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# The Development of a Large-Scale Synthesis of Matrix Metalloproteinase Inhibitor, ABT-518

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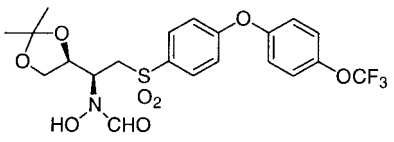
**Abstract:**

**A process for the preparation of matrix metalloproteinase inhibitor ABT-518 has been developed. Significant improvements have been made to the first generation synthesis and are described here. The new process is very robust and efficient; multikilogram quantities of the title compound have been synthesized for clinical trials. ABT-518 was prepared by this six-step synthetic sequence in 51% overall yield with >99% ee.**

## Introduction

ABT-518,[1] **1** is a potent inhibitor of gelatinase A and gelatinase B, two matrix metalloproteinase (MMP) enzymes involved in tumor growth and metastasis.[2,3] ABT-518 has demonstrated robust antitumor activity in a variety of animal models. This compound is a potent and selective inhibitor of these enzyme targets. To support continued development of ABT-518, multikilogram quantities of **1** were required for further biological studies and clinical trials. The original six-step synthesis was convergent and quite efficient.[1] We have made further improvements, and these have been demonstrated on pilot-plant scale in the preparation of ABT-518 in high yield with >99% ee.[4] Several issues associated with the first-generation synthesis such as cryogenic reaction conditions, multiple isolations, column chromatography, and several operational protocols not amendable to scale-up were addressed and are discussed here.

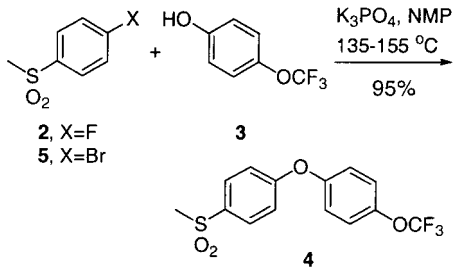


**1**, ABT-518

## Results and Discussion

**Biaryl Ether Preparation.** The original synthesis accomplished the biaryl ether formation using KO$^t$Bu/DMSO with fluorosulfone **2** and the requisite phenol **3**. The reaction proceeded in 1 h at 120 °C. A primary issue in this process was the *t*-BuOH byproduct, which caused emulsion problems during the workup. KO$^t$Bu could be replaced with KOH to alleviate this problem; however, 4-methoxy derivative **6** was generated as an impurity at ∼0.3%. Its removal was necessary at this stage because it had been shown to carry through the entire process. At present, the source of the methanol causing the formation of this side product is unknown. Another issue was the fluoride ion produced by the reaction of fluorosulfone **2** as it presented corrosion issues. The switch was made to bromosulfone **5**, which is much less reactive than **2**, and thus modified reaction conditions were required (Scheme 1).

***Scheme 1***

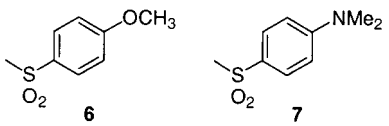


**2**, X=F
**5**, X=Br

**3**

**4**

Numerous solvents and base combinations were screened to find conditions that would provide practical reaction rates (e.g. the reaction of **5** and **2** with **3** took several days at 100 °C in water). The reaction rate using DMF/$K_3PO_4$ at 100−120 °C was found to be appropriate for scale-up; however, at these elevated temperatures DMF decomposed to a small extent and generated dimethylamine, which led to dimethylaniline **7**. This problem was avoided by the use of NMP/$K_3PO_4$. The isolation of **4** was also simplified by precipitating the product with water at the end of the reaction; this procedure provided **4** in 95% yield and excellent purity.



**6** **7**

Having the biaryl ether moiety in hand, the next task was to couple it with the suitably functionalized counterpart. An obvious approach is the condensation of the α-sulfonyl anion of **4** with protected glyceraldehyde **8a**. However, because of the intrinsic stability problems of **8a,** finding a viable commercial source proved to be problematic. Hence, the

(1) Wada, C. K.; Holms, J. H.; Curtin, M. L.; Dai, Y.; Florjancic, A. S.; Garland, R. B.; Guo, Y.; Heyman, H. R.; Stacey, J. R.; Steinman, D. H.; Albert, D. H.; Bouska, J. J.; Elmore, I. N.; Goodfellow, C. L.; Marcotte, P. A.; Tapang, P.; Morgan, D. W.; Michaelides, M. R.; Davidsen, S. K. *J. Med. Chem.* **2002**, *45*, 219.
(2) Michaelides, M. R.; Curtin, M. L. *Curr. Pharm. Des.* **1999**, *5*, 787.
(3) Foda, H. D.; Zucker, S. *Drug Discovery Today* **2001**, *6*, 478.
(4) Gupta, A. K.; Hill, D. R.; Chang, S.; Fernando, D.; Wittenberger, S. J.; King, S. *Abstracts of Papers*, 221st National Meeting of the American Chemical Society, San Diego, April 1−5, 2001; American Chemical Society: Washington, DC, 2001; ORGN 327.

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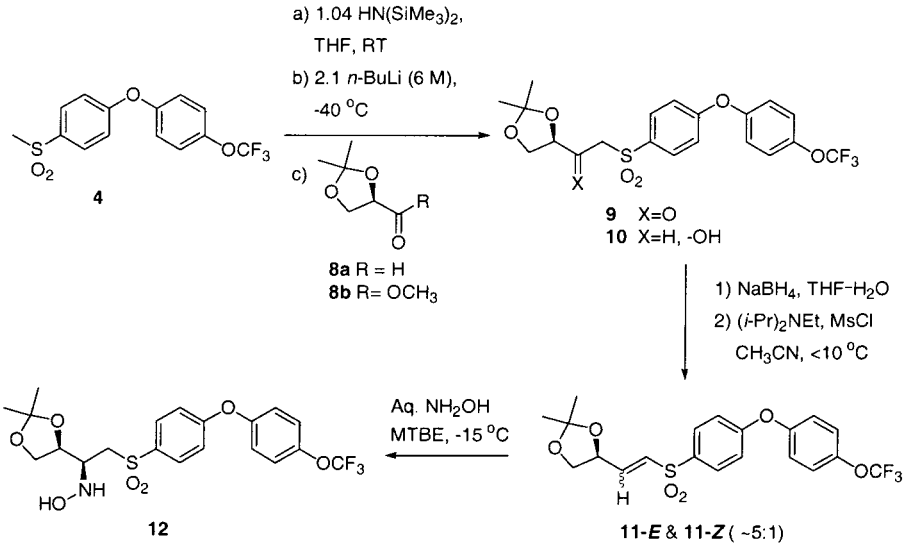
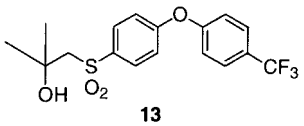
***Scheme 2***




synthetic protocol of generation of ketone **9** from glycerate **8b,** followed by reduction, elimination, and Michael addition of $NH_2OH$ to generate the *N*-hydroxyl derivative was pursued successfully.

**Preparation of *N*-Hydroxylamine 12.** The general sequence of reactions shown in Scheme 2 had been demonstrated as a means to efficiently assemble the backbone of ABT-518. Our focus was to eliminate unnecessary isolations and minimize the level of impurities. For the condensation of **4** with **8b**, the following criteria were deemed to be critical: (1) the choice and amount of base required to generate the anion of **4**, (2) the reaction temperature, and (3) various reaction and workup parameters important to prevent product degradation; in particular, the loss of enantiomeric purity of the ketone and hydrolysis of the acetonide.

In the original process, generation of the lithiosulfone anion of **4** was accomplished at temperatures below −60 °C using 1 mol equiv of *n*-BuLi. The anion mixture was transferred at low temperature to a solution of **8b**. However, it was envisioned that maintaining the low temperature during this transfer would be difficult to achieve in the pilot plant. We showed that inverse addition, that is, addition of **8b** to the anion, worked equally well, thus eliminating the requirement of a low-temperature transfer. We also found that at temperatures above −60 °C only partial conversion of **4** to **9** could be accomplished. The rationale for this observation is as follows. The initial product of the reaction of the sulfone anion of **4** and **8b** is the tetrahedral intermediate, which collapses at temperatures above −60 °C to **9**. The ketone is rapidly deprotonated by the remaining sulfone anion, resulting in the recovery of ∼50% **4**. It was postulated that a second equivalent of base would intercept the ketone to generate its enolate and conserve sulfone anion. We found that this strategy worked with varying degrees of success, depending on the base combination used. Of the base systems screened, the mixture of 1 equiv of *n*-BuLi and 1 equiv of LiHMDS was shown to be superior. In practice, the lithiosulfone anion was generated by the addition of 2 equiv of *n*-BuLi to **4** in the presence of 1 equiv HMDS, which simplified the handling of reagents. Examination of the reaction at temperatures above −40 °C showed that increasing amounts of an impurity formed, while yield of **9** decreased. The impurity was identified as tertiary alcohol **13**, the product of sulfone anion condensation with acetone. Acetone is presumably the product of enolization/$\beta$-elimination of **8b**.[5]

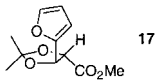


**13**

Controlling the quench of the reaction was found to be critical with respect to both acetonide hydrolysis and maintaining high optical purity. Final pH ranges of the reaction mixture following the acid quench from 2 to 11 were carefully studied. It was found that exposure to a pH above 7 resulted in erosion of the ee of **9** (e.g., a decrease from >99% ee to ca. 50% ee over 51 h was observed when the pH was adjusted to 8.7). At a pH below 2, significant acetonide hydrolysis resulted. We therefore targeted a pH range of 4−6 for the reaction workup. A streamlined procedure was achieved by eliminating the use of cosolvents and employing a series of aqueous washes that gave good phase separation and no losses of product to aqueous layers. The resulting wet THF solution (ca. 7% $H_2O$ by KF analysis) was used directly in the subsequent ketone reduction.

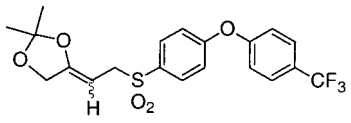
Consistent and rapid conversion of **9** to **10** was accomplished with $NaBH_4$ (0.35 equiv) at 0−10 °C. The workup was modified to a single wash of the reaction mixture with 27 wt % $K_2CO_3$ solution. Clear layer-separation was achieved, and residual boron levels in isolated product samples were found to be below the detection limit by

(5) The decomposition of **17**, a lithium ester enolate related to **8b**, via a $\beta$-elimination mechanism to form acetone at temperatures ≥−50 °C has been reported. Leighton J. L. Ph.D. Thesis, Harvard University, Cambridge, MA, 1994.



**17**

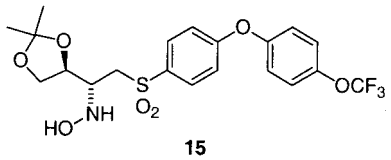
combustion analysis. We attempted to employ the wet solution of **10** directly in the dehydration reaction. Unfortunately, the solution was too wet for a number of reactive derivatizing reagents (e.g., MsCl, $(CF_3CO)_2O$, $SOCl_2$). Acetic anhydride treatment gave the corresponding acetate diastereomers, but the conditions necessary for elimination also caused isomerization of vinyl sulfone **11** to the thermodynamically more stable allyl isomer **14**.[6] A variety of other bases were screened for the elimination; weaker bases (e.g., triethylamine, *N*-methyl piperidine, or DABCO) did not promote the elimination. Another strong base, tetramethyl guanidine, eliminated the acetate but then added into the vinyl sulfone to produce the TMG-adduct.



**14**

To accomplish dehydration to vinyl sulfone **11**, the crude solution of **10** was dried by azeotropic distillation using acetonitrile to <10 mol % $H_2O$ (by KF analysis). At *atmospheric pressure* acetonitrile has a very favorable azeotrope for removal of water; at reduced pressure the fraction of water in the distillate is much lower.[7] The dried acetonitrile solution of **10** was treated with diisopropylethylamine followed by slow addition of methanesulfonyl chloride. After consumption of **10**, the reaction mixture was warmed to 55 °C to effect the elimination. With ~2 h of heating the reaction went to completion, and <2% peak area of allyl isomers **14** was formed. On extended heating time only minor increases in the allyl sulfone **14** were observed. Interestingly, when triethylamine was used as the base, the elimination occurred at lower temperature (0 °C to ambient); however, higher levels of allyl isomers **14** were formed (~2−10% peak area).

The optimized conditions for the Michael addition step for laboratory preparations were to add aqueous hydroxylamine to a dilute solution of vinyl sulfone **11** in MTBE at temperature below −15 °C. The diastereoselectivity for the addition under these conditions was typically ~5:1 *syn*:*anti*. After a solvent-switch to ethyl acetate to avoid emulsions during the aqueous workup, and then a second solvent-switch back to MTBE, the desired *syn* product **12** was isolated by crystallization from MTBE-heptane to give 60−65% yield of material containing 3−5% of *anti* isomer **15**. Experiments to find reaction conditions to achieve improved diastereoselectivity in the Michael addition as well as a simpler workup protocol and more robust crystallization conditions were sought prior to running in the pilot plant.

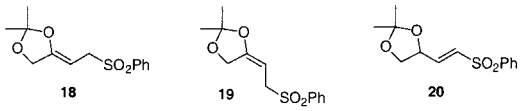


**15**

A wide variety of reaction conditions were screened to try to increase the diastereoselectivity of the Michael addition. These included solvent, hydroxylamine source, temperature, additives, addition rate, and addition order. None of these variables significantly increased the intrinsic diastereoselectivity of the reaction. It was noted during this investigation that the *syn:anti* ratio early in the reaction was higher than the *syn:anti* ratio of the isolated product. A possible explanation for this behavior is that the addition is initially selective and that the final ratio is a result of epimerization during the reaction. Alternatively, vinyl sulfone isomers **11-*E*** and **11-*Z*** might show different selectivity and reactivity. After verification that products **12** and **15** are stable to the reaction conditions, a 1:1 mixture of the *Z:E* vinyl sulfones was obtained by chromatography. This mixture was then subjected to the reaction conditions, and the product formation was followed by HPLC. Figure 1 shows that **11-*Z*** reacts significantly faster and more selectively than **11-*E***, resulting in an increased *syn:anti* ratio early in the reaction. Attempts to increase the *Z:E* ratio of **11** were unsuccessful so that it was not possible to exploit this phenomenon. Attention was then turned to a reliable method to isolate the product and remove undesired *anti* product **15**.

In laboratory runs, **12** was isolated by crystallization from MTBE−heptane. In preparation to move into the pilot plant, this crystallization was found to be difficult to reproduce. In cases where the material crystallized as expected, extending the stir time for as little as a few hours resulted in the solid becoming oily and difficult to stir. An extensive solubility study revealed that *syn* diastereomer **12** has low solubility in toluene−cyclohexane solvent mixtures. The crystallized solid remained a free-flowing slurry over extended stir times. Incorporation of toluene early in the workup also significantly streamlined the procedure. The final workup for the reaction was to add a portion of toluene to the crude reaction mixture and separate the existing aqueous layer. Any hydroxylamine remaining in the organic phase would be removed during solvent concentration. MTBE was removed and chased with a toluene distillation. Cyclohexane was added until the solution became saturated and then the addition of seed crystals resulted in the formation of a fine white to yellow solid. The concentration of **12** in solution could be adjusted by the addition of cyclohexane. In the pilot plant campaign, **12** was obtained with a *syn*:*anti* ratio of 73:1, and a potency adjusted yield was 65% from **4** over four steps.

(6) Calculations done using CambridgeSoft's *Chem3D Pro* energy minimization software indicated that model allyl sulfone isomers **18** and **19** were significantly thermodynamically more stable than vinyl sulfone **20**. This was demonstrated experimentally as treatment of **11-*E*** with DBU in $CH_3CN$ at 35 °C caused rapid and complete isomerization to a mixture of **14-*Z*** and **14-*E***.



**18** 9.21 kcal/mole **19** 10.44 kcal/mole **20** 19.31 kcal/mole

(7) *Azeotropic Data-III*; L. H. Horsley, Ed.; Advances in Chemistry Series 116; American Chemical Society: Washington, DC, 1973; p 14. At 750 mmHg the composition of water in the azeotrope (bp 76 °C) is 15.85−17.1 wt % At 50 mmHg, the composition of water in the azeotrope (bp 12 °C) decreases to 5.8 wt %.

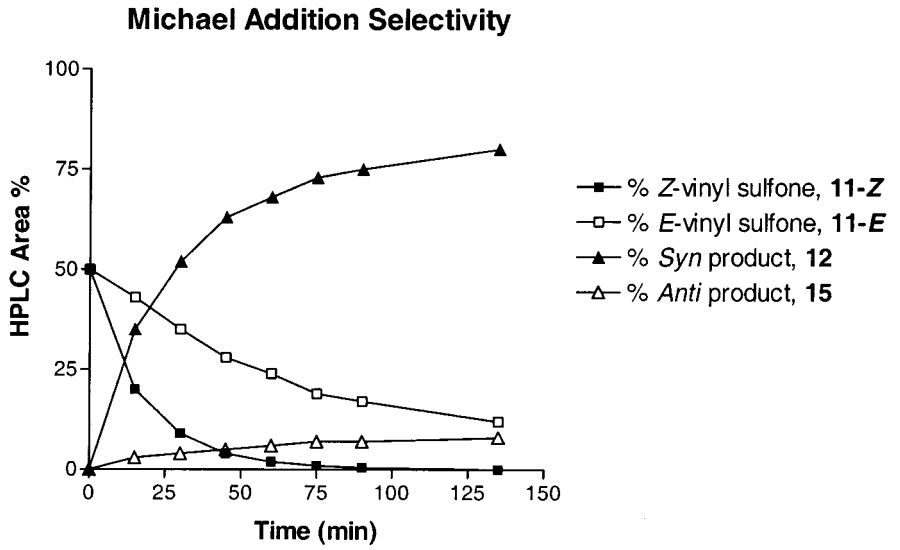
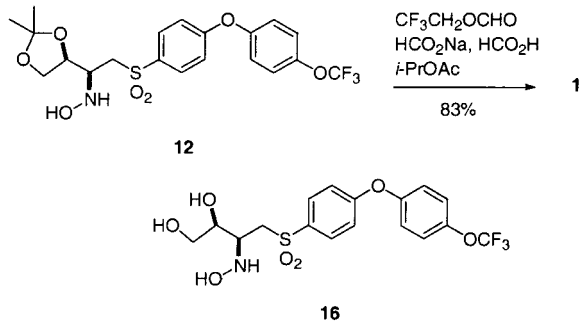



***Figure 1.***

***N*-Formylation and the Final Product Isolation.** Conversion of **12** to the API required *N*-formylation of the *N*-hydroxylamine moiety. A careful examination of various formylation reagents and conditions from the literature showed that none were ideally suited for our purpose. In general, other reagents proved to be too unreactive (e.g., alkyl formates) or produced large amounts of *O*-formyl adducts (e.g., aryl formates, etc.) that were slow to isomerize to the desired *N*-formyl isomer under sufficiently mild conditions. We recently reported the use of 2,2,2-trifluoroethylformate (TFEF) for the formylation of alcohols, amines and *N*-hydroxylamines.[8] In the reaction of TFEF with *N*-hydroxylamines there is a kinetic competition between formylation on oxygen and nitrogen. The *N*-formyl isomer is favored thermodynamically. To enhance the rate of the interconversion of the *O*-formyl isomer to the *N*-formyl isomer under the reaction conditions, a small amount of formic acid was added to the reaction mixture. For acid-sensitive substrates such as **12** (acetonide hydrolysis) the medium can be buffered with sodium formate. In the case of **12** this was necessary because diol **16** was very difficult to remove from the product, ABT-518, by crystallization. The optimized procedure entailed treatment of **12** with TFEF (6 equiv) in isopropyl acetate (*i*-PrOAc) containing formic acid and sodium formate at 60 °C for several hours (Scheme 3).

There are stringent limits on residual 2,2,2-trifluoroethanol (TFE) and TFEF in the final product (<0.01wt %). Somewhat surprisingly, simple concentration of the organic solvent or crystallization or both were not effective enough at removing these impurities to meet these requirements. For an early delivery, multiple chase distillations were performed with *i*-PrOAc, and the impurity levels were monitored by GC. This was a tedious and time-consuming procedure. Most recently this problem was addressed by initial solvent concentration to remove the bulk of the TFE and TFEF, followed by two crystallizations. The product after the first crystallization showed 100−150 ppm TFE. After a second crystallization the residual level of TFE was reduced to below the detection limit (<30 ppm). In the pilot plant, ABT-518 (**1**) was obtained in 83% isolated yield with very high purity (>99.9% HPLC peak area, >99.5% potency, >99.8% ee).

***Scheme 3***




## Conclusions

A six-step synthetic sequence has been developed and demonstrated for the preparation of multikilogram quantities of ABT-518 in 51% overall yield and with >99%ee. Highlights of the sequence include the carefully optimized addition of a lithiosulfone anion (from **4**) to a glycerate ester (**8b**) to provide the ketone product **9**, elimination of the derived alcohol **10** to the vinyl sulfones **11-*E*** and **11-*Z*** while minimizing isomerization to the thermodynamically more stable allylic sulfone **14**, and subsequent Michael addition of *N*-hydroxylamine. 2,2,2-Trifluoroethyl formate was used to introduced the *N*-formyl moiety under mild conditions.

## Experimental Section

Melting points were measured with a capillary apparatus and are uncorrected. All IR spectra were measured from KBr pellets. $^1$H NMR spectra were taken in $CDCl_3$ unless otherwise indicated with $CHCl_3$ (7.26 ppm) used as an internal standard. All reactions were performed under a positive pressure of nitrogen. Most of the HPLC analyses, unless otherwise indicated, were run on a Zorbax SB-C8 4.6 mm × 25 cm column; mobile phase was a gradient of 70%

(8) Hill, D. R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 111.

water with 0.1% $H_3PO_4$/30% acetonitrile to 30% water with 0.1% $H_3PO_4$/70% acetonitrile, flow rate 1−1.5 mL/min, column temperature 25−35 °C, UV detection at 240−245 nm.

**Preparation of Biaryl ether (4).** To a 100-gal reactor were charged 4-bromophenyl methyl sulfone **5** (15.45 kg, 65.7 mol), potassium phosphate (28 kg, 132 mol), NMP (29 kg), and 4-trifluoromethoxyphenol **2** (12.05 kg, 67.6 mol). The heterogeneous mixture was heated to an internal temperature of 145 ± 15 °C for 8 h. The reaction mixture was cooled to 25 °C, and water (∼46 kg) was added over 10 min to quench the reaction. The internal temperature increased to ∼39 °C as the solid phophate salts dissolved. The remaining water (∼46 kg) was added slowly (over 1 h); in this case, after ∼60% of the water had been added (temp at 32 °C) the product began to crystallize from the mixture. Following the water addition, the mixture was stirred while cooling to ambient temperature. The product was collected by filtration. The filter cake was washed with water until the eluant was neutral by pH test strips. The cake was dried by suction and then transferred to a vacuum oven and dried (at ∼100 mmHg with nitrogen bleed at <45 °C) to provide **4**, 20.85 kg, (95% yield, 100% potency vs a standard): mp 74−75 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, $J$ = 9.1 Hz, 2H), 7.26 (br d, $J$ = 9.2 Hz, 2H), 7.09 (d, $J$ = 8.9 Hz, 4H), 3.06 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.4, 153.0, 134.5, 129.5, 122.7, 121.4, 121.1, 118.9, 117.7, 44.9. IR (KBr) 1589, 1503, 1274, 1245, 1148, 961, 837, 763 cm$^{-1}$; MS (APCI) 350 $[M + NH_4]^+$. Anal. Calcd for $C_{14}H_{11}F_3O_4S$: C, 50.60; H, 3.34; F, 17.15; O, 19.26; S, 9.65. Found: C, 50.49; H, 3.22; F, 17.31; S, 10.22.

**Preparation of *N*-Hydroxylamine (12). (a) Ketone Formation (9).** A 100-gal reactor was charged with biaryl ether **4** (8.5 kg, 25.6 mol) and THF (64.6 kg), and the mixture was stirred to dissolve the material. 1,1,1,3,3,3-Hexamethyldisilazane, (HMDS) (4.3 kg, 26.6 mol) was charged to the reactor, and the resulting solution was cooled to −40 °C with stirring. *n*-BuLi in hexane (6 M, 6.35 kg, 53.7 mol) was charged to the reaction mixture via a pressure canister at a rate such that the temperature remained less than −30 °C. The canister was rinsed with hexanes (5.0 kg), and the rinse was added to the reaction. The reaction mixture was stirred for 30 min, maintaining a temperature of −40 °C. A second canister was charged with (*R*)-Me-*O*-isopropylidene glycerate **8** (4.6 kg, 28.7 mol) and THF (5.4 kg), and the contents were mixed. The solution of **8** was added to the reaction mixture slowly, maintaining a reaction temperature below −30 °C. The canister was rinsed with additional THF (4.4 kg), which was transferred to the reaction mixture. The reaction was sampled at 30-min intervals and analyzed for completion by HPLC. In this case, the 30-min sample showed the reaction to be complete. The −40 °C reaction solution was quenched with an initial 3.0-kg portion of 2 M $H_2SO_4$. A pH probe, calibrated with pH 7.00 and pH 4.00 buffers prior to use, was placed into the reaction mixture. 2 M $H_2SO_4$ was slowly charged to the reaction while maintaining a temperature of greater than +5 °C, to the target range pH 4−6. The mixture was stirred for 30 min, and then the phases were allowed to settle and were separated. The organic phase was washed with 15 wt % NaCl (57 kg), 15 wt % $KHCO_3$ (42 kg), and 15 wt % NaCl (57 kg) solutions in succession. The product solution (∼7 wt % water by KF titration) was assayed by HPLC against a working standard for 11.1 kg of **9** (96.3% yield) and used directly in the next step. Crude **9** was evaluated by chiral HPLC for enantiomeric purity and was found to be >99% ee. [Chiral HPLC method: Chiralpak AS (4.6 mm × 25 cm) column, isocratic, 10% EtOH−hexanes, 1.0 mL/min, 25 min run time, 35 °C column temperature. Retention times: desired (*R*) 18 min, undesired (*S*) 21 min.] A sample of **9** was crystallized from *i*-PrOH for characterization: mp 81−82 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91−7.87 (m, 2H), 7.30−7.26 (m, 2H), 7.13−7.07 (m, 4H), 4.61 (d, $J$ = 14.8 Hz, 1H), 4.55 (dd, $J$ = 4.8, 7.6 Hz, 1H), 4.31 (d, $J$ = 14.8 Hz, 1H), 4.17 (dd, $J$ = 7.6, 8.8 Hz, 1H), 4.12 (dd, $J$ = 4.8, 8.8 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 3H). IR (KBr) 1737, 1503, 1295, 1147, 832 cm$^{-1}$. $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.7, 162.6, 153.4, 146.2, 133.2, 131.3, 123.2, 121.8, 120.4 (q, $J_{13C19F}$ = 257 Hz), 117.9, 111.7, 80.3, 66.0, 62.5, 26.2, 25.0. Anal. Calcd for $C_{20}H_{19}F_3O_7S$: C, 52.17; H, 4.16; F, 12.38; O, 24.32; S, 6.96. Found: C, 52.10; H, 4.09; F, 12.27; S, 7.09.

**(b) Ketone Reduction (10).** A 100-gal reactor was charged with the wet ketone **9**−THF solution prepared in step 2a (11.1 kg **9** by assay, 24.1 mol) and was chilled to 0 ± 5 °C. $NaBH_4$ (333 g, 8.8 mole) was added via a solid addition funnel at such a rate that the internal temperature was maintained at less than +10 °C; following the addition, the mixture was stirred for 30 min before a sample was taken to monitor the reaction progress. The reaction was judged to be complete at <1% peak area remaining ketone **9**. The completed reaction was quenched by the addition of 27 wt % $K_2CO_3$ solution (prepared from 14 kg of $K_2CO_3$ dissolved in 38 kg of water) at such a rate that the internal temperature was maintained at greater than +35 °C. The mixture was stirred for 30 min, and then the phases were allowed to settle and were separated. The organic (top) phase was transferred to a polylined drum (85.4 kg) and assayed by HPLC for alcohol **10** versus a working standard: 11.3 kg of alcohols **10** (100% yield, ∼3:1 mix of diastereomers). A sample was purified by silica gel chromatography for characterization. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10−8.05 (m, 2H), 7.49−7.42 (m, 2H), 7.32−7.22 (m, 4H), 4.41−4.32 (m, 0.5H), 4.25−4.05 (m, 3.5H), 3.71 (dd, $J$ = 1.1, 14.3 Hz, 0.75H), 3.65−3.63 (m, 0.75H), 3.52 (dd, $J$ = 8.6, 14.3 Hz, 0.25H), 3.45 (dd, $J$ = 2.9, 14.3 Hz, 0.25H), 3.36 (dd, $J$ = 9.5, 14.3 Hz, 0.75H), 3.22−3.19 (m, 0.25H), 1.59 (s, 0.75H), 1.50 (s, 0.75H), 1.46 (s, 2.25H), 1.39 (s, 2.25H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.4, 153.4, 146.1, 133.1, 130.6, 123.2, 121.6, 118.1, 110.0, 77.5, 67.9, 66.7, 59.5, 26.7, 25.1, (*C*-$OCF_3$ not observed). Anal. Calcd for $C_{20}H_{21}F_3O_7S$: C, 51.95; H, 4.58. Found: C, 52.05; H, 4.52.

The solution of **10** (primarily THF) was concentrated at reduced pressure to one-quarter volume. Acetonitrile (101 kg) was charged, and the resulting solution was distilled at atmospheric pressure to ca. 20% volume. Acetonitrile was added (26 kg to give an approximately 25 wt % solution),

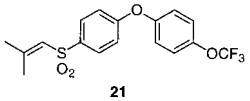
and a sample was taken for Karl Fischer determination of water content; a target of ≤10% mol water versus **10** was achieved.

**(c) Mesylation/Elimination to Vinyl Sulfone (11).** The acetonitrile solution of **10** from step 2b (11.1 kg **10** by assay, 24.3 mol) was chilled to ca. 0 °C. EtN(*i*-Pr)$_2$ (13 kg, 100.6 mol) was added in one portion, followed by MsCl (5.38 kg, 46.9 mol) added at a rate such that the internal temperature was maintained at below +10 °C. Following the addition, the mixture was stirred for 30 min, at which point a sample was taken to monitor the progress of the mesylate formation. The mesylation reaction was judged complete when there was <3% peak area combined alcohol **10** diastereomers. The internal temperature was adjusted to 55 ± 5 °C for 2 h, at which point a sample was taken to monitor the progress of the elimination reaction.[9] Upon completion, the reaction mixture was cooled to <30 °C, and water (78 kg) was added. The mixture was concentrated at reduced pressure to remove the bulk of the acetonitrile. After the distillation was judged complete, methyl *tert*-butyl ether (MTBE, 35 kg) was added, and the contents of the reactor were mixed and then allowed to settle. The layers were separated, and the upper organic phase was set aside. The lower aqueous portion was extracted with MTBE (19 kg) as above. Silica sand (9 kg) and silica gel (10 kg) were loaded into a suitable filter. The combined organic extracts were filtered through the silica gel pad and collected. The container was rinsed with MTBE (18 kg), and the rinse was filtered through the silica gel pad and combined with the filtrates. A sample of the combined filtrate and rinse (72.6 kg) was assayed for **11** by HPLC versus working standards: 10.28 kg **11** (90.1% yield). The MTBE solution was used directly in the next step. A sample of ***E*-11** was purified by silica gel chromatography. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85 (d, $J$ = 9.0 Hz, 2H), 7.30 (br d, 2H), 7.10 (m, 4H), 6.90 (dd, $J$ = 6.0, 15.0 Hz, 1H), 6.65 (dd, $J$ = 1.5, 15.0 Hz, 1H), 4.70 (m, 1H), 4.20 (dd, $J$ = 7.5, 9.0 Hz, 1H), 3.70 (dd, $J$ = 7.5, 9.0 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.8, 153.4, 142.2, 134.0, 131.7, 130.2, 129.9, 123.0, 121.4, 121.3, 118.0, 110.6, 73.9, 68.5, 26.3, 25.6, 21.8. IR (KBr) 1580, 1504, 1312, 1220, 1147, 839 cm$^{-1}$.

**(d) Michael Addition (12).** In a 100-gal *glass-lined*[10] reactor, the MTBE solution of **11** (net 72.6 kg, 10.28 kg **11** by assay, 23.1 mol) was diluted with MTBE (64 kg) to give a 7.5 wt % solution that was cooled to −16 °C. Aqueous $NH_2OH$ (50 wt %, 6.10 kg, 92.4 mol) was added over a 30-min period. The mixture was stirred at less than −13 °C until less than 1% peak area **11** remained by HPLC analysis. Toluene (55 kg) was added, and the reaction was warmed to 22 °C. Once at room temperature, the mixture was allowed to settle. The lower aqueous layer was removed, and the organic layer was assayed for **12** versus a known standard. The assay indicated 9.31 kg **12** (84.3%) and a 5.8:1 *syn*:*anti* ratio. The solution was concentrated under reduced pressure to a total volume of approximately 35 L. Toluene (50 kg) was added, and the solution was concentrated to approximately 25 L. The solution was assayed, and toluene (21 kg) was added to give a 25 wt % solution. Cyclohexane (67 kg) was added in portions until the solution become cloudy. Seed crystals (50 g) were added, and the mixture was stirred at room temperature for 8 h. The supernatant was assayed and was determined to contain 11.6 mg/mL of the *syn* product **12** and a 1:1 *syn*:*anti* ratio. The product was isolated by centrifugation and was washed with 21 kg of 1:4 toluene−cyclohexane. The solid was dried in vacuo (~100 mmHg, 35 °C) to a constant weight and assayed versus a standard. This procedure resulted in the isolation of 7.2 kg **12** (65% yield from **4**, *syn:anti* 73:1): mp 109−110 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 8.9 Hz, 2H), 7.29 (d, $J$ = 10.0 Hz, 2H), 7.13−7.10 (m, 4H), 5.78 (br s, 2H), 4.39 (ddd, $J$ = 5.9, 6.0, 6.6 Hz, 1H), 4.06 (dd, $J$ = 6.6, 8.7 Hz, 1H), 3.81 (dd, $J$ = 6.0, 8.8 Hz, 1H), 3.64 (dd, $J$ = 8.5, 14.3 Hz, 1H), 3.49 (ddd, $J$ = 3.2, 5.9, 8.5 Hz, 1H), 3.12 (dd, $J$ = 3.2, 14.3 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.6, 152.8, 145.5, 133.1, 130.1, 122.7, 121.1, 120.1 (q, $J_{13C19F}$ = 256 Hz), 117.7, 109.2, 74.8, 66.0, 58.6, 53.4, 26.7, 25.1. IR (KBr) 3491, 2989, 1505, 1279, 1156, 846 cm$^{-1}$. Anal. Calcd for $C_{20}H_{22}F_3NO_7S$: C, 50.31; H, 4.64; N, 2.93. Found: C, 50.47; H, 4.65; N, 2.82.

**Formylation (Preparation of ABT-518).** To a 100-gal glass-lined reactor were charged **12** (12.25 kg, 25.6 mol), sodium formate (1.3 kg, 19.1 mol), *i*-PrOAc (106.6 kg), 2,2,2-trifluoroethylformate (22.40 kg, 162 mol), and formic acid (1.84 kg, 40 mol). The resultant reaction mixture was heated to an internal temperature of 60 °C and maintained at this temperature with continuous stirring. The reaction was monitored by HPLC until the peak area of **12** was <0.5% (8.5 h) [HPLC sample prep: 20 $\mu$L of reaction mixture diluted to 1.0 mL with $CH_3CN$. HPLC conditions: Zorbax SB-C8 4.6 mm × 25 cm column at 35 °C; mobile phase was a gradient of 55% water with 0.1% $H_3PO_4$/45% acetonitrile to 35% water with 0.1% $H_3PO_4$/65% acetonitrile, Flow rate 1.0 mL/min, UV detection at 210 nm]. The reaction was cooled to <30 °C and 5 wt % NaCl solution (61 kg) was added and mixed well, and the layers were separated. The organic layer was washed twice with 5 wt % $NaHCO_3$ solution (ca. 61 kg portions) and with 5 wt % NaCl solution (61 kg). The organic phase was filtered to remove some interfacial materials and assayed by HPLC versus a working standard for **1**: 11.47 kg (86.9% yield). The solution was concentrated in vacuo to about 45 L. Precipitated **1** was redissolved by warming the mixture (to 70 °C), and then the solution was cooled to room temperature over 2 h during which time **1** crystallized. Heptanes (47 kg) were added slowly, and the resultant slurry was further cooled to 0 °C.

(9) In addition to the *E*- and *Z*-vinyl sulfone products **11**, minor amounts of the allyl isomers **14** (*E* and *Z*) may be observed at 12.2 min and the butenyl sulfone **21** at 12.0 min (from elimination of the tertiary alcohol impurity **13**).

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(10) On the basis of DSC and ARC experiments conducted in our Process Safety Laboratory, we chose to run reactions with 50 wt % aqueous *N*-hydroxylamine only in glass-lined equipment. Solutions of $NH_2OH$ have been shown in certain circumstances to generate gas and heat when brought into contact with metals and metal impurities (i.e., rust).

After stirring at 0 °C for 1 h, the slurry was filtered. The solids were washed with a pre-cooled (0 °C) 1:1.5 mixture of *i*-PrOAc−heptanes (25 kg). The residual amounts of TFE in the dried sample at this stage of isolation were typically found to be 100−150 ppm by GC. The wet cake was transferred to a 100-gal glass-lined reactor fitted with a mechanical stirrer. *i*-PrOAc (107 kg) was added, and the mixture was heated to ∼60 °C to dissolve the solids. The solution was polish-filtered to remove any extraneous matter. The filtrate was concentrated in vacuo to about 35 L of volume. The concentrated reaction mixture was heated to ∼80 °C to dissolve precipitated solids and then cooled to room temperature over 3 h. Heptanes (47 kg) were added slowly, and the resultant slurry was further cooled to 0 °C. After stirring at 0 °C for 1 h the slurry was filtered. The solids were washed with pre-cooled (0 °C) 1:1.5 mixture of *i*-PrOAc−heptanes (25 kg). The product was dried (ca. 100 mmHg with a $N_2$ purge at 55 °C); **1** obtained weighed 10.83 kg (83.3% yield, 99.8% HPLC peak area, >99.5% potency, >99.8% ee), and TFE/TFEF was undetectable (detection limit ∼30 ppm): mp 130−131 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.87 (br s, 0.7H), 8.38 (s, 0.3H), 7.89−7.84 (m, 2.7H), 7.58 (br s, 0.3H), 7.29−7.24 (m, 2H), 7.13−7.07 (m, 4H), 4.81 (ddd, $J$ = 3.2, 4.6, 10.4 Hz, 0.3H), 4.30−4.25 (m, 1.7H), 4.10 (dd, $J$ = 6.3, 9.2 Hz, 0.7H), 4.04 (dd, $J$ = 6.6, 9.2 Hz, 0.3H), 3.90−3.75 (m, 2H), 3.32 (dd, $J$ = 3.2 14.8 Hz, 0.3H), 3.11 (dd, $J$ = 1.7, 14.8 Hz, 0.7H), 1.40 (s, 2.1H), 1.40 (s, 0.9H), 1.31 (s, 2.1H), 1.29 (s, 0.9H). $^{13}$C NMR (125 MHz, $CDCl_3$) major rotomer: $\delta$ 162.3, 157.7, 153,3, 145.9, 132.9, 130.3, 122.9, 121.4, 120.4, 118.1, 109.9, 74.5, 65.7, 56.8, 51.8, 26.5, 24.6; minor rotomer: ä 162.7, 162.5, 153.1, 146.0, 131.4, 130.8, 123.0, 121.5, 120.4, 117.9, 109.8, 75.2, 65.5, 51.1, 26.2, 24.5. Anal. Calcd for $C_{21}H_{22}F_3NO_8S$: C, 49.90; H, 4.39; N, 2.77; F, 11.28; O, 25.32; S, 6.34. Found: C, 49.86; H, 4.31; N, 2.62; F, 11.56; S, 6.60.

**Synthesis of Tertiary Alcohol (13).** A 250-mL three-neck round-bottom flask fitted with $N_2$ inlet, thermocouple, and overhead stirrer was charged with **3** (10.123 g, 30.46 mmol). The reaction vessel was purged with $N_2$ for 30 min, and under an $N_2$ atmosphere, charged with anhydrous THF (65.0 mL). The resulting solution was cooled with stirring to −78 °C. *n*-BuLi in hexanes (5.8 M, 5.51 mL, 32.0 mmol) was added to the reaction via syringe pump at a rate such that the internal reaction temperature was maintained below −70 °C. The resulting mixture was stirred for an additional 37 min and then a THF solution of acetone (2.51 mL, 32.4 mmol acetone in 6.0 mL of THF) was charged at a rate such that the internal reaction temperature was maintained below −70 °C, and the mixture was stirred for an additional 26 min. Completion of the reaction was determined by HPLC at this point. The reaction mixture was warmed to −40 °C and quenched by slow addition of 2 M $H_2SO_4$ (20 mL), while allowing the reaction temperature to warm to ca. 10 °C. The organic phase was separated and washed successively with 15 wt % brine (40 mL), 15 wt % $KHCO_3$ (40 mL), and 15 wt % brine (40 mL). HPLC assay of the product solution versus an internal standard indicated 11.9 g (100%) of **13**. The product solution was concentrated to an oil under reduced pressure and then dissolved in EtOAc and azeotropically dried by concentration under reduced pressure (50 mL EtOAc, three cycles). Thorough drying in vacuo gave a viscous pale oil. The material obtained by this procedure was identical by HPLC retention time, UV spectra, and $^1$H NMR spectra to the impurity formed during the ketone formation. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91−7.87 (m, 2H), 7.29−7.26 (m, 2H), 7.12−7.08 (m, 4H), 3.67 (s, 1H), 3.32 (s, 2H), 1.47 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.5, 152.9, 145.5, 134.9, 129.7, 122.7, 121.2, 120.4 (q, $J_{13C19F}$ = 257 Hz), 117.7, 70.2, 66.6, 29.9. Anal. Calcd for $C_{17}H_{17}F_3O_5S$: C, 52.30; H, 4.39. Found: C, 52.26; H, 4.47.


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This paper is dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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