Pivaloyl-Directed Regioselective Syntheses of 2,3,6-Trioxygenated Benzamides: Phenolic Metabolites of Remoxipride

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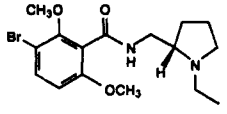
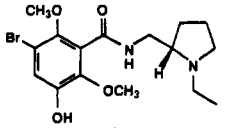
The regioselective syntheses of (*S*)-5-bromo-2,6-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-hydroxybenzamide (**2**) and (*S*)-5-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-hydroxy-6-methoxysalicylamide (**3**) from 2,6-dimethoxybenzoic acid and 4-methoxycatechol are described. The latter compound was protected and ortho-lithiated to introduce the carboxyl function in a regioselective manner. Regiocontrol in bromination and demethylation was achieved by introduction of a bulky pivaloyl group. This strategy also enabled the use of a common intermediate as an alternative synthesis of the catechol **3**.

Introduction

Remoxipride (**1**)[1,2] is an atypical antipsychotic agent of the substituted benzamide class[2-6] that has been found to be as efficacious as haloperidol in the treatment of acute schizophrenia.[7] Notably, remoxipride was associated with a considerably lower degree of extrapyramidal side effects (EPS).[7] In man and dog the dominating metabolic reactions involve oxygenation of the α-carbons in the pyrrolidine moiety which results in N-dealkylation and/or pyrrolidone and hydroxypyrrolidone derivatives.[8,9] In rodents, remoxipride is primarily metabolized in the benzamide system which leads to demethylated and/or oxidized compounds.[8] The major metabolites in rat are 5-hydroxylated remoxipride **2** and the catechol **3**, which are mainly excreted in a conjugated form in the urine.[8]



remoxipride (1)



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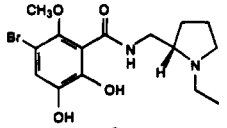

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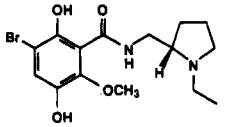

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Originally, the hydroquinone **4** and the catechol **3** could not be distinguished in the metabolic studies, which led to the need for regiochemically well-defined reference compounds. This paper describes regiospecific syntheses of the phenolic metabolites **2** and **3** by methods that permit convenient gram-scale preparation. We have recently described the last steps in the synthesis of the related hydroquinone **4**.[10]

Suitably protected 2,3,6-trioxygenated benzoic acid derivatives **5a** and **5b** are key intermediates which can be transformed to the corresponding amides and then brominated, or following the reverse order, to give **2** and **3** (Scheme I). The acids **5** can be obtained by regiospecific ortho-metalation of protected **6**, which takes advantage of the well-known cooperative effects of the meta-positioned groups (route A). The phenol group may be introduced by Bayer–Villiger oxidation of the easily accessible derivatives **7**. Alternatively, the 2,6-dioxygenated benzoic acids **8** can be acylated and subjected to a Bayer–Villiger oxidation (route B). This shorter path is well suited for the symmetrical 2,6-dimethoxybenzoic acid (**8b**). On the other hand, the synthesis of catechol **5a** preferably follows route A, avoiding the lack of regiocontrol in the acylation of the unsymmetrical **8a** in route B.

Ideally, **6a** should be protected with groups that are able to participate in several steps (Scheme I): (i) give regioselective ortho-lithiation of **6a**, (ii) allow amidation of a sterically hindered acid, (iii) give regioselective bromination, and (iv) be removed without affecting the bromine or the easily demethylated methoxy group in the formation of **3**. It seemed attractive to utilize the catechol grouping and lithiate cyclic protected ketals and silyl ethers. However, either the introduction of the protective groups in the sensitive 3,4-dihydroxyanisol (**6a**) was inadequate or problems in selective deprotection were experienced. We also considered, among others, the 3,4-bis(pivaloyloxy)anisol and 3,4-bis((2,6-dichlorobenzyl)-oxy)anisol, but we were unable to lithiate these derivatives. Thus, we used a sequence of blocking and deblocking steps.

A third possibility to reach **2** and **3** was based on the finding that the [(1-ethyl-2-pyrrolidinyl)methyl]amide was an exellent ortho-director (route C).[11] Even with bulky

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(1) Florvall, L.; Ögren, S.-O. *J. Med. Chem.* **1982**, *25*, 1280–6.

(2) (a) Ögren, S.-O.; Florvall, L.; Hall, H.; Magnusson, O.; Ångeby-Möller, K. *Eur. J. Pharmacol.* **1984**, *102*, 459–74. (b) Ögren, S.-O.; Florvall, L.; Hall, H.; Magnusson, O.; Ångeby-Möller, K. *Acta Psychiat. Scand.* **1990**, *82* (Suppl. 358), 21–6. (c) Köhler, C.; Hall, H.; Magnusson, O.; Lewander, T.; Gustafsson, K. *Acta Psyciat. Scand.* **1990**, *82* (Suppl. 358), 27–36.

(3) (a) Högberg, T. *Drugs Future* **1991**, *16*(4), 333–57. (b) Högberg, T. *Drug Design Discov.*, in press.

(4) Högberg, T.; Rämsby, S.; Ögren, S.-O.; Norinder, U. *Acta Pharm. Suec.* **1987**, *24*, 289–328.

(5) Ögren, S.-O.; Högberg, T. *ISI Atlas of Science: Pharmacology* **1988**, 141–7.

(6) Theodorou, A. E.; Crockett, M.; Jenner, P.; Marsden, C. D. *J. Pharm. Pharmacol.* **1980**, *32*, 441–4.

(7) Lewander, T.; Westerbergh, S.-E.; Morrison, D. *Acta Psychiat. Scand.* **1990**, *82* (Suppl. 358), 92–8 and other papers in the same supplement.

(8) Widman, M.; Nilsson, L. B.; Bryske, B.; Lundström, J. *Arzneimittel-Forschung* **1993**, *43*, 287–97.

(9) (a) Gawell, L.; Hagberg, C.-E.; Högberg, T.; Widman, M. *Acta Chem. Scand.* **1989**, *43*, 476–80. (b) Gawell, L.; Ström, P.; Högberg, T. *Acta Chem. Scand.* **1992**, *46*, 981–4.

(10) Högberg, T.; Bengtsson, S.; de Paulis, S.; Johansson, L.; Ström, P.; Hall, H.; Ögren, S.-O. *J. Med. Chem.* **1990**, *33*, 1155–63.

(11) (a) Bengtsson, S.; Högberg, T. *J. Org. Chem.* **1989**, *54*, 4549–53. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

0022-3263/93/1958-3538$04.00/0

Scheme I

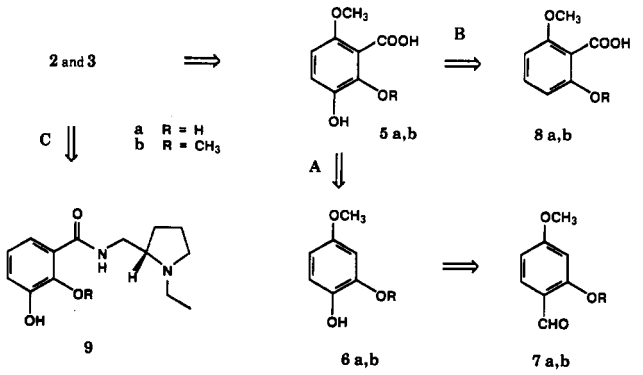
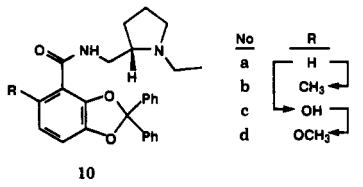


Chart I



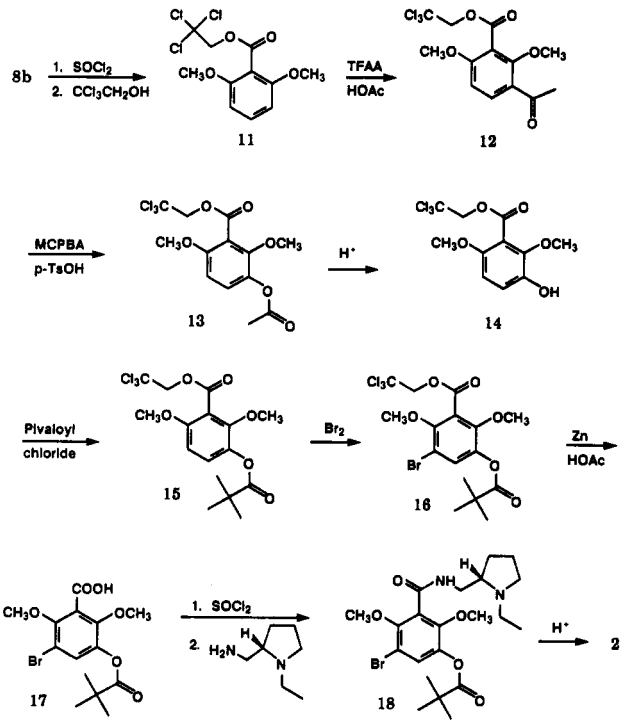
substituents as in **10a**, **10b** can be obtained in quite a good yield after metalation and methylation.[11] We synthesized **10c** via sequential treatment with n-BuLi, $B(OBu)_3$, and H_2O_2, although the yield was fairly low. However, the following methylation of the phenol under a number of conditions failed to produce **10d** in isolable amounts. This is in accordance with the failure to O-methylate other 6-methoxysalicylamides (unpublished results), which might be due to the coplanar arrangement of the intramolecularly H-bonded salicylamide. Consequently, route C was abandoned.

Results and Discussion

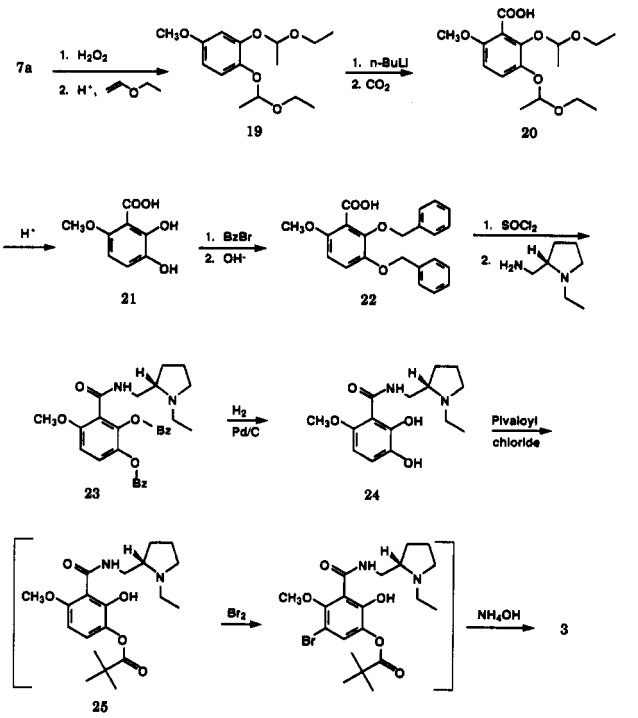
The route for preparation of the 2,6-dimethoxy-3-hydroxybenzamide **2** is outlined in Scheme II. Thus, 2,6-dimethoxybenzoic acid (**8b**) is transformed to its 2,2,2-trichloroethyl ester, which serves as an excellent protecting group in the subsequent steps and can be easily removed. C-Acetylation in the 3-position of the benzoate **11**, Bayer–Villiger oxidation of **12** giving the 3-acetoxy derivative **13**, and hydrolysis to **14** were performed in 71% overall yield, including the initial protecting step. Direct bromination of the free phenol gave a mixture of the 4- and 5-isomers (cf. the 5-hydroxy-6-methoxysalicylamide discussed below). Thus, we had to introduce a sterically bulky group in the 3-position of **14** and found the pivaloyl group to be suitable for this purpose. The bromination of **15** was performed to give compound **16** exclusively, in good yield. Reductive removal of the 2,2,2-trichloroethyl group with zinc in acetic acid and conversion of the substituted benzoic acid **17** into the corresponding acyl chloride, followed by addition of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine,[12] produced the benzamide **18**. Finally, the pivaloyl directing group was removed to give the hydrochloride of **2** in an overall yield of 22% from **8b**.

The main synthetic route to the 3-hydroxy-6-methoxysalicylamide **3** is presented in Scheme III. The 1-ethoxyethyl-protected catechol **19** was lithiated regiospecifically with n-BuLi in THF at −15 °C and quenched with solid

Scheme II



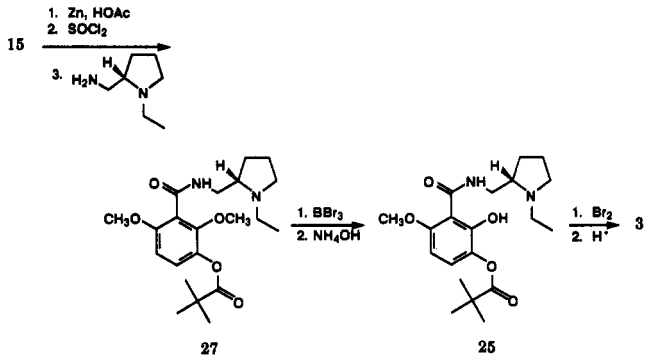
Scheme III



carbon dioxide. The resulting benzoic acid **20** was deprotected *in situ* to give the 3-hydroxy-6-methoxysalicylic acid (**21**) in a fair yield. Neither **21** nor **20** could withstand the following amidation conditions. Thus, compound **21** was treated with base and an excess of benzyl bromide and the obtained 2,3-bis(benzyloxy)-6-methoxybenzoic acid benzyl ester was hydrolyzed to give **22**. The conversion to the benzamide **23**, as well as the following hydrogenation to **24**, proceeded almost quantitatively. An excess of pivaloyl chloride was required for a complete acylation of the 3-hydroxy group in **24**. No acylation at the adjacent oxygen was observed. Thus, the following bromination was conducted *in situ* in the reaction mixture

(12) Högberg, T.; Rämsby, S.; Ström, P. *Acta Chem. Scand.* **1989**, *43*, 660–4.

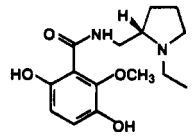
Scheme IV



with pivaloyl chloride present in order to ascertain total protection throughout the reaction. Deblocking afforded **3** as its oxalate salt in an overall yield of 13% from **7a**. The two bromo regioisomers were formed in a 2:1 ratio when the bulky pivaloyl group was absent.

An alternative route to **3** also takes advantage of the steric hindrance induced by the pivaloyl group (Scheme IV). We have shown earlier that 2,6-dimethoxy-substituted benzamides could be mono-demethylated with boron tribromide with preference for the sterically most hindered position.[13] Thus, the previously used **15** (Scheme II) was selectively deprotected and the benzoic acid **26** transformed to the amide **27**. This amide was monodemethylated to give the desired regioisomer **25** exclusively. Introduction of the bromine must be done as the subsequent step, and not earlier in the sequence, to ensure the selectivity in the demethylation step. Hydrolysis of the pivaloyl ester leads to **3** in an overall yield of 19% from 2,6-dimethoxybenzoic acid.

The synthesis of the 5-hydroxy-6-methoxysalicylamide **4** was mainly performed in accordance with the regioisomer **3** (cf. Scheme III) in an overall yield of 16% from 2-methoxyhydroquinone. The only difference was that, contrary to **24**, the (*S*)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-hydroxy-6-methoxysalicylamide (**28**) could be brominated regioselectively without the need of the bulky pivaloyl directing group.



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In summary, the regiospecific syntheses of **2** and **3** were performed in 11 and 12 steps, respectively. In addition, a key intermediate (**15**) in the synthesis of **2** could also be employed in an alternative route to the catechol **3**. The use of bulky directing groups to ensure regiocontrol in demethylation and halogenation of this type of heavily substituted oxygenated benzoic acid derivatives was found to be effective.

Experimental Section

Melting points were determined in open capillary tubes on a Mettler FP 61 apparatus and are uncorrected. ^{13}C NMR spectra were recorded on a Gemini 300 spectrometer and ^1H NMR on the same instrument or on a Varian EM 360 A spectrometer using Me_4Si as an internal standard. GLCs were run on an DB5 or CP Sil 19B capillary column. Preparative, centrifugally accelerated, TLCs were conducted on a Chromatotron from Harrison Research. Elemental analyses were performed by Mikro Kemi AB, Uppsala.

2,2,2-Trichloroethyl 2,6-Dimethoxybenzoate (11). 2,6-Dimethoxybenzoic acid (12.8 g, 70 mmol) dissolved in toluene was treated with an excess of thionyl chloride and a few drops of dimethylformamide. The solvent and the excess of thionyl chloride were evaporated, and the residual 2,6-dimethoxybenzoyl chloride was dissolved in dichloromethane. A solution of 2,2,2-trichloroethanol (12.6 g, 95 mmol) in dichloromethane was added. After the solution was stirred overnight, the solvent and excess 2,2,2-trichloroethanol were evaporated leaving a residue of crude **11** (97% on GLC). An analytical sample was recrystallized from EtOH: mp 72–74 °C; ^1H NMR ($CDCl_3$) δ 7.34 (1 H, t, J = 8.6 Hz), 6.59 (2 H, dd, J = 8.6 and 1.8 Hz), 4.98 (2 H, s), 3.83 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 165.4, 158.3, 132.2, 111.7, 104.2, 95.1, 74.7, 56.0. Anal. Calcd for $C_{11}H_{11}Cl_3O_4$: C, 42.13; H, 3.54. Found: C, 42.1; H, 3.3.

2,2,2-Trichloroethyl 3-Acetyl-2,6-dimethoxybenzoate (12). Crude **11** was heated with 50 mL of trifluoroacetic anhydride and 20 mL of acetic acid at 40 °C for 8 h followed by 16 h at room temperature. Chloroform was added, and the mixture was washed three times with water and 2 N NaOH (to get pH 6). Separation and evaporation of the organic solvent and flash chromatography of the residue on a short SiO_2 column afforded 23.3 g containing 90% (NMR) of the desired compound, which was used in the next step without further purification. The calculated yield was 83% from 2,6-dimethoxybenzoic acid. Recrystallization of a small amount from i-Pr_2O gave pure **12**: mp 85–86 °C; ^1H NMR ($CDCl_3$) δ 7.85 (1 H, d, J = 8.9 Hz), 6.79 (1 H, d, J = 8.9 Hz), 5.01 (2 H, s), 3.90 (3 H, s), 3.88 (3 H, s), 2.62 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 198.1, 164.6, 161.1, 159.1, 134.3, 125.8, 117.5, 107.1, 94.7, 75.0, 64.1, 56.3, 29.9. Anal. Calcd for $C_{13}H_{13}Cl_3O_5$: C, 43.91; H. 3.68. Found: C, 43.9; H, 3.4.

2,2,2-Trichloroethyl 3-Acetoxy-2,6-dimethoxybenzoate (13). To a solution of crude **12** (23.7 g, 65 mmol) in chloroform were added *m*-chloroperbenzoic acid (26.0 g, 150 mmol) and a catalytic amount (0.2 g) of *p*-toluenesulfonic acid. After the solution was stirred for 24 h at room temperature, water was added and the pH adjusted to 9 with aqueous NaOH. The organic layer was separated, washed twice with water, dried (Na_2SO_4), and evaporated. A small amount was purified by centrifugally accelerated TLC on SiO_2 with i-Pr_2O as eluent: ^1H NMR ($CDCl_3$) δ 7.13 (1 H, d, J = 9.2 Hz), 6.69 (1 H, d, J = 9.2 Hz), 4.98 (2 H, s), 3.87 (3 H, s), 3.83 (3 H, s), 2.33 (3 H, s): ^{13}C NMR ($CDCl_3$) δ 169.5, 164.1, 155.5, 151.1, 150.1, 137.2, 126.0, 117.5, 106.8, 94.7, 74.7, 62.1, 56.2, 20.6. Anal. Calcd for $C_{13}H_{13}Cl_3O_6$: C, 42.02; H, 3.53; O, 25.83. Found: C, 41.9; H, 3.3; O, 25.4.

2,2,2-Trichloroethyl 2,6-Dimethoxy-3-hydroxybenzoate (14). A solution of crude **13** in 150 mL of acetone was heated with 50 mL of 4 N HCl at 60 °C for 6 h. The acetone was evaporated and more water added followed by extraction three times with Et_2O. The combined organic phases were washed twice with water and some aqueous NH_3 (to get pH 7). Drying (Na_2SO_4) and evaporation of the solvent gave 19.2 g (85% from **12**) of the title compound with a purity of 95% (NMR). Centrifugally accelerated TLC on SiO_2 with i-Pr_2O as eluent furnished an analytical sample: ^1H NMR ($CDCl_3$) δ 7.01 (1 H, d, J = 9.2 Hz), 6.64 (1 H, d, J = 9.2 Hz), 5.3 (1 H, br), 4.96 (2 H, s), 3.90 (3 H, s), 3.79 (3 H, s): ^{13}C NMR ($CDCl_3$) δ 164.8, 151.3, 145.4, 143.1, 118.3, 116.3, 108.1, 94.8, 74.9, 62.4, 56.6. Anal. Calcd for $C_{11}H_{11}Cl_3O_5$: C, 40.09; H, 3.36; O, 24.27. Found: C, 39.8; H, 3.2; O, 24.2.

2,2,2-Trichloroethyl 2,6-Dimethoxy-3-pivaloylbenzoate (15). Pivaloyl chloride (10.8 mL, 90 mmol) was reacted with **14** (15.6 g, 45 mmol) in 30 mL of trifluoroacetic acid and 30 mL of chloroform at 60 °C for 16 h. The mixture was cooled, diluted with more chloroform, and washed four times with aqueous NH_3. Drying (Na_2SO_4) and evaporation of the solvent and purification by flash chromatography (SiO_2, i-Pr_2O) afforded 11.2 g (89%) of the desired product. A small amount was recrystallized from i-Pr_2O: mp 83–84 °C; ^1H NMR ($CDCl_3$) δ 7.08 (1 H, d, J = 9.2 Hz), 6.69 (1 H, d, J = 9.2 Hz), 4.98 (2 H, s), 3.86 (3 H, s), 3.83 (3 H, s), 1.38 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 177.2, 164.3, 155.5,

(13) de Paulis, T.; Hall, H.; Kumar, Y.; Rämsby, S.; Ögren, S.-O.; Högberg, T. *Eur. J. Med. Chem.* **1990**, *25*, 507–17.

150.4, 137.9, 126.0, 117.8, 107.0, 94.8, 74.9, 62.6, 56.4, 39.1, 27.1. Anal. Calcd for $C_{16}H_{19}Cl_3O_6$: C, 46.46; H. 4.63. Found: C, 47.1; H, 4.8.

2,2,2-Trichloroethyl 5-Bromo-2,6-dimethoxy-3-pivaloylbenzoate (16). Bromine (1.5 mL, 26 mmol) was added with cooling to 15 (8.28 g, 20 mmol) dissolved in 15 mL of trifluoroacetic acid and 15 mL of chloroform. After the solution was stirred for 4.5 h at room temperature, chloroform and aqueous NH_3 were added and the separated organic phase was washed twice with water. Drying (Na_2SO_4) and evaporation of the solvent followed by flash chromatography gave 11.5 g (90%) of 16: ^1H NMR ($CDCl_3$) δ 7.37 (1 H, s), 5.00 (2 H, s), 3.93 (3 H, s), 3.85 (3 H, s), 1.38 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 176.6, 163.3, 152.8, 149.5, 141.0, 130.0, 124.2, 111.4, 94.5, 75.1, 62.6, 39.1, 27.0. Anal. Calcd for $C_{16}H_{18}BrCl_3O_6$: C, 39.01; H, 3.68; O, 19.49. Found: C, 39.3; H, 3.7; O, 19.7.

5-Bromo-2,6-dimethoxy-3-pivaloylbenzoic Acid (17). Zinc powder (5.0 g, 76 mmol) was added in one portion at −5 °C to a solution of 16 (10.8 g, 22 mmol) in 150 mL of THF and 30 mL of 50% aqueous acetic acid. The mixture was stirred on an icebath for 3.5 h. After filtration the organic solvent was evaporated at 30 °C and the remaining aqueous residue was partitioned between Et_2O and water. The ether phase was washed with water and extracted with aqueous NH_3 followed by back extraction with Et_2O at pH 5. Flash chromatography of the residue on SiO_2 with i-Pr_2O/THF/HCOOH (40:10:0.4) yielded 5.0 g (63%): ^1H NMR ($CDCl_3$) δ 7.37 (1 H, s), 3.95 (3 H, s), 3.88 (3 H, s), 1.38 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 176.8, 169.9, 152.8, 149.9, 141.1, 129.6, 124.8, 111.6, 62.7, 62.6, 39.1, 27.0. Anal. Calcd for $C_{14}H_{17}BrO_6$: C, 46.56; H, 4.74; O, 26.58. Found: C, 46.6; H, 5.0; O, 26.7.

(*S*)-5-Bromo-2,6-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-pivaloylbenzamide (18). A solution of the acid 17 (4.70 g, 13 mmol), thionyl chloride (10 mL, 115 mmol), and 10 drops of DMF in 70 mL of toluene was stirred at 60 °C for 1.5 h. The solvent was evaporated, and the residue was dissolved in 100 mL of dichloromethane and evaporated again. The residual acyl chloride was dissolved in 100 mL of dichloromethane, and a solution of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[12] (2.44 g, 19 mmol) in 40 mL of dichloromethane was added with cooling. After the solution was stirred overnight, the solvent was evaporated and the residue was partitioned between 0.5 M HCl and Et_2O. The ether phase was extracted with water, and the combined water phases were made alkaline and extracted repeatedly with Et_2O. Drying (Na_2SO_4) and evaporation of the solvent gave 5.32 g (86% yield) of the pure (NMR) amide 18 as an oil: ^1H NMR ($CDCl_3$) δ 7.27 (1 H, s), 6.4 (1 H, br), 3.89 (3 H, s), 3.82 (3 H, s), 3.8-1.7 (11 H, m), 1.37 (9 H, s), 1.08 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 176.8, 164.4, 152.4, 149.1, 141.0, 128.9, 128.1, 111.5, 62.5, 62.4, 62.2, 53.4, 47.8, 40.8, 39.0, 27.9, 26.9, 22.4, 13.6. Anal. Calcd for $C_{21}H_{31}BrN_2O_5$: C, 53.51; H, 6.63; O, 16.97. Found: C, 53.7; H, 6.6; O, 17.6.

(*S*)-5-Bromo-2,6-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-hydroxybenzamide (2). The compound 18 (4.71 g, 10 mmol) was heated in 40 mL of 6 M HCl at 80 °C for 4 h. Ice was added, and the pH was adjusted to 9 with NH_3. The aqueous mixture was extracted five times with 200-mL portions of dichloromethane, and the combined organic phases were dried (Na_2SO_4) and evaporated to give 3.39 g (88%) of the base: ^1H NMR ($CDCl_3$) δ 7.28 (1 H, s), 6.6 (1 H, br), 3.84 (3 H, s), 3.82 (3 H, s), 3.8–1.7 (11 H, m), 1.10 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 166.1, 148.2, 146.2, 145.0, 127.3, 121.7, 111.3, 63.2, 62.4, 61.4, 53.3, 48.4, 40.7, 27.7, 22.4, 12.9. The base was dissolved in 50 mL of acetone and treated with HCl/EtOH affording 2.75 g (65% from 18) of the hydrochloride, mp 209–210 °C, after recrystallization from acetone. Anal. Calcd for $C_{16}H_{23}ClBrN_2O_4$: C, 45.35; H, 5.71; N, 6.61; O, 15.10. Found: C, 45.4; H, 5.8; N, 6.6; O, 15.1.

4-Methoxycatechol was synthesized according to the method by Paulsen[14] in 88% yield: ^1H NMR ($CDCl_3$) δ 6.74, 6.42 and 6.24 (3 H, AB^2), 3.60 (3 H, s).

1,2-Bis(1-ethoxyethoxy)-4-methoxybenzene (19). 4-Methoxycatechol (9.0 g, 64 mmol) was reacted with ethyl vinyl ether (14.2 g, 0.19 mol) and a catalytic amount (0.2 g) of trichloroacetic acid in 50 mL of dichloromethane at room temperature for 4 days. The mixture was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to give 15.8 g (82%) of crude product containing 5% of the monoprotected isomers: ^1H NMR ($CDCl_3$) δ 7.05, 6.74 and 6.52 (3 H, AB^2, J = 9.2 and 2.8 Hz), 5.40 (1 H, q), 5.26 (1 H, q), 3.73 (3 H, s), 1.45 (6 H, dd), 1.18 (3 H, t).

3-Hydroxy-6-methoxysalicylic Acid (21). To a stirred solution of crude 19 (9.6 g, 32 mmol) and *N,N,N',N'*-tetramethylethylenediamine (6.0 mL, 40 mmol) in 70 mL of anhydrous THF kept under N_2 was added *n*-butyllithium (26.7 mL of 1.5 M in hexane, 40 mmol) dropwise at −15 °C. After being stirred for 3 h the reaction mixture was poured into solid carbon dioxide in THF and left overnight. The mixture, containing 2,3-bis(1-ethoxyethoxy)-6-methoxybenzoic acid (20), was cooled to −10 °C. Concd HCl was added dropwise, and the mixture was stirred at room temperature for 6 h. The organic layer was separated, dried (Na_2SO_4), and concentrated affording 4.58 g (77%) of crystalline almost pure (NMR) 21. An analytical sample was prepared by recrystallization from i-Pr_2O: mp 128–129 °C; ^1H NMR ($CDCl_3$) δ 7.09 and 6.43 (2 H, AB, J = 9.2 Hz), 4.04 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.9, 151.8, 151.6, 140.9, 120.3, 101.7, 101.0, 56.8. Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.3; H, 4.5.

2,3-Bis(benzyloxy)-6-methoxybenzoic Acid (22). To a solution of 21 (4.41 g, 24 mmol) in 25 mL of dimethylformamide stirred at 60 °C were added 45% NaOH (4.5 mL, 72 mmol) and benzyl bromide (17.4 mL, 144 mmol) in portions during 5 h. After the reaction mixture was stirred at 60 °C overnight dichloromethane and water were added and the organic layer was washed with water and aqueous NaOH repeatedly. The obtained benzyl ester of 22 was heated in a mixture of 30 mL of 8 M NaOH, 90 mL of ethanol and 40 mL of dioxane at 80 °C for 5 h followed by stirring overnight at room temperature. The organic solvents were evaporated and the residue partitioned between water and Et_2O. The aqueous layer was acidified and extracted with Et_2O, and the organic phase was dried (Na_2SO_4) and evaporated. Recrystallization of the product from i-Pr_2O afforded 3.76 g (43%): mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 7.42–7.26 (10 H), 7.02 and 6.64 (2 H, AB, J = 9.0 Hz), 5.16 (2 H, s), 5.10 (2 H, s), 3.83 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.1, 151.8, 147.4, 146.4, 137.2, 137.1, 129.0, 128.8, 128.6, 128.3, 127.9, 118.7, 117.8, 106.9, 76.1, 72.2, 56.4. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 71.8; H, 5.5.

(*S*)-2,3-Bis(benzyloxy)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxybenzamide (23). Preparation from 22, by the procedure used for 18, gave the desired product in 89% yield after recrystallization from i-Pr_2O: mp 93–94 °C; ^1H NMR ($CDCl_3$) δ 7.44–7.27 (10 H), 6.93 and 6.59 (2 H, AB, J = 9.0 Hz), 6.2 (1 H, br), 5.08 (4 H, s), 3.78 (3 H, s), 3.8–1.6 (11 H, m), 1.00 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 166.0, 151.3, 146.8, 146.4, 137.7, 137.2, 128.8, 128.7, 128.4, 128.2, 128.1, 127.8, 123.4, 115.9, 106.5, 76.1, 71.8, 62.4, 56.0, 53.4, 47.8, 40.6, 27.7, 22.4, 13.7. Anal. Calcd for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22; N, 5.90; O, 13.48. Found: C, 73.5; H, 7.4; N, 5.9; O, 13.7.

(*S*)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-3-hydroxy-6-methoxysalicylamide (24) was prepared by hydrogenation (0.45 L of H_2, 20 mmol) of 23 (4.77 g, 10 mmol) in 70 mL of EtOH at normal pressure with palladium on charcoal (5%, 0.6 g) as catalyst. Filtration and evaporation gave 2.50 g (85%) after recrystallization from i-Pr_2O: mp 101–102 °C; ^1H NMR ($CDCl_3$) δ 9.0 (1 H, br), 6.94 and 6.29 (2 H, AB, J = 9.1 Hz), 5.08 (4 H, s), 3.87 (3 H, s), 3.7–1.6 (11 H, m), 1.13 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 170.9, 152.1, 151.8, 140.5, 116.7, 104.3, 100.2, 62.1, 56.2, 53.8, 48.0, 40.9, 28.6, 23.1, 14.3. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52; O, 21.74. Found: C, 61.5; H, 7.7; N, 9.5; O, 21.7.

(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-hydroxy-6-methoxysalicylamide (3). Method A. Pivaloyl chloride (1.80 mL, 15 mmol) and a catalytic amount (10 mg) of 4-(dimethylamino)pyridine (DMAP) were added to a cooled (ice bath) solution of the catechol 24 (1.47 g, 5.0 mmol) and pyridine (1.20 mL, 15 mmol) in chloroform (30 mL), and the reaction mixture was stirred for 18 h at room temperature. To the 3-pivaloyl derivative 25 obtained were added bromine (0.33 mL, 6.0 mmol) dissolved in 30 mL of chloroform and more pyridine (0.48 mL, 6.0 mmol), and the reaction mixture was stirred for another 5 h. The solvent was evaporated, and the residue was dissolved in 50 mL of MeOH and 7 mL (100 mmol) of concd NH_3

(14) Paulsen, A. *Medd. Norsk. Farm. Selskap* **1959**, *21*, 157–9.

and heated to 50 °C for 1 h. After evaporation of the MeOH, the residue was partitioned between Et_2O and aqueuos NH_3. The aqueous phase was extracted with another portion of ether and the combined organic phases were extracted repeatedly with water at pH 3 (dilute sulfuric acid). The combined aqueous phases were made alkaline with aqueous NH_3 and the product extracted with Et_2O. *n*-Hexane was added, and the solution was washed repeatedly with water to remove traces of pyridine and then dried (Na_2SO_4) and evaporated: ^1H NMR ($CDCl_3$) δ 8.9 (1 H, br), 7.17 (1 H, s), 3.83 (3 H, s), 3.8–1.6 (11 H, m), 1.13 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 169.3, 150.1, 148.2, 143.3, 120.7, 108.5, 104.8, 62.0, 61.9, 53.5, 47.9, 40.6, 28.5, 22.6, 14.1.

The semioxalate was prepared from the base dissolved in MeOH by addition of an oxalic acid solution (1.0 equiv). Recrystallization from MeOH afforded 1.35 g (65%): mp 165–166 °C. Anal. Calcd for $C_{16}H_{22}BrN_2O_6$: C, 45.95; H, 5.30; N, 6.70; O, 22.95. Found: C, 45.9; H, 5.2; N, 6.7; O, 22.8.

Method B. Bromination (0.15 mL, 2.7 mmol) of **25** (0.72 g, 1.9 mmol) in analogy with **16** gave 0.52 g (60%) of (*S*)-5-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxy-3-pivaloylsalicylamide after flash chromatography: ^1H NMR ($CDCl_3$) δ 8.8 (1 H, br), 7.32 (1 H, s), 3.89 (3 H, s), 3.7–1.7 (11 H, m), 1.37 (9 H, s), 1.07 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 176.9, 169.4, 155.4, 153.9, 137.5, 130.4, 110.0, 103.9, 62.7, 61.9, 53.4, 48.5, 40.5, 39.0, 28.4, 27.0, 22.4, 13.0. This intermediate (0.50 g, 1.10 mmol) was hydrolyzed in 2.5 mL of 6 M HCl and 1.5 mL of THF at 80 °C for 3 h. Ice was added, the pH adjusted to pH 9 with NH_3, and the mixture extracted five times with dichloromethane. The combined organic phases were extracted with aqueous HCl followed by back extraction from the aqueous phase by dichloromethane at pH 9. Drying (Na_2SO_4) and evaporation afforded the desired base. The semioxalate was prepared and recrystallized from MeOH, yield 0.20 g (44%). The benzamide **3** achieved by this route had spectroscopic and physical properties as above.

2,6-Dimethoxy-3-pivaloylbenzoic acid (26) was prepared from **15** in analogy with the bromo analog **17** in 67% yield: mp 125–126 °C; ^1H NMR ($CDCl_3$) δ 7.08 (1 H, d, J = 9.0 Hz), 6.71 (1 H, d, J = 9.0 Hz), 3.88 (3 H, s), 3.87 (3 H, s), 1.38 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 177.3, 170.0, 155.4, 150.6, 138.2, 125.9, 118.0, 107.1, 62.7, 56.5, 39.0, 27.1. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 58.9; H, 6.1.

(*S*)-2,6-Dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-pivaloylbenzamide (27) was prepared from **26**, by the procedure used for **18**, in 79% yield. An analytical sample had: mp 133–134 °C (*i*-Pr_2O); ^1H NMR ($CDCl_3$) δ 6.97 (1 H, d, J = 8.9 Hz), 6.65 (1 H, d, J = 8.9 Hz), 6.3 (1 H, br), 3.83 (3 H, s), 3.80 (3 H, s), 3.7–1.7 (11 H, m), 1.37 (9 H, s), 1.07 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 177.4, 165.5, 154.9, 149.8, 137.9, 124.0, 122.7, 106.6, 62.5, 62.3, 55.9, 53.4, 47.8, 40.5, 38.9, 27.7, 27.0, 22.4, 13.6. Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; O, 20.38. Found: C, 64.2; H, 8.2; O, 20.5.

(*S*)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-6-methoxy-3-pivaloylsalicylamide (25). A solution of **27** (0.79 g, 2.0 mmol) and HCl (2.0 mmol in Et_2O) in 20 mL of dichloromethane was treated with BBr_3 (2.0 mmol) in 4 mL of dichloromethane at 5–10 °C. The reaction mixture was stirred for 2 h at room temperature and quenched with 10 mL of 2 M NH_3. Extraction with dichloromethane, drying (Na_2SO_4), and evaporation of the solvent followed by flash chromatography (*i*-PrOH/THF/concd NH_3 (60:60:1)) gave 0.67 g (89%) of pure **25** as an oil. No 6-hydroxy-2-methoxy isomer could be detected by GLC or NMR: ^1H NMR ($CDCl_3$) δ 8.9 (1 H, br), 7.03 (1 H, d, J = 9.0 Hz), 6.34 (1 H, d, J = 9.0 Hz), 3.92 (3 H, s), 3.7–1.7 (11 H, m) 1.38 (9 H, s), 1.13 (3 H, t); ^{13}C NMR ($CDCl_3$) δ 177.5, 170.4, 156.6, 134.5, 128.2, 125.9, 105.2, 99.6, 62.0, 56.0, 53.6, 47.9, 40.6, 39.0, 28.3, 27.1, 22.9, 13.9. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 8.00. Found: C, 63.0; H, 8.5.

1,4-Bis(1-ethoxyethoxy)-2-methoxybenzene (29) was prepared from 2-methoxyhydroquinone analogous to **19** in a yield of 89%: ^1H NMR ($CDCl_3$) δ 7.13 and 6.99 (1 H), 6.72–6.47 (2 H), 5.36 (1 H, q), 5.26 (1 H, q), 3.86 (3 H, s), 3.66 (4 H, q), 1.47 (6 H, d), 1.22 (6 H, t).

3,6-Dihydroxy-2-methoxybenzoic acid (30) was obtained as an almost pure oil (NMR) in 71% yield by preparation from **29** in analogy with **21**. An analytical sample had: mp 154–155 °C ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.18 and 6.72 (2 H, AB), 4.03 (3 H, s). Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38; O, 43.44. Found: C, 52.1; H, 4.3; O, 43.3.

3,6-Bis(benzyloxy)-2-methoxybenzoic acid (31) was prepared from **30** in analogy with **22**: yield 65%; mp 118–119 °C (*i*-Pr_2O); ^1H NMR ($CDCl_3$) δ 7.44–7.30 (10 H), 6.95 and 6.65 (2 H, AB, J = 9.2 Hz), 5.10 (2 H, s), 5.07 (2 H, s), 3.99 (3 H, s). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53; O, 21.95. Found: C, 72.7; H, 5.5; O, 22.3.

(*S*)-3,6-Bis(benzyloxy)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxybenzamide[10] (32) was synthesized from **31** by the procedure used for **18** in 90% yield: mp 124–125 °C (*i*-Pr_2O); ^1H NMR ($CDCl_3$) δ 7.44–7.30 (10 H, m), 6.89 and 6.59 (2 H, AB, J = 9.2 Hz), 5.07 (2 H, s), 5.04 (2 H, s), 3.96 (3 H, s), 3.8–1.6 (11 H, m), 1.08 (3 H, t). Anal. Calcd for $C_{29}H_{34}N_2O_4$: C, 73.39; H. 7.22; N, 5.90. Found: C, 73.2; H, 7.2; N, 5.8.

(*S*)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-5-hydroxy-6-methoxysalicylamide[10] (28). Dibenzyl ether **32** (4.7 g, 10 mmol) was dissolved in 100 mL of EtOH and hydrogenated for 1 h (0.45 L, 20 mmol, H_2) at normal pressure with Pd on charcoal (5%, 0.7 g) as catalyst. After filtration and evaporation the residue solidified upon treatment with Et_2O to give 2.7 g (92%) of **28**: mp 107–108 °C; ^1H NMR ($CDCl_3$/MeOD) δ 7.13 and 6.67 (2 H, AB, J = 9.2 Hz), 3.99 (3 H, s), 3.9–1.7 (11 H, m), 1.13 (3 H, t). Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.2; H, 7.6; N, 9.5.

(*S*)-3-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-hydroxy-6-methoxysalicylamide[10] (4). To a stirred solution of compound **28** (1.48 g, 5.0 mmol) in 10 mL of dioxane and 5 mL of acetic acid was added a solution of bromine (0.29 mL, 5.5 mmol) in 10 mL of dioxane dropwise at 0 °C. The reaction mixture was stirred for 0.5 h at room temperature and then partitioned between 400 mL of water and 75 mL of Et_2O. The aqueous layer was made alkaline with NH_3 to pH 9.5 and extracted with four 100-mL portions of Et_2O. The combined organic phases were dried (Na_2SO_4), concentrated to 200 mL, and treated with HCl/Et_2O to give 1.22 g of crude hydrochloride. Recrystallization from acetone/MeOH afforded 0.96 g (47%): mp 189–190 °C; ^1H NMR (base, $CDCl_3$) δ 12.2 (br), 9.2 (br), 7.40 (1 H, s), 3.94 (3 H, s), 3.9–1.4 (11 H, m), 1.15 (3 H, t); ^{13}C NMR (base, $CDCl_3$) δ 169.3, 152.9, 145.9, 141.4, 125.4, 108.6, 106.5, 62.5, 61.7, 53.5, 48.3, 40.9, 28.6, 22.7, 13.6. Anal. Calcd for $C_{15}H_{22}BrClN_2O_4$: C, 43.97; H, 5.41; N, 6.84; Br, 19.50. Found: C, 43.9; H, 5.5; N, 6.9; Br, 19.6.