

Practical Synthesis of FR195752, the Side Chain of Micafungin, Utilizing a Regioselective Conversion of Diaryl- β -diketone to 3,5-Diarylisoxazole

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Abstract:

The practical synthesis of FR195752, the side chain of Micafungin, was established utilizing a highly regioselective conversion of diaryl- β -diketone to 3,5-diarylisoxazole via the corresponding β -keto enamine intermediate whose disfavored regioisomer could be recycled efficiently after its hydrolysis. In addition, the related substance of FR195752 could be strictly controlled by the purification of its intermediate.

Introduction

Micafungin (Funguard) **3** launched by Fujisawa Pharmaceutical Co. in 2002 has shown its significant activities for the treatment of systemic *Candidiasis* and *Aspergillosis* without any concerns of side effects,¹ while satisfying unmet medical needs and making a contribution to the treatment of invasive fungal infections. Micafungin is a new class of lipopeptide compounds synthesized by the acylation of the fermentative product **2** with FR195752, 1-[[4-[5-(4-pentyl-oxyphenyl)isoxazol-3-yl]benzoyl]-1-*H*-benzotriazole (**1**) (Scheme 1).² The original synthesis of **1** employed by medicinal chemists² involved 1,3-dipolar cycloaddition of hydroxymoyl chloride to phenylacetylene derivative which was one of the well-known methods of preparing asymmetric 3,5-diarylisoxazole³ (Scheme 2). However, phenylacetylene derivatives are usually unavailable, so it is generally prepared by utilizing a cross coupling reaction such as the Sonogashira reaction⁴ under the pollutive metal catalyzed conditions. As a consequence, the original synthesis involved several problems to be overcome from the viewpoints of industrial manufacturing: (1) the use of pollutive metals, PdCl₂(PPh₃)₂–CuCl, (2) cytotoxicity of some acetylene intermediates, (3) the use of an expensive starting material, methyl 4-formylbenzoate,

(4) no reproducibility in biphasic chlorination reaction of aldoxime intermediate, (5) low yield through the whole process (50%).

Especially, possible contamination of drug substance with pollutive metals is a serious concern for pharmaceutical industries. These issues urged us to develop not only a more environmentally friendly but also a cost-effective synthesis for industrial scale production. The details of which are described herein. Here, we disclose a new, practical, and environmentally friendly synthesis of **1**, utilizing a regioselective conversion of diaryl- β -diketone **6a** to 3,5-diarylisoxazole **4a** via the corresponding β -keto enamine intermediate **10a** (Scheme 3).

Results and Discussion

Synthetic Strategy of Asymmetric Isoxazole 4a. To eliminate the problems mentioned above, we started to build up a new strategy involving a regioselective synthetic method for the isoxazole moiety. There were two other well-known methods for synthesis of isoxazoles. The first one involved the oxidation of 4,5-dihydroxyisoxazole resulting from the intramolecular cyclization of α,β -unsaturated oximes, and second was the oximation of β -diketones followed by a cyclization process. The former method has been often used for a regioselective synthesis of isoxazoles; however the usage of pollutive metals such as palladium complex,⁵ lead-(IV) acetate,⁶ and tetrakis(pyridine)cobalt(II)dichromate⁷ is unavoidable. In addition, we noticed that the application of this method to the synthesis of **1** required an expensive starting material, methyl 4-acetylbenzoate. In the latter method, on the other hand, there is no need to use metals and the easy access to the starting materials for the asymmetric β -diketones (**6a**).⁸ However, this method is usually used for the synthesis of *symmetric* diarylisoxazoles, because the oximation of asymmetric β -diketones might produce two isomeric diarylisoxazoles whose separation was deemed to be difficult. For example, Bandiera and co-workers⁹ reported that 1-(4-nitrophenyl)-3-(4-methoxyphenyl)-1,3-propanedione (**6b**) reacted with hydroxylamine hydrochloride to give a mixture of the corresponding two

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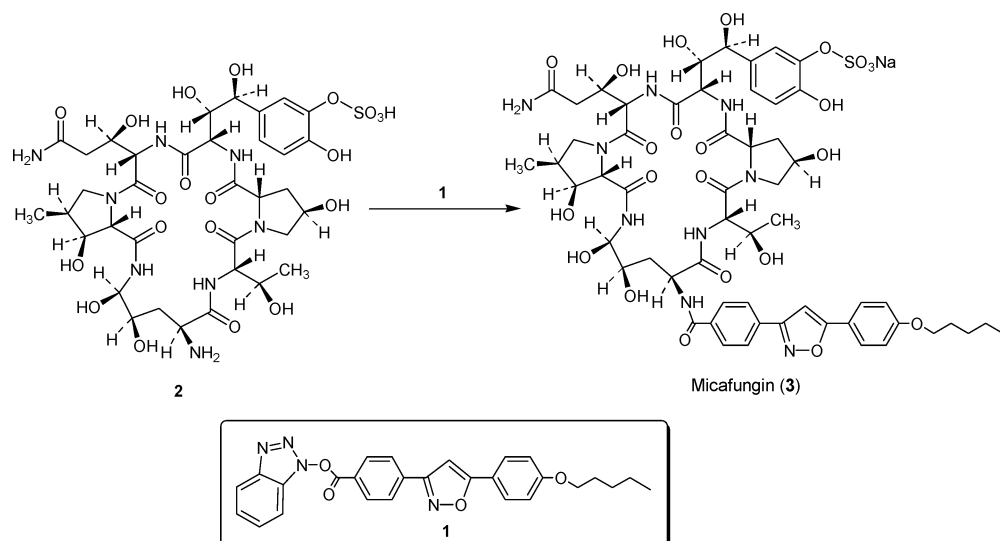
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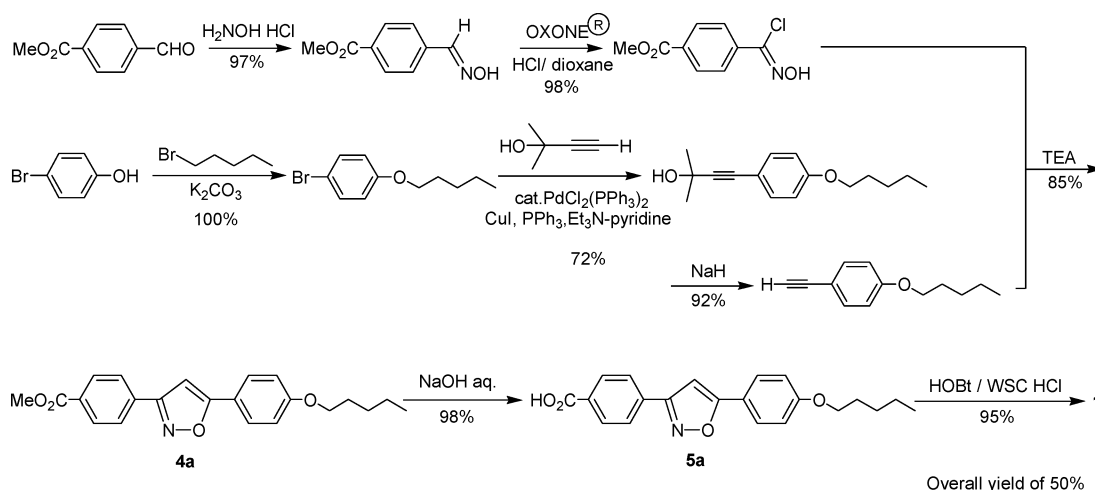
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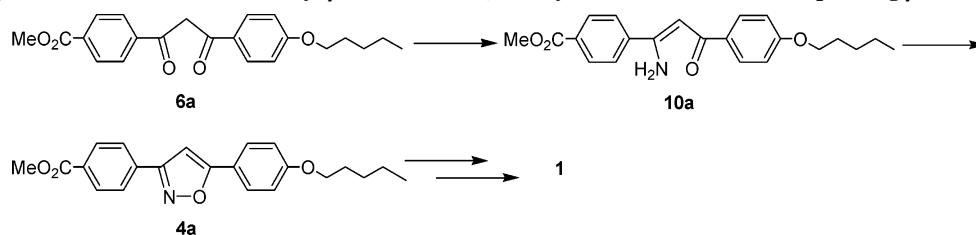
Scheme 1. Synthesis of Micafungin



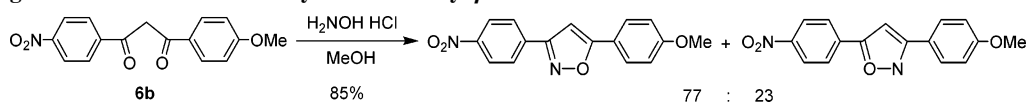
Scheme 2. Original synthesis of 1



Scheme 3. Regioselective conversion of diaryl- β -diketone to 3,5-diarylisoxazole via the corresponding β -keto enamine



Scheme 4. Regioselective conversion of asymmetric diaryl- β -diketone to isoxazole



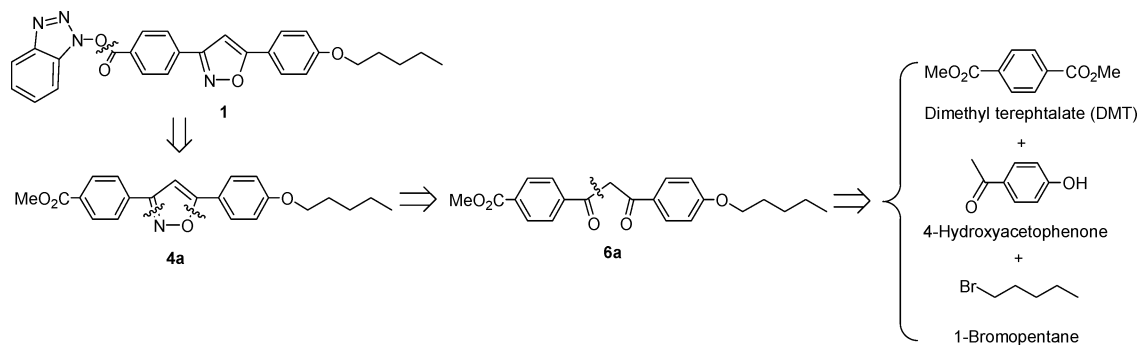
isomeric isoxazoles with moderate regioselectivity (77:23) (Scheme 4), and no method was reported to separate these isomers from the mixture. As they reported, an electron-withdrawing substituent like the nitro group increased the reactivity of the nearest ketones to afford a major isomer.

On the basis of these experimental results and information, we decided to utilize a 1,3-asymmetric diaryl- β -diketone **6a**. Thus, compound **1** could be broken into three commercially available and inexpensive fragments, 4-hydroxyaceto-

phenone, 1-bromopentane, and dimethyl terephthalate (DMT) (Scheme 5).

Synthesis of Diaryl- β -diketone 6a. We began with the alkylation of 4-hydroxyacetophenone with 1-bromopentane (Scheme 6). The oily product **7** was obtained quantitatively and used without any purification for the next aldol condensation to afford diaryl- β -diketone **6a**. The aldol condensation was optimized with 1.6 equiv of cheap DMT in the presence of *t*-BuOK, and then **6a** was isolated in 88%

Scheme 5. Retrosynthesis of 1



Scheme 6. Synthesis of 6a

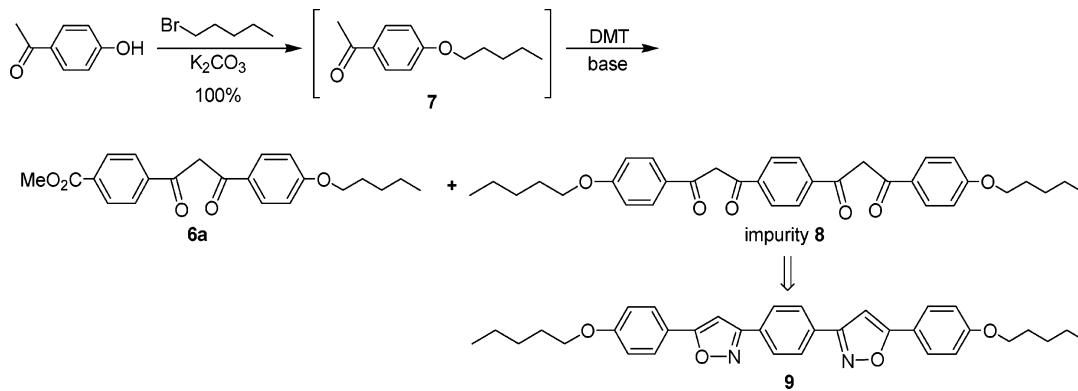


Table 1. Aldol condensation of 7 to β -diketone 6a^a

entry	DMT (equiv)	base (equiv)	conditions	isolated yield (%)	impurity 8 (%)
1	1.3	MeONa (1.5)	40–45 °C 24 h	74	1.8
2	1.3	<i>t</i> -BuOK (1.5)	20–25 °C 3 h	75	2.6
3	1.6	<i>t</i> -BuOK (1.5)	20–25 °C 3 h	88	0.8
4	2.5	<i>t</i> -BuOK (1.5)	20–25 °C 3 h	82	0.6

^a DMF was used as the solvent in all entries, and no DMT was observed in each 6a.

yield including 0.8% of impurity 8 by the crystallization in MeOH to get rid of the residual DMT (Table 1, entry 3). Increasing the equivalent of DMT by more than 1.6 was not effective in eliminating 8 (Table 1, entry 4). In addition, neither changing the kind of solvent nor diluting the reaction solution was satisfactory with low yield.

This diacylated compound 8 also was converted into impurity 9 in the next step, which resulted in one of the major related compounds in the final product 1, as mentioned later.

Regioselective Conversion of Diaryl- β -diketone 6a to Isoxazole 4a. After considering the conversion of diaryl- β -diketone 6a to isoxazole 4a with hydroxylamine hydrochloride, we envisaged that the desired regioselectivity would be recognized by the synergistic effect of the electron-withdrawing substituent ($-\text{CO}_2\text{Me}$) and electron-donating substituent ($-\text{O}(\text{CH}_2)_4\text{CH}_3$). Under optimized reaction con-

ditions,¹⁰ 6a was best converted into 4a in 74% isolated yield, including 11% of its isomer (4b). However, this process had to be abandoned because it proved to be impossible to obtain pure 4a from the mixture of two isomers with any practical purification methods. During the research of regioselective activation of 6a, we discovered that β -diketone 6a readily reacted with AcONH_4 to give a mixture of enamine 10a and 11a, which could be isolated as a stable crystalline form (Scheme 7). This offered a great possibility that isomerically pure β -keto enamine 10a would activate a regioselective oximation followed by a spontaneous intramolecular cyclization to afford the asymmetric isoxazole 4a. To realize this methodology, a regioselective enamination of β -diketone 6a became the most important matter.

Various primary amines with alkyl or aryl substituents were examined for a regioselective enamination of 6a (Table 2). As shown in entries 1 and 2, only ammonium salts gave the satisfactory results with moderate regioselectivity. Other amines except for ammonium salts made the reaction slow and did not show any regioselectivity (entries 3–7). Acetic or formic acid might activate the more electron-withdrawing ketone of 6a. In the workup and following an isolation study, fortunately the crystallization treated with the AcOEt/n -heptane (1/5) solvent system afforded an almost sole isomer 10a in 70% yield due to the difference of the solubility of each isomer. As around 2.5% of 11a was included in the isolated 10a, it was still unsatisfactory for use in the next cyclization step. Accordingly, crude 10a was recrystallized successfully with AcOEt/n -heptane (1/5) to give a high quality of 10a in 86% isolated yield (Scheme 7). As an end

(10) Conducted with hydroxylamine hydrochloride (5 equiv) in *N*-methyl-2-pyrrolidone at 60 °C for 30 h.

Scheme 7. Regioselective conversion of diaryl- β -diketone **6a** to 3,5-diarylisoazole **4a** via the corresponding β -keto enamine intermediate **10a** and its recovery system

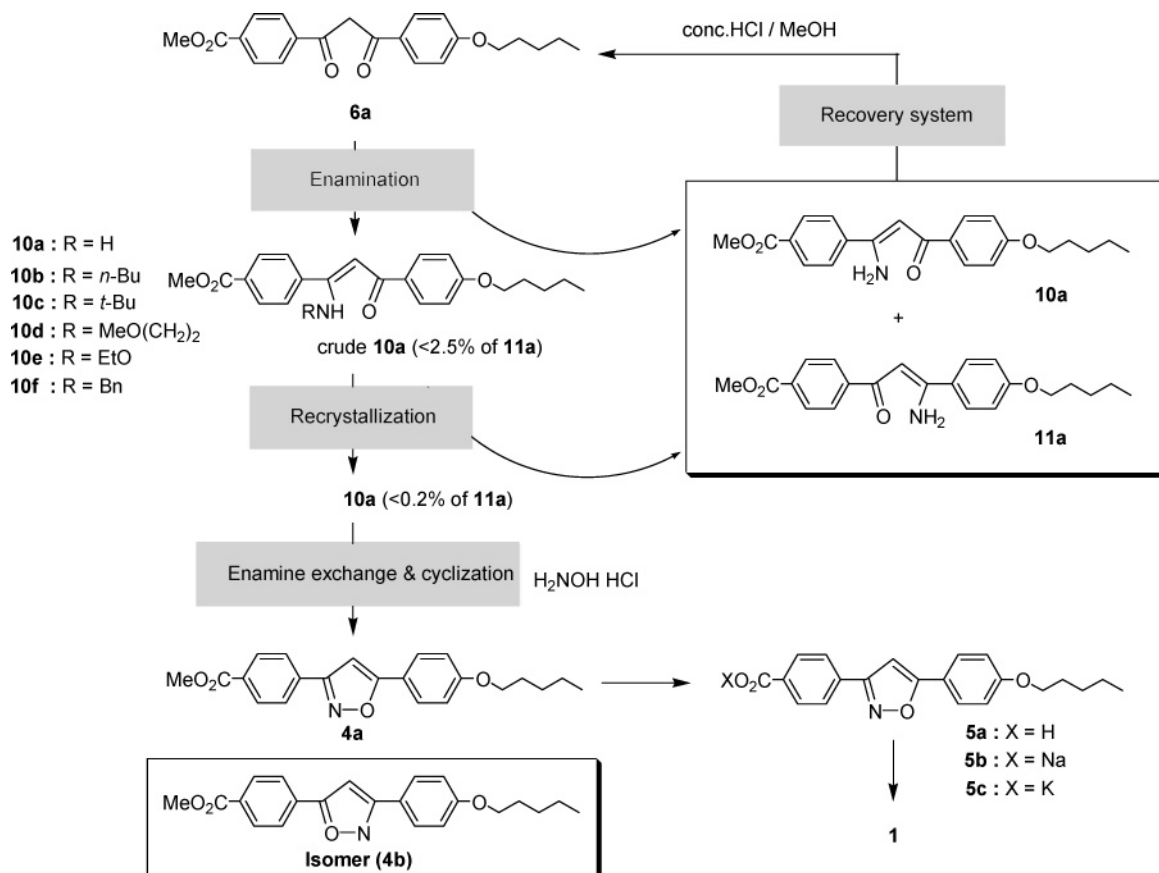


Table 2. Regioselective enamination of **6a** to **10a–f** with various amines^a

entry	amine	time (h)	conversion (%)	R	reaction selectivity		isolated yield (%)
					10	11	
1	HCO_2NH_4	4.5	96	H	83	17	70 ^b
2	AcONH_4	4.5	94	H	82	18	
3	$\text{HCO}_2\text{H}/n\text{-BuNH}_2$	24	NR ^c	<i>n</i> -Bu			
4	$\text{HCO}_2\text{H}/t\text{-BuNH}_2$	24	NR ^c	<i>t</i> -Bu			
5	$\text{MeO}(\text{CH}_2)_2\text{NH}_2$	74	41	$\text{MeO}(\text{CH}_2)_2$	50	50	
6	EtONH_2	3.5	NR ^c	EtO			
7	BzNH_2	73	36	Bz	50	50	

^a Amine (5 equiv), DMF at 100 °C were used in all entries. ^b Including 2.5% of isomer **11a**. ^c Not reacted.

result, the specification of **10a** in terms of **11a** was determined to be not more than 0.2%. In the next step with hydroxylamine hydrochloride, β -keto enamine **10a** was highly regioselectively converted into 3,5-diarylisoazole **4a** free of its isomer **4b**. The enamine exchange followed by spontaneous cyclization reaction prior to oximation of β -keto enamine **10a** proceeded smoothly in 96% isolated yield.

Although β -diketone **6a** was successfully converted into **10a** of high quality in 60% isolated yield after the recrystallization, the combined mother liquor still contained as much as 30% of **10a** and **11a** based on **6a**. To recycle the enamines **10a** and **11a** in the mother liquor, it was concentrated under reduced pressure and the resulting residue was easily hydrolyzed by treatment with aqueous hydrochloric

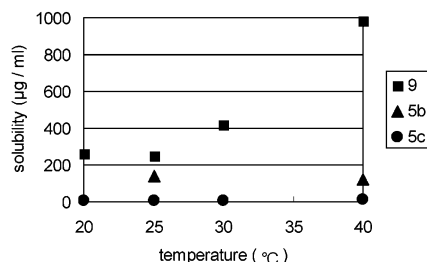
acid/MeOH solution to give **6a** of high quality in 90% yield (Scheme 7).

Synthesis of 1 and Removal of 9. Thus, an isomerically pure 3,5-diarylisoazole **4a** was converted into **1** by the hydrolysis of methyl ester with aqueous sodium hydroxide, followed by esterification with 1-hydroxybenzotriazole (HOBt)/1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSC·HCl) in 100% and 95% yield, respectively. At this stage, another issue on the quality of **1** emerged as a new related substance **9** derived from impurity **8** was identified at a level of 2%, and this highly insoluble related substance caused not only a deterioration of the quality of **1** but also a difficulty of cleaning facilities used for the coupling reaction of **1** and **2**, the critical step of **3**. Thus we had to remove **9** from **1** before the critical steps.

Table 3. Solubility data for **9**, **5b**, and **5c**

substrate	solubility ($\mu\text{g/mL}$) ^a				
	acetone	AcOEt	DMF	MeOH	THF
9	20	40	60	3	250
5b	2	8	50	600	140
5c	1	1	60	330	7

^a All solubility data were measured at room temperature.

**Figure 1.** Solubility of **9**, **5b**, and **5c** in THF.

To eliminate the contamination of **9** from **1**, we examined what stage of the manufacturing process of **1** is most effective. As **9** has a symmetric and nonionizable structure, we expected a solubility difference in the alkaline salts of **5a**. Table 3 shows the preliminary solvent screening for the discrimination of **9** from **5b** and **5c**. We have found that the combination of THF and potassium salt **5c** shows the best selectivity.

Furthermore, the solubility of **9** in THF is highly dependent on the temperature, and at 40 °C, its solubility increased three times compared to the room temperature solubility whilst the solubility of **5c** remained the same (Figure 1). Thus, we chose insoluble **5c** as the intermediate for the esterification step and then conducted the reslurry washing in THF at 40 °C effectively. As a result, the quality of **1** prepared via potassium salt **5c** met its specification, free of both regioisomer and **9**.

Conclusions

Compound **1** was thus manufactured in 60% overall yield from 4-hydroxyacetophenone including the recovery of **6a**. The present method is advantageous over the original methods from the viewpoints of a large scale manufacturing; we obtained the following advantages: (1) elimination of troublesome metals and impurities, (2) improvement of overall yield and cost-efficiency, (3) efficient use of disfavored regioisomer, utilizing a regioselective conversion of diaryl- β -diketone **6a** to 3,5-diarylisoaxazole **4a** via the corresponding β -keto enamine **10a**. This process could be successfully applied for industrial scale manufacturing (50 kg scale).

Experimental Section

Solvents and reagents were obtained from commercial sources and were used without any purification. ¹H NMR spectra were obtained on a Bruker Biospin DPX200 using tetramethylsilane as internal standard. IR spectra were recorded on a Horiba FT-720 Fourier transform infrared spectrometer. Mass spectra were recorded on a Hewlett-

Packard 1100LC/MSD mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer CHN elemental analyzer.

Methyl 4-{3-Oxo-3-[4-(pentyloxy)phenyl]propanoyl}-benzoate (6a**).** 4-Hydroxyacetophenone (35.0 kg), DMF (175 L), 1-pentylbromide (42.7 kg), and potassium carbonate (42.6 kg) were combined in a reaction vessel. The mixture was stirred at 65–70 °C for 4 h, and then water (525 L) and *n*-heptane (280 L) were added to the reaction mixture at below 30 °C. The organic layer was separated and washed with aqueous sodium hydroxide solution (sodium hydroxide 3.4 kg in water 168 L), following aqueous hydrochloric acid solution (35% hydrochloric acid 7 L and water 168 L), water (175 L), and aqueous sodium chloride solution (sodium chloride 35.0 kg in water 175 L) successively. The organic layer was treated with anhydrous magnesium sulfate (7.0 kg). The mixture was filtered, and magnesium sulfate cake was washed with *n*-heptane. The combined organic filtrates were concentrated under vacuum to remove *n*-heptane. To the concentrated oily residue DMF (840 L), dimethyl terephthalate (79.9 kg), and potassium *tert*-butoxide (43.3 kg) were added at 20–25 °C and stirred at the same temperature for 4 h. The mixture was diluted with methanol (2135 L) at 20–30 °C and then quenched and crystallized by slow addition of aqueous hydrochloric acid solution (35% hydrochloric acid 53 L and water 53 L) at 5–15 °C. The mixture was filtered, washed with methanol (280 L), and water (280 L). The wet crystal was dried under vacuum at 40–60 °C to give 83.3 kg of **6a** (88% yield).

¹H NMR (200 MHz, CDCl₃-*d*, δ) 0.96 (3H, t, *J* = 6.5), 1.35–1.51 (4H, m), 1.76–1.86 (2H, m), 3.96 (3H, s), 4.04 (2H, t, *J* = 6.5 Hz), 4.60 (0.05H, s, keto CH₂), 6.82 (0.95H, s, enol CH), 6.97 (2H, dd, *J* = 8.5, 2.0 Hz), 7.97 (2H, dd, *J* = 7.0, 2.0 Hz), 8.02 (2H, dd, *J* = 6.5, 2.0 Hz), 8.14 (2H, dd, *J* = 7.5, 2.0 Hz), 16.89 (0.9H, s, enol OH) (**6a** exists as its keto–enol tautomer.); IR (ATR) 2955, 2926, 1719, 1605, 1586, 1281, 1107 cm⁻¹; MS (EI) *m/z* 391 [*M* + Na]⁺. Anal. Calcd for C₂₂H₂₄O₅: C, 71.72; H, 6.57. Found: C, 71.84; H, 6.42.

Methyl 4-{1-Amino-3-[4-(pentyloxyphenyl)-3-oxo-1-propenyl]benzoate (Crude **10a).** Compound **6a** (83.3 kg), DMF (417 L), and ammonium formate (71.3 kg) were combined in a reaction vessel, and the mixture was stirred at 100–105 °C for 4 h. Ethyl acetate (2083 L) and water (2083 L) were added to the mixture at 20–30 °C, and then the organic layer was separated and washed with aqueous sodium chloride solution (sodium chloride 208 kg in water 2083 L) and another aqueous sodium chloride solution (sodium chloride 417 kg in water 2084 L) successively. The organic layer was concentrated to about 417 L under vacuum. The resultant solution was heated to 50–55 °C, and then *n*-heptane (2083 L) was added dropwise for 1–1.5 h for crystallization. The slurry was cooled to 20–25 °C and stirred for 1 h. The mixture was filtered and washed with the mixture of ethyl acetate (70 L) and *n*-heptane (350 L). The wet crystal was dried under vacuum at 40–60 °C to give 58.2 kg of crude **10a** (70% yield).

Purification of 10a. Crude **10a** (58.2 kg) and ethyl acetate (291 L) were combined in a reaction vessel. The mixture was stirred at 50–70 °C to dissolve, and then *n*-heptane (1455 L) was added at 50–55 °C for 1–1.5 h for crystallization. The mixture was cooled to 20–30 °C and stirred for 1 h. The mixture was filtered and washed with the mixture of ethyl acetate (58 L) and *n*-heptane (290 L). The wet crystal was dried under vacuum at 40–60 °C to give 50.1 kg of **10a** (86% yield).

¹H NMR (200 MHz, CDCl₃-*d*, δ) 0.94 (3H, t, *J* = 7.2), 1.34–1.52 (4H, m), 1.74–1.83 (2H, m), 3.95 (3H, s), 4.01 (2H, t, *J* = 6.5 Hz), 6.12 (1H, bs), 6.97 (2H, dd, *J* = 8.0, 2.0 Hz), 7.70 (2H, dd, *J* = 8.5, 2.0 Hz), 7.93 (2H, dd, *J* = 8.5, 2.0 Hz), 8.12 (2H, dd, *J* = 8.5, 2.0 Hz); IR (ATR) 3420, 2952, 2929, 1715, 1706, 1594, 1528, 1492, 1278 cm⁻¹; MS (EI) *m/z* 390 [M + Na]⁺. Anal. Calcd for C₂₂H₂₅NO₄: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.91; H, 7.01; N, 3.84.

Methyl 4-{5-[4-(Pentyloxy)phenyl]-3-isoxazolyl}benzoate (4a). Compound **10a** (50.1 kg), DMF (401 L), and hydroxylamine hydrochloride (18.9 kg) were combined in a reaction vessel, and the mixture was stirred at 60–65 °C for 4 h. The mixture was cooled to 20–40 °C, and acetonitrile (501 L) was added at this temperature for 30 min and then water (501 L) for 30 min for crystallization. The resulting precipitate was cooled to 20–25 °C then filtered and washed with aqueous acetonitrile solution (acetonitrile 125 L and water 125 L). The wet cake was dried under vacuum at 40–60 °C to give 47.8 kg of **4a** (96% yield).

¹H NMR (200 MHz, CDCl₃-*d*, δ) 0.95 (3H, t, *J* = 6.5 Hz), 1.35–1.53 (4H, m), 1.76–1.86 (2H, m), 3.95 (3H, s), 4.02 (2H, t, *J* = 6.5 Hz), 6.74 (1H, s), 6.99 (2H, d, *J* = 8.5 Hz), 7.77 (2H, dd, *J* = 8.5, 2.0 Hz), 7.93 (2H, d, *J* = 8.5 Hz), 8.15 (2H, d, *J* = 8.5 Hz); IR (ATR) 2961, 2944, 1716, 1612, 1278, 1107 cm⁻¹; MS (EI) *m/z* 388 [M + Na]⁺. Anal. Calcd for C₂₂H₂₃NO₄: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.39; H, 6.41; N, 3.87.

4-{5-[4-(Pentyloxy)phenyl]-3-isoxazolyl}benzoic Acid (5a). Compound **4a** (47.8 kg), THF (478 L), methanol (72 L), and aqueous potassium hydroxide solution (potassium hydroxide 11.6 kg in water 72 L) were combined in reaction vessel. The suspension solution was stirred at 50–60 °C for 2 h, and THF (956 L) was added at this temperature. The mixture was cooled to 40–45 °C and then filtered and washed with THF (478 L) to give a wet cake (crude **5c**). The obtained wet cake and THF (956 L) were charged into a reaction vessel. The mixture was stirred at 50–60 °C for 20 min and cooled to 40–45 °C. The mixture was filtered and washed with THF (478 L) to give a wet cake (**5c**) and eliminate compound **9**. The obtained wet cake, water (382 L), and THF (382 L) were charged into a reaction vessel. The aqueous hydrochloric acid solution (35% hydrochloric acid 20.1 L and water 219 L) and water (478 L) were added to the mixture at 40–55 °C for crystallization. And then, the mixture was cooled at 25–35 °C, filtered, and washed with water (378 L) and then acetone (239 L). The wet crystal was dried under vacuum at 40–60 °C to give 42.7 kg of **5a** (93% yield).

¹H NMR (200 MHz, DMSO-*d*₆, δ) 0.91 (3H, t, *J* = 7.0 Hz), 1.27–1.48 (4H, m), 1.61–1.82 (2H, m), 4.05 (2H, t, *J* = 6.5 Hz), 7.12 (2H, d, *J* = 9.0 Hz), 7.54 (1H, s), 7.85 (2H, d, *J* = 9.0 Hz), 8.03 (2H, d, *J* = 9.0 Hz), 8.10 (2H, d, *J* = 8.5 Hz); IR (ATR) 2938, 2867, 1677, 1613, 1248 cm⁻¹; MS (EI) *m/z* 352 [M + 1]⁺. Anal. Calcd for C₂₁H₂₁NO₄: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.72; H, 6.04; N, 3.96.

1-[[4-[5-(4-Pentyloxyphenyl)isoxazol-3-yl]benzoyl]-1-*H*-benzotriazole (1). Compound **5a** (42.7 kg), THF (427 L), DMF (342 L), and HOBt (23.0 kg) were combined in a reaction vessel and then WSC·HCL (39.6 kg) was added and stirred for 4 h at 20–30 °C. The mixture was cooled, and ethyl acetate (1708 L) was added and then water (427 L) was added at 0–25 °C followed by stirring for 1 h at 2–7 °C. The mixture was filtered and washed with acetonitrile (68 L). The wet crystal was dried under vacuum at 40–45 °C to give 54.1 kg of **1** (95% yield).

¹H NMR (200 MHz, CDCl₃-*d*, δ) 0.95 (3H, t, *J* = 7.0 Hz), 1.32–1.54 (4H, m), 1.76–1.90 (2H, m), 4.03 (2H, t, *J* = 6.5 Hz), 6.81 (1H, s), 7.01 (2H, dd, *J* = 9.0, 2.5 Hz), 7.42–7.62 (3H, m), 7.79 (2H, dd, *J* = 9.0, 2.5 Hz), 8.11 (2H, d, *J* = 8.5 Hz), 8.12 (1H, dd, *J* = 8.0, 1.0 Hz), 8.39 (2H, d, *J* = 8.5 Hz); IR (ATR) 3116, 2948, 1773, 1251 cm⁻¹; MS (EI) *m/z* 469 [M + 1]⁺. Anal. Calcd for C₂₇H₂₄N₄O₄: C, 69.22; H, 5.16; N, 11.96. Found: C, 68.90; H, 5.44; N, 11.78.

Recovery of 6a. The combined filtrates both of crude **10a** step and its purification step were concentrated under vacuum. To the resulting residue, methanol (833 L) and 35% (w/v) hydrochloric acid (83 L) were added. The mixture was stirred at 60–65 °C for 3 h, then cooled at 20–25 °C, filtered, and washed with methanol (350 L). The wet crystal was dried under vacuum at 40–60 °C to give **6a** (27% yield based on the starting material 4-hydroxyacetophenone).

¹H NMR (200 MHz, CDCl₃-*d*, δ) 0.95 (3H, t, *J* = 7.0), 1.35–1.51 (4H, m), 1.76–1.86 (2H, m), 3.96 (3H, s), 4.04 (2H, t, *J* = 6.5 Hz), 4.60 (0.05H, s, keto CH₂), 6.82 (0.95H, s, enol CH), 6.97 (2H, dd, *J* = 9.0, 2.0 Hz), 7.98 (2H, dd, *J* = 7.0, 2.0 Hz), 8.02 (2H, dd, *J* = 6.5, 2.0 Hz), 8.14 (2H, dd, *J* = 8.5, 2.0 Hz), 16.89 (0.9H, s, enol OH) (**6a** exists as its keto–enol tautomer); IR (ATR) 2956, 2927, 1718, 1605, 1586, 1281, 1107 cm⁻¹; MS (EI) *m/z* 391 [M + Na]⁺. Anal. Calcd for C₂₂H₂₄O₅: C, 71.72; H, 6.57. Found: C, 71.74; H, 6.64.

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Note Added after ASAP Publication: In the version published on the Internet February 11, 2005, the asterisk and e-mail address for one of the authors were not present. The final version published February 15, 2005, and the print version are correct.

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