JOC The Journal of Organic Chemistry

Note

Synthesis of HIV-Maturation Inhibitor BMS-955176 from Betulin by an Enabling Oxidation Strategy

Adrian Ortiz, Maxime Soumeillant, Scott A. Savage, Neil A. Strotman, Matthew Haley, Tamas Benkovics, Jeffrey Nye, Zhongmin Xu, Yichen Tan, Sloan Ayers, Qi Gao, and Susanne Kiau

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00438 • Publication Date (Web): 13 Apr 2017

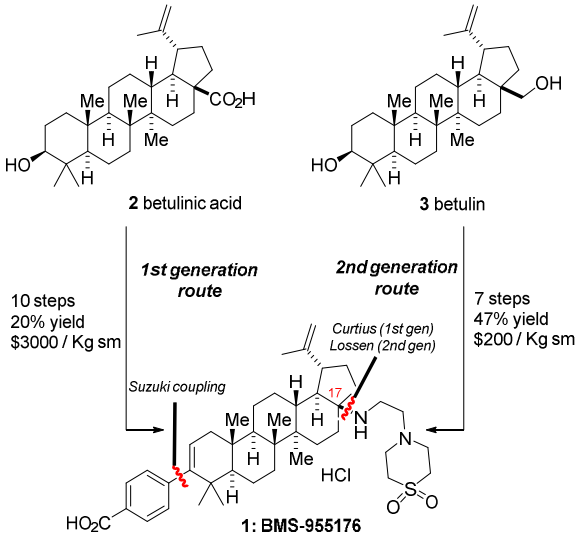
ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of HIV-Maturation Inhibitor BMS-955176 from Betulin by an Enabling Oxidation Strategy

*Adrian Ortiz, Maxime Soumeillant, Scott A. Savage, Neil A. Strotman, Matthew Haley, Tamas Benkovics, Jeffrey Nye, Zhongmin Xu, Yichen Tan, Sloan Ayers, Qi Gao, and Susanne Kiau

Bristol-Myers Squibb, Chemical and Synthetic Development, 1 Squibb Drive, New Brunswick, NJ, 08903.



Abstract

A concise and scalable 2nd generation synthesis of HIV maturation inhibitor BMS-955176 is described. The synthesis is framed by an oxidation strategy highlighted by a Cu^{I} mediated aerobic oxidation of betulin, a highly selective PIFA mediated dehydrogenation of an oxime, and a subsequent Lossen rearrangement which occurs through a unique reaction mechanism for the installation of the C17 amino functionality. The synthetic route proceeds in 7 steps, 47% overall yield, and begins from the abundant and inexpensive natural product betulin.

.

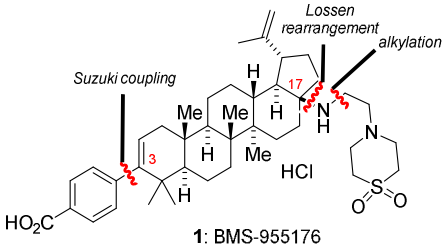


Figure 1: Key bond disconnections of the synthesis of BMT-955176 (**1**).

According to the World Health Organization, there are >35 million people infected with the HIV virus worldwide,[1] a staggering number despite significant advancements in treatments option made available as

a result of over 3 decades of research and development. While many patients respond well to highly active antiretroviral therapy (HAART), a standard of care therapy that acts to reduce viral load in the blood, there are a growing number of patients demonstrating resistance to this treatment. In fact, more than 25% of newly infected patients contract a therapy resistant strain of the HIV virus.[2] Therefore, it is important to continue to identify and evaluate new therapies including more potent anti-retrovirals as well as those possessing new modes of action. BMS-955176 (**1**, Figure 1) is a second generation HIV-maturation inhibitor possessing a recently validated novel mode of action[2] and currently under Phase IIb clinical evaluation. The discovery, design, and 1st generation synthesis of **1** were recently disclosed by researchers at Bristol-Myers Squibb[3] which utilized a semi-synthetic route starting from the natural product betulinic acid (**2**). This synthetic route was successfully implemented to produce initial clinical supplies, however, when considering the requirements of a potential commercial manufacturing route, this strategy possessed a single fundamental shortcoming, namely, the use of betulinic acid as starting material. As summarized in Figure 2, the use of **2** enabled the "purchase" of a fully oxidized C28 synthetic handle suitable for nitrogen introduction at the requisite C17 position, along with the ability for facile chemoselective differentiation between the C3 and C17 functional groups (i.e. 2^o -OH vs -CO_2H). However, when compared to a structurally similar relative, betulin (**3**), **2** came at the expense of a relatively high cost (10 X greater than **3**), and questionable sustainable availability. And while both molecules are derived from the Birch tree, only **3** is naturally abundant (30-40 wt% of **3** vs 1 wt% of **2** in the dry extract)[4,5]. Moreover, many commercial sources actually obtain **2** from **3** via synthetic means[6a-c]. Although many incremental improvements are conceivable within the 1st generation approach, the major driving force for a 2nd generation route was to enable the use of **3** instead of **2** as a raw material. To accomplish this task, a synthetic strategy was required which enabled both the chemoselective differentiation between the C3 and C17 positions of betulin and the appropriate oxidation strategy to enable the eventual introduction of the C17 amino group.

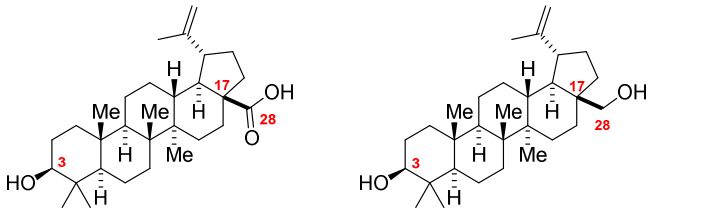
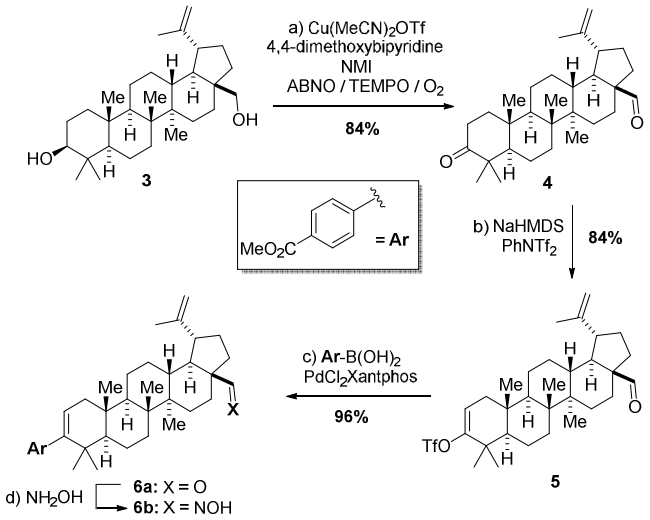


Figure 2: Comparison of natural products betulinic acid (**2**) and betulin (**3**) as semisynthetic starting materials for the preparation of **1**.

The synthesis of **1** commenced (Scheme 1) with the oxidation of betulin (**3**) to the corresponding keto-aldehyde (**4**) using a Cu(I) / ABNO / TEMPO catalyzed aerobic oxidation transformation [CH_2Cl_2 / CH_3CN (10:1), 220 psi of 10% O_2 / 90% N_2, 40 °C, 2 h, 84% yield] that was inspired by the work of the Stahl group.[7,8] The use of this unusual combination of nitroxyl radical catalyst precursors (2% ABNO / 10% TEMPO) was critical to the success of the reaction - ABNO enabling the oxidation of the uniquely hindered hydroxy groups of the betulin core and TEMPO, utilized not as a typical oxidant for hydroxyl groups, but as a highly effective stabilizing reagent capable of inhibiting undesired oxidation of the tertiary aldehyde and alkene moieties.[9] Traditional stoichiometric oxidations such as Cr^{IV} (PCC) and Ru

(TPAP) based reagents and activated DMSO type oxidations (Moffatt / Parikh-Doering) all performed satisfactorily, but a catalytic oxidation using dioxygen was preferred for process "greenness" considerations. Next, Keto-aldehdye **4** was subjected to triflation conditions ($PhNTf_2$, NaHMDS, MTBE, -10 to 0 °C) generating enol triflate **5** in 84% yield. Triflation of the ketone served to accomplish two goals: (1) facile preparation of the required electrophile for subsequent Suzuki coupling, and (2) a strategically necessary and simple chemoselective solution needed to differentiate the C3 and C17 positions of the betulin core. **5** was then united with commercially available (4-(methoxycarbonyl)phenyl) boronic acid under standard Suzuki coupling conditions (1.5 mol% $XantphosPdCl_2$, aq. K_3PO_4, THF, 60 °C, 5 h) to give the corresponding Suzuki product (**6a**).



Scheme 1: Preparation of Oxime (**6b**) from betulin (**3**).

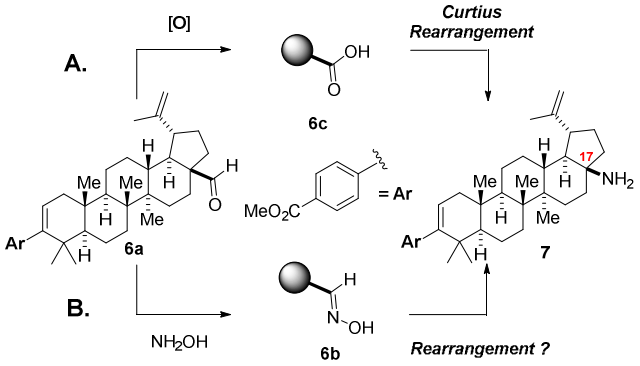
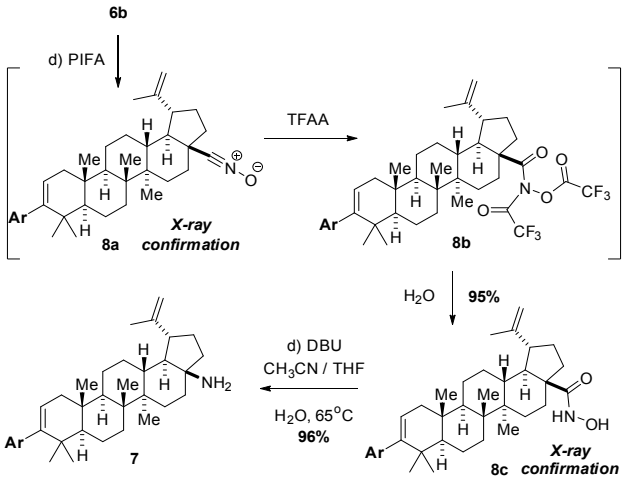


Figure 3. Initial (**A**) and alternative (**B**) strategies to install the C-17 amino group.

Having now successfully differentiated the two halves of the molecule and completed the functionalization of the A-ring, we turned our attention to address the transformation of the C-17 aldehyde into the corresponding amino group. The obvious approach (Figure 3, **A**) of an oxidation (**6a→6c**) followed by a Curtius rearrangement (**6c→7**) to install the C-17 amino group was initially explored. However, this standard protocol was unsuccessful primarily with the oxidation step rather than the subsequent Curtius rearrangement. A failure due to a combination of functional group instability with electrophilic oxidants (i.e. NaOCl) and/or the unfavorable physical properties inherent in these

pentacyclic triterpenoid intermediates resulting in triphasic mixtures, for example when Pinnick oxidation conditions[10] were explored. And while this strategy worked in principle, it was not amenable to multi-gram or Kg scale synthesis. Consequently, an alternative approach (Figure 3, **B**) was envisioned in which the corresponding oxime (**6b**) could be potentially rearranged to the desired amine (**7**), but the exact method to do so was not immediately clear. We were initially inspired by the work by the Rawal group in their synthesis of N-methylwelwitindolinone[11] in which a tertiary oxime was converted / rearranged to the isothiocyanate via the intermediacy of a chloro-oxime (R-CH=NOH→ R-CCl=NOH→ R-N=C=S) and hoped that a similar strategy could be employed to grant access to the requisite amine (**7**). To this end, oxime **6b**, which was generated most efficiently by exposure of the crude Suzuki reaction stream to aq. NH_2OH (IPA, pH = 6.5, 40 °C, 96% overall yield from **5**), was treated with various chloronium based reagents (e.g., NCS, dichlorohydantoin, NaOCl, and Chloramine-T) in an attempt to produce the corresponding chloro-oxime. However, this approach proved unsuccessful, consistent with our previous attempts at chloronium based oxidations of **6a.**



Scheme 2: Preparation of hydroxamic acid **8c** and Lossen rearrangement to amine **7**.

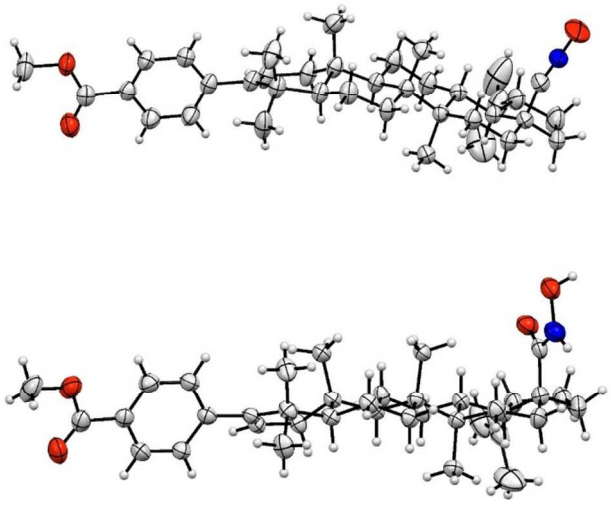
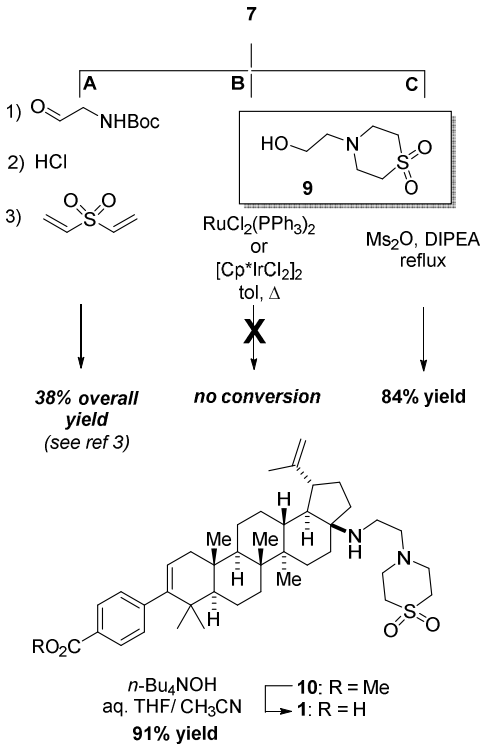


Figure 4: ORTEP representations of nitrile oxide **8a** (top) and hydroxamic acid **8c** (bottom), with 50% probability level.

We next considered the possibility of a dehydrogenation / hydration sequence of **6b** to access hydroxamic acid **8c**, a functional group that would enable exploration of the desired C to N migration by a Lossen rearrangement. Fortunately, it was discovered that treatment **6b** with PIFA (acetone / CH_3CN, 0 °C to rt, 30 min, Scheme 2) very cleanly resulted in dehydrogenation and formation of the corresponding and surprisingly stable nitrile oxide (**8a**), an outcome confirmed by X-ray crystallographic analysis (Figure 4, top).[12] Next, the mild hydration of the nitrile oxide to hydroxamic acid **8c** was carried out by a 2-step sequence beginning with the addition of TFAA (3.5 eq, 10 °C, 30 min) to give the resultant *N,O*-bis(trifluoroacetyl)hydroxamic ester **8b**[13] followed by the addition of H_2O. The role of H_2O was two-fold: acting to facilitate the hydrolysis of the two trifluoroacetyl groups of **8b** and then functioning as an anti-solvent to enable the isolation of **8c** (Figure 4, bottom)[12] in an impressive 95% overall yield from **6b** and as a single flask operation. At this point in the synthesis, it should be noted that the oxidation state of the C28 position of **8c**, which began oxidatively deficient due to the required use of **3**, had now been effectively raised to that of the carboxylic acid present in **2**, via a Cu^{II} mediated aerobic oxidation followed by the PIFA mediated dehydrogenation / hydration sequence (**6b→8c**). The combined sequence culminated in a highly selective, safe, and scalable alternative to more traditional oxidation strategies. Furthermore, the use of NH_2OH alleviated the safety concerns over the potential presence of hydrazoic acid intrinsic with any azide based reagent protocol. With the hydroxamic acid in place we were now poised to explore its rearrangement to **7** via a Lossen rearrangement. Traditional Lossen rearrangements occur most commonly through the activation of the hydroxamic acid with dehydrating reagents[14] leading to isocyanate products. However, recent reports have demonstrated base-mediated Lossen rearrangements, and are believed to proceed through a self-propagating mechanism that directly lead to primary amines[15-17]. Over the course of our work, we identified exceptionally mild base-catalyzed conditions (25 mol% DBU, CH_3CN /THF, 65°C, 4h) that could efficiently and fully convert hydroxamic acid **8c** *directly* to amine **7** without the observation of isocyanate and in excellent yield (96% yield, crystallized by addition of H_2O). The mechanism of this transformation was found to employ a novel mode of activation, and the complete details of this study is disclosed in an accompanying article in this same issue.[18]



Scheme 3: Methods evaluated for the Installation of thiomorpholine side chain **9** to prepare **10** and final conversion to **1**.

The next key step (Scheme 3) required a formal mono-alkylation of the recently generated C-17 amino group using an activated version of commercially available thiomorpholine **9** (**7** → **10**). In order to avoid the seemingly inevitable issue of over alkylation, we first investigated the possibility of reductive amination approaches. In our initial route (**A**, see ref. 3), a step-wise reductive amination sequence installed the desired side chain (3 steps, 38% overall yield) but required the use of divinyl sulfone, a skin sensitizer which proved difficult to source, thus prohibiting its use. Similarly, the use of Ir or Ru based "borrowing hydrogen" protocols[19] (**B**) were unsuccessful resulting in either decomposed or unreacted **7**, presumably due to the instability of the aldehyde derived from **9** which could not be prepared by standard oxidation protocols (swern, SO_3-pyr, TPAP, etc). Fortunately, after screening various activation modes of **9** (-OTs, Cl, I, Br, OTf) we found that conversion to its mesylate (**C**, Ms_2O, DIPEA, 0 °C, CH_2Cl_2) resulted in a relatively stable alkylating reagent that readily reacted with **7** to produce **10** in 84% yield after crystallization of its oxalate salt from THF. Furthermore, the use of the mesylate resulted in very high selectivity for the desired mono-alkylation of **7**, demonstrating typically <2% of the bis-alkylation side product, a result that can be attributed to both the relatively low reactivity of the mesylate with the uniquely hindered environment of the C-17 amino group of the betulin core. Finally subjection of **10** to hydrolytic conditions (*n*-Bu_4NOH, aq. in THF, 20 °C) gave BMS-955176 (**1**) in 91% yield (isolated as an HCl salt) and completed the synthesis of this experimental HIV maturation inhibitor.

Conclusion:

In summary, we have demonstrated a novel, economical, and highly efficient synthesis of BMS-955176 (**1**) starting from Betulin (**3**) in 7 steps and 47% overall yield. Critical to the success of this program was identifying a safe, effective, and scalable "oxidation strategy" to enable the use of betulin (**3**) as a starting material instead of the more expensive, less abundant, but more highly oxidized derivative, betulinic acid

(**2**). This case study also serves to demonstrate the effective and scalable use of the copper/nitroxyl radical mediated aerobic oxidations of hydroxyl groups as well as the implementation of the Lossen rearrangement instead of the more common Curtius reaction when C to N bond migration is tactically required.

Experimental Section:

General Remarks: All starting materials and reagents were corrected for potency and used as is. HPLC was carried out on a Shimadzu Prominence LC to determine reaction converison. The term "vol" refers to ml solvent / g substrate of limiting reagent. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker Ultrashield 400 spectrophotometer and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.27, C_2D_5HSO: δ 2.50). Data is reported as follows: chemical shift [multiplicity (app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants(s) in Hertz, integration]. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker Ultrashield 400 spectrophotometer and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances in the NMR solvent ($CHCl_3$: δ 77.0, C_2D_5HSO: δ 39.5). Data is reported as follows: chemical shift. High resolution mass spectrometry was performed on a ThermoFisher Scientific LTQ Orbitrap^{TM} mass spectrometer.

Keto-Aldehyde 4: To a 3-L buchi reactor was added CH_2Cl_2 (1.2 L) and MeCN (120 mL), followed by the addition of 4,4'-dimethoxybipyridine (3.11 g, 0.1 eq.), tetrakisacetonitrile copper (I) triflate (5.27 g, 0.1 eq.), NMI (2.20 g, 0.2 eq.), TEMPO (2.10 g, 0.1 eq.), ABNO (0.39 g, 0.02 eq.) and then betulin (**3**) (60g, 1.0 eq.). The reaction mixture was pressurized to 15 bar with 10% O_2 in N_2, and heated at 40 °C with overhead stirring (1500 rpm) for 18 h. After the completion of the reaction as indicated by HPLC, the pressure was slowly released and the reactor was purged with nitrogen (3 bar). The reaction stream was transferred to a 5-L reactor, and the reaction mixture was washed with of 5% EDTA and 10% aq. K_2HPO_4 solution (2 x 600 mL). Solvent was removed under vacuum and then the crude mixture was subjected to carbon treatment (10wt% Cuno-5 / 600 mL acetone). Carbon was removed by filtration and the filtrate was concentrated to a final volume of 300 mL. The resulting mixture was heated to 50 °C and H_2O (60 mL) was added over 1 h, stirred for an additional 1 h at this temperature and then an additional 60 mL of water added slowly to facilitate the crystallization of the product. After completion of the addition, the mixture was cooled to ambient temperature. The resulting slurry was filtered and washed with Acetone/H_2O (2:1, 250 mL) to afford **4** (49.83 g, 84% yield) as an off-white crystalline solid. **4**: mp = 160-163 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.66 (d, J = 1.6 Hz, 1H), 4.75 (m, 1H), 4.62 (m, 1H), 2.87 (td, J = 11.2, 5.9, 1H), 2.48 (J = ddd, 17.4, 9.9, 7.6 Hz, 1H), 2.39 (ddd, J = 15.7, 7.6, 4.3 Hz, 1H), 2.09 (m, 1H), 2.05 (m, 1H), 1.89 (m, 1H), 1.87 (m, 1H), 1.77 (m, 1H), 1.76 (m, 1H), 1.73 (m, 1H), 1.69 (s, 1H), 1.48 (m, 1H), 1.46 (m, 1H), 1.44 (m, 1H), 1.44 (m, 1H), 1.44 (m, 1H), 1.43 (m, 1H), 1.41 (m, 2H), 1.37 (m, 1H), 1.33 (m, 1H), 1.30 (m, 1H), 1.28 (m, 1H), 1.19 (m, 1H), 1.06 (s, 1H), 1.05 (m, 1H), 1.01 (s, 1H), 0.98 (s, 1H), 0.95 (s, 1H), 0.92 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 218.3, 206.8, 149.9, 110.4, 59.5, 55.1, 50.0, 48.2, 47.7, 47.5, 42.8, 41.0, 39.8, 39.0, 37.1, 34.3, 33.8, 33.4, 30.0, 29.3, 29.0, 26.8, 25.7, 21.5, 21.2, 19.8, 19.2, 16.2, 15.9, 14.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{30}H_{47}O_2$ 439.3566; Found 439.3571 (1.0 ppm error).

Enoltriflate 5: To a 20-L reactor was added **4** (556.0 g, 1.0 eq.) and Phenylbistriflimide (549.0g, 1.20 eq.) and MTBE (5.5 L). The resulting mixture was cooled to -10 °C and NaHMDS (1.0 M in THF, 1600 mL, 1.25 eq.) was added by addition funnel or pump at such a rate that the internal temperature is

maintained below -5 °C. Upon completion of the addition, the reaction was stirred an additional 30 min, and then quenched with 30wt% aq. NH_4OAc solution (1600 mL). The layers were split and the organic stream was concentrated under reduced pressure to a final volume of 2800 mL and heated to 40 °C. IPA was added (2800 mL), followed by the slow addition of H_2O (1600 mL) resulting in a crystalline slurry. The resulting slurry was cooled to ambient temperature, held at that temperature for 6 h, and then filtered (solids washed with 2800 mL of 70:30 IPA/H_2O) to yield **5** (637 g, 84% yield) as a partial THF solvate. **5**: mp = 130 °C (decomp); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.66 (d, J = 1.4 Hz, 1H), 5.55 (dd, J = 6.8, 1.9 Hz, 1H), 4.76 (m, 1H), 4.63 (m, 1H), 2.88 (td, J = 11.2, 5.9 Hz, 1H), 2.15 (dd, J = 17.1, 6.8 Hz, 1H), 2.08 (m, 1H), 2.06 (m, 1H), 1.87 (m, 1H), 1.78 (m, 1H), 1.76 (m, 1H), 1.74 (m, 1H), 1.74 (m, 1H), 1.70 (s, 1H), 1.47 (m, 1H), 1.46 (m, 1H), 1.45 (m, 1H), 1.43 (m, 1H), 1.43 (m, 1H), 1.42 (m, 1H), 1.41 (m, 1H), 1.37 (m, 1H), 1.34 (m, 1H), 1.34 (m, 1H), 1.31 (m, 1H), 1.21 (m, 1H), 1.20 (m, 1H), 1.11 (s, 1H), 1.05 (m, 1H), 1.00 (s, 1H), 0.97 (s, 1H), 0.94 (s, 1H), 0.90 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.7, 155.6, 149.9, 118.6 (q, J = 319.5 Hz), 113.9, 110.5, 59.5, 53.4, 49.1, 48.1, 47.7, 42.8, 40.9, 40.5, 38.9, 38.1, 36.5, 33.5, 33.4, 30.0, 29.3, 29.0, 27.6, 25.7, 21.5, 19.6, 19.2, 19.2, 16.4, 15.8, 14.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{31}H_{46}F_3O_4S$ 571.3063; Found 571.3069 (0.9 ppm error).

Oxime 6b: To a clean reactor inerted with nitrogen, was added a mixture of compound **5** (145.0 g, 1.0 eq.) in degassed THF (1286 mL) followed by 4-(methoxycarbonyl)phenylboronic acid (61.5 g, 1.5 eq.), nitrogen degassed THF (244.4 mL), $PdCl_2$Xantphos (2.58 g, 1.5 mol%) and nitrogen degassed THF (112.2 mL). After a 15 minutes subsurface nitrogen sparging 30 wt% aq. K_3PO_4 (483.5g, 3.0 eq.) and the overall reaction mixture was subjected to three vacuum/nitrogen pressure swings to inert the system whereupon the mixture was heated to 60 °C for 90 min. Upon complete conversion to intermediate **6a**, the mixture was cooled to 45 °C and diluted with MTBE (633 mL) and treated with a solution of *N*-acetyl cysteine (9.29 g, 0.25 eq.) in water (165 mL) for 45 min at 45 °C. The lower aqueous layer was removed by extraction and 50 wt% aq. hydroxylamine (30.1 g, 2.0 eq.) was added to the organic layer and the pH was adjusted to 7-8 by addition of acetic acid (0.2 to 0.25 eq. was typical). The reaction mixture was agitated for 2-3 hours at 45 °C until less than 1% of compound **6a** remained relative to compound **6b** based on HPLC analysis. Upon cooling to 25 °C the reaction mixture was washed with water (362 mL) and the lower aqueous layer was discarded. The upper organic layer was concentrated under reduced pressure to a final volume of 1.5 L, whereupon the residual THF was exchanged with 2-propanol (IPA) by constant volume distillation with an IPA feed under reduced pressure. To the resulting mixture at 45 °C was added water (825 mL) resulting in a slurry. The slurry was cooled to 20 °C for 3 hours and the product was collected by filtration, washed twice with IPA/water 3/2 (v/v) to yield compound **6b** as an off-white to pale yellow solid (127.0 g, 96% yield). **6b**: mp = 175°C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.57 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.40 (s, 1H), 7.23 (d, J = 8.2 Hz, 2H), 5.23 (dd, J = 6.2, 1.4 Hz, 1H), 4.71 (d, J = 2.0 Hz, 1H), 4.58 (m, 1H), 3.84 (s, 1H), 2.57 (td, J = 11.3, 5.1 Hz, 1H), 2.06 (dd, J = 17.3, 6.4 Hz, 1H), 1.89 (m, 1H), 1.88 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.70 (m, 1H), 1.68 (m, 1H), 1.67 (m, 1H), 1.67 (s, 1H), 1.62 (t, J = 11.5 Hz, 1H), 1.51 (m, 1H), 1.46 (m, 1H), 1.44 (m, 1H), 1.42 (m, 2H), 1.39 (m, 1H), 1.38 (m, 1H), 1.35 (m, 1H), 1.34 (m, 1H), 1.24 (m, 1H), 1.19 (m, 1H), 1.06 (m, 1H), 1.05 (m, 1H), 0.98 (s, 2H), 0.93 (s, 1H), 0.88 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.2, 152.6, 149.8, 148.2, 145.7, 130.0, 128.3, 127.6, 123.7, 109.9, 52.2, 52.0, 49.1, 48.6, 48.6, 47.3, 42.4, 41.0, 40.2, 37.9, 37.0, 36.6, 35.7, 33.1, 32.1, 29.3, 29.2, 27.5, 24.8, 20.9, 20.8, 19.3, 18.9, 16.2, 15.5, 14.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{38}H_{54}NO_3$ 572.4098; Found 572.4085 (2.3 ppm error).

Hydroxamic acid (8c): To a 10-L reactor was added oxime **6b** (400.0 g, 1.0 eq.) and acetone (6 L, 15 vol). The resulting thin slurry was stirred at 20 °C and PIFA (359.0 g, 1.2 eq.) was added. The resulting slurry, which initially became homogenous upon PIFA addition, slowly resulted in a 2nd slurry after crystallization of the corresponding nitrile oxide **8a** (see below for characterization). The reaction mixture

was aged for 30 min and then cooled to 10 °C. TFAA (337.0 mL, 3.5 eq.) was added slowly over 20 min by addition funnel and then aged for 1 h. Water (1.2 L, 5 vol) was then added resulting in the crystallization of the product and the slurry was aged for 12 h at ambient temperature before being isolated by filtration (cake washed with 3:1 acetone /H_2O) to yield hydroxamic acid **8c** (390.5 g, 95% yield) as an off-white crystalline solid. **8a:** mp = 260 °C (decomp); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 5.29 (dd, J = 6.3, 1.7 Hz, 1H), 4.77 (br d, 1H), 4.66 (m, 1H), 3.90 (s, 1H), 2.59 (td, J = 11.1, 6.0 Hz, 1H), 2.13 (m, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 2.01 (m, 1H), 1.85 (m, 1H), 1.79 (m, 1H), 1.78 (m, 1H), 1.69 (s, 1H), 1.67 (m, 1H), 1.59 (m, 1H), 1.58 (m, 1H), 1.56 (m, 1H), 1.55 (m, 1H), 1.52 (m, 1H), 1.50 (m, 1H), 1.48 (m, 2H), 1.47 (m, 1H), 1.39 (m, 1H), 1.35 (m, 1H), 1.22 (m, 1H), 1.13 (s, 1H), 1.10 (m, 1H), 0.99 (s, 1H), 0.98 (s, 1H), 0.93 (s, 1H), 0.92 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.4, 148.9, 148.3, 146.5, 130.3, 128.7, 128.1, 124.1, 111.2, 53.0, 52.2, 52.0, 50.3, 49.6, 49.1, 42.5, 42.2, 41.9, 41.6 (v br), 40.7, 37.7, 37.0, 36.5, 33.8, 32.3, 29.9, 29.7, 29.6, 25.3, 21.3, 21.2, 19.9, 19.9, 16.7, 16.0, 15.1. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{38}H_{52}NO_3$ 570.3942; Found 570.3946 (0.7 ppm error).

8c: mp = 225 °C (decomp); ^{1}H NMR (600 MHz, 1:1 DMSO-d_6:$CDCl_3$): δ 10.32 (br s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 5.21 (dd, J = 6.3, 1.6 Hz, 1H), 4.63 (d, J = 2.1 Hz, 1H), 4.50 (m, 1H), 3.82 (s, 1H), 3.04 (td, J = 10.8, 4.3 Hz, 1H), 2.57 (m, 1H), 2.05 (m, 1H), 2.04 (m, 1H), 1.80 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.63 (m, 1H), 1.61 (s, 1H), 1.47 (m, 1H), 1.46 (m, 1H), 1.42 (m, 1H), 1.40 (m, 1H), 1.38 (m, 2H), 1.36 (m, 1H), 1.36 (m, 1H), 1.34 (m, 1H), 1.31 (m, 1H), 1.25 (m, 1H), 1.22 (m, 1H), 1.16 (m, 1H), 1.08 (m, 1H), 0.94 (s, 1H), 0.93 (m, 1H), 0.92 (s, 1H), 0.92 (s, 1H), 0.86 (s, 1H), 0.86 (s, 1H). ^{13}C NMR (150 MHz, 1:1 DMSO-d_6:$CDCl_3$): δ 173.1, 166.0, 150.4, 148.0, 145.5, 129.6, 127.9, 127.3, 123.6, 108.9, 53.4, 52.1, 51.5, 50.0, 48.9, 46.0, 41.7, 41.0, 40.0, 37.7, 36.8, 36.8, 35.6, 33.0, 32.0, 30.2, 29.0, 28.8, 25.1, 20.8, 20.6, 19.2, 18.8, 16.0, 15.5, 14.1. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{38}H_{54}NO_4$ 588.4047; Found 588.4031 (2.8 ppm error).

Amine (7): To a 250 mL reactor was added hydroxamic acid **8c** (25.0 g, 1.0 eq.), a mixture of THF / CH_3CN (1:1, 100 mL), and water (2.5 g, 3.4 eq.). The resulting mixture was heated to 65 °C and then DBU (1.61 g, 0.26 eq.) was added and the resulting mixture was aged at that temperature for 2 h. CH_3CN (150 mL) was added 65 °C to facilitate the crystallization and the resulting slurry was cooled to 0 °C aged for 12 h, and then filtered (cake washed with CH_3CN) to produce **7** (21.4 g, 96% yield) as an off-white crystalline solid. **7**: mp = 240-243 °C; ^{1}H NMR (600 MHz, 1:0.7 DMSO-d_6:$CDCl_3$): δ 7.84 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 5.22 (dd, J = 6.2, 1.3 Hz, 1H), 4.66 (d, J = 2.1 Hz, 1H), 4.52 (br s, 1H), 3.83 (s, 1H), 2.52 (td, J = 11.0, 5.9 Hz, 1H), 2.06 (dd, J = 17.2, 6.4 Hz, 1H), 1.96 (m, 1H), 1.73 (m, 1H), 1.72 (m, 1H), 1.65, (m, 1H), 1.64 (m, 1H), 1.63 (s, 1H), 1.50 (m, 1H), 1.49 (m, 1H), 1.46 (m, 1H), 1.43 (m, 1H), 1.42 (m, 2H), 1.40 (m, 1H), 1.39 (m, 1H), 1.37 (m, 1H), 1.35 (m, 1H), 1.33 (m, 1H), 1.28 (m, 1H), 1.24 (m, 1H), 1.18 (m, 1H), 1.05 (s, 1H), 1.03 (m, 1H), 1.03 (m, 1H), 0.94 (s, 1H), 0.93 (s, 1H), 0.88 (s, 1H), 0.87 (s, 1H). ^{13}C NMR (150 MHz, 1:0.7 DMSO-d_6:$CDCl_3$): δ 166.0, 149.7, 148.0, 145.5, 129.6, 127.9, 127.3, 123.5, 109.2, 59.2, 52.1, 51.5, 48.7, 47.9, 47.1, 41.6, 41.0, 40.0, 39.3, 37.1, 36.8, 35.6, 34.5, 32.9, 28.9, 28.9, 26.3, 24.6, 20.8, 20.6, 19.1, 18.9, 16.0, 15.3, 13.6. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{37}H_{54}NO_2$ 544.4149; Found 544.4133 (2.9 ppm error).

Diamine (10): To a 1-L reactor was added thiomorpholine **9** (21.1 g, 1.6 eq.), DIPEA (15.8 g, 1.65 eq.), and CH_2Cl_2 (180 mL, 4.5 vol). The resulting mixture was cooled to -10 °C and a CH_2Cl_2 (100 mL, 2.5 vol) solution of Ms_2O (21.8 g, 1.65 eq.) was added and the resulting mixture was aged at -10 °C for 10 min then **7** (40.0 g, 1.0 eq.) and DIPEA (16.3, g, 1.7 eq.) was added and the mixture was refluxed for 22-24h. After the reaction was determined complete based on HPLC analysis, the mixture was diluted with CH_2Cl_2 (240 mL, 6 vol) and aq. NaOH (1N, 320 mL, 8 vol) was added. The layers are split and the

organic stream was washed with aq. AcOH (10 wt%, 320 mL, 8 vol), then again with aq. NaOH (1N, 320 mL, 8 vol), and finally washed once with water (320 mL, 8.0 vol). The CH_2Cl_2 was exchanged for THF (12 vol) under reduced pressure. The resulting THF stream was heated to 35°C and water was added (4.4 g, 3.3 eq.) followed by the slow addition oxalic acid (7.0 g, 1.1 eq.) as a solution in THF (160 mL, 4 vol) over 4 h. Upon completion of the addition, the resulting slurry was cooled to ambient temperature, aged for 6 h, then filtered to yield oxalic acid salt **10** (48.8 g, 84% yield) as a white crystalline solid. **10:** mp = 214 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.88 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 5.24 (dd, J = 6.1, 1.6, 1H), 4.73 (br s, 1H), 4.62 (br s, 1H), 3.84 (s, 1H), 3.15/3.07 (m, 2H), 3.08 (m, 2H), 2.96 (m, 1H), 2.91 (m, 1H), 2.76 (m, 1H), 2.75 (m, 1H), 2.08 (m, 1H), 2.04 (m, 1H), 2.03 (m, 1H), 1.92 (m, 1H), 1.87 (m, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.68 (s, 1H), 1.64 (m, 1H), 1.58 (m, 1H), 1.54 (m, 1H), 1.50 (m, 1H), 1.47 (m, 1H), 1.46 (m, 1H), 1.45 (m, 1H), 1.43 (m, 1H), 1.41 (m, 1H), 1.41 (m, 1H), 1.39 (m, 1H), 1.27 (td, J = 13.1, 4.1, 1H), 1.21 (m, 1H), 1.19 (m, 1H), 1.10 (s, 1H), 1.06 (m, 1H), 1.02 (s, 1H), 1.01 (s, 1H), 0.96 (s, 1H), 0.89 (s, 1H), 0.89 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.1, 164.1 (oxalate), 148.9, 148.1, 145.7, 130.0, 128.2, 127.6, 123.6, 110.5, 68.4, 52.1, 52.0, 50.4, 50.0, 49.2, 48.5, 48.2, 45.3, 41.7, 41.0, 40.2, 39.0, 37.0, 36.7, 36.1, 35.7, 33.2, 31.9, 29.2, 28.1, 25.7, 24.6, 20.9, 20.8, 19.2, 18.8, 16.3, 15.8, 14.0. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{43}H_{65}N_2O_4S$ 705.4660; Found 705.4644 (2.2 ppm error).

BMS-955176 (1): To a 1-L jacketed reactor was charged diamine **10** (50.0 g, 62.9 mmol, 1 eq.), THF, (200 mL), and TBAOH (95 mL, 55 wt% solution in water, 3.1 eq.). The solution was stirred for 1 h at 20 °C. After completion of the reaction, HCl (48.2 mL, 6 mol/L in water, 4.6 eq.) was added followed by MeCN (200 mL). The solution was heated to 40 °C. Water (165 mL) was added to achieve a solvent ratio of 4:5:4 (THF:water:MeCN). The crystallization was seeded followed by a subsequent addition of water (350 mL) over 4 h. The final solvent ratio was 4:12:4 (THF:water:MeCN). After water addition was complete, the slurry was cooled to 20 °C, filtered, and washed with 3:1 water:MeCN (200 mL). The solids were then dried in a vacuum oven overnight at 30 °C to yield **1** as a white solid (44.8 g, 60.1 mmol, 91% yield). **1**: mp = 95 °C (decomposition); ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.86 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 5.24 (dd, J = 6.1, 1.2, 1H), 4.75 (br s, 1H), 4.64 (br s, 1H), 3.17/3.08 (m, 3H), 3.15 (m, 2H), 3.09 (m, 1H), 3.08 (m, 1H), 2.16 (m, 1H), 2.09 (dd, J = 17.1, 6.1, 1H), 2.08 (m, 1H), 1.92 (m, 1H), 1.91 (m, 1H), 1.88 (m, 1H), 1.70 (m, 1H), 1.69 (s, 1H), 1.68 (m, 1H), 1.68 (m, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 1.46 (m, 1H), 1.46 (m, 1H), 1.43 (m, 1H), 1.42 (m, 1H), 1.42 (m, 1H), 1.41 (m, 1H), 1.39 (m, 1H), 1.27 (m, 1H), 1.23 (m, 1H), 1.21 (m, 1H), 1.09 (m, 1H), 1.09 (s, 1H), 1.02 (s, 1H), 0.96 (s, 1H), 0.89 (s, 1H), 0.89 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 167.2, 148.7, 147.7, 145.9, 129.8, 128.7, 128.4, 123.5, 110.7, 70.3, 52.1, 49.9, 48.8, 48.5, 47.9, 44.9, 41.7, 41.0, 40.2, 39.1, 37.0, 36.3, 35.8, 33.2, 31.6, 29.2, 28.0, 26.3, 25.6, 24.6, 20.9, 20.8, 19.2, 18.9, 16.3, 15.9, 14.0. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{42}H_{63}N_2O_4S$ 691.4503; Found 691.4487 (2.4 ppm error).

Associated content:

The supporting information is available free of charge on the ACS Publications website at DOI: XXXXXXXXX.

Copies of the of ^{1}H and ^{13}C NMR spectra for all new compounds.

Author Information:

*E-mail: Adrian.Ortiz@BMS.com

Acknowledgements

We would also like to thank Dr's Martin D. Eastgate, David A. Kronenthal, and Robert Waltermire for their support of this work.

References:

1. Qian, K., Morris-Matschke, S.L., Lee, K.; *Medicinal Research Reviews*. **2009**, 29, 2, 369-393.
2. Qian, K., Kuo, R., Chen, C., Huang, L., Morris-Natschke, S. L., Lee, K.; *J. Med. Chem*. **2010**, 53, 3133-3141.
3. Regueiro-Ren, A., Liu, Z., Chen, Y., Sin, N., Sit, S., Swidorski, J.J., Chen, J., Venables, B.L., Juliang, Z.,Nowicka-Sans, B., Protack, T., Lin, Z., Terry, B., Samanta, H., Zhang, S., Li, Z., Beno, B.R., Huang, X.S., Rahematpura, S., Parker, D.D., Haskell, R., Jenkins, S., Santone, K.S., Cockett, M.I., Krystal, M., Meanwell, N.A., Hanumegowda, U., Dicker. I.B.; *ACS Med. Chem. Lett*. **2016**, 7, 568-572.
4. Jager S, Laszczyk M.N, Scheffler A.; *Molecules*. **2008**, 13: 3224-3235.
5. Dehelean, C.A., Şoica. C., Ledeţi, I., Aluaş, M., Zupko, I., Găluşcan, A., Pinzaru, S., Munteanu, M.; *Chemistry Central Journal*. **2012**, 6, 137.
6. For selected examples of betulin oxidation see: (a) "Method for Preparation of Betulinic acid": Tulisalo, J., Wickholm, N., Pirtimaa, M., Alakurtti, S., Kauhauluoma, J.Y.; WO2013038312 A1, **2013**; (b) Melnikova, N., Burlova, I., Kiseleva, T., Klabukova, I, Gulenova, M., Tanaseichuk, B.; *Molecules*, **2012**, 17, 11849-11863; (c) Pichette, A., Liu, H., Roy, C., Tnaguay, S., Lavoie, S., *Syn.Comm.*, **2004**, 34, 21, 3925-3937.
7. Steves, J.E., Stahl, S.S.; *J. Org. Chem*. **2015**, 80, 11184-11188.
8. Steves. J.E., Stahl, S.S.; *J. Am. Chem. Soc.* **2013**, 135, 15742-15745.
9. Ayers, S., Benkovics, T., Marshall, J., Tan, Y., Strotman, N.A., Kiau, S., *J. Nat. Prod*. **2016**, 79, 2758-2761.
10. Dalcanale, G., Montanari, F.; *J. Org. Chem*. **1986**, 51, 567-569.
11. Allan, K. M., Kobayashi, K., Rawal, V.H.; *J. Am. Chem. Soc.* **2012**, 134, 1392-1395.
12. Full crystallographic data for **8a** and **8c** have been deposited to the Cambridge Crystallographic Data Center (CCDC reference numbers: 1534529, 1534530). Copies of the data can be obtained free of charge via the internet at **http://www.ccdc.cam.ac.uk**.
13. Proposed structure of **8b** is supported both by ^{19}F NMR, see supporting info, and chemical conversion tests (**8c** + TFAA → **8b**).
14. Dube, P. Nathel, N.F.F., Vetelino, M., Couturier, M., Aboussafy, C.L., Pichette, S., Jorgensen, M.L., Hardink, M.; *Org. Lett*. **2009**, 11, 24, 5622-5625.
15. Hoshino, Y., Okuno, M., Kawamura, E., Honda, K., Inoue, S.; *Chem. Commun.* **2009**, 2281-2283.
16. Hoshino, Y., Shimbo, Y., Ohtsuka, N., Honda, K., *Tet. Lett*. **2015**, 710-712.
17. Ohtsuka, N., Okuno, M., Hoshino, Y., Honda, K., *Org. Biomol. Chem*. **2016**. *14,* 9046-9054.
18. Strotman, N.A., Ortiz, A., Savage, S., Wilbert, C., Ayers, S., and Kiau. S., *submitted manuscript*. DOI: XXXXXXX.
19. For a review of such transformations see: Leonard, J., Blacker, A.J., Marsden, S.P., Jones, M.F., Mulholland, K.R., Newton, R.; *Org. Process. Res. Dev*. **2015**, 19, 1400-1410.