A Versatile Solid Phase Synthesis of Lavendustin A and Certain Biologically Active Analogs

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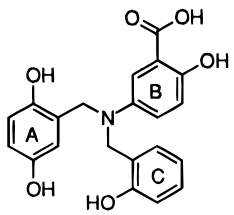
Reaction of aminomethylated polystyrene resin (**8**) with succinic anhydride, followed by esterification of the free carboxylic acid of the product **9** with 2,5-dihydroxybenzaldehyde (**4**), afforded the resin-linked aldehyde intermediate **10**. The key intermediate **10** was converted into the protein-tyrosine kinase inhibitor lavendustin A and certain analogs through reductive amination and reductive alkylation steps, followed by cleavage from the resin. This method enables the preparation of a wide variety of lavendustin A analogs using combinatorial chemistry and parallel synthesis techniques.

Combinatorial organic synthesis has increasingly become a valuable tool for the preparation of structurally diverse chemical libraries for both lead discovery and lead development.[1] The value of solid phase synthesis in the generation of large libraries of oligomeric compounds such as peptides[2] and oligonucleotides[3] has long been recognized. Recently, a considerable amount of attention has been focused on adapting and exploiting the advantages of solid phase synthesis for the production of libraries of nonoligomeric, small organic molecules for biological screening.[1,4] The development of general, high-yielding, solid phase reactions is crucial to these efforts. In addition, new methodologies that avoid extensive workup, recrystallization, and chromatographic purification of the material after cleavage from resin are of premium value to the chemist involved in multiple, parallel organic synthesis efforts. We report a solid phase synthesis of the natural product lavendustin A (**1**), a potent protein-tyrosine kinase inhibitor which was first isolated from *Streptomyces griseolavendus*.[5] The synthetic methodology has been developed to provide access to lavendustin A combinatorial libraries.



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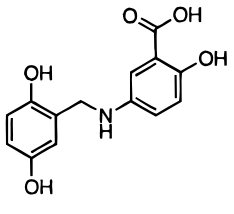

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Protein-tyrosine kinases (PTKs) play crucial roles in many signal transduction pathways within cells.[6] The abnormal expression or function of PTKs can lead to several disorders of cell proliferation including cancer.[7] Thus there is considerable interest in the development of PTK inhibitors as anticancer agents.[8] Lavendustin A and its biologically active pharmacophore, benzylamine **2**, are potent inhibitors of both receptor and nonreceptor PTKs.[5,9] Structure−activity relationship studies have revealed that the 2,5-hydroxy substituents on ring A are important for activity and their deletion and/or their conversion into *O*-methyl ethers results in a loss of inhibitory activity against certain PTKs.[10] In addition, modification of the carboxylic acid on ring B with hydrophobic aromatic substituents was shown to increase the inhibitory activity against epidermal growth factor receptor PTK-stimulated DNA synthesis in a cellular system.[11] We wished to develop a solid phase synthetic methodology that would incorporate and/or conserve these structural features in the final products. The previously reported solid phase synthesis of lavendustin analogs by Green utilized the carboxylic acid as a handle to link to the solid support and *O*-methylated fragments in ring A, B, and C for the analog synthesis.[12] Lavendustin A itself was prepared by cleaving the *O*-methyl ethers with BBr_3, followed by workup with methanol. In contrast, our strategy utilizes a free phenolic hydroxyl group for attachment to the resin, which frees the carboxylic acid for chemical manipulation on solid support and allows an additional site for generating chemical diversity. In addition, this synthesis is performed without protection of the free phenolic hydroxyl groups, thus avoiding the necessity for phenol deprotection.

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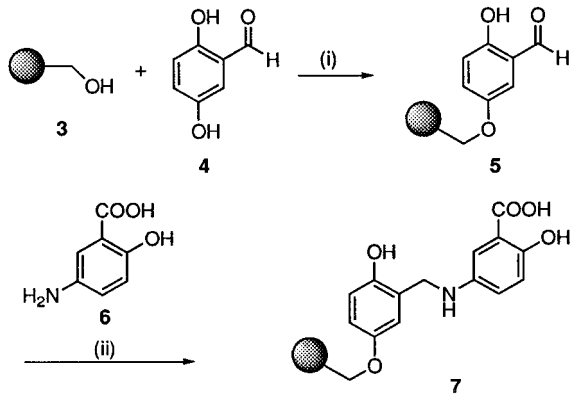
Scheme 1[a]



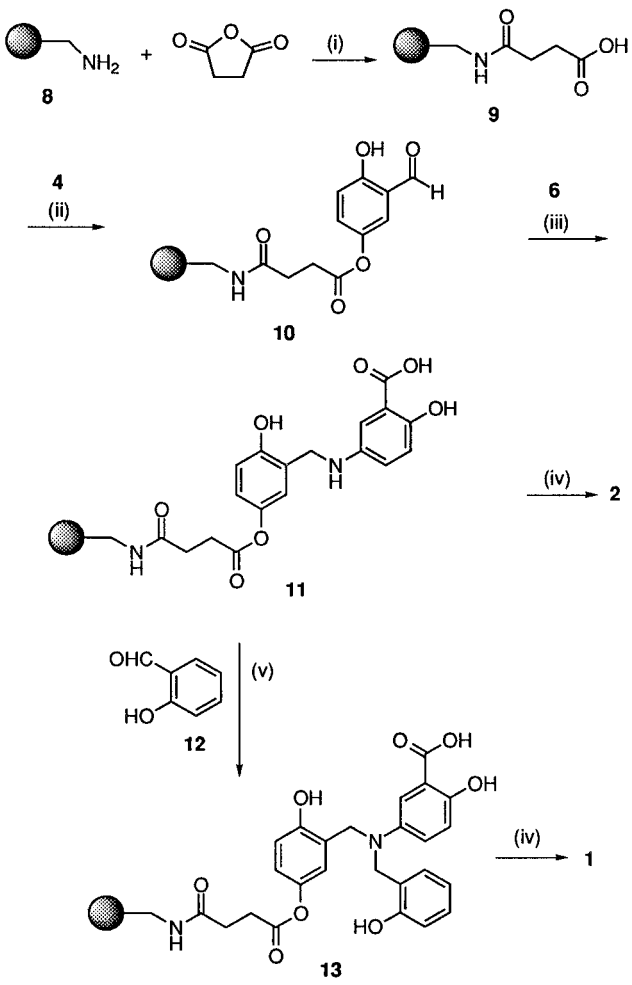
[a] Reagents and conditions: (i) Ph_3P, DEAD, THF, 24 h; (ii) $NaCNBH_3$, 1% AcOH in DMAc, 48 h.

Results and Discussion

Our initial studies were conducted using the TFA-labile Wang polystyrene resin[13] (**3**) (Scheme 1). A Mitsonobu coupling[14] of the benzyl alcohol of Wang's resin (**3**) with either of the phenolic hydroxyls of 2,5-dihydroxybenzaldehyde (**4**) was expected to provide the acid cleavable alkylaryl ether linkage.[15] Reaction of benzaldehyde **4** with Wang's resin using the standard Mitsonobu coupling reagents, triphenylphosphine and DEAD, afforded the desired support-bound benzaldehyde **5**. In this case it was of no consequence which of the two hydroxyls formed the ether link with the benzyl alcohol of Wang's resin, since both would be susceptible to TFA cleavage. Independent to our investigation, another group has recently reported a similar Mitsonobu coupling with hydroxybenzaldehydes.[16] Under conditions similar to those reported above, they found that the Mitsonobu coupling of Wang's resin with 2-hydroxybenzaldehyde was unsuccessful. On the basis of their observation, it seems likely that the ether formation of the benzyl alcohol of Wang's resin occurs with the non-hydrogen-bonded 5-hydroxyl group of 2,5-dihydroxybenzaldehyde. The efficiency of loading was determined to be 72% on the basis of the recovery of pure 2,5-dihydroxybenzaldehyde obtained by cleavage of resin **5** with CH_2Cl_2/TFA/Me_2S (50/45/5) at room temperature for 1.5 h. The presence of dimethyl sulfide in the cleavage mixture was essential in order to prevent decomposition of the cleaved material.

A reductive amination[5,17] of support-bound benzaldehyde **5** with 5-aminosalicylic acid (**6**), followed by cleavage from the resin, would afford the lavendustin A active pharmacophore (**2**). The reductive amination reaction was conducted in 1% AcOH in *N*,*N*-dimethylacetamide (DMAc) using a large excess of both the amine (6−7 equiv) and sodium cyanoborohydride (18−20 equiv) as the reducing agent to afford the support-bound benzylamine **7**. Unfortunately, the attempted cleavage of the desired product **2** from the solid support with CH_2Cl_2/TFA/Me_2S (50/45/5) led to considerable degradation and unacceptable levels of product purity. In an attempt to minimize this decomposition, several variables were explored, including decreasing the concentration of TFA, increasing the amount of dimethyl sulfide in the cleavage cocktail, and decreasing the time required for cleavage. In all instances, the product purity was compromised significantly due to the formation of highly colored degradation products. The extensive column chromatographic techniques that would be required to purify the product after cleavage from the resin and the low yields made this route highly unattractive and prompted the investigation of other linker strategies for the synthesis of the desired compounds.

Scheme 2[a]



[a] Reagents and conditions: (i) pyridine, 24 h; (ii) method A, DCC, HOBt, pyridine, 2,5-dihydroxybenzaldehyde (**4**), DMF, 24 h; method B, DCC, DMAP, **4**, CH_2Cl_2, DMF, 24 h; (iii) 5-aminosalicylic acid (**6**), $NaCNBH_3$, 1% AcOH in DMAc, 48 h; (iv) MeOH/Et_3N/Me_2S (75/15/10), 6 × 3 h; (v) method A, *o*-hydroxybenzaldehyde (**12**), $NaCNBH_3$, 4 Å seives, 1% AcOH in DMAc, 72 h; method B, **12**, $NaBH(OAc)_3$, AcOH, 4 Å seives, AcOH, CH_2Cl_2, DMF, 72 h.

Commercially available aminomethyl polystyrene resin (**8**) was acylated with succinic anhydride (3 equiv) in pyridine for 24 h at room temperature (Scheme 2). After the resin was subjected to a second round of reaction and a negative Kaiser test was ensured, the IR spectrum (KBr) of the derivatized resin **9** revealed two new absorptions at 1721 and 1655 cm^{-1}, indicating that the desired substitution had occurred. Two different reaction conditions were explored for the esterification of the

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support-bound acid with 2,5-dihydroxybenzaldehyde. Coupling of **9** with DCC (3 equiv), hydroxybenzotriazole (3 equiv), and 2,5-dihydroxybenzaldehyde (**4**) (3 equiv) in DMF/pyridine (9/1) as the solvent afforded the desired support-bound benzaldehyde ester (**10**). In a similar manner, a modified Steglich esterification[18] of resin **9** with DCC (3 equiv), DMAP (3.5 equiv), and **4** (3 equiv) in DMF/CH_2Cl_2 (4/1) also afforded **10**. It was found that a double-coupling protocol consistently provided much higher loading of the aldehyde onto the solid support. Reductive amination of support-bound benzaldehyde **10** with 5-aminosalicylic acid (**6**) under the conditions reported above (room temperature, 48 h) afforded the benzylaniline-linked solid support **11**. Several basic cleavage conditions were then explored to release the desired product **2** from the solid support in high yield and purity. Attempted hydrolysis of the ester with varying concentrations of NH_4OH in dioxane resulted in degradation, and none of the desired product could be isolated. Nonhydrolytic transesterification protocols were next attempted with ca. 0.25 equiv of sodium methoxide in methanol[19] and 10% triethylamine in methanol.[20] A qualitative (TLC) estimation of the progress of transesterification indicated that although the desired product **2** was formed, it was accompanied by highly colored, polar degradation products, with better results being obtained with 10% triethylamine in methanol.

Optimization of the cleavage conditions with Et_3N in methanol proved to be challenging. Subjection of the loaded resin **11** to cleavage for 30 min with 10% Et_3N in MeOH at room temperature afforded the desired product **2** in good purity (>95%). However, less than 10% yield of the product was obtained. Longer reaction times inevitably led to the formation of highly colored degradation products which compromised the purity of the product. Heating the reaction mixture to 50 °C in order to accelerate the rate of cleavage resulted in the formation of a deep red solution and complete degradation of the product. These results suggested that compounds containing a 2,5-dihydroxy substitution pattern are readily susceptible to degradation under the basic conditions of cleavage and probably oxidize to quinones through free radicals and/or other mechanisms. In an attempt to circumvent this problem, dimethyl sulfide (Me_2S) was incorporated in the cleavage cocktail, and the desired product was cleaved from the resin in small portions using repeated reactions, thus minimizing the contact of the cleaved material with the cleavage cocktail. Treatment of resin **11** six times with MeOH/Et_3N/Me_2S (75/15/10) for 3 h at room temperature under an argon atmosphere each time afforded the desired lavendustin A active pharmacophore **2** in 86% yield (based on incorporation of 2,5-dihydroxybenzaldehyde on the resin) and excellent purity (98%) after filtration through silica gel. This general method involving repeated cleavage reactions, to minimize contact time with the cleavage cocktail, was used in subsequent steps and consistently provided materials in good yields and purity.

The synthesis of lavendustin A (**1**) on solid support required a reductive alkylation of resin **11** with 2-hydroxybenzaldehyde (**12**). This reaction proved to be very sluggish due the unreactivity of both the aldehyde employed and the secondary aromatic nitrogen undergoing the reaction. Reductive alkylation using the conditions reported above failed to afford any product, and the starting material was recovered intact. Longer reaction times and addition of 4 Å molecular sieves to the reaction mixture led to a better conversion of the starting material. The desired support-bound lavendustin A (**13**) was thus obtained by driving the reaction to completion by subjecting the resin to the reductive alkylation conditions three times. Cleavage of the loaded resin **13** under the standard conditions reported above afforded the natural product lavendustin A (**1**) in 82% purity and 72% yield. We also investigated the use of sodium triacetoxyborohydride [$NaBH(OAc)_3$] as a reducing agent in the reductive alkylation.[17c,21] Reaction of support-bound benzylaniline **11** with *o*-hydroxybenzaldehyde (6 equiv) and $NaBH(OAc)_3$ (8 equiv) in CH_2Cl_2/DMAc (4/1) at room temperature for 72 h did not afford any of the desired product on cleavage, and only unreacted starting material was observed in the cleavage mixture. However, addition of AcOH (10 equiv) and 4 Å molecular sieves to the reaction mixture did increase the rate of reaction and after three rounds of reductive amination afforded the desired support-bound lavendustin A (**13**). In comparison to the $NaCNBH_3$ method of reductive amination, the $NaBH(OAc)_3$ method provided for a modest increase in the yield (77%) of lavendustin A (**1**).

This solid phase synthetic methodology was extended to the synthesis of a few lavendustin A analogs. A double reductive amination of benzaldehyde-linked solid support **10** with 3-aminobenzoic acid (**14**) and $NaCNBH_3$ in 1% AcOH in DMAc afforded the desired benzylaniline-linked solid support **15** (Scheme 3). Cleavage of resin **15** under the standard conditions afforded the deshydroxy lavendustin A active pharmacophore **16** in 88% yield and 92% purity. A triple reductive amination of resin **15** with benzaldehyde (6 equiv), $NaCNBH_3$ (18 equiv), and 4 Å molecular sieves in 1% AcOH in DMAc afforded the desired support-bound dibenzylaniline **17**. Cleavage of this resin under the standard conditions afforded the lavendustin A analog **18** in 73% yield.

The free carboxylic acid functionality in resin **15** presented an additional site for chemical modification. As mentioned before, modification at this site with hydrophobic side chains has resulted in analogs with superior activity against epidermal growth factor receptor PTK. Amide bond formation was investigated with phenethylamine in the presence of BOP-Cl, DIC, or EDCI as the coupling agent. Excellent results were obtained when resin **15** was reacted with 5 equiv of phenethylamine in the presence of EDCI (4 equiv), hydroxybenzotriazole (4 equiv), and iPr_2NEt (5 equiv) in a DMF/CH_2Cl_2 (1/1) mixture (Scheme 4). The support-bound phenethyl amide **19** was obtained following a double-coupling protocol to ensure complete conversion of all the acid sites to the amide. After the resin **19** was subjected to the standard cleavage conditions, the desired analog **21** was obtained in good yield (85%) and purity (93%) following filtration through silica gel. In a similar manner, the support-bound benzyl amide **22** was obtained by cleavage of resin **20** formed from the reaction of resin **15** with benzylamine. The next step was to introduce a benzyl group on the secondary nitrogen atom present in the support-bound amide **19** in an attempt to

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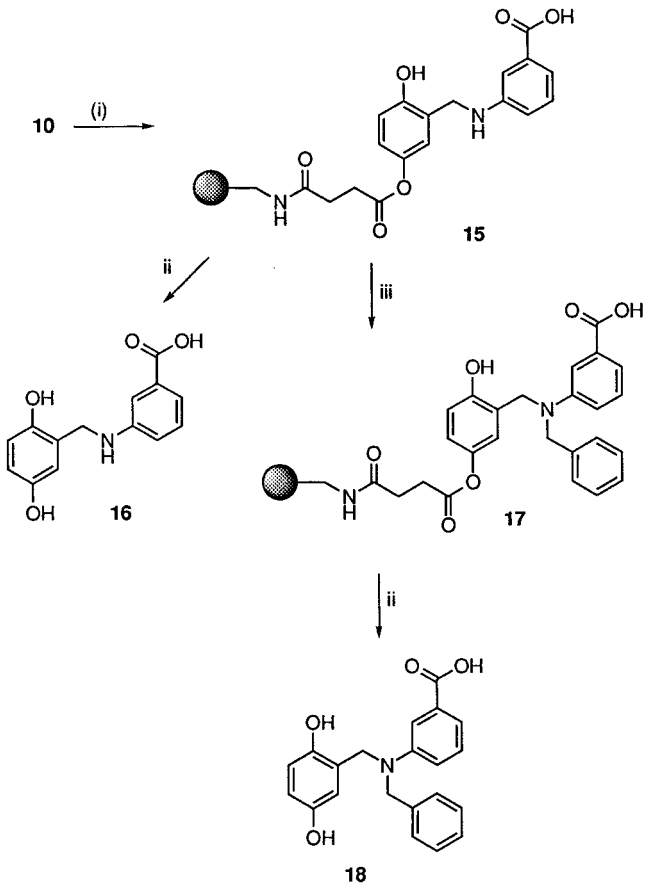
Scheme 3[a]



[a] Reagents and conditions: (i) 3-aminobenzoic acid (**14**), $NaCNBH_3$, 1% AcOH in DMAc, 48 h; (ii) $MeOH/Et_3N/Me_2S$ (75/15/10), 6 × 3 h; (iii) benzaldehyde, $NaCNBH_3$, 4 Å seives, 1% AcOH in DMAc, 72 h.

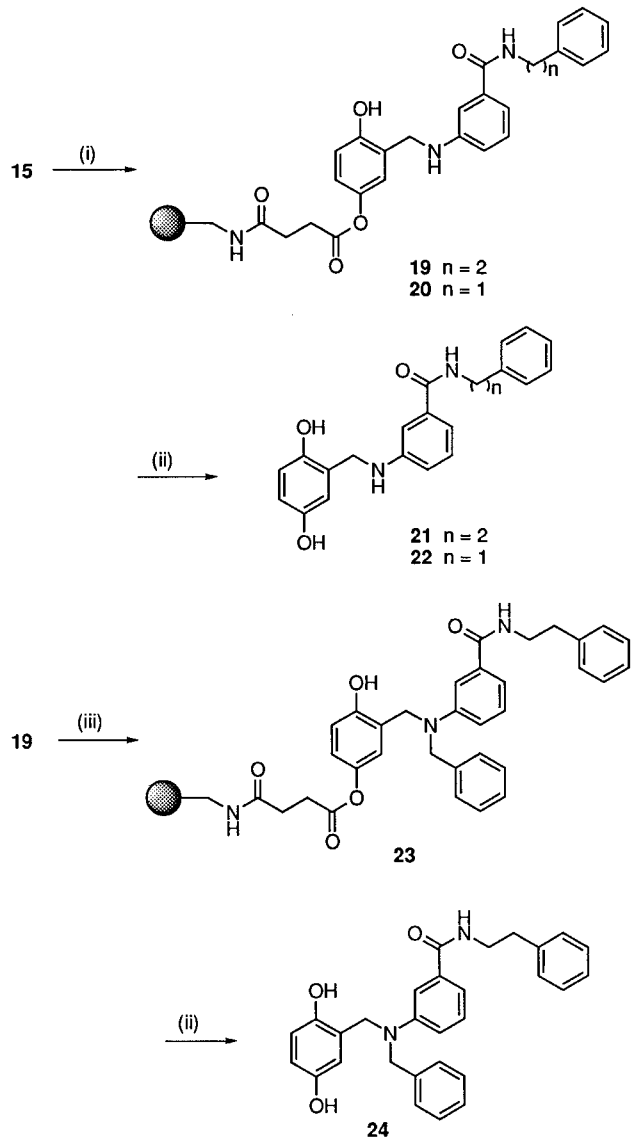
synthesize a fully functionalized lavendustin A analog. A nucleophilic displacement strategy was chosen in favor of the rather sluggish reductive amination protocol utilized previously for resins **11** and **15**. Reaction of support-bound phenethyl amide **19** twice with benzyl bromide (4 equiv) and proton sponge (1.2 equiv) as the base in anhydrous DMSO at room temperature for 8 h afforded the support-bound dibenzylaniline amide **23**. Cleavage of resin **23** under the standard conditions afforded the desired product **24** in very good purity (94%) and yield (80%) after filtration through silica gel.

In conclusion, we have demonstrated a convenient solid phase synthesis of the potent PTK inhibitor lavendustin A and representative analogs via a base-labile linker approach utilizing commercially available starting materials and avoiding protection/deprotection steps. In addition, the careful optimization of the cleavage conditions furnished the rather sensitive para-hydroxylated phenolic target molecules in good yields and superior purities. This methodology, together with the ready commercial availability of substituted amines, benzaldehydes, and benzyl halides offers the potential for the synthesis of a large library of structurally related analogs as PTK inhibitors.

Experimental Section

Analytical thin-layer chromatography was performed on Whatman silica gel 60 K6F glass-coated plates with fluorescent indicator, and spots were visualized with UV light at 254 or

Scheme 4[a]



[a] Reagents and conditions: (i) phenethylamine (for **19**) or benzylamine (for **20**), EDCl, HOBt, iPr_2NEt, DMF, CH_2Cl_2, 6 h; (ii) $MeOH/Et_3N/Me_2S$ (75/15/10), 6 × 3 h; (iii) benzyl bromide, proton sponge, DMSO, 8 h.

365 nm. Column chromatography was carried out using Merck silica gel (230−400 mesh). Analytical reverse phase high-performance liquid chromatography was done with a diode-array detector or a UV/vis detector at 254 nm. *p*-(Benzyloxy)benzyl alcohol (Wang's) resin (substitution 0.96 mmol/g) and aminomethyl polystyrene resin (substitution 0.81 mmol/g) were purchased from Calbiochem-Novabiochem International. Commercially available starting materials and reagents were purchased from Aldrich Chemical Company, Inc. All solvents were dried over 4 Å molecular sieves before use. DMF was distilled from calcium hydride. Pyridine was stored over KOH pellets.

Mitsonobu Coupling of 2,5-Dihydroxybenzaldehyde (4) to Wang's Resin (3) To Afford Loaded Resin 5. A solution of **4** (0.28 g, 2 mmol) and triphenylphosphine (0.53 g, 2 mmol) in anhydrous THF (6 mL) was added to a suspension of washed (THF) Wang's resin (0.96 mmol/g, 1.04 g, 1 mmol) preswelled in THF (10 mL). This was followed by the slow addition of DEAD (0.35 g, 2 mmol) in THF (3 mL). The mixture was gently stirred for a period of 24 h at room temperature and filtered. The resin was washed with THF (3 × 15 mL), DMF (3 × 15 mL), MeOH (3 × 15 mL), THF (3 × 15 mL), and CH_2Cl_2 (3 × 15 mL) and dried under reduced pressure. The entire procedure was repeated again to afford

support-bound benzaldehyde. The loading on solid support was determined to be 0.62 mmol/g (72%) by cleavage of loaded resin **5** twice with CH_2Cl_2/TFA/Me_2S (50/45/5) for 1.5 h and isolation of pure 2,5-dihydroxybenzaldehyde.

Reductive Amination of 5 with 5-Aminosalicylic Acid To Form Loaded Resin 7. Derivatized resin **5** (0.62 mmol/g, 0.32 g, 0.2 mmol) was washed with 1% AcOH in DMAc (2 × 5 mL). 5-Aminosalicylic acid (0.19 g, 1.2 mmol) was added to a preswelled suspension of the resin **5** in 1% AcOH in DMAc (7 mL). Solid $NaCNBH_3$ (0.23 g, 3.6 mmol) was added in portions over a period of 3 h and the suspension gently stirred for 48 h at room temperature. The resin was filtered, washed well with 1% AcOH in DMAc, DMAc, CH_2Cl_2, and EtOH (3 × 7 mL, each), and dried under reduced pressure to afford the benzylaniline-linked solid support **7**. Attempted cleavage of the desired product **2** from this resin resulted in considerable degradation.

Derivatization of Aminomethylated Polystyrene Resin (8) with Succinic Anhydride To Yield 9. Commercially available aminomethylated polystyrene resin **8** (manufacturer's substitution 0.81 mmol/g, 2.47 g, 2 mmol) was preswelled in pyridine (35 mL). A solution of succinic anhydride (0.6 g, 6 mmol) in pyridine (12 mL) was added to this suspension and the mixture gently stirred for 24 h at room temperature. The resin was then filtered and washed well with pyridine, DMF, CH_2Cl_2, and EtOH (3 × 20 mL each). The resin was then dried under reduced pressure over KOH pellets and subjected to another round of reaction to afford the desired succinic acid-derivatized resin **9**: IR (KBr) 1721, 1655 cm^{-1}.

Esterification of Resin 9 with 2,5-Dihydroxybenzaldehyde To Give 10. Method A. Solid DCC (1.24 g, 6 mmol) and HOBt (0.81 g, 6 mmol) were added to a suspension of resin **9** in DMF/pyridine (9/1, 30 mL). Solid 2,5-dihydroxybenzaldehyde (**4**, 0.83 g, 1.2 mmol) was added next and the mixture gently stirred at room temperature for 24 h. The resin was filtered, washed with pyridine (1 × 25 mL) and DMF, CH_2Cl_2, and EtOH (3 × 25 mL each), and dried under reduced pressure over KOH pellets. This procedure was repeated again on this resin to afford the benzaldehyde-linked solid support **10**.

Method B. To a suspension of dried resin **9** in DMF/CH_2Cl_2 (4/1, 30 mL) were added DCC (1.24 g, 6 mmol) and DMAP (0.86 g, 7 mmol) followed by 2,5-dihydroxybenzaldehyde (0.83 g, 1.2 mmol). The suspension was gently stirred for 24 h at room temperature and filtered. The resin was washed with DMF, CH_2Cl_2, and EtOH (3 × 25 mL each) and then dried under reduced pressure. This coupling protocol was repeated again to afford the support-bound benzaldehyde **10**.

Cleavage of 2,5-Dihydroxybenzaldehyde (4) from Solid Support 10. The cleavage cocktail was prepared by degassing a solution of MeOH (7.5 mL) and Et_3N (1.5 mL) with argon. Dimethyl sulfide (1 mL) was then added to this mixture, and the cleavage cocktail was used immediately. This solution (4 mL) was added to dried resin **10** (100 mg) obtained from method A, and the mixture was gently stirred under argon for 3 h at room temperature. The resin was filtered and washed with MeOH (2 mL) and the filtrate evaporated at once under a stream of argon. The resin was subjected to this procedure a total of six times. The combined residue was filtered through a syringe packed with silica gel (1.5 × 4 cm) using 4/1 $CHCl_3$/MeOH as the solvent. The filtrate was evaporated under a stream of argon to afford 8.8 mg (92%) of the desired product **4** as a yellow solid: mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.61 (s, 1 H), 9.82 (s, 1 H), 7.08 (dd, 1 H, J = 3, 9 Hz), 7.01 (d, 1 H, J = 3 Hz), 6.91 (d, 1 H, J = 9 Hz), 4.95 (s, 1 H); low-resolution FABMS m/z 139 (MH^+).

In a similar manner the cleavage of resin **10** (100 mg) obtained by method B afforded 8 mg (84%) of pure 2,5-dihydroxybenzaldehyde (**4**).

Reductive Amination of Resin 10 with 5-Aminosalicylic Acid To Afford 11. 5-Aminosalicylic acid (**6**) (0.28 g, 1.8 mmol) was added to a suspension of resin **10** (0.43 g, 0.3 mmol assuming 100% reaction over the previous steps) in 1% AcOH in DMAc (8 mL). Solid $NaCNBH_3$ (0.34 g, 5.4 mmol) was added in portions over 3 h to the suspension and the reaction continued for 48 h at room temperature. The resin was filtered, washed well with 1% AcOH in DMAc, H_2O, DMAc, EtOH, and CH_2Cl_2 (3 × 10 mL each), and dried, and the reductive amination procedure was repeated to afford the benzylaniline-linked solid support **11**.

Cleavage of Lavendustin A Active Pharmacophore 2 from Solid Support 11. Resin **11** (100 mg) was subjected to cleavage (using freshly prepared cleavage mixture) in a manner similar to that reported above for the cleavage of **4** from resin **10**. The residue was filtered through a syringe containing silica gel (1.5 × 4 cm) using $CHCl_3$/MeOH (4/1) as the solvent. The filtrate was evaporated under a stream of argon, reevaporated from anhydrous EtOH (2×), and then further dried under reduced pressure over $CaSO_4$ to afford 13.8 mg (86%, based on the loading of **4** on solid support) of lavendustin A active pharmacophore (**2**). HPLC analysis (25−75% MeOH in 0.1% aqueous TFA over 30 min, flow rate 1 mL/min, Phenomenex C-8 column) indicated this material (retention time = 9.04 min) to be 98% pure: ^{1}H NMR (300 MHz, CD_3OD) δ 7.89 (s, 1 H), 7.58 (d, 1 H, J = 2.7 Hz), 7.11 (dd, 1 H, J = 2.7, 8.7 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 6.70 (d, 1 H, J = 8.7 Hz), 6.67 (d, 1 H, J = 3 Hz), 6.62 (dd, 1 H, J = 3, 8.7 Hz), 4.29 (s, 2H); low-resolution FABMS m/z 276 (MH^+); high-resolution FABMS calculated MH^+ 276.0872, found 276.0866.

Reductive Alkylation of Resin 11 with *o*-Hydroxybenzaldehyde To Afford 13. Method A. Support-bound benzylaniline **11** (0.16 g, 0.1 mmol assuming 100% conversions) was suspended in 1% AcOH in DMAc (5 mL). *o*-Hydroxybenzaldehyde (**12**, 0.09 g, 0.7 mmol) was added to this suspension followed by 4 Å molecular sieves (0.08 g). After 1 h, solid $NaCNBH_3$ (0.13 g, 2.1 mmol) was added in portions over 2 h to this suspension and the reaction continued for 72 h at room temperature. The resin was filtered, washed with 1% AcOH in DMAc, H_2O, DMAc, EtOH, and CH_2Cl_2 (3 × 8 mL each), and dried under reduced pressure. This procedure of reductive alkylation was repeated twice on the dried resin to afford lavendustin A-linked solid support **13**.

Method B. *o*-Hydroxybenzaldehyde (**12**, 0.73 g, 0.6 mmol) and 4 Å molecular sieves (0.08 g) were added to a suspension of the loaded resin **11** (0.16 g, 0.1 mmol) in CH_2Cl_2/DMF (4/1, 5 mL). Glacial AcOH (57 μL, 1 mmol) was then added and the reaction continued for 1 h. Solid $NaBH(OAc)_3$ (0.21 g, 1 mmol) was added in portions to this suspension over a period of 2 h and the reaction continued for 72 h at room temperature. The resin was filtered, washed with DMF, H_2O, EtOH, and CH_2Cl_2 (3 × 8 mL each), dried, and resubjected to the same procedure twice more to afford the desired solid support **13**.

Cleavage of Lavendustin A (1) from Solid Support 13. The loaded resin **13** (100 mg) obtained by method A was subjected to cleavage, using freshly prepared cleavage mixture, in a manner similar to that reported above for the cleavage of **4** from loaded resin **10**. The residue was filtered through a syringe containing silica gel (1.5 × 4 cm) using $CHCl_3$/MeOH (4/1) as the solvent. The filtrate was evaporated under a stream of argon and re-evaporated from anhydrous EtOH (2×) to afford the desired product **1** as a light brownish-gray solid. HPLC analysis (35−90% MeOH in 0.1% aqueous TFA over 30 min, flow rate 1 mL/min, Phenomenex C-8 column) of this material indicated it (retention time = 10.72 min) to be 82% pure. An analytical sample was obtained by further purifying this residue on silica gel (1.5 × 5 cm), eluting with $CHCl_3$/MeOH (4/1). Evaporation under a stream of argon afforded 14.9 mg (72%, based on loading of **4** on solid support) of lavendustin A (**1**): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.68 (d, 1 H, J = 2.7 Hz), 7.25 (dd, 1 H, J = 2.7, 8.8 Hz), 7.14 (dd, 1 H, J = 7.5, 8.0 Hz), 7.04 (d, 1 H, J = 7 Hz), 6.81 (d, 1 H, J = 8.0 Hz), 6.73 (2 overlapping d, 2 H, J = 7, 8.8 Hz), 6.66 (d, 1 H, J = 8.7 Hz), 6.58 (dd, 1 H, J = 3, 8.7 Hz), 6.52 (d, 1 H, J = 3 Hz), 4.66 (s, 2 H), 4.60 (s, 2 H); low-resolution FABMS m/z 382 (MH^+); high-resolution FABMS calculated MH^+ 382.1291, found 382.1291.

In a similar manner cleavage of resin **13** (100 mg), obtained by method B, afforded after purification on silica gel (as mentioned above) 15.9 mg (77%) of lavendustin A identical in all respects to the sample obtained above.

Reductive Amination of Resin 10 with 3-Aminobenzoic Acid To Give 15. The reductive amination was per-

formed as described for the synthesis of resin **11** using 6 equiv of 3-aminobenzoic acid (**14**) and 18 equiv of $NaCNBH_3$. After a second round of reductive amination, the resin was dried under reduced pressure to afford the desired support-bound benzylaniline **15**.

Cleavage of Analog 16 from Resin 15. Resin **15** (100 mg) was subjected to cleavage (using freshly prepared cleavage mixture) in a manner similar to that reported above for the cleavage of compound **4** from resin **10**. The residue was filtered through a syringe containing silica gel (1.5 × 4 cm) using $CHCl_3$/MeOH (4/1) as the solvent. The filtrate was evaporated under a stream of argon, evaporated twice again after addition of anhydrous EtOH each time, and then further dried under reduced pressure to afford 13.4 mg (88%, based on the loading of **4** on solid support) of lavendustin A active pharmacophore analog **16**. HPLC analysis (25−75% MeOH in 0.1% aqueous TFA over 30 min, flow rate 1 mL/min, Phenomenex C-8 column) indicated that this material was 92% pure (retention time = 10.45 min): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.31 (d, 1 H, J = 3 Hz), 7.26 (d, 1 H, J = 7.8 Hz), 7.15 (dd, 1 H, J = 7.5, 8.1 Hz), 6.83 (dd, 1 H, J = 3, 7.5 Hz), 6.71 (d, 1 H, J = 3 Hz), 6.63 (d, 1 H, J = 8.8 Hz), 6.50 (dd, 1 H, J = 3, 8.8 Hz), 4.27 (s, 2 H); low-resolution FABMS m/z 259 (M^+); high-resolution FABMS calculated M^+ 259.0845, found 259.0842.

Reductive Alkylation of Resin 15 with Benzaldehyde To Provide Loaded Resin 17. A triple reductive amination of resin **15** with benzaldehyde (6 equiv) and $NaCNBH_3$ (18 equiv) was performed as described above for the synthesis of resin **13** to give the dibenzylaniline-linked polystyrene support **17**.

Cleavage of Analog 18 from Resin 17. Cleavage of resin **17** (100 mg) using the standard procedure reported above, followed by filtration through silica gel, afforded **18** as a yellow solid. HPLC analysis (35−90% MeOH in 0.1% aqueous TFA over 30 min, flow rate 1 mL/min, Phenomenex C-8 column) indicated that this material (retention time = 22.06 min) was 78% pure. This sample was further purified on silica gel (1.5 × 5 cm), eluting with $CHCl_3$/MeOH (4/1). Evaporation of the solvent under a stream of argon afforded 14 mg (73%, based on the substitution level of resin **10**) of lavendustin A analog **18** as a pale yellow solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.0 (d, 1 H, J = 8.4 Hz), 7.15−7.58 (m, 7 H), 6.88 (dd, 1 H, J = 3, 8.4 Hz), 6.64 (d, 1 H, J = 8.4 Hz), 6.52 (overlapping d and dd, 2 H, J = 3 Hz and J = 3, 8.4 Hz), 4.70 (s, 2 H), 4.60 (s, 2 H); low-resolution FABMS m/z 349 (M^+); high-resolution FABMS calculated M^+ 349.1314, found 349.1307.

Amidation of Resin 15 with Phenethylamine To Afford Loaded Resin 19. Resin **15** (0.31 g, 0.2 mmol, assuming 100% conversion) was suspended in DMF/CH_2Cl_2 (1/1, 6 mL), and diisopropylethylamine (176 μL, 1 mmol) was added to this suspension. Solid EDCI·HCl (0.15 g, 0.8 mmol) and HOBt (0.11 g, 0.8 mmol) were added to the mixture, followed immediately by the addition of phenethylamine (125 μL, 1 mmol). The reaction was continued for 6 h at room temperature. The resin was then filtered and washed with DMF, EtOH, and CH_2Cl_2 (3 × 8 mL each). The resin was dried under reduced pressure, and the coupling protocol was repeated again on this resin to afford the phenethylamide-linked solid support **19**.

Amidation of Resin 15 with Benzylamine To Yield 20. In a manner similar to that described above for the synthesis of solid support **19**, benzylamine was coupled with resin **15** to afford benzylamide-linked solid support **20**.

Cleavage of Analog 21 from the Loaded Resin 19. Utilizing the standard conditions reported above, the loaded resin **19** (100 mg) was cleaved to afford an oil, which was filtered through a syringe containing silica gel (1.5 × 4 cm) using $CHCl_3$/MeOH (8/1). The filtrate was evaporated under a stream of argon, re-evaporated from anhydrous EtOH (2×), and dried under reduced pressure to afford 17 mg (85%, based on the loading of **4** on solid support) of lavendustin A analog **21** as a dark yellow solid. HPLC analysis (35−90% MeOH in 0.1% aqueous TFA over 30 min, flow rate 1 mL/min, Pheneomenex C-8 column) indicated that the solid (retention time = 15.40 min) was 93% pure: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.1−7.3 (m, 6 H), 7.02 (m, 1 H), 6.94 (d, 1 H, J = 7.5 Hz), 6.76 (dd, 1 H, J = 8 Hz), 6.71 (d, 1 H, J = 3 Hz), 6.63 (d, 1 H, J = 8.4 Hz), 6.50 (dd, 1 H, J = 3, 8.4 Hz), 4.26 (s, 2 H), 3.54 (t, 2 H, J = 7.5 Hz), 2.87 (t, 2 H, J = 7.5 Hz); low-resolution FABMS m/z 363 (MH^+); high-resolution FABMS calculated MH^+ 363.1709, found 363.1717.

Cleavage of Analog 22 from Resin 20. In a manner similar to that reported above for the cleavage resin **19**, resin **20** (100 mg) was cleaved to afford 15.7 mg (82%) of the lavendustin A analog **22** as a yellowish-orange solid. HPLC analysis (20−95% CH_3CN containing 0.05% H_3PO_4 in 0.05% aqueous H_3PO_4 over 35 min, flow rate 1 mL/min, Vydac C-18 column) indicated that this material (retention time = 17.65 min) was 82% pure: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.02−7.35 (m, 7 H), 6.77 (m, 1 H), 6.71 (d, 1 H, J = 3 Hz), 6.62 (d, 1 H, J = 9 Hz), 6.50 (dd, 1 H, J = 3, 9 Hz), 4.53 (s, 2 H), 4.26 (s, 2 H); low-resolution FABMS m/z 349 (MH^+); high-resolution FABMS calculated MH^+ 349.1476, found 349.1468.

Alkylation of Resin 19 with Benzyl Bromide To Afford 23. Benzyl bromide (48 μL, 0.4 mmol) and proton sponge (20 mg, 0.12 mmol) were added to a suspension of the dried resin **19** (0.17 g, 0.1 mmol) in anhydrous DMSO (3 mL). This suspension was gently stirred at room temperature for 8 h. The resin was filtered and washed well with DMSO, EtOH, and CH_2Cl_2 (3 × 5 mL each). The resin was dried and the alkylation procedure repeated again to afford the benzylated solid support **23**.

Cleavage of Analog 24 from Resin 23. Utilizing the standard conditions reported above, resin **23** (100 mg) was cleaved to afford an oil which was filtered through silica gel (1.5 × 4 cm) using $CHCl_3$/MeOH (8/1). The filtrate was evaporated under a stream of argon, re-evaporated twice from anhydrous EtOH, and dried to afford 18.9 mg (80%) of lavendustin A analog **24** as a dark yellow solid. HPLC analysis (35−90% MeOH in 0.1% aqueous TFA over 30 min, flow rate 1 mL/min, Phenomenex C-8 column) indicated that this material (retention time = 26.07 min) was 94% pure: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.12−7.33 (m, 12 H) 6.96 (d, 1 H, J = 7.5 Hz), 6.81 (dd, 1 H, J = 3, 7.5 Hz), 6.65 (d, 1 H, J = 8.1 Hz), 6.51 (overlapping peaks, 2 H), 4.69 (s, 2 H), 4.59 (s, 2 H), 3.51 (t, 2 H, J = 7.2 Hz), 2.84 (t, 1 H, J = 7.2 Hz); low-resolution FABMS m/z 453 (MH^+); high-resolution FABMS calculated MH^+ 453.2178, found 453.2160.

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Supporting Information Available: ^{1}H NMR spectra and HPLC traces of **1**, **2**, **16**, **18**, **21**, **22**, and **24** (14 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.

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