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Process Research and Development of TP-808: A Key Intermediate for the Manufacture of Synthetic Tetracyclines

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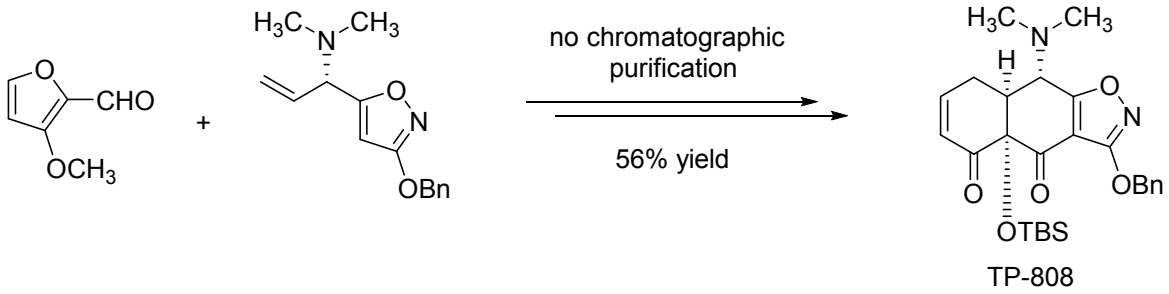

CHO
OCH3
+
H3C
N
CH3
O
N
OBn
no chromatographic
purification
56% yield
H3C
N
CH3
H
O
N
O
O
OBn
OTBS

TP-808

Abstract

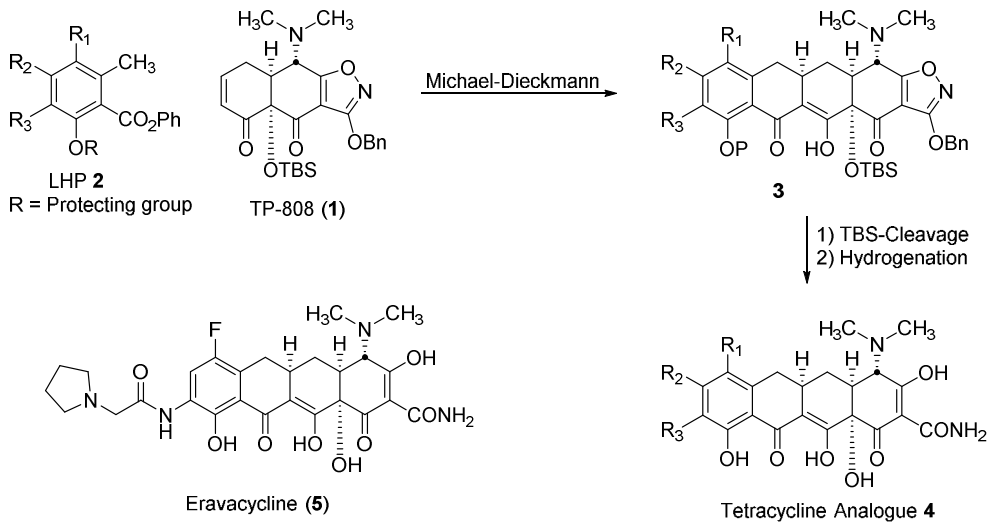
Process research, development and manufacture of TP-808 (**1**), a key intermediate for the discovery and manufacture of tetracycline analogs is described. The process used for the preparation of **1** avoids chromatographic purifications and has been substantially improved over the previously reported preparation. The robustness of the process was demonstrated in a 76.1 kg manufacturing campaign with 56% overall yield.

Key words: tetracycline, magnesiation, isoxazole, Omura-Sharma-Swern oxidation, Parikh-Doehring, enone, eravacycline

Introduction

As part of an ongoing effort to develop an efficient process for the manufacture of novel fully synthetic tetracyclines unavailable from traditional semi synthetic routes, our group has extensively investigated the process for the manufacture of enone **1**, a key intermediate for the synthesis of tetracyclines of wide structural diversity (Scheme 1).[1] Several synthetic approaches to the tetracycline antibiotics have been published previously, however most suffer from low overall yields as well as lengthy linear sequences.[2] The convergent, discovery-enabling synthetic approach to the tetracycline class of antibiotics reported by Myers group combines **1** and **2**, a substituted phenyl benzoate, in a base-promoted Michael-Dieckmann reaction to give pentacyclic intermediates **3** followed by deprotections to give the tetracycline analogues **4**. Our lead compound, eravacycline (**5**) is manufactured using this approach.[3]

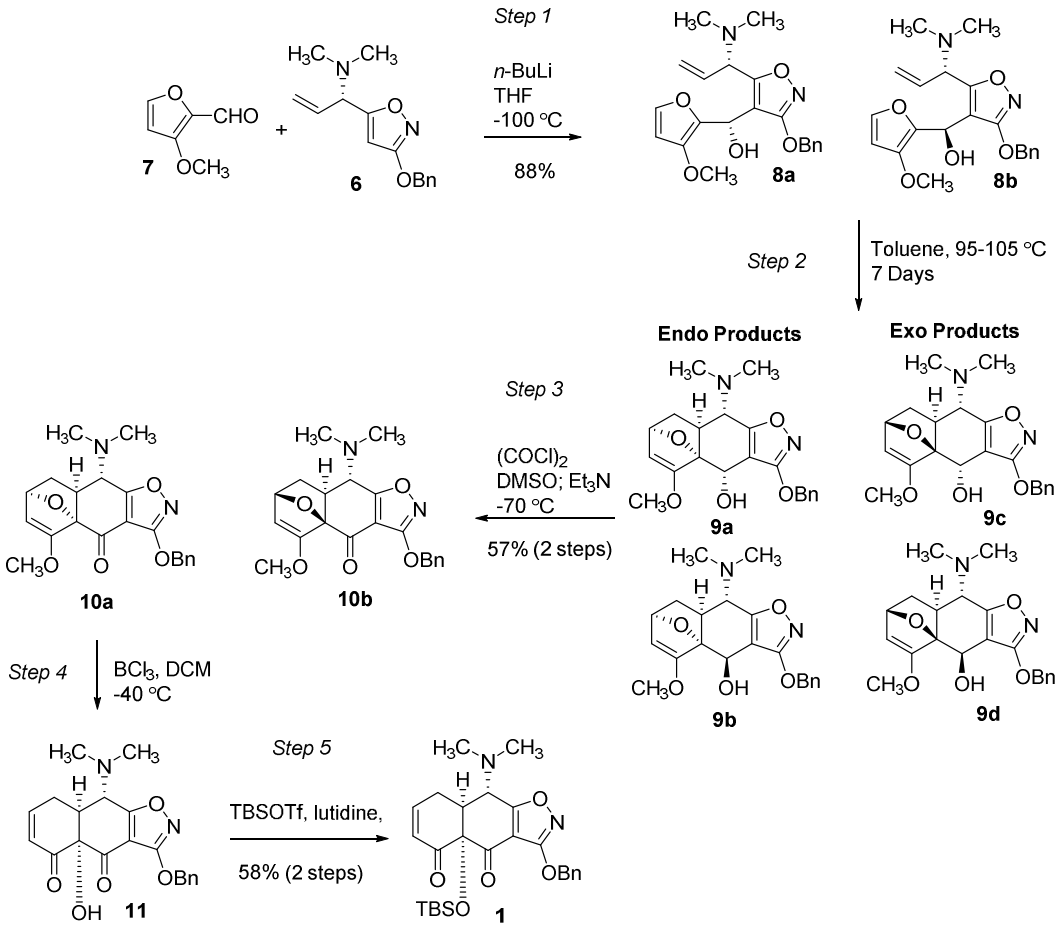
Scheme 1. Myers' Route to Tetracycline Analogues and the Structure of Eravacycline.



In 2007 Myers and Brubaker published a rapid and convergent route to **1** from two heterocyclic precursors, isoxazole **6** and 3-methoxy-2-furaldehyde (**7**) (Scheme 2).[4] This route was used to generate the first batches of material for research at Tetraphase, but all the steps needed improvement for large scale manufacturing. The lithiation of the isoxazole **6** and addition of the resulting anion to aldehyde **7** to give a mixture of alcohols **8a** and **8b** required a temperature of −100 °C; above this temperature the deprotonation is not regioselective leading to deleterious side reactions. The intramolecular Diels-Alder reaction of the mixture of **8a** and **8b** required a minimum of 7 days to reach completion. The overall selectivity for the favored endo isomers **9a** and **9b** relative to the unfavored exo isomers **9c** and **9d** was modest (~3:1) and the subsequent oxidation of the alcohols (**9a-d**) utilized cryogenic Swern conditions. The boron trichloride-promoted demethylation/ring opening step was not robust and at times provided low yields of **11a**. After each operation the desired product was isolated by silica gel chromatography. **10a** and **10b** were particularly difficult to separate in this manner. An overall yield of 29% was reported.

As Tetraphase's lead candidate, eravacycline (**5**) progressed through development, the demand for **1** required significant improvements in its manufacturing process.

Scheme 2. The Myers-Brubaker route to **1**



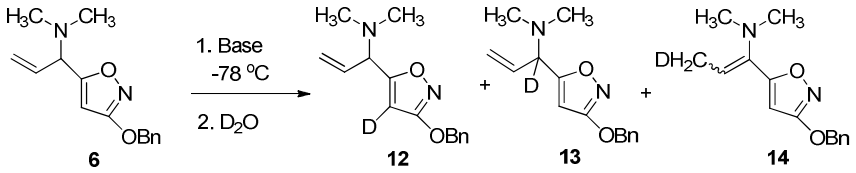
Results and Discussion

Step 1 Coupling:

At temperatures higher than −100 °C, allylic metallation (i.e., removal of proton α to the dimethylamino group) of **6** is competitive with metallation of the isoxazole ring. We attempted to improve the regio-selectivity of the deprotonation of **6** by using different reagents including *n*-butyllithium, *n*-hexyllithium, phenyllithium, methyllithium, KHMDS, and LiTMP in different solvents including THF, ethyl ether, DME and toluene. We also explored the use of additives such as TMEDA. To determine the regioselectivity of deprotonation, the reaction was quenched

with D_2O (Scheme 3) and the selectivity was determined by ^1H NMR. It was found that *n*-hexyl lithium using THF as solvent gave the best selectivity at −78 ºC (82% **12**, 18% **13** and **14**) which was slightly better than when *n*-BuLi was used. An analogous distribution of products was seen when the resulted anions reacted with furaldehyde **7**. All other conditions gave lower regioselectivity. In many cases the deprotonation of the allylic position was predominant.

Scheme 3. NMR Determination of Regio-Selectivity



We proceeded to investigate the direct magnesiation of **6** using a magnesium base. Hauser,[5] and later Eaton[6] and Knochel[7] have investigated the use of magnesium dialkylamides for the direct magnesiation of acidic C-H bonds. These bases have been used in the direct and selective magnesiation of acidic C-H bonds within arenes, heteroarenes and even certain alkenes and alkanes under mild conditions. To our knowledge, no metallations of isoxazoles had been examined with these types of bases at the initiation of this work.

Three different bases derived from tetramethylpiperidine (TMP), TMPMgCl·LiCl, TMPMgBr·LiBr and TMPMgBr·LiCl[8] were examined with regards to the regioselective metallation of **6** and the subsequent reaction of the organomagnesium species derived from **6** (will be referred to as **6**-anion) towards aldehyde **7** with respect to both conversion and stereoselectivity. The stereoselectivity of the addition of **6** to **7** plays a key role in the stereoselctivity of the Diels-Alder reaction (vide infra). All three bases metallated **6** exclusively

on the isoxazole ring at moderate temperature.[9] The bases containing bromide counter ion, TMPMgBr·LiBr and TMPMgBr·LiCl, provided slightly more favorable ratios of **8a** to **8b**, however the reactions with these bases were often incomplete and less clean, thus offered no advantage over TMPMgCl·LiCl, whose reactivity was superior in terms of providing the most consistent high yielding coupling reactions. For these reasons TMPMgCl·LiCl was chosen for further investigation and scale up.

Regioselective deprotonation of **6** proceeded rapidly at 0 °C using 1.2 to 1.4 equiv of TMPMgCl·LiCl. The furaldehyde **7** (1.1 equiv) was then added at –30 to –20 ºC to furnish the coupled product with ~2.3 : 1 ratio of **8a** to **8b**. These reaction conditions were successfully scaled to 1.6 kg scale with ~80% assay yields. An ensuing larger scale manufacturing run provided a 10 ~ 20% lower yield. We suspected that **6** and/or **6-**anion might be unstable under these conditions. To investigate the stability, three experiments were performed. After deprotonation of **6** with 1.4 equiv of TMPMgCl·LiCl at 0 ºC, the reactions were quenched at 0 °C at 0.5h, 1h and 2h, respectively. Although no significant impurities were detected by HPLC and ^{1}H NMR, the recovered assay yields of all three samples were approximately 15% lower than expected, indicating some non-specific decomposition under these conditions. The fact that deprotonation would not achieve completion without the extra 0.2 to 0.4 equiv of base suggested that at 0 °C the decomposition occurred concurrently to the deprotonation and consumed base. We proceeded to examine the metallation at a lower temperature. The magnesiation of **6** using 1.4 equiv of TMPMgCl·LiCl was carried out at approximately –25 ºC and was complete in ~ 40 min. The aldehyde **7** (1.1 equiv) was added and an IPC indicated ~30% of **6** was not consumed after overnight at room temperature. Additional **7** (0.3 equiv) was added leading to nearly quantitative consumption of **6** without the previously observed non-specific decomposition of **6**.

This indicated substantial stability of **6**-anion even at room temperature. We speculate that **7** reacts stoichiometrically with the excess TMPMgCl·LiCl first and consequently both the base and aldehyde **7** are not available for reaction with **6**-anion. Indeed, adding a slight excess of **7** relative to TMPMgCl·LiCl in general leads to a smooth and complete coupling. We noted that **7** was partially recovered after quench. In house experimentation revealed that the amount of TMPMgCl·LiCl and **7** used in this coupling could be lowered to 1.1 equiv each without sacrificing conversion and yield with the benefit of not wasting substantial amounts of **7**. Without the extra base the metallation took longer but still reached completion in 1.5 h. During the manufacturing normally 1.2 to 1.3 equiv of base is needed possibly due to generally less anhydrous conditions.

Table 1. Coupling Reaction selectivity and conversion

Entry*	Solvent	Additive	Temperature (°C)	Selectivity **8a/8b**	Conversion of **6**
1	THF		–70	5.0:1	14%
2	THF		–60	4.1 to 1	46%
3	THF		–50	3.3 to 1	53%
4	THF		–70 to –10	3.5 to 1	99%
5	2-MeTHF		–70 to –10	3.2 to 1	93%
6	toluene		–70 to –10	3.3 to 1	85%
7	THF	LiCl (2equiv)	–70	5.1 to 1	16%
8	2-MeTHF	LiBr (3equiv)	–70	6.4 to 1	16%
9	2-MeTHF	$MgBr_2$ (2equiv)	–70	5.9 to 1	19%
10	2-MeTHF	LiBr (3equiv)	–70 to –10	3.7 to 1	98%
11	2-MeTHF	$MgBr_2$ (2equiv)	–70 to –10	4.1 to 1	93%

*All reactions used 1.2 equiv of base and 1.2 equiv of furaldehyde **7**.

Another aspect of the reaction concerns the stereoselectivity since the *S*-alcohol (**8a**) is favored in the subsequent Diels-Alder reaction (vide infra). Our results for the coupling between **6** and **7** are summarized in Table 1. The coupling at −70 °C (entry 1) using TMPMgCl·LiCl provided the most favorable ratio of **8a/b** observed (5:1), however the reaction stalled with 86% of **6** remaining. Raising the temperature of the reaction to −60 °C and −50 °C (entries 2 and 3) provided somewhat better conversion but with decreased diastereoselectivity. The best compromise between stereoselectivity and conversion was achieved by addition of **7** to a cold solution (−70 °C) of **6**-anion and allowing the reaction temperature to gradually rise to −10 °C (entry 4). The use of other solvents, toluene and 2-methyltetrathydrofuran (2-MeTHF) (entries 5 and 6), suffered lower selectivity and lower conversion. Reactions with additives were also investigated.[10] The reactions in 2-MeTHF with LiBr and $MgBr_2$ as additives gave better selectivity at low temperature, whereas the selectivity did not change in THF with LiCl as additive (entries 7-9). The use of LiBr in THF improved the ratio slightly when the reaction was gradually warmed up from −70 °C to −10 °C (entry 10). Although the selectivity of **8a/b** was improved to 4.1:1 with $MgBr_2$ as additive, it was negated by lower conversion (about 7% of **6** recovered, entry 11). Other additives (e.g. Me_3Al, Et_2AlCl, BF_3OEt_2, $TiCl_4$, and $Ti(O\text{-}iPr)_4$) were examined, however none improved the selectivity significantly. Overall none of the additives benefited the reaction. Our optimal conditions employ THF as solvent with the metallation of **6** conducted at −25 °C and the subsequent coupling of **7** with **6**-anion conducted from −70 °C to −10 °C to give a mixture of **8a/b** with 3.5:1 selectivity favoring **8a**. The products **8a** and **8b** are not stable below pH 6 thereby the use of mineral acids for work up must be avoided. We also

observed that the presence of residual tetramethylpiperidine is detrimental to the subsequent Diels-Alder reaction. Using saturated aqueous ammonium chloride solution for quenching the reaction avoids strong acidic conditions and also effectively removes the tetramethylpiperidine from the organics during phase cuts. In a typical manufacturing, **8a/b** are obtained in greater than 90% purity by HPLC and ~90% yield, and the mixture can be directly used in the next step without further purification.

Step 2 Diels-Alder Reaction

The originally reported Diels-Alder conditions for the conversion of **8a/b** to **9a-d** required 7 days and provided modest endo selectivity (**8a** gave **9a** and **9c** in a ratio of 6.2 to 1 and 8**b** gave **9b** and **9d** in a ratio of 1.6 to 1). Additionally, the volumetric efficiency was low as 26 volumes of solvent were required and increasing the initial concentration of **8a/b** provided lower selectivity. We proceeded to investigate improving the endo/exo selectivity, the volumetric efficiency and the reaction rate in order to reduce the manufacturing cycle.

We briefly investigated the effect of Lewis and mild Brönsted acids with regards to reaction time and endo/exo selectivity.[11] Lewis acids ($Yb(OTf)_3$, $Al(O\text{-}iPr)_3$ and silica gel) as additives as well as halogenated alcohols[12] ($(CF_3)_2CHOH$, CF_3CH_2OH and $ClCH_2CH_2OH$) as solvents were examined. In line with our previous observations of the acid sensitivity of **8a/b**, these additives/solvents generally led to substantial decomposition of the starting materials. We proceeded with an extensive solvent screen in the presence of 1.1 equiv of diisopropylethylamine and 1% of BHT (Table 2). Reactions in chlorobenzene and α,α,α-trifluorotoluene gave a similar product distribution as toluene (entries 1 to 3). Excellent endo-selectivity was obtained at small scale in acetonitrile (entry 4). However, at larger scale the selectivity dropped unexpectedly

(entry 5). The reaction could be accelerated at higher temperature by using a sealed tube or microwave reactor (entries 6 and 7). Notwithstanding the lower selectivity at higher temperature, this provided quick access to Diels-Alder products. Excellent endo selectivity was also observed when isopropyl acetate, methyl isobutyl ketone, butyl acetate, or *t*-butyl acetate was employed at small scale (entries 8 to 11), however the selectivity was not realized at a larger scale (entry 12). The inconsistent results discouraged us from investigating these solvents for further scale up.

Table 2. Diels-Alder Reaction Conditions and Results

Entry[a]	Solvent	Temperature	**9a**/**9c** (from **8a**)[b]	**9b**/**9d** (from **8b**)[b]	*endo*/*exo* selectivity[c]	Reaction time
1	Toluene	95 - 110 °C	6:1	1.6:1	78.5:21.5	7 days
2	chlorobenzene	95 °C	7:1	1.4:1	78.7:21.3	6 days
3	α,α,α-trifluorotoluene	95 °C	7:1	1.9:1	80.8: 19.2	6 days
4	acetonitrile	reflux	37:1	2:1	89.9:10.1	4 days
5[d]	acetonitrile	reflux	13:1	2:1	84.9:15.1	5 days
6	acetonitrile	105 °C	8:1	1.5:1	80.2:19.8	40 h
7	acetonitrile	150 ºC (microwave)	7:1	1.3:1	78.1:21.9	1.5h
8	isopropyl acetate	95 - 100 °C	34:1	1.7:1	86.8:13.2	5days
9	methyl isobutyl ketone	95 - 100 °C	35:1	1.6:1	86.5:13.5	5 days
10	*n*-butyl acetate	95 - 100 °C	32:1	1.7:1	86.6:13.4	5 days
11	*t*-butyl acetate	95 - 100 °C	26:1	1.7:1	86.2:13.8	5 days
12[e]	isopropyl acetate	95 °C	17:1	1.3:1	83.1:16.9	6 days

13	2-propanol (IPA)	reflux	30:1	1:1	82.7:17.3	6 days
14	*t*-butanol	95 °C	29:1	1:1	82.5:17.5	6 days
15	1,3-propanediol	95 °C	23:1	1:1.1	81.2:18.8	1 day
16	Ethylene glycol	95 °C	11:1	1:1.1	78.3:21.7	20 h
17	1,4-dioxane	95 °C	30:1	1:1	81.5:18.5	3 days
18	DMF	95 °C	25:1	1.1:1	81.6:18.4	2 days
19	DMSO	95 °C	45:1	1: 1	83.4:16.6	2 days
20	$EtN(iPr)_2$	95 °C	10:1	1.1:1	79.3:10.7	2 days

a: All the reactions used 30 vol of solvents, 1.1 equiv of *i*-Pr_2NEt and 1% of BHT. Unless noted, 100mg of starting material was used.

b: The selectivity is determined by the integration of the methoxy group by ^1H NMR.

c: The endo/exo selectivity is calculated based on the endo/exo selectivity**,** and the 2.3 : 1 ratio of **8a** to **8b** (*S*-8 to *R*-8) in the starting material.

d: Starting material: 17 g.

e: Starting material: 10 g.

In alcoholic solvents (IPA and *t*-butanol, entries 13 and 14), reaction of **8a** gave excellent selectivity (~30:1), while **8b** was not selective (~1:1). The reaction proceeded without the formation of substantial impurities by HPLC, however some tarry materials were observed at kilogram scale. These materials could be removed by a filtration through a small pad of silica gel. We were gratified that the reaction rate and selectivity were not affected by lowering the solvent volume from 30 vol to 10 vol. Thus IPA was chosen as the solvent for a laboratory scale campaign (1.5 kg) and larger scale pilot plant runs. This Diels-Alder reaction was complete in 6 days at gram scale but needed 7 to 8 days in the pilot plant. After distillation the residue was purified by passage through a short silica gel (3x) column. We investigated the use of other, higher boiling point alcohols for decreasing the reaction time. The use of primary alcohols (*n*-

butanol, 3-methyl-1-butanol) resulted in decomposition of starting materials and/or products. If the reaction temperature was kept at ~95 ºC, other secondary and tertiary alcohols (e.g., *t*-amyl alcohol, 3-pentanol) gave similar results as the use of IPA. When the reaction was conducted at 110 ºC all reactions were complete in 2 days with increased impurities and lower selectivity (**8a**, 15:1 endo/exo*;* **8b**: 1:1 endo/exo*).* The reactions in ethylene glycol and in 1,3-propanediol were attractive because of the shorter reaction time (<1 day, entries 15 and 16), however the workups were complicated by the formation of emulsions and consequently the yields were low.

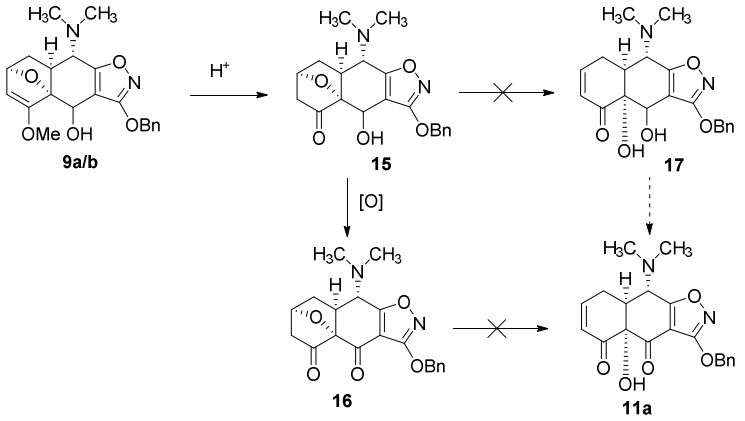
Examination of the Diels-Alder reaction in polar aprotic solvents dioxane, DMF and DMSO gave good selectivity and the process was substantially accelerated (entries 17-19). The use of DMSO was particularly attractive, as the oxidation in the next step uses a substantial amount of DMSO as a reagent. The reaction in DMSO was completed after 2 days at 95 °C. After the reaction reached completion, it was stressed by keeping the reaction at 100 ºC for additional 2 days. Even after this extended reaction time, yield and purity were not compromised. We tested these conditions with crude **8a/b** containing residual **6** and **7** and monitored the process closely by ^{1}H NMR and LC/MS. Only products and impurities carried over from the starting material were observed with both residual **6** and **7** unchanged. The reaction was run using 3, 5 and 10 volumes of DMSO respectively and no significant difference in selectivity or reaction rate was noted. Because MTBE, ethyl acetate or isopropyl acetate could be used as an extraction solvent for the coupling step, one volume of isopropyl acetate, ethyl acetate or MTBE was added to the reaction respectively and again no adverse effect was observed.

In the presence of water, we observed in the course of these studies the formation of a substantial byproduct **15** (Scheme 4) which, unfortunately, is not a productive intermediate. In fact, **15** could be easily prepared by treatment of **9a/b** with acids (HCl, HCOOH or TFA) and

water. In our hands **15** did not undergo any productive ring opening reactions, nor did ketone **16** which was independently prepared by oxidation of **15**.

As water is also detrimental to the subsequent oxidation step, the moisture content before Diels-Alder is controlled at <0.1% by KF, a level that ensures both steps proceed smoothly. If the coupling product contains too much water it can be dried with a desiccant (e.g., 4 Å molecular sieves) or by azeotropic distillation. For large scale manufacturing, isopropyl acetate is selected as the extraction solvent for the coupling step because it is efficient for azeotropic removal of water. After the Diels-Alder reaction is complete the reaction mixture is diluted with 10 volumes of ethyl acetate and the resultant solution is used directly in the next step.

Scheme 4. Formation and Attempted Use of **15**



Step 3. Oxidation of Diels-Alder Products

Although the Swern oxidation of alcohols **9a-d** to ketones **10a/b** using oxalyl chloride and DMSO as reagents under cryogenic conditions was reported to proceed with good yield, on multiple occasions in our hands this reaction condition gave significant byproducts. We postulated that since in the Swern process the base (i.e., triethylamine) was added at the end, the

reaction environment could be acidic which was known to be detrimental to **9a-d** and **10a/b**. We investigated two other DSMO based oxidation methods. The Parikh-Doehring[13] oxidation ($DMSO/SO_3.Py/EtN(i\text{-}Pr)_2$) could be performed at room temperature and provided an essentially quantitative yield with 2 equivalents of SO_3·Py. After the Diels-Alder reaction was completed, to the reaction mixture extra amine base and SO_3·Py were simply added at mild temperatures (20 to 40 °C) to furnish the oxidation product. When this material was used to complete the synthesis of enone **1** an impurity was present that could not be removed by our normal purification (short column chromatography followed by heptane slurry). This impurity was identified as BCl_3.pyridine complex, confirmed by simply mixing pyridine and BCl_3 together. This complex was difficult to quench, surviving treatment with acids or bases. To prevent the formation of this byproduct, pyridine must be completely removed after SO_3·Py/DMSO oxidation. Azeotropic distillation with toluene effectively removed most of the pyridine but not completely. The pyridine could be extracted by washing the organics with aqueous $CuSO_4$, but emulsions formed at larger scales. The need to deliver **1** in excellent quality prompted us to continue screening oxidation methods. As an alternative we investigated the possibility of using the Omura-Sharma-Swern oxidation [Trifluoroacetic anhydride (TFAA)/DMSO/base].[14] To assure a basic environment throughout the reaction, the reagent charging sequence normally used in the literature (i.e., alcohol is added to premixed DMSO and TFAA followed by an amine base at the end) was modified. We investigated a reagent charging sequences in which TFAA was added to a mixture of **9a-d**, DMSO and base (NEt_3 or $i\text{-}Pr_2NEt$) in a solvent. This charging sequence proved effective on larger laboratory scales. It also allows for the Diels-Alder reaction mixture, which contains starting materials **9a-d**, $i\text{-}Pr_2NEt$ and DMSO, to be directly used in the oxidation without work up. Charging additional amine base followed by TFAA to the reaction mixture

after dilution with an appropriate solvent provides **10a/b**. The reaction is complete as soon as the charging of TFAA is complete. Typically 1.6 equiv of TFAA is sufficient to provide a complete reaction on laboratory scales. Since the product is not stable under acidic conditions, sufficient base should be added first to ensure that the mixture never becomes acidic. However, during large scale manufacturing, the reactions using TFAA often stalled with ~3% of **9a** remaining even after 3 equiv of TFAA were charged, presumably because the reaction mixture was less anhydrous at large scale. As a result the assay yield of the TFAA oxidation is generally 5% lower compared to that of SO_3·Py oxidation. Additionally for the TFAA reaction, a temperature range of 0 - 10 °C needs to be maintained to ensure a clean reaction and to avoid DMSO freezing. For these reasons SO_3·Py is preferred although charging liquid is operationally preferred in a plant setting. Using either TFAA or SO_3·Py, the same solvents and work up procedure can be used. Several solvents performed satisfactorily for this oxidation including THF, DCM, toluene and ethyl acetate. Ethyl acetate was selected as the solvent due to the ease of phase cuts during workup. In addition, we observed that when using ethyl acetate as the organic phase during the workup, DMSO and residual **7** from the coupling step above are easily extracted into the aqueous washes. After extraction the crude ethyl acetate solution is filtered through a pad of silica gel to remove any trace of polar impurities and then concentrated.

Only **10a** is a productive intermediate for the manufacture of enone **1**. The two isomers are not easily separated chromatographically. We discovered that the compound resulting from continued operations on **10b** could easily be removed after the last step of the manufacturing route of **1** (vide infra), allowing the mixture to be carried forward without purification in our earlier manufacturing campaigns. Since ethyl acetate is not compatible with BCl_3 in the next step, the residual ethyl acetate is completely removed by azeotropic distillation with toluene.

If the oxidation product is not purified, the final product **1** needs to be purified by column chromatography followed by a heptane slurry. In order to remove chromatography from the entire process, recrystallization of the crude oxidation product was investigated. A recrystallization of **10a/b** was developed using an ethanol/MTBE mixture yielding pure **10a**. This process is capable of purging impurities resulting from early manufacturing using un-optimized reaction conditions, however ~20% of **10a** is lost to the mother liquor. After optimizing the three steps leading to **10a/b**, especially when SO_3·Py was used, the purity of the crude material improved and an alternative recrystallization/re-slurry process using toluene and heptane was developed. After the work up, the ethyl acetate solution is concentrated followed by switching the solvent to toluene. The ratio of toluene to **10a** (mL/g) is determined by IPC using NMR and should be between 3 and 6. To the toluene solution, heptane (10 vol) is added at 70 to 80 °C followed by cooling to room temperature. The isolated product is typically > 90% pure as a light brown solid, containing 1 to 7% of **10b** depending on the quantity of toluene used. The yield loss to mother liquor is normally 2 to 5%. This recrystallization reduced impurity carry over, resulted in better control in subsequent reactions and allowed us to purify enone **1** without chromatography. In addition, it completely removed the residual pyridine resulting from the use of SO_3·Py.

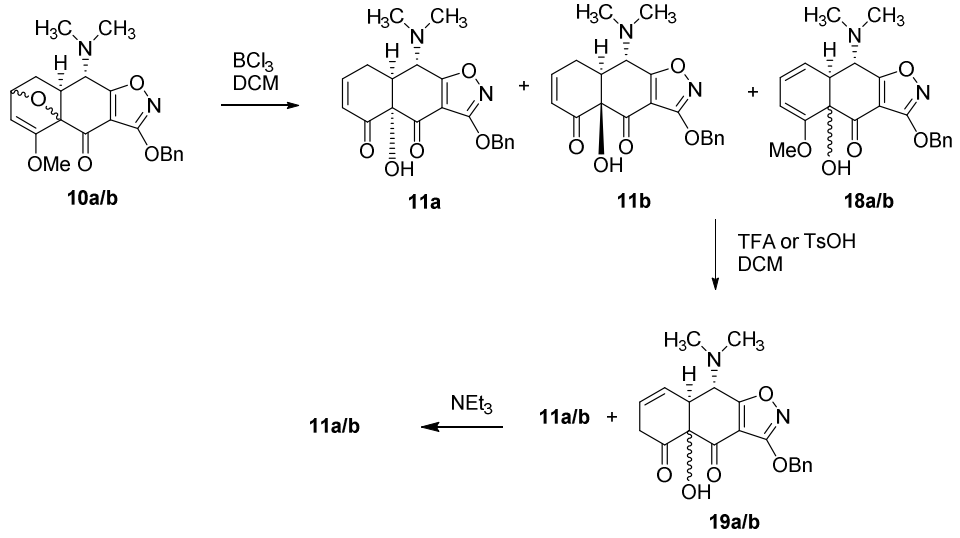
This two-step (Diels-Alder and oxidation) in one pot process has been successfully scaled up with a typical **10a** yield of 70%.

Step 4. Demethylative Oxygen Bridge Opening

Treating **10a/b** with BCl_3 at −40 °C gave crude tertiary alcohol **11a/b** in moderate yield along with varying amounts (up to 40%) of diene-containing side products **18a** and presumably minor

amount of **18b** (Scheme 5). In general, more **18a/b** is formed at lower reaction temperatures. The quality and source of BCl_3 also affected the outcome of the products. However, we could not explain or predict the variation of the amount of **18a**/**b** formed.

Scheme 5. Conversion of **10a/b** to **11a/b**



Since the amount of **18a/b** formed is significant and variable, conversion of **18a/b** to **11a/b** was seen as critical. Experimentation revealed that the vinyl ether **18a/b** could be easily converted to **11a/b** with acid. Variable amounts (1 to 10%) of β,ϒ-enone **19a/b** were observed when **18a/b** was treated with TFA or TsOH in DCM, or HCl in methanol. Since DCM is used as solvent in the ring opening reaction and work-up, it is easy to execute the conversion of **18a/b** to **11a/b** by addition of TFA or TsOH to the DCM solution after workup. Typically, treatment of **18a/b** with TFA in DCM gives the least amount of **19a/b** (1 to 5%) whereas TsOH gives up to 10%. However, the hydrolysis usually required 5 equiv of TFA and the reaction time varied significantly (6 to 21 h) dependent on the water content of the reaction mixture. On the other

hand, the hydrolysis only needs 2 equiv of $TsOH.H_2O$, and the reaction consistently reached completion in 2h irrespective of the water content.

A time course study confirmed enone **11a**, as well as the newly formed **19a/b,** were stable under the TFA or TsOH condition for >24h. The downstream product arising from **19a/b** is difficult to purge from **1** thus we examined the possibility of converting **19a/b** to **11a/b**. In the presence of catalytic amount (10 mol%) of Et_3N, isomerization of **19a/b** to **11a/b** was complete at room temperature in 1 h. Weaker organic bases such as 2,6-lutidine were not effective for this conversion.

We next examined the BCl_3 reaction parameters such as equivalents, reaction temperature and work-up. The ring opening reaction typically required 1.1 equiv of BCl_3 if purified **10a** was used and 1.3 equiv of BCl_3 when crude **10a/b** was used. Excess BCl_3 led to benzyl ether cleavage as evidenced by the appearance of a benzyl chloride peak on HPLC, however other side-products were not detected indicating further nonspecific decomposition of the molecule other than the benzyl removal. The effect of the purity of the starting material on the yield of the reaction was also evaluated. When the oxidation product was purified by chromatography or recrystallization, the yield of BCl_3 reaction was improved by 5 to 10%. Later, it was found that a simple filtration of the crude oxidation product through a silica gel pad (2x) removed the baseline polar impurities and this resulted in a similar high yield. It is hypothesized that the baseline impurities may partially quench BCl_3 rendering it ineffective for the demethylative ring opening reaction while still leading to nonspecific decompositions of the reaction intermediates.

The reaction rate at different temperatures was studied using 1.3 equiv of BCl_3 relative to the sum of **10a** and **10b** (Table 3). The reaction was rapid at 0 to –25 °C (entries 1-2) but slower below –35 ºC (entries 3-5). There was no benefit when the reaction was started at low

temperature and then warmed (entry 6). To examine the product stability under reaction conditions, a time course to monitor the yield of reactions was performed. At –10 to 0 °C the yield at 2 h was significantly lower than it was at 0.5 h but at below –20 °C the yield did not change with extended reaction time. Therefore, a temperature range of –20 to –30 °C is selected for this reaction.

Table 3: Temperature Effect on BCl_3 Reaction

Entry	Conditions[a]	**11a**[b] yield	**10a**[c]
1	–15 °C, 45 min	81%	0%
2	–25 °C, 30 min	80%	1.6%
3	–35 °C, 45 min	73%	11%
4	–45 °C, 45 min	63%	28%
5	–55 °C, 45 min	55%	34%
6	–70 to –25 °C, 80 min	77%	10%

a. Crude starting material was used. After the ring opening reaction, **18a** was converted to **11a** by TFA treatment.
b. Yield was determined by HPLC assay analysis.
c. Amount of SM after BCl_3 treatment.

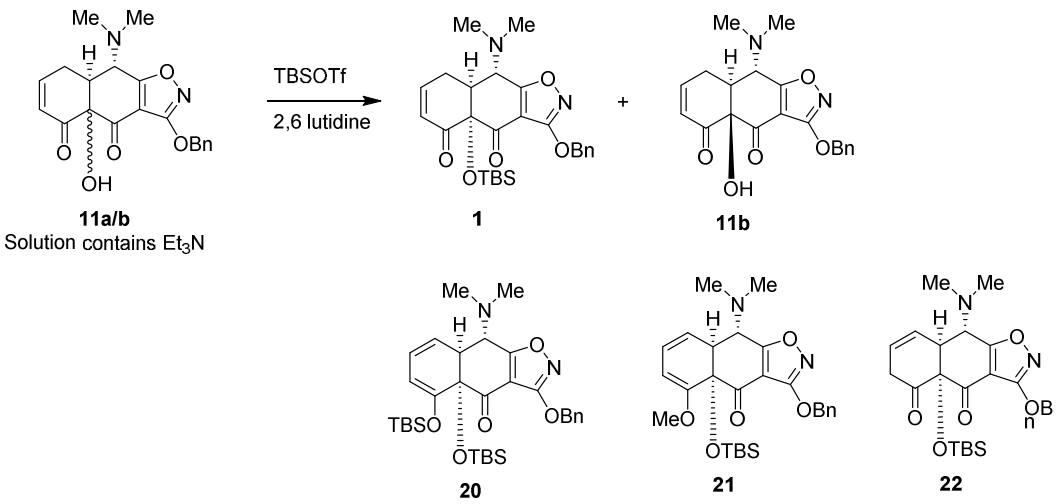
Although **11a** is stable toward acid, lower recoveries of **11a** were obtained if the reaction mixture was exposed to acidic conditions, e.g., when the reaction was quenched with water the yield of **11a** was low. This indicated that the intermediate before quench, presumably a borate complex, is susceptible to the acid generated from reaction of BCl_3 and water. A stress study in which aqueous potassium phosphate tribasic was added over an extended period also resulted in low yield. To ensure a basic environment during the work up a reverse quench was instituted for manufacturing. To our satisfaction, addition of the reaction mixture into an aqueous potassium phosphate tribasic solution at 30 to 40 ºC consistently gave high yields.

The quality of BCl_3 is critical for this reaction. We have encountered very low yield (< 30%) of **11a** with older BCl_3 solution presumably due to the HCl generated from the hydrolytic decomposition of BCl_3. To confirm this hypothesis HCl in dioxane was added to **10a/b** in anhydrous DCM solution and this indicated that **10a/b** decomposed quickly to many low level impurities. Other acids (i.e, TFA, MsOH, $PPh_3 \cdot HBr$) also decomposed **10a/b** under anhydrous conditions. High quality BCl_3 solution in DCM is not commercially available on large scale and therefore must be freshly prepared from neat BCl_3 and used immediately. We tested other BCl_3 solutions (toluene and heptane) without success. As a cost effective and practical alternative, we developed the direct use of vaporized BCl_3 from a cylinder. In contrast to BCl_3 in DCM solution neat BCl_3 in a cylinder is stable, readily available in large quantities and easy to handle during manufacturing. It is imperative that the BCl_3 should be condensed in the head space of the reactor. If it is bubbled into the reaction mixture the locally excess BCl_3 may cause product decomposition.

With control of the temperature, equivalents of BCl_3, and using neat BCl_3, yields of ~ 90% have been consistently achieved at laboratory and manufacturing scales.

Step 5. TBS Protection

Scheme 6. TBS Protection



The reaction solution from the previous step could be used directly in the TBS protection of the tertiary alcohol within **11a** (Scheme 6). If β,Ɣ-enone **19a** content was >2%, triethylamine was added before silylation to isomerize **19a** to desired **11a**. The reaction of **11a** with TBSOTf in the presence of NEt_3 gives some silyl enol ether **20** as a side-product but by controlling the reaction temperature at 0 to 10 ºC, impurity **20** could be controlled at ~1%. Residual **18a** and **19a** are converted to **21** and **22** respectively. Additionally, we discovered that **11b** does not react with TBSOTf under these conditions presumably due to the steric hindrance of the molecule and can be removed by a silica gel filtration. Indeed no reaction occurred when pure **11b** was treated with excess TBSOTf and 2,6-lutidine at room temperature. In our earlier manufacturing, the crude enone was purified by a two stage purification process. Unreacted **11b** and other polar impurities are first removed by a short column using 5x silica gel followed by removal of residual 2,6-lutidine and less polar impurities including **20**, **21** and **22** by a re-slurry in heptane. The desired product is isolated as a white to off-white solid with greater than 99% HPLC purity. In our earlier development manufacturing up to 26 kg scale of **1**, chromatography was needed but a method to avoid the cumbersome and costly procedure was desired.

After optimization of all steps, crude **1** after work up was generally > 90% pure on HPLC and this crude material could be purified by a simple silica gel filtration followed by methanol/water slurry to give **1** with > 98% HPLC purity. However, in many instances the product was darker and had baseline impurities by TLC. After screening we found that the baseline TLC spot and color could be removed by treatment of the crude material with charcoal and silica gel in toluene. As a switch of solvent from toluene to methanol is difficult and azeotropic distillation of toluene with IPA is effective we investigated using IPA instead of MeOH for the crystallization of **1**. We found that enone **1** has better solubility in IPA at high temperature (70 to 80 °C) and a true recrystallization in IPA/water yielded better quality material than a methanol/water slurry. After a combination of silica gel/charcoal pre-treatment and IPA/water recrystallization, the material is generally >99% pure. The major impurities **20, 21** and **22** are normally completely purged to the mother liquor. To maximize the benefit of toluene, which requires less TBSOTf in the protection step compared to DCM presumably because toluene distillation removes some volatile impurities, and streamline the process, we designed the process as follows: the DCM solution from the previous step is distilled to a minimum volume, toluene is charged and the residual DCM is removed by azeotropic distillation. To the toluene solution, 0.1 equiv of triethylamine is added to facilitate the conversion of **19a** to **11a**. After isomerization, silylation is performed by adding 2,6-lutidine and TBSOTf at 0 to 10 °C. After aqueous work up, the toluene solution is slurried with 1.5x silica gel and 1x charcoal to remove color and baseline impurities. After removal of charcoal and silica, the filtrate is distilled and the residual toluene is removed by azeotropic distillation with IPA resulting in a clear hot IPA solution at 70 to 80 °C. To this hot solution 20% (volume relative to that of IPA) of water is added followed by cooling to 0 °C. The desired product is collected by filtration. The loss to the mother liquor is generally <5%.

It is worth noting that when **10a/b** and enone **1** are purified by recrystallization, the chiral purity is enhanced and the chiral purity of enone **1** is consistently close to 100%.

Conclusion:

We have developed an improved, robust process for manufacture of enone **1**, a key intermediate for synthetic tetracyclines, and demonstrated the process by manufacturing of 76.1 kg of enone **1** with 56% overall yield (Step 1, 95.2%; Step 2/3, 73.9%; Step 4, 90.1%; Step 5, 88.4%). Key improvements include: 1) mild coupling conditions using TMP.LiCl.MgCl as base with 3.5 :1 stereoselectivity; 2) shorter Diels-Alder reaction using DMSO as solvent with higher endo to exo selectivity, allowing the resulting reaction mixture to be used in subsequent step as a one pot procedure; 3) a mild dose-control oxidation condition and a recrystallization process with high recovery; 4) tighter control of the demethylation/ring opening reaction and subsequent conversion of diene to desired product to ensure high yield; 5) using neat BCl_3 from a cylinder resulting in much lower material cost as well as a simple operation; 6) an IPA/water crystallization process to provide high quality enone **1** with minimal product loss. These improvements enabled a synthetic sequence with no column chromatography.

Experimental Section

General. The experiments outlined below provide representative procedure of enone 1 synthesis for what was run on scale in the pilot-plant facilities. ^{1}H NMR spectra were recorded on a JEOL ECX-400 400 MHz spectrometer. Achiral HPLC analyses were performed on an Agilent SunFire C18 (150 mm × 4.6 mm, 5 μm) column with 10–100% CH_3CN/H_2O (+0.1%

TFA) as mobile phase over 21 min at flow rate of 1.5 mL/min. Chiral HPLC analysis were performed on Shimadzu IA (250 mm × 4.6 mm, 5 μm) column using Hex/IPA/Ethansulfonic acid (30:70:0.14) as mobile phase over 15 min at flow rate of 0.5 mL/min.

Free base 6. The L-Tartrate of compound **6**[15] (115 kg, 281.6 mol, 1.0 equiv) and water (610 kg) were added to a 3000 L reactor and the mixture was cooled to 0-10 °C. To the mixture 6 M NaOH aqueous solution (96 kg, 563.2 mol, 2.1 equiv) was added over a period of 1 h while maintaining the temperature at 0-10 °C. After addition the pH of the mixture was approximate 10 indicated by pH paper. After stirring for another 10 min, the mixture was extracted with toluene twice (472 kg and 196 kg). The combined organics were washed with water (196 kg). The toluene solution was distilled under reduced pressure (< –0.085MPa) at below 65 °C to give 86.6 kg of product as a toluene solution. The water content was measured at 0.05% by KF.

Coupling Product 8a/b. The above toluene solution of **6** (281.6 mol, 1.0 equiv) was dissolved in THF (226 kg) and then the mixture was cooled to –20 to –30 °C at which temperature TMPMgCl·LiCl (320 kg, 309.6 mol, 1.10 equiv) was charged over a period of 1 h. After addition, the mixture was stirred for another 90 min at which time IPC indicated that ~7.4% of **6** were not deprotonated. Additional TMPMgCl·LiCl (24.0 kg, 23.2 mol, 0.08 equiv) was added over 15 min and then the reaction mixture was stirred for another 30 min at –20 to –30℃. IPC deemed the deprotonation was complete. The mixture was cooled to between –70 and –80 °C at which temperature a solution of compound **7** (42.5 kg, 337.0 mol, 1.2 equiv) in THF (240 kg) was added. After addition the reaction was stirred for 2 h and then was gradually warmed up to –15°C over a period of 8 h and stirred at –15 °C for another 2h. The reaction was quenched with

670 kg of saturated NH_4Cl. The mixture was filtered through a layer of celite. The celite was washed with 200 kg of water followed by 396 kg of isopropyl acetate. The organic layer was separated and the aqueous layer was extracted with 302 kg of isopropyl acetate. The combined organics were washed sequentially with saturated NH_4Cl twice (400 kg each), water (268 Kg) and brine (266 Kg). The resulting isopropyl acetate solution was concentrated under reduced pressure at below 50 °C until the water content was 0.06% by KF. During the distillation additional 178 kg of isopropyl acetate was added. An isopropyl acetate solution (164 kg with a HPLC assay of 62.86% corresponding to 103.1 kg of **8a**/**b** and 95.2% yield) was obtained. The ratio of **8a** to **8b** was 3.57:1 as determined by HPLC (74.3% of **8a** and 20.8% of **8b**). The ^1H NMR spectral data were consistent with those reported.[4]

Ketone 10a. The above **8a**/**b** solution in isopropyl acetate (103.1 kg of **8a/b**, 268.1 mol, 1.0 equiv), DMSO (526 Kg, KF=0.05%), diisopropylethylamine (39.1 kg, 294.9 mol, 1.1 equiv) and BHT (930 g, 2.7 mol, 0.01 equiv) were mixed in a 2000 L reactor. After the mixture was purged with argon it was stirred at 90 °C for 24 h and then at 95 °C for 24 h at which time HPLC analysis deemed the Diels-Alter reaction was complete. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (412 kg, KF=0.02%) followed by diisopropylethylamine (138 kg, 1067 mol, 4.0 equiv). Sulfur trioxide pyridine complex (120.6 kg, 758.7 mol, 2.8 equiv) was added in portions at below 30 °C over a period of 1.5 h. After the addition, the mixture was stirred at 20 to 30 °C for 16 h at which time the reaction was deemed complete by HPLC analysis. Water (310 kg) was added over a period of 1 h at below 30 °C to quench the reaction. The mixture was transferred to a bigger reactor and additional water (814 kg) and ethyl acetate (690 kg) were added. The mixture was filtered through a layer of celite and

the celite was washed with ethyl acetate (484 kg). The organic layer was separated and the aqueous layer was extracted with ethyl acetate twice (536 kg and 236 kg). The combined organics were washed with water (432 kg) and brine (432 kg), and then filtered through a 60.0 kg silica plug. The silica gel was washed with 588 kg of ethyl acetate. The crude solution was concentrated to about 300 L under reduced pressure (< –0.085 MPa) at below 50 ℃. To the residue toluene (640 kg) was added and the resulting solution was again distilled to ~ 300 L. The residue was diluted with 160 kg of toluene. ^{1}H NMR determined that the ratio of toluene to **10a** was approximately 4.5 L per 1 kg based on the integration of CH_3 groups in toluene and **10a**. Additional toluene (50 Kg) was added and then the toluene solution was heated to 70-80 ℃ at that temperature heptane (742 kg, approximately 10x volume of theoretical **10a/b**) was added over a period of 3 h. After addition, the mixture was cooled slowly to 10-20 ℃ at which temperature it was stirred for 12 h. Sample was analyzed by ^{1}H NMR which indicated a 5.4:10 (vol/vol) ratio of toluene and heptane. The slurry was filtered, washed with heptane twice (82 kg each) and dried under vacuum at 40-50 ℃ to afford 79.14 kg of **10a** as a light brown solid with a HPLC assay of 95.77 % corresponding to 75.8 kg and 73.9% yield). HPLC showed 99.1% of **10a** and 0.9% of **10b**.The ^{1}H NMR spectral data were consistent with those reported.[4]

Unprotected enone 11a. In a 500 L cryogenic reactor, the above **10a** (39.5 kg solution with an assay of 95.77% corresponding to 37.8 kg of **10a**, 98.9 mol, 1.0 equiv) was dissolved in 380 kg of anhydrous DCM. The solution was cooled to –50 to –40 ℃. At this temperature vaporized neat BCl_3 (13.2 Kg, 1.14 equiv) from a cylinder was directly conducted into the reactor head space and condensed/dissolved into the reaction mixture. After addition, the mixture was warmed to –30 to –20 ℃ and then stirred at this temperature for 15 minutes at which time the

reaction was deemed complete by HPLC. The reaction mixture was transferred into a reactor containing 502 kg of 20% K_3PO_4 aqueous solution while maintaining the temperature at 35 to 40 ℃. The mixture was cooled to 15-25 ℃ and then combined with another reaction mixture with the same batch size for workup.

The organic layer was separated and the aqueous layer was extracted with 180 kg of DCM. The combined organics were washed with 460 kg of brine. To the DCM solution was added TsOH.H_2O (75.6 kg, 397.4 mol, 2.0 equiv) and then stirred at 15-25 ℃ for 5 h at which time HPLC showed all diene **18a** was consumed. To the mixture was added 910 kg of 20% K_3PO_4 solution to adjust the pH to > 8. The organic layer was separated and the aqueous layer was extracted with 182 kg of DCM. The combined DCM solutions were washed with 552 kg of brine and distilled to give 644 kg solution of **11a** with a HPLC assay of 10.2% corresponding to 65.7 kg of **11a** and 90.1% yield. HPLC purity: 96.5%. The ^{1}H NMR spectral data was consistent with those reported.[4]

TP-808 (Enone 1). The above solution of **11a** (65.7 kg of **11a**, 178.3 mol, 1.0 equiv) was distilled to a minimum volume. To the residue toluene (210 kg) was added and the mixture was distilled under reduced pressure (< –0.085MPa) at below 60 ℃ to a minimum volume. The distillation cycle was repeated until the water content of the residue was 0.02%. To the residue 390 kg of toluene was added followed by triethylamine (1.96 kg, 0.1 equiv). The mixture was stirred at 15-25 ℃ for 2 h and then was cooled to 0 to10 ℃. At this temperature 2,6-lutidine (38 Kg, 354.8 mol, 2.0 eq) was added followed by TBSOTf (76.5 Kg, 288.8 mol, 1.6 equiv). After stirring for 30 min at 0 to10 ℃ the reaction was deemed complete by HPLC and was quenched with water (312 kg). The two layers were separated. The aqueous layer was extracted with

toluene (143 kg). The combined toluene layers were washed with brine (390 kg). To the toluene solution was added silica gel (117 kg) and charcoal (78 kg). The slurry was stirred at 20-30℃ for 3 h and filtered. After filtration, the filter cake was washed with toluene (977 kg) until TLC showed no product remained on the filter cake. The combined organic solutions were distilled under reduced pressure (< –0.085MPa) at below 60 ℃ to approximately 100 L. To the residue 326 kg of isopropyl alcohol was added and again the solution was distilled to ~100 L. This process was repeated for another cycle. To the residue 327 kg of IPA was added and the solution was analyzed by GC which indicated 0.14% of residual toluene. The mixture was heated to 75 °C and the solution was analyzed by ^{1}H NMR which determined the ratio of IPA and enone **1** was approximately 5.3 L per kg. Additional IPA (272 kg, 4.5 V) was added to make up a solution with 10x volume of IPA assuming 90% yield. The mixture was heated to 75-85 ℃, and to the resulting clear solution water (156 kg, 2.0 V) was added. The solution was cooled to 0 to 5 ℃ over a period of 6 h at which temperature the slurry was stirred for another 2 h. The slurry was filtered, washed with IPA/water twice (54 kg each, V/V=5:1), and dried in a vacuum oven at 45-55 ℃ for 36 h to give 76.1 kg (88.4 % yield) of enone **1**. The ^{1}H NMR spectral data were consistent with those reported.[4] HPLC purity: 100%; Chiral HPLC purity: 100%; LC/MS: $[M+H]^+$ 483.2; Anal. Calcd for $C_{26}H_{34}N_2O_5Si$: C, 64.70; H, 7.10; N, 5.80. Found: C, 64.77; H, 7.29; N, 5.82.

A total of 936 kg mother liquor was obtained with an assay of 0.31%. The loss to the mother liquor is 2.9 kg.

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