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Convergent, Fit-For-Purpose, Kilogram-Scale Synthesis of a 5-Lipoxygenase Inhibitor

Stéphane G. Ouellet,*[,†] Danny Gauvreau,[†] Mark Cameron,[‡] Sarah Dolman,[†] Louis-Charles Campeau,[†] Gregory Hughes,[†] Paul D. O'Shea,[†] and Ian W. Davies[‡]

[†]Department of Process Research, Merck Frosst Canada, Kirkland, Quebec H9H 3L1, Canada

[‡]Department of Process Research, Merck & Co., Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: Process research and development of a synthetic route towards a novel 5-lipoxygenase inhibitor is described. The synthetic route provided **1** in 27% yield in nine steps (seven steps in the longest linear sequence) and was performed on kilogram scale. The synthesis began with the preparation of the coumarin core via an efficient von Pechmann condensation. The triazole fragment was obtained via a regioselective copper-catalyzed [3 + 2] cycloaddition between a chiral alkyne and the coumarin azide.

INTRODUCTION

The 5-lipoxygenase (5-LO) pathway is characterized by a series of biochemical reactions in which arachidonic acid is transformed into pro-inflammatory mediators called leukotrienes[1] which are known to exhibit diverse biological actions and are believed to be involved in many disease states.[2] Several studies have highlighted the role of leukotrienes in the pathogenesis of asthma; consequently, the development of pharmaceutically active agents with the ability to inhibit the synthesis and/or the action of leukotrienes is being pursued for the treatment of asthma. Our discovery efforts in this field identified **1** as a potent 5-LO inhibitor.[3] To support preclinical and clinical development, a practical synthesis of **1** suitable for multi kilogram-scale preparation of the active pharmaceutical ingredient was required.

RESULTS AND DISCUSSION

We focused our efforts on two synthetic strategies outlined in Scheme 1. In both routes to **1**, we envisioned that the 1, 4-substituted triazole would be constructed using a regioselective [3 + 2] cycloaddition between a chiral alkyne (**2**) and the coumarin azide **3**. For the construction of the coumarin core, we considered two complementary routes. The azido-coumarin **3** could be obtained from a Suzuki cross-coupling reaction between a functionalized coumarin and a boronic acid or be prepared in a more expedite way via a von Pechmann cyclization of a ketoester with 3-methylphenol.

Early work to support medicinal chemistry efforts and early preclinical profiling were focused on designing a synthetic sequence that would allow for maximum flexibility. Summarized in Scheme 2, the synthetic route utilized for the preparation of the azido-coumarin **3** allows for facile modification of the 4-aryl component which proved to be an important pharmacophore. Cresol **6** was first acylated and underwent a Fries rearrangement[4] under Lewis acidic conditions to provide aryl ketone **8**. Following a Masamune chain extension,[5] the resulting keto-lactone was trapped with triflic anhydride to provide the vinyl triflate **9**.

This intermediate underwent a palladium-catalyzed Suzuki cross-coupling reaction with 3-fluorophenyl boronic acid to provide coumarin **10**. Finally, the benzylic position was activated using NBS/$(BzO)_2$, and the resulting benzyl bromide was displaced with NaN_3 to give the coumarin azide **3** in an overall yield of 23% (seven steps). Using this sequence, we were able to successfully prepare this active pharmaceutical ingredient (API) on ~100 g scale.

While the late introduction of the functionalized aryl substituent was strategically beneficial from a SAR standpoint, a shorter, more efficient and scalable approach was desired in order to support further development of this compound. Realizing the inherent inefficiency in forming the coumarin core, followed by installation of the *m*-fluorophenyl side chain, we explored methods to synthesize the coumarin which would directly incorporate the requisite substitution pattern. To achieve this goal, we considered a von Pechmann reaction[6] between a functionalized keto-ester and *m*-cresol (Scheme 3). Preparation of keto-ester **12** was achieved via a chain extension[5] of the activated 3-fluorobenzoic acid in the presence of potassium ethylmalonate, triethylamine, and magnesium chloride. The unreacted starting materials could easily be rejected during the workup, and the crude reaction mixture was used directly in the following step. The coumarin synthesis was achieved by successfully adapting a methodology that was initially used for the synthesis of MK-0633.[7] The keto-ester **12** reacted smoothly with *m*-cresol in methanesulfonic acid at 40−45 °C to afford the key methyl-coumarin **10**. Following an aqueous workup, the methyl-coumarin **10** was precipitated out of a mixture of DCM/IPA to provide the desired product in 72% isolated yield with an excellent purity profile (>99 LCAP). Bromination using a small excess of NBS and a catalytic amount of benzoyl peroxide was performed in acetonitrile at 80 °C.

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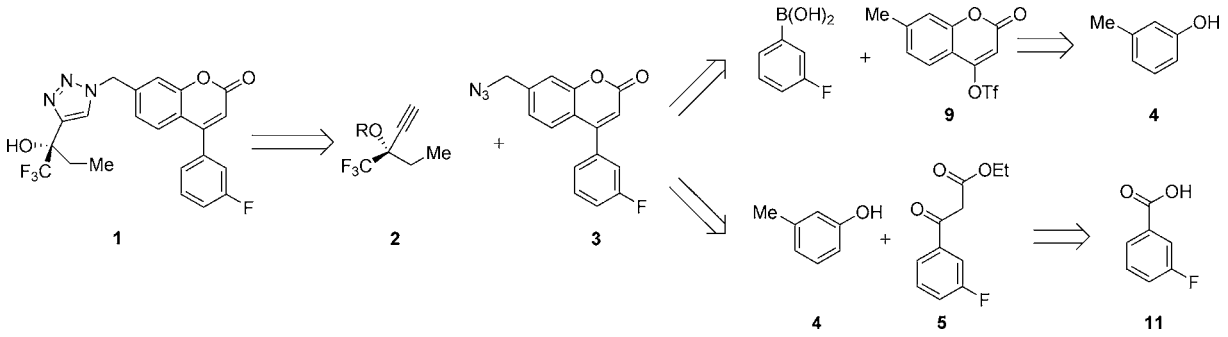
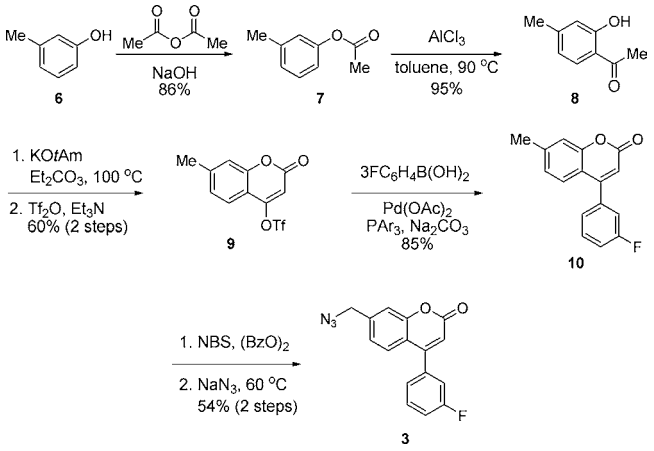
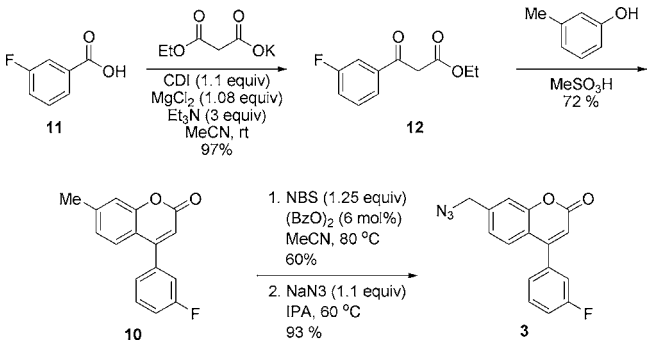
Scheme 1. Retrosynthetic analysis



Scheme 2. First synthetic route developed to access the coumarin 3



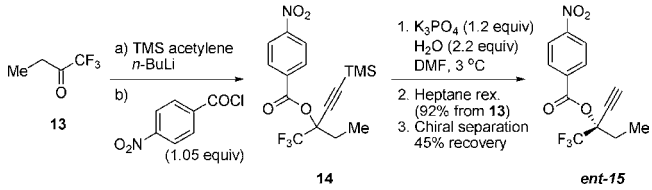
Scheme 3. Preparation of the azido-coumarin 3 via a von Pechmann cyclization



Under these optimized conditions, we typically observed about 85% conversion to the desired monobromide along with 5−8% unreacted **10** and 7−10% dibromide (LCMS). Upon cooling of the reaction mixture, the monobromide crystallized in 60% yield with good rejection of the dibromide (<0.2 LCAP) but is contaminated with 1−2% of the starting material (**10**). Nevertheless, this purity profile was deemed suitable as these levels of methylcoumarin **10** can easily be rejected downstream. Finally, the displacement of the benzylic bromide with NaN_3 in ethanol afforded the azido-coumarin **3** in 55−65% yield over both steps. This robust and straightforward approach provided **3** in four steps from 3-fluorobenzoic acid (**11**) in 39% overall yield on >2.5 kg scale.

In the preparation of *ent*-**15**, we opted for a chiral resolution of the racemic material which could be prepared in a straightforward manner (see Scheme 4). Addition of lithium (trimethylsilyl)acetylene to 1,1,1-trifluoro-2-butanone had to be performed with careful control of the reaction temperature to ensure the stability of the lithium-acetylide. In order to achieve reproducible results, temperatures below −50 °C were required during the lithiation/addition sequence. For the electrophilic quench with *p*-nitrobenzoyl chloride, the reaction mixture could be warmed up to −30 °C without any effect on the reaction efficiency or the overall purity. We selected *p*-nitrobenzoyl chloride because it could be cleaved under mild conditions and both enantiomers could be easily separated by chiral HPLC.

Scheme 4. Preparation of the chiral acetylene *ent*-15



While initial work on desilylation of the alkyne used HF·Et_3N, we elected to develop an alternative protocol to allow for this transformation to be run in glass reactors. We found that the TMS could be cleaved under a variety of mild basic conditions (K_3PO_4 or K_2CO_3 in DMF/water mixture). However, ester hydrolysis was found to be a significant side reaction. To address this issue, an improved protocol needed to be developed. The optimal set of conditions involved the use of 1.2 equiv of K_3PO_4 in DMF at 3 °C with a slow addition of water. Upon completion of the reaction, a reverse quench into cold MTBE/3 N HCl prevented further hydrolysis of the ester. Under these conditions, the ester hydrolysis byproduct formation was reduced to less than 1.5 LCAP. To further upgrade the purity of *rac*-**15** (and to reject the undesired hydrolysis byproduct), the alkyne was recrystallized from heptane to provide *rac*-**15** with an overall isolated yield of 92%. The racemic alkyne was resolved by chiral HPLC to provide the desired alkyne in >99% ee with a 45% recovery.

The final three chemical steps in the synthesis of this API were developed as a through-process starting from the azido-coumarin **3** and the chiral alkyne *ent*-**15**. A copper-catalyzed regioselective [3 + 2] cycloaddition[8] allowed for the efficient formation of the triazole **20**. While these reactions were often run with a very high catalyst loading (>25 mol % of CuI), we successfully demonstrated that <5 mol % was sufficient to obtain high conversion with acceptable reaction time (24 h at rt). In order to further decrease the catalyst loading while

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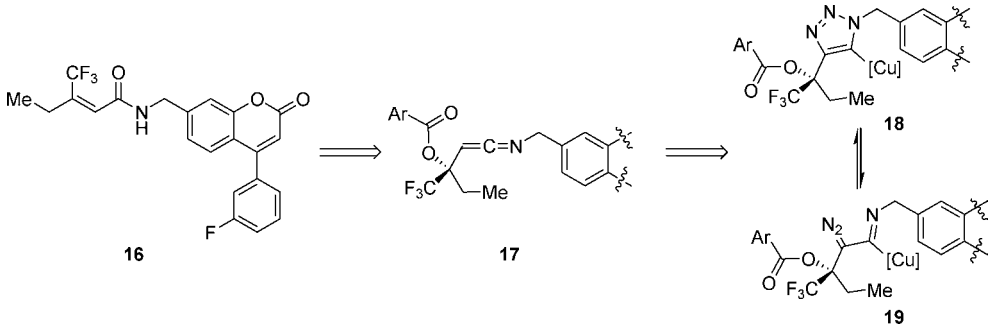
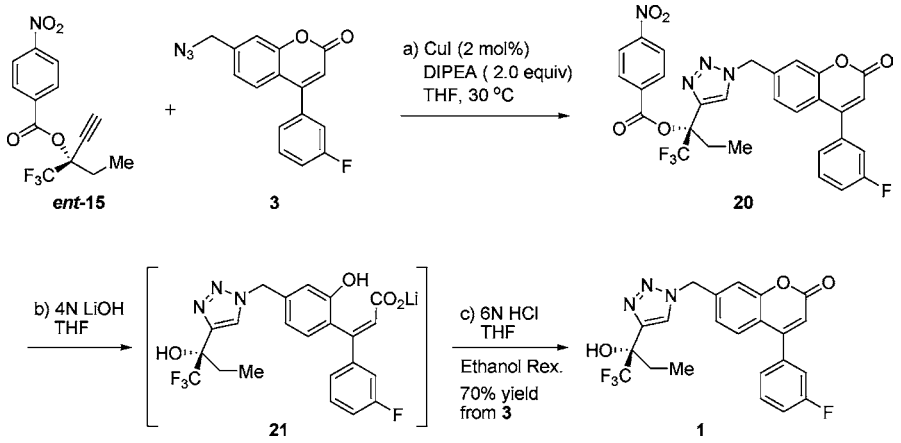
Scheme 5. Possible pathway leading to the formation of the byproduct 16



Scheme 6. End-game through-process to access the 5-lipoxygenase inhibitor 1



maintaining acceptable reaction times, we explored the effect of temperature on the reaction profile. The reaction rate was found to be significantly increased upon raising the reaction temperature to 40 °C. Under these conditions, we found that 3 mol % of catalyst was sufficient to allow the reaction to reach complete conversion in about 1.5 h and that 1 mol % of CuI would lead to full conversion in about 18 h. Unfortunately, when the temperature was increased further, we observed the formation of an impurity which tracked to the final API and was difficult to reject by recrystallization. Somewhat surprisingly, this impurity was identified as being alkene **16** (Scheme 5).[9] Electron-rich azides typically react selectively with alkynes to afford the 1,2,3-triazole. However, it is known that electron-deficient azides, such as Ts-N_3, react with alkynes to afford rearranged amine products. On the basis of our observations and recent literature precedent,[10] we believe that impurity **16** could arise from such a rearrangement. Triazolyl copper species **18**, the first intermediate formed in the cycloaddition, could undergo a Dimroth rearrangement to ketenimine **17** via the hetero-Wolff rearrangement of the α-diazoimino species **19**.[11] This ketenimine could then undergo a hydrolysis followed by an elimination of the benzoyl group to provide the unsaturated amide **16**. This is consistent with the observation that amide **16** is only observed after the 4 N LiOH treatment and reacidification with 6 N HCl. These observations warn of the potential formation of such contaminants which may form even when using electron-rich alkyl azides in this chemistry. Fortunately, on the basis of our previous optimization of temperature and catalyst loading, we were able to control the formation of this impurity by selecting 30 °C and 3 mol % of CuI. These conditions provided the best balance between low catalyst loading, convenient reaction rate, and low level (<0.6%) of the impurity **16** (Scheme 6).

Once the cycloaddition was found to be complete, the reaction mixture was cooled to −10 °C, and the *p*-nitrobenzoate was hydrolyzed by addition of aqueous 4 N LiOH which also resulted in the ring-opening of the coumarin core. The lactone was efficiently regenerated upon acidification of the reaction mixture. Finally, on the 5 kg batch, a recrystallization (IPAc/heptane) afforded a highly crystalline white solid (**1**) in 70% isolated yield (from **3**) with an acceptable purity profile (97.6 LCAP, purities >97% were typically observed).

■ CONCLUSION

In summary, we developed a practical and scalable synthesis of a 5-LO inhibitor. The azido-coumarin fragment was prepared via two complementary routes. On kilogram scale, this was achieved via a von Pechmann condensation (four steps, 39% overall yield). Careful study of the [3 + 2] cycloaddition between the chiral alkyne *ent*-**15** and the coumarin azide **3** revealed the formation of an unexpected impurity which could be controlled by selecting the appropriate temperature and catalyst loading, resulting in the formation of triazole heterocycle **20** in high yield and selectivity. This chemistry was demonstrated on multikilogram scale and provided the desired API in good overall yield (27%) and high chemical purity (97.6% LCAP, 99.5% ee).

■ EXPERIMENTAL SECTION

General Procedure. It is worth noting that the appropriate safety evaluations were carried out and that under the reaction conditions described, the risk was deemed acceptable.

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The azide **3**, the nitro-alkyne **15**, and the API (**1**) were found to be not shock sensitive. The azide **3** was tested in presence of ethanol and showed no exothermic activity below 200 °C (maximum temperature recommended for drying the azide was set at 40 °C). DSC testing of the API (**1**) slurried in THF showed a small exotherm at 175 °C and a larger one around 250 °C. Since the triazole formation will be carried out below 66 °C (boiling point of THF), these exotherms should not be encountered.

Intermediates were analyzed on an Agilent 1100 series instrument using the following conditions: 4.6 mm × 50 mm Zorbax SB-C18 column, 1.8 μm, gradient elution (0.1% H_3PO_4/CH_3CN 90:10 to 10:90 over 8 min, then hold 4 min, flow rate = 1.5 mL/min, detection = 215 nm, T = 35 °C, samples were diluted in MeCN, and a 10 μL sample was injected. HPLC conditions used for the chiral separation of *rac*-**15**: (11 cm × 25 cm DAC column packed with Chiralpak OD). The feed was about 29 mg/mL in v/v 13/87 isopropyl alcohol/heptane, the injection volume ranged from 1.0 to 1.2 L with elution performed using 15% v/v isopropyl alcohol/heptane at a flow rate of 800 mL/min, UV detection at 295 nm. The second eluting enantiomer (*S*-isomer) was the desired one.

*1-Ethyl-1-(trifluoromethyl)-3-(trimethylsilyl)prop-2-yn-1-yl 4-nitrobenzoate (**14**).* A mixture of TMS−acetylene (7.06 kg, 1.5 equiv) and MTBE (24 L) was cooled to −67 °C, and *n*-BuLi (2.26 M, 22.3 L, 1.05 equiv) was added over 6 h (keeping the reaction mixture below −51 °C). The mixture was aged 45 min, allowing the mixture to cool to −65 °C. 1,1,1-Trifluoro-2-butanone (6.5 L, 1.0 equiv) was added over 4 h (keeping the internal temperature below −50 °C). The mixture was aged 20 min, and *p*-nitrobenzoyl chloride (9.33 kg, 1.05 equiv) was added over 2.5 h as a THF solution (14 L) (keeping the reaction mixture below −33 °C). The mixture was stirred for 4 h. The reaction was quenched by adding water (18 L, exotherm observed) over 60 min. To the reaction mixture was added Solka Floc (500 g, 8 wt %), and the mixture was stirred for 20 min. The biphasic mixture was filtered over Solka Floc, and the organic layer was washed with half-saturated $NaHCO_3$ (2 × 30 L) and brine (30 L). The crude reaction mixture was used directly into the following step (the crude was concentrated under vacuum and solvent switched to DMF, temperature was kept below 35 °C, and final volume was about 45 L). **^{1}H NMR** (400 MHz, DMSO-d_6): 8.37 (d, J = 8.4 Hz, 2 H), 8.16 (d, J = 8.4 Hz, 2 H), 2.45−2.22 (m, 2 H), 1.06 (t, J = 7.6 Hz, 3 H), 0.17 (s, 9 H). **^{13}C NMR** (101 MHz, DMSO-d_6): 160.8, 150.7, 133.8, 130.9, 124.2, 122.9 (q, J = 284.9 Hz), 96.6, 95.0, 77.4 (q, J = 31.1 Hz), 27.1, 8.1, −0.8. **HRMS** (ESI): m/z calcd for $C_{16}H_{18}NO_4F_3SiNa$ (M + Na) 396.0849; found 396.0869. **Melting point**: 49.7 °C. **IR** (neat, cm^{-1}): 2964, 1733, 1527, 1349, 1274, 1251, 1097, 715.

*1-Ethyl-1-(trifluoromethyl)prop-2-yn-1-yl 4-nitrobenzoate (**15**).* A solution of TMS−acetylene-ester **14** (8.85 kg, 1.0 equiv) in DMF (36 L) was cooled to 0 °C, and solid K_3PO_4 (6.04 kg, 1.2 equiv) was added followed by water (940 mL, 2.2 equiv, added over 60 min to control the exotherm). The mixture was aged 30 min at 0 °C and quenched by pouring the DMF stream onto a precooled (2 °C) mixture of MTBE (27 L) and 3 N HCl (32 L). The residual K_3PO_4 was decanted off. The mixture was filtered on Solka Floc and rinsed with MTBE (9 L). The organic layer was washed with water (2 × 35 L), half-saturated $NaHCO_3$ (35 L), and brine (35 L) to give a quantitative assay yield of *rac*-**15** (98.5 LCAP). A suspension of *rac*-**15** (7.14 kg, 1.0 equiv) in heptane (32 L) was heated to 65 °C which allowed for the complete dissolution of the acetylene-ester. The solution was cooled to 1 °C over a period of 15 h to allow for a slow crystallization of the acetylene-ester (seeds were added at 56 °C). The crystallized acetylene-ester was filtered, rinsed with cold heptane (2 × 8 L), and dried under a flow of nitrogen. The recovery of *rac*-**15** was 6.56 kg (92% yield). The losses to the mother liquors were estimated to be about 4.8% (378 g). **^{1}H NMR** (400 MHz, DMSO-d_6): 8.36 (d, J = 8.8 Hz, 2 H), 8.15 (d, J = 8.8 Hz, 2 H), 4.23 (s, 1 H), 2.46−2.26 (m, 2 H), 1.06 (t, J = 7.5 Hz, 3 H). **^{13}C NMR** (101 MHz, DMSO-d_6): 160.9, 150.7, 133.7, 130.9, 124.2, 122.9 (q, J = 285.9 Hz), 82.4, 77.2 (q, J = 31.2 Hz), 74.1, 27.1, 8.0. **HRMS** (ESI): m/z calcd for $C_{13}H_{11}NO_4F_3$ (M + H) 302.0635; found 302.0640. **Melting point** (heptane): 103.8 °C. **IR** (neat, cm^{-1}): 1738, 1523, 1349, 1278, 1196, 1089, 711.

*Ethyl 3-(3-fluorophenyl)-3-oxopropanoate (**12**).(Flask A: 22 L).* To a suspension of 3-fluorobenzoic acid (**11**, 2.00 kg, 1.0 equiv) in CH_3CN (6 L) was added CDI (2.60 kg, 1.1 equiv, added portion-wise, gas evolution was observed, and the temperature of the reaction mixture decreased from 14 to 5 °C). This solution was stirred for 4 h (temperature of the batch was raised to 22 °C).

(Flask B: 100 L). To a solution of potassium ethylmalonate (3.17 kg, 5 equiv) in CH_3CN (30 L) was added $MgCl_2$ (1.47 kg, 1.08 equiv) in portions over 15 min (batch temperature rose from 18 to 41 °C). The mixture was stirred at 35 °C for 30 min and then cooled to 25 °C and Triethylamine (6.0 L, 3.0 equiv) was added. After the addition of about 2 L of TEA, the reaction mixture became very thick, and mechanical stirring was more challenging. The slurry was stirred for 30 min. The solution in flask A was then transferred to the slurry in flask B over 5 min. The batch temperature rose form 24 to 32 °C, and gas evolution was observed. The reaction mixture was stirred for 1.5 h, cooled to 7 °C, and quenched with 3 N HCl (32 L), while maintaining the batch temperature <20 °C. The resulting by-phasic solution was distilled to remove volatiles (CH_3CN) and the resulting concentrate extracted with MTBE (35 L). The organic phase was washed with water (8 L), 5% $NaHCO_3$ (8 L), and 20% NaCl (8 L). The organic solution was concentrated under reduced pressure to give an orange-colored oil (2.921 kg) in 97% yield.[12]

*4-(3-Fluorophenyl)-7-methyl-2H-chromen-2-one (**10**).* To a solution of *m*-cresol (**6**, 2.35 kg, 1.0 equiv) in methanesulfonic acid (16 L) was added the keto-ester **12** (4.85 kg, 1.06 equiv) over 30 min (internal temperature rose from 19 to 39 °C). The mixture was stirred for 3 h (39−33 °C), heated at 40−45 °C for 2 h, and allowed to cool to room temperature overnight. The reaction mixture was partitioned between CH_2Cl_2 (20 L) and water (20 L), and the aqueous layer was back-extracted with CH_2Cl_2 (8 L). The combined organic layers were washed with 1 N NaOH (16 L) and water (16 L). The organic solution was concentrated under reduced pressure to about 10 L. IPA (12 L) was added, and volatiles were evaporated until a volume of ∼18 L of slurry was obtained. The suspension was stirred overnight. The product was isolated by filtration (the filter cake was washed with IPA (2 × 2 L)). The product was dried on the filter pot under a flow of nitrogen for 8 h and then transferred to drying trays and dried in a vacuum oven at 40 °C under a gentle nitrogen sweep to give **10** (4.05 kg, 100 wt % 99.8 LCAP) in 72% isolated yield. **^{1}H NMR** (400 MHz, DMSO-d_6): 7.63−7.55 (m, 1 H), 7.42−7.30 (m, 3 H), 7.30−7.23 (m, 2 H), 7.12 (d, J = 8.09 Hz, 1 H), 6.35 (s, 1 H), 2.38 (s, 3 H). **^{13}C NMR** (101 MHz, DMSO-d_6): 162.0 (d, J = 245.4 Hz), 159.6,

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153.6, 153.4 (d, J = 2.1 Hz), 143.2, 136.9 (d, J = 8.2 Hz), 130.9 (d, J = 8.2 Hz), 126.2, 125.6, 124.7 (d, J = 2.7 Hz), 117.0, 116.5 (d, J = 21.1 Hz), 115.6 (d, J = 2.6 Hz), 115.4, 114.1, 21.0. **HRMS** (ESI): m/z calcd for $C_{16}H_{12}O_2F$ (M + H) 255.0816; found 255.0825. **Melting point** (IPA): 103.9 °C. **IR** (neat, cm^{-1}): 3055, 1729, 1584, 1440, 1359, 1265, 1253, 1179, 1147, 1115, 967, 716.

7-(Bromomethyl)-4-(3-fluorophenyl)-2H-chromen-2-one. To a stirred suspension of methylcoumarin **10** (4.05 kg, 1.0 equiv) in CH_3CN (10.0 L) was added NBS (3.32 kg, 1.16 equiv) followed by $(BzO)_2$ (192 g, 0.05 equiv) and the mixture was heated to reflux (78−82 °C) for 2 h. At this time, the heating source was turned off and the batch stirred overnight which allowed the product to precipitate out of solution. The crystallized product was then isolated by filtration and the filter cake washed with IPA (2 × 4 L) and dried under a flow of nitrogen to give monobrominated product (3.21 kg, 97 wt % 2 mol % **10** by H/F NMR) in 60% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.58−7.49 (m, 1 H), 7.50−7.42 (m, 2 H), 7.33−7.22 (m, 3 H), 7.18 (d, J = 9.2 Hz, 1 H), 6.39 (s, 1 H), 4.55 (s, 2 H). **^{13}C NMR** (101 MHz, $CDCl_3$): 162.7 (d, J = 249.2 Hz), 160.0, 154.0, 153.6 (d, J = 1.6 Hz), 142.3, 136.8 (d, J = 7.6 Hz), 130.7 (d, J = 8.3 Hz), 127.1, 125.0, 124.1 (d, J = 2.9 Hz), 118.3, 117.6, 116.8 (d, J = 20.7 Hz), 115.7, 115.5 (d, J = 22.3 Hz), 31.5. **HRMS** (ESI): m/z calcd for $C_{16}H_{11}O_2FBr$ (M + H) 332.9921; found 332.9930. **Melting point** (MeCN): 103.8 °C. **IR** (neat, cm^{-1}): 3032, 1723, 1579, 1373, 1254, 1221, 1148, 900, 720.

*7-(Azidomethyl)-4-(3-fluorophenyl)-2H-chromen-2-one (**3**).* To a suspension of bromomethylcoumarin (3.22 kg, 1.0 equiv) in ethanol (32 L) was added NaN_3 (0.65 kg, 1.05 equiv) and the mixture heated at 60 °C for 3 h. At this point, the batch was cooled to 10−15 °C. Water (30 L) was added slowly, and the batch was stirred for an additional 60 min. The residual slurry was transferred onto a filter pot, and the cake was washed with water (2 × 10 L) and allowed to dry under a flow of nitrogen overnight. The product was then transferred onto drying trays and dried to constant weight (vacuum oven 40 °C, nitrogen sweep) to provide the azidemethylcoumarin (**3**, 2.65 kg, 97 wt %, 98.1 LCAP) in 93% isolated yield. **^{1}H NMR** (400 MHz, acetone-d_6): 7.64 (q, J = 7.1 Hz, 1 H), 7.52 (d, J = 8.2 Hz, 1 H), 7.48−7.30 (m, 5 H), 6.39 (s, 1 H), 4.63 (s, 2 H). **^{13}C NMR** (101 MHz, acetone-d_6): 163.6 (d, J = 246.7 Hz), 160.1, 155.1, 154.4 (d, J = 2.1 Hz), 141.7, 138.2 (d, J = 8.0 Hz), 131.8 (d, J = 8.5 Hz), 128.1, 125.5 (d, J = 2.9 Hz), 124.9, 119.1, 117.3 (d, J = 21.1 Hz), 117.2, 116.4 (d, J = 22.9 Hz), 116.3, 54.1. **HRMS** (ESI): m/z calcd for $C_{16}H_{11}N_3O_2F$ (M + H) 296.0830; found 296.0835. **Melting point** (water): 90.7 °C. **IR** (neat, cm^{-1}): 2116, 2096, 1724, 1579, 1417, 1349, 1276, 1254, 1183, 1144, 890.

*(1S)-1-(1-{[4-(3-Fluorophenyl)-2-oxo-2H-chromen-7-yl]-methyl}-1H −1,2,3-triazol-4-yl)-1-(trifluoromethyl)propyl 4-nitrobenzoate (**1**).* To a solution of azidemethylcoumarin **3** (5.0 kg, 1.0 equiv) in THF (25 L) was added alkyne *ent*-**15** (5.44 kg, 1.1 equiv) and di-isopropylethylamine (5.74 L, 2.0 equiv). This reaction mixture was degassed by bubbling nitrogen for 20 min. To this solution was added CuI (62.5 g, grounded with a mortar and pestle) in one portion and the reaction mixture was degassed for an additional 5 min before to be heated up to 30 °C and stirred for 24 h (complete consumption of the azide was observed). At this point the reaction mixture was cooled to −10 °C and 4 N LiOH (15 L) was added (small exotherm observed but easily controlled by rate of addition). After 4 h, the reaction mixture was transferred into a 160 L extractor (6 L THF used to rinse the flask) and cooled to 0 °C. To this cold solution was added 6 N HCl (15 L, small exotherm observed but easily controlled by rate of addition), and the reaction mixture was stirred vigorously at rt for 18 h. MTBE (50 L) and water (10 L) were added, and the layers were separated. The organic layer was washed with Na_2CO_3 (2 × 40 and 20 L, three layers were observed during the first wash, only the lower layer was rejected) and half-saturated brine (2 × 20 L). The reaction mixture was solvent switched to ethanol (<0.5% THF vs ethanol was detected, final volume was 8 mL/g) and heated until complete dissolution (67 °C). The reaction mixture was slowly cooled down to rt (seeded at 45−47 °C) and aged for 6 h (at this point, the solubility in the mother liquor was 25 mg/mL). This suspension was filtered and the residual solid washed with the mother liquor (10 L), ethanol/water (30 L of 4:6), and heptane (40 L). The beige solid was dried under a flow of N_2 overnight and transferred into a vacuum oven at 50 °C under a gentle sweep of nitrogen. 5.15 kg of **1** was obtained (70% yield from *ent*-**15** and **3**, beige solid, 97.6 LCAP, 33 ppm Cu, 99.5% ee, 0.5% water, 0.3% ethanol). **^{1}H NMR** (400 MHz, acetone-d_6): 8.50 (s, 1 H), 8.37 (d, J = 8.4 Hz, 2 H), 8.27 (d, J = 8.4 Hz, 2 H), 7.65−7.57 (m, 1 H), 7.48 (d, J = 8.2 Hz, 1 H), 7.40−7.22 (m, 5 H), 6.37 (s, 1 H), 5.84 (s, 2 H), 3.07−2.97 (m, 1 H), 2.88−2.77 (m, 1 H), 1.11 (t, J = 7.4 Hz, 3 H). **^{13}C NMR** (101 MHz, acetone-d_6): 163.5 (d, J = 245.7 Hz), 162.6, 160.0, 155.1, 154.2 (d, J = 1.9 Hz), 151.9, 143.6, 141.1, 138.0 (d, J = 8.1 Hz), 135.7, 131.9 (d, J = 8.0 Hz), 131.8, 128.2, 125.5, 125.4 (d, J = 3.0 Hz), 125.1 (d, J = 285.3 Hz), 124.7, 124.5, 119.2, 117.3 (d, J = 21.4 Hz), 117.1, 116.6, 116.4 (d, J = 22.8 Hz), 82.3 (d, J = 29.4 Hz), 53.6, 25.9, 7.8. **HRMS** (ESI): m/z calcd for $C_{29}H_{21}N_4O_6F_4$ (M + H) 597.1392; found 597.1403. **Melting point** (ethanol): 133.9 °C. $[\alpha]^D_{20}$: −48.1° (c = 10.0, DCM). **IR** (neat, cm^{-1}): 1727, 1527, 1349, 1268, 1253, 1182, 1118, 917, 867, 715.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete characterization data and spectra for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

stephane_ouellet@merck.com.

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