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Article

Synthesis and Biological Activity of Allosteric Modulators of $GABA_B$ Receptors Part 3. 3-(2,6-Bis-*iso*-propyl-4-hydroxyphenyl)propanols

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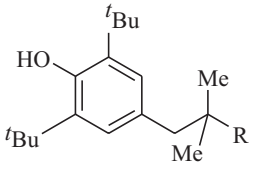
Uma série de seis derivados do propan-1-ol 2,2-disubistituído 3-[3,5-di-*iso*-propil-4-hydroxifenil] foi preparada para avaliação como moduladores alostéricos de receptores $GABA_B$. A maior atividade (EC_{50} 30 μM) encontrada na série foi para os análogos do dimetil, mas os compostos *iso*propilfenil foram, de maneira geral, mais fracos que os compostos *t*-butílicos. A metilação do grupo fenólico levou à uma perda de atividade.

A series of six 2,2-disubstituted 3-[3,5-di-*iso*-propyl-4-hydroxyphenyl]propan-1-ol derivatives have been prepared for evaluation as allosteric modulators of $GABA_B$ receptors. The activity (EC_{50} 30 μM) was greatest for the dimethyl analogue, but the *iso*propylphenyl compounds were generally weaker than the corresponding *t*-butyl compounds. Methylation of the phenolic group led to loss of activity.

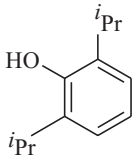
Keywords: propofol analogue, allosteric positive modulation, $GABA_B$

Introduction

Following a random mass screening, Urwyler *et al.*[1] recently reported that 2,6-di-*tert*-butyl-4-(3-hydroxyphenyl)-2,2-dimethylpropionaldehyde, CGP 13501, (**1**) acted as a positive allosteric modulator for $GABA_B$ receptors,[2,3] and its reduction product, the corresponding alcohol CGP 7930 (**2**) was found to be even more potent. Because of our interest in such modulators,[2,4,5] we speculated that the latter could be regarded as a hybrid of propofol (**3**) and hydroxybutyric acid (GHB, **4**). Propofol[6,7] is a short-acting hypnotic agent ($GABA_A$ modulator), effective for induction and maintenance of anaesthesia when administered intravenously either as repeated bolus injections or by continuous infusion. GHB is best known as a drug of abuse,[8] and is a GABA analogue. Accordingly, we have recently synthesized a series of compounds modifying the structure **2**, all of which acted as positive modulators at $GABA_B$ receptors.[9] The most active was the cyclohexyl analogue (**5**), which was 2 to 3 times as active as the lead compound (**2**). Our working hypothesis for the lead compound (**2**) is that it acts through the 3-hydroxyphenylpropyl moiety, with the hydroxyphenyl group corresponding to the carboxyl group of GHB, in addition to providing hydrophobic properties that would facilitate transport across cell membranes.



1 R=CHO
2 R=CH_2OH



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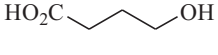

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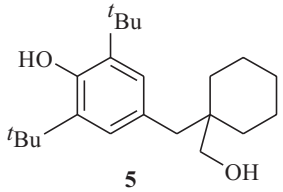

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Since our previous work[9] was concerned mainly with an examination of the effect of changing the hydrophobicity and steric bulk near the hydroxyl end of the molecule, we now report the preparation of some variants at the phenolic portion of the molecule; at this stage little is known of the pharmacokinetics of these compounds, and their therapeutic potential is uncertain. The basic synthetic approach continues to be basically that of Urweyler *et al.*[1]

Discussion

Chemical synthesis

2,6-Di-*iso*propyl-4-methoxymethylphenol (**6**) reacted with carbonyl compounds in methanol more slowly than the *t*-butyl analogue.[9] The resulting carbonyl compounds (**7a**-**d**) were either reduced with sodium borohydride to the alcohols (**8a**, **8b**, **9a**, **9c**), or reacted with alkyllithium reagents to give a mixture of diastereoisomers of alcohol (**9b**) (Scheme 1).

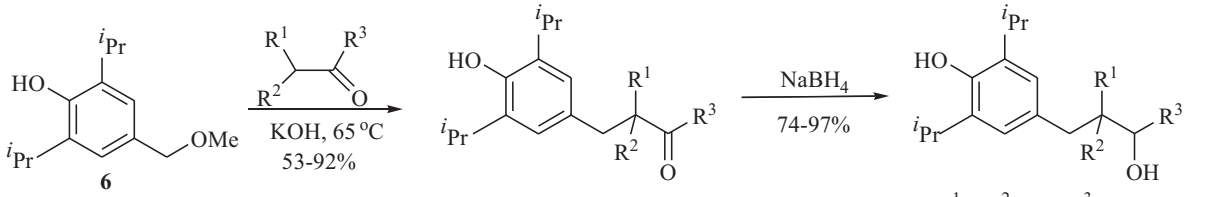
Since we suspected that these compounds were GABA mimics, it was desirable to synthesise at least one example of a primary amine, and the reductive amination method of Borch *et al.*[10] was chosen.

Reaction of the aldehyde **7b** with ammonium acetate and sodium cyanoborohydride,[10] gave a good yield, not of the desired primary amine **10**, but of the secondary amine **11**. We suspect that the initially formed **10** reacted with **7b** faster than with ammonium acetate, leading to the new intermediate **13**, reduction of which gave the observed product **11**, as shown in Scheme 2.

The subtle difference in the decreased activating effect of *iso*propyl groups compared to *tert*-butyl groups was noted when the reaction of ether **6** with 3-methylbutan-2-one failed to occur to any significant extent under basic conditions. However, the use of trifluoroacetic acid in refluxing dichloromethane allowed efficient reaction of the ether with ketones, and indeed also gave cleaner reaction products with aldehydes, leading to products **7a**-**7c**.

The requirement for an acidic or hydrogen-bonding centre on the phenyl group was probed by methylation of **8a** in this series to give **14**, but attempt to synthesize methyl ethers from tertiary butyl derivatives failed.

In order to further examine the suspected importance of the bulkiness of the aryl substituents in these compounds, the synthesis of methyl analogues was investigated. However, as reported in the literature,[11] the

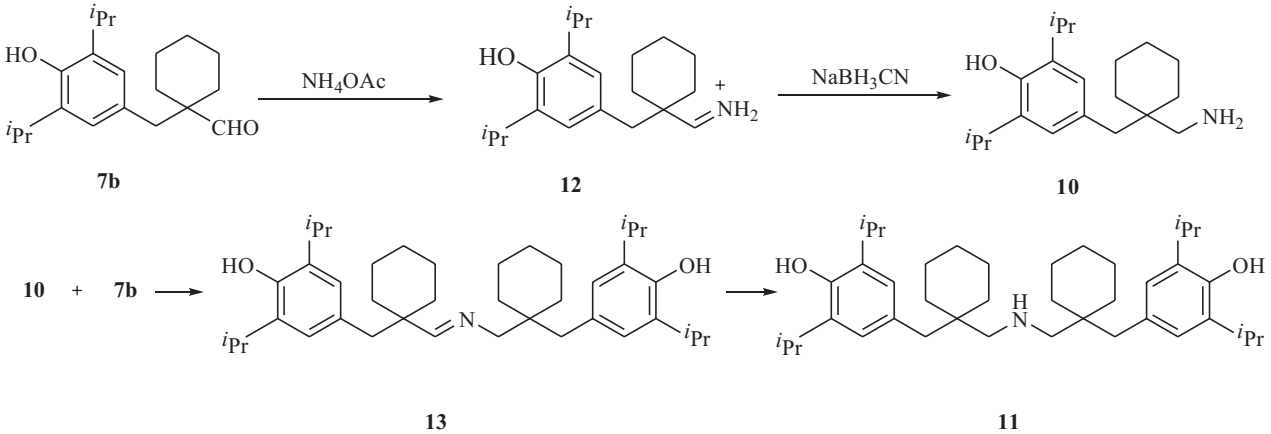


6

7a R^1, R^2=Me, R^3=H
7b R^1, R^2= -$(CH_2)_5$-, R^3= H
7c R^1 = Me, R^2= H, R^3= 4-ClPh
7d R^1, R^2, R^3= Me

8a R^1, R^2=Me, R^3=H
8b R^1, R^2=-$(CH_2)_5$-, R^3= H
9a R^1, R^2, R^3=Me
9b R^1, R^2=-$(CH_2)_5$-, R^3= Me
9c R^1 = Me, R^2=H, R^3= 4-ClPh

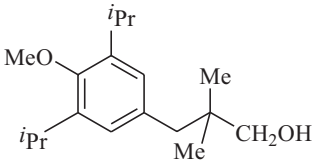
Scheme 1.



7b **12** **10**

13 **11**

Scheme 2.



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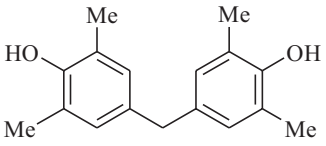

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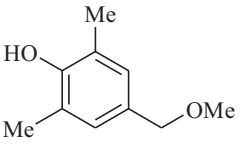

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base catalysed condensation of 2,6-dimethylphenol with formaldehyde in basic methanol gave 4,4'-dihydroxy-3,5,3',5'-tetramethylphenylmethane **15** instead of the desired 2,6-dimethyl-4-methoxymethylphenol **16**, and this area was not pursued further.

Biological evaluation

As described previously,[4,12,13] the compounds prepared above were examined for their pharmacological effects in enhancing baclofen-induced hyperpolarizing responses at $GABA_B$ post-synaptic receptors, and as potentiators of baclofen actions in reducing electrically-evoked release of [^{3}H]-GABA or [^{3}H]-glutamate at presynaptic receptors, mediated via $GABA_B$ auto or heteroreceptors, respectively, in rat neocortical slice preparations.[14,15] Baclofen is a classical selective agonist at $GABA_B$ receptor sites,[16,17] and is commonly used in rat brain preparations to stimulate these receptors to induce a neuronal response. Herein (Table 1) we summarise the results of the effects of the test compounds in modulating baclofen mediated function using grease gap recording in rat neocortical slices.[12,13] The responses induced by baclofen are dose-dependent, with baclofen generating an EC_{50} value of approximately 10 μM.[12] The EC_{50} value for the agonist baclofen is calculated as the concentration of baclofen inducing 50% of the maximum hyperpolarizing response. Using this fixed concentration of baclofen at 10 μM, the concentration-response curves of differing concentrations of the test compounds are subsequently constructed. From these curves, the EC_{50} values of the test compounds in potentiating the baclofen response are measured, the values representing the concentration of the compound needed to induce 50% of the maximal potentiated responses.

All the new 3-(hydroxyphenyl)propanol derivatives had relatively low activity with EC_{50} typically around 30-100 μM. As with the *t*-butyl compounds reported earlier,[9] this may be a reflection of their extremely low solubility even in DMSO/water mixtures, leading to partial precipitation during the testing procedure: real activities possibly may be somewhat greater. The methyl ethers were of very low activity, and their solubility was even lower. The *tert*-butyl derivatives reported previously[9] appeared to be two to three times more active than the *iso*propyl series, but still several orders of magnitude lower than that of the *N*-(phenylpropyl)-1-arylethylamines. [2]

Table 1.[a] Pharmacological activity (EC_{50}) of 3-(4-hydroxyaryl)propanols as $GABA_B$ potentiators

Compound	Activity
5	4 μM
8a	50 μM
8b	40 μM
9a	30 μM
9b	75 μM
9c	200 μM
14	Nil[b]
2	10 μM

[a] All numerical data on the concentration-response curves were expressed as approximate EC_{50} values (n=6-12); [b] Essentially insoluble in test procedure

Conclusion

Generally, it can be concluded that 3-(4-hydroxy-3,5-dialkylphenyl)propanols represent a new distinct classes of $GABA_B$ receptor modulators, limited at this stage by very poor solubility. The 3,5-di *i*-propyl analogues are less active than the corresponding *t*-butyl compounds. However, these $GABA_B$ modulators may still represent a novel therapeutic strategy for the treatment of various neurological and pathological diseases mentioned previously, without the side effects of full $GABA_B$ receptor agonists.

Experimental

All solvents used were freshly distilled and dried according to the methods of Perrin and Armarego.[18] Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Gemini Varian 300 spectrometer in deuteriochloroform with tetramethylsilane as internal standard, unless otherwise stated. Infrared spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrophotometer, measured as films or KBr disks. Mass spectra and high resolution mass spectra were recorded on a Kratos MS25RF spectrometer.

*3-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-2,2-dimethylpropanal (**7a**)*

2,6-Di*iso*propyl-4-methoxymethylphenol (**6**)[19] (0.5 g), potassium hydroxide (0.10 g) and *iso*butyraldehyde (0.5 g) were heated under N_2 at 100 °C for 2h. The reaction mixture was poured into 1% acetic acid (20 mL), and extracted with dichloromethane. The extracts were washed with water, dried and evaporated, and the product recrystallised from hexane as white needles (0.39 g, 65%), mp 67-68 °C. Found $(M+H-H_2O)^+$ 245.1895. $C_{17}H_{25}O$ requires 245.1900. ^{1}H NMR δ 1.06 (s, 6H), 1.24 (d, *J* 6.8 Hz, 12H), 2.71 (s, 2H), 3.12 (sep, *J* 6.8 Hz, 2H), 4.62 (bs, 1H), 6.75 (s, 2H), 9.59 (s, 1H). ^{13}C NMR δ 21.3, 22.7, 27.0, 43.1, 46.9, 125.2, 128.5, 133.3, 148.5, 206.5. FT-IR (KBr) ν_{max}/ cm^{-1}: 3518, 2960, 2869, 1716, 1470, 1199, 1154, 884.

*3-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-2,2-dimethylpropanol (**8a**)*

A mixture of **7a** (131 mg) and sodium borohydride (48 mg) in dry ethanol (4 mL) was refluxed overnight. Water (10 mL) was added, the mixture extracted with dichloromethane, and the combined extracts washed with water, dried, and evaporated to give **8a**, which was recrystallised from hexane as colourless crystals (121 mg, 91%), mp 96-97 °C. Found $(M+H)^+$ 265.2158. $C_{17}H_{29}O_2$ requires 265.2168. ^{1}H NMR δ 0.87 (s, 6H), 1.26 (d, *J* 6.8 Hz, 12H), 2.50 (s, 2H), 2.93 (bs, 2H), 3.15 (sept, *J* 6.8 Hz, 2H), 3.33 (s, 2H), 6.82 (s, 2H). ^{13}C NMR δ 22.8, 23.9, 27.0, 36.3, 44.6, 71.4, 125.3, 130.4, 133.0, 148.1. FT-IR (KBr) ν_{max}/cm^{-1}: 3417, 3241, 2961, 2866, 1462, 1359, 1203, 1167, 1034.

*1-[4-Hydroxy-3,5-bis(1-methylethyl)phenylmethyl] cyclohexanecarboxaldehyde (**7b**)*

Method 1

2,6-Di*iso*propyl-4-methoxymethylphenol (6)[19] (1.0 g), potassium hydroxide (0.10 g) and cyclohexanecarboxaldehyde (1.5 g) were heated under N_2 at 110 °C for 3h. The reaction mixture was poured into 1% acetic acid (20 mL), and extracted with dichloromethane. The extracts were washed with water, dried and evaporated, and the product chromatographed on silica (dichloromethane:hexane, 1:1) to yield colourless crystals (0.98 g, 72%), mp 67-68 °C. Found $(M+H-H_2O)^+$ 285.2216. $C_{20}H_{29}O$ requires 285.2218. ^{1}H NMR δ 1.23 (d, *J* 6.8 Hz, 12H), 1.20-1.36 (m, 4H), 1.48-1.72 (m, 4H), 1.83-1.94 (m, 4H), 2.65 (s, 2H), 3.10 (sep, *J* 6.8 Hz, 2H), 4.68 (bs, 1H), 6.70 (s, 2H), 9.50 (s, 1H). ^{13}C NMR δ 22.7, 25.6, 27.0, 31.1, 43.5, 50.6, 125.2, 127.9, 133.2, 148.5, 207.8. FT-IR (KBr) ν_{max}/ cm^{-1}: 3520, 2960, 2866, 2712, 1716, 1596, 1383, 1362, 1343, 1306, 1284, 1263, 1125, 1107, 1071, 1033, 959, 938, 882, 863, 847, 831, 812. Mass spectrum *m/z* 302 (M), 192, 191, 175, 161, 105, 91, 55.

Method 2

2,6-Di*iso*propyl-4-methoxymethylphenol (0.2 g), cyclohexanecarboxaldehyde (0.2 g), and trifluoroacetic acid (0.1 g) were refluxed in dry dichloromethane (5 mL) under N_2 for 3h. The reaction mixture was evaporated, and the product chromatographed on silica (dichloromethane:hexane, 1:1) to yield colourless crystals (0.21 g, 75%), mp 67-68°C, identical with those obtained above.

*3-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-2-(1,1-spirocyclohexyl)propanol (**8b**)*

A mixture of **7b** (200 mg) and sodium borohydride (50 mg) in dry ethanol (5 mL) was refluxed overnight. Water (10 mL) was added, the mixture extracted with dichloromethane, and the combined extracts washed with water, dried, and evaporated to give **8b** as a pale yellow oil (177 mg, 88%). Found $(M+H-H_2O)^+$ 287.2378. $C_{20}H_{31}O$ requires 287.2376. ^{1}H NMR δ 1.26 (d, *J* 6.8 Hz, 12H), 1.25-1.37 (m, 6H), 1.38-1.62 (m, 4H), 2.58 (s, 2H), 3.13 (sep, *J* 6.8 Hz, 2H), 3.36 (s, 2H), 4.50 (bs, 2H), 6.86 (s, 2H). ^{13}C NMR δ 21.6, 22.8, 26.4, 27.0, 32.3, 38.4, 41.7, 67.6, 125.3, 130.3, 133.1, 148.1. FT-IR (film) ν_{max}/ cm^{-1}: 3412, 2960, 1595, 1383, 1362, 1264, 1123, 1107, 1073, 974, 940, 926, 883, 812. Mass spectrum *m/z* 304 (M), 192, 191, 177, 149, 105, 85, 83, 55.

*4-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-3-(1,1-spirocyclohexyl)butan-2-ol (**9b**)*

To a solution of aldehyde **7b** (75 mg) in dry ether (4 mL) at 0 °C was added dropwise a solution of 1.5 mol L^{-1} methyllithium (mL in hexane) under N_2. After 30 min at 0 °C, the mixture was stirred at rt for 15 min, and water (5 mL) added at 0 °C. The mixture was extracted with ether, the extracts washed with water, dried and evaporated to give **9b** as colourless crystals (75 mg, 95%), mp 106-107 °C. Found $(M+H-H_2O)^+$ 301.2533. $C_{21}H_{33}O$ requires 301.2535. ^{1}H NMR δ 1.19 (d, *J* 6.6 Hz, 3H), 1.24 (d, *J* 6.8 Hz, 12H), 1.21-1.63 (m, 10 H), 2.58 (d, *J* 13.6 Hz, 1H), 2.75 (d, *J* 13.6 Hz, 1H), 3.13 (sep, *J* 6.8 Hz, 2H), 3.73 (q, *J* 6.6 Hz, 1H), 4.70 (bs, 2H), 6.86 (s, 2H). ^{13}C NMR δ 17.3, 21.4, 21.5, 22.8, 26.3, 27.0, 30.3, 30.8, 37.7, 40.7, 71.0, 125.6, 130.6,

133.1, 148.0. FT-IR (KBr) ν_{max}/ cm^{-1}: 3417, 2865, 1594, 1382, 1362, 1309, 1282, 1266, 1152, 1098, 1052, 1008, 946, 934, 897, 852 . Mass spectrum *m/z* 318 (M), 192, 191, 177, 149, 91, 83, 67, 55.

*1-(4-Chlorophenyl)-3-[4-hydroxy-3,5-bis(1-methylethyl) phenyl]- 2-methylpropan-1-one (**7c**)*

2,6-Di*iso*propyl-4-methoxymethylphenol (**6**)[19] (0.7 g), potassium hydroxide (0.12 g) and 4-chloropropiophenone (1.3 g) were heated under N_2 at 110 °C for 3h. The reaction mixture was poured into 1% acetic acid (20 mL), and extracted with dichloromethane. The extract were washed with water, dried and evaporated, and the product recrystallised from hexane as colourless crystals (0.71 g, 62%), mp 73-76 °C. Found (M+H)$^+$ 359.1765. $C_{22}H_{28}ClO_2$ requires 359.1778. ^{1}H NMR δ 1.20 (d, *J* 6.9 Hz, 3H), 1.24 (d, *J* 6.9 Hz, 12H), 2.69 (dd, *J* 14.4, 6.9 Hz, 1H), 3.01-3.16 (m, 1H), 3.69 (dd, *J* 14.4, 6.9 Hz, 1H), 4.7 (bs, 1H), 6.84 (s, 2H), 7.48 (d, *J* 8.5Hz, 2H), 7.82 (d, *J* 8.5Hz, 2H). ^{13}C NMR δ 17.9, 23.1, 27.5, 40.2, 43.4, 124.3, 129.1, 130.1, 131.8, 134.0, 135.6, 139.5, 148.6, 203.7. FT-IR (KBr) ν_{max}/ cm^{-1}: 3443, 3068, 2965, 2925, 2866, 1669, 1589, 1569, 1471, 1400, 1376, 1362, 1291, 1255, 1208, 1152, 1176, 1091, 1043, 1012, 977, 953, 910, 876, 863, 840, 816, 747, 684 . Mass spectrum *m/z* 360 (M+2), 358 (M), 193, 191, 175, 139, 111.

*3-(3,5-Bis(1-methylethyl)-4-hydroxyphenyl)-1-(4-chlorophenyl)-2-methyl-1-propanol (**9c**)*

A mixture of **7c** (200 mg) and excess sodium borohydride (53 mg) in dry ethanol (10 mL) was refluxed overnight, water (12 mL) was added and the mixture was extracted with dichloromethane (30 mL). The extract was washed with water, dried and evaporated to give *ca.* 1:1 mixture of diastereo-isomers of **9c** as a colourless oil (170 mg, 85%). ^{1}H NMR δ 0.71 (d, *J* 6.9 Hz, 3H in isomer A), 0.86 (d, *J* 6.9 Hz, 3H in isomer B), 1.28 (d, *J* 6.9Hz, 12H), 2.11-2.15 (m, 1H), 2.29-2.41 (m, 1H in two isomers), 2.73 (dd, *J* 13.5, *J* 6.3 Hz, 1H in isomer A), 2.94 (dd, *J* 13.5, 4.2 Hz, 1H in isomer B), 3.16 (sep, *J* 6.9 Hz, 2H), 4.52 (d, *J* 6.9 Hz, 1H in isomer A), 4.64 (d, *J* 4.5 Hz, 1H in isomer B), 4.8 (bs, 1H), 6.84 (s, 2H, in isomer A), 6.85 (s, 2H, in isomer B), 7.27 (d, *J* 8.7 Hz, 2H), 7.34 (d, *J* 8.7Hz, 2H). ^{13}C NMR δ 13.6, 15.4, 22.8, 27.1, 29.7, 38.6, 39.3, 42.2, 42.3, 76.0, 78.1, 123.9, 124.2, 127.5, 128.1, 128.2, 128.3, 132.1, 132.2, 132.7, 133.1, 133.4, 133.5, 141.7, 142.2, 148.0. FT-IR (film) ν_{max}/ cm^{-1}: 3437, 2962, 2936, 2877, 1597, 1491, 1470, 1383, 1200, 1152, 1091, 1013, 835 . Mass spectrum *m/z* 362 (M+2), 360 (M), 342, 300, 299, 220, 219, 192, 191, 178, 177, 163, 149, 141, 107, 91, 77.

*4-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-3,3-dimethyl-2-butanone (**7d**)*

2,6-Di*iso*propyl-4-methoxymethylphenol (**6**)[19] (600 mg), potassium hydroxide (100 mg) and 3-methyl-2-butanone (600 mg) were heated under N_2 at 100 °C for 2h. The reaction mixture was poured into 1% acetic acid (10 mL), and extracted with dichloromethane. The extracts were washed with water, dried and evaporated, and the product recrystallised from hexane as a white solid (620 mg, 82%), mp 76-77 °C. ^{1}H NMR δ 1.1 (s, 2H), 1.24 (d, *J* 6.8Hz, 12H), 2.09 (s, 3H), 2.73 (s, 2H), 3.13 (sep, *J* 6.8Hz, 2H), 4.45 (bs, 1H), 6.75 (s, 2H). ^{13}C NMR δ 22.77, 24.15, 26.33, 26.95, 45.49, 48.69, 125.14, 129.37, 133.14, 148.39, 214.47. FT-IR (KBr) ν_{max}/ cm^{-1}: 3488, 2962, 2869, 1696, 1595, 1470, 1363, 1310, 1281, 1202, 1153, 1114. Found (M+H-Me_2CHCOMe)$^+$ 191.1436 requires (M+H-Me_2CHCOMe)$^+$ 191.1430. Mass spectrum *m/z* 276 (M), 261, 233, 192, 191, 175, 147, 105, 91, 55.

*4-[4-Hydroxy-3,5-bis(1-methylethyl)phenyl]-3,3-dimethyl-2-butanol (**9a**)*

A mixture of **7d** (138 mg) and sodium borohydride (48 mg) in dry ethanol (4 mL) was refluxed for 1h. Water (10 mL) was added, the mixture extracted with dichloromethane, and the combined extracts washed with water, dried, and evaporated to give **9a**, which was recrystallised from hexane as a white solid (122 mg, 87%). ^{1}H NMR δ 0.81 (s, 3H), 0.86 (s, 3H), 1.19 (d, *J* 6.4Hz, 3H), 1.26 (d, *J* 13.2Hz, 1H), 2.60 (d, *J* 13.2Hz, 1H), 3.15 (sep, *J* 6.8Hz, 2H), 3.55 (q, *J* 6.4Hz, 1H), 4.25 (bs, 2H), 6.84 (s, 2H). ^{13}C NMR δ 17.89, 21.73, 22.83, 22.99, 26.95, 38.62, 44.31, 74.17, 125.60, 130.50, 132.96, 148.06. FT-IR (KBr) ν_{max}/ cm^{-1}: 3421, 2963, 2870, 1472, 1383, 1201, 1092. Found (M+H-H_2O)$^+$ 261.2219 requires (M+H-H_2O)$^+$ 261.2218. Mass spectrum *m/z* 278(M), 260, 233, 192, 191, 177, 161, 149, 105, 91, 77, 55.

3-(3,5-Bis(1-methylethyl)-4-methoxyphenyl)-2,2-dimethylpropanal

A mixture of 3-(3,5-bis(1-methylethyl)-4-hydroxy-phenyl)-2,2-dimethylpropanal (300 mg) and potassium hydroxide (65 mg) in ethanol (5 mL) was stirred vigorously at room temperature. Then dimethyl sulfate (360 mg, excess) was added to the mixture which was stirred vigorously at 20 °C for 1 h. The mixture was warmed for 30 min at 60-70 °C in order to complete the methylation. After cooling, 10% NaOH (45 mL) was added with vigorous stirring. The product was extracted

with dichloromethane (30 mL), washed, and dried over Na_2SO_4. Removal of the solvent gave the title compound as a colourless viscous oil (290 mg, 92%). ^{1}H NMR δ 1.1 (s, 6H), 1.23 (d, *J* 6.9Hz, 12H), 2.75 (s, 2H), 3.32 (sep, *J* 6.9Hz, 2H), 3.73 (s, 3H), 6.81 (s, 2H), 9.61 (s, 1H). ^{13}C NMR ä 21.33, 24.09, 26.30, 43.27, 46.91, 62.2, 125.92, 132.58, 141.19, 153.12, 206.16. FT-IR (film) ν_{max}/ cm^{-1}: 2963, 2925, 2828, 2699, 1726, 1471, 1363, 1283, 1214, 1164, 1119, 1016, 884 . Mass spectrum *m/z* 276 (M), 274, 259, 225, 217, 205, 202, 192, 189, 177, 175, 174, 91, 83, 69, 57, 55, 43, 41.

*3-(3,5-Bis(1-methylethyl)-4-methoxyphenyl)-2,2-dimethylpropanol (**14**)*

A mixture of 3-(3,5-bis(1-methylethyl)-4-methoxyphenyl)-2,2-dimethylpropanal (290 mg) and sodium borohydride (100 mg, excess) in dry ethanol (5 mL) was refluxed overnight. Water was added to the mixture, which was then extracted with dichloromethane (30 mL), and the extract washed with water and dried over Na_2SO_4. Removal of the solvent gave a colourless solid which was recrystallised from n-hexane mp 66-68 °C (260 mg, 89%). ^{1}H NMR δ 0.87 (s, 6H), 1.22 (d, *J* 7Hz, 12H), 2.52 (s, 2H), 3.28-3.34 (m, 4H), 3.71 (s, 3H), 6.85 (s, 2H). ^{13}C NMR δ 23.33, 24.79, 25.50, 27.10, 36.30, 61.02, 63.15, 125.18, 127.02, 134.46, 140.81. FT-IR (KBr) ν_{max}/ cm^{-1}: 3497, 3016, 2965, 2920, 2871, 1472, 1362, 1283, 1211, 1163, 1116, 1055, 1013, 881, 795. Mass spectrum *m/z* 278 (M), 206, 205, 189, 175, 163, 91.

Reaction of 2,6-dimethylphenol with formaldehyde

A solution of potassium hydroxide (3.2 g in 3.2 mL water) was added under nitrogen to a solution of 2,6-dimethylphenol (5.0 g, 0.04 mol) and 36 % formaldehyde (8 mL) in methanol (50 mL). The solution was refluxed for 30 min under a current of nitrogen, cooled to room temperature and the precipitated **16** was collected and washed with cold water as pale yellow crystals, mp 174-176 °C (lit.[20] mp 172-176°C). ^{1}H NMR δ 2.24 (s, 12H), 3.72 (s, 2H), 6.80 (s, 4H, ArH). ^{13}C NMR δ 15.9, 4 × CH_3; 40.2, CH_2; 122.9, ArC; 128.8, ArCH; 133.4, ArC; 150.3. FT-IR (KBr) ν_{max}/ cm^{-1}: 3463, 3008, 2916, 2848, 1608, 1474, 1484, 1437, 1375, 1304, 1186, 1146, 882, 731.

*Di-[3-{4-hydroxy-3,5-bis(ethylmethyl)phenyl}-2-spirocyclohexyl]propylamine (**11**)*

Aldehyde **7b** (410 mg), ammonium acetate (1.54 g), and sodium cyanoborohydride (168 mg, 2 equiv.) in methanol (5 mL) were stirred at rt for 48 h. The reaction mixture was evaporated to dryness, and water (10 mL) added. The mixture was extracted with ether (3×10 mL) and the dried extract evaporated. The residue (386 mg) was chromatographed on silica (dichloromethane:methanol 1:1) to give **11** as a white solid (250 mg, 61%), mp 75-80 °C. Found $(M+H)^+$ 590.4941. $C_{40}H_{64}NO_2$ requires 590.4937. ^{1}H NMR δ 1.24 d, *J* 6.8 Hz, 24H), 1.25-1.66 (m, 20H), 2.60 (s, 4H), 2.71 (s, 4H), 3.12 (sep, *J* 6.8 Hz, 4H), 5.65 (bs (exch), 2H), 6.81 (s, 4H). ^{13}C NMR δ 21.4, 22.7, 25.6, 27.1, 33.1, 37.0, 42.1, 57.7, 125.6, 128.9, 133.6, 148.8. FT-IR (KBr) ν_{max}/ cm^{-1}: 3362, 3199, 2959, 2930, 2866, 1469, 1383, 1361, 1285, 1202, 1152, 1124, 910.

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