Organic Process Research & Development

ARTICLE

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Development of a Practical Synthesis of Stearoyl-CoA Desaturase (SCD1) Inhibitor MK-8245

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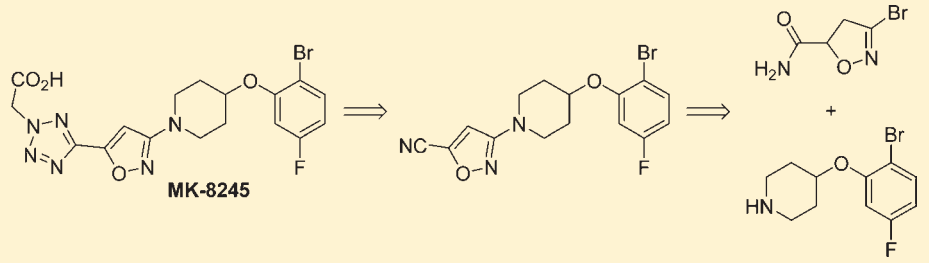
ABSTRACT:



A practical kilogram scale chromatography-free synthesis of stearoyl-CoA desaturase 1 (SCD1) inhibitor MK-8245 is described. The key features of this sequence include an efficient addition−elimination reaction of a piperidine fragment with a 3-bromoisoxaline followed by an iodine-mediated oxidation to the corresponding isoxazole. The development of a safe and scalable tetrazole formation protocol is also presented.

INTRODUCTION

The stearoyl-CoA desaturase 1 (SCD1) enzyme plays a pivotal role in the biosynthesis of monounsaturated fatty acids, essential components of membrane phospholipids, cholesterol esters, and triglycerides.[1] The potential of SCD1 inhibitors in the treatment of type II diabetes, dyslipidemia, obesity, and metabolic diseases has been demonstrated in rodents and humans.[2−4] However, the preclinical development of SCD1 inhibitors has been limited due to adverse events associated with skin and eye tissues.[3] To address these toxicity liabilities, our medicinal chemistry colleagues designed MK-8245, a potent and *liver-targeted* SCD1 inhibitor[5] that incorporates a 2-substituted pharmacophore, known to be biologically active for a number of indications.[6]

To support both preclinical and clinical development, we required a practical synthesis of MK-8245, suitable for the kilogram scale preparation of the active pharmaceutical ingredient (API). Evaluation of the first generation synthesis used by the medicinal chemistry group revealed several problematic steps (Scheme 1). The sequence featured an unacceptably low-yielding three-component coupling between functionalized amine **3**, dibromoformaldoxime **4**, and ethyl propiolate. Improvement of this key step was deemed essential to facilitate preparation on large scale. Additionally, an alternative to the Mitsunobu reaction used to prepare amine **3** would improve efficiency. The use of acid in combination with sodium azide for the formation of tetrazole **7** was a major safety concern. Finally, the overall yield was further reduced at the penultimate step, where HPLC separation was required to separate regioisomers of alkylated tetrazole **8**. Considering these shortcomings, the need for an alternative second generation synthesis to provide a more efficient and safe route was clear.

RESULTS AND DISCUSSION

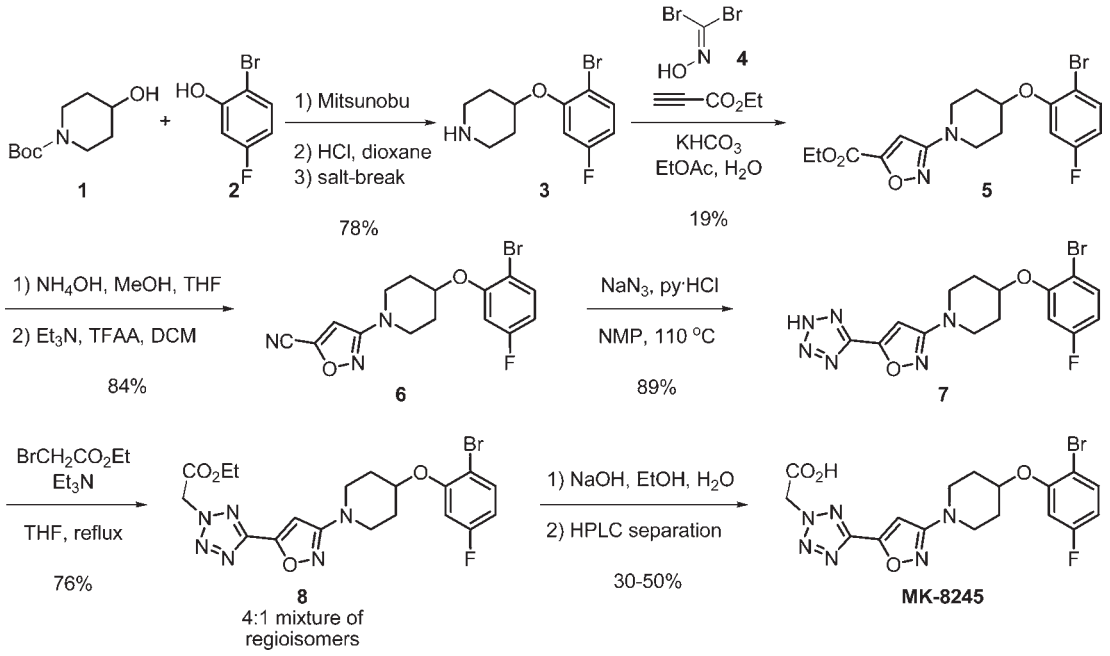
The first generation synthesis began with a Mitsunobu reaction between *N*-Boc-protected hydroxypiperidine **1** and phenol **2**. To render the step more efficient, we explored the possibility of forming the aryl−oxygen bond *via* a nucleophilic aromatic substitution (S_NAr) reaction. Bromo-difluorobenzene **10** was found to be a suitable partner for an S_NAr reaction with hydroxypiperidine **1**.[7] Moreover, hydroxypiperidine **9** was shown to be equally efficient when a hindered alkoxide base (KO*t*Bu, Scheme 2) was used. Thus, the need for a deprotection step was eliminated. When the S_NAr reaction was performed at reflux in THF, 2−4% of the regioisomer (from displacement at the 4-fluoro position) was observed. This minor regioisomer could be rejected at this stage by selective formation of the HCl salt, but this was unnecessary due to successful removal later in the synthesis.

Dibromoformaldoxime **4** was readily prepared on scale according to literature procedures (Scheme 3).[8] The modest yield obtained can be explained in part by the volatility of the product. To minimize exposure to the noxious solid **4**, after workup the

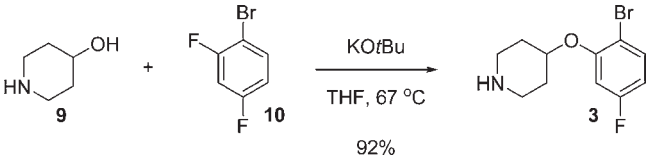
Received: July 11, 2011
Published: August 23, 2011

dx.doi.org/10.1021/op200186d | *Org. Process Res. Dev.* 2011, 15, 1073−1080

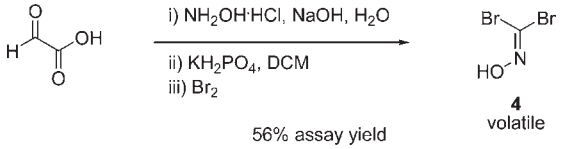
Scheme 1. First Generation Synthesis of MK-8245



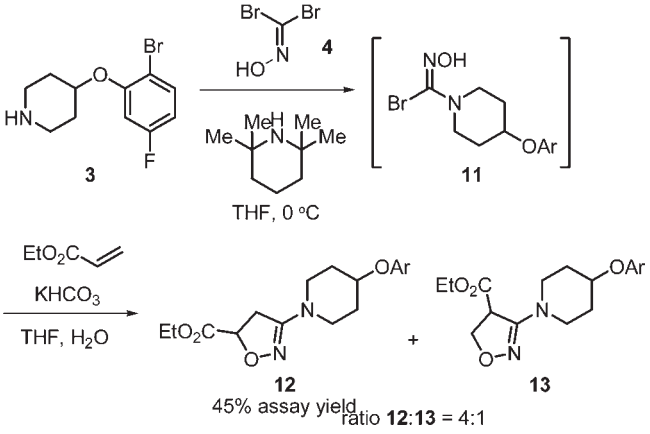
Scheme 2. Preparation of Piperidine 3



Scheme 3. Preparation of Dibromoformaldoxime 4



Scheme 4. One-Pot Three-Component Coupling to 3-Aminoisoxazoline 12



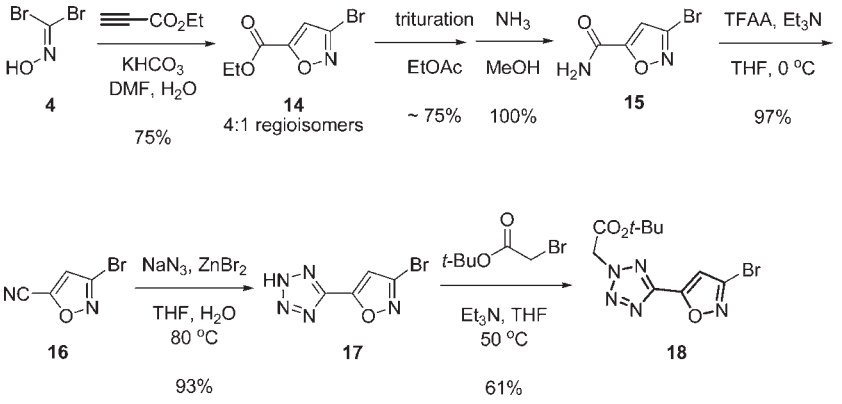
solvent of the crude organic layer was simply switched to DMF, and the resulting solution was used without purification.

With amine fragment **3** and dibromoformaldoxime **4** in hand, we focused on improvement of the isoxazole synthesis. The existing three-component coupling suffered from a lack of regioselectivity (1:1 mixture of 4- and 5-regioisomers). While it was found that appropriate choice of base and solvent could vastly improve the yield of intermediate oxime **11**,[9] significant improvement in regioselectivity was achieved only when ethyl acrylate was used in place of ethyl propiolate (Scheme 4). Thus, isoxazoline **12** was obtained in 45% assay yield, with 4:1 regioselectivity for the desired 5-isomer.

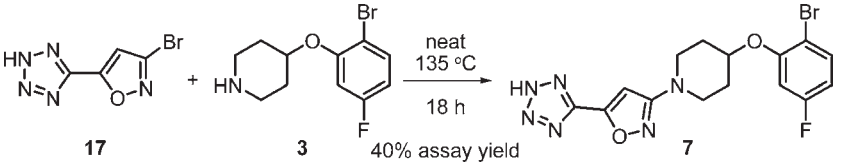
Still dissatisfied with this low yield and poor regioselectivity, we chose to separate the three-component coupling into two separate reactions. The [3 + 2] cycloaddition of ethyl propiolate and dibromoformaldoxime **4** *via* its nitrile oxide afforded 4:1 regioselectivity for the desired 3-bromoisoxazole **14** in 75% yield (Scheme 5).[10] The undesired regioisomer was rejected by trituration of the regioisomeric mixture in ethyl acetate. Functionalization of the ethyl ester **14** proved straightforward to provide access to amide **15**, nitrile **16** and tetrazoles **17** and **18**. With these various 3-bromoisoxazoles in hand, we set out to form the key C3−N bond of the desired 3-aminoisoxazole. Various attempts at copper- and palladium-catalyzed amination of 3-bromoisoxazoles **15**−**18** all met with failure.[11] Only under various base-promoted S_NAr reaction conditions were the desired products observed.[12] Despite extensive optimization efforts, the yields culminated with a modest 40% in the case of a neat reaction of tetrazole **17** at 135 °C (Scheme 6). Unfortunately, the extended reaction time (>24 h) and high temperature required for the S_NAr reaction led to extensive decomposition, which both lowered yield and complicated purification of the desired product **7** from byproducts.

dx.doi.org/10.1021/op200186d |*Org. Process Res. Dev.* 2011, 15, 1073–1080

Scheme 5. Synthesis of 3-Bromoisoxazoles



Scheme 6. S_NAr Approach to 3-Aminoisoxazole 7



Scheme 7. Synthesis of 3-Aminoisoxazoline 21

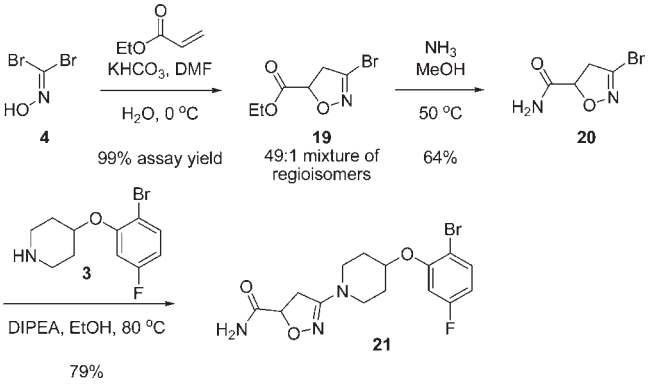
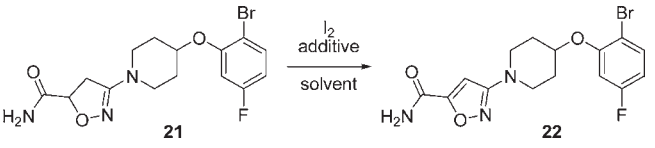
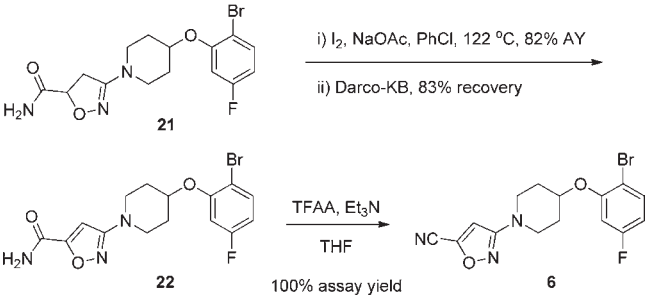


Table 1. Optimization of the Oxidation



entry	solvent (T in °C)	additive	convn (%)	assay yield (%)
1	DMSO (90)	none	68	40
2	PhCl (132)	none	60	35
3	PhCl (105)	none	33	30
4	DMSO (105)	Et_3N (2 equiv)	0	ND
5	PhCl (105)	$KHCO_3$ (3 equiv)	5	ND
6	PhCl (105)	NaOAc (5 equiv)	99	86

Scheme 8. Synthesis of Nitrile 6



Faced with the challenging formation of 3-aminoisoxazoles, we envisioned the formation of the key C3−N bond on a 3-bromoisoxazoline, which would exhibit greater reactivity.[13] The desired isoxazole could then be accessed by subsequent oxidation. Cycloaddition of ethyl acrylate and dibromoformaldoxime **4** afforded 3-bromoisoxazoline **19** with excellent regioselectivity (49:1) and high yield (99% assay yield, Scheme 7). Ethyl ester **19** was treated with ammonia in methanol and the resulting primary amide **20** precipitated from a mixture of MTBE:heptane. We were delighted to observe a substantial increase in reactivity of isoxazoline **20** as compared to isoxazole **15**. Addition−elimination of piperidine **3** with 3-bromoisoxazoline **20** proceeded in the presence of 2.5 equiv of DIPEA in ethanol at 80 °C in 22 h. The resulting 3-aminoisoxazoline **21** was precipitated using 1 N HCl and isolated in 79% yield.

A variety of oxidants[14] provided the desired isoxazole **22**, albeit in modest yield. We chose to focus on the reaction from iodine in DMSO, which afforded 68% conversion and 40% HPLC assay yield (Table 1, entry 1).[15] Similar levels of conversion and

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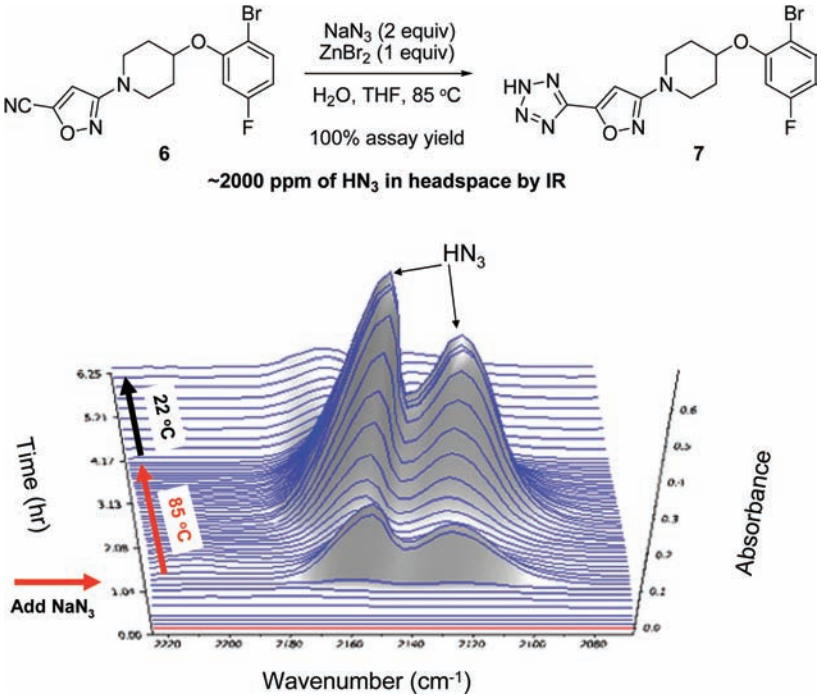


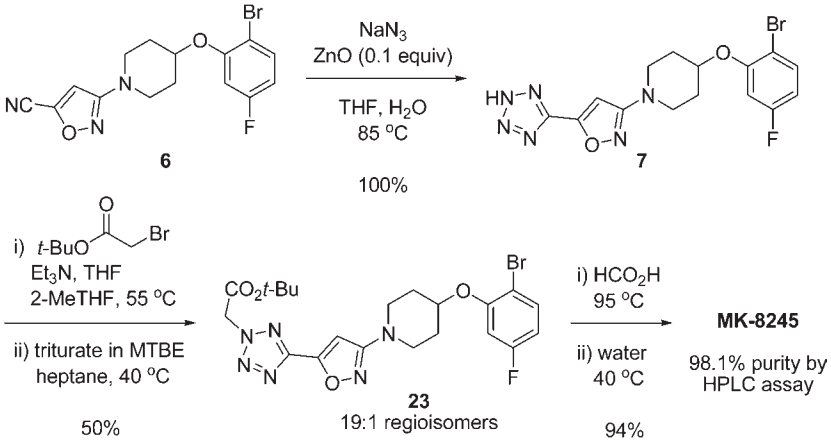
Figure 1. Stacked IR spectra of the reactor headspace during $ZnBr_2/NaN_3$-mediated tetrazole formation.

degradation were observed in chlorobenzene at reflux (entry 2); however, when the temperature was lowered to 105 °C, the product was formed cleanly, such that assay yield matched conversion (entry 3). Study of this reaction by ^{1}H NMR revealed that at 33% conversion 2 equiv of the HI salt of the starting material (**21**·HI) was present, which is consistent with the reaction stoichiometry. We postulated that **21**·HI could be prone to decomposition under more forcing conditions. In order to circumvent the undesired pathway, we explored the addition of base. While Et_3N and $KHCO_3$ were found to inhibit the reaction (entries 4 and 5), NaOAc afforded the desired isoxazole **22** in 86% assay yield. On kilogram-scale the oxidation was run at 122 °C to shorten reaction time to <4 h (Scheme 8), and a Darco treatment used post-workup to remove color and various minor, unidentified impurities. Dehydration of amide-isoxazole **22** using TFAA afforded nitrile **6** in quantitative yield.

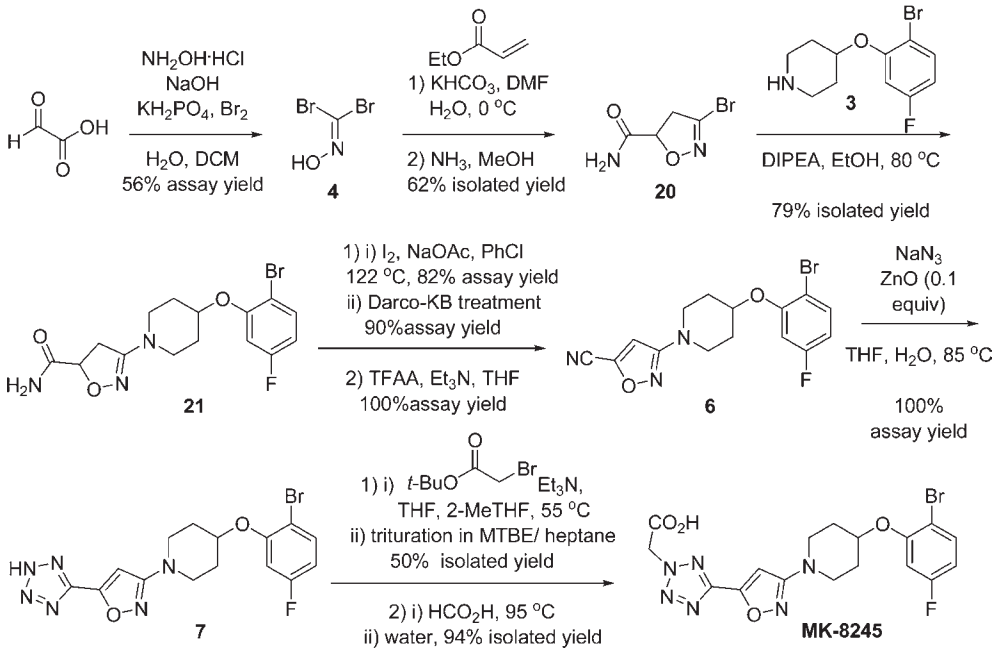
In the first generation synthesis, nitrile **6** was reacted with sodium azide (NaN_3) in the presence of pyridinium hydrochloride. These acidic conditions raised an important safety concern due to the formation of hydrazoic acid, known for its toxicity and extreme shock sensitivity (reported to detonate from audible speech).[16] A safer protocol has been proposed by Sharpless et al., using zinc(II) bromide and NaN_3 in refluxing water.[17] These conditions were reported to be slightly alkaline and to minimize the liberation of hydrazoic acid. When similar conditions were applied to nitrile **6**,[18] online infrared spectroscopy of the reactor headspace revealed the presence of ~2000 ppm hydrazoic acid (Figure 1). Although this level is below the detonation threshold (~15,000 ppm), we wanted to evaluate the possibility to further lower the amount of hydrazoic acid liberated. The most obvious way to achieve this goal was to buffer the reaction media. To this end, K_3PO_4 was added (pH increased from 5 to 9), and the reaction still proceeded to full conversion in 18 h. A significant amount of precipitate formed under these conditions, which was suspected to be zinc(II) oxide. This led to an interesting finding: a catalytic amount of ZnO (0.1 equiv) also facilitated the cyclization (Scheme 9). This modification ensured the safety of the reaction as the pH increased from 5 to 8 and only ~2 ppm hydrazoic acid was detected in the headspace. It should be noted that in this case there was a significant background reaction for converting nitrile **6** to tetrazole **7**. When the zinc catalyst was omitted, the reaction still proceeded to 72% conversion in 24 h (for comparison, full conversion was obtained with 0.1 equiv ZnO in 24 h). Alkylation of the tetrazole with *tert*-butylbromoacetate provided intermediate **23**, the high crystallinity of which facilitated purification and allowed a regioisomer ratio (from 4:1 to 19:1) upgrade *via* crystallization. The synthesis of MK-8245 was completed by cleavage of the *tert*-butyl ester in refluxing formic acid. When full conversion was reached, seeds and water were added. After ageing for 14 h at 40 °C, the crystalline API was isolated in 94% yield with the desired purity for preclinical and clinical use.

In conclusion, a second generation synthesis was developed and successfully utilized to complete the kilogram-scale chromatography-free synthesis of MK-8245 (Scheme 10). The major issues of the first generation synthesis were addressed. A protecting-group free S_NAr reaction of difluorobenzene **10** with hydroxypiperidine **9** replaced the inefficient Mitsunobu reaction to access **3**. Several alternatives to the low-yielding three-component coupling used to generate 3-aminoisoxazole **5** were studied, leading to the development of a robust two-step sequence: addition−elimination of piperidine **3** onto 3-bromoisoxazoline **20** to afford **21**, followed by oxidation and dehydration to access isoxazole **6**. Neutral conditions were developed and shown to minimize hydrazoic acid generation to ensure safe conditions for preparation of tetrazole **7**. Post-alkylation, the desired regioisomer of **23** was isolated by selective crystallization, and MK-8245 was obtained by a deprotection step, followed by direct crystallization of the pure API. These improvements resulted in overall yield of 9.5% to access >2.5 kg of MK-8245, in a longest linear sequence of 9 steps.

Scheme 9. Tetrazole 7 Formation and Functionalization



Scheme 10. Synthesis of MK-8245



EXPERIMENTAL SECTION

All reactions were performed in glass reaction vessels equipped with a mechanical stirrer and a thermocouple under an atmosphere of nitrogen. Commercially available reagents and solvents were used without further purification. ^{1}H NMR spectra were recorded on 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (DMSO-d_6: δ 2.49). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, td = triplet of doublets, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (DMSO-d_6: δ 39.5). ^{19}F NMR spectra were recorded on a 375 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with α,α,α-trifluorotoluene added as an internal reference (δ −62.7). All compounds were characterized using the same HPLC conditions: gradient elution (0.1% H_3PO_4/CH_3CN 70:30 to 5:95 over 25 min, hold 5 min), flow rate = 2.0 mL/min, T = 35 °C, UV detection at 210 nm.

3-Bromo-4,5-dihydro-isoxazole-5-carboxylic Acid Ethyl Ester (19). To a solution of dibromoformaldoxime **4** (3.42 kg, 16.9 mol) in DMF (10.3 L) at −15 °C were added ethyl acrylate (2.19 L, 20.2 mol) and then aq $KHCO_3$ (3.38 kg, 33.7 mol in 13.6 L water) over 1 h 45 min (internal temperature rising to 0 °C). After ageing for 75 min at 0 °C, the mixture was transferred to an extractor, and water (17 L) and MTBE (17 L) were added. The layers were separated, and the aqueous layer was extracted with MTBE (2 × 10 L). The combined organic layers were washed

dx.doi.org/10.1021/op200186d |Org. Process Res. Dev. 2011, 15, 1073–1080

with a mixture of brine and water (10 L each), assayed by HPLC (3.71 kg, 99% assay yield), combined with a second batch of similar size, and concentrated under reduced pressure to a yellow oil. ^{1}H NMR (400 MHz, acetone-d_6) δ 5.19 (dd, J = 11.6, 6.9 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 3.70 (dd, J = 17.6, 11.6 Hz, 1 H), 3.53 (dd, J = 17.6, 6.9 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (126 MHz, acetone-d_6) δ 169.3, 137.4, 78.9, 62.0, 44.8, 14.0. 38, 1046. HRMS (ESI) m/z calcd for $C_6H_9BrNO_3$ $[M + H]^+$ 221.9760, found 221.9767.

3-Bromo-4,5-dihydro-isoxazole-5-carboxylic Acid Amide (20). A solution of ester **19** (10.5 kg, 47.3 mol) in ammonia (2 M in MeOH, 28.4 L, 56.7 mol) was heated to 50 °C and aged for 2.5 h. The mixture was allowed to cool to ambient temperature and aged for 16 h. It was purged with a stream of nitrogen (the flask was connected to a scrubber containing H_2SO_4). The mixture was then cooled to 0 °C and diluted with MTBE (10.5 L) before addition of heptane (31.5 L) over 75 min. The slurry was aged at 0 °C for 2 h. The precipitate was recovered by filtration and washed with a 3:1 mixture of heptane/MTBE (2 × 5.25 L). A white solid was obtained (5.82 kg, 64% yield, 20:1 mixture of regioisomers by ^{1}H NMR). Characterization data in complete accord with literature precedent.[5]

4-(2-Bromo-5-fluoro-phenoxy)-piperidine (3). To a solution of 4-hydroxypiperidine (6.58 kg, 65.0 mol) in THF (32.9 L) was added *t*-BuOK (8.02 kg, 71.5 mol) with the internal temperature rising from 13 to 24 °C. The mixture was heated to reflux and aged for 25 min. Heating was stopped, and 1-bromo-2,4-difluorobenzene (8.08 L, 71.5 mol) was added over 1 h 40 min, which maintained a gentle reflux. After ageing 15 min, the mixture was cooled to 22 °C over 1 h and was transferred to an extractor charged with water (16.5 L). The flask was rinsed with MTBE (32.9 L), and this was also charged to the extractor. The layers were separated, and the organic layer was washed with a mixture of brine and water (8 L brine, 4 L water). The organic layer was assayed by HPLC (16.36 kg, 92% yield). The solution was concentrated under reduced pressure and azeotroped with iPrOAc (20 L) and ethanol (25 L) to afford an orange oil (48.7 wt %; ^{19}F NMR showed the presence of 2.3% of the regioisomer). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (dd, J = 8.8, 6.4 Hz, 1 H), 7.13 (dd, J = 11.2, 2.8 Hz, 1 H), 6.73 (td, J = 8.5, 2.8 Hz, 1 H), 4.61−4.53 (m, 1 H), 2.96−2.88 (m, 2 H), 2.56 (ddd, J = 12.6, 8.9, 3.2 Hz, 2 H), 2.05 (br, 1 H), 1.88−1.81 (m, 2 H), 1.53−1.42 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, J_{CF} = 247 Hz), 154.6 (d, J_{CF} = 3.5 Hz), 133.8 (d, J_{CF} = 10 Hz), 109.0 (d, J_{CF} = 21 Hz), 107.9 (d, J_{CF} = 4.2 Hz), 103.3 (d, J_{CF} = 26 Hz), 74.0, 42.7, 30.9. ^{19}F NMR (377 MHz, DMSO-d_6) δ −118.3 (desired regioisomer), −112.7 (minor regioisomer). HRMS (ESI) m/z calcd for $C_{11}H_{13}BrFNO$ $[M + H]^+$ 274.0237, found 274.0238.

3-[4-(2-Bromo-5-fluoro-phenoxy)-piperidin-1-yl]-4,5-dihydro-isoxazole-5-carboxylic Acid Amide (21). To a solution of piperidine **3** (8.89 kg, 32.4 mol) in ethanol (28.5 L) were added 3-bromoisoxazoline **20** (5.69 kg, 29.5 mol) and DIPEA (12.8 L, 74.0 mol). The mixture was heated to reflux for 22 h, cooled to 5 °C, and transferred to an extractor. Aqueous HCl (1 N, 39.8 L) was added over 1 h 15 min (internal temperature rising to 7 °C). After ageing for 2 h at 0 °C, the precipitate was recovered by filtration and was washed with a 1:1 mixture of EtOH/1 N HCl (2 × 4.5 L), followed by water (8.5 L) and finally heptane (8.5 L). A beige solid was obtained (8.97 kg, 79% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.58 (dd, J = 8.8, 6.3 Hz, 1 H), 7.04 (dd, J = 10.9, 2.8 Hz, 1 H), 6.98 (s, 1 H), 6.71 (td, J = 8.4, 2.8 Hz, 1 H), 6.59 (s, 1 H), 4.83−4.76 (m, 2 H), 3.53−3.46 (m, 2 H), 3.35 (dd, J = 16.0, 10.7 Hz, 1 H), 3.31−3.23 (m, 3 H), 1.87−1.79 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.0, 162.2 (d, J_{CF} = 244 Hz), 160.3, 154.2 (d, J_{CF} = 11 Hz), 133.7 (d, J_{CF} = 10 Hz), 108.9 (d, J_{CF} = 23 Hz), 106.9 (d, J_{CF} = 3.8 Hz), 103.6 (d, J_{CF} = 28 Hz), 78.0, 72.8, 36.8, 29.1.

3-[4-(2-Bromo-5-fluoro-phenoxy)-piperidin-1-yl]-isoxazole-5-carboxylic Acid Amide (22). To a suspension of isoxazoline **21** (4.31 kg, 11.2 mol) and NaOAc (2.38 kg, 29.0 mol) in chlorobenzene (21.6 L) was added iodine (3.68 kg, 14.5 mol). The mixture was heated to reflux for 3 h 45 min, cooled to 73 °C over 1 h, and transferred to an extractor charged with 2-MeTHF (43 L) that had been warmed to 50 °C. The resulting suspension was cooled to 45 °C before addition of aqueous NaS_2O_3 (21.6 L, 10 wt %). The dark mixture was stirred for 5 min (34 °C) and filtered through solka floc. The cake was washed with 2-MeTHF (21.6 L). The filtrate was returned to the extractor, and the layers were separated easily. The organic layer was washed with brine (21.6 L) and assayed by HPLC (3.53 kg, 82% yield). Darco-KB (2.47 kg) was added to the crude solution, which was stirred for 3 h and then filtered through solka floc. The cake was rinsed with THF (20 L). The filtrate was assayed by HPLC (3.19 kg, 90% recovery). The material was combined with a second batch of similar size, solvent switched with toluene (40 L) and THF (40 L), and subjected to a second treatment with 50 wt % Darco-KB (92% recovery). The filtrate was concentrated under reduced pressure to 18 wt % and used directly in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1 H), 7.85 (s, 1 H), 7.64−7.58 (m, 1 H), 7.24 (d, J = 11.0 Hz, 1 H), 6.91 (s, 1 H), 6.82−6.76 (m, 1 H), 4.81 (s, 1 H), 3.53−3.45 (m, 2 H), 3.33−3.25 (m, 2 H), 2.02−1.94 (m, 2 H), 1.79−1.70 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.1, 163.8, 162.8 (d, J_{CF} = 245 Hz), 158.0, 154.7 (d, J_{CF} = 11 Hz), 134.2 (d, J_{CF} = 10 Hz), 109.4 (d, J_{CF} = 22 Hz), 107.5 (d, J_{CF} = 2.8 Hz), 104.1 (d, J_{CF} = 28 Hz), 98.5, 73.3, 44.2, 29.3. HRMS (ESI) m/z calcd for $C_{15}H_{15}BrFN_3O_3$ $[M + H]^+$ 384.0354, found 384.0352.

3-[4-(2-Bromo-5-fluoro-phenoxy)-piperidin-1-yl]-isoxazole-5-carbonitrile (6). To the crude solution of **22** (18 wt %, 34.3 kg, 16.1 mol) was added Et_3N (4.49 L, 32.2 mol), and the mixture was cooled to 2 °C. Trifluoroacetic anhydride (3.35 L, 24.1 mol) was added over 35 min keeping the internal temperature below 15 °C. After 25 min, more Et_3N (225 mL, 3.22 mol) was added. After 30 min more, TFAA (112 mL, 1.21 mol) was added. After ageing for 30 min, the mixture was transferred to an extractor and partitioned between MTBE (64 L) and water (16 L). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 16 L). The pH values of the washes were 6.5 and 8.1, respectively. The organic layer was then washed with a mixture of water (8 L) and brine (8 L) and assayed by HPLC (6.39 kg, 100% assay yield). The crude solution was concentrated under reduced pressure to 56 wt % and used directly in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63−7.57 (m, 1 H), 7.60 (s, 1 H), 7.23 (dd, J = 11.0, 2.8 Hz, 1 H), 6.81−6.76 (m, 1 H), 4.85−4.78 (m, 1 H), 3.56−3.48 (m, 2 H), 3.53−3.13 (m, 2 H), 2.03−1.96 (m, 2 H), 1.80−1.72 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 162.8 (d, J_{CF} = 244 Hz), 154.7 (d, J_{CF} = 10 Hz), 141.2, 134.2 (d, J_{CF} = 11 Hz), 109.6 (d, J_{CF} = 3.0 Hz), 109.4, 107.5 (d, J_{CF} = 3.0 Hz), 107.3, 104.1 (d, J_{CF} = 26 Hz), 73.1, 44.2, 29.3. HRMS (ESI) m/z calcd for $C_{15}H_{13}BrFN_3O_2$ $[M + H]^+$ 366.0248, found 366.0250.

4-(2-Bromo-5-fluoro-phenoxy)-1-[5-(2*H*-tetrazol-5-yl)-isoxazol-3-yl]-piperidine (7). In a reaction vessel connected to a

scrubber containing 3 N NaOH were added the crude nitrile **6** (56 wt %, 10.96 kg, 16.8 mol), ZnO (137 g, 1.68 mol), THF (6.2 L), and water (31 L). Sodium azide (1.20 kg, 18.5 mol) [**CAUTION**: sodium azide is extremely toxic and may generate hydrazoic acid in the presence of acid. Hydrazoic acid is shock-sensitive, volatile, and toxic (see ref 16 for further details). Ensure that all aqueous solutions of sodium azide are kept above pH 7, wash all equipment with copious aqueous base post-use, and ensure all azide-containing waste is collected separately, kept basic, and disposed of separately] was dissolved in water (3.1 L) and added via an addition funnel to the reaction mixture over 20 min. The mixture was then heated to 78 °C for 15 h, cooled to ambient temperature, and transferred to an extractor charged with saturated aqueous $NaHCO_3$ (16 L), brine (16 L), and 2-MeTHF (31 L). The organic layer was separated and assayed by HPLC (6.88 kg, 100% assay yield). The 25 wt % crude solution was used directly in the next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (dd, J = 8.8, 6.4 Hz, 1 H), 7.23 (dd, J = 11.1, 2.8 Hz, 1 H), 6.77 (td, J = 8.5, 2.7 Hz, 1 H), 6.54 (s, 1 H), 4.79 (s, 1 H), 4.05 (s, 1 H), 3.53−3.47 (m, 2 H), 2.01−1.95 (m, 2 H), 1.77−1.71 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.7, 162.2 (d, J_{CF} = 244 Hz), 156.5, 154.2 (d, J_{CF} = 11 Hz), 133.7 (d, J_{CF} = 10 Hz), 109.0 (d, J_{CF} = 23 Hz), 107.0, 103.6 (d, J_{CF} = 26 Hz), 97.1, 72.8, 43.7, 28.8.

(5-{3-[4-(2-Bromo-5-fluoro-phenoxy)-piperidin-1-yl]-isoxazol-5-yl}-tetrazol-2-yl)-acetic Acid *tert*-Butyl Ester (23). To the crude solution of tetrazole **7** (25 wt %, 22 kg, 13.4 mol) was added Et_3N (3.3 L, 23.5 mol), and the mixture was heated to 55 °C. *tert*-Butylbromoacetate (3.0 L, 20.5 mol) was added over 20 min, and the internal temperature rose to 63 °C over the course of the addition. The mixture was aged for 2 h 30 min at 58 °C and then cooled to 35 °C. It was transferred to an extractor charged with aqueous HCl (1 N, 30 L). The layers were separated, and the organic layer was washed with a mixture of water and brine (15 L each) and assayed by HPLC (5.03 kg, 71% assay yield and 1.25 kg of the desired 1-regioisomer). The solution was filtered through a 1.0 μm inline filter, concentrated under reduced pressure, flushed with heptane (20 L), and concentrated to give a thick beige slurry (47 wt %). MTBE (25 L) and heptane (5.8 L) were added to the slurry, and the resultant suspension was warmed to 47 °C. After ageing for 16 h, the slurry was cooled to 39 °C and the precipitate was recovered by filtration, rinsing with a 3:1 mixture of MTBE/heptane (2.0 L). A light beige solid was obtained (3.52 kg, 20:1 regioisomers, 70% isolated yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (dd, J = 8.8, 6.3 Hz, 1 H), 7.24 (d, J = 14.8 Hz, 2 H), 6.78 (td, J = 8.5, 2.8 Hz, 1 H), 5.85 (s, 2 H), 4.83−4.79 (m, 1 H), 4.03 (s, 1 H), 3.59−3.52 (m, 2 H), 2.03−1.97 (m, 2 H); 1.79−1.73 (m, 2 H); 1.43 (s, 9 H).^{13}C NMR (126 MHz, DMSO-d_6) δ 166.7, 164.7, 162.3 (d, J_{CF} = 245 Hz), 157.2, 155.3, 154.3 (d, J_{CF} = 10 Hz), 133.7 (d, J_{CF} = 10 Hz), 109.0 (d, J_{CF} = 23 Hz), 107.0 (d, J_{CF} = 2.5 Hz), 103.6 (d, J_{CF} = 26 Hz), 97.0, 83.3, 72.9, 54.3, 43.7, 28.9, 27.5.

(5-{3-[4-(2-Bromo-5-fluoro-phenoxy)-piperidin-1-yl]-isoxazol-5-yl}-tetrazol-2-yl)-acetic Acid (MK-8245). A suspension of *tert*-butyl ester **23** in formic acid (17 L) was heated to 95 °C for 2 h. The solution was cooled to 77 °C, and 80 g of seed was added. The suspension was aged for 1 h, and water (6.5 L) was added over 1 h. It was allowed to cool to 40 °C, aged for 14 h, and then filtered. The cake was washed with water (17 L) and dried in a vacuum oven at 70 °C (2.87 kg, 94% isolated yield, 98.1% pure as measured by HPLC at 210 nm). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (dd, J = 8.8, 6.3 Hz, 1 H), 7.25−7.19 (m, 2 H), 6.77 (td, J = 8.5, 2.7 Hz, 1 H), 5.83 (s, 2 H), 4.82−4.78 (m, 1 H), 3.59−3.53 (m, 2 H), 2.03−1.97 (m, 2 H), 1.78−1.71 (m, 2 H). ^{13}C NMR and HRMS data obtained are in complete accord with literature precedent.[5]

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ACKNOWLEDGMENT

We thank Claude Briand, Richard Desmangles, and Wayne Mullett for analytical support. Also, we would like to express our appreciation to Theintu Lam for helpful safety discussions.

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tetramethylpiperidine (TMP) was uniquely able to promote the condensation without competing as reactant with dibromooxime **4**. A solvent screen (acetonitirile, ethyl acetate, dichloromethane, toluene, and dimethylformamide) was then used to identify optimal conditions.

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