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# Enrichment, Characterization and Absolute Configuration of the Enantiomers of 1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol

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The racemate and enriched enantiomers of 1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol have been obtained via reduction of the respective ketone with $LiAlH_4$ and with $BH_3$ in the presence of oxazaborolidines. Enriched enantiomers were characterized by $^1H$ NMR spectroscopy, together with the Eu-*d*-(hfbc)$_3$ reagent, and by polarimetry. The absolute configuration was obtained by $^1H$ and $^{13}C$ NMR spectroscopy from the (*S*)-MTPA esters. The configuration of the esters was optimized by force-field calculation.

In our earlier study on the biologically active compounds obtained from the stilbenes of the bark of Picea abies some combretastatin-like compounds were prepared.[1] Among these was obtained the antileukemia-active 1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol (**1**) in very low yield. To confirm the structure and activity as well as the possible activity dependence on the stereostructure of **1** we have synthesized it as a racemic mixture as well as in both enantiomeric forms.

There are not many enantiomer characterizations of this type of compound reported in the literature. Pettit *et al.* have synthesized the natural (−)-combretastatin but they obtained the enantiomers via a semipreparative HPLC technique.[2] We preferred the asymmetric reduction of the intermediate ketone **10** (Scheme 1).[3]

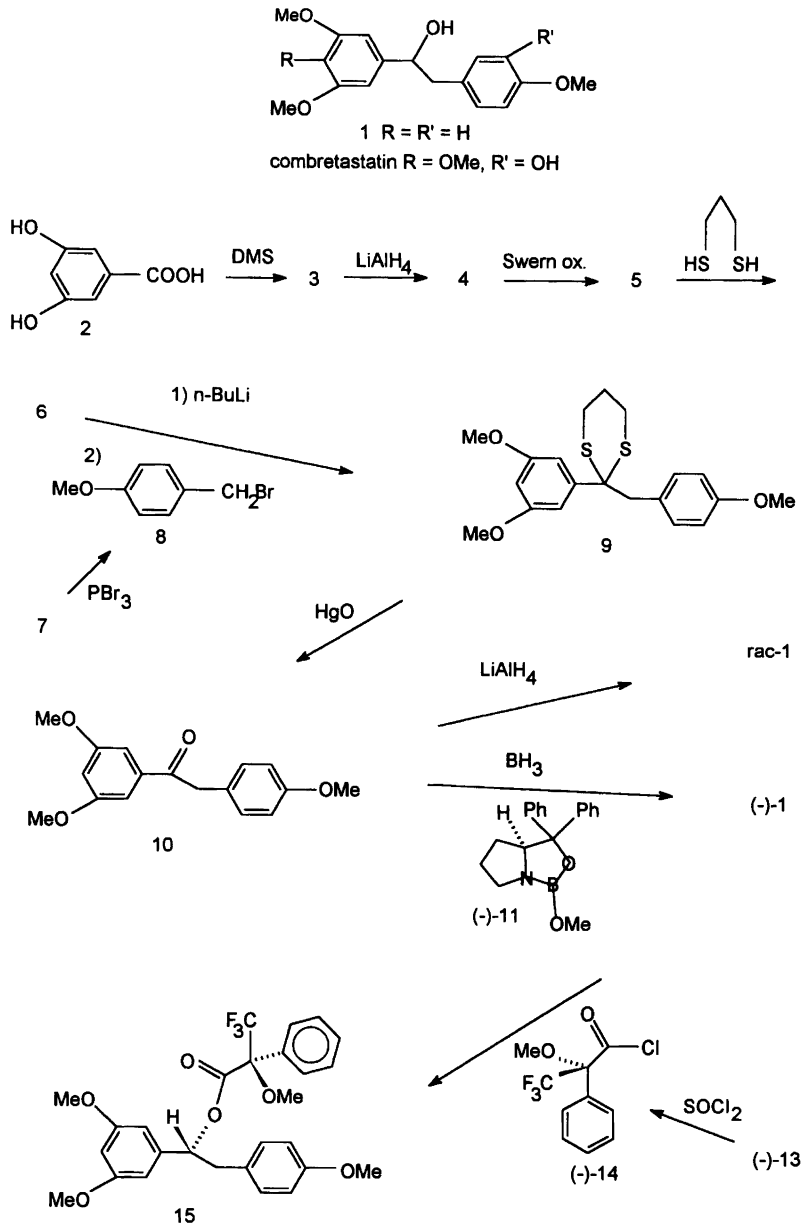
## Results and discussion

The intermediate ketone **10** was prepared using known reactions[4] (Scheme 1). $LiAlH_4$ reduction of **10** gave racemic **1**. The enriched enantiomers of **1** were obtained via $BH_3$ reduction of **10** in the presence of oxazaborolidine catalyst (**11**).[3,5] The presence of (*S*)-(−)-**11** led to enrichment of (−)-**1** and the presence of (*R*)-(+)-**11** to enrichment of (+)-**1**.[3]

The enantiomeric composition (ec)[6] was elucidated by use of $^1H$ NMR spectroscopy together with Eu-*d*-(hfbc)$_3$ (**12**).[7] When the molar ratio of *rac*-**1**:**12** was 0.1–0.2 and the concentration of **1** 1–2 mM, a splitting of the signals of the 2- and 6- protons, as well as some signals of the multiplet of the β-protons could be obtained. Significantly higher concentrations of **1** or shift reagent destroyed the resolution of the $^1H$ NMR spectrum. From these splittings an enantiomeric composition of 70% for enriched (+)-**1** and 85% for (−)-**1** was estimated by integration. The optical activity measurement gave specific optical rotation $[\alpha]_D^{20} = 3°$.

To elucidate the absolute configuration of **1** we prepared the (*S*)-(−)-2-methoxy-3,3,3-trifluoro-2-phenylpropionyl ester[8](15) of the enriched (−)-**1** by using (*R*)-(−)-2-methoxy-3,3,3-trifluoro-2-phenylpropionyl chloride (**14**). In the $^1H$ NMR spectrum of the obtained mixture all the signals of the protons on the 1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol skeleton of both diastereoisomers could be assigned. At the 4′-substituted end of the molecule the signals of the (+)-enantiomer ester had smaller δ values than those of the (−)-enantiomer ester, but at the 3,5-disubstituted end of the molecule the situation was reversed. In the $^{13}C$ NMR spectrum the same trend was observed (Table 1).

If the geometry of the ester proposed by Mosher is accepted (α-carbon−carbinol proton−carbonyl bond−$CF_3$ group in the same plane[8,9]) the differences of all the chemical shifts of proton and carbon signals mentioned above can be explained by shielding – deshielding effects of the three benzene rings. Based on these considerations we assign the *S* configuration to the (+)-enantiomer and the *R* configuration to the (−)-enantiomer. To support our conclusion we have optimized the ester structures **15** and **16** by force-field calculations (Fig. 1). In our opinion the absolute config-




*Scheme 1.*

uration of all the 1,2-diphenylethanol derivatives together with different phenyl residues can be resolved spectroscopically by NMR according to these principles.

## Experimental

MS and HRMS: Varian MAT 731 and Varian 311A instruments, 70 eV. $^1H$ and $^{13}C$ NMR: Varian VRX 200, Bruker AM 300 and Varian VXR 500 instruments; $Me_4Si$ as an internal standard. Optical rotations: Perkin-Elmer 241 polarimeter. TLC and flash chromatography: standard laboratory equipment, Macherey–Nagel TLC plates and T. J. Baker silica gel. Force-field calculations were performed using the program PC Model Pi (Version 3.0).

*Methyl 3,5-dimethoxybenzoate* (**3**). From 3,5- dihydroxybenzoic acid (**2**).[10]

*3,5-Dimethoxybenzyl alcohol* (**4**). From **3**.[11]

*3,5-Dimethoxybenzaldehyde* (**5**). From **4**.[12]

*2-(3,5-Dimethoxyphenyl)-1,3-dithiane* (**6**). From **5**.[13]

*4-Methoxybenzyl bromide* (**8**). From 4-methoxybenzyl alcohol (**7**).[14]

*2-(4-Methoxybenzyl)-2-(3,5-dimethoxyphenyl)-1,3-dithiane* (**9**). From **6** (560 mg, 2.5 mmol) and **8** (450 mg, 2.2 mmol) with the aid of BuLi following the procedure for similar compounds.[4] Purification by flash chromatography (silica gel–$CH_2Cl_2$), colourless oil. Yield of **9**: 480 mg (60%). MS (70 eV): *m/z* (%) 376 (3) ($M^+$), 256 (20), 255 (100), 182 (**11**), 181 (15), 121 (5). $^1H$ NMR ($CDCl_3$): δ 6.95 (d, 2 H), 6.70 (AB, 4 H), 6.37 (t, 1 H), 3.80 (s, 2 H), 3.75 (s, 3 H), 3.72 (s, 6 H), 2.80–2.55 (m,

*Table 1.* $^{13}C$ NMR chemical shifts (δ-values) and proposed assignment of the signals for compounds **9**, **10**, **1**, **15**, and **16** (partially).

| Assignment | 9 | 10 | 1 | 15 | 16 |
|---|---|---|---|---|---|
| 3 | 160.81 | 160.88 | 160.84 | 160.77 | |
| 5 | 160.81 | 160.88 | 160.84 | 160.77 | |
| 4′ | 158.67 | 158.58 | 158.44 | 158.57 | 158.41 |
| 1 | 143.54 | 138.57 | 146.48 | 141.51 | 141.15 |
| 2′ | 131.92 | 130.42 | 130.50 | 130.52 | |
| 6′ | 130.92 | 130.42 | 130.50 | 130.52 | |
| 1′ | 126.60 | 126.54 | 129.94 | 129.36 | |
| 3′ | 112.77 | 114.19 | 113.97 | 113.93 | 113.73 |
| 5′ | 112.77 | 114.19 | 113.97 | 113.93 | 113.73 |
| 2 | 107.67 | 106.50 | 103.79 | 104.19 | 104.75 |
| 6 | 107.67 | 106.50 | 103.79 | 104.19 | 104.75 |
| 4 | 99.40 | 105.36 | 99.60 | 100.56 | |
| α | 60.25 | 197.64 | 75.45 | 79.80 | 79.20 |
| O-$CH_3$ | 55.43 | 55.58 | 55.36 | 55.26 | |
| O-$CH_3$ | 55.43 | 55.58 | 55.36 | 55.26 | |
| O-$CH_3$ | 55.16 | 55.26 | 55.29 | 55.26 | |
| β | 50.60 | 44.78 | 46.07 | 42.25 | 41.76 |
| R | 27.44 | | | 165.81 | |
| | 27.44 | | | 132.21 | |
| | 24.44 | | | 129.36 | |
| | | | | 128.17 | |
| | | | | 127.31 | |
| | | | | 30.34 | |
| | | | | 29.71 | |

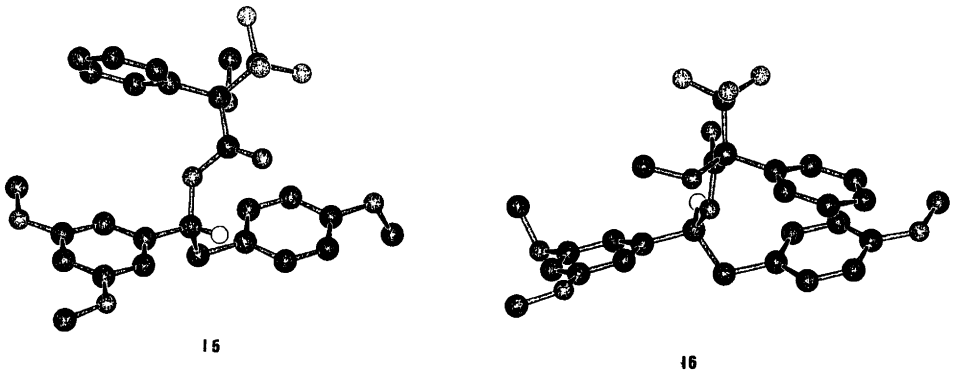



*Fig. 1.* Schakal plot of **15** and **16** after force-field calculation.

4 H), 2.0–1.8 (m, 2 H). $^{13}C$ NMR (Table 1). $C_{20}H_{24}O_3S_2$: Calc. 376.1167. Found 376.1166 (MS).

*1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl) ethanone* (**10**). From **9** (150 mg, 0.4 mmol) by treatment with HgO in THF–$H_2O$ and $BF_3$–$Et_2O$ according to the procedure given for similar compounds.[4] Purification by flash chromatography (silica gel–petroleum ether–diethyl ether, 30:20 vol%), light yellow oil. Yield of **10**: 70 mg (61%). MS (70 eV): *m/z* (%) 286 (30) ($M^+$), 166 (**11**), 165 (100), 137 (15), 122 (10), 121 (30). $^1H$ NMR ($CDCl_3$): δ 7.17 (d, 2 H), 7.15 (d, 2 H), 6.84 (d, 2 H), 6.62 (t, 1 H), 4.19 (s, 2 H), 3.83 (s, 6 H), 3.79 (s, 3 H). $^{13}C$ NMR (Table 1). $C_{17}H_{18}O_4$: Calc. 286.1205. Found 286.1205.

rac-*1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl) ethanol* (*rac*-**1**). From **10** (16 mg, 0.021 mmol) by $LiAl_4$ reduction in $Et_2O$. Purification by preparative TLC (silica gel–pentane–$Et_2O$; 50:50 vol%), colourless oil. Yield of *rac*-**1**: 5 mg (82%). $^1H$ NMR and MS.[1] $^{13}C$ NMR (Table 1) $^1H$ NMR (1.0 mg rac-**1**/1.1 mg Eu-*d*-(hfbc)$_3$, tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium(III) derivative ($CDCl_3$): δ 7.18 (d, 2 H), 6.86 (d, 2 H), 6.63/6.61 (d/d, 1/1, 2 H), 6.39 (t, 1 H), 5.04 (m, 1 H), 3.78 (s, 3 H), 3.77 (s, 6 H), 3.08 (m, 2 H). $C_{17}H_{20}O_4$: Calc. 288.1362. Found 288.1361 (MS).

(S)-(+)-*1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-ethanol* [(+)-**1**]. From **10** (17 mg, 0.059 mmol) and the $BH_3$–THF reagent in the presence of 3.2 mg of [(*R*)-(+)-oxazaborolidine catalyst (*R*)-(+)-**11**] according to the procedure given by Corey *et al.*[5] at 40 °C for 1.5 h. Purification by preparative TLC (silica gel–petroleum

ether–diethyl ether (50:50 vol%) gave 10 mg of **10** and 5.2 mg (31%) of (+)-**1** (colourles oil). $^1$H NMR [1.0 mg enriched (+)-**1**, 0.8 mg Eu-*d*-(hfbc)$_3$, $CDCl_3$)]: δ 7.15 (d, 2 H), 6.86 (d, 2 H), 6.57/6.56 (d/d, 3/1, 2 H), 6.39 (t, 1 H), 4.90 (m, 1 H), 3.8 (s, 3 H), 3.79 (s, 6 H), 3.02 (m, 2 H); estimated enantiomeric composition 70%.

(R)-*(−)-1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-ethanol* [(−)-**1**]. From **10** (75 mg, 0.26 mmol) and the $BH_3$–THF reagent in the presence of 13 mg of (*S*)-(−)-oxazaborolidine catalyst (**11**) as described above at 35 °C for 1.5 h. Purification as above gave 50 mg of **10** and 12.8 mg (9.6%) of enriched (−)-1 (colourless oil). Enantiomeric purity determination as above gave 85%. Optical rotation: 8.7 mg (ec 85%) in 1 ml $CDCl_3$ gave α −0.022 °; specific optical rotation $[\alpha]_D^{20} = -3$ °. $^1$H NMR [0.8 mg enriched (−)-**1**, 0.9 mg Eu-*d*-(hfbc)$_3$, $CDCl_3$]:δ 7.26 (d, 2 H), 6.90 (d, 2 H), 6.79/6.75 (d/d, 1/5.8, 2 H), 5.30 (m, 1 H), 3.81 (s, 3 H), 3.80 (s, 6 H), 3.21 (m, 2 H); estimated enantiomeric composition 85%.

(R)-*(−)-2-methoxy-3,3,3-trifluoro-2-phenylpropionyl chloride* (**14**) was prepared from (*S*)-(−)-2-methoxy-3,3,3-trifluoro-2-phenylpropionic acid (**13**) (Fluka) (250 mg, 1.1 mmol) in an excess of thionyl chloride according to the method given by Mosher *et al.*[8] After removal of the excess of thionyl chloride **14** was obtained in a quantitative yield and was used without distillation.

(S)-*(−)-2-Methoxy-3,3,3-trifluoro-2-phenylpropionyl ester of the enriched* (R)-(−)-*1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl) ethanol* (**15, 16**). From enriched (−)-**1** (8.7 mg, mmol and (−)-**14** (about a tenfold molar excess) in $CH_2Cl_2$, pyridine and 4-(dimethylamino)pyridine according to a method given in the literature[15] in an overnight reaction at room temperature. Preparative TLC purification (petroleum ether–$Et_2O$, 2:1 vol%) of the reaction mixture gave 1.5 mg of the unchanged (−)-**1** and further purification by preparative TLC (petroleum ether – ethyl acetate (4:1 vol%) gave 6.6 mg (43%) of **15/16** (5:1) as a colourless oil. $^1$H NMR **15** (in the 5:1 mixture, $CDCl_3$): δ 7.36–7.11 (m, 5 H), 7.13 (d, 2 H), 6.82 (d, 2 H), 6.39 (s/m, 3 H), 6.01 [m (X), 1 H), 3.80 (s, 3 H), 3.71 (s, 6 H), 3.32 (d, 3 H), 3.17–3.01 [m (AB), 2 H], $^1$H NMR **16** (in the 1:5 mixture, $CDCl_3$): δ 7.36–7.11 (m, 5 H), 6.96 (d, 2 H), 6.71 (d, 2 H), 6.47 (d, 2 H), 6.40 (t, 1 H), 6.08 [m (X), 1 H], 3.77 (s, 3 H), 3.74 (s, 6 H), 3.37 (d, 3 H), 3.13–2.96 [m (AB), 2 H]. MS of the mixture (5:1) (70 eV): *m/z* (5) 504 (22) ($M^+$), 271 (43), 270 (89), 189 (100), 166 (13, 121 (69). $^{13}$C NMR (Table 1). $C_{27}H_{27}F_3O_6$: Calc. 504.1760. Found 504.1759.

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