JOC The Journal of Organic Chemistry

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CRTH2 Antagonist MK-7246: A Synthetic Evolution from Discovery through Development

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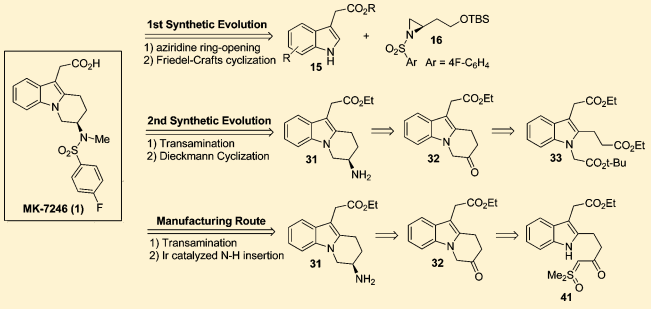
Supporting Information

ABSTRACT: In this paper, we report the development of different synthetic routes to MK-7246 (**1**) designed by the Process Chemistry group. The syntheses were initially designed as an enabling tool for Medicinal Chemistry colleagues in order to rapidly explore structure−activity relationships (SAR) and to procure the first milligrams of diverse target molecules for in vitro evaluation. The initial aziridine opening/cyclodehydration strategy was also directly amenable to the first GMP deliveries of MK-7246 (**1**), streamlining the transition from milligram to kilogram-scale production needed to support early preclinical and clinical evaluation of this compound. Subsequently a more scalable and cost-effective manufacturing route to MK-7246 (**1**) was engineered. Highlights of the manufacturing route include an Ir-catalyzed intramolecular N−H insertion of sulfoxonium ylide **41** and conversion of ketone **32** to amine **31** in a single step with excellent enantioselectivity through a transaminase process. Reactions such as these illustrate the enabling impact and efficiency gains that innovative developments in chemo- and biocatalysis can have on the synthesis of pharmaceutically relevant target molecules.



INTRODUCTION

CRTH2 (*c*hemo-attractant *r*eceptor expressed on *Th2* cells) is one of the two high-affinity transmembrane receptors for prostaglandin d2 (PGD2) that have been identified to date.[1] PGD2 has been implicated as a mediator of allergic inflammation and diseases including asthma, allergic rhinitis, and atopic dermatitis.[2] The first PGD2 receptor characterized, DP, is known mainly for its role in vasodilatation.[3] By contrast the more recently identified CRTH2 has been found to play a role in leukocyte activation.[4] Biological and genetic data suggest that the downstream events triggered by activation of CRTH2 through binding to PGD2 play a key role in stimulating late-phase allergic inflammation.[5] The hypothesis that blockade of the CRTH2 receptor could provide a novel mechanism for treatment of chronic allergic disease is being aggressively pursued by the pharmaceutical industry. Many companies have engaged in CRTH2 antagonist programs which have reached various stages of preclinical and clinical development.[6]

Recently, Merck researchers disclosed MK-7246 (**1**) as a potent and selective CRTH2 antagonist for the potential treatment of respiratory disease (Figure 1).[7] In this paper, we report the development of different synthetic routes to MK-7246 (**1**) designed by the Process Chemistry group. The syntheses were initially designed as an enabling tool for Medicinal Chemistry colleagues in order to rapidly explore structure−activity relationships (SAR) and to procure the first milligrams of diverse target molecules for in vitro evaluation. This collaboration allowed the program to quickly advance and identify MK-7246 (**1**) as the drug candidate, and therefore, the chemistry was driven to evolve substantially to become the optimum scalable route capable of supplying the large quantities needed for further development through clinical trials.

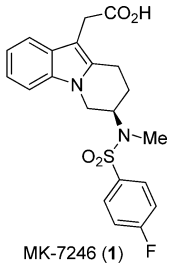


Figure 1. Structure of MK-7246 (**1**).

RESULTS AND DISCUSSION

Original Synthesis. The synthetic approach originally utilized by Medicinal Chemistry in support of SAR studies is outlined in Scheme 1.[7a,8] Reduction ($LiAlH_4$) of ester **2** followed by oxidation (MnO_2) of the resulting alcohol generated aldehyde **3**, which was elaborated over a further three steps to provide

Received: December 19, 2011
Published: February 15, 2012

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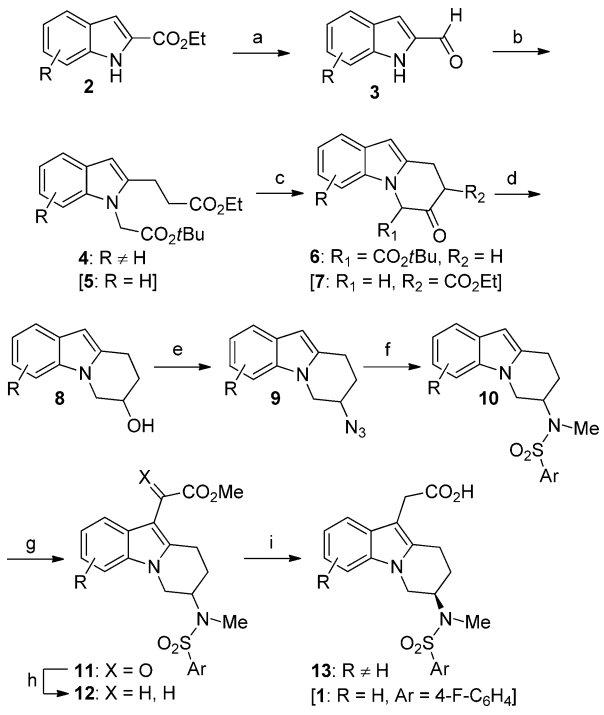
Scheme 1. Original Synthesis of MK-7246 (1) and Analogues (13)



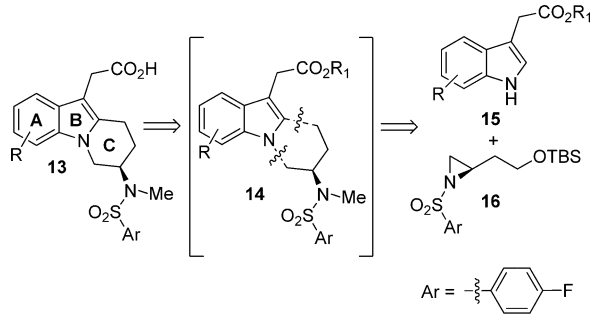
Reagents: (a) 1. $LiAlH_4$; 2. MnO_2; (b) 1. Ph_3PCHCO_2Et; 2. $BrCH_2CO_2t$-Bu, Cs_2CO_3; 3. H_2, Pd/C; (c) KO*t*-Bu; (d) 1. silica gel, toluene, reflux; 2. $NaBH_4$; (e) 1. MsCl, Et_3N; 2. NaN_3; (f) 1. H_2, Pd/C; 2. $ArSO_2Cl$, Et_3N; 3. NaH, MeI; (g) 1. $(COCl)_2$; 2. MeOH; (h) 1. $NaBH_4$; 2. Et_3SiH, TFA; (i) 1. chiral HPLC; 2. LiOH, THF.

orthogonally protected diester **4**. Treatment of **4** with KO-*t*-Bu in THF resulted in Dieckmann cyclization to afford tricyclic ketone **6**. Hill and co-workers had previously reported that cyclization of the unsubstituted indole substrate **5** (R = H) proceeded with high regioselectivity, with only trace quantities of the alternative Dieckmann product **7** being formed (vide infra).[9] Deprotection of the *tert*-butyl ester group with concomitant decarboxylation by heating in the presence of silica gel was followed by reduction with $NaBH_4$ to provide tricyclic alcohol **8** in racemic form. The hydroxyl group was converted to the corresponding azide **9** via a standard activation/displacement sequence and then further elaborated to give sulfonamide **10**. Intermolecular Friedel–Crafts acylation at the indole C3-position with oxalyl chloride and then methanolysis of the intermediate α-keto acid chloride produced ketoester **11**. The two-stage reductive removal of the ketone group ($NaBH_4$ then Et_3SiH/TFA) gave racemic penultimate ester **12**, the enantiomers of which could be separated by preparative HPLC on a chiral stationary phase. A final ester hydrolysis step then completed the synthesis.

Although the described original chemistry route did provide access to specific target structures, from the perspective of enabling rapid SAR work this route was hampered by a number of limitations. In particular, the synthesis was linear with the indole core being incorporated in the first step, limiting the possibilities for subsequent diversification of this motif. Furthermore, at 18 steps (~10% overall yield), including many flash chromatography purifications and a late-stage chiral separation (resolution), the synthesis time per analogue was long (3–4 weeks), a significant drawback during lead optimization. A more versatile and expedient synthesis was therefore desired.

First Synthetic Evolution. A more convergent route was envisaged in which a four-carbon subunit of the C-ring would be appended on to the indole core (Scheme 2). The proposed

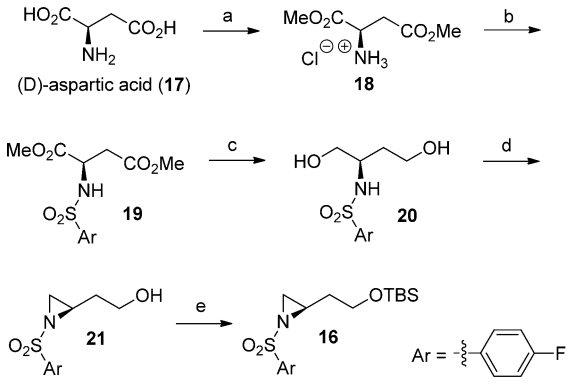
Scheme 2. Retrosynthetic Analysis: Aziridine Ring-Opening Reaction as the Key Coupling Strategy



transformations to achieve this were intermolecular aziridine ring-opening and subsequent Friedel–Crafts cyclization onto the indole C2 position.[10,11] This strategy would provide several advantages. Because there are many indoles and azaindoles **15** commercially available, the probing of SAR around this ring system would be facilitated. Also, an enantiopure preparation of aziridine **16** would allow us to set the stereocenter on the molecules eliminating any need for chiral separations. Finally, since the 4-fluorobenzenesulfonamide group was present in many of the target compounds (**13**) of interest, this substituent was incorporated into aziridine **16**, thus serving the dual purposes of both activating the ring toward nucleophilic opening and eliminating downstream protecting group manipulations.

Aziridine **16** was prepared from D-aspartic acid (**17**) in five steps (Scheme 3) utilizing a modification of a route reported by

Scheme 3. Preparation of Aziridine 16



Reagents: (a) $SOCl_2$, MeOH, 99%; (b) $ArSO_2Cl$, Et_3N, THF, 93%; (c) $NaBH_4$ (5 eq), EtOH, 60%; (d) ADDP, *n*-Bu_3P, THF, 77%; (e) TBSCl, Et_3N, THF, 84%.

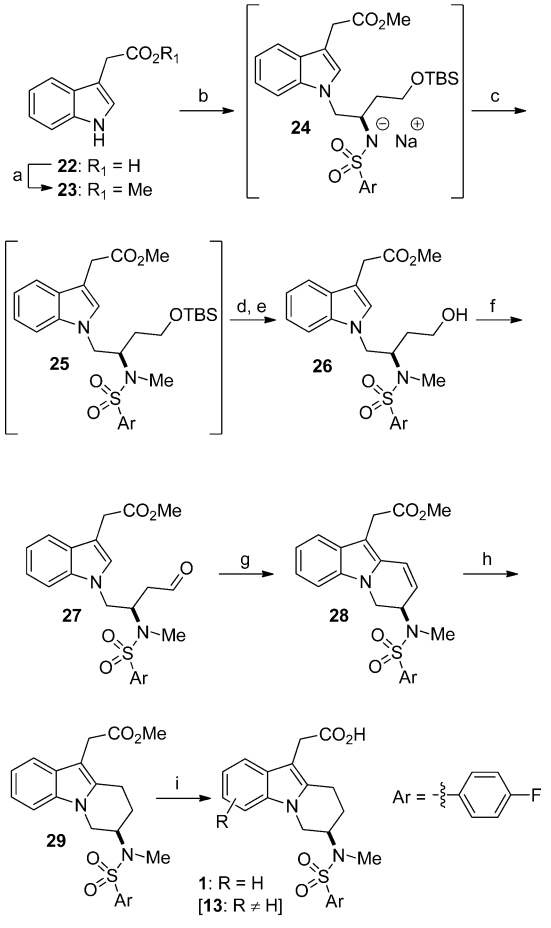
Bisai and Singh for the preparation of the corresponding *p*-toluenesulfonyl analogue.[12] Esterification of D-aspartic acid (**17**) using thionyl chloride and methanol[13] was followed by sulfonylation to afford diester **19** (an oil) in 94% overall yield. Reduction of both ester groups to give diol **20** (also an oil) was accomplished with 5 equiv of $NaBH_4$ in EtOH (60% yield).[14] The workup of this reaction was complicated by the high

dx.doi.org/10.1021/jo202620r | J. Org. Chem. 2012, 77, 2299–2309

aqueous solubility of diol **20** and by removal of boron salts, thus requiring many unit operations. Cyclization of diol **20** under Mitsunobu conditions, using 1,1′-(azodicarbonyl)dipiperidine (ADDP) and tri-*n*-butylphosphine in THF,[15] selectively afforded aziridine **21** in 77% yield. Protection of the resulting primary alcohol as the corresponding TBS ether under standard conditions then provided the key intermediate **16**.

With the requisite aziridine in hand, we next turned our attention to the preparation and elaboration of the indole fragment. Addition of aziridine **16** to the *N*-anion generated from indole acetic ester **23** (prepared in one step from the corresponding acid **22**) in DMF resulted in regioselective ring-opening to afford sulfonamide anion **24** (Scheme 4).[16] The

Scheme 4. Synthesis of MK-7246 (1) Using the Aziridine Ring-Opening Strategy



Reagents: (a) MeOH, cat H_2SO_4, 81%; (b) 1. KHMDS, DMF; 2. **16**; (c) MeI; (d) HCl, 63% (69 LCAP) from **16**; (e) reslurry in EtOAc/MTBE/*n*-heptane, 96% (83 LCAP); (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (g) PPTS, toluene, 60 °C, 80% from **26**; (h) H_2, Pd/C, EtOAc, 91%; (i) LiOH, THF, 97%.

relative stoichiometry and order of addition of the coupling partners **16** and **23** was important in this process.[17] Intermediate **24** could, in turn, be alkylated in situ by the addition of a sufficiently reactive alkylating agent (MeI) to give *N*-methyl derivative **25**. Quenching of the reaction using 2 M aq HCl resulted in concomitant removal of the TBS group to furnish alcohol **26** which, after aqueous workup, could be crystallized from the organic layer. The yield for this three-step, one-pot procedure was 63%, however with low purity (69 LCAP[18]). The isolated material was then reslurried in EtOAc/MTBE/*n*-heptane to upgrade the purity of the product from 69 to 83 LCAP (96% recovery of **26**, 60% overall yield from **23**).[19]

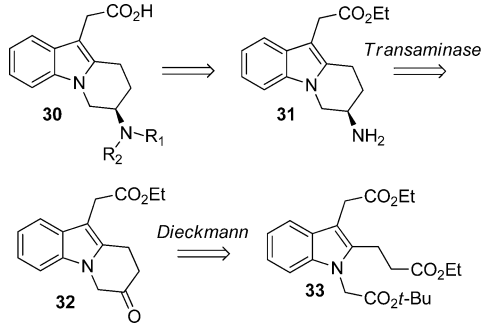
On the basis of a report by Guazzelli and Settambolo[20] describing the facile Friedel–Crafts cyclization of (indol-1-yl)-butanals,[21] aldehyde **27** was anticipated to be the substrate of choice for cyclization onto the indole core.[22] Oxidation of alcohol **26** to aldehyde **27** under Swern conditions proceeded uneventfully; after aqueous workup, the crude product was filtered through a pad of silica (to remove Et_3N·HCl) and the solvent switched from CH_2Cl_2 to toluene. Exposure of the solution to mildly acidic conditions (cat PPTS, 60 °C) resulted in cyclization of aldehyde **27** and subsequent dehydration to form allylic sulfonamide **28**, which was isolated in 80% overall yield for the two steps.[23] Alkene hydrogenation followed by basic hydrolysis of the ester group then completed the synthesis of MK-7246 (**1**).

At only six steps, and less than 1 week processing time on laboratory scale, from a common *chiral* aziridine intermediate **16** (overall 11 steps, 15% yield from D-aspartic acid **17**) and with the potential for structural diversification at many sites, this second-generation route was applied to the synthesis of many analogues **13**, driving much of the early lead optimization work.[7c,24] The synthesis was also scalable to the extent that 1–10 kg quantities of MK-7246 (**1**) could be prepared, enough to supply the early phase I clinical trials and animal toxicity studies needed to support an eventual regulatory filing.

However, there were limitations; moderate yields, processing difficulties for several steps, and instability of certain intermediates combined to render this route impractical for the production of the significantly larger quantities (>10 kg) of MK-7246 (**1**) needed for late-stage development into phase II and beyond. Concurrently, efforts were also continuing within Medicinal Chemistry to identify other candidates as potential backups to MK-7246 (**1**). From an SAR perspective this route was limiting in that the substituents on the alkyl nitrogen could not be readily varied. Further revision to the chemistry was therefore mandated.

Second Synthetic Evolution. Rather than follow the chiral-pool approach, an asymmetric synthesis was planned that called for the direct installation of the chiral amine functionality from prochiral ketone precursor **32** in a single step (Scheme 5).

Scheme 5. Retrosynthetic Analysis: An Enzymatic Reaction Installs the Amine-Bearing Stereocenter in a Single Step

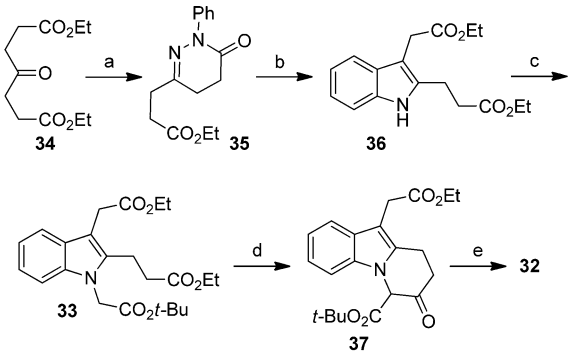


The strategy was to leverage a biocatalytic transamination technology[25] that was recently employed for the commercial production of sitagliptin (Januvia).[26,27] Ketone **32** could, in turn, be prepared following the Dieckmann cyclization strategy to access the general tricyclic core structure (vide supra).

dx.doi.org/10.1021/jo202620r | J. Org. Chem. 2012, 77, 2299–2309

Commercially available ketone **34** was converted in two steps, via isolated pyridazinone **35**, into diester **36** using a modification of a two-step protocol reported by Sapi and co-workers (Scheme 6).[28] *N*-Alkylation using *tert*-butyl bromoacetate

Scheme 6. Preparation of Transaminase Ketone Precursor 32: Dieckmann Cyclization Route



Reagents: (a) $PhNHNH_2$•HCl, toluene, reflux, 87%; (b) H_2SO_4, EtOH, reflux, 75%; (C) $BrCH_2CO_2t$-Bu, Cs_2CO_3, DMF, 93%; (d) KO*t*-Bu, THF, 64%; (e) silica gel, toluene, reflux, 88%.

then furnished the Dieckmann precursor **33** which, when treated with KO-*t*-Bu in THF[9] generated the desired ketoester **37** as the major cyclization product in 64% isolated yield after column chromatography. Significant amounts of byproduct **38** and **39** (Figure 2) were generated during the Dieckmann reaction;[29]

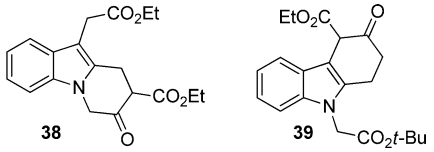
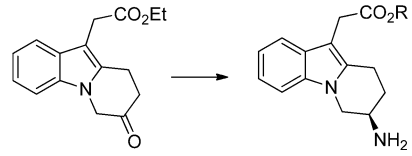


Figure 2. Competing byproducts **38** and **39** formed during the cyclization of triester **33**.

evidently, triester **33** is a more challenging substrate than the simpler diester substrate **5** (Scheme 1) due to the greater number of plausible competing cyclization pathways.[30] Regioselective ester hydrolysis/decarboxylation of ketoester **37** then afforded ketone **32**.

Ketone **32** could then be screened against an in-house library of *R*-selective transaminases previously developed for the sitagliptin project. Gratifyingly, minimal time was required for this endeavor as a hit was found with one of the first enzyme variants evaluated, namely CDX-017.[31] Under the optimized reaction conditions shown in Scheme 7, ketone **32** was converted to amine **31** in 98–99% ee and 81% HPLC assay yield in a single step. This excellent enantioselectivity was achieved using a readily available enzyme variant, which had not been engineered for the specific substrate **32**, demonstrating the potential broader utility of this methodology. Careful pH control was required during the reaction and workup to minimize ester hydrolysis.[32] The reaction was performed with a constant N_2 sweep through the reaction flask headspace; this eliminated the formation of oxidation byproduct arising from α-hydoxylation of ketone **32** under the basic conditions and also shifted the transaminase reaction equilibrium in favor of amine **31** by removing the acetone coproduct formed from *i*-Pr_2NH.

Scheme 7. Transaminase Reaction of Ketone 32

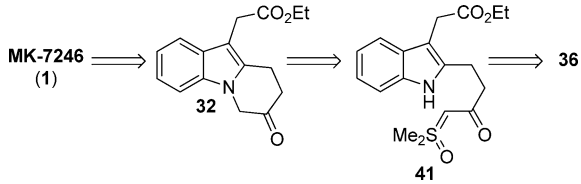


Conditions: CDX-017 (4.3 wt%), PLP, *i*-$PrNH_2$, pH 8.5 Et_3N buffer, aq DMSO, 45 °C, 80 – 81 % assay yield of **31**, 98 – 99% ee.

Amine **31** was readily prepared in laboratory-scale quantities using the route shown in Schemes 6 and 7. This amine was highly valuable for our Medicinal Chemistry colleagues since it allowed subsequent SAR of positions R_1 and R_2 of compound **30** in only two steps. For a larger scale synthesis of MK-7246 (**1**), however, the drawbacks of this approach to ketone **32** were immediately apparent: the relatively high number of steps, the paucity of crystalline intermediates and need for chromatographic purification after each step, and the lack of regioselectivity in the cyclization reaction. The chemistry was re-evaluated again, and one final round of synthesis evolution was performed to arrive at the preferred manufacturing route to MK-7246 (**1**).

MK-7246 Manufacturing Route. Recently published research from these laboratories has demonstrated the utility of δ-keto sulfoxonium ylides as carbenoid precursors for metal-catalyzed intermolecular and intramolecular X–H insertion processes, mitigating potential safety and processing concerns surrounding the more traditionally employed α-diazoketone precursors.[33] As applied to the preparation of MK-7426 (**1**), this process would manifest itself as the conversion of sulfoxonium ylide **41** to tricyclic ketone **32** (Scheme 8).[34] An

Scheme 8. Revised Retrosynthetic Analysis: N–H Carbenoid Insertion Approach to Tricyclic Ketone 32



appealing route to sulfoxonium ylide **41** presented itself in the form of regioselective functionalization of one of the ester groups in indole **36**. Precedent from Sapi and co-workers describing hydrolysis and reduction transformations of the dimethyl ester analogue of **36**, with moderate to high regioselectivity, suggested that this may indeed be a viable possibility.[28]

The manufacturing route to MK-7246 (**1**) that was developed is illustrated in Scheme 9. A more expedient preparation of indole diester **36** was discovered that employed a direct Fisher indolization under mild conditions.[35] Treatment of ketone **34** with a stoichiometric amount $ZnCl_2$ as promoter in toluene at 105 °C cleanly generated diester **36** in 93% HPLC assay yield, with <1% pyridazinone **35** being formed.[36] After aqueous workup, the crude diester **36** was used directly in the next step.[37]

Ylide **41** was prepared in a single step from indole diester **36**, employing conditions developed by Nugent and co-workers.[38] Thus, Me_3SOI and a 1 M solution of KO-*t*-Bu in THF[39] were

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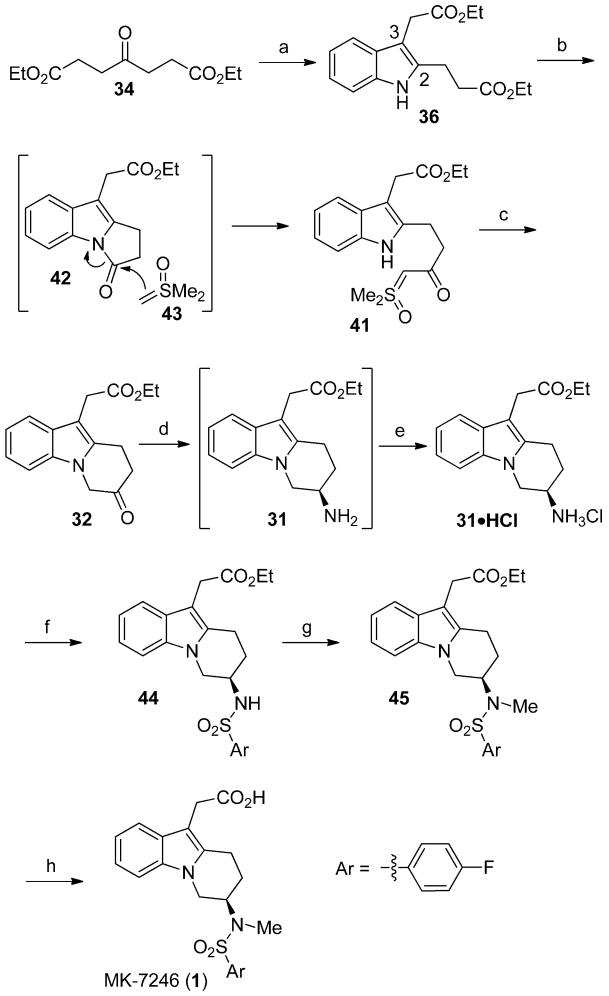
Scheme 9. Manufacturing Route to MK-7246 (1)



Reagents: (a) $PhNHNH_2$•HCl, $ZnCl_2$, toluene, 105 °C; (b) Me_3SOI, KO*t*-Bu, THF, 77% from **34**; (c) $[IrCl(COD)]_2$ (1 mol%), toluene/DMF, 85 °C, 83%; (d) CDX-017 (4.3 wt%), PLP, *i*-$PrNH_2$, pH 8.5 Et_3N buffer, aq DMSO, 45 °C, 81% AY, 98-99%ee; (e) HCl, IPA/CPME, 76% from **32**; (f) $ArSO_2Cl$, aq Na_2CO_3, IPAc, 89%; (g) MeI, K_2CO_3, DMF, 96%; (h) aq LiOH, THF/EtOH, 99%.

combined and heated to 65 °C for 2 h, the slurry was then cooled, and diester **36** was added as the crude solution in toluene. The reaction proceeded to completion in 2 h,[40] with ylide **41** being isolated after workup in 83% yield by crystallization from EtOAc/hexanes. Small amounts of by-product **46** and **47** (Figure 3, < 5% each) were observed during

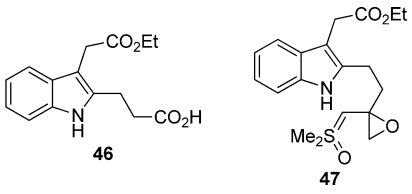
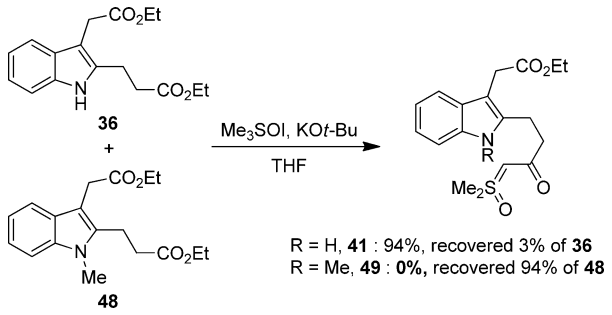


Figure 3. Impurities **46** and **47** generated during the formation of sulfoxonium ylide **41**.

the reaction[41] but were efficiently rejected during the workup and crystallization of the product **41**. The preheating stage was essential, as the reaction performed very poorly if the whole process was run at room temperature.

The ylide formation was found to be highly regioselective; no products derived from reaction at the ester group pendant at the indole C-3 position were seen. Arguably of equal interest was the fact that either of the ester groups reacted at all, as esters of aliphatic acids typically react only sluggishly under these reaction conditions.[39] The regioselectivity of other transformations of diester **36** had previously been attributed to electronic effects, with the indole ring exerting a higher positive inductive effect at the C-3 position relative to C-2, disfavoring nucleophilic attack at the C-3 substituent.[28] We propose an alternative rationale in which lactam **42** is formed by rapid cyclization under the basic reaction conditions, and serves as an activated carbonyl intermediate for opening by ylide species **43**. Lactam **42** could not be observed by HPLC–MS analysis during the reaction, though indirect evidence for its role in facilitating the ylide formation was provided by the competition experiment illustrated in Scheme 10. Thus, when a

Scheme 10. Competition Experiment between Indoles 36 and 48 in Sulfoxonium Ylide Formation



1:1 mixture of indoles **36** and **48** was exposed to the reaction conditions, indole **36** reacted smoothly to give the expected ylide product **41** while the *N*-methylated derivative **48**, which cannot undergo lactamization to **49**, was recovered almost quantitatively.

The Ir-catalyzed N–H insertion reaction of ylide **41** could be performed in good yield with only slight modifications to the general literature procedure (Scheme 9).[33] Addition of a solution of ylide **41** in DMF to a warm solution of $[IrCl(COD)]_2$ (1 mol %) over 6 h gave ketone **32** in 90% HPLC assay yield.[42,43] After aqueous workup and crystallization from IPA/water ketone **32** was isolated in 83% yield. Ketone **32** isolated in this manner contained relatively high levels of residual Ir (typically 4000–7000 ppm), but this did not impact downstream processing and the metal contaminant was effectively rejected during subsequent isolations.[44]

A rhodium-catalyzed insertion reaction of diazoketone **50** was also evaluated on small scale and used in the early synthesis of some analogue structures[7c] (Scheme 11). In our hands, the sulfoxonium ylide process was favored due to the higher yield and elimination of potential safety concerns regarding the generation and manipulation of diazo intermediates on larger scale.

The transaminase step performed reproducibly on scale following the procedure outlined above. At the end of the reaction, the mixture was acidified to precipitate the enzyme which was then removed by filtration. Following an extractive workup protocol, crude amine **31** was obtained as a dark brown solution in cyclopentylmethyl ether (CPME).[45] To facilitate isolation of the product, crystalline salt **31**•**HCl** was identified

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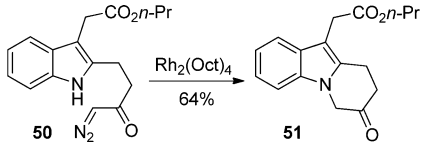
Scheme 11. Rhodium-Catalyzed Insertion Reaction



and could be generated from the crude stream using HCl in IPA. This isolation process effected good rejection of colored impurities and Ir residues, with good product recovery (76% isolated yield from ketone **32**), and also enhanced the ee of the product to >99%.

Sulfonylation of amine salt **31·HCl** under Schotten–Baumann conditions (IPAc/aq Na_2CO_3) gave sulfonamide **44** in 89% yield after workup and crystallization from IPAc/hexanes. Methylation of sulfonamide **44** was effected using MeI and K_2CO_3 in DMF. Since this was a heterogeneous reaction mixture it was found that the use of powdered K_2CO_3 was critical to achieving reproducibility. The use of K_2CO_3 with a larger particle size (e.g., granular material) gave inconsistent results or stalled reactions. At the end of reaction (100% HPLC assay yield), the product **45** was isolated by filtration to remove inorganic salts and subsequent crystallization by the addition of water (96% isolated yield). Finally, basic hydrolysis of ester **45** followed by acidification and crystallization afforded MK-7246 (**1**) in excellent yield (99%) and purity (>99 wt %, >99% ee).

This route proceeded in eight steps and 49% overall yield from commercially available starting materials, required no chromatographic purifications, and was amenable to pilot-plant scale production (>100 kg).[46]

■ CONCLUSION

In summary, the chemical synthesis of MK-7246 (**1**) has undergone substantial development in order to support the evolving demands of the CRTH2 antagonist program at Merck. The first- and second-generation Process Chemistry routes were designed for flexibility and speed to enable the rapid production of analogues to support SAR, thereby accelerating the identification and selection of the pharmaceutical candidate MK-7426 (**1**). The initial aziridine opening/cyclodehydration strategy was also directly amenable to the first GMP deliveries of MK-7246 (**1**), streamlining the transition from milligram- to kilogram-scale production needed to support early preclinical and clinical evaluation of this compound. Subsequently, a more scalable and cost-effective manufacturing route to MK-7246 (**1**) was engineered. This route features a dramatically improved overall yield and productivity, coupled with a significantly reduced environmental burden, as compared to all the preceding approaches to the target compound **1**. Highlights of the manufacturing route include an Ir-catalyzed intramolecular N–H insertion of sulfoxonium ylide **41** and conversion of ketone **32** to amine **31** in a single step with excellent enantioselectivity through a transaminase process. Reactions such as these illustrate the enabling impact and efficiency gains that innovative developments in chemo- and biocatalysis can have on the synthesis of pharmaceutically relevant target molecules.

■ EXPERIMENTAL SECTION

(2*R*)-1,4-Dimethoxy-1,4-dioxobutan-2-aminium Chloride (18).[13] $SOCl_2$ (57.6 mL, 789 mmol) was added dropwise over 10 min to a stirred mixture of D-aspartic acid **17** (75.0 g, 563 mmol) and MeOH (75 mL) at 0 °C. The mixture was warmed to rt and stirred for 16 h before being concentrated. The residue was triturated with Et_2O (300 mL), filtered, washed with Et_2O (1 × 200 mL), and dried at rt under vacuum to give the title compound (110.0 g, 99% yield) as a white waxy solid.

Dimethyl (2*R*)-2-[[(4-Fluorophenyl)sulfonyl]amino]-butanedioate (19). To a stirred suspension of diester HCl salt **18** (55.0 g, 278 mmol) and 4-fluorobenzenesulfonyl chloride (59.6 g, 306 mmol) in THF (220 mL) was added Et_3N (120 mL, 863 mmol) at rt. After 16 h, the slurry was filtered, and 1 M aq HCl (200 mL) was added to the filtrate. The layers were separated, and the aqueous layer was extracted with MTBE (1 × 200 mL). The combined organic layers were washed with satd aq NaCl (1 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to give the title compound (83.0 g, 93% yield) as a yellow oil which was used without further purification in the next step: $[\alpha]_D^{25}$ −2.7 (*c* 0.3, $CHCl_3$); IR (neat) 1733, 1591, 1494, 1224, 1166, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 8.5, 5.0 Hz), 7.22 (2H, dd, *J* = 8.5, 8.5 Hz), 5.74 (1H, d, *J* = 8.0 Hz), 4.20 (1H, ddd, *J* = 8.5, 4.5, 4.5 Hz), 3.70 (3H, s), 3.64 (3H, s), 3.02 (1H, dd, *J* = 17.0, 4.5 Hz), 2.90 (1H, dd, *J* = 17.0, 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 165.7 (d, *J* = 254.0 Hz), 134.3, 130.8 (d, *J* = 9.0 Hz), 116.3 (d, *J* = 23.0 Hz), 53.0, 52.2, 52.1, 37.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.8; HRMS calcd for $C_{12}H_{15}FNO_6S$ $[M + H]^+$ 320.0599, found 320.0603.

***N*-[(2*R*)-1,4-Dihydroxybutan-2-yl]-4-fluorobenzenesulfonamide (20).** To a stirred mixture of diester **19** (75.0 g, 235 mmol) in EtOH (750 mL) was added $NaBH_4$ (44.4 g, 1174 mmol) in three portions at 0 °C. The mixture was stirred for 16 h, quenched by the addition of satd aq NaCl (375 mL), and filtered. The filtrate was concentrated to remove EtOH, and then NaCl was added to the residual aqueous solution until the mixture was saturated. The solids from the preceding filtration were suspended in EtOAc (750 mL), stirred at rt for 1 h, and then filtered. The organic filtrate was used to extract the NaCl-saturated aqueous layer. The aqueous layer was further extracted with fresh EtOAc (2 × 375 mL). The combined organic layers were washed with satd aq NaCl (1 × 250 mL), dried ($MgSO_4$), filtered, and concentrated. The crude solid product was slurried in acetone (375 mL) at rt, and the mixture filtered through a pad of Solka Floc to remove boron salts. The filtrate was concentrated to afford the title compound (37.0 g, 60% yield) as a colorless oil which was used without further purification in the next step: $[\alpha]_D^{25}$ +2.7 (*c* 0.7, $CHCl_3$); IR (neat) 3253, 2494, 1460, 1290, 1109, 1091 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6 δ 8.20 (2H, dd, *J* = 8.5, 5.0 Hz), 7.59 (2H, dd, *J* = 8.5, 8.5 Hz), 6.71 (1H, m), 4.11 (1H, dd, *J* = 5.5, 5.5 Hz), 3.89 (1H, dd, *J* = 5.5, 5.5 Hz), 3.81–3.74 (3H, m), 3.72–3.65 (2H, m), 2.08–1.97 (1H, m), 1.92–1.80 (1H, m); ^{13}C NMR (125 MHz, acetone-d_6 δ 164.7 (d, *J* = 255.0 Hz), 138.3, 129.7 (d, *J* = 9.0 Hz), 115.9 (d, *J* = 23.0 Hz), 64.1, 58.3, 53.5, 34.5; ^{19}F NMR (376 MHz, acetone-d_6) δ −108.6; HRMS calcd for $C_{10}H_{14}FNO_4S$ $[M]^+$ 263.0628, found 263.0632.

2-[(2*R*)-1-[(4-Fluorophenyl)sulfonyl]aziridin-2-yl]ethanol (21). To a stirred mixture of diol **20** (75.7 g, 288 mmol) and ADDP (72.5 g, 288 mmol) in THF (1.45 L) was added *n*-Bu_3P (70.9 mL, 288 mmol) dropwise over 30 min. After a further 30 min, the mixture was filtered and the cake washed with THF (300 mL). Water (363 mL) was added to the filtrate and the resulting solution stirred at rt for 1 h. NaCl was then added to form a biphasic mixture, and the layers were separated. The organic layer was washed with satd aq NaCl (1 × 300 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was triturated in MTBE (300 mL) to precipitate *n*-Bu_3PO and filtered and the filtrate concentrated. The residue was triturated again using EtOAc/hexanes (1:1, 300 mL), filtered, and concentrated. The residue was finally purified by column chromatography (gradient elution from 25 to 75% EtOAc in hexanes) to give the title compound (54.4 g, 77% yield) as a light yellow oil: $[\alpha]_D^{25}$ −0.6 (*c* 0.6, $CHCl_3$); IR (neat) 3420, 2929, 1590, 1494, 1320, 1291, 1231, 1166, 1090 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.06 (2H, dd, *J* = 8.5, 5.0 Hz), 7.45 (2H, dd, *J* = 8.5, 8.5 Hz), 3.68–3.62 (1H, m), 3.58–3.45 (2H, m), 2.95–2.88 (1H, m), 2.64 (1H, d, *J* = 7.0 Hz), 2.25 (1H, d, *J* = 4.5 Hz), 1.84–1.74 (1H, m), 1.56–1.47 (1H, m); ^{13}C NMR (125 MHz, acetone-d_6) δ 165.0 (d, *J* = 253.0 Hz), 134.8, 131.0 (d, *J* = 9.0 Hz), 116.3, 59.0, 38.0, 34.3, 33.1;

dx.doi.org/10.1021/jo202620r | J. Org. Chem. 2012, 77, 2299–2309

^{19}F NMR (376 MHz, $CDCl_3$) δ −106.6; HRMS calcd for $C_{10}H_{13}FNO_3S$ $[M + H]^+$ 246.0595, found 246.0589.

(2*R*)-2-(2-[[*tert*-Butyl(dimethyl)silyl]oxy]ethyl)-1-(4-fluorobenzenesulfonyl)aziridine (16). To a stirred solution of alcohol **21** (54.4 g, 222 mmol) in THF (1.09 L) were added TBSCl (36.8 g, 244 mmol) and imidazole (33.2 g, 488 mmol) at rt. After 1 h, the slurry was filtered and the cake washed with MTBE (1 × 300 mL). The filtrate was washed with 1 M aq HCl (2 × 110 mL) and satd aq NaCl (2 × 110 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (10% EtOAc in hexanes) to give the title compound (67.2 g, 84%) as a white solid: mp 54 °C; $[\alpha]_D^{25}$ +0.7 (*c* 0.2, $CDCl_3$; IR (neat) 2955, 2854, 1590, 1494, 1320, 1127, 1165, 1078 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−7.99 (2H, m), 7.25 (2H, dd, *J* = 8.5, 8.0 Hz), 3.63−3.50 (2H, m), 2.95−2.92 (1H, m), 2.72 (1H, dd, *J* = 5.6, 1.5 Hz), 2.19 (1H, d, *J* = 2.0 Hz), 1.86−1.72 (1H, m), 1.60−1.55 (1H, m), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7 (d, *J* = 254.0 Hz), 134.3, 130.8 (d, *J* = 9.0 Hz), 116.3, 60.3, 38.3, 34.6, 33.8, 25.8, 18.2, −5.4; ^{19}F NMR (400 MHz, $CDCl_3$) δ −104.00; HRMS calcd for $C_{16}H_{27}FNO_3SSi$ $[M + H]^+$ 360.1465, found 360.1473.

Methyl 1*H*-Indol-3-ylacetate (23). To a stirred mixture of indole acid **22** (80.0 g, 457 mmol) and MeOH (400 mL) was added concd H_2SO_4 (4.87 mL, 91 mmol) dropwise at 20−25 °C (CAUTION: addition is exothermic). The mixture was stirred at rt for 2.5 h then cooled in an ice bath, and 2 M aq NaOH (41.1 mL, 82 mmol) was added dropwise below 10 °C. The solution was diluted with water (400 mL), and then K_2CO_3 was added in portions until pH = 7. The solution was then extracted with MTBE (2 × 500 mL), and the combined organic layers were washed with water (2 × 300 mL) and satd aq NaCl (1 × 200 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in MTBE (120 mL), and hexanes (320 mL) was added dropwise over 1 h, seeding with crystalline product **23** during the addition. Additional hexanes (600 mL) was added over 2 h and the resulting slurry stirred for a further 16 h. Another portion of hexanes (600 mL) was added over 2 h and the resulting slurry stirred for a further 1 h before being filtered. The cake was washed with hexanes (200 mL) and dried at rt under vacuum to give the title compound (69.6 g, 81% yield) as a light orange solid: mp 50 °C; IR (neat) 3354, 1713, 1455, 1430, 1332, 1299, 1216, 1153, 1102 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (1H, s), 7.66 (1H, d, *J* = 8.0 Hz), 7.37 (1H, d, *J* = 8.0 Hz), 7.24 (1H, dd, *J* = 8.0, 8.0 Hz), 7.18 (1H, dd, *J* = 8.0, 8.0 Hz), 7.16 (1H, s), 3.83 (2H, s), 3.75 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 163.1, 127.2, 123.2, 122.2, 119.7, 118.8, 111.3, 108.3, 52.0, 31.2; HRMS calcd for $C_{11}H_{12}NO_2$ $[M + H]^+$ 190.0868, found 190.0869.

Methyl (2*R*)-2-(1-[2-[4-Fluoro-*N*-methylphenylsulfonamido]-4-hydroxybutyl]-1*H*-indol-3-yl)acetate (26). A solution of ester **23** (50.5 g, 267 mmol) in DMF (240 mL) at 0 °C was added dropwise over 30 min to a stirred mixture of KHMDS (53.5 g, 267 mmol) and DMF (240 mL). After 15 min, a solution of aziridine **16** (48.0 g, 134 mmol) in DMF (240 mL) was added dropwise over 40 min. After a further 1 h, MeI (25.0 mL, 401 mmol) was added in one portion and stirring continued for 1 h. Aqueous HCl (2 M, 467 mL, 935 mmol) was then added dropwise over 30 min (exotherm to 16 °C). After a further 1.5 h, the mixture was diluted with half-saturated aq NaCl (500 mL) and extracted with MTBE (1 × 500 mL) and then with EtOAc (1 × 500 mL then 1 × 300 mL). The combined organic layers were concentrated, and the residue was stirred to induce crystallization of the product **26**. The suspension was diluted with 4:1 MTBE/EtOAc (250 mL), and then *n*-heptane (250 mL) was added dropwise over 1 h and the slurry stirred at rt for an additional 16 h. The mixture was filtered, and the cake was washed with *n*-heptane (1 × 200 mL) then dried at rt under vacuum to give the title compound (46.3 g, 81 wt %, 69LCAP, 63% corrected yield) as a brown solid. This product was slurried in 4:1 MTBE/EtOAc (250 mL), then *n*-heptane (250 mL) was added dropwise over 1 h and the mixture stirred at rt for an additional 4 h. The mixture was filtered, and the cake was washed with *n*-heptane (1 × 200 mL) then dried at rt under vacuum for 16 h to give the title compound (38.5 g, 94 wt %, 83 LCAP, 96% recovery, 60% overall corrected yield from **23**) as a tan solid: mp 121 °C; $[\alpha]_D^{25}$ −2.9 (*c* 0.3, $CDCl_3$); IR (neat) 3530, 1741, 1590, 1494, 1318, 1226, 1146, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.0 Hz), 7.70−7.52 (6H, m), 7.14 (2H, dd, *J* = 8.0, 8.0 Hz), 4.48−4.40 (2H, m), 4.13 (3H, s), 4.10−3.98 (4H, m), 3.29 (3H, s), 2.25−2.10 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 164.6 (d, *J* = 253.0 Hz), 136.1, 135.1, 129.3 (d, *J* = 9.0 Hz), 127.9, 126.4, 122.4, 119.7, 119.2, 115.7 (d, *J* = 23.0 Hz), 109.1, 107.8, 58.2, 53.9, 52.0, 48.0, 32.5, 30.7, 28.0; ^{19}F NMR (400 MHz, $CDCl_3$) δ −106.00; HRMS calcd for $C_{22}H_{26}FN_2O_5S$ $[M + H]^+$ 449.1546, found 449.1540.

Methyl (2*R*)-2-(7-[4-Fluoro-*N*-methylphenylsulfonamido]-6,7-dihydropyrido[1,2-*a*]indol-10-yl)acetate (28). DMSO (5.14 mL, 72.5 mmol) was added dropwise to a stirred solution of oxalyl chloride (3.04 mL, 34.8 mmol) in CH_2Cl_2 (65 mL) below −60 °C. After 30 min, a solution of alcohol **26** (13.0 g 29.0 mmol) in CH_2Cl_2 (104 mL) was added dropwise. After a further 30 min, Et_3N (16.2 mL, 116 mmol) was added dropwise, and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched by the addition of satd aq $NaHCO_3$ (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with satd aq NaCl (1 × 50 mL), dried (Na_2SO_4), filtered through a pad of silica gel (100 g), and concentrated to give crude aldehyde **27** (9.6 g) as a yellow foam. Crude aldehyde **27** was dissolved in toluene (130 mL), PPTS (1.5 g, 5.8 mmol) was added, and the mixture was heated at 60 °C for 16 h (reaction flask protected from light). The mixture was cooled to rt, diluted with water (100 mL), and extracted with EtOAc (1 × 100 mL). The aqueous layer was extracted again with EtOAc (1 × 100 mL), and the combined organic layers were washed with satd aq NaCl (1 × 100 mL), dried (Na_2SO_4), filtered, and concentrated to give a sticky foam. The crude product was purified by column chromatography (gradient elution 20−40% EtOAc in hexanes). Product-containing fractions were concentrated to give a light yellow foam which was dissolved in EtOAc (20 mL) and triturated by the dropwise addition of MTBE (50 mL) followed by *n*-heptane (70 mL). The product was collected by filtration and dried at rt under vacuum to give the title compound (9.1 g, 73% yield) as an off-white solid. The filtrate was concentrated and the residue purified by column chromatography to provide an additional 0.9 g (7% yield) of compound **28** also as an off-white solid. Combined allylic sulfonamide (10.0 g, 80% yield): mp 140 °C; $[\alpha]_D^{25}$ −16.8 (*c* 0.3, $CDCl_3$); IR (neat) 2957, 2928, 2857, 1592, 1495, 1331, 1168, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 8.0, 5.5 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.32−7.25 (3H, m), 7.18−7.13 (2H, m), 6.87 (1H, d, *J* = 8.0 Hz), 5.49 (1H, dd, *J* = 8.0, 4.0 Hz), 5.10 (1H, dd, *J* = 8.5, 4.0 Hz), 4.19 (1H, dd, *J* = 10.0, 5.0 Hz), 4.14 (1H, dd, *J* = 10.0, 5.0 Hz), 3.74 (2H, s), 3.68 (3H, s), 2.68 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 165.2 (d, *J* = 250.0 Hz), 136.5, 135.7, 130.4, 129.8 (d, *J* = 9.0 Hz), 123.4, 122.2, 120.5, 120.3, 119.5, 116.6 (d, *J* = 23.0 Hz), 108.7, 106.5, 52.1, 51.0, 44.3, 30.2, 29.8, 26.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.0; HRMS calcd for $C_{22}H_{22}FN_2O_4S$ $[M + H]^+$ 429.1284, found 429.1272.

Methyl [(7*R*)-7-[[(4-Fluorophenyl)sulfonyl](methyl)amino]-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl]acetate (29). 10% Pd/C (0.492 g) was added to a stirred solution of allylic sulfonamide **28** (10.0 g, 23.1 mmol) in EtOAc (100 mL) at rt, and the flask was purged with N_2. The mixture was then purged with H_2 and stirred under an atmosphere of H_2 (balloon) in the dark for 24 h. The mixture was then filtered through a plug of Celite 545, washing with EtOAc (2 × 50 mL), and the combined filtrates were concentrated to give a yellow foam. The crude product was purified by column chromatography (gradient elution 20−40% EtOAc in hexanes) to give the title compound (9.2 g, 98 wt %, 91% corrected yield) as a light yellow amorphous foam: $[\alpha]_D^{25}$ +5.6 (*c* 0.2, $CDCl_3$); IR (neat) 1728, 1587, 1460, 1339, 1164, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, dd, *J* = 8.0, 5.5 Hz), 7.56 (1H, d, *J* = 8.0 Hz), 7.33−7.25 (2H, m), 7.24−7.14 (3H, m), 4.57−4.46 (1H, m), 4.24 (1H, dd, *J* = 11.0, 6.0 Hz), 3.88−3.61 (3H, m), 3.69 (3H, s), 3.20−3.15 (1H, m), 2.93 (3H, s), 2.90−2.84 (1H, m), 1.97−1.75 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 165.2 (d, *J* = 254.0 Hz), 135.7, 135.5, 132.2, 129.7 (d, *J* = 9.0 Hz), 121.2, 120.1, 118.1, 116.6 (d, *J* = 22.0 Hz), 108.6, 102.8, 52.8, 52.0, 44.2, 30.0, 29.4, 25.0, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.0; HRMS calcd for $C_{22}H_{24}FN_2O_4S$ $[M + H]^+$ 431.1441, found 431.1438.

dx.doi.org/10.1021/jo202620r | *J. Org. Chem.* 2012, 77, 2299−2309

[(7*R*)-7-[[(4-Fluorophenyl)sulfonyl](methyl)amino]-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl]acetic acid (1, MK-7246). *Method A: Hydrolysis of Methyl Ester **29**.* To a stirred solution of ester **29** (9.0 g, 20.5 mmol) in THF (45 mL) was added 1 M aq LiOH (61.5 mL, 61.5 mmol) dropwise over 15 min at rt. After a further 16 h, 1 M aq HCl (200 mL, 200 mmol) was added dropwise over 1 h. The resulting crystalline product was collected by filtration, washed with 1 M aq HCl (1 × 50 mL), and dried at rt under vacuum to give the title compound (8.4 g, 99 wt %, 97.2 LCAP, 97% corrected yield) as a pale green powder.

*Method B: Hydrolysis of Ethyl Ester **45**.* EtOH (38 mL) was added to a stirred solution of ester **45** (15 g, 33.7 mmol) in THF (113 mL) at rt, and the light yellow solution was then sparged with N_2 for 15 min. Aqueous LiOH (2 M, 56.2 mL, 105 mmol) was added dropwise over 15 min at a temperature below 15 °C. The mixture was then allowed to warm to rt and stirred for 4 h. Aqueous HCl (1 M, 100 mL, 100 mmol) was added dropwise over 30 min at 15−20 °C to reach pH 6.5−7.0. The solution was then seeded with crystalline product **45** (50 mg) and the slurry aged for 1 h. Dropwise addition of additional 1 M aq HCl (35 mL) was then continued over 2 h until pH 2.5−3.5 was reached. The slurry was then cooled to 0 °C and stirred for 1 h. The product was collected by filtration, washed with 2:1 water/EtOH (1 × 30 mL) and then EtOH (1 × 30 mL), and dried at rt under vacuum to give the title compound (13.98 g, >99 wt % purity, 99% corrected yield) as a white powder: mp 225 °C; $[\alpha]_D^{25}$ +11.6 (*c* 0.2, acetone); IR (neat) 1699, 1590, 1488, 1341, 1264, 1166, 1089 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 12.13 (1H, br s), 8.04−8.02 (2H, m), 7.50−7.46 (3H, m), 7.29 (1H, d, J = 8.0 Hz), 7.08 (1H, dd, J = 8.0, 1.0 Hz), 7.03 (1H, dd, J = 8.0, 1.0 Hz), 4.47−4.41 (1H, m), 4.13 (1H, dd, J = 11.5, 5.5 Hz), 3.88 (1H, dd, J = 11.5, 11.5 Hz), 3.56 (2H, abq, J = 13.0 Hz), 3.04 (1H, ddd, J = 16.5, 5.0, 2.5 Hz), 2.83 (3H, s), 2.80 (1H, ddd, J = 16.5, 12.5, 5.5 Hz), 1.83 (1H, ddd, J = 12.5, 12.5, 5.0 Hz), 1.52−1.50 (1H, m); ^{13}C NMR (125 MHz, d_6-DMSO) δ 172.9, 164.6 (d, J = 252.0 Hz), 135.3, 135.3 (d, J = 3.0 Hz), 132.8, 130.0 (d, J = 9.5 Hz), 128.0, 120.3, 119.3, 117.8, 116.8 (d, J = 22.5 Hz), 108.9, 102.9, 52.5, 43.9, 29.7, 29.3, 23.8, 20.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.2; HRMS calcd for $C_{21}H_{22}FN_2O_4S$ $[M + H]^+$ 417.1284, found 417.1287.

Ethyl 3-(6-Oxo-1-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)-propanoate (35). $PhNHNH_2$·HCl (30 g, 207 mmol) was added to a solution of ketone **34** (44.2 mL, 207 mmol) in toluene (180 mL), and the mixture was heated at reflux under Dean−Stark conditions for 16 h. The solution was then cooled to rt and concentrated. The residue was purified by column chromatography (gradient elution 10−75% EtOAc in hexanes) to give the title compound (53.1 g, 93 wt %, 87% corrected yield) as an orange oil: IR (neat) 2977, 2905, 1728, 1677, 1595, 1320, 1302, 1211, 1170, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.42 (2H, m), 7.29−7.25 (2H, m), 7.14−7.10 (1H, m), 4.02 (2H, q, J = 7.0 Hz), 2.61−2.51 (4H, m), 2.50−2.39 (4H, m), 1.11 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 164.6, 154.6, 140.7, 127.7, 125.5, 123.8, 59.9, 30.8, 29.4, 27.3, 25.1, 13.7; HRMS calcd for $C_{15}H_{19}N_2O_3$ $[M + H]^+$ 275.1396, found 275.1393.

Ethyl 3-[3-(2-Ethoxy-2-oxoethyl)-1*H*-indol-2-yl]propanoate (36). *Method A: From Pyridazinone **35**.* Concentrated H_2SO_4 (30 mL, 563 mmol) was added over 2 min to a solution of pyridazinone **35** (15 g, 54.7 mmol) and EtOH (120 mL) (CAUTION: exotherm from rt to 70 °C was observed upon the addition of H_2SO_4). The mixture was heated to gentle reflux (90−92°(C) for 2.5 h, cooled to 5 °C, and neutralized to pH = 7.0 by the addition of aq NaOH (stock solution prepared by diluting 25 mL 50 wt % aq NaOH with 100 mL water), maintaining the temperature below 18 °C. The slurry was then concentrated to remove most of the EtOH, and the residue was partitioned between MTBE (200 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with MTBE (1 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10−20% EtOAc in hexanes) to give the title compound (12.47 g, 75% yield) as an orange oil.

Method B: Direct Indole Synthesis. $PhNHNH_2$·HCl (40 g, 277 mmol) then $ZnCl_2$ (56.6 g, 415 mmol) were added to a stirred solution of ketone **34** (58.9 mL, 277 mmol) in PhMe (375 mL) at rt. The slurry was then heated to 105 °C over 30 min and maintained at that temperature for 1.5 h. The mixture was cooled to 35 °C, and water (300 mL) was added in one portion. Stirring was continued at rt for 5 min until all the solid material had dissolved to give a biphasic solution. The layers were separated, and the orange organic layer was washed with water (1 × 150 mL), concentrated, and flushed with toluene (200 mL) to a final volume of ∼150 mL. HPLC assay indicated 78 g (93% assay yield) product **36** in the final organic solution, which was used directly in the ylide formation step: IR (neat) 3385, 2979, 2935, 1716, 1621, 1461, 1155, 1030, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (1H, br s), 7.60−7.57 (1H, m), 7.31−7.29 (1H, m), 7.16 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.11 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 4.19 (2H, q, J = 7.0 Hz), 4.13 (2H, q, J = 7.0 Hz), 3.71 (2H, s), 3.11−3.08 (2H, m), 2.75−2.71 (2H, m), 1.28 (3H, t, J = 7.0 Hz), 1.25 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.9, 135.7, 135.1, 128.1, 121.5, 119.4, 118.4, 110.6, 104.6, 60.9, 60.7, 34.1, 30.4, 20.7, 14.2, 14.1; HRMS calcd for $C_{17}H_{21}NO_4Na$ $[MNa]^+$ 326.1368, found 326.1364.

Ethyl 3-[1-(2-*tert*-Butoxy-2-oxoethyl)-3-(2-ethoxy-2-oxoethyl)-1*H*-indole-2-yl]propanoate (33). To a stirred solution of diester **36** (11.0 g, 36.3 mmol) in DMF (44 mL) was added Cs_2CO_3 (14.1 g, 43.5 mmol) in one portion at 5 °C, followed by *tert*-butyl bromoacetate (6.43 mL, 43.5 mmol) dropwise over 2 min. The mixture was warmed to rt, stirred for 16 h, and then partitioned between MTBE (100 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with MTBE (2 × 50 mL). The combined organic layers were washed with water (1 × 50 mL) and satd aq NaCl (1 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10−20% EtOAc in hexanes) to give the title compound (14.15 g, 93% yield) as an orange oil: IR (neat) 2980, 2927, 1727, 1467, 1368, 1224, 1152, 1030, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, d, J = 7.5 Hz), 7.20−7.18 (2H, m), 7.16−7.13 (2H, m), 4.77 (2H, s), 4.17 (2H, q, J = 7.0 Hz), 4.14 (2H, q, J = 7.0 Hz), 3.76 (2H, s), 3.13 (2H, dd, J = 8.0, 8.0 Hz), 2.69 (2H, dd, J = 8.0, 8.0 Hz), 1.45 (9H, s), 1.27 (3H, t, J = 7.0 Hz), 1.25 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.5, 167.6, 136.5, 136.2, 127.7, 121.5, 119.6, 118.5, 108.5, 105.5, 82.2, 60.4 (2C), 45.6, 38.8, 30.6, 27.7, 19.4, 13.9 (2C); HRMS calcd for $C_{23}H_{32}NO_6$ $[M + H]^+$ 418.2230, found 418.2236.

***tert*-Butyl 10-(2-Ethoxy-2-oxoethyl)-7-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-6-carboxylate (37).** A solution of indole **33** (14.0 g, 33.5 mmol) in THF (90 mL) was added dropwise over 15 min to a stirred mixture of THF (100 mL) and KO-*t*-Bu (1 M in THF, 36.9 mL, 36.9 mmol) at −25 °C. After a further 15 min at −20 °C, the reaction was quenched by the addition of 1 M aq HCl (120 mL). The mixture was warmed to rt and partitioned between MTBE (80 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with MTBE (1 × 80 mL). The combined organic layers were washed with satd aq NaCl (1 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10−15% EtOAc in hexanes) to give the title compound (7.94 g, 64% yield) as a yellow oil: IR (neat) 2979, 2941, 1724, 1463, 1368, 1147, 1028, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (1H, dd, J = 7.0, 1.5 Hz), 7.22−7.14 (3H, m), 5.37 (2H, s), 4.11 (2H, q, J = 7.0 Hz), 3.72 (2H, abq, J = 10.0 Hz), 3.31 (1H, ddd, J = 16.0, 6.0, 4.0 Hz), 3.18 (1H, ddd, J = 16.0, 12.5, 4.0 Hz), 2.86 (1H, ddd, J = 16.0, 4.0, 4.0 Hz), 2.61 (1H, ddd, J = 16.0, 12.5, 6.0 Hz), 1.38 (9H, s), 1.22 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 171.0, 164.5, 134.9, 132.4, 128.2, 121.3, 120.1, 118.3, 108.2, 103.5, 83.2, 66.0, 60.2, 36.2, 29.8, 27.2, 18.7, 13.8; HRMS calcd for $C_{21}H_{26}NO_5$ $[M + H]^+$ 372.1811, found 372.1812.

Ethyl (7-Oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)-acetate (32). *Method A: Decarboxylation of Ester **37**.* Silica gel (24 g) was added to a stirred solution of ester **37** (8 g, 21.5 mmol) in PhMe (240 mL) at rt. The mixture was heated to reflux for 70 min, cooled rt, and filtered. The cake was washed with EtOAc (2 × 50 mL), and the combined filtrates

were concentrated. The residue was purified by flash chromatography (gradient elution 20−33% EtOAc in hexanes) to give the title compound (5.12 g, 88% yield) as a yellow oil that solidified upon standing at rt for 48 h.

Method B: N−H Insertion of Ylide ***41***. A round-bottomed flask equipped with a thermocouple, mechanical stirrer, addition funnel, and N_2 inlet was charged with toluene (1.275 L) and the solution sparged with N_2 for 15 min at rt. In a glovebox, $[IrCl(COD)]_2$ (1.44 g, 2.06 mmol) was charged into a 40 mL vial and slurried with toluene (35 mL). This slurry was then added to the round-bottomed flask, rinsing with toluene (40 mL). The resulting stirred orange solution was sparged with N_2 for 10 min and then heated to 85 °C. In a separate flask a dark red solution of ylide **41** (75 g, 206 mmol) in DMF (150 mL) was prepared, sparged with N_2 for 15 min at rt, and then transferred to the addition funnel. The ylide solution was then added dropwise to the hot catalyst solution over 6 h. The resulting solution was stirred at 85 °C for a further 1 h, cooled to rt, then washed with water (2 × 300 mL). The organic layer was concentrated to ∼300 mL and then was flushed with IPA while maintaining a constant volume of ∼300 mL until less than 5 vol % of PhMe remained (monitored by ^{1}H NMR, 750 mL of IPA was used for the flush), during which time the product began to crystallize. The resulting slurry was stirred at rt for 30 min, and then water (300 mL) was added dropwise over 1 h. The slurry was then cooled to 0 °C and aged for 30 min. The product was collected by filtration, washed with cold (0°(C) 1:1 IPA/water (1 × 150 mL), and dried at rt under vacuum to give the title compound (49.1 g, 95 wt % purity, 83% corrected yield) as an off-white powder: mp 69−69.5 °C; IR (neat) 2961, 2872, 1717, 1610, 1468, 1247, 1144, 1036, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, dd, J = 7.5, 1.5 Hz), 7.23−7.17 (3H, m), 4.67 (2H, s), 4.15 (2H, q, J = 7.0 Hz), 3.75 (2H, s), 3.27 (2H, dd, J = 8.0, 6.5 Hz), 2.81 (2H, dd, J = 8.0, 6.5 Hz), 1.27 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 171.7, 135.2, 132.6, 128.2, 121.6, 120.2, 118.7, 108.3, 103.3, 60.8, 51.9, 37.5, 30.3, 19.6, 14.2; HRMS calcd for $C_{16}H_{18}NO_3$ $[M + H]^+$ 272.1287, found 272.1277.

Ethyl (2-[4-[Dimethyl(oxido)-λ^4-sulfanylidene]-3-oxobutyl]-1*H*-indol-3-yl)acetate (41). Me_3SOI (91 g, 411 mmol) was added in two equal portions over 5 min to a stirred solution of KO-*t*-Bu (1 M in THF, 424 mL, 424 mmol). The slurry was heated to 65−67 °C over 20 and maintained at that temperature for 2 h. The slurry was then cooled to 3 °C, and a solution of crude indole **36** (78 g assay, 257 mmol) in PhMe (total indole solution volume ∼150 mL) was dropwise over 1 h at a temperature below 10 °C. The slurry was then allowed to warm to rt over 2 h and then transferred over 15 min into stirred, chilled (10°(C) water (900 mL). The mixture was diluted with EtOAc (300 mL) and stirred for a further 10 min at rt. The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 500 mL). The combined organic layers were washed with water (1 × 300 mL), concentrated, and flushed with EtOAc (500 mL) to a target volume of ∼400 mL, during which time the product began to crystallize. The resulting slurry was aged at rt for 30 min, hexanes (450 mL) was added dropwise over 3 h, and the slurry was aged for a further 3 h. The slurry was then filtered, and the product was washed with 4:1 hexanes/EtOAc (2 × 250 mL) and dried at rt under vacuum for 2 h to give the title compound (75.9 g, 97.5 wt %, 77% corrected yield for the two steps from ketone **34**) as a beige powder: mp 133 °C; IR (neat) 3174, 2921, 1724, 1552, 1398, 1158, 1020, 760 cm^{-1}; ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.42 (1H, ddd, J = 8.0, 1.0, 1.0 Hz), 7.25 (1H, ddd, J = 8.0, 1.0, 1.0 Hz), 7.03 (ddd, J = 8.0, 7.0, 1.0 Hz), 6.97 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 3.70 (2H, s), 3.32 (6H, s), 3.01 (2H, dd, J = 8.0, 7.0 Hz), 2.50 (2H, dd, J = 8.0, 7.0 Hz), 1.21 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ 191.4, 174.5, 137.9, 137.2, 129.7, 122.0, 120.0, 119.0, 111.7, 104.9, 61.9, 41.5, 41.3 (2C), 31.2, 24.0, 14.7; HRMS calcd for $C_{18}H_{24}NO_4S$ $[M + H]^+$ 350.1426, found 350.1426.

Ethyl [(7*R*)-7-Amino-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl]acetate Hydrochloride (31·HCl). A triethanolamine/isopropylamine buffer solution was prepared by dissolving triethanolamine (0.32 mL) in water (24 mL). The solution was cooled to 5 °C, and *i*-PrNH$_2$ (3.11 mL) was added over 20 min. MSA (2 mL) was added over 25 min to adjust the pH of the solution from 12.2 to 9.0. The buffer solution was then charged at rt to a 50 mL Multimax vessel equipped with an overhead stirrer, thermocouple, pH probe, and N_2 inlet. Pyridoxal-5-phosphate (PLP, 40 mg) was added, and the mixture was gently agitated to give a clear yellow solution at pH 8.0−8.3. CDX-017 enzyme (115 mg) was then added and dissolved with gentle agitation in a few min. DMSO (7.5 mL) was then charged over 5 min to the agitated (400 rpm) solution at rt, and then the mixture was heated to 45 °C and adjusted to pH 8.5 using 4 M aq *i*-PrNH$_2$. A solution of ketone **32** (2.67 g, 96 wt % purity, 9.44 mmol) in DMSO (8 mL + 0.5 mL rinse) was added over 4 h via syringe pump, and the reaction was aged at 45 °C for 48 h under constant N_2 sweep and maintaining the solution pH at 8.3−8.5 by the metered addition of 4 M aq *i*-PrNH$_2$. The mixture was cooled to rt and adjusted to pH 7.0 using MSA (0.45 mL), then cooled to 12 °C, acidified to pH 2.0 with another portion of MSA (0.2 mL), and aged for 3 h at 12 °C and 1000 rpm. The mixture was filtered, rinsing with chilled (10 °C) 60:40:1 water/DMSO/MSA (3 × 10 mL). The filtrate was washed with CPME (1 × 40 mL) and the organic layer discarded. CPME (70 mL) was added to the aqueous layer and the mixture adjusted to pH 10.5 using 5 M aq NaOH (5.5 mL). The layers were separated, and the aqueous layer was extracted with CPME (1 × 40 mL). The combined organic layers (HPLC assay 2.09 g amine freebase **31**, 81% assay yield, 98−99% ee) were washed with satd aq NaCl (1 × 20 mL), concentrated, and flushed with CPME (24 mL) to a final volume of 24 mL. The solution was then cooled to 0 °C and seeded with product HCl salt **31·HCl** (24 mg), and HCl (5.5 M in IPA, 1.76 mL) was added over 2 h until a nominal pH of 6.0 was reached. The slurry was further aged at 0 °C for 1 h, filtered, washed with CPME (2 × 5 mL), and dried at rt under vacuum to give the title compound (2.272 g, 98 wt %, >99% ee, 76% corrected yield from ketone **32**) as a cream powder: mp 196−199 °C dec; $[\alpha]_D^{25}$ +20.5 (*c* 1.6, EtOH); IR (neat) 2925, 2862, 1717, 1518, 1459, 1268, 1159, 738 cm^{-1}; ^{1}H NMR (500 MHz, d_4-MeOH) δ 7.48 (1H, ddd, J = 8.0, 1.0, 1.0 Hz), 7.32 (1H, ddd, J = 8.0, 1.0, 1.0 Hz), 7.14 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.08 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 4.40 (1H, dd, J = 12.0, 5.0 Hz), 4.12 (2H, q, J = 7.0 Hz), 4.02 (1H, dd, J = 12.0, 7.5 Hz), 3.94−3.90 (1H, m), 3.70 (2H, s), 3.10 (1H, ddd, J = 17.0, 6.0, 6.0 Hz), 3.00 (1H, ddd, J = 17.0, 8.5, 6.0 Hz), 2.35−2.29 (1H, m), 2.13−2.05 (1H, m), 1.23 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, d_4-MeOH) δ 174.3, 137.7, 133.4, 129.8, 122.4, 121.1, 119.1, 109.8, 104.9, 62.1, 47.6, 45.8, 30.7, 25.9, 19.7, 14.7; HRMS calcd for $C_{16}H_{21}N_2O_2$ $[M + H]^+$ 273.1603, found 273.1602.

Ethyl [(7*R*)-7-[[(4-Fluorophenyl)sulfonyl]amino]-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl]acetate (44). To a stirred solution of Na_2CO_3 (20.59 g, 194 mmol) in water (180 mL) were added IPAc (330 mL) and amine salt **31·HCl** (24 g, 78 mmol) at rt. After 5 min, a solution of 4-fluorobenzenesulfonyl chloride (15.13 g, 78 mmol) in IPAc (50 mL) was added dropwise over 1.5 h. The biphasic mixture was stirred at rt for a further 2 h, and then the layers were separated. The organic layer was washed with water (1 × 60 mL) and was then concentrated and flushed with IPAc (100 mL) to a final volume of ∼100 mL. The solution was seeded with product **44** (50 mg) and the resulting slurry aged at rt for 1 h. Hexanes (300 mL) was added over 1.5 h, and then the slurry was aged for a further 1.5 h. The product was collected by filtration, washed with 5:1 hexanes/IPAc (2 × 80 mL), and dried at rt under vacuum to give the title compound (30.91 g, 96.5 wt %, 89% corrected yield) as an off-white powder: mp 128.5−129.5 °C; $[\alpha]_D^{25}$ +66.7 (*c* 1.5, $CHCl_3$); IR (neat) 3341, 1726, 1592, 1462, 1153, 1092, 836, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.80 (2H, m), 7.53−7.52 (1H, m), 7.15−7.08 (4H, m), 7.07−7.04 (1H, m), 5.55 (1H, d, J = 7.5 Hz), 4.11 (2H, q, J = 7.0 Hz), 4.04 (1H, dd, J = 12.0, 4.5 Hz), 3.84−3.81 (1H, m), 3.65 (1H, dd, J = 12.0, 7.0 Hz), 3.63 (2H, s), 3.00 (1H, ddd, J = 17.0, 6.5, 6.5 Hz), 2.86 (1H, ddd, J = 17.0, 7.0, 6.5 Hz), 1.94−1.88 (1H, m), 1.80−1.73 (1H, m), 1.25 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 165.0 (d, J = 255.5 Hz), 136.7 (d, J = 3.0 Hz), 135.5, 132.2, 129.5 (d, J = 9.5 Hz), 128.0, 120.9, 120.0, 118.0, 116.4 (d, J = 22.5 Hz), 108.5, 103.0, 60.8, 48.3, 47.1, 30.0, 26.8, 19.0, 14.2; ^{19}F NMR (471 MHz, $CDCl_3$)

dx.doi.org/10.1021/jo202620r | *J. Org. Chem.* 2012, 77, 2299−2309

−104.8; HRMS calcd for $C_{22}H_{24}FN_2O_4S$ $[M + H]^+$ 431.1441, found 431.1446.

Ethyl [(7*R*)-7-[[(4-fluorophenyl)sulfonyl](methyl)amino]-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl]acetate (45). K_2CO_3 (powdered, 12.96 g, 94 mmol) was added in two equal portions over 5 min to a stirred solution of sulfonamide **44** (24.6 g, 96.5 wt % purity, 55.1 mmol) in DMF (123 mL) at rt. MeI (5.86 mL, 94 mmol) was then added dropwise over 5 min and the slurry aged for 2 h. The mixture was then filtered, washing with DMF (1 × 15 mL). Water (20 mL) was added dropwise over 5 min to the stirred filtrate at rt and the solution seeded with crystalline product **45** (100 mg). The slurry was aged at rt for 1 h, and then additional water (72 mL) was added dropwise over 2 h and the mixture aged for a further 1 h. The product was collected by filtration, washed with 1:1 DMF/water (1 × 70 mL) then IPA (2 × 50 mL), and dried at rt under vacuum to give the title compound (24.29 g, 99 wt %, 96% corrected yield) as a white powder: mp 114−115 °C; $[\alpha]_D^{25}$ +103.5 (*c* 1.22, $CHCl_3$); IR (neat) 2938, 1723, 1590, 1460, 1325, 1164, 1156, 822, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.88 (2H, m), 7.56 (1H, dd, *J* = 7.0, 1.5 Hz), 7.28−7.22 (2H, m), 7.19−7.12 (3H, m), 4.52−4.44 (1H, m), 4.21 (1H, dd, *J* = 11.0, 5.5 Hz), 4.13 (2H, q, *J* = 7.0 Hz), 3.78 (1H, dd, *J* = 11.0, 11.0 Hz), 3.65 (2H, abq, *J* = 16.5 Hz), 3.16 (1H, ddd, *J* = 17.0, 5.0, 2.5 Hz), 2.90 (3H, s), 2.86 (1H, ddd, *J* = 17.0, 12.5, 5.5 Hz), 1.87 (1H, ddd, *J* = 12.5, 12.5, 5.0 Hz), 1.79−1.76 (1H, m), 1.25 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 165.2 (d, *J* = 255.0 Hz), 135.6, 135.5 (d, *J* = 3.5 Hz), 132.2, 129.6 (d, *J* = 9.5 Hz), 128.1, 121.1, 120.0, 118.2, 116.6 (d, *J* = 22.5 Hz), 108.5, 102.9, 60.7, 52.7, 44.1, 30.2, 29.3, 24.9, 21.4, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) −104.7; HRMS calcd for $C_{23}H_{26}FN_2O_4S$ $[M + H]^+$ 445.1605, found 445.1597.

Ethyl 3-[3-(2-Ethoxy-2-oxoethyl)-1-methyl-1*H*-indol-2-yl]-propanoate (48). NaH (0.58 g of a 60% dispersion in mineral oil, 14.5 mmol) was added in portions over 1 min to a stirred solution of indole **36** (4.0 g, 13.2 mmol) in DMF (24 mL) at 5 °C. After 15 min, MeI (0.99 mL, 15.82 mmol) was added in one portion, and the reaction mixture was diluted with additional DMF (4 mL). The mixture was warmed to rt, aged for 30 min, and then poured into 1:1 MTBE/water (100 mL). The biphasic mixture was diluted with MTBE (100 mL), and the layers were separated. The organic layer was washed with water (1 × 40 mL) and satd aq NaCl (2 × 40 mL), then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10−20% EtOAc in hexanes) to give the title compound **48** (2.41 g, 94 wt % purity, 54% corrected yield) as a pink oil: IR (neat) 2979, 2929, 1727, 1642, 1471, 1368, 1158, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz), 7.31 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz), 7.26 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 7.19 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 4.23 (2H, q, *J* = 7.0 Hz), 4.20 (2H, q, *J* = 7.0 Hz), 3.82 (2H, s), 3.71 (3H, s), 3.24−3.20 (2H, m), 2.72−2.68 (2H, m), 1.33 (3H, t, *J* = 7.0 Hz), 1.32 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.7, 136.5, 136.2, 127.3, 121.1, 119.1, 118.2, 108.7, 104.4, 60.4 (2C), 33.9, 30.4, 29.3, 19.7, 13.9; HRMS calcd for $C_{18}H_{23}NO_4$ $[M + H]^+$ 318.1703, found 318.1705.

*Ylide Formation Competition Experiment between Indoles **36** and **48**.* A three-necked round-bottomed flask equipped with a magnetic stir bar, thermocouple, condenser and N_2 inlet was charged with Me_3SOI (546 mg, 2.48 mmol) and THF (5 mL) at rt. KO-*t*-Bu (1 M in THF, 2.56 mL, 2.56 mmol) was then added in one portion. The slurry was then heated to a target temperature of 65−67 °C over a period of 10 min using a heating mantle, then maintained at that temperature for 2 h. The slurry was then cooled to 6 °C. A solution of indoles **36** (470 mg, 1.55 mmol) and **48** (492 mg, 1.55 mmol) in THF (2 mL) was added dropwise over 2 min. The reaction was then allowed to warm to rt over 30 min, aged for a further 40 min, and then quenched by the addition of water (5 mL) and EtOAc (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with satd aq NaCl (1 × 10 mL), dried ($MgSO_4$), and filtered. Quantitative HPLC analysis of the filtrate indicated the presence of 516 mg of ylide **41** (94% yield), 461 mg of N−Me indole **48** (94% recovery), and 20 mg of N−H indole **36** (3% recovery). The mixture was not processed further.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods, chiral SFC analysis of amine **31**, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

[§]The research described was partially carried out at the former Merck Frosst Canada, Department of Process Research, Merck, 16711 Autoroute Transcanadienne, Kirkland, Québec, Canada H9H 3L1.

■ ACKNOWLEDGMENTS

We thank Dr. Wayne Mullett and Mr. Ravi Sharma for analytical support, Dr. Tom J. Novak for assistance with HRMS analysis, and Drs. Nobuyoshi Yasuda and Cheng-yi Chen for helpful discussions.

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(17) Aziridine **16** was added to an excess (2 equiv) of the anion derived from indole **23**. Lower amounts of indole **23**, or reversing the order of addition, led to competing opening of another molecule of aziridine **16** by sulfonamide anion intermediate **24**, and the consequent formation of oligomeric products.

(18) LCAP = HPLC area percent monitored at 220 nm determined by comparison to an authentic standard.

(19) Performance (with respect to yield and impurity generation) of the upgraded material in the remaining steps to MK-7246 (**1**) was significantly superior than the 69 LCAP alcohol **26** initially isolated by crystallization.

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(28) Sapi and co-workers generated the dimethyl ester analogue of indole **36** from pyridazinone **35** using HCl in MeOH at reflux; see: Bascop, S.-I.; Laronze, J.-Y.; Sapi, J. *Synthesis* **2002**, 1689−1694.

(29) Compounds **38** and **39** were formed as the major byproduct (approximately 10% yield each) under the conditions shown in Scheme 5 and were not isolated. Yield estimates and structural assignments were made on the basis of HPLC−MS analysis alone. Many other lower level impurities were also generated.

(30) The product distribution could not be improved despite extensive variation of the reaction parameters (base, solvent, temperature).

(31) Available from Codexis, Inc., 200 Penobscot Dr, Redwood City, CA 94063.

(32) At pH 8.5, the level of amino acid byproduct **40** formed was typically 1% during the reaction.

(33) (a) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. *Org. Lett.* **2009**, *11*, 3566−3569. (b) Mangion, I. K.; Weisel, M. *Tetrahedron Lett.* **2010**, *51*, 5490−5492.

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(36) Substoichiometric amounts of $ZnCl_2$ or lower temperatures resulted in slower or stalled reactions. A one-pot Fisher indole synthesis from ketone **34** could also be effected using conc. H_2SO_4 in EtOH but was lower yielding. The use of other Brønsted acids proved less successful; Lewis acids other than $ZnCl_2$ were not screened.

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(39) The use of commercially available THF solutions of KO-*t*-Bu was preferred over the solid base reagent, as with the latter much higher levels of acid byproduct **46** were observed.

(40) Significantly longer reaction times (e.g., overnight) resulted in some product degradation.

(41) Tentative assignment based on HPLC−MS analysis.

(42) Slow addition of ylide **41** and rigorous degassing of the reaction mixture were essential to ensure consistent performance in this step. A minimum catalyst loading of 1 mol % (2 mol % of Ir) was required to drive the reaction to completion.

(43) Toluene as solvent gave the highest yield for this reaction (superior to the chlorinated solvents described in the literature protocols). However, to minimize overall solvent volume and cost for the process, ylide **41** was added as a concentrated solution in DMF due to the low solubility of this substrate in toluene alone.

(44) The specification for residual Ir levels in batches of MK-7246 (**1**) destined for use in clinical trials was 200 ppm or less.

(45) MTBE could be used instead of CPME for the workup. The use of IPAc resulted in higher mother liquor losses in the subsequent HCl salt formation.

(46) The procedures described in the Experimental Section for the manufacturing route were scaled up, with only minor modifications, to more than 100 kg scale in the pilot plant.