Reductive Amination with Tritylamine as an Ammonia Equivalent: Efficient Preparation of the 5-[4-[[(9-Fluorenylmethyloxycarbonyl)-amino]methyl]-3,5-dimethoxyphenoxy]valeric Acid (PAL) Handle for Peptide Synthesis[1]

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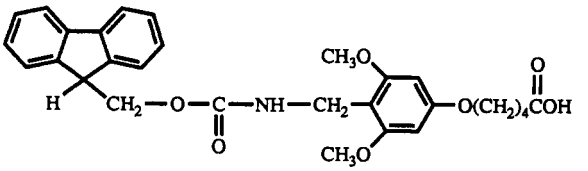
Many naturally occurring peptides exist as *C*-terminal peptide amides, and synthetic peptide substrates and probes for enzymological or immunological studies are often required with this end group. The recent popularity of methods of solid-phase peptide synthesis[4] which use the 9-fluorenylmethyloxycarbonyl (Fmoc) group for N^{α}-amino protection[4c-f,5] has created a need for companion anchoring linkages and handles directed toward peptide amides. This need has been met by the introduction of the acid-labile 5-[4-[[(9-fluorenylmethyloxycarbonyl)-amino]methyl]-3,5-dimethoxyphenoxy]valeric acid[6] (PAL) handle 1 from one of our laboratories[7] and by additional useful compounds and resins from us[8] or others.[9] The tris(alkoxy)benzyl theme has also borne fruit with a highly acid-sensitive handle (HAL) for anchoring peptide acids,[10] and 2,4,6-trimethoxybenzyl (Tmob) protecting groups for the side chains of asparagine, glutamine, and cysteine.[11,12]



PAL, 1 [*para* isomer as drawn]
1' [*ortho* isomer, CH_3O and $O(CH_2)_4CO_2H$ are switched]

The present note describes novel alternatives to the published routes[7] for the preparation of PAL. The new routes are variations on reductive aminations;[13,14] these procedures reveal several interesting features which may therefore provide generality beyond this application to peptide chemistry.

Results and Discussion

Initial Studies and Controls on Reductive Amination. A key transformation in the earlier-described syntheses of PAL[7] and Tmob-NH_2[11] is the reductive conversion of a hindered electron-rich carbonyl to an aminomethyl group. This can be accomplished in two steps by catalytic hydrogenolysis of an isolated oxime intermediate (Scheme IA); yields are reasonable but scale-up is occasionally cumbersome. An obvious alternative which might simplify these procedures involves reductive amination with ammonia or an ammonium salt (Scheme IA*). Initial experiments toward this end in one of our laboratories proved futile,[7b] but an independently initiated effort[2a] prior to our joint work gave more encouraging results. Thus, reaction of representative aldehyde precursors **2** with ammonium acetate in refluxing methanol in the presence of molecular sieves, followed by treatment with sodium cyanoborohydride,[13] provided among other products the desired tris(alkoxy)benzylamines **3**. Although **3** could be isolated by silica gel chromatography and carried forward to useful products (e.g., **1** and **1'** obtained in series **d** and **c'**, respectively), the yields were marginal even in the best cases. Systematic studies in several systems and under a variety of conditions revealed that the *major* product from reductive amination is the secondary amine **6**[15] resulting from further reaction of amine **3** with starting aldehyde **2**. The molar ratios of **3** to **6** ranged from 1:3 to 1:1, meaning that although **2**

(1) The following abbreviations are used: DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; FABMS, fast atom bombardment mass spectrometry; Et_2O, diethyl ether; EtOAc, ethyl acetate; Fmoc, 9-fluorenylmethyloxycarbonyl; HOAc, acetic acid; HPLC, high performance liquid chromatography; MeOH, methanol; OSu, *N*-succinimidyl ester; PAL, title handle of this paper; Tmob, 2,4,6-trimethoxybenzyl; TFA, trifluoroacetic acid; Trt, triphenylmethyl (trityl); t_R, retention time. All solvent ratios and percentages are volume/volume unless stated otherwise.

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(4) Reviews: (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154. (b) Merrifield, R. B. *Science* **1986**, *232*, 341–347. This is an updated version of Merrifield's Nobel Prize lecture, which has been reprinted in several other journals. (c) Barany, G.; Kneib-Cordonier, N.; Mullen, D. G. *Int. J. Pept. Protein Res.* **1987**, *30*, 705–739. (d) Atherton, E.; Sheppard, R. *Solid Phase Peptide Synthesis: A Practical Approach*, IRL Press, Oxford, 1989. (e) Fields, G. B.; Noble, R. L. *Int. J. Pept. Protein Res.* **1990**, *35*, 161–214. (f) Fields, G. B.; Tian, Z.; Barany, G. In *Synthetic Peptides: A User's Guide*; Grant, G. A., Ed.; Chapter 3; W. H. Freeman and Co.: New York, 1992; pp 77–183.

(5) (a) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409. (b) Meienhofer, J.; Waki, M.; Heimer, E. P.; Lambros, T. J.; Makofske, R. C.; Chang, C.-D. *Int. J. Pept. Protein Res.* **1979**, *13*, 35–42.

(6) Since 1988, the title handle and closely allied structures have been made commercially in >100-g lots and marketed by Milligen/Biosearch under the user-friendly acronym PAL (*P*eptide *A*mide *L*inker). The corresponding functionalized support is marketed as PAL-resin.

(7) (a) Albericio, F.; Barany, G. *Int. J. Pept. Protein Res.* **1987**, *30*, 206–216. (b) Albericio, F.; Kneib-Cordonier, N.; Biancalana, S.; Gera, L.; Masada, R. I.; Hudson, D.; Barany, G. *J. Org. Chem.* **1990**, *55*, 3730–3743. (c) Albericio, F.; Barany, G. *Int. J. Pept. Protein Res.* **1993**, *41*, 307–312, and refs cited in all of these papers.

(8) (a) Hammer, R. P.; Albericio, F.; Gera, L.; Barany, G. *Int. J. Pept. Protein Res.* **1990**, *36*, 31–45. (b) Bontems, R. J.; Hegyes, P.; Bontems, S. L.; Albericio, F.; Barany, G. In *Peptides: Chemistry and Biology*; Smith, J. A.; Rivier, J. E., Eds.; Escom: Leiden, The Netherlands, 1992; pp 601–602.

(9) (a) Sieber, P. *Tetrahedron Lett.* **1987**, *28*, 2107–2110. (b) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787–3790. (c) Funakoshi, S.; Murayama, E.; Guo, L.; Fujii, N.; Yajima, H. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2791–2800. (d) Stüber, W.; Knolle, J.; Breipohl, G. *Int. J. Pept. Protein Res.* **1989**, *34*, 215–221. (e) Penke, B.; Nyerges, L. *Pept. Res.* **1991**, *4*, 289–295. (f) Pátek, M.; Lebl, M. *Tetrahedron Lett.* **1991**, *31*, 3891–3894. This listing, while not exhaustive, highlights the most significant approaches.

(10) Albericio, F.; Barany, G. *Tetrahedron Lett.* **1991**, *32*, 1015–1018.

(11) The 2,4,6-trimethoxybenzyl (Tmob) protecting group for the N^{ω}-carboxamide side chains of asparagine and glutamine was reported by Derek Hudson at the 10th American Peptide Symposium, St. Louis, MO, May 23–28, 1987.

(12) Munson, M. C.; García-Echeverría, C.; Albericio, F.; Barany, G. *J. Org. Chem.* **1992**, *57*, 3013–3018.

(13) The seminal paper on reductive aminations with sodium cyanoborohydride is: Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904. In this paper, amine, aldehyde, and $NaBH_3CN$ are stirred together with molecular sieves in dry MeOH for 48 h at 25 °C; for the present work, we find that chemically equivalent results are obtained, more rapidly, by carrying out reactions at reflux. There was no difference when amine and aldehyde were preincubated prior to addition of reducing agent.

(14) Reviews: (a) Lane, C. F. *Synthesis* **1975**, 135–146. (b) Klyuev, M. V.; Khidekel', M. L. *Russ. Chem. Rev.* **1980**, *49*, 14–27.

(15) The formation of secondary amines during reductive amination with ammonia has been reported previously; see discussions in Borch *et al.* (ref 13) as well as: March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; pp 898–900.

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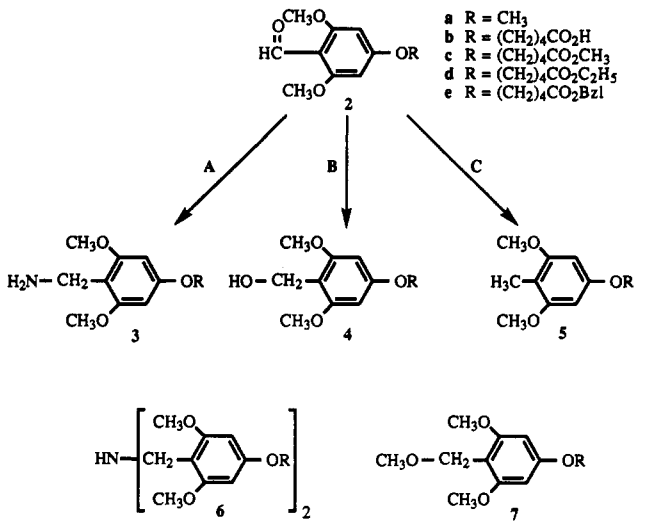
Scheme I[a,b]

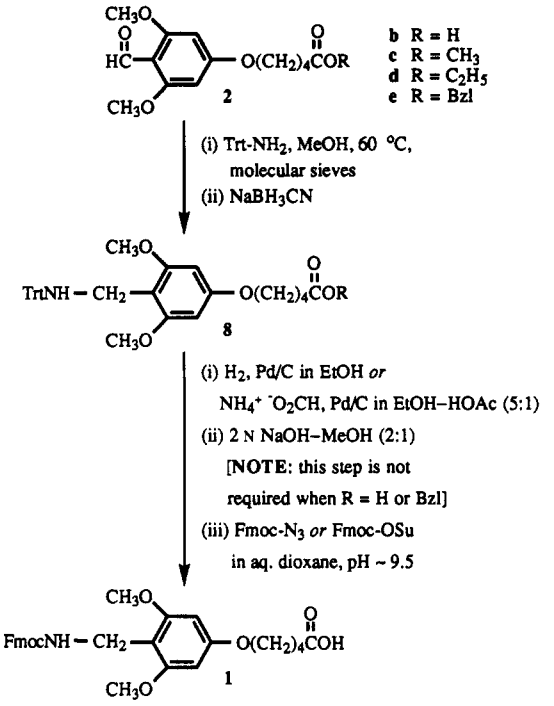


[a] *Conditions*: (A) Two steps: (i) NH_2OH + base, (ii) H_2, Pd/C (refs 7, 11); (A*) NH_4OAc + $NaBH_3CN$ in MeOH, forms **3** as well as secondary amine **6**, although little or no **4** (this work, see text and ref 16). Substitution of NH_4Cl for NH_4OAc gave essentially identical results; (B) $NaBH_4$ in 2 N NaOH–MeOH (1:1) (refs 10, 12) or neat MeOH (ref 16); (B*) $NaBH_3CN$ in MeOH–HOAc (20:1), forms principally methyl ester **7**, as well as some alcohol **4** (this work, see text); (C) $NaBH_3CN$ in HOAc (this work, see text and ref 16). [b] As appropriate, only the *para* isomers are drawn. The corresponding chemistry also applies for the *ortho* isomers; these latter compounds are designated by the same structural formula number, with a prime (′) added. Pathway A has been demonstrated in series **b**, **b′**, **d**, **d′**; pathway A* in series **a**, **b**, **b′**, **c′**, **d**; pathway B in series **a**, **b**, **d**; pathway B* in series **d**; and pathway C in series **a**, **b**, **b′**, **c′**, **d**.

could be converted completely, *at most* only one-third of this material was retained as the desired mono-adduct **3**.[16]

The initial work on the reductive amination theme paralleled our interest in the direct reduction (absence of ammonia source) of aldehydes **2** to provide the corresponding benzyl alcohols **4** (Scheme IB).[10,12] In fact, the mechanistic requirements of these two transformations are quite distinct. When ammonium acetate was omitted from reduction conditions with sodium cyanoborohydride that would otherwise convert **2** to a mixture of **3** and **6**, no reaction took place (i.e., starting **2** recovered and no **4** formed). On the other hand, reductions of **2** carried out in *neat* acetic acid resulted in clean conversions of the formyl group to a methyl group, as in structures **5** (Scheme IC),[17] *irrespective* of the presence or absence of ammonium salts. Compounds **5** are explained readily by assuming that alcohols **4** are intermediates; in acid, these are protonated, lose water to form a highly stabilized tris(alkoxy)benzyl carbonium ion, and are finally quenched by hydride from the reducing agent. In support of this idea, alcohols **4** were the minor product (15%) from cyanoborohydride reduction of aldehydes **2** in the presence of *dilute* acetic acid (Scheme IB*); major products in this variation were the methyl ethers **7** (85%) resulting from trapping of the tris(alkoxy)benzyl carbonium ion with the solvent, methanol.

Scheme II[a]



[a] Shown for *para* isomer (compare to legend to Scheme I). Scheme II as shown was carried out for series **c′**, **d**, and **e′**. Series **b** was not effective in practice, for reasons discussed in the text.

Reductive Amination with Tritylamine as an Ammonia Equivalent. The triphenylmethyl function, also known as trityl (Trt), is a valuable sterically bulky protecting group for peptide, carbohydrate, and nucleotide chemistry.[18] Trityl groups confer acid-labile protection onto alcohols, thiols, and amines; occasionally, effective removal can also be achieved by catalytic hydrogenolysis. Recently, triphenylmethylamine (tritylamine, Trt-NH_2), was reported as an ammonia equivalent for the preparation of novel imine intermediates.[19] We reasoned that a one-pot reductive amination reaction of tritylamine with aldehydes **2** would provide tritylated aminobenzyl monoadducts **8**, without the further dialkylation described previously when ammonium salts were applied (Scheme IA*). This prediction was borne out in practice; conditions were developed to achieve the desired transformation in excellent yield and purity (Scheme II, first stage).

Application to Preparation of PAL, and Additional Variations and Improvements. Tritylated derivatives **8**, available by reductive amination, were converted readily in three further steps, carried out in high yield without isolation of intermediates, to provide the target PAL compounds **1** (Scheme II, second stage). The critical step was detritylation,[18] since ester saponification and introduction of the Fmoc group were entirely precedented in earlier work.[7a,b] Attempted removal of Trt under various *acid* conditions was unsuccessful in several ways, as

(16) Due to space limitations further discussion and/or experimental documentation on this theme is found with the supplementary material.

(17) Precedents for this transformation include: (a) reduction of 2,4,6-trimethoxybenzaldehyde (**2a**) with H_2 and Pt in ether to give 2,4,6-trimethoxytoluene (**5a**); see: Freudenburg, K.; Harder, M. *J. Liebigs Ann. Chem.* **1926**, *451*, 213–222. (b) Hydrogenolysis of electron-rich benzaldehydes (especially 3,4-dimethoxybenzaldehyde) and benzophenones with BH_3 in the presence of BF_3, to yield the corresponding hydrocarbons; see: Breuer, E. *Tetrahedron Lett.* **1967**, *20*, 1849–1854. (c) Reductive conversions of various alkyl substituted benzaldehydes with Li/NH_3 to the corresponding toluenes; see: Hall, S. S.; Bartels, A. P.; Engman, A. M. *J. Org. Chem.* **1972**, *37*, 760–762.

(18) Reviews: (a) Gross, E.; Meienhofer, J., Eds., *The Peptides: Analysis, Synthesis, Biology*; *Vol. 3: Protection of Functional Groups in Peptide Synthesis*; Academic Press: New York, 1981. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley-Interscience, New York, 1991.

(19) Soroka, M.; Zygmunt, J. *Synthesis* **1988**, 370–372.

emphasized by the unexpected finding that the ester could be cleaved while the tritylamine function remained unaffected. Harsher acid conditions gave rise to tritylamine from undesired N–CH_2 bond cleavage, and additional trityl-derived coproducts or byproducts from trityl–N bond cleavage. Fortunately, the wanted removal of Trt from 8 was accomplished readily by catalytic *hydrogenolysis*, both in the standard[18] and catalytic transfer (with ammonium formate as the hydrogen source[20]) modes.

A further simplification of the PAL synthesis was achieved in the benzyl ester series **e**.[21] The prior saponification step [Scheme II, second stage, step (ii)] could now be omitted, since the catalytic hydrogenolysis step removed the *N*-trityl and *O*-benzyl groups simultaneously. However, the simplest alternative, namely working with the free acids (series **b**, R = H), was impractical because attempted detritylation of **8b** was very sluggish, perhaps due to the low solubility of the substrate. Such a reaction sequence provided little **1**, with considerable levels of **8b** recovered as well as additional byproducts formed.[22] Finally, attempts to repeat the title route (Scheme II) using benzylamine in place of tritylamine as an ammonia equivalent were unsatisfactory, for a variety of reasons.[16]

Experimental Section

General Procedures. Materials, solvents, instrumentation, and general methods were essentially as described in recent previous publications.[7,8,12] ^{1}H NMR spectra were obtained on Varian EM-390, Megnachem A-200, IBM NR-200, IBM NR-300, or Varian VXR-300 spectrometers. Mass spectra were determined on Finnigan MAT Model 8430 or VG 7070E-HF instruments. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Analytical HPLC was carried out with a Beckman instrument using a Vydac C-18 column, detection at 215 or 280 nm, and linear gradients over 15 min of 0.1% TFA in CH_3CN and 0.1% aqueous TFA from 1:9 to 3:1, flow rate 1.2 mL/min.

5-[4-[[(Fmoc)amino]methyl]-3,5-dimethoxyphenoxy]valeric Acid (1). Method A. (Scheme II, series **d**, second stage with catalytic transfer hydrogenolysis to remove Trt group). Trityl precursor **8d** (1.0 g, 1.8 mmol) was suspended in a mixture of absolute EtOH (60 mL) and glacial HOAc (12 mL), and ammonium formate (1.34 g, 21 mmol) was added. Reduction began with the addition of 10% Pd/C (100 mg) and continued with stirring for 50 h at 25 °C. TLC revealed that the reaction was almost complete, although a small amount of starting material remained. The reaction mixture was filtered, concentrated, and triturated with *n*-hexane (3 × 10 mL) to remove starting material and triphenylmethane. The residue, a light-green oil (0.47 g, 1.26 mmol, 70%), was essentially pure amine **3d** (as its acetate salt) suitable for carrying forward to the next step without purification, TLC R_f 0.24 [acetone–EtOH–H_2O (12:1:1), yellow to ninhydrin spray]. This product was dissolved in a mixture of dioxane (10 mL) and 2 N NaOH (10 mL) and stirred for 2 h at 25 °C (no starting ester remained by TLC). A solution of Fmoc-N_3 (0.35 g, 1.3 mmol) in dioxane (6 mL) was added dropwise over 25 min, and the reaction mixture was stirred for an additional 2 h at 25 °C, while maintaining the pH at 9.5 by the addition of 10% aqueous Na_2CO_3 (w/v). H_2O (150 mL) was then added and the solution was acidified carefully to pH 3.0 using 6 N aqueous HCl under cooling. The aqueous solution was extracted with EtOAc (2 × 20 mL), and the combined organic phases were washed with saturated NaCl (2 × 30 mL) and H_2O (1 × 30 mL), dried ($MgSO_4$), and concentrated to give a yellow powder: yield 0.50 g (55%, based on **8d**). An analytical sample was obtained from EtOH: mp 174–176 °C (lit.[7b] 178–180 °C); HPLC t_R 20.0 min; ^{1}H NMR ($CDCl_3$) δ 7.25–7.75 (m, 8H), 6.11 (s, 2H), 5.15 (broad, NH), 4.33–4.43 (m, 5H), 3.98 (t, 2H), 3.61 (s, 6H), 2.45 (t, 2H), 1.84 (m, 4H). Anal. Calcd for $C_{29}H_{31}NO_7$, MW 505.57: C, 68.90; H, 6.18; N, 2.77. Found: C, 68.76; H, 6.20; N, 2.84.

Method B. (Scheme II, series **c**, second stage with standard catalytic hydrogenolysis). The title product was obtained on a 0.93-mmol scale in 82% yield by following the procedure given immediately below for the *ortho* isomer 1′: mp 175–176 °C; ^{1}H NMR ($CDCl_3$) identical to material by method A. Anal. Calcd for $C_{29}H_{31}NO_7$, MW 505.57: C, 68.90; H, 6.18; N, 2.77. Found: C, 69.00; H, 6.17; N, 2.82.

5-[2-[[(Fmoc)amino]methyl]-3,5-dimethoxyphenoxy]valeric Acid (1′). A suspension of trityl precursor **8c′** (0.5 g, 9.28 mmol) in a mixture of EtOAc (75 mL) and glacial HOAc (10 mL) was hydrogenated for 2 h at 25 °C at atmospheric pressure in the presence of 10% Pd/C (100 mg) (reaction complete as judged by TLC). The reaction mixture was filtered and diluted with H_2O (50 mL), and the organic layer was discarded. The aqueous layer was washed further with EtOAc (2 × 50 mL) to remove traces of triphenylmethane, and then diluted with MeOH (25 mL). Solid NaOH (4 g, 0.1 mol) was added, and saponification proceeded (net 2 N base) with stirring at 25 °C for 3 h (complete as judged by TLC in EtOH). The pH was adjusted to 9.5 using 6 N HCl, and Fmoc-OSu (0.31 g, 9.3 mmol) dissolved in dioxane (5 mL) was added slowly over 15 min. The solution was stirred for an additional 4 h, with the pH maintained at 9.5 by addition of 10% aqueous Na_2CO_3. The mixture was acidified carefully under cooling with 6 N HCl to pH 3.0, and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried ($MgSO_4$), and concentrated to give a white solid. Recrystallization (two crops) from MeOH provided 0.39 g (82%) of title product: mp 114–116 °C (lit.[7b] 116–118 °C); ^{1}H NMR ($CDCl_3$) δ 7.25–7.75 (m, 8H), 6.11 (d, 2H), 5.27 (t, NH), 4.14–4.43 (m, 5H), 3.97 (t, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.46 (t, 2H), 1.79–1.92 (m, 4H); isobutane CIMS *m/z* 505 ($M^{+\cdot}$), 327, 282. Anal. Calcd for $C_{29}H_{31}NO_7$, MW 505.57: C, 68.90; H, 6.18; N, 2.77. Found: C, 69.12; H, 6.35; N, 2.75.

Reductive Amination of Aldehydes with Ammonium Chloride or Acetate. (Scheme IA*). As described in the text, bis-adducts **6** predominated, despite attempts to maximize the formation of the mono-adducts **3**. Numerous reaction parameters, including nature of ammonium salt, concentrations of reagents, reaction temperatures, etc., were varied, with no significant difference in outcome. Either a two-stage [compare to later procedures for **8**] or a one-stage[13] method gave similar results. Representative experiments are provided in the supplementary material, which includes spectral characteristics of products and information on acetylated and/or Fmoc-derivatives which were prepared to facilitate differentiation of **3**, **4**, and **6**.

Treatment of Ethyl 5-(4-Formyl-3,5-dimethoxyphenoxy)valerate (2d) with $NaBH_3CN$ in MeOH–HOAc (20:1) (Scheme IB*). Aldehyde **2d**[7b] (0.25 g, 0.81 mmol) was dissolved in dry MeOH (10 mL), glacial HOAc (0.5 mL) was added, and $NaBH_3CN$ (76 mg, 1.2 mmol) was then added portionwise. The reaction mixture was stirred under N_2 for 4 h at 25 °C and then diluted with H_2O (75 mL) and extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with H_2O (3 × 75 mL) and brine (2 × 75 mL), dried (Na_2SO_4), and concentrated to an oil (0.25 g, quantitative). ^{1}H NMR indicated a mixture of **ethyl 5-[4-(hydroxymethyl)-3,5-dimethoxyphenoxy]valerate (4d)** and **ethyl 5-[4-(methoxymethyl)-3,5-dimethoxyphenoxy]valerate (7d)** in a ratio of about 3:17. For **4d**: ^{1}H NMR ($CDCl_3$) δ 6.08 (s, 2H), 4.67 (s, 2H), 4.11 (q, 2H), 3.95 (t, 2H), 3.78 (s, 6H), 2.36 (t, 2H), 1.80 (m, 4H), 1.23 (t, 3H). For **7d**: δ 6.08 (s, 2H), 4.45 (s, 2H), 4.11 (q, 2H), 3.95 (t, 2H), 3.78 (s, 6H), 3.32 (s, 3H), 2.36 (t, 2H), 1.80 (m, 4H), 1.23 (t, 3H).

Reduction of Aldehyde Groups to Methyl Groups with $NaBH_3CN$ in Acetic Acid (Scheme IC). Results were uniform with both the *para* and *ortho* (′) series, and there was no difference whether the ω-carboxyl was free (series **b**) or esterified (series **c**,

(20) Review: Ram, S.; Ehrenkaufer, R. E. *Synthesis* 1988, 91–95.

(21) Benzyl 5-chlorovalerate and benzyl 5-bromovalerate are new compounds, made by straightforward esterification of the corresponding ω-halovaleric acid (ref 16). These were used to alkylate 4-formyl-3,5-dimethoxyphenol or 2-formyl-3,5-dimethoxyphenol by precedented chemistry (ref 7b), providing starting materials **2e** and **2e′** for Scheme II.

(22) Even if the just-discussed chemistry (Scheme II, second stage, series **b**) were more successful, this approach would represent no significant saving of effort because substrates **2b** are anyhow derived by saponification of esters **2c** or **2d**. We showed earlier (ref 7b) that direct alkylation of appropriate phenolic precursors with 5-bromovaleric acid gave desired products in poor yields.

d). There follows a typical procedure (series d). Scale, yields, and analytical data from other experiments are with the supplementary material.

$NaBH_3CN$ (0.25 g, 4.0 mmol) was added portionwise over 10 min under ambient conditions to a stirred solution of ethyl 5-(4-formyl-3,5-dimethoxyphenoxy)valerate (**2d**)[7b] (0.25 g, 0.8 mmol) in glacial HOAc (8 mL). The vigorous reaction was accompanied by a dissipation of yellow color. Stirring continued under N_2 at 25 °C for 4 h; TLC [EtOAc–hexane (2:1)] indicated complete conversion of **2d** (R_f 0.46) to product **5d** (R_f 0.74). The reaction mixture was diluted with H_2O (75 mL) and extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with H_2O (3 × 75 mL) and brine (2 × 75 mL), dried (Na_2SO_4), and concentrated to give NMR- and TLC-pure product **ethyl 5-(3,5-dimethoxy-4-methylphenoxy)valerate (5d)** (0.24 g, quantitative) as an oil: HPLC t_R 20.4 min; ^1H NMR ($CDCl_3$) δ 6.11 (s, 2H), 4.12 (q, 2H), 3.95 (t, 2H), 3.78 (s, 6H), 2.38 (t, 2H), 2.00 (s, 3H), 1.81 (m, 4H), 1.25 (t, 3H). Anal. Calcd for $C_{16}H_{24}O_5$, MW 296.37: C, 64.84; H, 8.16. Found: C, 64.63; H, 8.18.

Ethyl 5-[4-[(Tritylamino)methyl]-3,5-dimethoxyphenoxy]valerate (8d). A solution of aldehyde **2d**[7b] (1.6 g, 5.1 mmol) and tritylamine (1.55 g, 6.0 mmol) in absolute MeOH (30 mL) was placed over 3-Å molecular sieves (100 mg) and refluxed for 6 h under N_2. The mixture was cooled to 25 °C, and $NaBH_3CN$ (0.5 g, 7.7 mmol) was added in small portions over 15 min. The reaction mixture was stirred further, under N_2 for 2 h, and then quenched with an equal volume of H_2O. Partial concentration *in vacuo* removed MeOH and provided an aqueous suspension which was extracted with EtOAc (3 × 20 mL). The combined organic phases were separated, washed with H_2O (50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield 2.78 g (98%) of a TLC-pure yellow oil: R_f 0.40 [*n*-hexane–EtOAc (4:1)]. An analytical sample was recrystallized from hot MeOH (plus decolorizing charcoal): shiny white needles, mp 105–106 °C; HPLC t_R 20.1 min; ^1H NMR ($CDCl_3$) δ 7.15–7.60 (m, 15H), 6.09 (s, 2H), 4.11 (q, 2H), 3.95 (t, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.16 (s, 2H), 2.36 (t, 2H), 1.61 (m, 4H), 1.25 (t, 3H). Anal. Calcd for $C_{35}H_{39}NO_5$, MW 553.70: C, 75.92; H, 7.10; N, 2.53. Found: C, 75.63; H, 6.81; N, 2.65.

5-[4-[(Tritylamino)methyl]-3,5-dimethoxyphenoxy]valeric Acid (8b). Title compound was obtained similarly to **8d**, using aldehyde **2b**[7b] (0.25 g, 0.89 mmol). Yield: 0.26 g (57%), a white solid; HPLC t_R 18.0 min; ^1H NMR ($CDCl_3$) δ 7.2–7.6 (m, 15H), 6.09 (s, 2H), 3.96 (t, 2H), 3.73 (s, 6H), 3.22 (s, 2H), 2.42 (t, 2H), 1.82 (m, 4H); high resolution FABMS, calcd for $C_{33}H_{35}NO_5$ 525.2515, found *m/z* 526.2596 (MH^+).

Methyl 5-[2-[(Tritylamino)methyl]-3,5-dimethoxyphenoxy]valerate (8c′). Title compound was prepared in an analogous manner to **8d**, using aldehyde **2c′**[16] (4.0 g, 13.5 mmol). Crude product, a light yellow oil, was recrystallized from MeOH and obtained as a white solid (6.5 g, 89%): mp 113–115 °C; ^1H NMR ($CDCl_3$) δ 7.1–7.6 (m, 15H), 6.10 (d, 2H), 3.88 (t, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.22 (s, 2H), 2.29 (t, 2H), 1.69 (m, 4H); high resolution EIMS, calcd for $C_{34}H_{37}NO_5$ 539.2671, found *m/z* 539.2666. Anal. Calcd for $C_{34}H_{37}NO_5$, MW 539.68: C, 75.67; H, 6.91; N, 2.60. Found: C, 76.22; H, 6.87; N, 2.64.

Benzyl 5-[2-[(Tritylamino)methyl]-3,5-dimethoxyphenoxy]valerate (8e′). Title compound was prepared on a 9.4-mmol scale in 79% yield by the same general procedures as for **8d**, starting with **2e′**.[16,21] The title product was an oil: R_f 0.76 [EtOAc–hexanes (1:1)]; ^1H NMR ($CDCl_3$) δ 7.05–7.60 (m, 20H), 6.08 (d, 2H), 3.84 (t, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.62 (s, 2H), 3.22 (s, 2H), 2.28 (t, 2H), 1.62–1.75 (m, 4H).

Attempted Acidolytic Detritylation of Ethyl 5-[4-[(Tritylamino)methyl]-3,5-dimethoxyphenoxy]valerate (8d). Substrate **8d** (0.25 g, 0.45 mmol) was stirred for 24 h in 12 N aqueous HCl–acetone (1:1, 4 mL), after which the red-orange darkened reaction mixture (indicative of trityl-derived polymerization) was diluted with H_2O (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic phases were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated to provide a mixture which was principally the *N*-trityl free acid **8b** (0.18 g, 75%): HPLC t_R 18.0 min; ^1H NMR as before; FABMS, calcd for $C_{33}H_{35}NO_5$ 525.3, found *m/z* 526.3 (MH^+). Similar reactions in glacial HOAc led to recovered starting **8d** (t_R 20.1 min), whereas use of 12 N aqueous HCl–HOAc (1:1) gave acid **8b** as well as Trt-NH_2 (t_R 13.7 min) and Trt-OH (t_R 20.0 min), but negligible desired amine **3b** (t_R 9.3 min).

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Supplementary Material Available: Results, discussion, and experimental procedures pertaining to preparation of aldehyde precursors **2**, reductive amination of aldehydes with ammonium salts, reduction of aldehyde groups to methyl groups with $NaBH_3CN$ in acetic acid, reductive amination using benzylamine as the ammonia equivalent, hydrogenolytic cleavage of *N*-benzylamines, and preparation of additional compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.