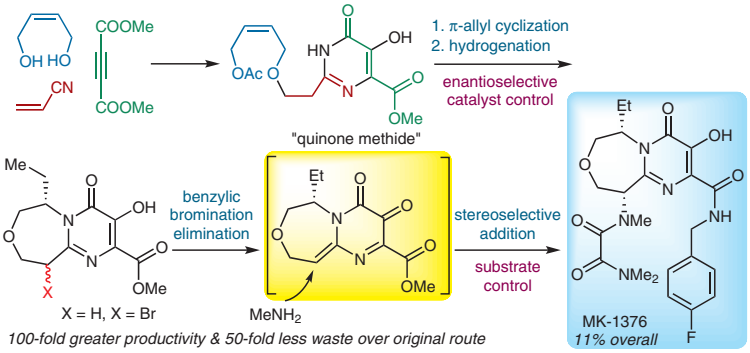
Synthesis P. E. Maligres et al. Special Topic

Synthesis of Fused Oxepane HIV Integrase Inhibitor MK-1376

Peter E. Maligres[*a]
Zhiguo Jake Song[*]
Neil A. Strotman
Jinquin Yin
Tao Pei[1]
Hallena R. Strotman[2]
Tetsuji Itoh
Edward C. Sherer
Guy R. Humphrey

Department of Process Research and Development, Merck & Co., Inc., Kenilworth, NJ 07033, USA
peter_maligres@merck.com

Published as part of the Special Topic *Synthesis in Industry*



Received: 22.01.2020
Accepted after revision: 20.02.2020
Published online: 16.03.2020
DOI: 10.1055/s-0040-1707994; Art ID: ss-2020-c0045-st

Abstract Controlling the absolute and relative stereochemistry of a seven-membered oxepane in the formation of HIV integrase inhibitor MK-1376 was accomplished through a strategy involving the use of asymmetric allylation and stereoconvergent, substrate-directed installation of an amine fragment. Surprising reactivity was demonstrated during the asymmetric allylation in which the allyl-pyrimidone product was formed reversibly. The stereoconvergent amine addition was accomplished through an elimination/addition sequence involving a quinone methide reactive intermediate, and nucleophilic trapping of the reactive quinone methide intermediate with methylamine. This novel approach delivered MK-1376, offering 100-fold greater productivity and 50-fold less waste than the initial synthetic chemistry route.

Key words HIV integrase inhibitor, oxepane, pyrimidine, π-allyl cyclization, quinone methide

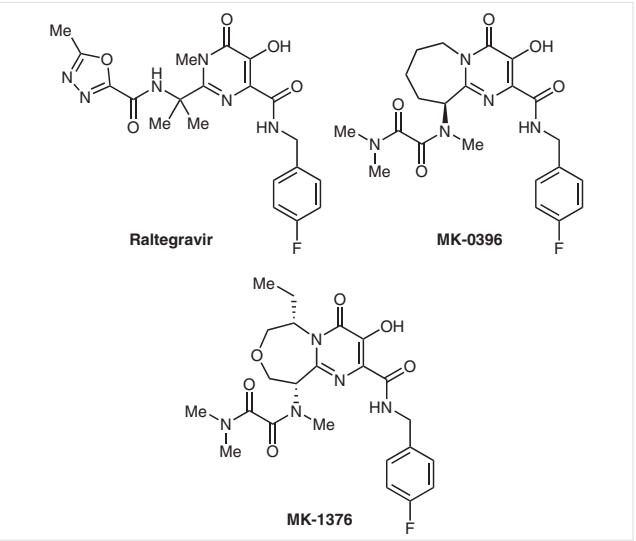


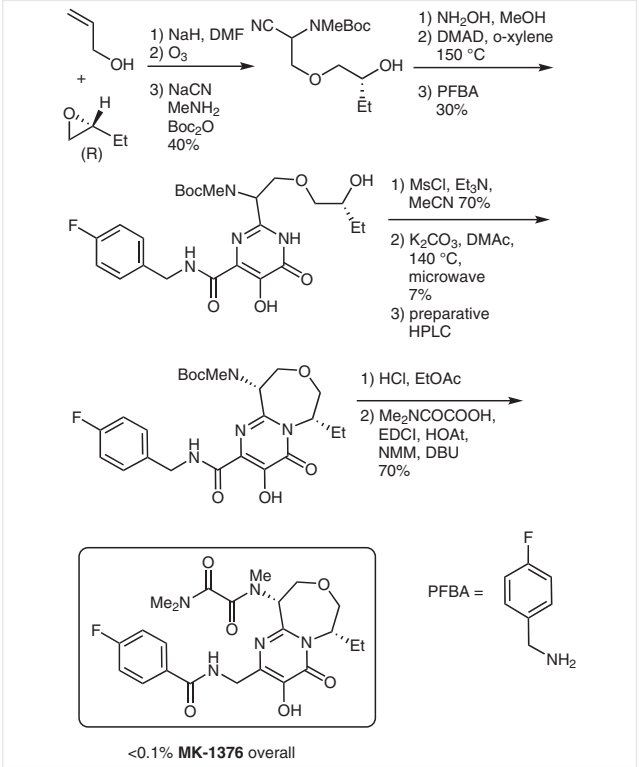
Figure 1 HIV Integrase inhibitors

Global estimates from the Joint United Nations Program on HIV/AIDS indicate that, as of 2018, over 76 million people have become infected with HIV, and 37 million have died from AIDS related illnesses since the 1981 start of the epidemic.[3] In 2017 alone, nearly 37 million people were living with AIDS, 1.8 million new cases had been diagnosed, and nearly 1 million people had died as a result. These discouraging statistics have spurred rapid expansion in HIV/AIDS research, with the discovery of multiple drugs targeting reverse transcriptase and protease to achieve successful combinational therapies. Despite the advances afforded by these approaches, drug resistance inevitably becomes a problem. More recently, HIV integrase has been targeted, with MSD's integrase inhibitor Raltegravir (Figure 1) representing an especially potent option.[4] More elaborate HIV integrase inhibitors bearing an oxepane fused pyrimidine have subsequently been identified, including MK-0396, bearing a stereogenic center[5] and MK-1376, bearing two stereogenic centers.[6]

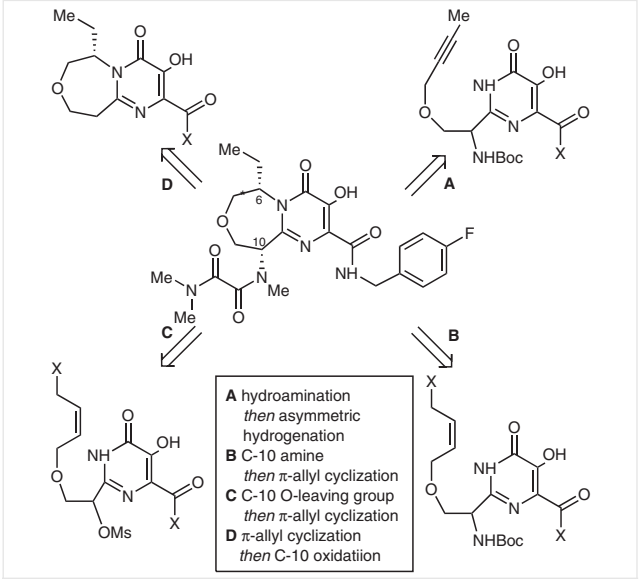
The original route for MK-1376 (Scheme 1) utilized commercially available, but expensive, 1,2-epoxybutane for the efficient preparation of an advanced intermediate that was an epimeric mixture at the nitrogen-bearing stereocenter. An intense effort was required for production of gram quantities of final product through an inefficient synthesis, mostly due to low cyclization yields, preparative chromatography to separate the diastereomers, and the complication of oxepane epimerization.

This existing chemistry was not amenable to scale, as preparation of a single kilogram of MK-1376 would generate more than 60 metric tons of waste. As a result, a new route was required to enable the preparation of clinical

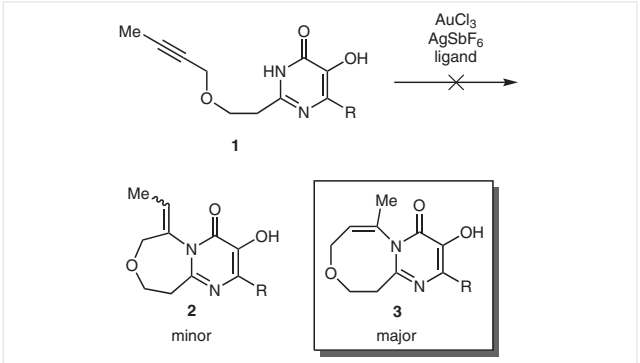
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 Initial route for HIV integrase inhibitor MK-1376



Scheme 2 Retrosynthetic strategy

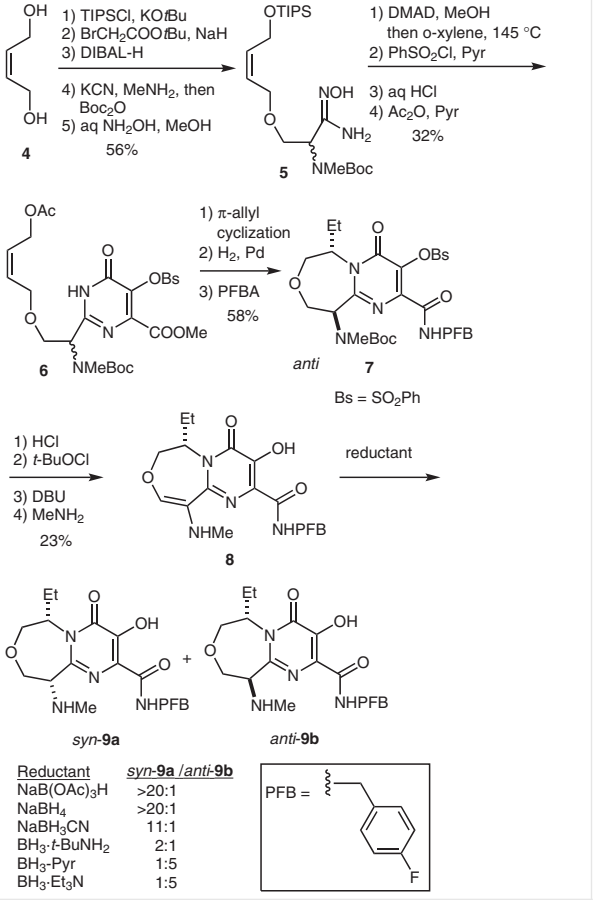


Scheme 3 Alkyne hydroamination

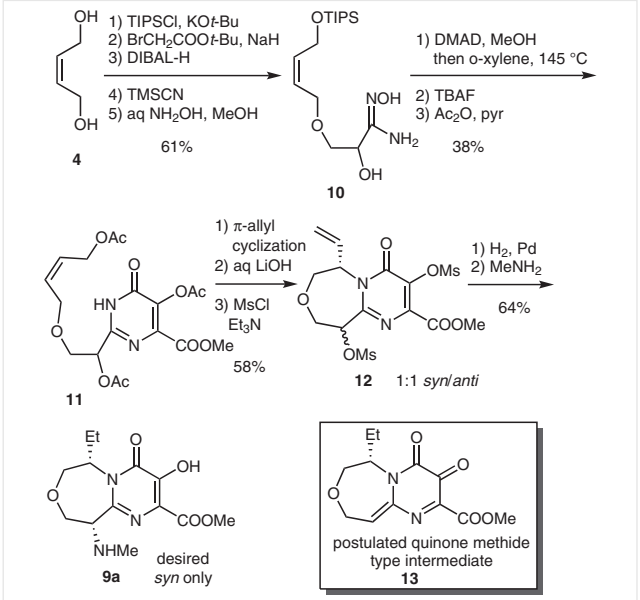
supplies of MK-1376. Several retrosynthetic routes were envisioned (Scheme 2). Our initial strategy was to introduce the C-10 amine center asymmetrically, followed by cyclization to the oxepane, and finally, asymmetric introduction of the C-6 center through either a hydroamination (route A) or a π-allylation approach (route B). The C-10 amine could also be installed later via displacement of the corresponding mesylate (route C). Alternatively, an approach was envisioned with oxidative installation of the C-10 center after having installed the C-6 center via the π-allylation (route D).

Our attempts at intramolecular hydroamination of a representative propargylic ether **1** to form the seven-membered azepane were unsuccessful (Scheme 2, route A). There was a strong preference for cyclization to form the eight-membered ring, providing only traces of the desired azepane **2** (Scheme 3).

Given this result, we turned our attention (Scheme 2, route B) to the intramolecular π-allyl cyclization of allylic acetate **6**, which is readily available from inexpensive *cis*-butene diol **4** (Scheme 4). Since earlier studies had suggested that the C-10 stereocenter of intermediates **5**, **6**, and **7** was prone to epimerization, the desired stereochemistry would need to be established later in the synthesis. Initially the π-allyl cyclization was run in a racemic sense to allow rapid exploration of downstream chemistry, yielding exclusively the *trans* isomer.[7] We hoped that the C-10 stereochemistry could be inverted through a sequence similar to that used for the preparation of MK-0396 (Figure 1) involving oxidation to the chloroamine followed by elimination to an imine/enamine intermediate[5b] and subsequent *syn*-selective reduction. Computations suggested a preference for the *anti*-addition transition state of sodium triacetoxyborohydride to imine to give *syn* **9a** by 14 kcal/mol, providing hope for a stereoselective reduction. While selectivity varied based on the hydride source employed (Scheme 4, bottom), the use of sodium borohydride and sodium triacetoxyborohydride both offered >20:1 *syn*-selectivity for the desired product. Unfortunately, upon reinvestigation of the π-allyl cyclization to render the route asymmetric, no successful conditions were identified. We hypothesized that the significant steric bulk imparted by the Boc-methylamine substituent was partially responsible for the poor selectivity of the π-allyl cyclization, leading us to investigate installation of this group at a later stage.



Scheme 4 C-10 Amine oxidation/stereoselective reduction



Scheme 5 Stereoselective C-10 displacement with $MeNH_2$

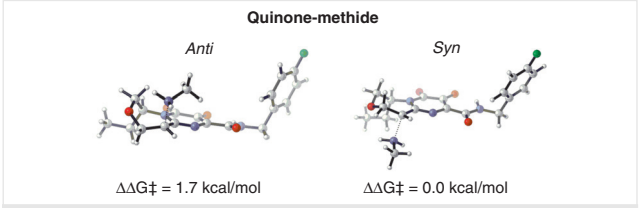
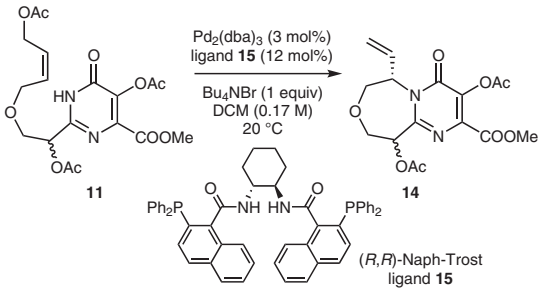


Figure 2 Transition states leading to *syn* and *anti* addition of methylamine to **13**

To this end, we focused our efforts on C-10 oxygenated systems featuring less steric hindrance at C-10 instead of protected C-10 amines (Scheme 2, route C). We envisioned activation of the C-10 center via conversion into a leaving group, taking advantage of the latent phenol to reveal a quinone methide system, which eliminates the need for stereocontrol at the originating sp^3 C-10 center (Scheme 5).[8] Trapping of the quinone methide by methylamine could afford exclusively the *syn* isomer through this stereoconvergent approach. While the hydride addition was shown to occur from the *anti* face, initial transition-state modeling of the quinone methide and methylamine suggested that the transition state leading to the desired product ***syn*-9a** was favored by 1.7 kcal versus the corresponding *anti* transition state (Figure 2). We envisioned that the C-6 enantioenriched mesylate **12** could be accessed via a cyanohydrin-based route involving asymmetric allylation (Scheme 5).

Initial screens of intramolecular asymmetric allylation of acetate **11** to form oxepane **14** revealed some surprising results (Table 1). While reactions with the naphthyl-Trost ligand **15** and Pd_2dba_3 in DCM (CH_2Cl_2) gave no C-6 enantioselectivity under typical conditions, the addition of Bu_4NBr resulted in high enantioselectivity and modest diastereoselectivity at moderate conversions (entries 1 vs. 2). It was also found that the activity was highest with a large ratio of the ligand to metal (2:1), despite the use of a bidentate phosphine.[9] In fact, at a ratio of 1:1, no conversion was observed (entry 3). Reactions in other solvents showed either low reactivity or poor enantioselectivity (entries 4–7). Lowering the temperature showed a modest increase in selectivity, but a concomitant decrease in conversion, while raising the temperature showed the converse (entries 8 and 9). Upon extended aging, reactions reached moderately higher conversion, but showed severe degradation of ee (entry 10). To understand the effect of Bu_4NBr, other halides (Cl, I), tetrafluoroborate, and tetrabutylphosphonium ion were investigated, but all were inferior (entries 11–15). Higher levels of Bu_4NBr resulted in slight improvements in ee, but decreased reactivity (entries 16 and 17). Higher catalyst loading was effective in achieving higher conversion but led to decreased ee and *cis*/*trans* ratio, likely due to product epimerization.[10]

Table 1 Optimization of Allylic Amination on C-10 Acetoxy Intermediate **11**

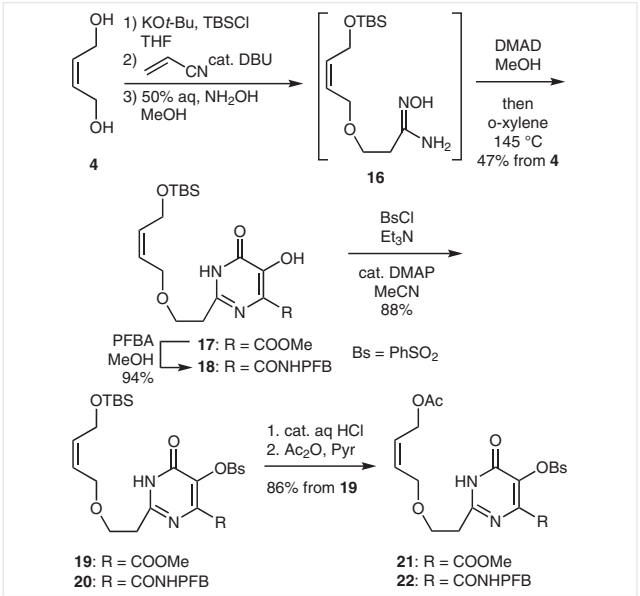


Entry	Change from standard[a]	Conv (%)	*cis*/*trans*	*cis* ee (%)	*trans* ee (%)
1	none	40	57:43	92	86
2	no Bu_4NBr	100	41:59	<5	<5
3	1:1 L/Pd	<2	ND	ND	ND
4	MeCN	<2	ND	ND	ND
5	MeCN, no Bu_4NBr	100	39:61	54	44
6	THF, no Bu_4NBr	100	37:63	<5	<5
7	toluene, no Bu_4NBr	79	55:45	<5	<5
8	10 °C	25	58:42	95	93
9	40 °C, 8 h	64	48:52	89	53
10	40 °C, 22 h	75	37:63	68	33
11	Bu_4NI	37	42:58	62	61
12	Bu_4NCl	82	41:59	33	28
13	Bu_4PBr	51	55:45	91	78
14	Bu_4PI	44	47:53	73	53
15	Bu_4NBF_4	91	39:61	<5	<5
16	0.5 equiv Bu_4NBr, 2 mol% Pd	46	57:43	96	87
17	2 equiv Bu_4NBr, 2 mol% Pd	29	58:42	98	93
18	2 equiv Bu_4NBr, 5 mol% Pd	88	47:53	91	77

[a] Standard conditions: Naph-Trost ligand **15** (12 mol%), Pd_2dba_3 (3 mol%), (2:1 L/M), Bu_4NBr (1 equiv), substrate **11** (0.17 M), 20 °C, 14–22 h.

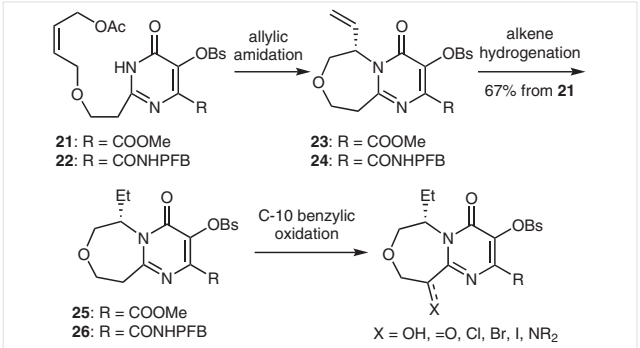
This surprising observation hinted at unprecedented reactivity by which the allylation step was reversible. Material that was >90% (*S*)-configuration at C-6 was carried forward to mesylate **12** as a ca. 1:1 mixture of C-10 epimers. Despite this starting mixture, deacylation and activation as the mesylate **12**, leading to quinone methide **13** gave exclusively the *syn* product upon attack by $MeNH_2$. Ultimately, while this approach delivered the desired material, challenges related to ee erosion at high conversion of the π-allylation led us to investigate an alternative approach.

The previous route provided proof of concept that a π-allyl cyclization could be employed to set the C-6 stereocenter, and this group could direct attack of methylamine on a quinone methide to afford the desired *syn* selectivity. This reactivity could be leveraged in a more efficient route involving a benzylic oxidation at the C-10 position (Scheme 2, route D). Pyrimidinone silyl ether **17** was prepared in four steps from inexpensive 1,4-*cis*-butenediol and isolated as a crystalline solid (Scheme 6). The ester functionality could either be retained or converted into the corresponding amide **18**. Products **21** and **22** were obtained after a sequence involving benzenesufonylation, desilylation, and *O*-acylation.



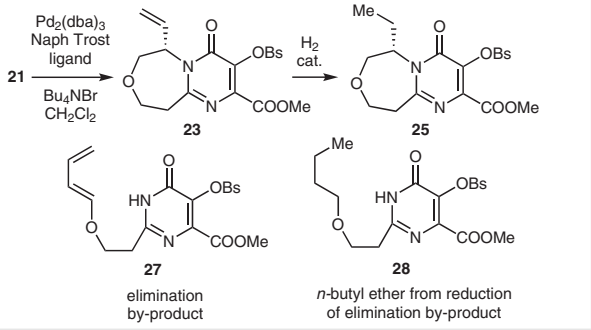
Scheme 6 π-Allyl substrate preparation

It was envisioned that compounds **21** and **22** could undergo a similar sequence as with acetate **11** involving asymmetric allylic amination and alkene hydrogenation to give bicycles **23** and **24**, respectively, bearing no substitution at the C-10 position (Scheme 7). Subsequent oxidation could intercept the chemistry in Scheme 5 at the quinone methide intermediate (**13**).



Scheme 7 π-Allyl cyclization and benzylic oxidation

Applying what was learned from C-10 acetate **11**, optimal asymmetric allylation conditions were developed for unsubstituted allylic acetate **21** after further screens involving 0.75% mol Pd_2dba_3, 3.15% mol (*R*,*R*)-Naph-Trost ligand (**15**), and 10% mol Bu_4NBr at 0.17 M in DCM and 22 °C. In only 7 h, these conditions gave 98.5% conversion and 96.2% ee, with 2.6% of elimination by-product **27** (Scheme 8).[11] However, as before, prolonged reaction times were found to lead to erosion of ee from reversible ring closure, and, in this system, also resulted in formation of diene **27** from elimination. Since the pyrimidinone can act as a leaving group, the allylic product is also susceptible to formation of the π-allyl Pd species. To our knowledge, this is the first example of reversibility in a π-allylation reaction. To suppress the epimerization and elimination processes post reaction, a series of additives were explored, but most showed little effect. Leveraging our previous observation that a low L/M ratio suppressed catalysis, we found that the addition of 1.5 mol% $Pd(OAc)_2$ immediately halted further reaction (productive and unproductive).



Scheme 8 Optimized π-allyl cyclization and hydrogenation

Our goal was to identify effective hydrogenation conditions on the crude reaction mixture to produce ethyl-substituted product **25**, rather than isolating vinyl intermediate **23**, to ensure configurational stability of the C-6 stereocenter.[12] Initial attempts to perform hydrogenation with the remaining Pd catalyst led to only 4% product, and formation of 6% of a new *n*-butyl ether by-product **28**, resulting from reduction of the diene **27** (Table 2). A screen of hydrogenation conditions revealed that reduction of the desired alkene took place in the presence of sulfided palladium on carbon, while minimizing ring opened by-products and avoiding epimerization. After hydrogenation, the optical purity can be upgraded from 94% ee to >99% ee through crystallization of the much less soluble racemate from *i*-PrOAc. After filtration from the racemate, recrystallization from isopropanol results in 74% isolated yield of compound **25** over two steps from acetate **21**.

Extensive screening of C-10 oxidation on ester **25** and amide **26** was performed. A variety of reagents and conditions were investigated, targeting a benzylic halide, alcohol, ketone, or amine derivative.[13] Use of amide **26** gave rise to

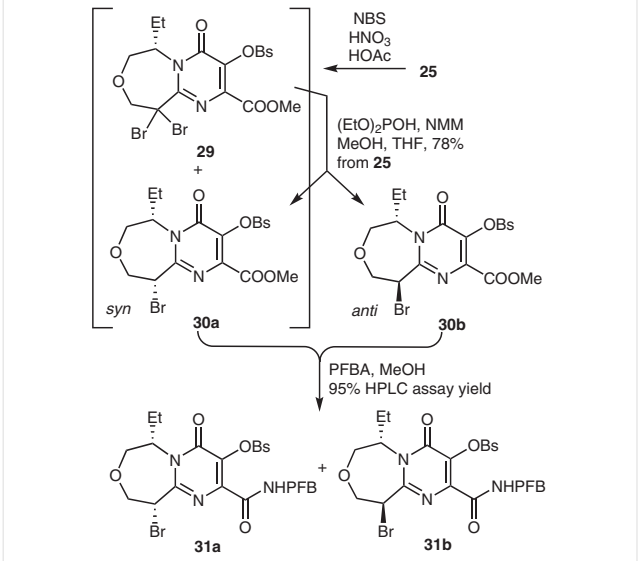
Table 2 Screen of Hydrogenation of **23**[a]

Catalyst	Unreacted SM **23** (%)	Product **25** (%)	*n*-Butyl ether **28** (%)
none	90	4	6
5% Pt/C	9	72	19
5% Pt/alumina	3	73	24
5% Pd(S)/C	0	93	7
IrO_2	88	4	8
2% Ir/C	59	28	13
5% Pd/$BaSO_4$	4	81	15
5% Pt(S)/C	1	79	20

[a] Reaction conditions: Crude allylic amination stream in *i*-PrOAc treated with $Pd(OAc)_2$. Added 5 wt% of heterogeneous catalyst relative to olefin **23**, 40 psi H_2, 16 h, 25 °C.

complex mixtures of by-products, probably due to the presence of an additional benzylic center, while employment of ester **25** gave encouraging results with NBS, Br_2, NIS and Pyr_2INO_3. The best results were obtained in HOAc with partial conversion into exclusively the *syn*-C-10 halide.

At this point, evidence from the Pyr_2INO_3 halogenations indicated an auxiliary oxidant could be beneficial in driving the halogenation to completion. Optimal conditions were identified involving NBS and HNO_3 in HOAc, resulting in complete conversion into a mixture of C-10 *syn*-mono- and dibrominated products **30a** and **29**, respectively (*anti*-monobromide **30b** was undetectable) (Scheme 9). A determination needed to be made whether the mono- or dibrominated product would offer a more effective path forward, although obtaining selectivity for either species alone proved challenging. The chemistry of the dibromide **29** was

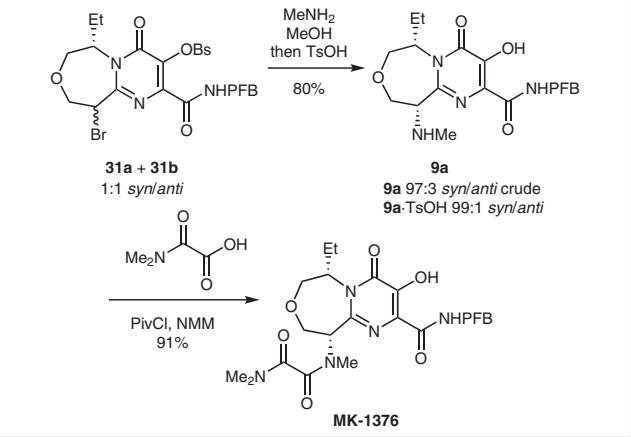


Scheme 9 Bromination of **25**

explored to determine whether a path involving an enamine or ketone was viable. Reactions of dibromide with methylamine were messy, while attempts to hydrolyze to the ketone resulted mostly in ring-opened product. The dibromide was also found to readily lose bromine (even oxidizing HBr to Br_2) to give mixtures of monobromide diastereomers. This serendipitous observation revealed the possibility that the dibromide could be selectively debrominated and offer a more robust path to the monobromide.

A screen of reducing agents showed diethyl phosphite to be the most effective reducing agent, chemoselectively reducing dibromide **29** to monobromides **30a** and **30b** without overreduction to starting material **25**. The 2:1 mixture of monobromide esters **30a** and **30b**, respectively, could then be converted into the corresponding PFB amides **31a** and **31b** via direct Me_3Al mediated ester amidation in the presence of the benzenesulfonate and bromide (Scheme 9).

As seen previously (Scheme 9), reaction of $MeNH_2$ with the electrophilic C-10 center of amide **31a** and **31b** gave the *syn* isomer, independent of the original stereochemistry at C-10, consistent with the intermediacy of a quinone methide. After further optimization, it was found that the reaction of $MeNH_2$ with the mixture of PFB amides **31a** and **31b** gave a 97:3 *syn*/*anti* ratio of the corresponding methylamines, with concomitant cleavage of the benzenesulfonate. Crystallization of **9a** as the *p*-toluenesulfonic salt provided the *syn* product phenol in 80% overall yield from **31** with 99:1 *syn*/*anti* ratio (no loss of ee). The final coupling was accomplished via a mixed anhydride intermediate, providing MK-1376 in 90% yield from penultimate **9a** with >99% dr, >99% ee, and >99% purity by HPLC (Scheme 10).



Scheme 10 Stereoselective methylamine displacement

In conclusion, a concise asymmetric synthesis of MK-1376 was developed, providing 11% overall yield from *cis*-1,4-butenediol and inexpensive, readily available starting materials and reagents, without the need for any chromatographic purifications. The key feature of this synthesis is an intramolecular asymmetric π-allyl palladium complex substitution by the pyrimidinone nitrogen to form a seven-membered heterocycle, which is reversible, requiring control through a combination of modified reaction conditions and an unusual post-reaction quench using $Pd(OAc)_2$. A benzylic bromination, followed by displacement with methylamine via a quinone methide intermediate, serves as a critical transformation to drive a stereoconvergent route to the *syn* oxepane of MK-1376. This novel strategy offered 100-fold greater productivity and 50-fold less waste than the initial medicinal chemistry route and laid the groundwork for critical scale-up efforts.[14]

Assay yields were obtained using analytical standards prepared by recrystallization or preparative chromatography. All isolated yields reflect correction for purity based on quantitative HPLC assays. Solkafloc was obtained from Seidler Chemical Co., Newark, NJ. All reagents and solvents were used as received without further purification unless otherwise stated. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of nitrogen gas. In general, glassware was not specially dried prior to use. Solvent switch refers to constant volume distillation with continuous addition of the new solvent. Ratios and percentages of solvents used for chromatography, TLC, HPLC and workups are by volume. High-pressure liquid chromatography (HPLC) analysis was performed with a Hewlett Packard series 1100 HPLC system; HPLC method for reported retention times: Zorbax Eclipse plus C18 50 × 4.6mm 1.8µm column eluted at 1.5 mL/min gradient 10→95% MeCN in 0.1% aq H_3PO_4 over 5 min then hold isocratic with detection at 210 nm. Analytical TLC was performed using Merck Kieselgel G60 F254 precoated plates (0.25 mm) followed by visualization with UV light (254 nm), staining with iodine vapor or staining with a solution of 14% ammonium molybdate and 0.5% ceric sulfate in 10% aqueous sulfuric acid then heat. Flash column chromatography was performed using silica gel (Merck, 70–230 mesh ASTM). Optical rotations were obtained with a Perkin–Elmer 241 polarimeter at 20 °C. Melting points were obtained with a Barnstead/Thermolyne MEL-TEMP® apparatus and are uncorrected. ^1H and ^{13}C NMR chemical shifts are reported in ppm; coupling constants are reported in Hz. ^1H and ^{13}C NMR spectra were recorded with Bruker AM and AMX systems. Elemental analyses were obtained from Shanghai Institute of Organic Chemistry Chinese Academy of Sciences and Quantitative Technologies Inc, Whitehouse, NJ.

(*Z*)-3-((4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)propanenitrile

A 75 L three-necked RB flask was charged with THF (27.5 L) and *t*-BuOK (95wt%, 6.10 kg, 51.6 mol) at r.t. to give a white slurry. *cis*-2-Butene-1,4-diol (**4**; 4.55 kg, 51.6 mol) was added as neat liquid over 0.5 hour maintaining the temperature below 20 °C. The resulting slurry was aged at r.t. for 30 minutes and TBS-Cl (7.00 kg, 46.5 mol) dissolved in THF (3.5 L) was added over 0.5 hour, keeping the temperature below 30 °C. The reaction mixture was aged at r.t. for 1–2 hours and quenched into a stirred mixture of water (25 L) and *t*-BuOMe (25 L). The layers were separated, the organic layer was washed with 5% aq NH_4Cl (18 L) and 5% aq NaCl (2 × 18 L). The *t*-BuOMe layer was concentrated to an oil in a 50 L three-necked RB flask. Heptane (20 L) was added and the mixture was concentrated to an oil to afford the *cis*-2-butene-1,4-diol mono-TBS ether,[15] which was used without further purification in the next step. ^1H NMR spectroscopic analysis indicated this crude oil contained 88 mol% of the mono-TBS ether (54.4 mol)

and 12 mol% of the bis-TBS ether. Acrylonitrile (68.1 mol, 4.46 L) and DBU (0.684 L, 4.54 mol) were added at r.t. and the reaction mixture was heated to 60 °C for 16 hours. The reaction mixture was cooled to r.t., diluted with *t*-BuOMe (25 L), transferred into a 100 L extractor and washed with 5% aqueous KH_2PO_4 (20 L). The layers were separated, the organic phase was washed with water (2 × 18 L) and concentrated to 10 L. The solution was solvent switched to MeOH to afford the coupled nitrile (10.5 kg, 91% assay yield from *cis*-2-butene-1,4-diol mono-TBS ether) as a solution in MeOH (30 L total volume), which was used as is in the next step. A sample of the crude solution was evaporated to provide a colorless oil.

HPLC: t_R = 4.92 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68–5.80 (m, 1 H), 5.51–5.65 (m, 1 H), 4.25 (d, *J* = 6.02 Hz, 2 H), 4.13 (d, *J* = 6.27 Hz, 2 H), 3.65 (t, *J* = 6.40 Hz, 2 H), 2.61 (t, *J* = 6.40 Hz, 2 H), 0.91 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.5, 126.1, 117.9, 67.0, 64.7, 59.6, 25.9, 19.0, 18.4, 5.12.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{26}NO_2Si$: 256.1733; found: 256.1732.

(*E*)-3-(((*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)-*N*′-hydroxypropanimidamide (16)

A 75 L three-necked RB flask was charged with a crude solution of the coupled nitrile from the previous step (10.42 kg, 40.8 mol in 30 L of MeOH). Hydroxylamine (50% aqueous, 2.75 L, 44.9 mol) was added at r.t. in one portion and the resulting solution was heated to 60 °C for 6 hours (99.8 A% conversion). The reaction mixture was cooled to r.t. and transferred into an extractor containing *t*-BuOMe (35 L) and water (35 L). The layers were separated (pH ~9) and the organic phase was washed with 5% brine (2 × 18 L). The aqueous portion was back extracted with *t*-BuOMe (15 L). The combined organic layers were concentrated to an oil and solvent switched to MeOH (3 L/kg solution) to afford a solution of the amidoxime, which was used as is in the next step. A sample of the crude solution was evaporated to provide **16** as a colorless oil.

HPLC: t_R = 2.60 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.60–5.65 (m, 1 H), 5.48–5.53 (m, 1 H), 4.94 (br, 2 H), 4.16 (d, *J* = 6.02 Hz, 2 H), 3.99 (d, *J* = 6.27 Hz, 2 H), 3.55 (t, *J* = 5.71 Hz, 2 H), 2.32 (t, *J* = 5.65 Hz, 2 H), 0.83 (s, 9 H), 0.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.67, 132.87, 126.55, 68.33, 66.82, 59.50, 31.91, 31.32, 25.94, –5.15.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{29}N_2O_3Si$: 289.1947; found: 289.1944.

Dimethyl 2-(((*E*)-(1-Amino-3-(((*Z*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)propylidene)amino)oxy)but-2-enedioate

A 75 L three-necked RB flask was charged with crude amidoxime **16** solution from the previous step (10.95 kg, 38 mol in 27 L of MeOH). The reaction mixture was cooled to –20 °C and dimethyl acetylenedicarboxylate (DMAD, 4.67 L, 38 mol) was added over 45 minutes keeping the temperature below 5 °C. The reaction mixture was concentrated, and solvent switched to *o*-xylene to make a 50 wt% solution of the DMAD adduct (16.4 kg, 100% assay yield). A sample of the crude solution was evaporated to provide a colorless oil containing the two isomers in 1:1 ratio.

HPLC: t_R = 5.02 and 5.07 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (d, *J* = 1.38 Hz, 0.2 H), 5.60–5.74 (m, 3 H), 5.48–5.59 (m, 1 H), 5.28 (br, 0.3 H), 4.21 (d, *J* = 6.02 Hz, 2 H), 4.03–4.14 (m, 2 H), 3.88 (d, *J* = 1.25 Hz, 0.5 H), 3.83–3.85 (m, 2 H), 3.70 (d, *J* = 1.25 Hz, 2 H), 3.67 (d, *J* = 1.38 Hz, 0.5 H), 3.58–3.66 (m, 2 H), 2.33–2.45 (m, 2 H), 2.02 (d, *J* = 1.25 Hz, 1 H), 1.24 (d, *J* = 7.15 Hz, 0.5 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

LC-MS (EI, 70 eV): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{35}N_2O_7Si$: 431.2; found: 431.3.

(*Z*)-Methyl 2-(2-((4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)ethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (17)

A 100 L three-necked RB flask was charged with *o*-xylene (55 L) and heated to 143–145 °C (heating mantle, gentle reflux). The crude DMAD adduct in xylene (7.40 kg assay, 16.7 mol, 50 wt% *o*-xylene solution) from the previous reaction was added over 2 hours to the hot *o*-xylene solution. The reaction mixture was aged 3 additional hours at the end of the addition, allowed to cool slightly to 130 °C and *o*-xylene (15 L) distilled under partial reduced pressure (internal temp 120–130 °C). The reaction mixture was allowed to cool to r.t. to give a tan mobile slurry of crystallized pyrimidinone. The slurry was aged overnight at r.t. Heptane (45 L) was added over 2 hours and then aged for 2 hours. The slurry was filtered, and the cake was washed with 1:1 toluene/heptane (15 L) and then with heptane (10 L). The cake was dried under vacuum and a stream of nitrogen for three days at r.t. to give the TBS-pyrimidinone **17** (3.75 kg, >97 A%, 85 wt%, 47% yield) as a white crystalline solid.

R_f = 0.15 (EtOAc/EtOH/HOAc, 15:4:1); mp 132–134 °C; HPLC: t_R = 4.11 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.15 (br, 1 H), 10.68 (br, 1 H), 5.67–5.73 (m, 1 H), 5.53–5.58 (m, 1 H), 4.20 (d, *J* = 6.53 Hz, 2 H), 4.12 (d, *J* = 6.40 Hz, 2 H), 4.01 (s, 3 H), 3.76 (t, *J* = 5.58 Hz, 2 H), 2.93 (t, *J* = 5.65 Hz, 2 H), 0.87 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.73, 158.60, 150.14, 149.66, 133.45, 126.08, 125.94, 66.99, 66.82, 59.43, 53.51, 35.22, 25.87, 18.27, –5.22.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}N_2O_6Si$: 399.1951; found: 399.1944.

(*Z*)-Methyl 2-(2-((4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)ethyl)-6-oxo-5-((phenylsulfonyl)oxy)-1,6-dihydropyrimidine-4-carboxylate (19)

TBS pyrimidinone (7.20 kg, 85 wt%, 15.4 mol) was charged to a 100 L RB flask. Pyridine (10.5 kg) was added at r.t., followed by the addition of benzenesulfonyl chloride (3.70 kg, 20.9 mol) over 30 minutes while maintaining the temperature at 25–30 °C. The solution was stirred at 25–30 °C for 2 hours. The batch was cooled to 20 °C and MeOH (21 L) was added followed by water (17.5 L). The slurry was stirred at 28–30 °C for 30 minutes. Water (17.5 L) was added at 20–25 °C. The slurry was aged 30 minutes and filtered. The filter cake washed with MeOH/water (3:5 v/v, 30 L). The cake was dried in a nitrogen stream on the filter pot overnight to give TBS besylate **19** (10.3 kg, 71wt%, 88% yield) as a white crystalline solid.

R_f = 0.52 (*t*-BuOMe); mp 112–115 °C; HPLC: t_R = 4.93 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.19 (br, 1 H), 7.92 (d, *J* = 7.2 Hz, 2 H), 7.57–7.61 (m, 1 H), 7.45–7.49 (m, 2 H), 5.59–5.63 (m, 1 H), 5.42–5.45 (m, 1 H), 4.11 (d, *J* = 5.96 Hz, 2 H), 4.03 (d, *J* = 5.96 Hz, 2 H), 3.74 (s, 3 H), 3.67 (t, *J* = 5.65 Hz, 2 H), 2.83 (t, *J* = 5.65 Hz, 2 H), 0.78 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.10, 158.83, 157.57, 146.04, 136.66, 135.41, 134.40, 133.80, 129.00, 128.61, 125.62, 67.12, 66.17, 59.45, 53.19, 35.27, 25.90, 18.30, –5.21.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{35}N_2O_8SSi$: 539.1883; found: 539.1874.

(*Z*)-Methyl 2-(2-((4-Acetoxybut-2-en-1-yl)oxy)ethyl)-6-oxo-5-((phenylsulfonyl)oxy)-1,6-dihydropyrimidine-4-carboxylate (21)

TBS besylate **19** (9.90 kg, 71wt%, 13.1 mol) and acetonitrile (18 L) were charged to a 50 L RB flask. Concd HCl (95 mL, 1.14 mol) was added and the solution was stirred at 15–18 °C for 1 hour. The mixture was washed with heptane (2 × 9 L) to remove TBS-OH. The acetonitrile layer containing the desilylated intermediate (HPLC: t_R = 2.68 min) was charged to a 72 L RB flask and pyridine (190 mL, 2.36 mol) was added. The solution was concentrated to approximately 15 L and flushed with acetonitrile (18 L) by distillation under reduced pressure (50 °C). Acetic anhydride (4.5 kg, 44.1 mol) was added and the solution was warmed to 75 °C for 3 hours. *i*-PrOH (30 L) was added and the batch was concentrated under reduced pressure (50 °C) to remove 20 L solvent. *i*-PrOH was added to obtain a final volume of 55 L at 50 °C. The solution was treated with Darco-G60 (activated carbon, 900 g), stirred at 50 °C for 1 hour and filtered warm through a small solka-floc pad into a 100 L RB flask. The filter cake was washed with *i*-PrOH (10 L) at 50 °C. The combined filtrates were stirred, cooled to 30 °C and seeded with product **21** (1 g). The slurry was cooled to 20 °C over 1 hour and then cooled to 2 °C and aged 1 hour. The slurry was filtered and washed with *i*-PrOH (10 L) and heptane (10 L). The cake was dried to give the acetate-besylate **21** (5.2 kg, >98wt%, 86% yield) as a white crystalline solid.

R_f = 0.20 (*t*-BuOMe); mp 71–73 °C; HPLC: t_R = 3.31 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.39 (br, 1 H), 8.03 (t, *J* = 5.20 Hz, 2 H), 7.66–7.73 (m, 1 H), 7.53–7.61 (m, 2 H), 5.64–5.78 (m, 2 H), 4.62 (t, *J* = 2.80 Hz, 2 H), 4.18 (t, *J* = 2.80 Hz, 2 H), 3.83 (s, 3 H), 3.75–3.82 (m, 2 H), 2.96 (t, *J* = 5.80 Hz, 2 H), 2.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.25, 163.19, 158.85, 158.19, 146.26, 136.70, 135.32, 134.51, 129.98, 129.14, 128.67, 127.53, 66.69, 60.05, 53.28, 35.39, 21.03.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_9S$: 467.1124; found: 467.1115.

Methyl 4-Oxo-3-((phenylsulfonyl)oxy)-6-vinyl-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepine-2-carboxylate (23)

A solution of the acetate besylate **21** (2.50 kg, 5.36 mol) and tetrabutylammonium bromide (173 g, 0.536 mol) in CH_2Cl_2 (20 L) was degassed with nitrogen. Degassed CH_2Cl_2 (6.8 L) was added to a mixture of Pd_2dba_3 (37 g, 0.040 mol) and (*R*,*R*)-naphthyl Trost ligand (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-1-naphthoyl) (**15**; 134 g, 0.169 mol). After stirring for 10 minutes, the catalyst solution was transferred to the stirred reaction vessel, and the reaction mixture was aged for about 8 h. Solid $Pd(OAc)_2$ (60 g, 0.27 mol) was added to quench the reaction. The resultant solution of allylated product **23** was carried forward to the next step. A second batch was run at the same scale. A sample of the crude solution was washed with water, filtered through a plug of silica gel and crystallized from *i*-PrOAc to provide **23** as a white crystalline solid.

R_f = 0.38 (*t*-BuOMe); mp 90–94 °C; HPLC: t_R = 3.46 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–8.07 (m, 2 H), 7.65–7.75 (m, 1 H), 7.51–7.62 (m, 2 H), 6.07 (ddd, *J* = 17.41, 10.76, 3.70 Hz, 1 H), 5.88 (dd, *J* = 3.51, 2.38 Hz, 1 H), 5.36 (dd, *J* = 10.79, 2.51 Hz, 1 H), 5.05 (dd, *J* = 17.44, 2.26 Hz, 1 H), 4.33 (dd, *J* = 13.93, 4.14 Hz, 1 H), 3.85 (s, 3 H), 4.04–4.16 (m, 1 H), 3.60–3.73 (m, 2 H), 3.46–3.58 (m, 1 H), 3.07 (dd, *J* = 15.43, 4.89 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.99, 161.14, 158.17, 143.69, 136.55, 134.53, 134.15, 131.67, 129.08, 128.62, 118.77, 71.45, 66.69, 57.07, 53.26, 40.63.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_7S$: 407.0913; found: 407.0907.

(*S*)-Methyl 6-Ethyl-4-oxo-3-((phenylsulfonyl)oxy)-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepine-2-carboxylate (25)

5% Pd (S)/C (828 g) was added to the crude CH_2Cl_2 solution of allylated product **23** from the previous step (2.03 kg, 5.00 mol assuming 100% yield for the allylation). The slurry was charged to a 10 gallon stirred autoclave. The reaction vessel was pressurized with hydrogen to 45 psi and heated at 30 °C until hydrogen uptake showed complete conversion. This was repeated on a second batch. The two hydrogenation batches were combined, *t*-BuOMe (2.5 L) was added and the mixture was then stirred with $MgSO_4$ (0.8 kg) and K_2HPO_4 (0.8 kg) for 30 minutes. The mixture was filtered through silica (6 kg). The silica pad was washed with 9:1 CH_2Cl_2/*t*-BuOMe (25 L). The combined filtrates were concentrated, and solvent switched to isopropyl acetate (13 L). The mixture was cooled to 22 °C over 1 hour. The resulting slurry was filtered on a pad of silica (0.25 kg) and the filter cake of racemate was washed with *i*-PrOAc (4 L) to give, on drying, the racemic ethyl oxepanopyrimidinone (0.17 kg, 10–20% ee). The filtrates were concentrated, and solvent switched to *i*-PrOH (13 L). The mixture was treated with Darco G60 (0.3 kg) at 80 °C for 1 hour. The mixture was filtered hot through a pad of solka-floc and washed with hot *i*-PrOH (4 L) and acetone (1.3 L). The combined filtrates were solvent switched to *i*-PrOH at 60–80 °C and cooled to 23 °C over 3 hours. The slurry was cooled to 10 °C over 2 hours and filtered. The cake was washed with *i*-PrOH (3 L) at 10 °C. The cake was dried under nitrogen stream to give the oxepanopyrimidinone **25** (3.186 kg, 95wt% purity, 74% from allylic acetate **21**) as a white crystalline solid.

R_f = 0.40 (*t*-BuOMe); mp 99–103 °C; $[\alpha]_D$ 57.7° (*c* = 1 in $CHCl_3$); HPLC: t_R = 3.51 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–8.05 (m, 1 H), 7.65–7.72 (m, 1 H), 7.51–7.61 (m, 2 H), 5.12–5.17 (m, 1 H), 4.05–4.21 (m, 2 H), 3.83 (s, 3 H), 3.42–3.66 (m, 3 H), 3.14 (dd, *J* = 15.81, 4.39 Hz, 1 H), 1.97–2.10 (m, 1 H), 1.84–1.95 (m, 1 H), 0.90 (t, *J* = 7.47 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.05, 160.63, 158.50, 143.33, 136.64, 134.48, 134.22, 129.07, 128.60, 70.84, 66.73, 57.80, 53.21, 40.95, 22.42, 10.59.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}N_2O_7S$: 409.1069; found: 409.1052.

(*S*)-Methyl 10,10-Dibromo-6-ethyl-4-oxo-3-((phenylsulfonyl)oxy)-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepine-2-carboxylate (29) and (6*S*,10*S*)-Methyl 10-Bromo-6-ethyl-4-oxo-3-((phenylsulfonyl)oxy)-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepine-2-carboxylate (30a)

Oxepanopyrimidinone **25** (3.35 kg, 8.20 mol) was suspended in acetic acid (24.6 L) in a 100 L four-neck RB flask. NBS (4.38 kg, 24.6 mol) was added followed by concentrated nitric acid (2.46 L, 38.5 mol). The mixture was warmed to 75 °C over 1 h and the resulting homogenous orange mixture was maintained at 72–80 °C for 3 hours. The mixture was concentrated under vacuum (50 Torr at 75–45 °C) to remove 6 L orange distillate, leaving a pale-yellow residual solution. The mixture was cooled to 35 °C, CH_2Cl_2 (12.3 L) and water (16.4 L) were added. The organic layer was separated and the aqueous phase was back-extracted with CH_2Cl_2 (4.1 L). The combined organic phases were washed with water (16.4 L) and 1.67 M aqueous K_2HPO_4 (24.5 L). The

combined CH_2Cl_2 extracts were dried over $MgSO_4$ (100 g), filtered and concentrated. The residue was solvent switched to 4.1 L THF containing a 4:3 mixture of di-bromo/mono-bromo products **29** and **30a**, which was used directly in the next step. A sample of the crude solution was evaporated and purified by flash column chromatography on silica gel (EtOAc/*n*-heptane = 1:4), which gave the dibromide **29** (97% LCAP) as a white crystalline solid.

R_f = 0.75 (*t*-BuOMe); mp 143–147 °C; $[\alpha]_D$ = 181.5° (*c* = 1 in $CHCl_3$); HPLC: t_R = 4.50 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–8.09 (m, 2 H), 7.69–7.77 (m, 1 H), 7.55–7.65 (m, 2 H), 5.04–5.12 (m, 1 H), 4.71 (d, *J* = 13.93 Hz, 1 H), 4.37 (dd, *J* = 14.18, 2.89 Hz, 1 H), 4.12 (d, *J* = 14.05 Hz, 1 H), 3.80 (s, 3 H), 3.68 (d, *J* = 14.18 Hz, 1 H), 2.40–2.48 (m, 1 H), 1.81–1.92 (m, 1 H), 0.96 (t, *J* = 7.47 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.14, 158.72, 155.18, 141.98, 136.55, 134.58, 134.23, 129.14, 128.55, 80.59, 70.79, 66.39, 60.93, 53.15, 23.46, 10.90.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}Br_2N_2O_7S$: 566.9259; found: 566.9243.

(6*S*)-Methyl *syn*- and *anti*-10-Bromo-6-ethyl-4-oxo-3-((phenylsulfonyl)oxy)-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepine-2-carboxylates (30a and 30b)

To the crude 4:3 mixture of di-bromo/mono-bromo oxepanopyrimidinones **29** and **30a** in THF from the previous step was added MeOH (16.4 L), NMM (631 g, 5.74 mol) and diethyl phosphite (741 g, 5.74 mol). The mixture was stirred for 1 hour at 25–40 °C. Water (19 L) was added dropwise over 2 hours while the mixture was gradually cooled to 17 °C. The resulting slurry was filtered, and the filter cake was washed with 1:1 MeOH/water (16.4 L) and dried to provide the 2:1 diastereomeric mixture of *syn*/*anti*-monobromides **30a** and **30b** respectively (3.16 kg, 78% from **25**) (mp 135–143 °C). A sample of the *syn*/*anti*-mixture was purified by flash chromatography on silica gel (EtOAc/*n*-heptane = 1:4), which gave the *syn* monobromide **30a** and the *anti* monobromide **30b** both as white crystalline solids. Both **30a** and **30b** undergo isomerization over time to ultimately give a 95:5 mixture of **30a** and **30b**, respectively.

syn-Monobromide 30a

R_f = 0.60 (*t*-BuOMe); mp 143–145 °C; $[\alpha]_D$ 188.8° (*c* = 1 in $CHCl_3$); HPLC: t_R = 4.08 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.78 Hz, 3 H), 7.67–7.74 (m, 1 H), 7.53–7.63 (m, 2 H), 5.29–5.36 (m, 1 H), 5.00 (br, 1 H), 4.36 (dd, *J* = 14.24, 3.20 Hz, 1 H), 4.24 (dd, *J* = 14.12, 2.82 Hz, 1 H), 4.02 (dd, *J* = 14.18, 1.25 Hz, 1 H), 3.60 (d, *J* = 14.31 Hz, 1 H), 3.81 (s, 3 H), 2.45–2.61 (m, 1 H), 2.04–2.10 (m, 1 H), 0.97 (t, *J* = 7.47 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.55, 158.69, 157.59, 142.92, 136.51, 134.67, 134.55, 129.11, 128.54, 72.39, 71.31, 60.35, 53.19, 52.38, 22.86, 10.80.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}BrN_2O_7S$: 487.0175; found: 487.0161.

anti-Monobromide 30b

R_f = 0.64 (*t*-BuOMe); mp 140–142 °C; $[\alpha]_D$ 193.2° (*c* = 1 in MeOH); HPLC: t_R = 4.10 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–8.06 (m, 2 H), 7.67–7.74 (m, 1 H), 7.51–7.61 (m, 2 H), 5.32 (dd, *J* = 2.70, 1.44 Hz, 1 H), 4.93–5.02 (m, 1 H), 4.33 (dd, *J* = 14.24, 3.20 Hz, 1 H), 4.22 (dd, *J* = 14.18, 2.89 Hz, 1 H), 4.01 (dd, *J* = 14.18, 1.38 Hz, 1 H), 3.77 (s, 3 H), 3.60 (d, *J* = 14.18 Hz, 1 H), 2.43 - 2.57 (m, 1 H), 1.95–2.11 (m, 1 H), 0.95 (t, *J* = 7.40 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.53, 158.68, 157.63, 142.87, 136.45, 134.60, 134.57, 129.13, 128.51, 72.35, 71.25, 60.35, 53.16, 52.47, 22.85, 10.80.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}BrN_2O_7S$: 487.0175; found: 487.0166.

(6*S*)-10-Bromo-6-ethyl-2-((4-fluorobenzyl)carbamoyl)-4-oxo-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepin-3-yl Benzenesulfonate (31a and 31b)

CH_2Cl_2 (10.5 L) was charged in a 50 L round-bottom flask. 4-Fluorobenzylamine (578 g, 4.62 mol) was added and the slightly yellow solution was degassed with N_2 for 1 h. Me_3Al (2 M, 2.3 L, 4.6 mol) was added slowly to the benzylamine solution over 1 h. The solution was aged at r.t. for 1 h. The diastereomeric mixture of *syn*/*anti*-monobromides **30a** and **30b** (1.5 kg, 3.08 mol) dissolved in CH_2Cl_2 (6 L) was added to the amine-Al complex solution over 20 min at 20–25 °C. The reaction mixture was aged at r.t. for 1 h and was pumped into a 50 L cylindrical vessel containing 1N HCl (15 L) at 10 °C. The relatively large exotherm and rapid gas evolution (methane) was controlled by the slow addition of the mixture to the aqueous HCl. The organics were washed with 1N HCl (2 × 15 L), saturated $NaHCO_3$ (15 L) and saturated brine (15 L) at r.t. The organic layer containing the amide products **31a** and **31b** (1.69 kg, 95% HPLC assay yield) was concentrated and solvent switched to methanol. The final volume of the MeOH solution was approximately 25 L and the solution of the amides was used in next step without further purification. A second batch was run at the same scale. A sample of the crude solution was evaporated and crystallized from *i*-PrOAc to provide a 2:1 mixture of **31a** and **31b** as a white crystalline solid.

Mp 117–129 °C; $[\alpha]_D$ 70.3° (*c* = 1 in $CHCl_3$); HPLC: t_R = 4.60 and 4.66 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.20 (t, *J* = 6.09 Hz, 1 H), 7.93 (dd, *J* = 8.41, 1.13 Hz, 2 H), 7.77–7.85 (m, 1 H), 7.62–7.70 (m, 2 H), 7.30 (dd, *J* = 8.60, 5.71 Hz, 2 H), 7.10–7.20 (m, 2 H), 5.57 (d, *J* = 1.00 Hz, 1 H), 4.81–4.95 (m, 1 H), 4.13–4.31 (m, 4 H), 4.04–4.12 (m, 1 H), 3.79 (d, *J* = 13.80 Hz, 1 H), 2.23–2.41 (m, 1 H), 1.94–2.03 (m, 1 H), 0.83 (t, *J* = 7.47 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.74 (d, *J* = 241 Hz, 1 C), 161.53, 160.53, 158.80, 157.99, 146.12, 136.49, 135.28, 135.22, 132.53, 129.90 (d, *J* = 7 Hz, 1 C), 128.58, 115.46 (d, *J* = 21 Hz, 1 C), 71.95, 70.49, 59.75, 54.37, 42.01, 22.75, 22.75, 10.82.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –115.84.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{24}BrFN_3O_6S$: 580.0553; found: 580.0548.

(6*S*,10*S*)-6-Ethyl-*N*-(4-fluorobenzyl)-3-hydroxy-10-(methylamino)-4-oxo-6,7,9,10-tetrahydro-4*H*-pyrimido[1,2-*d*][1,4]oxazepine-2-carboxamide 4-Methylbenzenesulfonate (9a·TsOH)

The methanol solution of the crude amides **31a** and **31b** from the previous step (3.0 kg, 5.17 mol) was charged to a 100 L flask and cooled to 5 °C. Methylamine solution in EtOH (33 wt%, 8 M, 3.23 L, 41.4 mol) was added over 15 minutes. The solution was aged 30 minutes at 5–10 °C, warmed to 20 °C and aged for about 4 hours until reaction was complete. A solution of toluenesulfonic acid (3.93 kg, 20.7 mol) in water (20 L) was added to the batch. The batch was seeded with salt product **9a**·TsOH (1 g), and aged 30 minutes. Water (9 L) was added over 30 minutes, aged for 30 minutes and additional water (60 L) add-

ed over 1 hour. The slurry was aged at r.t. for 1 hour, filtered, washed with 3:1 water/MeOH (10 L) and dried on a filter pot for 2 days with nitrogen flow. The crude dry cake was slurried in EtOAc (30 L) for 2 hours at r.t., filtered and washed with EtOAc (10 L). The cake was dried overnight to give amine salt **9a**·TsOH (2.32 kg, 80%) as a white crystalline solid.

Mp 202–204 °C; $[\alpha]_D$ 31.6° (c = 1 in $CHCl_3$); HPLC: t_R = 4.49 min (TsOH 1.10 min).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.42 (br. s., 1 H), 9.63 (d, J = 5.40 Hz, 1 H), 9.29 (br. s., 1 H), 8.85 (br. s., 1 H), 7.49 (d, J = 7.53 Hz, 2 H), 7.38 (dd, J = 8.28, 5.77 Hz, 2 H), 7.06–7.23 (m, 4 H), 5.10 (br. s., 1 H), 4.41–4.62 (m, 3 H), 4.00–4.17 (m, 2 H), 3.74–3.94 (m, 2 H), 2.71 (br. s., 3 H), 2.29 (s, 3 H), 2.14 (dt, J = 13.58, 6.70 Hz, 1 H), 1.77–1.94 (m, 1 H), 0.97 (t, J = 7.34 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.82, 161.57 (d, J = 242 Hz, 1 C), 157.89, 147.89, 145.25, 138.07, 134.55, 129.38 (d, J = 8 Hz, 1 C), 128.17, 125.48, 123.81, 115.19 (d, J = 22 Hz, 1 C), 67.91, 64.98, 60.50, 31.78, 22.00, 20.80, 11.24.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –115.56.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{24}FN_4O_4$: 391.1782; found: 391.1775.

Anal. Calcd for $C_{26}H_{31}FN_4O_7S$: C, 55.51; H, 5.55; F, 3.38; N, 9.96; S, 5.70; Found: C, 55.51; H, 5.60; F, 3.14; N, 9.81; S, 5.53.

MK-1376

A 50 L flask was charged with *N*,*N*-dimethyloxamic acid (0.66 kg, 5.64 mol), CH_2Cl_2 (14 L), and NMM (1.13 kg, 11.2 mol). The mixture was cooled to 15 °C. Pivaloyl chloride (0.64 kg, 5.31 mol) was added and aged 2 hours at r.t.. Amine salt **9a**·TsOH (2.01 kg, 3.58 mol) was added in one portion and aged 2 hours. The mixture was quenched with water (12 L) and 5 M HCl (0.21 L, 1.05 mol). The lower organic layer was separated and washed with water (2 × 12 L). The solution was concentrated to low volume and *i*-PrOH (8 L) was added. The solution was heated to 55–60 °C, seeded with MK-1376 (24 g, crystalline Form II), solvent switch continued at 55–60 °C by adding *i*-PrOH to maintain the volume at approximately 12 L. The slurry was aged at 55–60 °C for 6 hours, cooled to r.t. and filtered. The cake was washed with *i*-PrOH/heptane (10 L) and heptane (10 L) and dried *in vacuo* at 40 °C to afford MK-1376 as a white crystalline solid (1.62 kg, >98 wt% purity, 91% yield).

R_f = 0.50 (CH_2Cl_2/MeOH, 9:1); mp 142–144 °C; HPLC: t_R = 3.57 min (*anti* isomer 3.72 min).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.30 (s, 1 H), 9.63 (t, J = 6.3 Hz, 1 H), 7.37 (m, 1 H), 6.97 (m, 1 H), 5.82 (br s, 1 H), 4.62 (m, 1 H), 4.54 (d, J = 6.3 Hz, 2 H), 4.43 (m, 1 H), 4.20 (d, J = 3.1 Hz, 2 H), 4.13 (dd, J = 11.8, 2.7 Hz, 1 H), 3.07 (s, 3 H), 3.02 (s, 3 H), 2.85 (s, 3 H), 2.06 (m, 1 H), 1.83 (m, 1 H), 1.31 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.75, 166.74, 165.09, 162.47 (d, J_{CF} = 244.9 Hz), 159.45, 147.85, 144.38, 134.76 (d, J_{CF} = 3.1 Hz), 130.30 (d, J_{CF} = 8.0 Hz), 125.39, 115.57 (d, J_{CF} = 21.3 Hz), 67.89, 64.98 (br), 60.96, 54.78 (br), 42.76, 37.45, 34.00, 33.46 (br), 25.07, 11.70.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{29}FN_5O_6$: 490.2102; found: 490.2093.

Acknowledgment

We thank: C. Bazaral, R. S. Hoerner, T. Houck, and M. Weisel from the high pressure lab for their work on catalytic hydrogenation; M. Journet and R. Miller for alternate route exploration and scale-up lab work; G. Black, C. K. Esser, D. Henderson, J. F. Leone, J. Liu, L. Tan and D. Von Langen for scale-up of original route; M. Biba and T. Brkovic and Y. Liu for analytical support; R. Reamer for NMR support; S. D. Dreher, E. N. Guidry, S. Shultz, D. Steinhuebel, D. M. Tellers and M. Tudge for chemocatalysis, high-throughput screening and automation support; F. Fleitz for biocatalysis support; E. Choi and C. K. Maguire for molecular and materials characterization support; K. Emerson, E. Fisher and I. Lee for calorimetry and engineering support. We thank Jianjun Duan and Guiquan Liu at WuXi AppTec Co., Ltd. for characterization of intermediates. We are grateful to R. C. Ruck, P. G. Bulger, D. M. Tschaen and LC. Campeau for their useful edits, suggestions, and managerial support.

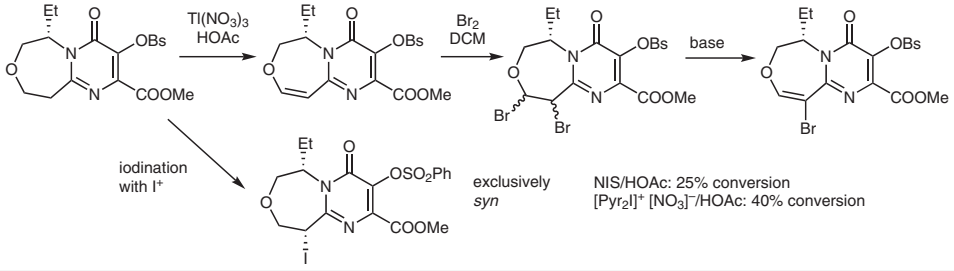
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707994.

References

(1) New address: Arrowhead Biopharmaceuticals, 502 South Rosa Road, Madison, WI 53719, USA
(2) New address: Colgate Palmolive Company, 909 River Rd, Piscataway, NJ 08854, USA
(3) (a) Kallings, L. O. *J. Intern. Med.* **2008**, *263*,03 218. (b) Global AIDS Monitoring 2019 Joint United Nations Programme on HIV/AIDS (UNAIDS) WHO; UNAIDS/JC2941; ISBN 978-92-9253-088-4. (c) HIV/AIDS Surveillance Report - 2017; Centers for Disease Control and Prevention, **2017**; Vol. 29.
(4) (a) Humphrey, G. R.; Pye, P. J.; Zhong, Y.-L.; Angelaud, R.; Askin, D.; Belyk, K. M.; Maligres, P. E.; Mancheno, D. E.; Miller, R. A.; Reamer, R. A.; Weissman, S. A. *Org. Process Res. Dev.* **2011**, *15*, 73. (b) For details of the thermal rearrangement mechanism of DMAD adduct, see: Pye, P. J.; Zhong, Y.-L.; Jones, G. O.; Reamer, R. A.; Houk, K. N.; Askin, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 4134.
(5) (a) Zhong, Y.-L.; Pipik, B.; Lee, J.; Kohmura, Y.; Okada, S.; Igawa, K.; Kadowaki, C.; Takezawa, A.; Kato, S.; Conlon, D.; Zhou, H.; King, A. O.; Reamer, R. A.; Gauthier, D. R. Jr.; Askin, D. *Org. Process Res. Dev.* **2008**, *12*, 1245. (b) Zhong, Y.-L.; Krska, S. W.; Zhou, H.; Reamer, R. A.; Lee, J.; Sun, Y.; Askin, D.; Ferrara, M. B. *Org. Lett.* **2009**, *11*, 369. (c) Ferrara, M.; Crescenzi, B.; Donghi, M.; Muraglia, E.; Nizi, E.; Pesci, S.; Summa, V.; Gardelli, C. *Tetrahedron Lett.* **2007**, *48*, 8379.
(6) Isaacs, R. C. A.; Thompson, W. J.; Williams, P. D.; Su, D.-S.; Venkatraman, S.; Embrey, M. W.; Fisher, T. E.; Wai, J. S.; Dubost, D. C.; Ball, R. G.; Choi, E. J.; Pei, T.; Trice, S. L.; Campbell, N.; Maddess, M.; Maligres, P. E.; Shevlin, M.; Song, Z. J.; Steinhuebel, D. P.; Strotman, N. A.; Yin, J. US 20100087419, **2010**.
(7) Subsequent studies using conditions optimized for asymmetric allylation showed only racemic product with this substrate.
(8) Toteva, M. M.; Richard, J. P. *Adv. Phys. Org. Chem.* **2011**, *45*, 39.
(9) Impact of L/M ratio and effect of Bu_4NBr in Trost allylation has been previously reported, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M. *Tetrahedron* **2015**, *71*, 5708. (c) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.
(10) Even under these optimized conditions for the π-allyl cyclization, Boc-methylamine species **6** still gave only racemic *trans*-product.

(11) Interestingly, when 1 equiv K_2CO_3 was added to the asymmetric allylation reaction, the rate increased and the sense of enantioselectivity completely switched from 96% ee (*R*) to –45% ee (*S*). This reversal in selectivity could signal a change in mechanism from one involving attack of the pyrimidone on Pd followed by reductive elimination to one involving intermolecular attack of the pyrimidone anion directly on the Pd-bound allyl fragment.
(12) No hydrogenation reaction was observed in dichloromethane.
(13) During this oxidation screen an interesting unprecedented oxidation was discovered using $Tl(NO_3)_3$ in HOAc, which oxidized the oxepane to the olefin (Scheme 11). This olefin could then be converted into the dibromide, which gave the vinyl bromide regioselectively upon base-mediated elimination. Further pursuit of this method was not attempted due to the toxicity of thallium; but, it was encouraging to note traces of the desired C-10 halogenated compound were observed after halogenations in the presence of $Tl(NO_3)_3$ using NBS, NCS and *t*-BuOCl. At this point, evidence from the thallium(III) catalyzed and Pyr_2INO_3 halogenations indicated an auxiliary oxidant may be beneficial in driving the halogenation to completion.
(14) Process mass intensity (PMI) was decreased from >60,000 to 1200.
(15) Bhunia, N.; Das, B. *Synthesis* **2015**, *47*, 1499.



Scheme 11