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Development of a Scalable Synthetic Route to BMS-986251. Part 1: Synthesis of the Cyclohexane Dicarboxylate Fragment

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ABSTRACT: The cyclohexane dicarboxylate unit of BMS-986251 (**1**), a potent and efficacious RORγt inverse agonist, was synthesized starting from Hagemann's ester in seven chemical transformations with five isolated intermediates. The synthesis involved an enzymatic kinetic resolution, a two-step telescoped enol tosylation followed by carboxylation using a benign CO surrogate for the installation of the second carboxylate functionality, and a Crabtree catalyst-mediated diastereoselective olefin hydrogenation. This process was successfully demonstrated to produce 3.6 kg of compound **3**.

KEYWORDS: *enzymatic ester hydrolysis, carboxylation using a CO surrogate, Crabtree hydrogenation, nuclear hormone receptors, RORγt*

INTRODUCTION

BMS-986251 (**1**) was discovered and developed within Bristol-Myers Squibb as a potent small molecule RORγt inverse agonist.[1] In order to supply the active pharmaceutical ingredient (API) for preclinical and early clinical studies, we needed a rapid, safe, and robust synthetic approach that would allow for the large-scale production of the structurally complex target **1**. Retrosynthetically, **1** can be derived by coupling advanced intermediate **2** with an appropriately substituted enantiomerically pure cyclohexane dicarboxylate unit (Scheme 1). While the discovery approach to **1** involved the coupling of the methyl ester **4** with the tricyclic fragment **2**, we chose to employ the phenyl ester **3** (vide infra). This manuscript details the synthesis of the cyclohexane dicarboxylate unit **3**, while the synthesis of the tricyclic fragment **2** and its subsequent coupling with the dicarboxylate fragment to ultimately produce BMS-986251 (**1**) will be described in the next paper.

We envisioned that the absolute configuration at C1 and C2 of **3** could be established via an enzyme-mediated kinetic resolution of an ester derived from readily available Hagemann's ester **6**.[2] A carbonylation reaction on intermediate **5** would install the phenyl ester functionality at C4, and a directed diastereoselective hydrogenation would provide access to the desired configuration at this position.

The discovery approach to the dicarboxylate fragment **4**[3] commenced with the synthesis of *t*-butyl Hagemann's ester (±)-**10** in two steps from *t*-butyl acetoacetate **7** and methyl vinyl ketone **8** (Scheme 2). This racemic compound was separated by supercritical fluid chromatography (SFC), and the desired enantiomer **11** was hydrogenated over Pd/C to afford the *cis* keto-ester **12**. Treatment of ketone **12** with a base and $PhNTf_2$ provided a mixture of regioisomeric enol triflates **13**, which were subjected to a Pd-catalyzed carbonylation reaction using CO gas[4] to yield a regioisomeric mixture of diesters **14**. A diastereoselective reduction of this mixture using Crabtree's catalyst[5,6] followed by TFA-mediated chemoselective cleavage of the *t*-butyl ester furnished the desired methyl ester **4**. The cyclohexane dicarboxylate unit **4** prepared via this sequence was coupled with the tricyclic core **2** to provide API **1** after hydrolysis of the methyl ester.

This sequence to synthesize **4** was demonstrated successfully on a multigram scale. As the molecule progressed into development, significantly higher quantities of materials were required, which necessitated a refinement of this synthetic route. This work needed to be accomplished expediently to enable the supply of API for preclinical and clinical studies. All of the intermediates in the synthetic route depicted in Scheme 2 (except **4**) were oils and required chromatographic purification. In addition, the absence of a chromophore in this synthetic sequence posed analytical challenges. We envisioned that the use of a phenyl ester at C4 would alleviate these concerns by imparting crystallinity to several of the intermediates, facilitating the use of HPLC analysis due to the presence of a chromophore, and promoting faster hydrolysis under milder conditions (after coupling with **2**) compared to the methyl ester analog. Therefore, dicarboxylate **3** containing a phenyl ester moiety at C4 was chosen as our target. We

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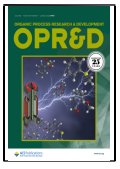

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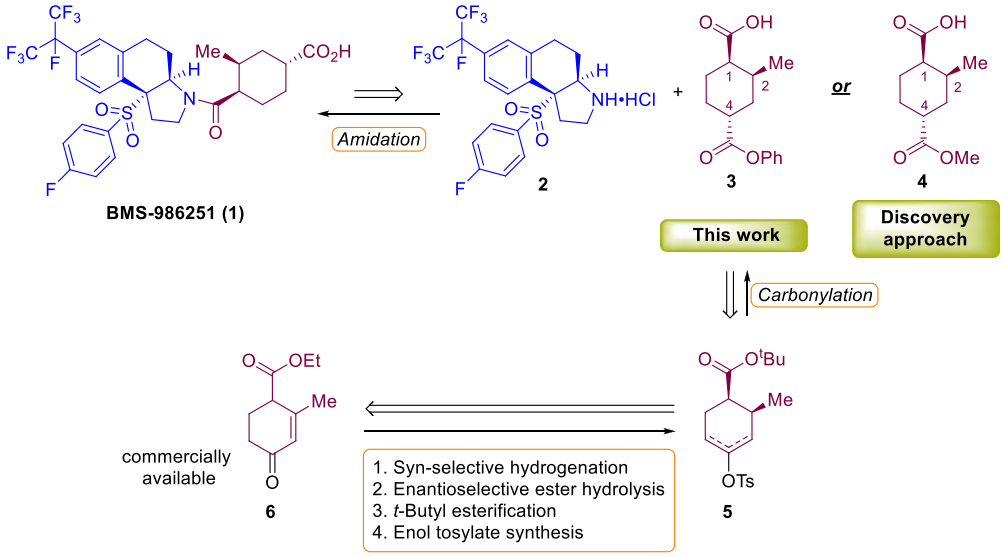
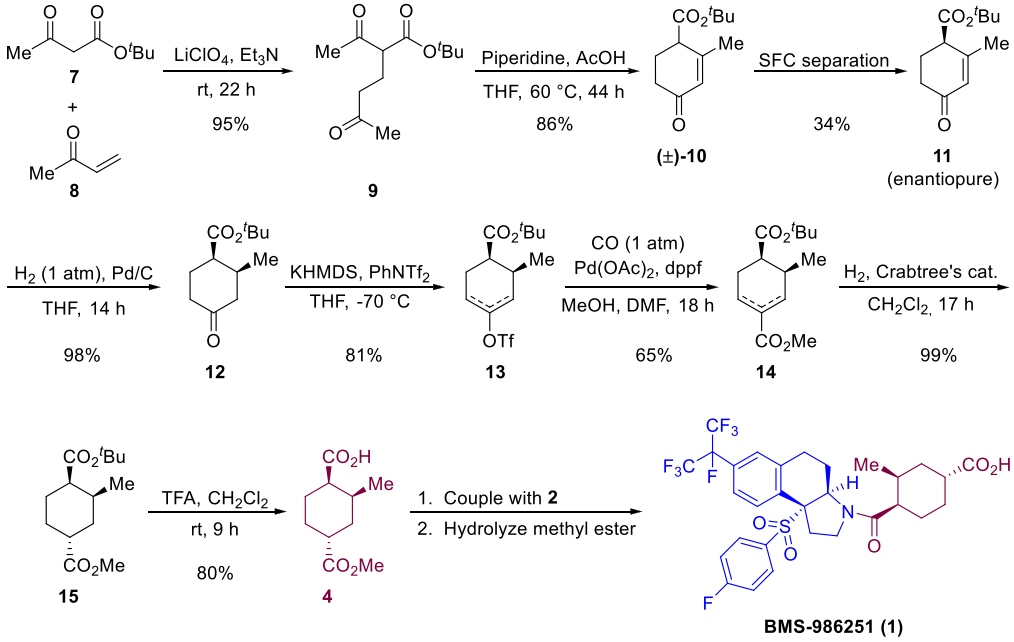
Scheme 1. Retrosynthetic Analysis for 1



Scheme 2. First-Generation Synthesis of 1 via Methyl Ester 4



sought to develop a process for the large-scale synthesis of **3** that would obviate the need for SFC separation as well as avoid the use of CO gas to install the carboxylate functionality at C4. Our efforts are described in this manuscript.

RESULTS AND DISCUSSION

We envisioned that an enzymatic approach could be leveraged to establish the absolute configuration at C1. Initial attempts at an enzymatic resolution by hydrolysis of the *t*-butyl cyclohexenone ester (±)-**10** and its cyclohexanone analog were not successful, thus prompting us to examine the corresponding ethyl esters. Commercially available cyclohexenone ester **6** was subjected to a transfer hydrogenation using Pd/C, formic acid (2.0 equiv), and *i*-Pr_2NEt (2.2 equiv)[7] in 2-methyltetrahydrofuran (2-MeTHF) at 25−35 °C to furnish *cis*-cyclohexanone ester (±)-**16** in an 86% yield (along with ∼2.5% *trans*-isomer (±)-**19**), as an oil. Our discovery colleagues had utilized pig liver esterase for this transformation;[1] however, its animal origin precluded its use in our synthesis. An array of readily available enzymes was screened in an attempt to selectively hydrolyze one of the enantiomers of **16**. Gratifyingly, several enzymes were effective for this kinetic resolution with esterase AR "Amano"[8] (10 wt %) in 0.1 M aqueous tris buffer (pH 8) providing the best result (desired acid enantiomer **17** in ∼92% ee at ∼40% conversion). After completion of the reaction, the enzyme was removed from the reaction mixture by filtration after a charcoal treatment, and the unreacted ester **18** was separated from the desired carboxylic acid **17** by extraction with 2-MeTHF at pH 8. Acidification of the aqueous layer followed by extraction with 2-MeTHF gave the required acid **17** in 92−94% ee. The enantiomeric purity was upgraded to 99% ee by recrystallization of the crude from ethyl acetate/*n*-heptane. This step was

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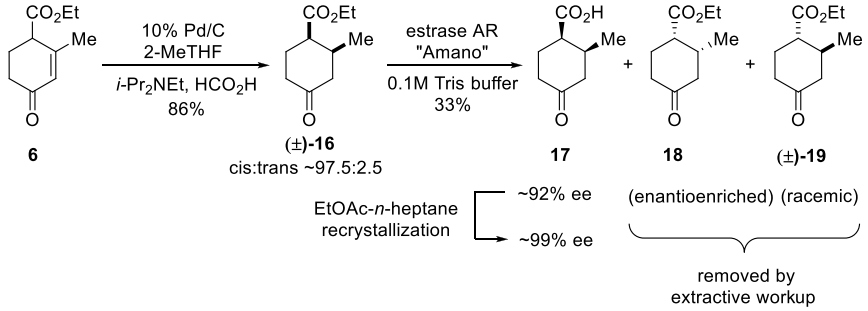
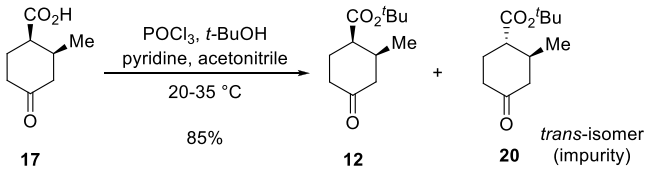
Scheme 3. Olefin Hydrogenation and Enzymatic Ester Hydrolysis



successfully demonstrated on multiple 25 kg batches in the pilot plant (Scheme 3).

It was necessary to mask the carboxylic acid in **17** as an ester in order to effect subsequent transformations. We chose to protect it as the *t*-butyl ester since that would impart hydrolytic stability to the molecule and provide the orthogonality needed for selective deprotection in downstream processing. Several conditions were attempted to effect the esterification; most of them either led to low conversions (e.g., $H_2SO_4/MgSO_4$/*t*-BuOH provided ~30% conversion) or led to epimerization of the carboxyl center (e.g., DMAP/Boc_2O/*t*-BuOH furnished a 2.8:1 ratio of **12**:**20** at 63% conversion). Eventually, enantiomerically enriched carboxylic acid **17** was converted to the corresponding *t*-butyl ester **12** in an 85% yield by treatment with $POCl_3$ (2.3 equiv), pyridine (12 equiv), and *t*-BuOH[9] in acetonitrile at 20−35 °C (Scheme 4). The *trans*-isomer impurity **20** was also formed in <0.5% by HPLC area due to partial epimerization and was carried through to the subsequent steps.

Scheme 4. *t*-Butyl Ester Synthesis



The addition of $POCl_3$ to a mixture of carboxylic acid **17**, pyridine, and *t*-BuOH in acetonitrile at 10 °C was exothermic with an adiabatic temperature rise of 68 °C and was found to be dosing-controlled. The addition was controlled such that the temperature of the reaction mixture did not exceed 25 °C. The mixture after product formation was thermally stable in the operating range and exhibited only a very minor self-heating event (1 °C/min) at 110 °C by ARSST. The reaction was quenched by the addition of water, which was also found to be only mildly exothermic with an adiabatic temperature rise of 8 °C. This transformation was successfully carried out on a 17 kg scale.

In the discovery approach, the carboxylate unit at C4 was introduced through conversion of ketone **12** to the corresponding mixture of enol triflates **13** followed by a Pd-catalyzed carboxylation with CO gas. From a scalability standpoint, this approach presented two major challenges: (1) the enol triflate preparation was capricious and led to several impurities, and (2) the use of CO gas on scale was not preferred. We hypothesized that the sequence could be carried out via enol tosylates **5** (which would be more stable than the corresponding enol triflates **13** and would also be amenable to monitoring by HPLC due to the presence of a chromophore). Further, carboxylation using a CO surrogate such as HCO_2Ph/Et_3N[10−12] would obviate the need to use a large excess of CO gas on scale (Scheme 5).

Enol tosylates **5** were initially synthesized via the addition of NaHMDS (2 M in THF, 1.4 equiv) to a solution of **12** in THF at below −50 °C to generate an isomeric mixture of the enolate intermediates. A solution of Ts_2O (1.75 equiv) in THF (10 vol) was added to the enolate, maintaining the temperature below −35 °C, and the mixture was allowed to warm to ambient temperature. This approach worked well in the laboratory, but the reaction provided inconsistent yields at a 1 kg scale. This problem was solved by simply modifying the addition sequence: addition of the enolate solution to a solution of Ts_2O in THF at below −5 °C (reverse addition) led to clean conversion to enol tosylates **5**. The reaction was quenched with water, the mixture was extracted with toluene, and the product-rich toluene layer was azeotropically dried and carried through to the carboxylation reaction.

To the solution of **5** in toluene, HCO_2Ph (2.5 equiv), Et_3N (2.5 equiv), $Pd(OAc)_2$ (0.03 equiv), and Xantphos (0.06 equiv) were added and heated at 85−95 °C for 20 h to provide phenyl esters **21** as a 1:1 mixture of inconsequential regioisomers after workup, treatment with SiliaMetS Thiol (in order to remove residual Pd that could interfere with the subsequent hydrogenation), and crystallization from aqueous methanol. It is important to note that CO gas is generated in situ during the reaction, and hence, the reactor outlet was

Scheme 5. Enol Tosylate Formation Followed by Carboxylation

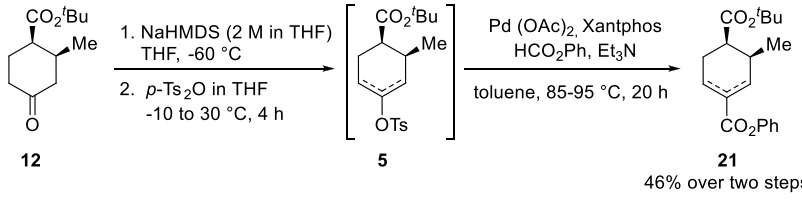


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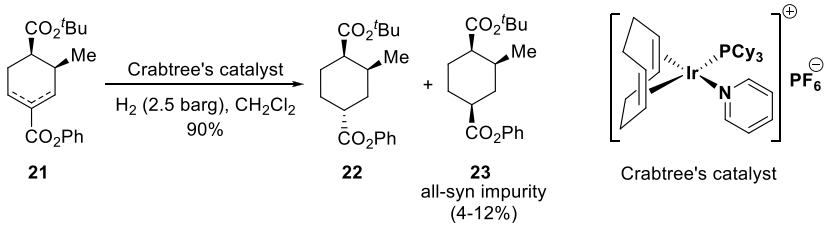
Table 1. Effect of Applied Hydrogen Pressure and Crabtree Catalyst Loading on the Diastereoselective Hydrogenation



			in process results (HPLC area %)		
entry	catalyst loading (mol %)	applied H_2 pressure (barg)	**21**	**22**	**23**
1	10	1	44.9	53.9	0.5
2	10	2.5	0.6	92.9	5.7
3	10	5	2.2	86.1	11.0
4	5	2.5	5.9	84.1	9.2
5	14	2.5	0.4	95.9	2.8

connected to an exhaust, and the processing area was equipped with CO sensors. This telescoped process was scaled up to 9 kg in the pilot plant to furnish the mixture of regioisomeric esters **21** as a crystalline solid in a 46% yield over two steps.

The discovery approach utilized a directed diastereoselective hydrogenation mediated by Crabtree's catalyst[5,6] (7 mol % Crabtree's catalyst in CH_2Cl_2 at 1 barg H_2 pressure) of a regioisomeric mixture of methyl esters **14** to establish the stereocenter at C4 (Scheme 2). In the process chemistry approach (this work), the reduction of phenyl esters **21** reliably went to completion on <10 g scales in a 200 mL hydrogenator under these conditions. However, as the reaction scale was increased beyond 100 g in a 10 L hydrogenator, the reaction took much longer (up to 72 h) and led to higher levels of unreacted **21** (up to 3% by HPLC area).[13] Simultaneous exploration of downstream processing conditions revealed that compound **21** was difficult to purge in subsequent steps, and consequently, we focused our efforts on identifying conditions that would reproducibly lead to <1.0 area % **21** remaining at the end of the reaction.

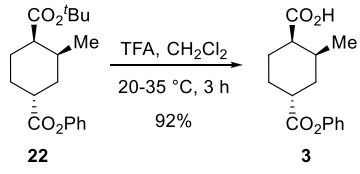
We examined the effect of hydrogen pressure (1, 2.5, and 5 barg) and catalyst loading (5, 10, and 14 mol %) on the rate and selectivity in the Crabtree hydrogenation, and our results are summarized in Table 1. These reactions were carried out in 10 volumes of CH_2Cl_2[14] wrt the phenyl esters **21**, in a 2 L hydrogenator with 30% occupancy. This occupancy was chosen considering the average batch sizes in the plant; higher occupancies (up to 60%) and lower concentrations (20 volumes of CH_2Cl_2) in laboratory-scale experiments exhibited similar reaction profiles. In general, the reactions were clean and produced only the desired compound **22** and the all-syn diastereomer **23**. In the first three reactions (entries 1−3, Table 1), the catalyst loading was held constant at 10 mol %, while the hydrogen pressure was varied. At 1 barg, the reaction remained incomplete after 7 h (~45 area % starting material **21**, entry 1). As the pressure was increased to 2.5 barg, the reaction proceeded to completion (0.55 area % **21** remaining after 7 h, entry 2). However, up to 5.7 area % of the all-syn isomer **23** was also observed under these conditions. Interestingly, increasing the pressure to 5 barg not only led to a slightly lower conversion (2.2 area % **21** remaining, entry 3) but also furnished ~11 area % of the all-syn isomer **23**. While up to 10 area % **23** at this stage could be effectively purged in downstream processing, its formation was detrimental to the overall yield.

The lower selectivity (higher all-syn formation) observed at higher pressures suggested a background reaction perhaps due to catalyst decomposition. We postulated that this selectivity issue could be addressed by increasing the catalyst loading. Accordingly, the next two reactions depicted in Table 1 were carried out under 2.5 barg pressure with varying catalyst loadings. At a 5 mol % loading, both the starting material **21** and the all-syn isomer **23** were observed above their acceptance criteria at 5.9 and 9.2 area %, respectively (entry 4). At a 14 mol % loading, the hydrogenation proceeded smoothly to >99% conversion (~0.4 area % **21** remaining), with excellent selectivity (2.8 area % **23**, entry 5); therefore, these conditions were chosen for the scale-up runs.

The gas−liquid mass transfer coefficient (kLa) for the 2 L lab-scale hydrogenators was measured to be <0.01 s^{-1}. The kLa for the pilot plant hydrogenator, as estimated using Dynochem correlations, was >0.3 s^{-1}; the higher kLa indicated better mass transfer on scale. The hydrogenation was successfully carried out in multiple batches up to an 8 kg scale in a 300 L hydrogenator (15 mol % catalyst, 20 volumes of CH_2Cl_2 at 2.5−3 barg H_2 pressure), and the product was isolated by treatment with SiliaMetS Thiol (to reduce the Ir content from ~11,000 to <400 ppm in isolated **22**) and crystallization from aqueous methanol. Under these conditions, phenyl esters **21** and the all-syn diastereomer **23** were controlled to <0.5 and <5 area %, respectively. The next step (hydrolysis of the *t*-butyl ester, vide infra) effectively purged the all-syn diastereomer **23** completely and also reduced the residual Ir content to <10 ppm.

Selective hydrolysis of the *t*-butyl ester in **22** was accomplished by treatment with trifluoroacetic acid[15,16] in CH_2Cl_2 (Scheme 6). Compound **3** was isolated in a 92% yield (>99.9% purity; >99.8% ee) after recrystallization from CH_2Cl_2/*n*-heptane; the all-syn diastereomer **23** carried from the Crabtree hydrogenation was completely purged during this step. The overall synthesis of **3** is depicted in Scheme 7.

Scheme 6. *t*-Butyl Ester Hydrolysis



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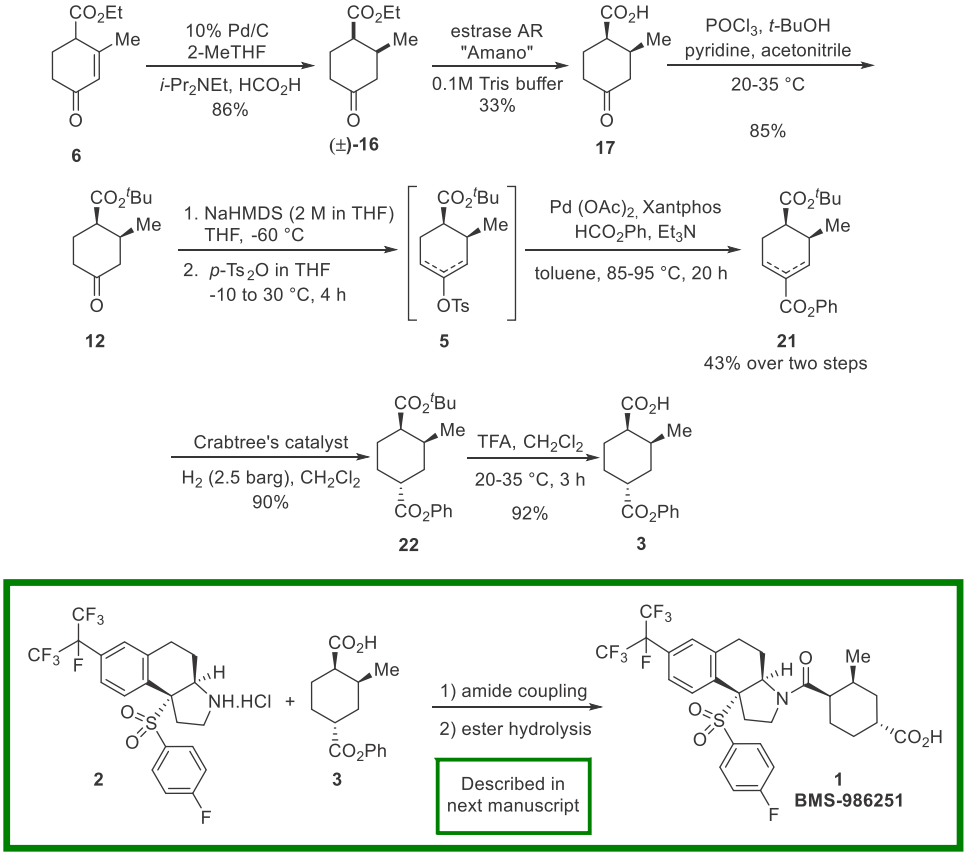
Scheme 7. Synthesis of Compound 3



SUMMARY

We rapidly developed a scalable approach to the stereochemically complex cyclohexyl fragment of BMS-986251. This compound was synthesized in seven steps from ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate **6**. The stereocenters in this molecule were established as follows: a transfer hydrogenation to set the relative stereochemistry at C1 and C2, an enzyme-mediated kinetic resolution to generate the absolute stereochemistry at C1 and C2, and a directed diastereoselective hydrogenation to install the stereocenter at C4. The key carboxylation reaction was effected using HCO_2Ph-Et_3N as a CO surrogate, thereby circumventing the need to use excess CO gas under pressure. The choice of the phenyl ester was significant: it provided a chromophore that rendered it amenable to HPLC analysis, which allowed for excellent purity control and impurity tracking, imparted crystallinity to several downstream intermediates, and most importantly, could be cleaved under mild conditions after coupling with the tricyclic core **2** (this is described in the next manuscript). The process described in this manuscript was successfully scaled up to produce 3.6 kg of dicarboxylate **3**.

EXPERIMENTAL SECTION

General Information. All reactions were performed under a nitrogen atmosphere. Reaction conversion was measured by GC and/or HPLC. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent ($CDCl_3$ = δ 7.29). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.01). Melting points were obtained using a Buchi B-545 instrument. HRMS was recorded on a Q Exactive Plus Orbitrap Thermo mass spectrometer.

Ethyl (*cis*)-2-Methyl-4-oxocyclohexane-1-carboxylate (±)-16. To a 600 L Hastelloy hydrogenation reactor, 2-MeTHF (330 L), ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate **6** (33.0 kg, 181.1 mol), *N*,*N*-diisopropylethylamine (51.5 kg, 398.5 mol, and 2.2 equiv), and 10% Pd/C 50% wet (6.6 kg, 20% wt/wt) were charged sequentially under an N_2 atmosphere. The reaction mixture was cooled to 10−15 °C, and formic acid (17.0 kg, 369.3 mol, and 2.0 equiv) was added to the reactor under a N_2 atmosphere. The reaction mass was warmed to 25−35 °C and stirred for 6 h. After completion of the reaction, the catalyst was removed by filtration through a bed of Celite. The reactor was rinsed with 2-MeTHF (230 L), and the rinse was filtered through the Celite bed and combined with the product-containing filtrate in a separate 600 L Hastelloy reactor. The solution was washed sequentially with 1.5 N aqueous hydrochloric acid (330 L), water (330 L), 10% aqueous $NaHCO_3$ (2 × 165 L), and 10% aqueous NaCl (2 × 165 L). The organic layer was concentrated in vacuo (at less than 55 °C) until the 2-MeTHF content was less than 5% by GC (actual 2-MeTHF content, 1.58%) to afford 30.4 kg of ethyl (*cis*)-2-methyl-4-oxocyclohexane-1-carboxylate (±)-**16** as a colorless liquid (86% assay-corrected yield, 97.3% purity by GC area %, 2.65% *trans*-isomer (±)-**19**, and 94.1% assay).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09 (m, 2H), 2.77 (dt, J = 8.4 Hz, 4.0 Hz, 1H), 2.48−2.39 (m, 2H), 2.35 (m, 2H), 2.27−2.18 (m, 1H), 2.11−1.90 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H).

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.4, 173.2, 60.2, 46.7, 43.9, 38.6, 33.6, 24.5, 16.3, 14.0.

HRMS (ESI) (m/z): $[M + H]^+$ calcd for $C_{10}H_{17}O_3$, 185.1172; found, 185.1170.

(1*R*,2*S*)-2-Methyl-4-oxocyclohexane-1-carboxylic Acid 17. Purified water (270 L) and tris(hydroxymethyl)-aminomethane (3.3 kg, 27.0 mol) were added to a 1500 L glass-lined reactor at 20−30 °C and stirred for 5 min. The pH of the mass was adjusted to less than 8.1 by adding hydrochloric acid (11 M, 1.5 L). Forty kilograms of this solution (tris buffer) was unloaded and kept aside, and the remaining solution was heated to 32−37 °C in the reactor. Ethyl 2-methyl-4-oxocyclohexane-1-carboxylate (±)-**16** (13.5 kg, 73.3 mol) was charged to the reactor followed by a solution of esterase AR "Amano" (1.35 kg) in 30.5 L of tris buffer, and the resulting mixture was stirred at 32−37 °C for 10 h. During this time, the pH of the reaction was maintained between 7.5 and 8.5 by the addition of 5 N aqueous sodium hydroxide every 30 min. At the end of the 10 h stirring period, the reaction mass was cooled to 25−30 °C, and 3.4 kg of activated charcoal was charged. The slurry was stirred for 1 h, filtered through a Celite bed, and washed with 68 L of 50% aqueous 2-MeTHF. The combined filtrate was extracted with 2-MeTHF (2 × 135 L) to remove the unreacted starting material. The aqueous layer was acidified with conc. HCl (4.5 L) to pH 2−3 and extracted with 2-MeTHF (4 × 68 L). The combined organic layer was filtered through a Celite bed, and the bed washed with 68 L of 2-MeTHF. The filtrate was washed with saturated brine solution (2 × 34 L) and concentrated in vacuo to a final volume of 13 L. *n*-Heptane (34 L) was added, and the reaction mass was concentrated in vacuo to a final volume of 13 L. *n*-Heptane (34 L) was charged to the concentrated mass and stirred at 20−35 °C for 1 h, and resulting slurry was filtered to give 4.6 kg of crude (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylic acid **17** as a white crystalline solid.

This solid was added to a Hastelloy reactor containing ethyl acetate (10 L), and the solution was maintained at 45−55 °C for 30 min. *n*-Heptane (50 L) was slowly added into the mass at 45−55 °C, and the slurry was cooled to 20−30 °C and allowed to granulate for 3 h. The resulting solid was filtered, washed with 67 L of *n*-heptane, and deliquored for 4 h to give 4.2 kg of (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylic acid **17** as a white crystalline solid (33% assay-corrected yield, 99.68% purity by chiral column GC, and 90.80% assay).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.10 (br s, 1H), 2.92 (m, 1H), 2.62−2.40 (m, 4H), 2.39−2.26 (m, 1H), 2.24−2.03 (m, 2H), 1.02 (d, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.7, 179.2, 46.8, 43.9, 38.6, 33.5, 24.3, 16.5.

HRMS (ESI) (m/z): $[M-H]^+$ calcd for $C_8H_{11}O_3$, 155.0714; found, 155.0704.

***tert*-Butyl (1*R*,2*S*)-2-Methyl-4-oxocyclohexane-1-carboxylate 12.** To a 1000 L glass-lined reactor, dry acetonitrile (180 L), (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylic acid **17** (17.2 kg, 94.5% assay, and 110.0 mol), pyridine (89.5 kg, 1131 mol, and 10.3 equiv), and dry *tert*-butyl alcohol (73.4 kg, 990 mol, and 9.0 equiv) were charged sequentially under a nitrogen atmosphere. The reaction mass was cooled to 0−10 °C, and $POCl_3$ (23.9 kg, 156.1 mol, and 1.42 equiv) was added maintaining the temperature below 25 °C. The reaction mixture was stirred at 20−35 °C, and the progress of the reaction was monitored by GC. Pyridine and $POCl_3$ were added portion-wise in 2 h intervals as follows: 32.8 kg of pyridine (415 mol, 3.8 equiv) and 8.6 kg of $POCl_3$ (56 mol, 0.5 equiv); 18.6 kg of pyridine (235 mol, 2.1 equiv) and 5.0 kg of $POCl_3$ (33 mol, 0.3 equiv); 14.9 kg of pyridine (188 mol, 1.7 equiv) and 4.0 kg of $POCl_3$ (26 mol, 0.24 equiv). After completion of the reaction, the mixture was cooled to <15 °C, and 180 L of purified water was added maintaining the temperature below 25 °C. The mixture was extracted with MTBE (3 × 86 L), and the combined organic layer was washed with 1 N aqueous HCl (3 × 86 L), 5% aqueous citric acid (2 × 690 L), 10% aqueous sodium bicarbonate (2 × 86 L), purified water (2 × 86 L), and saturated aqueous NaCl (86 L). The organic layer was concentrated in vacuo until the MTBE content was less than 5% by GC to afford 18.7 kg of *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate **12** (84.5% yield, 98.4% purity by chiral column GC) as a viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (dt, J = 8.8 Hz, 4.4 Hz, 1H), 2.55−2.39 (m, 4H), 2.30 (ddd, J = 6.4 Hz, 9.2 Hz, 14.8 Hz, 1H), 2.16−1.96 (m, 2H), 1.48 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 172.7, 80.6, 47.0, 44.9, 38.8, 33.9, 28.0, 24.6, 16.3.

HRMS (ESI) (m/z): $[M-H]^+$ calcd for $C_{12}H_{19}O_3$, 211.1340; found, 211.1336.

Mixture of 4-(*tert*-Butyl) 1-Phenyl (4*R*,5*S*)-5-Methylcyclohex-1-ene-1,4-dicarboxylate and 4-(*tert*-Butyl) 1-Phenyl (3*S*,4*R*)-3-Methylcyclohex-1-ene-1,4-dicarboxylate 21. *Tosylation.* To a 600 L Hastelloy reactor, THF (66 L, water content < 0.05%) and *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate **12** (6.0 kg, 28.3 mol) were charged and stirred at 20−30 °C. After 5 min, the solution was cooled to −60 °C, and a 2 M solution of NaHMDS in THF (22.2 kg, 48.3 mol, and 1.7 equiv) was added slowly while maintaining the temperature below −45 °C. At the end of the addition, the mixture was cooled to −60 °C and transferred slowly to a precooled (−10 to −5 °C) solution of *p*-toluenesulfonic anhydride (16.1 kg, 49.5 mol, and 1.75 equiv) in THF (60 L, water content < 0.05%) in a separate 600 L Hastelloy reactor while maintaining the temperature below 5 °C. The resulting thick slurry was warmed to 20−30 °C over 2 h and was stirred for an additional 2 h. The reaction was quenched by the addition of purified water (36 L) and extracted twice with toluene (60 and 36 L). The combined organic layer was washed with aqueous NaCl solution (4 × 30 L) and concentrated in vacuo to a final volume of 20 L. Toluene (60 L) was added, and the mixture was concentrated in vacuo to 20 L. This operation was repeated two more times to provide a solution of tosylates **5** in toluene (<0.5% v/v THF; <1.0% water).

Carboxylation. The solution of tosylates **5** in toluene in a 600 L Hastelloy reactor was subjected to five vacuum/N_2 purge cycles to remove headspace oxygen. Phenyl formate (8.7 kg, 71.2 mol, and 2.5 equiv wrt ketone **12**) and triethylamine (7.2 kg, 71.2 mol, and 2.5 equiv) were charged to the vessel, and the resulting solution was sparged with nitrogen via a dip tube for 10 min. $Pd(OAc)_2$ (192.0 g, 0.8 mol, and 0.03 equiv) was added followed by Xantphos (1.0 kg, 1.7 mol, and 0.06 equiv) and then sparged with nitrogen via a dip tube for 20 min. The reaction mixture was maintained at 85−95 °C for 20 h (Caution: CO gas is evolved in the reaction. The reactor outlet was connected to an exhaust, and the processing area was equipped with CO sensors). The reaction mixture was

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cooled to ambient temperature, and a kicker charge of phenyl formate (1.3 kg, 11.0 mol), triethylamine (1.1 kg, 11.0 mol), $Pd(OAc)_2$ (29.7 g, 0.13 mol), and Xantphos (154.5 g, 0.26 mol) was added. The reaction mixture was heated at 85−95 °C for an additional 14 h, cooled to 20−30 °C, and washed with purified water (31 L), 0.1 N aqueous HCl, (33 L), 10% aqueous *N*-acetylcysteine (33 L), 10% aqueous LiOH twice (23 and 13 L),[17] and purified water (3 × 30 L). The organic layer was stirred with 3 kg of silica gel (230−400 mesh) for 1 h at 20−30 °C and filtered through a Nutsche filter. The filter cake was washed with toluene (24 L), and the combined filtrate was concentrated in vacuo to 19 L under reduced pressure, diluted with *n*-heptane (72 L) and filtered through Celite to remove fine particulate residues, and concentrated in vacuo to 10 L. *n*-Heptane (30 L) and ethyl acetate (30 L) were added followed by SiliaMetS Thiol (1.5 kg) and activated charcoal (1.5 kg), and the resulting slurry was stirred for 2 h and filtered through Celite. The filtrate was concentrated in vacuo and swapped with methanol (3 × 50 L) to the final volume of 30 L (<0.5% v/v each of toluene, *n*-heptane, and ethyl acetate by Raman analysis). Purified water (11 L) was added to this solution over 20 min, and the resulting slurry was allowed to granulate at 0−5 °C for 2 h and filtered. The cake was washed with water (16 L), and the solid was dried at 55 °C under vacuum for 16 h to give 4.5 kg of a mixture of 4-(*tert*-butyl) 1-phenyl (4*R*,5*S*)-5-methylcyclohex-1-ene-1,4-dicarboxylate and 4-(*tert*-butyl) 1-phenyl (3*S*,4*R*)-3-methylcyclohex-1-ene-1,4-dicarboxylate (phenyl esters **21**, 46.2% yield from **12**, 93.41% purity by HPLC area) as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.8 Hz, 2H), 7.20 (m, 1.5H), 7.11 (m, 2.5H), 2.83 (m, 0.5H), 2.65−2.20 (m, 4.5H), 1.95 (m, 0.5H), 1.75 (m, 0.5H), 1.47 (s, 9H), 1.05 (d, J = 7.2 Hz, 1.5H), 0.96 (d, J = 6.9 Hz, 1.5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 173.2, 165.7, 165.6, 151.0, 145.1, 139.3, 129.4, 128.8, 128.1, 125.6, 121.7, 80.5, 80.4, 43.5, 42.6, 32.0, 31.2, 28.7, 28.1, 25.0, 24.1, 19.4, 15.4, 15.3.

HRMS (ESI) (m/z): $[M + H]^+$ calcd for $C_{19}H_{25}O_4$, 317.1747; found, 317.1744.

1-(*tert*-Butyl) 4-Phenyl (1*R*,2*S*,4*R*)-2-Methylcyclohexane-1,4-dicarboxylate 22. To a 300 L stainless steel hydrogenation reactor equipped with an induction stirrer, dichloromethane (162 L), a mixture of 4-(*tert*-butyl) 1-phenyl (4*R*,5*S*)-5-methylcyclohex-1-ene-1,4-dicarboxylate and 4-(*tert*-butyl) 1-phenyl (3*S*,4*R*)-3-methylcyclohex-1-ene-1,4-dicarboxylate (phenyl esters **21**, 7.9 kg, and 25.1 mol assay-corrected charge), and Crabtree's catalyst (3.2 kg, 4.0 mol) were charged sequentially. The reactor was purged with nitrogen (applied 1.0 barg pressure and evacuated for not less than 5 min; two cycles) and then hydrogen (applied 1.0 barg pressure and evacuated for not less than 5 min; two cycles). The reactor was then charged with hydrogen (2−3 barg pressure) and stirred for 15 h at 25−35 °C. After completion of the reaction, the mixture was transferred to a 600 L reactor, and 159 L of *n*-heptane was added. The solution was concentrated in vacuo to ∼80 L. *n*-Heptane (159 L) was charged, and the mixture was stirred for 1 h at 20−35 °C. This solution was filtered through a Celite bed to remove the precipitated catalyst-related residues. The reactor was rinsed with 79 L of *n*-heptane, and the rinse was passed through the Celite bed. The combined filtrate was transferred to a clean reactor. Dichloromethane (16 L) and SiliaMetS Thiol (8.1 kg) were added, and the mixture was stirred for 2 h. The slurry was filtered through Celite, and the cake was washed with a mixture of dichloromethane (8 L) and *n*-heptane (79 L). The combined filtrate was concentrated in vacuo to 24 L and swapped with methanol twice (79 and 64 L) to a final volume of 24 L. An additional 64 L of methanol was added, the contents were cooled to 5−15 °C, 79 L of purified water was added, and the resulting slurry was allowed to age for 2 h. The precipitated solids were filtered through a Nutsche filter, and the cake was rinsed with 79 L of water. The material was dried under vacuum at 50−55 °C for 18 h to give 7.8 kg of 1-(*tert*-butyl) 4-phenyl (1*R*,2*S*,4*R*)-2-methylcyclohexane-1,4-dicarboxylate **22** (90.0% yield, 93.3% purity by HPLC area, 5.94% all-syn isomer **23**, and 92.2% assay) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 0.2 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 2.74 (tt, J = 3.6 Hz, 12.0 Hz, 1H), 2.52−2.38 (m, 2H), 2.16 (m, 1H), 2.00 (m, 1H), 1.88−1.78 (m, 2H), 1.70 (dq, J = 3.6 Hz, 12.0 Hz, 1H), 1.62−1.48 (m, 1H), 1.45 (s, 9H), 0.97 (d, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 173.9, 150.8, 129.4, 125.7, 121.5, 80.1, 46.1, 37.4, 34.9, 29.8, 28.1, 27.8, 21.3, 13.9.

HRMS (ESI) (m/z): $[M + H]^+$ calcd for $C_{19}H_{27}O_4$, 319.1904; found, 319.1904.

(1*R*,2*S*,4*R*)-2-Methyl-4-(phenoxycarbonyl) Cyclohexane-1-carboxylic Acid 3. Dichloromethane (17 L), 1-(*tert*-butyl) 4-phenyl (1*R*,2*S*,4*R*)-2-methylcyclohexane-1,4-dicarboxylate **22** (3.2 kg, 10.0 mol corrected for assay) and trifluoroacetic acid (6.74 L) were charged into a 60 L glass-lined reactor, and the mixture was stirred at 20−35 °C for 3 h. Upon reaction completion the solution was concentrated in vacuo to 9 L. *n*-Heptane (30 L) was added, and the solution was concentrated to 9 L. This operation was repeated once more. Finally *n*-heptane (30 L) was added to the residue, and the resulting slurry was allowed to age at 20−35 °C for 1 h. The solids were filtered, washed with *n*-heptane (19 L) and deliquored for 6 h to afford 2.7 kg of crude **3**.

Crude **3** was dissolved in dichloromethane (4 L) in a 60 L glass-lined reactor. *n*-Heptane (26 L) was added to the reactor and the slurry was allowed to age at 20−35 °C for 1 h. The resulting solids were isolated by filtration through a Nutsche filter, and dried under vacuum at 50−55 °C for 18 h to afford 2.4 kg of (1*R*,2*S*,4*R*)-2-methyl-4-(phenoxycarbonyl) cyclohexane-1-carboxylic acid **3** (91.6% yield, 99.98% purity by HPLC area, 99.80% ee by chiral column HPLC, and 99.8% assay) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.66 (br s, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 2.81 (t, J = 11.6 Hz, 1H), 2.63 (m, 2H), 2.22 (d, J = 11.2 Hz, 1H), 2.09 (d, J = 13.6 Hz, 1H), 2.03−1.72 (m, 3H), 1.62 (q, J = 13.6 Hz, 1H), 1.07 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.9, 174.3, 150.7, 129.3, 125.7, 121.4, 45.2, 37.2, 34.6, 29.5, 27.4, 21.1, 14.0.

HRMS (ESI) (m/z): $[M-H]^+$ calcd for $C_{15}H_{17}O_4$, 261.1132; found, 261.1133.

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Notes

The authors declare no competing financial interest.

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