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Development of HIV-Integrase Inhibitor S-1360: Selection of the Protecting Group on the 1,2,4-Triazole Ring

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Abstract:

HIV-integrase inhibitor S-1360 was synthesized by Claisen-type reaction of 5-(4-fluorobenzyl)-2-furyl methyl ketone with N-protected 1*H*-1,2,4-triazole-3-carboxylate. The protecting group on the triazole ring is essential for the reaction to proceed. Tetrahydropyranyl and 1-methoxy-1-methylethyl groups were examined for manufacturing S-1360 on a large scale. High throughput and a convenient procedure were realized by using the 1-methoxy-1-methylethyl group.

Introduction

The human immunodeficiency virus (HIV) has reverse transcriptase, protease and integrase as enzymes for replication.[1] Inhibitors of the reverse transcriptase and the protease have already been used treat HIV infection. The combinational use of these inhibitors has greatly diminished both mortality and morbidity of HIV-infected patients. However, when complex combination therapy is continued, these inhibitors induce considerable toxicity, and their effectiveness is undermined by the emergence of drug-resistant strains of HIV. Consequently, there is a need for new inhibitors that can resolve these issues.[2] The latest inhibitor of integrase has been considered an attractive therapeutic target, because HIV cannot replicate without integrating with a host chromosome.[3] An inhibitor of integrase, compound S-1360 (**7**), was found by our colleagues.[4] To develop **7**, we needed a low-cost and reliable synthetic method by which **7** could be prepared on a large scale. Here we report the development of a manufacturing method of this integrase inhibitor with the focus on selection of the protecting groups of the triazole ring.[5]

Results and Discussion

In the absence of a protecting group on the triazole ring, the Claisen-type reaction of 5-(4-fluorobenzyl)-2-furyl methyl ketone (**3**)[6] and ethyl 1*H*-1,2,4-triazole-3-carboxylate (**4**)[7] did not proceed. At first, the trityl group was used to protect the 1,2,4-triazole, and a few kilograms of **7** were synthesized by the following route for non-clinical use (Scheme 1). Tritylation of triazole **4** by trityl chloride proceeded selectively[8] (isomers ratio = 10:1) to give ethyl 1-trityl-1*H*-1,2,4-triazole-3-carboxylate (**5a**), that is a crystalline substance,[9] making it easy to purify by crystallization to remove the isomer. However, trityl chloride is expensive for commercial manufacturing and lowers the atom economy, producing much waste. Furthermore deprotection of **6a** is accompanied by trityl fragments that are not easily separated from **7** by the crystallization. In order to remove the trityl moiety, **7** was dissolved in alkali aqueous solution, and then the solution was washed with organic solvent to remove it. Due to the oxidation at the benzylic position of **7** in the alkali solution, considerable amounts of oxidized by-products were contaminated. Thus, we searched for other protecting groups.

First, the tetrahydropyranyl (THP) group was examined instead of the trityl group. According to the previous patent, methyl 1-tetrahydropyranyltriazole-3-carboxylate was selectively obtained by the use of excess amount of 3,4-dihydropyran (3,4-DHP).[10] We have found when 1.1 molar equiv of 3,4-DHP reacted with the triazole **4**, a mixture of ethyl 1-tetrahydropyranyltriazole-3-carboxylate (**5b**) and ethyl 1-tetrahydropyranyltriazole-5-carboxylate (**8**)[11] was initially obtained,[12] and then the unstable isomer **8** isomerized to the stable isomer **5b** (Scheme 2).[13] Namely, in the presence of acid catalyst, the triazole **4** smoothly reacted with 3,4-DHP in THF to afford **5b**. Without purification, the Claisen-type condenzation of **5b**

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(8) The isomers ratio was estimated by ^{1}H NMR spectra. **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (3H, t, $J = 7.2$ Hz), 4.45 (2H, q, $J = 7.2$ Hz), 7.09–7.17 (6H, m), 7.30–7.39 (9H, m), 8.01 (1H, s). Ethyl 1-trityl-1*H*-1,2,4-triazole-5-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (3H, t, $J = 7.2$ Hz), 3.76(2H, q, $J = 7.2$ Hz), 7.10–7.17 (6H, m), 7.28–7.36 (9H, m), 8.00 (1H, s).

(9) The structure of **5a** was determined by the X-ray structural analysis. The detail data are included in Supporting Information.

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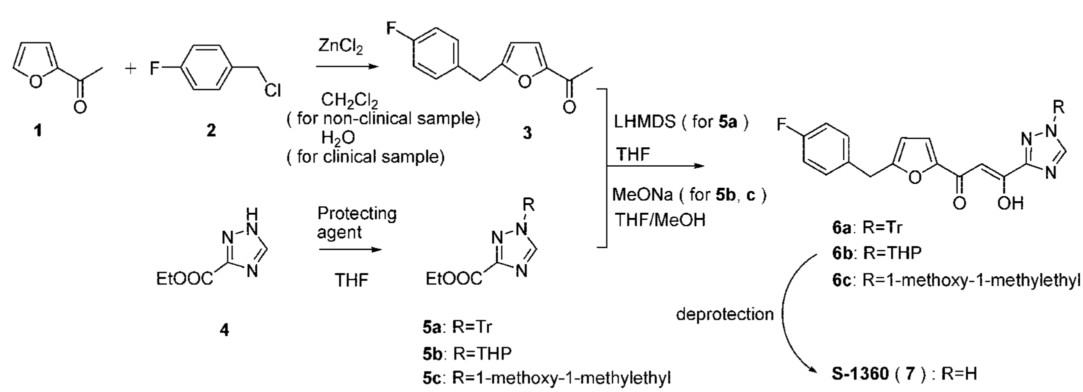
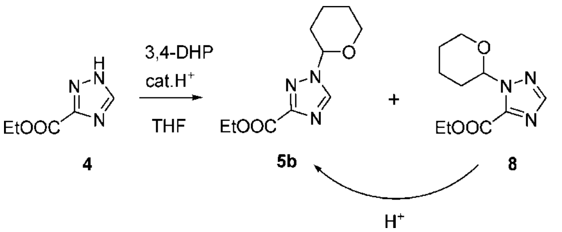
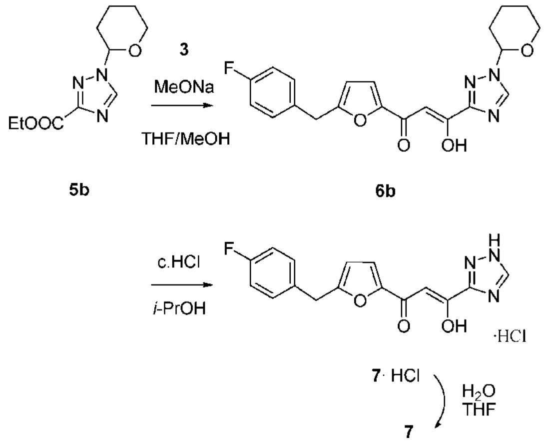
Scheme 1. **Synthesis of S-1360 for large scale**



Scheme 2. **Protection of the triazole**



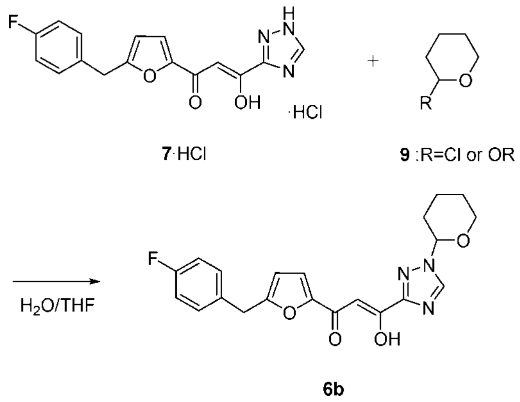
Scheme 3. **Synthesis of S-1360 using the THP protecting group**



gave N-protected S-1360 (**6b**),[14] which was isolated by direct crystallization from the Claisen reaction mixture (Scheme 1).

Deprotection of **6b** was examined under various conditions that involved catalytic acetic acid, pyridinium *p*-toluenesulfonate, hydrochloric acid or sulfuric acid in alcohol, but the deprotection was not completed, and the obtained **7** was accompanied by **6b** (ca. 0.7–2%). Although under the high dilution condition deprotection of **6b** proceeded completely, this procedure could not be adopted for commercial production where high throughput is required for cost reduction. We found that the deprotection of **6b** by using excess concentrated HCl in MeOH or isopropyl alcohol gave crystals of hydrochloride salt of S-1360 (**7**·HCl) without the contamination of **6b**, which remained in the mother liquid. The obtained **7**·HCl is easily converted to the free base **7** by contact with water, which acts as a base (Scheme 3). Namely, **7**·HCl was dissolved in THF/H_2O at 60 °C, and the solution was filtered with a membrane filter to remove insoluble particulates. Additional H_2O was added to the filtrate, and then the mixture was cooled to under 10°C to obtain crystals of **7**; ca. 40 kg of **7** was synthesized by the THP protecting method for first-clinical use.

Scheme 4. **Reproduction of 6b**



Although the THP group was chosen for first manufacturing of a clinical sample, this protecting group involved significant issues. THP fragments (**9**) were generated by the deprotection and remained in **7**·HCl obtained after centrifugal separation. In the final conversion to the free base, the obtained free S-1360 reacted with the fragments **9** to reproduce **6b** as a contaminant (Scheme 4).

We searched for another protecting group that could be completely deprotected. The final successful manufacturing route of S-1360 utilized 2-methoxypropene for the protection as shown in Scheme 1. Regioselective protection of **4** using 2-methoxypropene proceeded smoothly to give ethyl 1-(1-

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(12) (a) The isomers were estimated by triazole ring proton of ^1H NMR spectra. **5b**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (3H, t, $J = 7.2$ Hz), 1.62–1.79 (3H, m), 1.93–2.09 (2H,m), 2.17–2.29 (1H, m), 3.68–3.77 (1H, m), 4.05–4.12 (1H, m), 4.48 (2H, q, $J = 7.2$ Hz), 5.54 (1H, dd, $J = 0.3$ and 0.9 Hz), 8.38 (1H, s). Although the corresponding isomer **8** could not be isolated, a signal of δ 8.01 could be assigned to the triazole ring proton of **8**. For ^1H NMR spectra of similar triazole compounds, see: Vemishetti, P.; Leiby, R. W.; Abushanab, E.; Panzica, R. P. *J. Heterocycl. Chem.* **1988**, *25*, 651. (b) Ramasamy, K. S.; Tam, R. C.; Bard, J.; Averett, D. R. *J. Med. Chem.* **2000**, *43*, 1019. (c) Kim, M. J.; Chung, S. Y.; Chun, M. W. *Synth. Commun.* **2005**, *35*, 2653.

(13) Similarly, selective alkylation of methyl 1*H*-1,2,4-triazole-3-carboxylate has been reported; see: Zhang, P.; Dong, Z. E.; Cleary, T. P. *Org. Process Res. Dev.* **2005**, *9*, 583.

(14) The protecting group position of **6b** is confirmed by the HMBC correlation for the pyranyl methine proton to the triazole C-5 and without the HMBC correlation for the pyranyl methine proton to the triazole C-3. The detail data are included in Supporting Information.

methoxy-1-methylethyl)-1*H*-1,2,4-triazole-3-carboxylate (**5c**). Without further purification **5c** was allowed to react with ketone **3** to obtain the corresponding N-protected S-1360 derivative (**6c**) with good yield as crystals that were isolated directly by crystallization from the reaction mixture. The obtained crude **6c** was purified by recrystallization from MeOH. The purified **6c** was completely deprotected in aqueous acetone at 50–60 °C in the presence of a catalytic amount of acid to afford purified **7** as crystals without further purification.

The present new protective method has the following advantages compared with the THP method. (1) Carcinogenic by-product **9** (R = Cl) was eliminated. (2) Final crystals of **7** are obtained directly from the reaction mixtures without the recrystallization procedure. (3) For clinical use the final step involves filtration to remove insoluble particulates. As a result of the four times higher solubility of **6c** compared to that of **7**, a high concentration procedure (high throughout) was performed. As a result, final recrystallization volume was reduced by quarter.

Conclusion

The protecting group on the triazole ring is essential for the Claisen reaction, and a ketal protecting group on the triazole ring can be completely deprotected compared with the acetal group. By selection of the protective groups on the triazole ring, we developed an efficient process for manufacturing **7** that realizes a high throughput procedure without the need for a final recrystallization process.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 300 MHz FT NMR spectrometer and/or Varian Inova 500 MHz FT NMR spectrometer. The FT-IR spectra were recorded on a Bruker Vertex 70 spectrometer. Melting points were measured on a Büchi B-545 melting point apparatus.

1-[5-(4-Fluorobenzyl)-2-furyl]-3-[1-tetrahydropyranyl-1,2,4-triazol-3-yl]propan-1,3-dione (6b). To a stirred slurry of ethyl 1*H*-1,2,4-triazole-3-carboxylate (**4**) (20 kg, 142 mol), benzenesulfonic acid hydrate (600 g, 3.41 mol) and dry THF (53.3 kg) was added 3,4-dihydropyran (13.1 kg, 156 mol) dropwise while maintaining the reaction temperature under 45 °C, and then THF (8.9 kg) was added as a rinse. The solution was stirred at 45 °C for 1 h. 5-(4-Fluorobenzyl)-2-furyl methyl ketone (**3**) (30.9 kg, 142 mol) was added at 15 °C to the solution, 28% sodium methoxide (35.6 kg, 185 mol) in MeOH was added dropwise under 25 °C, and then the obtained brownish solution was stirred at 65 °C for 3 h. MeOH (79.1 kg) was added, and the mixture was cooled at 15 °C. Aqueous 13.7% acetic acid solution (92.7 kg, 211 mol) was added dropwise to neutralize to pH = 6. The mixture was stirred at 20 °C for 1 h to crystallize, and then the slurry was stirred at 5 °C for 1 h, filtered and washed with aqueous 60% MeOH solution (85.3 kg). The obtained yellow crystals were dried at 45 °C (jacket temperature) under vacuum to obtain 48.4 kg of N-protected S-1360 (**6b**) in 85.8% yield. Mp 122.6–123.2 °C. ^{1}H NMR (enol): (500 MHz, DMSO-d_6) δ 1.58 (2H, m), 1.69 (1H, m), 1.95 (1H, m), 2.02 (1H, m), 2.12 (1H, m), 3.69 (1H, m), 3.96 (1H, m), 4.15 (2H, s), 5.67 (1H, dd, J = 2.8 and 9.6 Hz), 6.47 (1H, d, J = ~4 Hz), 6.93 (1H, s), 7.18 (2H, t, J = 8.8 Hz), 7.34 (2H, dd, J = 5.5 and 8.7 Hz), 7.53 (1H, d, J = 3.5 Hz), 8.93 (1H, s). ^{1}H NMR (keto): (500 MHz, DMSO-d_6) δ 1.58 (2H, m), 1.69 (1H, m), 1.95 (1H, m), 2.02 (1H, m), 2.12 (1H, m), 3.69 (1H, m), 3.96 (1H, m), 4.15 (2H, s), 4.52 (2H,s) 5.67 (1H, dd, J = 2.8 and 9.6 Hz), 6.47 (1H, d, J = ~4 Hz), 7.18 (2H, t, J = 8.8 Hz), 7.34 (2H, dd, J = 5.5 and 8.7 Hz), 7.53 (1H, d, J = 3.5 Hz), 8.93 (1H, s). ^{13}C NMR (enol): (125 MHz, DMSO-d_6) δ 21.3, 24.3, 29.2, 32.8, 66.8, 85.2, 94.4, 110.4, 115.3 (d, $J_{C\text{-}F}$ = 21 Hz), 119.7, 130.5 (d, $J_{C\text{-}F}$ = 7.9 Hz), 133.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 145.3, 148.8, 157.0, 160.7, 161.0 (d, $J_{C\text{-}F}$ = 242 Hz), 171.9, 177.5. ^{13}C NMR (keto): (125 MHz, DMSO-d_6) δ 21.3, 24.3, 29.2, 32.8, 49.5, 66.8, 85.2, 110.4, 115.3 (d, $J_{C\text{-}F}$ = 21 Hz), 119.7, 130.5 (d, $J_{C\text{-}F}$ = 7.9 Hz), 133.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 145.3, 148.8, 157.0, 160.7, 161.4 (dd, $J_{C\text{-}F}$ = 242 Hz), 181.4, 187.3. IR (ATR) 1625, 1602, 1505, 1453, 1278, 1214, 1195, 1081 cm^{-1}. Anal. Calcd for $C_{21}H_{20}FN_3O_4$: C, 63.47; H, 5.07; F, 4.78; N, 10.57. Found: C, 63.40; H, 4.91; F, 4.41; N, 10.47.

(*Z*)-1-[5-(4-Fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1*H*-1,2,4-triazol-3-yl)propenone (S-1360). *First campaign procedure.* To a stirred slurry of N-protected S-1360 (**6b**) (25.0 kg, 62.9 mol) and 2-propanol (192.1 kg) was added concentrated HCl (32.8 kg, 315 mol). The mixture was warmed at 60 °C for 2 h and cooled at 25 °C for 1 h to crystallize. The slurry was filtered and washed with 2-propanol (98.2 kg) to give hydrochloride salt of S-1360 (**7**·HCl). The obtained wet hydrochloride salt was dissolved in THF (76.3 kg) and H_2O (12 kg), and then the solution was filtered with a Teflon membrane filter to remove insoluble particulates. THF (15.3 kg) was added to the filtrate as a rinse, and H_2O (160 kg) was added for crystallization. The slurry was stirred at 25 °C for 1 h and at 10 °C for 1 h. The slurry was filtered and washed with H_2O (342 kg). The obtained crystals were dried at 70 °C (jacket temperature) under vacuum to obtain 16.3 kg of S-1360 (**7**) in 82.6% yield. Mp 183 °C (TG-DTA). ^{1}H NMR (enol): (500 MHz, DMSO-d_6) δ 4.15 (2H, s), 6.48 (1H, d, J = 3.6 Hz), 6.95 (1H, s), 7.18 (2H, t, J = 8.8 Hz), 7.35 (2H, dd, J = 5.7 and 8.5 Hz), 7.53 (1H, br), 8.78 (1H, br), 14.73 (1H, brs), 15.6(1H, brs). ^{1}H NMR (keto): (500 MHz, DMSO-d_6) δ 4.09 (2H, s), 4.54 (2H, s), 6.42 (1H, d, J = 3.6 Hz), 7.16 (2H, t, J = 8.8 Hz), 7.31 (2H, dd, J = 5.7 and 8.5 Hz), 7.53 (1H, br), 8.31 (1H, br), 15.2 (1H, br). ^{13}C NMR (enol): (125 MHz, DMSO-d_6) δ 32.9, 94.2, 110.5, 115.4 (d, $J_{C\text{-}F}$ = 21 Hz), 119.5, 130.6 (d, $J_{C\text{-}F}$ = 8 Hz), 133.1 (d, $J_{C\text{-}F}$ = 3 Hz), 145.4, 148.8, 157.4, 160.5, 161.1 (d, $J_{C\text{-}F}$ = 242 Hz), 173.0, 177.3. ^{13}C NMR (keto): (125 MHz, DMSO-d_6) δ 32.9, 49.6, 109.8, 115.4 (d, $J_{C\text{-}F}$ = 21 Hz), 121.7, 130.6 (d, $J_{C\text{-}F}$ = 8 Hz), 133.0 (d, $J_{C\text{-}F}$ = 3 Hz), 145.4, 150.7, 157.4, 160.6, 161.1 (d, $J_{C\text{-}F}$ = 242 Hz), 181.6, 187.6. IR (KBr) 3100–3200, 1621, 1601, 1510, 1219, 1081, 770 cm^{-1}. Anal. Calcd for $C_{16}H_{12}FN_3O_3$: C, 61.34; H, 3.86; F, 6.06; N, 13.41. Found: C,61.48; H, 3.83; F, 6.07; N, 13.40.

(*Z*)-1-[5-(4-Fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1*H*-1,2,4-triazol-3-yl)propenone (S-1360). *Second campaign procedure.* To a stirred slurry of N-protected S-1360 (**6b**) (16.5 kg, 41.5 mol) and MeOH (65.2 kg) was added concentrated HCl (6.5 kg, 62.4 mol), and the mixture was warmed at 60 °C to dissolve. Additionally, concentrated HCl (15.1 kg, 145 mol) was added, and the obtained slurry was stirred for 2 h and cooled at 0 °C for 1 h. The slurry was filtered and washed with 2-propanol (168.9 kg) to give hydrochloride salt of S-1360 (**7**·HCl). The obtained hydrochloride salt was dissolved in THF (49.9 kg), H_2O (23 kg) and 8.5% aqueous Na_2CO_3 (22.9 kg,18.9 mol), and then the solution was filtered with a Teflon membrane filter to remove dust. To the filtrate was added aqueous THF (THF 8 kg/H_2O 2.25 kg) as a rinse and H_2O (68 kg) to crystallize. The slurry was stirred at 30 °C for 1 h and at 7 °C for 1 h. The slurry was filtered and washed with H_2O (225 kg). The obtained crystals were dried at 70 °C (jacket temperature) under vacuum to obtain 10.8 kg of S-1360 (**7**) in 82.6% yield.

1-[5-(4-Fluorobenzyl)-2-furyl]-3-[1-(1-methyl-1-methoxyethyl)-1,2,4-triazol-3-yl]propan-1,3-dione (6c). To a stirred slurry of ethyl 1*H*-1,2,4-triazole-3-carboxylate (**4**) (145 kg, 1027 mol), *p*-toluenesulfonic acid hydrate (1.78 kg, 9.36 mol) and dry THF (642 L) was added 2-methoxypropene (81.6 kg, 1132 mol) dropwise while maintaining reaction temperature under 5 °C. The solution was stirred at 5 °C for 1 h. 5-(4-Fluorobenzyl)-2-furyl methyl ketone (**3**) (204 kg, 935 mol) was added under 10 °C to the solution, 28% sodium methoxide (234 kg, 1212 mol) in MeOH was added dropwise under 10 °C, and THF (46 L) was added as a rinse. The obtained brownish solution was stirred at 60 °C for 3 h. MeOH (528 L) was added, and the mixture was cooled at 15 °C. Aqueous 13.8% acetic acid solution (598 kg, 1374 mol) was added dropwise to neutralize to pH = 6, and H_2O (528 kg) was added. The mixture was stirred at 25 °C for 1 h to crystallize, and then the slurry was stirred at 5 °C for 1 h, filtered and washed with aqueous 60% MeOH solution (660 L). The obtained wet crude N-protected S-1360 (**6c**) was dissolved at 55 °C in MeOH (2589 L). The solution was cooled at 30 °C, seed crystals of N-protected S-1360 **6c** (900g) were added, and then the slurry was stirred 30 °C for 1 h and at −10 °C for 1 h to crystallize. The slurry was filtered and washed with aqueous 60% MeOH solution (648 L). The obtained crystals were dried at 70 °C (jacket temperature) under vacuum to obtain 301.1 kg of N-protected S-1360 (**6c**) in 83.6% yield. Mp 107.7–107.8 °C ^{1}H NMR (enol): (500 MHz, DMSO-d_6) δ 1.81 (6H, s), 3.03 (3H, s), 4.15 (2H, s), 6.47 (1H, d, $J = 3.6$ Hz), 6.94 (1H, s), 7.19 (2H, t, $J = 8.7$ Hz), 7.35 (2H, dd, $J = 5.5$ and 8.7 Hz), 7.53 (1H, d, $J = 3.6$ Hz), 8.95 (1H, s). ^{1}H NMR (keto): (500 MHz, DMSO-d_6) δ 1.81 (6H, s), 3.03 (3H, s), 4.15 (2H, s), 4.52 (2H, s), 6.47 (1H, d, $J = 3.6$ Hz), 7.19 (2H, t, $J = 8.7$ Hz), 7.35 (2H, dd, $J = 5.5$ and 8.7 Hz), 7.53 (1H, d, $J = 3.6$ Hz), 8.95 (1H, s). ^{13}C NMR (enol): (125 MHz, DMSO-d_6) δ 25.3, 32.8, 50.1, 90.6, 94.3, 110.4, 115.3 (d, $J_{C\text{-}F} = 20.9$ Hz), 119.6, 130.5 (d, $J_{C\text{-}F} = 8.0$ Hz), 133.0 (d, $J_{C\text{-}F} = 3.0$ Hz), 144.6, 148.9, 156.8, 160.7, 161.0 (d, $J_{C\text{-}F} = 242$ Hz), 172.1, 177.6. ^{13}C NMR (keto): (125 MHz, DMSO-d_6) δ 25.3, 32.8, 49.5, 50.1, 90.6, 110.4, 115.3 (d, $J_{C\text{-}F} = 20.9$ Hz), 119.6, 130.5 (d, $J_{C\text{-}F} = 8.0$ Hz), 133.0 (d, $J_{C\text{-}F} = 3.0$ Hz), 144.6, 148.9, 156.8, 160.7, 161.0 (d, $J_{C\text{-}F} = 242$ Hz), 181.4, 187.4. IR (ATR) 1596, 1507, 1473, 1425, 1384, 1215, 1202, 1184, 1158, 1055,1010 cm^{-1}. Anal. Calcd for $C_{20}H_{20}FN_3O_4$: C, 62.33; H, 5.23; F, 4.93; N, 10.90. Found: C, 62.32; H, 5.07; F, 4.53; N, 10.96.

(*Z*)-1-[5-(4-Fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1*H*-1,2,4-triazol-3-yl)propenone (S-1360). *Last campaign procedure*. N-Protected S-1360 (**6c**) (145 kg, 376 mol) was dissolved in acetone (1012 L) and H_2O (153 L), and then the solution was filtered to remove insoluble particulates. Acetone (118 L) was added to the filtrate as a rinse, and the combined filtrate was heated at >55 °C. Next, 0.3% HCl (47.4 kg, 3.74 mol) solution was added, and the mixture was stirred at 58 °C for 1 h. Seed crystals of S-1360 (100g) and aqueous Na_2CO_3 [Na_2CO_3 (200 g, 1.88 mol) in H_2O (553 L)] solution were added at 55 °C to crystallize. The slurry was stirred at 2 °C for 1 h, filtered and washed with H_2O (588 L). The obtained crystals were dried at 70 °C (jacket temperature) under vacuum to obtain 115.2 kg of S-1360 (**7**) in 97.9% yield.

(*Z*)-1-[5-(4-Fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1*H*-1,2,4-triazol-3-yl)propenone (S-1360). *Planned procedure for commercial manufacturing*. (This experiment is 7/100,000 scale for the commercial production. The quality of this concentrated procedure was examined by using 10 lots of **6c** that had obtained in the last campaign. As compared with the last campaign, the quality of this procedure was equivalent.) N-Protected S-1360 **6c** (20.3g, 52.7 mmol) was dissolved at 40 °C in acetone (70.8 mL) and H_2O (10.7 mL), and then the solution was filtered to remove insoluble particulates. Acetone (6.5 mL) was added to the filtrate as a rinse, and the combined filtrate was heated at >55 °C. Next, 0.3% HCl (3.3g, 0.026 mmol) solution was added, and the reaction mixture was stirred at 58 °C for 1 h. Aqueous 0.036% Na_2CO_3 solution (38.7g, 0.013 mmol) was added at 53 °C. The resulting slurry was stirred at 25 °C for 1 h, filtered and washed with H_2O (82.4 mL). The obtained crystals were dried at 70 °C under vacuum to obtain 16.0 g of S-1360 (**7**) in 97.1% yield.

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Supporting Information Available

The X-ray structural analysis and data of **5a** and 2D proton–carbon correlation spectra (HMBC) of **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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