# Solid Phase Synthesis of Lavendustin A and Analogues

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*Received March 24, 1995*

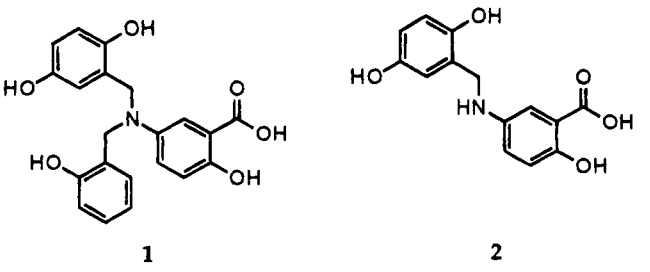
## Introduction

The emergence of combinatorial chemistry as a means of rapidly generating large numbers of diverse molecules has opened new pathways, particularly applicable to medicinal chemistry.[1] Molecular diversity generated by combinatorial synthesis may be used for two purposes, namely, lead discovery and lead development. Lead discovery by means of molecular diversity is exemplified by the use of large peptide[1,2] and oligonucleotide libraries,[3] as well as biopolymer mimetics[4] such as N-substituted oligoglycine (peptoids)[5] and oligocarbamates.[6] In this approach, the levels of diversity are high, the number of products is large (typically $10^3$–$10^7$), and the oligomeric nature of the products makes for practical synthesis using repetitive reaction conditions. When using combinatorial chemistry to develop existing leads, lesser diversity may be required ($10^1$–$10^4$ compounds) as the pharmacophore has already been identified. For example, recent reports on the combinatorial solid phase synthesis of hydantoins[7] and benzodiazepines[7,8] have been prompted by known therapeutic agents of these molecular classes. Approaches to such non-oligomeric molecules require that a wider variety of reaction types and conditions be evaluated on an appropriate solid support.[9] Herein the solid phase synthesis of the potent tyrosine kinase inhibitor lavendustin A (**1**)[10] is described (Figure 1). The methods developed have been applied to the combinatorial synthesis of 60 structurally related analogs.

## Discussion

Lavendustin A and the proposed pharmacophore **2**[10] are potent tyrosine kinase inhibitors. O-Methylated analogs of **1** and **2** are also of interest as tyrosine kinase inhibitors[11] and anti-proliferative agents.[12] Lavendustin A is a multihydroxylated aromatic carboxylic acid. Phenolic and carboxylic functional groups represent useful sites for linkage to a solid support, since these functional groups may be attached to and released from a solid support (e.g. functionalized polystyrene) using well-defined chemical methods. The lavendustin framework is synthetically accessible from three widely available subunits, making combinatorial synthesis a useful technique for the synthesis of large numbers of analogues of lavendustin A. Synthesis may be achieved from (i) an aromatic amino acid or amino phenol, (ii) an aromatic aldehyde, and (iii) an alkylating agent such as a benzylic bromide (Scheme 1). A large number of substituted variants of all three components are inexpensive and widely available, or can be easily prepared.

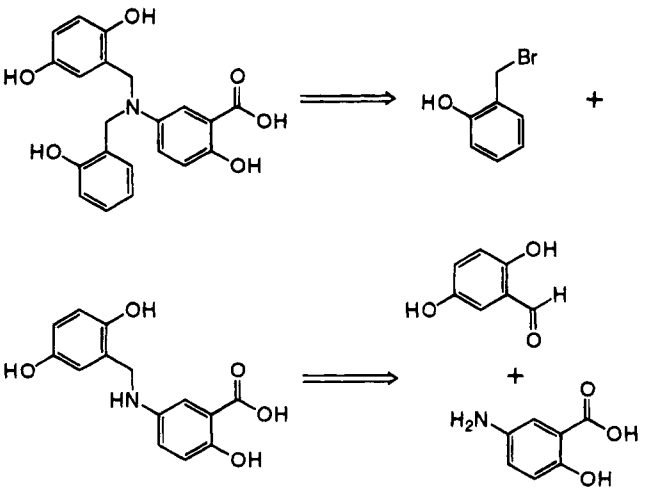
Initial studies were carried out using the TFA-labile Rink polystyrene resin[13] for convenience, since it was necessary to cleave small quantities of reaction products from the solid support for analysis, identification, and purity determination. The assembly of the lavendustin skeleton was achieved as outlined in Scheme 2. Attachment of the Fmoc-protected 5-amino-2-methoxybenzoic acid (prepared from 5-aminosalicylic acid in four steps) to the resin was achieved by means of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)[14] /HOBt activation in DMF. The degree of resin



**1** **2**

**Figure 1.**

**Scheme 1**



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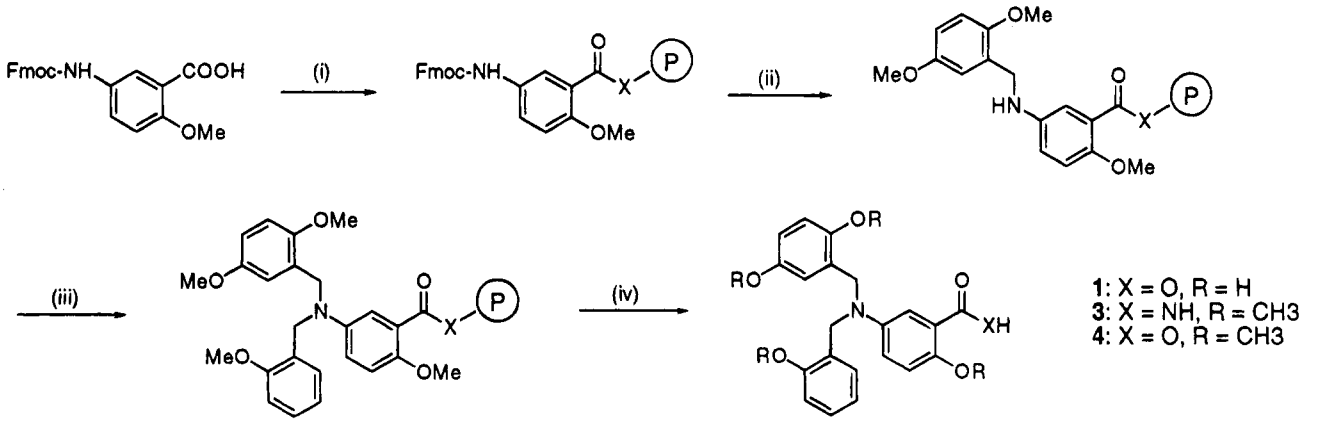
**Scheme 2**[a]




[a] R = $CH_3$, X = NH. Rink resin: (i) HBTU, HOBt, $^iPr_2NEt$, resin, DMA, 2 h; (ii) (a) 20% piperidine, DMA: (b) 2,5-dimethoxybenzaldehyde, $NaCNBH_3$, 1% AcOH, DMA; 18 h; (iii) 2-methoxybenzyl bromide, DBU, DMSO, 3 h; (iv) 5% TFA, $CH_2Cl_2$, 30 min. R = $CH_3$, X = O. Wang resin: (i) (a) $SOCl_2$, THF, reflux, 1 h; (b) Wang resin, THF, pyridine, DMAP, 2 h; (ii) (a) 20% piperidine, DMA: (b) 2,5-dimethoxybenzaldehyde, $NaCNBH_3$, 1% AcOH, DMA, 18 h; (iii) 2-methoxybenzyl bromide, DBU, DMSO, 3 h; (iv) 50% TFA, $CH_2Cl_2$, 30 min. R = H, X = O. (Hydroxymethyl)polystyrene: (i) (a) $SOCl_2$, THF, reflux, 1 h; (b) resin, THF, pyridine, DMAP, 2 h; (ii) (a) 20% piperidine, DMA: (b) 2,5-dimethoxybenzaldehyde, $NaCNBH_3$, 1% AcOH, DMA, 18 h; (iii) 2-methoxybenzyl bromide, DBU, DMSO, 3 h; (iv) 1.0 M $BBr_3$, $CH_2Cl_2$, 4 h. P indicates polymer support

substitution was verified by UV analysis of the Fmoc deprotection product, dibenzofulvene–piperidine adduct ($\epsilon$ = 7200 $mol^{-1}$ $dm^3$ $cm^{-1}$, determined experimentally). The resin-bound Fmoc-5-amino-2-methoxybenzoic acid was then deprotected with 20% piperidine in dimethylacetamide (DMA) and alkylated by reductive amination.[15] The resin was treated with 2,5-dimethoxybenzaldehyde (2–5 equiv) in 1% AcOH in DMA using $NaCNBH_3$ as reducing agent. A large excess of $NaCNBH_3$ (*ca.* 20 equiv) and overnight reaction at room temperature were necessary for complete reduction. The reaction was monitored by removing a small portion of resin and cleaving the resin-bound material with 5% TFA in $CH_2Cl_2$. HPLC analysis of the product gave a clear indication of the progress of the reductive amination. Incomplete reduction of the imine intermediate was apparent by the presence of aldehyde in the chromatogram, since the TFA treatment also cleaves the imine intermediate. When the reaction was complete, the resin-bound molecule was alkylated using 2-methoxybenzyl bromide (10 equiv) in DMSO with DBU (1.5 equiv) present as base. The use of DMA as solvent resulted in very low levels of alkylation. The product was detached from the resin by treatment with 10% TFA in $CH_2Cl_2$ for 30 min to afford the tetra-O-methylated lavendustin A amide **3** in 98% yield. Higher concentrations of TFA resulted in lower purity products, presumably due to degradation products, but no significant increase in product yield. Trial experiments showed that 85% of all cleavable material is removed in the first 30 min by 5% TFA in $CH_2Cl_2$.

Having determined reliable, high-yielding reactions in the preparation of **3** using Rink resin as the solid support, the synthesis was repeated on two other resin types, both of which yield the free acid as liberated product. Both Wang resin[16] and hydroxymethylated polystyrene were acylated using 5-Fmoc-amino-2-methoxybenzoyl chloride[17] in THF:pyridine (3:1) in the presence of DMAP. Subsequent reactions were carried out as described above. For Wang resin, cleavage was mediated by 50% TFA in $CH_2Cl_2$ to give the tetra-O-methylated lavendustin A **4**. Product purity is excellent and is estimated at greater than 95% by HPLC.

The synthesis performed on hydroxymethylated polystyrene resin was completed by treatment with an excess (*ca.* 40 equiv) of $BBr_3$ in $CH_2Cl_2$, resulting in simultaneous cleavage of the methyl ethers, as well as the

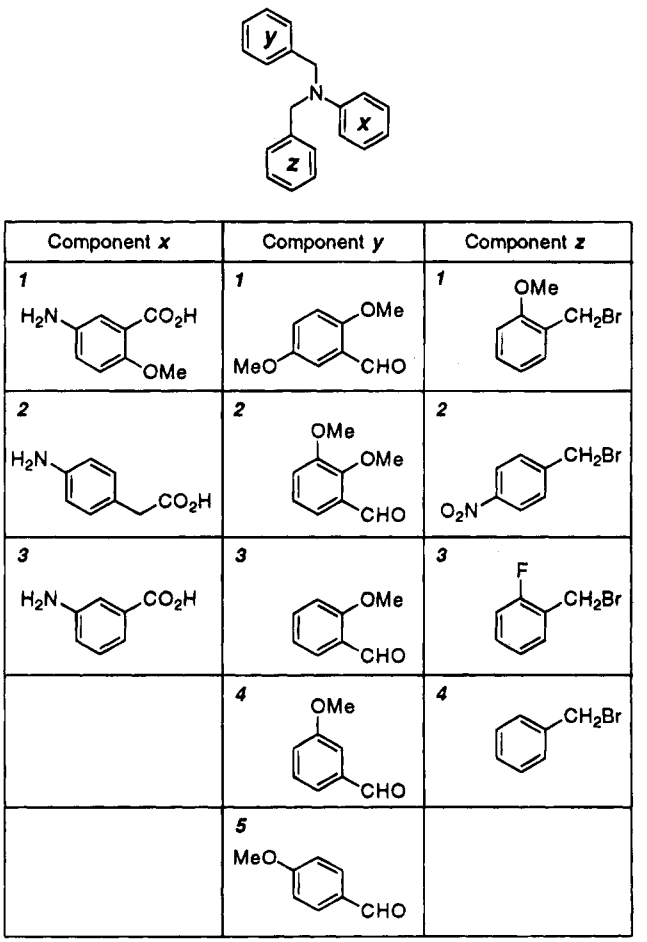



**Figure 2.**

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benzylic ester[18] link between the lavendustin molecule and the resin. Product was obtained in 90% yield, and purity of the crude product as obtained from this reaction was excellent (*ca.* 87% by HPLC).

The solid phase approach, successfully employed in the synthesis of **1** and the methylated derivatives **3** and **4**, has been applied to the combinatorial synthesis of 60 analogs of **4**. The reaction components are shown in Figure 2. These analogs were assembled from a group of three Fmoc-protected aromatic amino acids (component ***x***), five methoxy-substituted benzaldehydes (component ***y***), and four benzyl bromides (component ***z***), shown in Figure 2. The 60 compounds are numbered using a three-digit descriptor, ***xyz***, which identifies the three starting material components. Thus **4** is compound ***111***.

Synthesis was carried out on Wang resin as described above using basic laboratory equipment. Reactions were carried out in disposable polypropylene tubes held in a shaker for mixing (see Experimental Section). After cleavage of the products from the resin, product quality was assessed by HPLC and TLC, and yield was determined by $^1$H NMR using maleic acid as an internal standard. As shown in Table 1, yields varied from 10 to 76% based upon the substitution of the Fmoc-amino acid derivatized resin. In 59 of the 60 cases, the major product was the desired product. Product yield (by NMR) and product purity (by HPLC) correlate well.

In summary, this solid phase approach has been successfully employed in the synthesis of **1** and the methylated derivatives **3** and **4**, as well as analogs by combinatorial synthesis. The study and optimization of reaction conditions has allowed for the rapid assembly of these molecules in good yield and purity.

## Experimental Section

4-[(2′,4′-Dimethoxyphenyl)((fluorenylmethoxycarbonyl)amino)-methyl]phenoxypolystyrene resin (Rink resin) was purchased from Advanced Chemtech. *p*-Alkoxybenzyl alcohol (Wang resin) and hydroxymethyl polystyrene resins were purchased from Bachem Bioscience Inc. Solid phase synthesis reactions were carried out using a shaker apparatus (St. John Associates, Inc.) in a custom glass reaction vessel. Reaction vessels consist of a glass cylinder (*ca.* 10 × 80 mm) fitted with a screw thread at the top and a sintered coarse frit at the bottom. Below the frit is a 1 mm Teflon stopcock with a luer tip outlet. Multiple syntheses were carried out in disposable polypropylene tubes (Pharmacia PD-10) fitted with sintered polyethylene discs. Tubes were mounted in a Wheaton lab shaker and the contents mixed by 360° rotation. $^1$H (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Bruker ARX300 spectrometer in appropriate deuterated solvent. Microanalyses were performed by Robertson Microlit, Madison, NJ.

**Solid Phase Synthesis of Tetra-*O*-methyllavendustin A Amide (3). 1. Coupling of 5-((Fluorenylmethoxycarbonyl)amino)-2-methoxybenzoic Acid to Rink Resin.** Rink resin (0.66 mmol g$^{-1}$, 315 mg, 0.21 mmol) was washed with dimethylacetamide (DMA) (2 × 1 mL) and then shaken with 20% piperidine in DMA (2 mL) for 2 × 7 min. The resin was drained and washed with DMA (8 × 2 mL). 5-((Fluorenylmethoxycarbonyl)amino)-2-methoxybenzoic acid (256 mg, 0.66 mmol) and HOBt (104 mg, 0.68 mmol) were dissolved in dry DMF (2 mL). HBTU (253 mg, 0.67 mmol) and diisopropylethylamine (0.25 mL, 1.43 mmol) were added. The mixture was stirred for 1 min and then added to the resin. The mixture shaken for 1 h; then the resin was washed with DMA (5 × 2 mL) and $CH_2Cl_2$ (3 × 1 mL). UV analysis of the dibenzofulvene–piperidine adduct ($\epsilon$ 7200 mol$^{-1}$ dm$^3$ cm$^{-1}$, $\lambda$ 300 nm) showed a substitution of 0.557 mmol g$^{-1}$ (93% of theoretical, based on manufacturer's substitution).

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**Table 1**

| compd | yield, mg | TLC $R_f$[a] | HPLC purity | yield NMR | compd | yield, mg | TLC $R_f$[a] | HPLC purity | yield NMR |
|---|---|---|---|---|---|---|---|---|---|
| ***111*** | 40 | 0.49 | 91 | 70 | ***233*** | 50 | 0.29 | 54 | 60 |
| ***112*** | 32 | 0.44 | 92 | 68 | ***234*** | 44 | 0.29 | 73 | 57 |
| ***113*** | 34 | 0.45 | 97 | 68 | ***241*** | 49 | 0.30 | 73 | 62 |
| ***114*** | 35 | 0.46 | 95 | 83 | ***242*** | 51 | 0.28 | 42 | 57 |
| ***121*** | 34 | 0.48 | 91 | 73 | ***243*** | 42 | 0.28 | 49 | 55 |
| ***122*** | 35 | 0.41 | 90 | 63 | ***244*** | 42 | 0.28 | 56 | 54 |
| ***123*** | 30 | 0.44 | 94 | 72 | ***251*** | 49 | 0.30 | 70 | 63 |
| ***124*** | 32 | 0.44 | 92 | 65 | ***252*** | 57 | 0.28 | 44 | 50 |
| ***131*** | 30 | 0.48 | 91 | 72 | ***253*** | 11 | 0.26 | 74 | 10[b] |
| ***132*** | 31 | 0.43 | 95 | 64 | ***254*** | 50 | 0.28 | 66 | 58 |
| ***133*** | 26 | 0.44 | 97 | 71 | ***311*** | 39 | 0.33 | 85 | 68 |
| ***134*** | 24 | 0.46 | 93 | 62[b] | ***312*** | 36 | 0.31 | 56 | 37 |
| ***141*** | 33 | 0.46 | 95 | 73 | ***313*** | 25 | 0.31 | 62 | 42 |
| ***142*** | 36 | 0.39 | 93 | 70 | ***314*** | 31 | 0.33 | 66 | 51 |
| ***143*** | 25 | 0.41 | 97 | 76 | ***321*** | 32 | 0.35 | 80 | 74 |
| ***144*** | 26 | 0.44 | 93 | 72 | ***322*** | 27 | 0.29 | 44 | 22 |
| ***151*** | 28 | 0.48 | 94 | 74 | ***323*** | 27 | 0.31 | 48 | 33 |
| ***152*** | 29 | 0.39 | 74 | 48 | ***324*** | 28 | 0.33 | 60 | 48 |
| ***153*** | 27 | 0.42 | 95 | 65 | ***331*** | 36 | 0.35 | 81 | 78 |
| ***154*** | 30 | 0.44 | 97 | 68 | ***332*** | 27 | 0.31 | 50 | 34 |
| ***211*** | 35 | 0.29 | 78 | 42[b] | ***333*** | 26 | 0.32 | 57 | 38 |
| ***212*** | 55 | 0.29 | 45 | 56 | ***334*** | 26 | 0.33 | 65 | 40 |
| ***213*** | 48 | 0.28 | 54 | 54 | ***341*** | 33 | 0.35 | 57 | 53 |
| ***214*** | 49 | 0.29 | 63 | 54 | ***342*** | 26 | 0.31 | 39 | 25[b] |
| ***221*** | 61 | 0.31 | 72 | 69 | ***343*** | 25 | 0.31 | 40 | 27 |
| ***222*** | 54 | 0.29 | 42 | 51 | ***344*** | 23 | 0.32 | 56 | 29 |
| ***223*** | 44 | 0.29 | 50 | 52 | ***351*** | 36 | 0.35 | 80 | 61 |
| ***224*** | 53 | 0.30 | 54 | 60 | ***352*** | 27 | 0.29 | 30 | 10 |
| ***231*** | 52 | 0.31 | 79 | 62 | ***353*** | 22 | 0.31 | 31 | 19 |
| ***232*** | 53 | 0.29 | 45 | 60 | ***354*** | 24 | 0.33 | 39 | 24 |

[a] TLC recorded in 9:1 $CHCl_3$:MeOH. [b] Yield reduced due to material losses.

**2. Reductive Amination.** The derivatized resin (0.193 mmol) was deprotected with 20% piperidine in DMA (2 × 2mL) for 7 min each and washed with DMA (5 × 2 mL) and 1% AcOH in DMA (5 × 2 mL). 2,5-Dimethoxybenzaldehyde (102 mg, 0.61 mmol) was added to the resin followed by 1% AcOH in DMA (2 mL) and the mixture shaken for 5 min. $NaCNBH_3$ (215 mg, 3.42 mmol) was added in portions over a 2 h period and the mixture shaken overnight. The resin was filtered and washed with 1% AcOH in DMA (5 × 2 mL) and MeOH (4 × 1 mL).

**3. Alkylation.** The resin was washed with DMSO (4 × 2 mL); then a solution of 2-methoxybenzyl bromide (201 mg, 1.00 mmol) in DMSO (2.5 mL) was added. The mixture was shaken for 30 min; then DBU (45 $\mu$L, 0.30 mmol) was added. The reaction mixture was shaken for 2.5 h. The resin was then washed with DMSO (5 × 1 mL) and $CH_2Cl_2$ (6 × 2 mL) and dried under suction.

**4. Cleavage.** TFA (10%) in $CH_2Cl_2$ (4 mL) was added to the resin and the mixture shaken for 30 min. The resin was filtered and washed with 10% TFA in $CH_2Cl_2$ (2 × 1.5 mL), $CH_2Cl_2$ (3 × 1 mL), and $Et_2O$ (2 × 1 mL). The filtrate was evaporated to dryness to reveal a light brown oil, which was taken up in $CH_2Cl_2$ (5 mL) and reevaporated (×2). An analytical sample was purified on silica gel using 2% MeOH in $CH_2Cl_2$ as eluent: yield 113 mg, 98% (trifluoroacetate); $^1$H NMR ($d_6$-DMSO) $\delta$ 7.61 (1H, s), 7.43 (1H, s), 7.24–6.60 (10H, m), 4.53 (2H, s), 4.50 (2H, s), 3.81 (3H, s), 3.77 (3H, s), 3.76 (3H, s), 3.61 (3H, s); $^{13}$C NMR ($d_6$-DMSO) $\delta$ 166.7, 157.4, 153.5, 151.4, 149.2, 143.0, 128.3, 127.6, 127.1, 126.1, 123.0, 120.6, 116.0, 114.2, 113.9, 111.8, 111.3, 111.0, 102.8, 56.6, 56.0, 55.6, 55.5, 49.9, 49.8; MS (CI) m/z = 437 (M + H)$^+$; HRMS (EI) calcd for $C_{25}H_{28}N_2O_5$ 436.1998, found 436.1992. Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.55; H, 6.72; N, 6.39.

**Solid Phase Synthesis of Tetra-*O*-methyllavendustin A (4). 1. 5-((Fluorenylmethoxycarbonyl)amino)-2-methoxybenzoyl Chloride.** 5-((Fluorenylmethoxycarbonyl)amino)-2-methoxybenzoic acid (639 mg, 1.64 mmol) was suspended in dry THF (10 mL), and freshly distilled thionyl chloride (1.0 mL, 13.7 mmol) was added. The mixture was heated to reflux for 60 min to give a clear, slightly orange solution. The mixture was evaporated to dryness, and the crude acid chloride was placed in a desiccator over NaOH pellets and dried under vacuum for 1 h before use. The acid chloride was used without purification or analysis.

**2. Coupling of 5-((Fluorenylmethoxycarbonyl)amino)-2-methoxybenzoic Acid to Wang Resin.** *p*-Alkoxybenzyl alcohol resin (0.9 mmol $g^{-1}$; 294 mg, 0.26 mmol) was washed with DMA (2 × 2 mL) and THF (2 × 2 mL). Pyridine (1 mL) was added. The freshly prepared 5-((fluorenylmethoxycarbonyl)-amino)-2-methoxybenzoyl chloride was dissolved in dry THF (6.4 mL) and exactly half of this solution added to the resin. The mixture was shaken for 45 min prior to addition of DMAP (20 mg, 0.16 mmol). After a further 2 h, the resin was washed with DMA (6 × 1 mL) and $CH_2Cl_2$ (4 × 1 mL). Substitution was determined to be 0.575 mmol $g^{-1}$ (85%). The resin was treated with benzoyl chloride (0.1 mL) and pyridine (0.1 mL) in $CH_2Cl_2$ (2 mL) for 30 min and then washed with DMA (3 × 1 mL), MeOH (3 × 1 mL), and $CH_2Cl_2$ (3 × 1 mL).

**3. Reductive amination and alkylation** was carried out as described in the synthesis of **3**.

**4. Cleavage.** TFA (50%) in $CH_2Cl_2$ (5 mL) was added to the resin and the mixture shaken for 80 min. The resin was filtered and washed with 50% TFA in $CH_2Cl_2$ (3 × 1 mL) and $CH_2Cl_2$ (4 × 1 mL). The filtrate was evaporated to dryness to reveal 86 mg of a light brown oil. An analytical sample was purified on silica gel using 2% MeOH in $CH_2Cl_2$ as eluent: yield 86 mg, 78% (trifluoroacetate); $^1H$ NMR ($d_6$-DMSO) $\delta$ 12.37 (1H, br), 7.21–6.55 (10H, m), 4.54 (2H, s), 4.51 (2H, s), 3.81 (3H, s), 3.76 (3H, s), 3.69 (3H, s), 3.61 (3H, s); $^{13}C$ NMR ($d_6$-DMSO) $\delta$ 166.4, 155.7, 151.9, 149.7, 148.3, 141.1, 126.7, 125.9, 125.7, 124.4, 120.5, 119.0, 115.1, 113.3, 112.6, 112.4, 110.3, 109.9, 109.4, 55.2, 54.4, 54.0, 53.7, 48.4; EI MS *m/z* 437 ($M^+$); HRMS (EI) calcd for $C_{25}H_{27}NO_6$ 437.1838, found 437.1826. Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.64; H, 6.22; N, 3.20. Found: C, 68.40; H, 6.30; N, 3.19.

**Solid Phase Synthesis of Lavendustin A (1). 1. Acylation of (Hydroxymethyl)polystyrene.** (Hydroxymethyl)polystyrene resin (1.04 mmol $g^{-1}$; 250 mg, 0.26 mmol) was acylated with the remainder of the solution of the freshly prepared 5-((fluorenylmethoxycarbonyl)amino)-2-methoxybenzoyl chloride as described above. Substitution was determined to be 0.730 mmol $g^{-1}$ (97%).

**2. Reductive Amination and Alkylation.** Reactions were performed as described in the synthesis of **3**.

**3. Cleavage and Deprotection.** The resin was placed in a 25 mL flask and dried in a desiccator over NaOH pellets in vacuo for 48 h prior to cleavage and deprotection. The dried resin was cooled under $N_2$ to −78 °C. A 1.0 M solution of $BBr_3$ in $CH_2Cl_2$ (10 mL) was added, and the resulting mixture was stirred at −78 °C for 30 min and at room temperature for 3.5 h. The mixture was cooled to −78 °C, and the reaction was quenched by addition of MeOH (5 mL). The cooling bath was removed, and after 15 min the mixture was filtered and the filtrate evaporated to dryness. The residue was taken up in MeOH (5 mL) and reevaporated (×3) and then dried under high vacuum. The product co-eluted on HPLC with authentic **1** prepared by conventional means. An analytical sample was purified by HPLC on a Kromasil C8 column (20 × 250 mm) eluted at 12 mL/min with a gradient of 20–45% MeCN in 0.1% aqueous TFA over 25 min: yield 86 mg, 90%; $^1H$ NMR ($d_6$-DMSO, $D_2O$) $\delta$ 7.07–6.93 (4H, m), 6.78–6.72 (2H, m), 6.66 (1H, m), 6.57 (1H, m), 6.42 (2H, m), 4.46 (2H, s), 4.41 (2H, s); $^{13}C$ NMR ($CD_3OD$) $\delta$ 172.2, 164.2, 157.5, 152.1, 150.3, 133.1, 133.1, 130.0, 129.9, 126.0, 121.8, 120.6, 119.5, 119.3, 118.5, 118.1, 117.4, 116.5, 114.8, 61.4, 61.3; MS (FAB) *m/z* 382 $(M + H)^+$.

**Combinatorial Solid Phase Synthesis of Methylated Lavendustin A Analogs. ((Fluorenylmethoxycarbonyl)-amino)aryl Carboxylic Acid Chlorides.** ((Fluorenylmethoxycarbonyl)amino)aryl carboxylic acid chlorides were prepared from the corresponding Fmoc-amino acid (5.7 mmol) and redistilled thionyl chloride (4.0 mL, 55 mmol) as described above. The acid chloride was used without purification or analysis.

**Resin Esterification.** *p*-Alkoxybenzyl alcohol resin (0.9 mmol $g^{-1}$; 2.50 g, 2.25 mmol) was washed with DMA (2 × 10 mL) and THF (10 mL). Pyridine (3 mL) was added, followed by a solution of the freshly prepared acid chloride in dry THF (10 mL). The reaction was shaken for 30 min prior to addition of DMAP (50 mg, 0.4 mmol). After a further 30–90 min, the resin was washed with DMA (5 × 10 mL) and $CH_2Cl_2$ (4 × 10 mL). Substitution was determined by UV analysis of the dibenzofulvene–piperidine adduct.

**Fmoc-5-amino-2-methoxybenzoyl Resin.** The acylation reaction was carried out twice as the initial acylation resulted in a lower than expected level of substitution. Substitution: 0.423 mmol $g^{-1}$ (63%). Weight: 2.74 g.

**Fmoc-4-aminophenylacetyl Resin.** Substitution: 0.679 mmol $g^{-1}$ (96%). Weight: 3.07 g.

**Fmoc-3-aminobenzoyl Resin.** Substitution: 0.549 mmol $g^{-1}$ (76%). Weight: 2.56 g.

The resin-bound amino acids were N-deprotected using 20% piperidine in DMA (2 × 20 mL × 7 min), then washed with DMA (5 × 30 mL) and $CH_2Cl_2$ (4 × 20 mL), dried, and weighed. Each of the three derivatized resins was divided into five equal portions by weight (±10 mg) and placed into polypropylene tubes fitted with polyethylene frits. The tubes were placed in a shaker (360° rotation), and the resin samples were each washed with 1% AcOH in DMA (3 × 3 mL). The five aldehydes (2.0 mmol) in 1% AcOH in DMA (3 mL) were added to the three different resins and mixed by shaking for 15 min. $NaCNBH_3$ (15.0 g, 240 mmol) was added in approximately four equal portions over 2 h to the 15 samples. Thus each tube received approximately 1.0 g, 16 mmol, of $NaCNBH_3$. The reductions were mixed overnight. The resin samples were drained, washed with DMA (3 × 3 mL), MeOH (3 × 3 mL), and $Et_2O$ (3 × 3 mL), and dried under suction. Each was subdivided into four equal portions by weight (*ca.* 130–150 mg each). Each resin sample was washed with DMSO (3 × 2 mL); then a 0.3 M solution of the appropriate benzyl bromide in DMSO (2 mL) was added. The mixtures were shaken for 1 h, then DBU (30 $\mu$L, 0.2 mmol) was added to each. The mixtures were shaken for 5 h, then washed with DMSO (3 × 2 mL), DMA (3 × 2 mL), and $CH_2Cl_2$ (5 × 2 mL), and dried under suction. The products were cleaved from the resin by addition of 50% TFA in $CH_2Cl_2$ (2 mL) to the resins and the mixtures shaken for 60 min. Each reaction was filtered and the resin washed with 50% TFA in $CH_2Cl_2$ (2 × 1 mL), $CH_2Cl_2$ (2 × 1 mL), and $Et_2O$ (2 × 1 mL). The filtrate was evaporated to dryness under a stream of $N_2$ to reveal the products as light brown oils. Each product was dissolved in MeOH (5.0 mL) and analyzed by HPLC. Then 1.0 mL of each methanol solution was evaporated to dryness and the residue taken up in a 27.5 mM solution of maleic acid ($\delta$ = 6.27 ppm) in $d_6$-DMSO. $^1H$ NMR spectra were recorded at 300 MHz and the yield determined by relative integration of maleic acid and product benzylic $CH_2$ peaks. See Table 1.

**Acknowledgment.** The author thanks Dr. Andrew Tyler of the Harvard University Chemistry Department Mass Spectrometry Facility for mass spectra and Dr. Kwunmin Chen for an authentic sample of **1**.

**Supplementary Material Available:** Further experimental procedures, $^1H$ NMR spectra, and HPLC chromatograms of **1**, **3**, and **4** (9 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.

JO9505841