5-Trimethoxyphenyloxirane 6.** A solution of the monotosylate **5** (2 g, 5.22 mmol) in methylene chloride (30 mL) and a solution of sodium hydroxide (0.64 g, 16 mmol) and tetrabutylammonium hydrogen sulfate (100 mg) water (5mL) was stirred for 3 h. The mixture was diluited with ether and the organic phase was washed with brine, dried, and evaporated to afford a residue from which pure **6** (1.07 g, 97 % yield) was obtained by chromatography (H/EA 1:1) as an oil which solidified on standing: mp 47.5-49 °C; ^{1}H NMR δ: 2.74 (dd, *J* = 2;5.6 and 5.6 Hz, 1H), 3.11 (dd, *J* = 4.0 and 5.6 Hz, 1H), 3.81 (dd, *J* = 2.5 and 4.0 Hz, 3.83 (s, 3H), 3.86 (s, 6H), 6.51 (s, 2H); ^{13}C NMR δ: 51.61, 53.00, 56.58, 61.30, 102.71, 133.77, 138.38, 154.02; $[\alpha]_D$ +15.48 (c= 1.80, $CHCl_3$); Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7. Found: C, 62.9; H, 6.6.

1-Bromo-3-^{t}butyldimethylsilyloxy-4-methoxybenzene 8. Bromophenol **7**[4] (2 g, 9.85 mmol) was allowed to react with ^{t}butyldimethylsily chloride (1.5 g, 10 mmol) and imidazole (1.36 g, 20 mmol) in DMF (5 mL) for 16 h at room temperature. The mixture was partitioned between hexane and water; the organic phase was washed with water, dried and evaporated to afford pure **8** (2.62 g, 98 % yield) as an oil. The analytical sample was distilled bulb to bulb: bp 180-5 °C/0.1 torr. ^{1}H NMR δ: 0.15 (s, 6H), 0.99 (s, 9H), 3.77 (s, 3H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 1.7 Hz, 1H), 7.20 (dd, *J* = 8.4 and 1.7 Hz, 1H); ^{13}C NMR δ: -4.12, 19.00, 26.21, 56.14, 112.88, 113.74, 124.62, 124.97, 146.51, 150.99; Anal. Calcd. for $C_{13}H_{21}BrO_2Si$: H 6.7 C 49.2 ; Found: H, 6.8 C, 50.0.

***(R)*-2-(3-^{t}Butyldimethylsilyloxy-4-methoxy)phenyl-1-(3,4,5-trimethoxyphenyl)ethan-ol 9.** To a solution of silylated bromophenol **7** (1.6 g, 5.05 mmol) in dry tetrahydrofuran (30 mL) stirred under

nitrogen at -78 °C was added ^{t}butyllithium (10.1 mmol, 5.9 mL of a 1.7 M pentane solution). After 1 h epoxide **6** (1.0 g, 4.7 mmol) was added and the solution allowed to warm up to the room temperature over 3 h. After 12 h, the reaction mixture was partitioned between ether and water; the organic phase was washed with brine, dried and evaporated to afford a residue from which **9** (1.59 g, 75 % yield) was obtained after chromatography (H/EA 2:1) as an oil; ^{1}H NMR δ: 0.12 (s, 6H), 0.97 (s, 9H), 2.85-2.90 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 3.84 (s, 6H), 4.75 (dd, J = 5.4 and 7.8 Hz, 1H), 6.55 (s, 2H), 6.69-6.80 (m, 3H); ^{13}C NMR δ: -4.12, 18.93, 26.24, 45.73, 56.03, 56.53, 61.30, 75.97, 103.31, 112.57, 122.71, 123.20, 128.84, 130.89, 137.48, 140.19, 145.36, 150.23, 153.56; $[\alpha]_D$ -11.94 (c= 3.40, $CHCl_3$) (lit.[3] $[\alpha]_D$ -33.3). The e. e. (97.3 %) was determined by HPLC on a Chiracel OD-H column (25 cm, 0.46 cm i. d.) eluting with hexane/2-propanol 1:9. Anal. Calcd. for $C_{24}H_{36}O_6Si$: C, 64.2; H, 8.1; Found: C, 64.0; H, 8.3.

***(R)*-2-(3-hydroxy-4-methoxy)phenyl-1-(3,4,5-trimethoxyphenyl)ethanol (combretastatin) 1.** To a solution of the silylated alcohol **8** (1 g, 2.2 mmol) in tetrahydrofuran (15 mL) tetrabutylammonium fluoride (2.3 mmol, 2.3 mL of a 1 M terahydrofuran solution) was added. After 2 h the solution was partitioned between ether and diluite hydrochloric acid; the organic phase was washed with brine, dried and evaporatred to afford a residue from which pure **1** (0.72 g, 98% yield) was obtained by recrystallisation from ether hexane as a colorless solid: mp 128-130 °C (lit.[7] 129-131 °C); ^{1}H NMR δ: 2.85-3.03 (m, 2H), 3.84 (s, 3H), 3.85 (s, 6H), 3.86 (s, 3H), 4.77 (dd, J = 4.8 and 8.3 Hz, 1H), 6.58 (s, 2H), 6.67 (dd, J = 2.0 and 8.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H); ^{13}C NMR δ: 46.20, 56.65, 56.74, 61.50, 76.08, 103.37, 111.35, 116.14, 121.63, 131.79, 137.77, 140.28, 146.11, 146.30, 153.82; $[\alpha]_D$ -8.51 (c= 2.4, $CHCl_3$) (lit.[7] $[\alpha]_D$ -8.51 (c= 1.41, $CHCl_3$)). Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.7; H, 6.6. Found: C, 64.8; H, 6.5.

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