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A Practical Synthesis of 5-Lipoxygenase Inhibitor MK-0633

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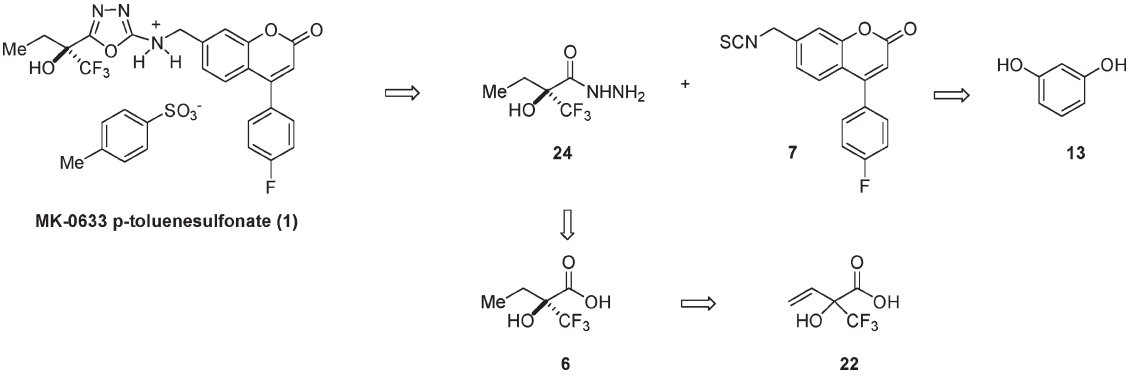

Practical, chromatography-free syntheses of 5-lipoxygenase inhibitor MK-0633 *p*-toluenesulfonate (**1**) are described. The first route used an asymmetric zincate addition to ethyl 2,2,2-trifluoropyruvate followed by 1,3,4-oxadiazole formation and reductive amination as key steps. An improved second route features an inexpensive diastereomeric salt resolution of vinyl hydroxy-acid **22** followed by a robust end-game featuring a through-process hydrazide acylation/1,3,4-oxadiazole ring closure/salt formation sequence to afford MK-0633 *p*-toluenesulfonate (**1**).

Introduction

Leukotriene metabolism plays a central role in inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and atherosclerosis.[1] In particular, the activation of the enzyme 5-lipoxygenase (5-LO) and its associated protein, 5-LO activating protein (FLAP), initiates a cascade that transforms arachidonic acid into inflammatory leukotrienes.[2] As part of a drug discovery program in our laboratories, MK-0633 *p*-toluenesulfonate (**1**) was identified as a potent and selective inhibitor of 5-LO (Figure 1).[3] Herein we wish to report two practical, chromatography-free syntheses that are suitable for the preparation of multikilogram amounts of 5-lipoxygenase inhibitor MK-0633.

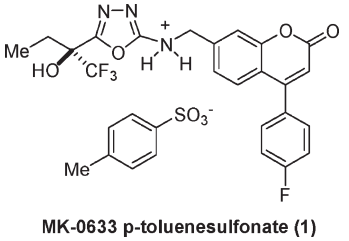

FIGURE 1. Structure of MK-0633 *p*-toluenesulfonate.

Results and Discussion

Two convergent synthetic approaches to MK-0633 are illustrated in Scheme 1. The first approach that we investigated

(1) Funk, C. D. *Science* **2001**, *294*, 1871.
(2) Evans, J. F.; Ferguson, A. D.; Mosley, R. T.; Hutchinson, J. H. *Trends Pharmacol. Sci.* **2008**, *29*, 72.
(3) Ducharme, Y.; Blouin, M.; Brideau, C.; Châteauneuf, A.; Gareau, Y.; Grimm, E. L.; Juteau, H. N.; Laliberté, S.; Mackay, D. B.; Massé, F.; Ouellet, M.; Salem, M.; Styhler, A.; Friesen, R. *ACS Med. Chem. Lett*. DOI: 10.1021/ml100029k. Published Online: April 13, 2010

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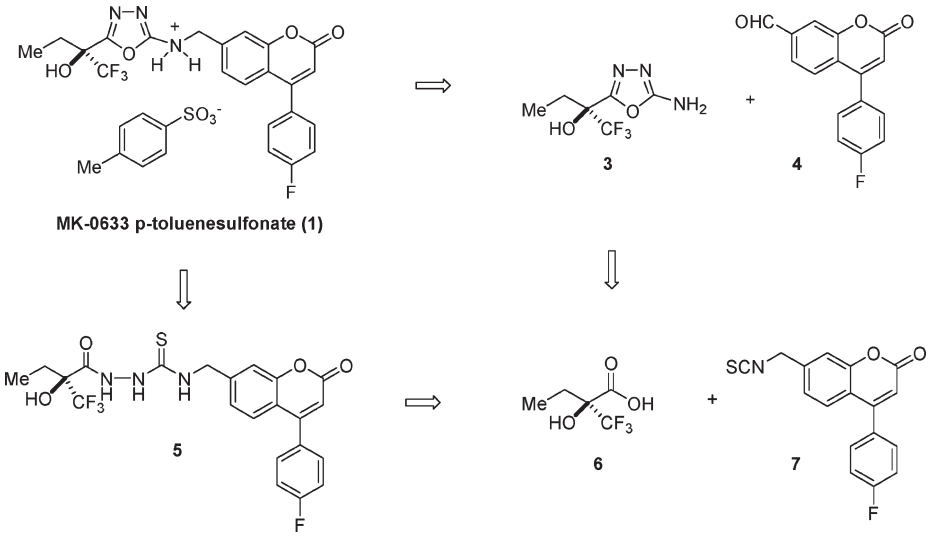
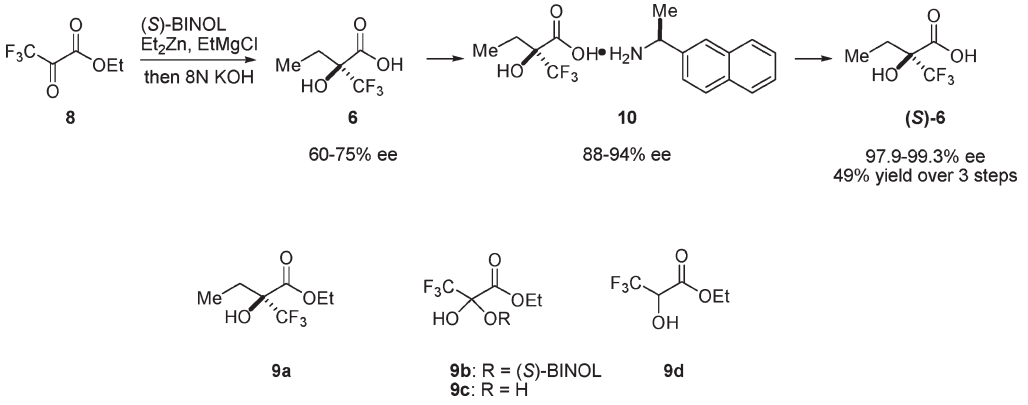
SCHEME 1. Retrosynthetic Analysis



SCHEME 2



and demonstrated on kilogram scale involved an asymmetric BINOL-ethylzincate addition to trifluoropyruvate followed by a late-stage reductive amination between 2-amino-1,3,4-oxadiazole **3** and aldehyde **4** as key steps. A second generation and complementary approach to MK-0633 involved a late-stage cyclization of mixed thiosemicarbazide **5**. Both approaches required the development of robust syntheses of chiral α-trifluoromethyl α-hydroxy-acid intermediate **6**. We established the second route described in this report as a potential manufacturing route to MK-0633.

Synthesis of Aminooxadiazole Intermediate. The synthesis of 2-amino-1,3,4-oxadiazole **3** began with organometallic addition to ethyl 2,2,2-trifluoropyruvate to form chiral ethyl hydroxy-acid **6** (Scheme 2). Few methods have been reported for asymmetric organometallic additions to α-keto esters.[4] Furthermore, the challenging asymmetric synthesis of chiral trifluoromethylated alcohols has received attention recently.[5−7]

To install the tertiary alcohol center found in MK-0633, we discovered and developed an asymmetric ethylzincate addition to ethyl 2,2,2-trifluoropyruvate **8** (Scheme 2).[8] Addition of EtMgCl to Et_2Zn at −20 °C led to complete formation of the corresponding chloromagnesium triethylzincate as ascertained by ^1H NMR analysis. Subsequent addition of $Et_3ZnMgCl$ to a slurry of (*S*)-(−)-1,1′-bi(2-naphthol) [(*S*)-BINOL] in 1,2-dichloroethane at −20 °C led to formation of a chiral (*S*)-BINOL-zincate complex.[9] Ethyl 2,2,2-trifluoropyruvate **8** was then added to this reagent over 4−6 h in order to obtain >95% conversion to the desired adduct (*S*)-hydroxy ester **6** in 60−75% ee. Slow addition

(4) (a) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781. (c) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. (d) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (e) Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 15453. (f) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718.

(5) For diastereoselective addition of CF_3TMS to a chiral α-keto ester, see: Song, J. J.; Tan, Z.; Xu, J.; Reeves, J. T.; Yee, N. K.; Ramdas, R.; Gallou, F.; Kuzmich, K.; DeLattre, L.; Lee, H.; Feng, X.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 292.

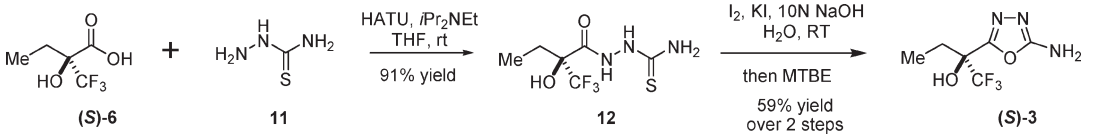
(6) For cinchonine ammonium fluoride catalyzed enantioselective addition of CF_3TMS to aldehydes and ketones, see: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137. (b) Caron, S.; Do, N. M.; Arpin, P.; Larivée, A. *Synthesis* **2003**, 1693. In our hands, the analogous reaction with ethyl 2-oxobutanoate afforded racemic **9a**.

(7) For a biocatalytic approach, see: Shaw, N. M.; Naughton, A.; Robins, K.; Tinschbert, A.; Schmid, E.; Hischier, M.-L.; Venetz, V.; Werlen, J.; Zimmermann, T.; Brieden, W.; de Riedmatten, P.; Roduit, J.-P.; Zimmermann, B.; Neumüller, R. *Org. Process Res. Dev.* **2002**, *6*, 497.

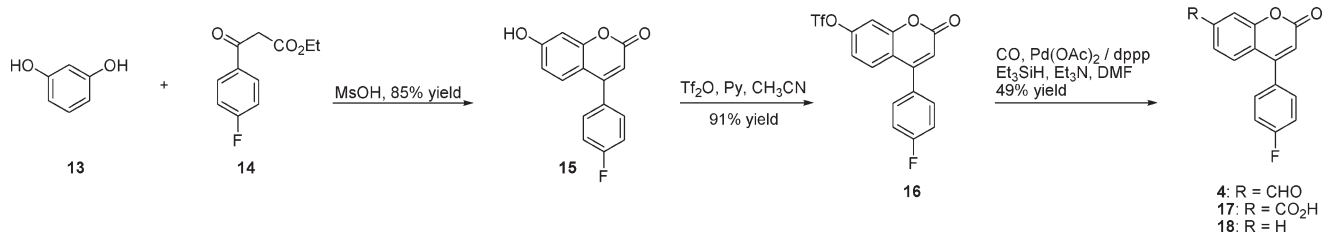
(8) Gosselin, F.; Britton, R. A.; Mowat, J.; O'Shea, P. D.; Davies, I. W. *Synlett* **2007**, 2193.

(9) For reviews on the use of BINOL in asymmetric synthesis, see: (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.

SCHEME 3. Synthesis of 2-Amino-1,3,4-oxadiazole 3



SCHEME 4. Synthesis of Aldehyde 4



of pyruvate **8** was required due to competing capture of the highly reactive pyruvate as a stable hemiketal **9b** (R = (*S*)-BINOL) as ascertained by ^{19}F NMR spectroscopic analysis.[10] In comparison, addition of pyruvate **8** over 5−10 min afforded at best 50% conversion to the desired ethyl adduct **9a**. Furthermore, the charge stoichiometry of Et_2Zn was found to be critical since excess reagent led to reduction of pyruvate **8** to form racemic alcohol **9d**.[11] Pyruvate hydrate **9c**, alcohol **9d**, and (*S*)-BINOL were removed in the basic aqueous workup. It was essential to remove (*S*)-BINOL from the crude reaction mixture prior to ester hydrolysis. Omitting removal of (*S*)-BINOL led to poor yields of hydroxy-acid **6**. Ester **9a** was hydrolyzed in situ by treating the crude product with aqueous KOH at reflux. The crude acid **6** was solvent-switched to toluene and the enantiomeric purity was upgraded to 88−94% ee via formation of a diastereomeric salt with (*S*)-1-(2-naphthyl)ethylamine. Salt break and recrystallization of the free acid in toluene gave (*S*)-**6** in 49% yield over 3 steps and 97.9−99.3% ee.

Amidation of hydroxy-acid (*S*)-**6** with HATU[12] activation and coupling with thiosemicarbazide **11** in THF gave hydrazide **12** in 91% yield (Scheme 3). A reslurry in acetone partially removed residual 1-hydroxy-7-azabenzotriazole (HOAt) and *N*,*N*,*N*′,*N*′-tetramethylurea coupling byproduct and provided **12** in 99% yield, suitable for the oxidant-mediated cyclization. Other peptide coupling reagents gave inferior results in terms of yield and purity: CDI (40−59% yield), EDC·HCl/HOBt (68−72% yield), TBTU[13] (46% yield), PyBOP[14] (68% yield).

Oxidant-mediated cyclization of thiosemicarbazide **12** with I_2/KI/aqueous NaOH proceeded to afford aminooxadiazole **3** in 66% yield (Scheme 3). Prolonged reaction time led to decomposition of **3** under basic conditions. Other oxidants gave inferior results: $Na_2WO_4 \cdot 2H_2O/H_2O_2$ (decomposition), Br_2 (55% yield), HIO_3 (34% yield). Recrystallization of (*S*)-aminooxadiazole **3** from MTBE removed colored impurities and gave enantiomerically pure **3** as ascertained by chiral SFC analysis.

Synthesis of Aldehyde Intermediate. The synthesis of the aldehyde component began with the von Pechmann reaction between resorcinol **13** and β-keto ester **14** in methanesulfonic acid to afford hydroxy-coumarin **15** (Scheme 4).[15,16] Reaction with triflic anhydride gave triflate **16** and reductive carbonylation[17] with $Pd(OAc)_2$/dppp/Et_3SiH/Et_3N gave aldehyde **4** contaminated with the corresponding acid **17** (~5A% HPLC) and reduced coumarin **18** (~10A% HPLC) as determined by LC-MS analysis. These impurities were readily removed by a reslurry of crude coumarin aldehyde **4** in acetone.

Reductive Amination End-Game. Although a plethora of reaction conditions for imine formation were evaluated, we found the reductive amination to be a challenging step (Scheme 5).[18] The difficulty observed in the formation of the imine **20** was attributed to the poor reactivity of 2-amino-1,3,4-oxadiazole **3** since aldehyde **4** readily formed imines with more nucleophilic amines such as benzylamine. Reaction conditions involving azeotropic removal of water with benzene as solvent and 10 mol % pyridinium *p*-toluenesulfonate as acid catalyst for 18 h gave up to 80% conversion and 70% yield on small scale. Extended reaction times led to increased conversion but lower yields of imine suggesting that **20** was thermally unstable. Imine formation with coumarin

(10) Hemiketals of ethyl 2,2,2-trifluoropyruvate prepared by reaction with the metal alkoxides of MeOH, 2-propanol, phenol, and BINOL exhibited a singlet with a chemical shift between δ −85.4 and −85.8 ppm by ^{19}F NMR spectroscopic analysis with benzotrifluoride as internal standard (δ −61.5 ppm).

(11) In contrast, the reagent obtained from lithium triethylzincate, formed by reaction of ethyllithium with diethylzinc, and (*S*)-BINOL gave the opposite sense of stereoselectivity (52% ee).

(12) HATU: 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium hexafluorophosphate 3-oxide: (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397. (b) Carpino, L. A.; El-Faham, A.; Minor, C. A.; Albericio, F. *J. Chem. Soc., Chem. Commun.* **1994**, 201. (c) Carpino, L. A.; Imazumi, H.; El-Faham, A.; Ferrer, F.; Zhang, C.; Lee, Y.; Foxman, F. M.; Henklein, P.; Hanay, C.; Mügge, C.; Wenschuh, H.; Klose, J.; Beyermann, M.; Bienert, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 441.

(13) TBTU: 1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium tetrafluoroborate 3-oxide: (a) Dourtoglou, V.; Ziegler, J.-C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269–1272. (b) Dourtoglou, V.; Ziegler, J.-C.; Gross, B. *Synthesis* **1984**, 572–574. (c) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927–1930.

(14) PyBOP: *O*-benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate: Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205.

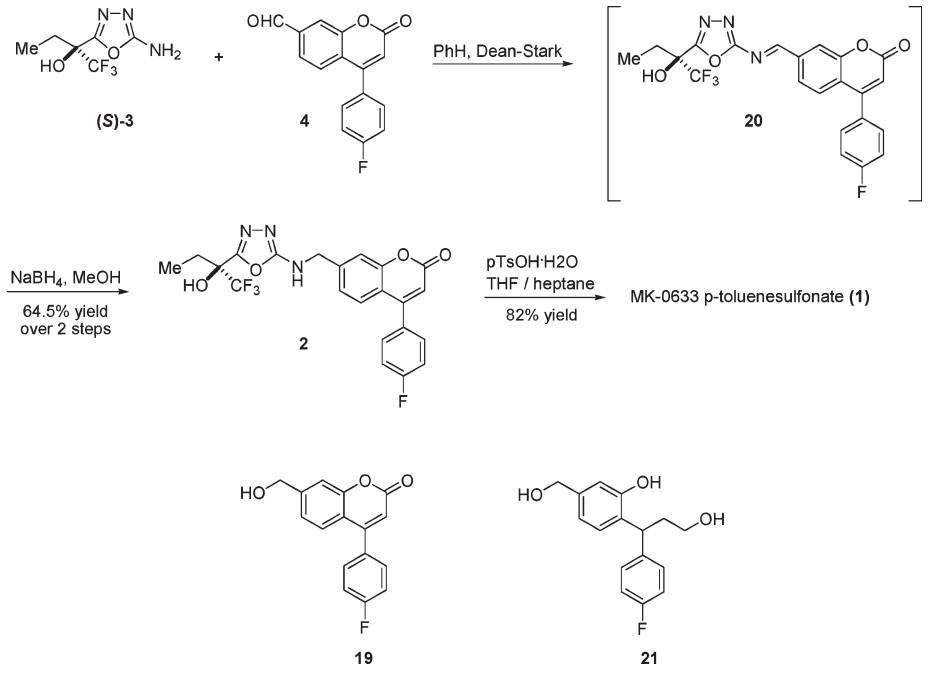
(15) von Pechmann, H.; Duisberg, C. *Chem. Ber.* **1884**, *17*, 929.

(16) The β-keto ester was prepared according to: Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72–73.

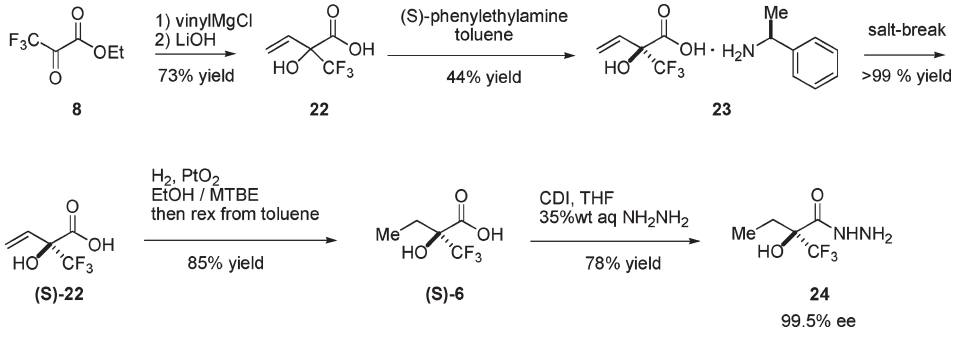
(17) Reviewed in: Ashfield, L.; Barnard, C. F. J. *Org. Process Res. Dev.* **2007**, *11*, 39.

(18) A thorough investigation of milder imine formation conditions with various dehydrating agents including $Ti(OEt)_4$, $Ti(OiPr)_4$, $TiCl_4$, $(MeO)_3CH$, $MgSO_4$, and $CuSO_4$ in toluene, 1,2-dichloroethane, or THF led to poor conversions to **20** (30−50%). Transimination via the *N*-TMS aldimine or N-H imine derivatives also proved fruitless.

SCHEME 5. Reductive Amination and Isolation of MK-0633 *p*-Toluenesulfonate



SCHEME 6. Hydrazide Synthesis



aldehyde **4** proceeded slower on scale and was attributed to the poor solubility of 2-amino-1,3,4-oxadiazole (*S*)-**3**[19] and afforded at best 65% conversion. Reduction with $NaBH_4$ in MeOH gave crude **2** in 64.5% assay yield. The stoichiometry of $NaBH_4$ relative to imine **20** was found to be critical since excess hydride (> 30 mol %) led to reduction of the coumarin ring to afford **19** and **21** as byproducts (Scheme 5).[20] Removal of benzene from the reaction stream was done via azeotropic removal with MeOH, followed by azeotropic removal of MeOH with THF for the final step. Complete elimination of benzene was achieved during the final salt formation step. The removal of benzene was carefully monitored by HPLC analysis throughout the process.

A robust purification step was required to remove substantial quantities of alcohol **19** (up to 26A% HPLC) formed in the reductive amination step. We identified MK-0633 *p*-toluenesulfonate salt (**1**) as a stable, crystalline, and bioavailable API form for safety assessment and clinical evaluation. Its crystallization allowed robust purification from crude free base **2** obtained with purities ranging from 60A% to 74A% HPLC. Thus, treatment of crude MK-0633 free base with *p*-toluenesulfonic acid hydrate in THF/heptane gave crystalline tosylate salt (**1**) as a white powder in 82% yield, 99.69 wt %, 99.81A% HPLC, 0.19A% HPLC benzyl alcohol **19**, > 99.9% ee, < 3 ppm residual Pd, PhH: not detected, < 2 ppm).

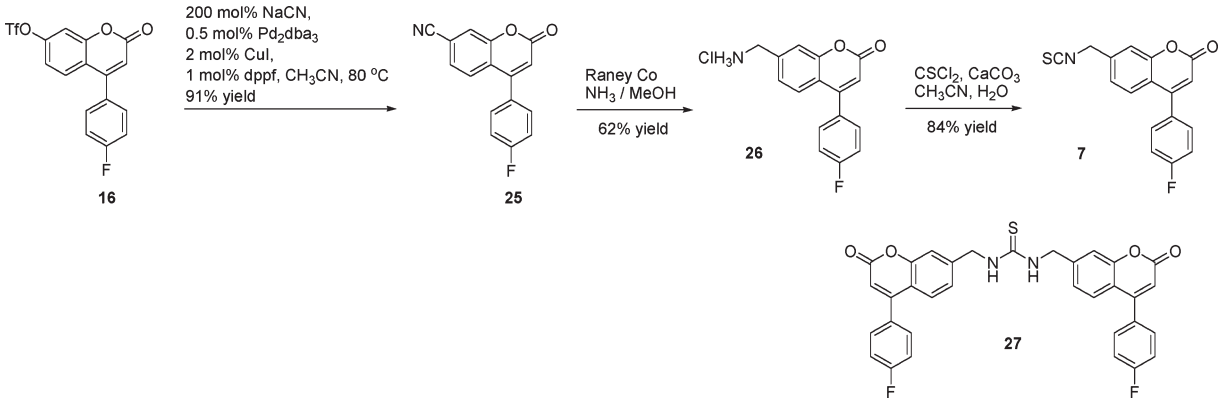
Although this initial synthetic route provided kilogram amounts of MK-0633 for preclinical evaluation, a number of attributes made it impractical and difficult to scale-up further than a few kilograms: (1) a highly work intensive and inefficient synthesis of the chiral hydroxy-acid (*S*)-**6**; (2) the expensive and not readily available peptide coupling agent HATU was used in the preparation of thiosemicarbazide **12**; (3) a sensitive cyclization to 2-amino-1,3,4-oxadiazole (*S*)-**3**; and (4) a difficult reductive amination penultimate step. To address these shortcomings, a second generation and complementary approach to MK-0633 involved a late-stage cyclization of mixed thiosemicarbazide **5** (Scheme 1).

Synthesis of Hydrazide Intermediate. Because of both economic and operational considerations the stoichiometric BINOL-zincate addition was deemed not viable for long-term

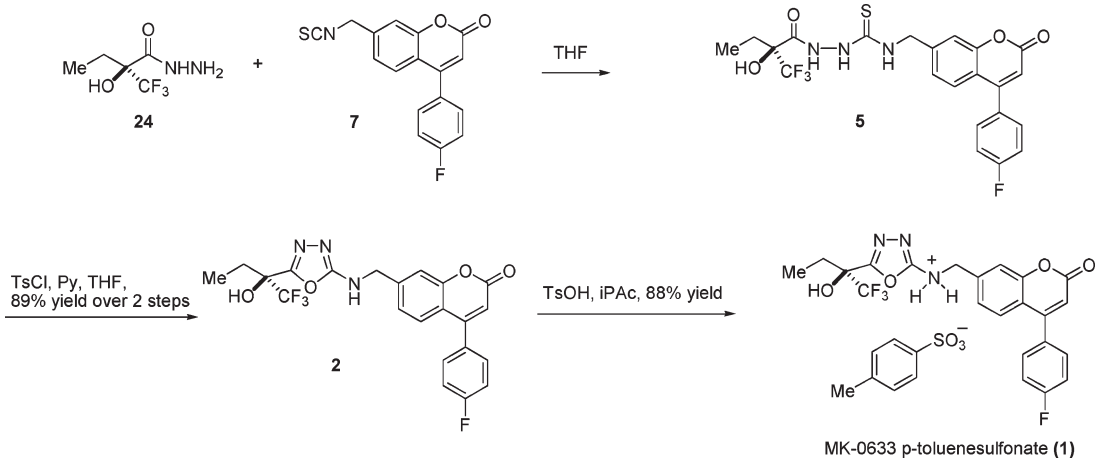
(19) Solid-state NMR analysis of (*S*)-**3** indicated a different crystal form vs material recrystallized from *i*PAc/heptane.

(20) The formation of byproduct **21** obtained from conjugate reduction was attributed to residual palladium in the coumarin aldehyde.

SCHEME 7. Coumarin Isothiocyanate Synthesis



SCHEME 8. Synthesis End-Game



manufacturing of MK-0633. We therefore evaluated a number of chemo- and biocatalytic approaches for the synthesis of ethyl hydroxy-acid intermediate **6** (see the Supporting Information for discussion). Ultimately, we found that a simple route involving diastereomeric salt resolution provided (*S*)-**6** (Scheme 6). Addition of vinylmagnesium chloride to ethyl 2,2,2-trifluoropyruvate **8** followed by in situ hydrolysis of the ethyl ester gave racemic acid **22** in 73% yield. Addition of 100 mol % (*S*)-phenylethylamine to a solution of acid in toluene at 90 °C gave the desired crystalline salt **23** in 43−45% yield and 92−94% ee. Attempted resolution with a number of other chiral amines gave inferior results. Hydrogenation of the olefin with either Pd/C or Pt/C afforded ethyl hydroxy-acid (*S*)-**6** in 88% yield after enantiomeric purity upgrade via recrystallization from toluene. In stark contrast, performing the diastereomeric resolution under a wide variety of conditions with ethyl hydroxy-acid **6** afforded 66% ee at best (with D-alaninol as chiral amine). Activation of the acid to its corresponding imidazolide with CDI and addition to 35% aqueous hydrazine at rt gave hydrazide **24** in 78−82% isolated yield after crystallization from toluene.

Synthesis of Isothiocyanate Intermediate. Coumarin triflate **16** was converted to the corresponding coumarin nitrile **25** by using Pd_2dba_3/dppf as catalyst and NaCN as cyanide source (Scheme 7). The desired coumarin nitrile **25** was isolated in 91% yield after simple precipitation from the reaction mixture. Alternatively, we found that the cyanation proceeded in 97% yield by using a catalyst prepared from $Pd(OAc)_2/Et_2Zn$/dppf. Attempted cyanation of triflate **16** in the absence of a catalyst either failed or led to competing hydrolysis of the sulfonate group.[21] Reduction of the nitrile with Raney cobalt in the presence of ammonia under 300 psi of H_2 at 90 °C gave complete conversion to the desired 7-aminomethyl-coumarin **26**. A modified protocol with Raney cobalt in $AcOH/H_2O$ as solvent was later devised due to instability of the coumarin amine free base in NH_3/MeOH. Formation of isothiocyanate **7** was initially performed with carbon disulfide and *p*-toluenesulfonyl chloride in THF.[22] Due to serious safety concerns toward handling hazardous CS_2 in the pilot plant we sought alternative conditions for the formation of **7**. We initially found that use of thiophosgene in CH_3CN/Et_3N gave a mixture of desired **7** and the corresponding coumarin thiourea dimer **27** (30−70%). Use of inorganic base in CH_3CN/water gave improved profile and yield. Ultimately we found that powdered $CaCO_3$ gave best results affording isothiocyanate **7** in 84% yield on kilogram scale after simple precipitation of product via addition of water.[23] Under these reaction conditions < 1% of the corresponding coumarin thiourea dimer **27** was formed.

(21) The corresponding 7-bromo-coumarin afforded nitrile **25** upon reaction with CuCN but required elevated temperatures (150 °C, 60 h) to reach complete conversion.

(22) Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969.

(23) Dyson, G. M.; Hunter, R. F. *Recl. Trav. Chim. Pays-Bas* **1926**, *45*, 422.

Through-Process End-Game. The end-game chemistry proceeded efficiently without isolation of intermediates (e.g., a through-process; Scheme 8). Thus, acylation of hydrazide **24** with isothiocyanate **7** in THF at rt and cyclization of thiosemicarbazide **5** with TsCl/pyridine[24] was followed by aqueous workup, carbon treatment, and solvent-switch to isopropyl acetate (*i*PAc) to afford crude MK-0633 free base **2**. Addition of **2** (~74A% HPLC) to a solution of *p*-toluenesulfonic acid monohydrate (1.0 equiv) in *i*PAc at 60 °C gave crystalline MK-0633 *p*-toluenesulfonate salt (**1**) (91.4% yield, 99.82A% HPLC) as a white powder.

Conclusion

In conclusion, we have developed a practical, chromatography-free route to MK-0633 featuring a through-process hydrazide acylation/1,3,4-oxadiazole ring closure/salt formation sequence to afford multikilogram amounts of MK-0633 *p*-toluenesulfonate (**1**). It is notable that although major efforts were directed toward developing practical asymmetric routes to chiral α-hydroxy-acid intermediate **6**, in the end a simple diastereomeric salt resolution emerged to provide **6** with improved productivity and ease of operation.

Experimental Section

(2*S*)-2-Hydroxy-2-(trifluoromethyl)butanohydrazide (24). Hydroxy-acid (*S*)-**6** (3.18 kg, mol) was dissolved in THF (8 L). The solution was added over 1 h to a stirred slurry of CDI (3.6 kg, mol) in THF (8 L). **Caution**: Gas evolution, ensure good venting of CO_2! After stirring for 1 h, the resulting homogeneous solution was added over 1 h to a stirred biphasic solution of 35 wt % aqueous hydrazine (3.9 L) in THF (8 L). The reaction was stirred at rt for 18 h and then diluted with *i*PAc (28 L). A portion of aqueous hydrazine separated from the organic layer (~1.7 kg) was drained off. The organic layer was then washed with citric acid (20% aqueous, 15 L then 3 L) and saturated aqueous $NaHCO_3$ (10 L). The layers were cut and solid NaCl was added to the combined aqueous layers until saturation. The aqueous layer was then back-extracted with *i*PAc (2 × 13 L). The combined aqueous layers were extracted with *i*PAc (5 L). The organic layers were combined, line-filtered, and concentrated. The solution was solvent-switched to toluene at 25 °C and the resulting gelatin-like slurry was filtered and washed with toluene (8 L) to give **24** as a crystalline solid (2.78 kg, 97.7A%, 96.3 wt %, 99.5% ee, 78% yield): mp 98−99 °C, $[\alpha]^{20}_D$ −26.7 (*c* 1.69, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.25 (br s, 1H), 6.61 (br s, 1H), 4.49 (br s, 2H), 2.02 (m, 1H), 1.68 (m, 1H), 0.82 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 165.4, 124.8 (q, *J* = 285 Hz), 77.3 (q, *J* = 26 Hz), 24.8, 6.7; ^{19}F NMR (DMSO-d_6) δ −78.6. Chiral GC analysis: column, Restek Rt-gammaDEX-sa, 30 m × 0.32 mm, 0.25 μm film (RTx-1701); injector, split 12×, cup linear with Siltek; inj., 1.0 μL at 230 °C; det., FID at 250 °C; carrier gas, He = 3.4 mL/min, flow 24 psi, 180 °C isothermal; (*S*)-hydrazide t_R = 7.9 min, (*R*)-hydrazide t_R = 9.3 min; HRMS calcd for $C_5H_{10}F_3N_2O_2$ [M + H] 187.0694, found 187.0688.

4-(4-Fluorophenyl)-7-(isothiocyanatomethyl)-2*H*-chromen-2-one (7). A visually clean 100 L round-bottomed flask equipped with a mechanical stirrer, a dropping funnel and a N_2 inlet was charged with coumarin amine hydrochloride **26** (4.68 kg, 15.31 mol) and powdered $CaCO_3$ (2.30 kg, 22.97 mol, 150 mol %). The solids were suspended in CH_3CN (23.4 L) and water (18.7 L) at rt to afford a white slurry that stirred well. Mixing caused an endotherm to 9.2 °C. A solution of thiophosgene (1.40 L, 18.37 mol, 120 mol %) in CH_3CN (1.40 L) was added dropwise over 45 min. **Caution**: proper venting is required due to gas evolution! The internal temperature rose from 9.2 to 24.5 °C during the addition of thiophosgene and gave a thick cream-colored slurry. The batch was stirred for 15 min and HPLC analysis showed >99% conversion to isothiocyanate **7**. Water (23.4 L) was added dropwise over 30 min and the slurry was filtered. The cake was washed with water (3 × 18.7 L) and dried on the frit for 3 h. The solids were dried under high vacuum/N_2 sweep at 30 °C. Isothiocyanate **7** was obtained as an off-white solid: 4.0 kg, 84% yield; mp 127−128 °C; ^{1}H NMR (DMSO-d_6) δ 7.62 (m, 2H), 7.49 (d, 2H, *J* = 8.0 Hz), 7.42 (dd, 2H, *J* = 9.0, 8.5 Hz), 7.36 (d, 1H, *J* = 8.5 Hz), 6.47 (s, 1H), 5.10 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 163.9, 161.9, 159.4, 153.6, 153.5, 139.3, 131.0, 130.8, 127.3, 123.2, 118.1, 116.0, 115.8, 115.5, 115.2; ^{19}F NMR (DMSO-d_6) δ −112.8; HRMS calcd for $C_{17}H_{11}FNO_2S$ [M + H] 312.0495, found 312.0489. HPLC analysis: column, Zorbax Extend C18 (4.6 × 150 mm, 5 μ); eluent 0.1% aqueous NH_4OH/CH_3CN; 5−40% over 8 min, hold 2.5 min, to 90% over 5 min, hold 5.5 min, post-time 4.5 min; flow = 1 mL/min; detection = 210 nm; temp = 40 °C; inj., 10 μL, coumarin amine **26** t_R = 11.4 min, coumarin thiourea dimer **27** t_R = 16.0 min, coumarin isothiocyanate **7** t_R = 16.3 min.

(1*S*)-*N*-{[4-(4-Fluorophenyl)-2-oxo-2*H*-chromen-7-yl]methyl}-5-[1-hydroxy-1-(trifluoromethyl)propyl]-1,3,4-oxadiazol-2-amine (2). A visually clean 100 L round-bottomed flask equipped with a mechanical stirrer, a thermocouple, and a N_2 inlet was charged with solid isothiocyanate **7** (2.00 kg, 6.43 mol) and hydrazide **24** (1.28 kg, 6.62 mol). The solids were dissolved in THF (32 L) and the amber solution was let stir at rt overnight. Internal temperature was 20 °C. HPLC analysis indicated >99% conversion to the desired mixed thiosemicarbazide **5** after ~15 h: mp 198.1−198.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (br s, 1H), 9.75 (br s, 1H), 7.99 (br s, 1H), 7.61 (dd, 2H, *J* = 5.6, 8.8 Hz), 7.37 (m, 4H), 7.23 (d, 1H, *J* = 8.8 Hz), 6.91 (s, 1H), 6.40 (s, 1H), 4.85 (m, 2H), 1.98 (m, 1H), 1.75 (m, 1H), 0.90 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.8, 161.9, 159.7, 153.8, 153.7, 144.5, 131.1, 131.0, 130.9, 126.4, 123.5, 123.1, 116.9, 115.9, 115.8, 114.8, 114.3, 77.9 (q, *J* = 26.1 Hz), 46.2, 25.5; ^{19}F NMR (375 MHz, DMSO-d_6) δ −77.8, −113.1. HRMS calcd for $C_{22}H_{19}F_4N_3O_4S$ [M + H] 498.1111, found 498.1114. IR (cm^{-1}, KBr pellet): 3303, 2980, 1701, 1617, 1543, 1510, 1420, 1374, 1282, 1239, 1194, 1005, 841; $[\alpha]^{20}_D$ −4.8 (*c* 1.08, EtOH). HPLC analysis: 4.6 mm ×150 mm Eclipse XDB Phenyl column, gradient elution (0.1% H_3PO_4/CH_3CN from 65:35 to 10:90 over 50 min, hold 10 min; run time = 60 min), flow rate = 1.0 mL/min, detection = 210 nm, *T* = 25 °C; sample preparation = an aliquot was withdrawn and diluted with CH_3CN/water (75/25). A 10 μL sample was injected, thiosemicarbazide **5** t_R = 22.68 min. Chiral HPLC: Chiralpak AS-RH (4.6 mm × 150 mm); isocratic method, CH_3CN/water = 37:63, flow rate = 1.0 mL/min, detection = 210 nm, *T* = 20 °C; sample preparation = an aliquot was withdrawn and diluted with CH_3CN/water (37/63), a 5 μL sample was injected: t_R = 21.7 min (major), 18.8 min (minor). The reactor was equipped with a reflux condenser and *p*-toluenesulfonyl chloride (1.47 kg, 7.72 mol) and pyridine (1.09 L, 13.51 mol) were charged. The batch was heated to reflux (internal temperature = 67 °C) for ~18 h. HPLC analysis indicated >95% conversion to MK-0633 free base **2**. The heat was shut off and the batch was cooled to 35 °C. The batch was line-transferred into 1 N aqueous HCl (30 L) and then diluted with *i*PAc (30 L). The layers were cut and the top organic layer was washed with water (2 × 30 L). The crude solution was combined with a batch of the same size to afford a total of ~6 kg of MK-0633 free base in *i*PAc/THF. The solution was treated with Darco KB-B (1.5 kg, 25 wt %) for 2 h at 18−19.7 °C and

(24) It is noteworthy that the corresponding semicarbazide analogue afforded only 20% assay yield of MK-0633 under the same conditions. We recently reported on the dramatically improved reactivity of thiosemicarbazides vs semicarbazides in the synthesis of aminooxadiazoles: Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2006**, *71*, 9548.

then filtered on solkafloc. The filter cake was washed with *i*PAc (3 × 10 L) and concentrated. The batch was solvent-switched to *i*PAc (3 × 20 L): mp 92.9−94.3 °C; $[\alpha]_D$ −4.5 (*c* 1.08, EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (t, 1H, J = 6.0 Hz), 7.60 (m, 2H), 7.38 (m, 4H), 7.31 (d, 2H, J = 8.4 Hz), 7.23 (s, 1H), 6.41 (s, 1H), 4.51 (d, 2H, J = 6.0 Hz), 2.08 (m, 1H), 1.97 (m, 1H), 0.88 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.1, 159.6, 156.1, 153.7, 153.6, 143.8, 131.0, 130.9, 126.8, 123.5, 117.4, 116.0, 115.8, 115.4, 114.7, 73.7 (q, J = 26.1), 45.4, 26.1; ^{19}F NMR (375 MHz, DMSO-d_6) δ −79.8, −113.1; IR (cm^{-1}, KBr pellet) 3309, 3068, 2945, 1701, 1617, 1510, 1420, 1372, 1329, 1280, 1238, 1190, 1160, 1108, 1079, 1014, 841. HRMS calcd for $C_{22}H_{17}F_4N_3O_4$ [M + H] 464.1233, found 464.1228. HPLC analysis: 4.6 mm × 150 mm Eclipse XDB Phenyl column, gradient elution (0.1% H_3PO_4/CH_3CN from 65:35 to 10:90 over 50 min, hold 10 min; run time = 60 min), flow rate = 1.0 mL/min, detection = 210 nm, T = 25 °C; sample preparation = an aliquot was withdrawn and diluted with CH_3CN/water (75/25). A 10 μL sample was injected. HPLC t_R = 17.65 min. Chiral HPLC retention time: major enantiomer t_R = 14.00 min, minor enantiomer t_R = 19.75 min.

(*1S*)-*N*-{[4-(4-Fluorophenyl)-2-oxo-2*H*-chromen-7-yl]methyl}-5-[1-hydroxy-1-(trifluoromethyl)propyl]-1,3,4-oxadiazol-2-aminium 4-Methylbenzenesulfonate (MK-0633 Tosylate, 1). The crude solution of MK-0633 free base **2** (5.4 kg according to HPLC after concentration) in *i*PAc (15.5 L) was diluted in *i*PAc (40 L) and was stirred at rt for 16 h. Stirring was stopped and solids settled rapidly at the bottom of the flask. The supernatant was filtered and analyzed by HPLC and ^{1}H NMR spectroscopy. HPLC assay of the solution indicated 54.4 kg at 9.72% wt in *i*PAc for a total mass 5.3 kg of free base **2**. ^{1}H NMR analysis showed a 1:8.74 wt ratio of free base: *i*PAc. Thus the free base solution already contained 52.89 L of *i*PAc. *p*-Toluenesulfonic acid·H_2O (2.17 kg, 11.42 mol) was dissolved in *i*PAc (13.2 L). The slurry was heated to 60 °C and stirred until complete dissolution of *p*TsOH·H_2O (∼20 min). The solution of free base **2** was added over 2 h to the hot solution of *p*TsOH·H_2O. After 20% of the crude MK-0633 free base solution was added the addition was stopped. MK-0633 tosylate **1** seeds (1 g) were added and the mixture was stirred for 10 min. Addition of crude free base was then continued. After the end of the addition, the batch was gradually cooled to rt over 2 h, then let stir at rt for 16 h and the slurry was filtered. The filter cake was suspended in *i*PAc (40 L), filtered, resuspended in *i*PAc (40 L) and filtered. The batch was dried under low vacuum on the frit for 4 h. The solids were then transferred in trays to a vacuum oven at 30 °C. The solids were dried to a constant weight under low vacuum/N_2 sweep. MK-0633 tosylate salt (**1**) was obtained as a white solid (6.64 kg, 91.4% yield): mp 164−165 °C; $[\alpha]^{20}_D$ − 0.86 (*c* 10.0, EtOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (1 H, t, J = 6.2 Hz), 7.62 (2 H, dd, J = 8.3, 5.4 Hz), 7.49 (2 H, d, J = 7.8 Hz), 7.47−7.38 (4 H, m), 7.33 (1 H, d, J = 8.3 Hz), 7.13 (2 H, d, J = 7.7 Hz), 6.44 (1 H, s), 4.53 (2 H, d, J = 5.6 Hz), 2.30 (3 H, s), 2.17−2.05 (1 H, m), 2.03−1.93 (1 H, m), 0.90 (3 H, t, J = 7.37 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.1, 162.9 (d, J = 246.8 Hz), 159.6, 156.1, 153.7, 153.6, 145.5, 143.7, 137.7, 131.1 (d, J = 3.5 Hz), 130.9 (d, J = 8.7 Hz), 128.1, 126.8, 125.4, 124.5 (q, J = 286.6 Hz), 123.5, 117.4, 115.9 (d, J = 22.0 Hz), 115.4, 114.7, 73.7 (q, J = 28.6 Hz), 45.4, 26.1, 20.8, 7.0; ^{19}F NMR (375 MHz, DMSO-d_6) δ −79.7, −113.1; HRMS calcd for $C_{22}H_{18}F_4N_3O_4$ [M + H] 464.1228, found 464.1246. IR (cm^{-1}, NaCl thin film) 3324, 3010, 2977, 1735, 1716, 1618, 1510, 1428, 1215, 1178. HPLC analysis: eclipse XDB-phenyl column 4.6 mm × 15 cm (0.1% aq H_3PO_4/CH_3CN 65:35 to 10:90 over 50 min, 1.0 mL/min, 210 nm, 25 °C); MK-0633 (**1**) t_R = 16.86 min. Chiral HPLC analysis: Chiralpak AD-H column 4.6 mm × 25 cm (EtOH/hexane 60:40, hold 15 min, 0.5 mL/min, 300 nm, 30 °C); (*S*)-enantiomer t_R = 9.5 min; (*R*)-enantiomer t_R = 11.5 min.

Supporting Information Available: Experimental procedures and characterization for compounds (*S*)-**3**, **4**, (*S*)-**6**, **12**, **15**, **16**, (*S*)-**22**, **25**, and **26** and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.