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Large-scale synthesis of SB-462795, a cathepsin K inhibitor: the RCM-based approaches

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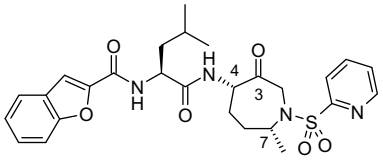
ABSTRACT

Two stereoselective syntheses of SB-462795, a highly potent cathepsin K inhibitor, are described. Both routes feature a C5–C6 disconnection by ring closing metathesis to construct an azepane ring and are amenable to large-scale manufacturing.

1. Introduction

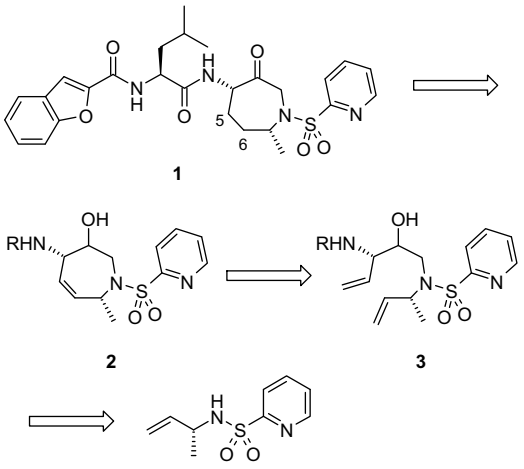
Cathepsin K is a cysteine protease of the papain super family that plays a crucial role in bone degradation. Synthesized by osteoclast cells, it dissolves the collagenous matrix after the bone has been demineralized by acid and its inhibition therefore suppresses bone destruction. Unlike bisphosphonate therapies that cause death of osteoclasts, cathepsin K inhibition does not affect the osteoclastic function of signaling for the replacement of resorbed bone by new bone, thus preventing bone loss while allowing bone reformation to continue. This characteristic of cathepsin K inhibitors provides a crucial advantage over bisphosphonates, the current market leader in osteoporosis treatment, and their development has attracted significant attention.[1] SB-462795 (**1**, Fig. 1) has recently emerged as a potent cathepsin K inhibitor and demonstrated significant therapeutic potential in the treatment of osteoporosis and osteoarthritis.[2] Its progression into clinical trials has necessitated a synthetic route that is amenable to large-scale synthesis.



1, SB-462795

Figure 1. Structure of SB-462795.

One of the main challenges in the synthesis of **1** exists in the azepanone ring bearing two stereocenters at C4 and C7. While several synthetic methods were successfully employed in the formation of this ring during our investigation, a group of routes based on a ring closing metathesis (RCM)[3–5] disconnection of the C5–C6 bond proved to be very efficient in constructing this moiety. As depicted in Scheme 1, the formation of the azepane ring **2** is



Scheme 1.

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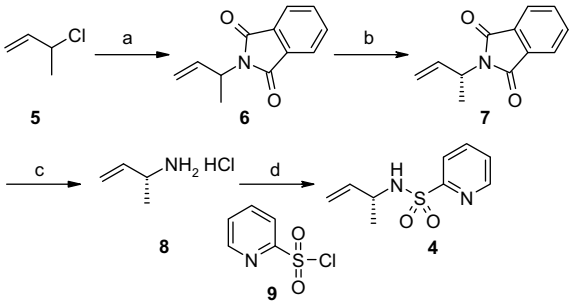
effected by RCM of a dienoaminoalcohol[6] of the general structure **3**, in which the C7 stereocenter is derived from allyl sulfonamide **4**. Herein we wish to report our efforts in the development of a scaleable route based on this RCM approach.

2. Results and discussion

2.1. Establishing the C7 stereocenter: synthesis of chiral allyl sulfonamide 4

Chiral allyl sulfonamide **4** was prepared from allyl chloride **5** in four steps, as shown in Scheme 2. Displacement of the chloride using potassium phthalimide provided racemic allylic phthalimide **6**, which was resolved by Simulated Moving Bed (SMB) chromatography[7] to afford chiral imide **7** in 48% yield and 98% ee. Deprotection using ethanolamine followed by HCl treatment gave chiral amine **8** as the HCl salt in 82% yield. Coupling with 2-pyridinesulfonyl chloride (**9**), prepared from 2-mercaptopyridine by oxidation,[8] afforded chiral sulfonamide **4** as a white crystalline solid in excellent yield and enantiomeric purity on >700 kg scale.

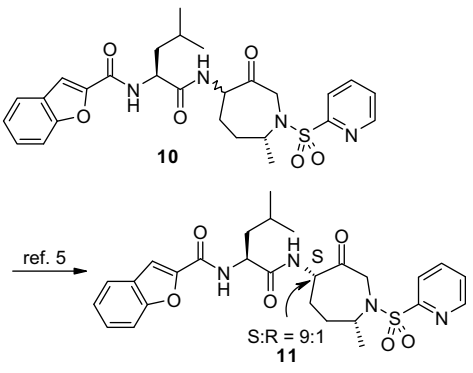


Scheme 2. (a) Potassium phthalimide, K_2CO_3, DMF, 83%; (b) SMB chromatography, 48%, 98% ee; (c) ethanolamine, EtOH, HCl, 82%; (d) **9**, CH_2Cl_2, Et_3N, 87%, 98% ee.

2.2. Synthesis of the azepane moiety: carbon chain assembly and RCM

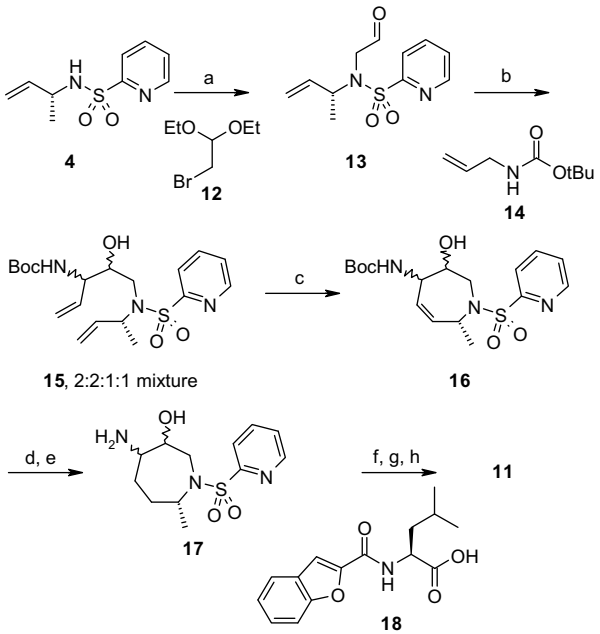
2.2.1. Epimerizablility of the C4 center and a nonstereoselective route

It should be noted that with the C7 stereocenter established, the C4 stereocenter of the azepanone is readily epimerizable and does not have to be synthetically defined. In the case of the diastereomeric mixture bearing a 7*R*-methyl group (**10**, Scheme 3), the cis diastereomer, which also happens to have the greater cathepsin K inhibitory potency, is strongly favored over the trans isomer in the epimerization equilibrium.[5,9]



Scheme 3.

This fortuitous property of ketone **10** provides the opportunity of constructing the carbon chain without defining the stereochemistry at C3 and C4, but establishing the C4 stereocenter by epimerization after the oxidation of the C3 carbinol. Not controlling the stereochemistry of these two carbons offers a great deal of potential in lowering the cost of the synthesis; and this possibility was extensively explored. One of the RCM-based routes that adopts this strategy is shown in Scheme 4.

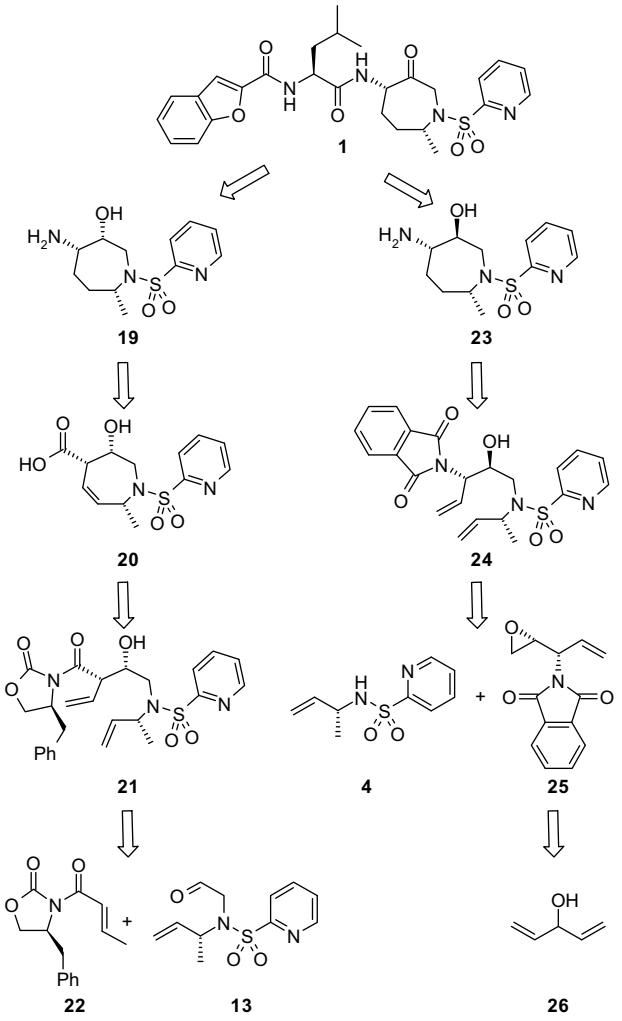


Scheme 4. (a) Cs_2CO_3, **12**, NMP; then H_2SO_4, 71%; (b) **14**, *sec*-BuLi (2.2 equiv), $ZnCl_2$ (1.1 equiv), THF, −20 °C, 95%; (c) 2nd generation Grubbs catalyst (14 mol %), CH_2Cl_2, 95%; (d) H_2, $RhCl(PPh_3)_3$, HCl, 75%; (e) aq K_2CO_3, CH_2Cl_2, 70%; (f) **18**, EDCI, HOOBt, NMM, CH_2Cl_2; (g) DMSO, Ac_2O; (h) Et_3N, MeOH, 94% yield, 61% purity (by HPLC) over three steps.

Alkylation of pyridinesulfonamide **4** with bromide **12** followed by hydrolysis of the acetal gave aldehyde **13** in 71% yield over two steps. The coupling between aldehyde **13** and the dianion of *N*-Boc-allylamine mediated by $ZnCl_2$[10] provided diene **15** in excellent yield, with inconsequentially low diastereoselectivity at the newly-formed stereogenic centers. Ring closure of the diastereomeric mixture was accomplished using Grubbs's second-generation catalyst. Hydrogenation of the resultant C5–C6 double bond followed by Boc removal gave a stereoisomeric mixture of aminoalcohols **17**. After coupling with side chain **18**, the product mixture was directly oxidized to the corresponding ketones and subjected to epimerization conditions. The desired product **1** was ultimately obtained, however, the overall purity of the product was low and attempts to purify it by crystallization were not successful.

The main challenge in the scale-up of this route stemmed from its non-stereoselective nature, which led to mixtures of stereoisomers for all of the later intermediates and made purifications virtually impossible without chromatography. The difficulty in purification eventually outweighed the potential economic benefit of not setting the C3 and C4 stereochemistry, and it was concluded that these two stereogenic centers would have to be carefully controlled in a route suitable for large scale manufacturing.

This realization led to two stereoselective routes to the target (Scheme 5), whereby the azepanone moiety is derived from either of the two C3-epimeric aminoalcohols **19** and **23**. The former would arise from an Evans aldol condensation between aldehyde **13** and crotonate imide **22**, to afford the *syn* product **21**. The stereochemistry at C4 would be preserved in a subsequent Curtius reaction to install the amino group. The C3/C4 stereocenters in **23**, however, would be derived from epoxide **25**, which in turn would be synthesized using Sharpless epoxidation of divinyl carbinol (**26**), with the C4 center inverted during the introduction of phthalimide via a Mitsunobu reaction. In both cases, the azepane ring formation would be effected using olefin metathesis.

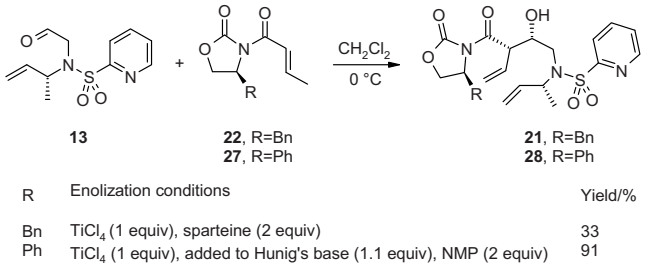


Scheme 5.

*2.2.2. Synthesis of aminoalcohol **19**: the aldol–RCM route*

The aldol–RCM disconnection via aminoalcohol **19** shown in Scheme 5 was based on a synthesis previously developed at GSK for the des-C7-methyl analog.[11] At the outset, it was anticipated that the current C7-methyl analog would also be accessible via this strategy, however, it was soon discovered that the key aldol–RCM–Curtius sequence posed significant challenges to efficient scale-up (vide infra) and had to be completely retooled.

The synthesis of aminoalcohol **19** began with an aldol reaction between aldehyde **13** and crotonate imide **22**.[12] The modified procedure by Crimmins was employed to mitigate the need for boron triflate and cryogenic temperatures during the aldol coupling.[13] Thus, crotonate **22** was treated with $TiCl_4$ to form a thick slurry, to which sparteine was added to generate the titanium enolate. Addition of aldehyde **13** gave the desired adduct **21** in 33% yield. The primary side product resulted from the dimerization of oxazolidinone **22**, presumably via a 1,4-addition to the $TiCl_4$-activated crotonate by the newly formed Ti enolate during the addition of base. Although the insoluble nature of the titanium complex of benzyl-substituted oxazolidinone **22** precluded the use of an inverse addition procedure, the complex between phenyl-substituted **27** and $TiCl_4$ was highly soluble in CH_2Cl_2. Using the phenyl derivative **27** in lieu of **22** in the aldol reaction thus allowed for an inverse-addition of its $TiCl_4$ complex to base for the enolate formation, which conveniently circumvented the dimerization side reaction. The desired product **28** was obtained in excellent yield, and the primary impurities were small amounts (<2%) of unconsumed **27** and the *anti* diastereoisomer (Scheme 6).

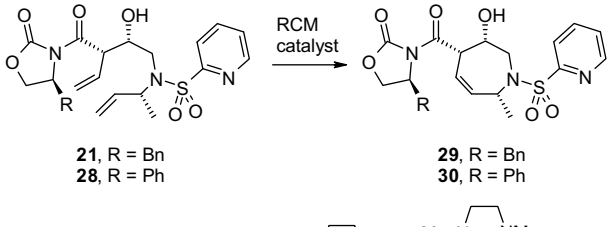


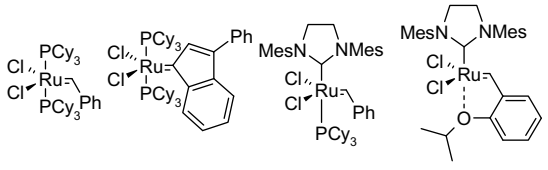
R	Enolization conditions	Yield/%
Bn	$TiCl_4$ (1 equiv), sparteine (2 equiv)	33
Ph	$TiCl_4$ (1 equiv), added to Hunig's base (1.1 equiv), NMP (2 equiv)	91

Scheme 6.

Initial studies showed that the RCM reaction of **21** (or **28**) required very high catalyst loadings (Table 1).[14] The reaction proceeded to completion with 10 mol % of Hoveyda's second generation catalyst **34**,[15] but lower loadings (5%) led to incomplete reaction (entries 1 and 2). Even lower conversion was observed with the Grubbs catalysts (**31**, **33**)[16] and indenylidene catalyst **32**.[17] When $Ti(Oi\text{-}Pr)_4$ was used as an additive with catalysts **31** or **33**,[18] it led to significant decomposition of the diene, not only by retro-aldol pathway but also cleavage of the oxazolidinone moiety by 2-propoxide.

Table 1
RCM of oxazolidinone-dienes **21** and **28**

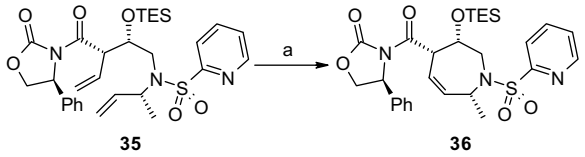




Entry	R	Catalyst	Loading/mol %	Conditions	Conv./%
1	Bn, Ph	**34**	10	Reflux, toluene	100
2	Bn	**34**	5	Reflux, toluene	60–79
3	Ph	**31**	5	DCM, 40 °C	6
4	Bn	**32**	5	DCE, rt to 80 °C	7
5	Ph	**33**	5	DCE, 80 °C	24

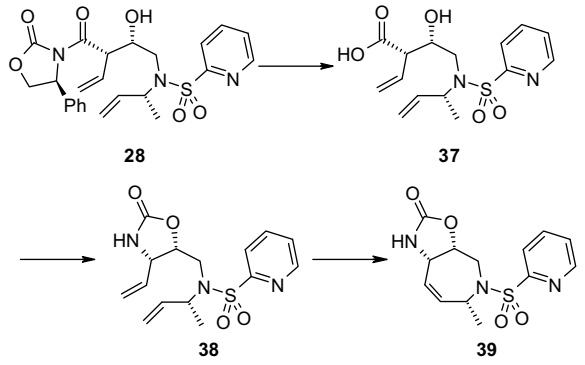
The high catalyst loading necessary for the completion of the reaction was detrimental to the scale-up of this process. The high cost of the catalyst aside, it proved extremely difficult to remove all residual ruthenium from the reaction. The product decomposed when the reaction mixture was treated with ruthenium scavenger $P(CH_2OH)_4Cl/NaOH$,[19] presumably via a retro-aldol pathway. Taking the crude product with a high ruthenium content forward was impractical from a safety standpoint, as the ensuing chemical transformations involved reagents or intermediates sensitive to heavy metals (H_2O_2 for oxazolidinone removal and the acyl azide intermediate in the Curtius reaction). The high catalyst loading in RCM and the issues it entailed, therefore, rendered the aldol–RCM–Curtius sequence originally used in the des-methyl analog virtually inapplicable in this investigation, and a new method was needed to convert the aldol adduct into aminoalcohol **19**.

It was rationalized that the electron rich oxazolidinone and free C3 hydroxyl group might coordinate to the ruthenium center and inhibit catalyst turnover, thus leading to the high catalyst loading. This hypothesis was supported by the observation that silylated analog **35** underwent complete RCM with a much lower catalyst loading (Scheme 7).[20]



Scheme 7. (a) **34** (2 mol %), reflux toluene, 4 h, 99% conversion.

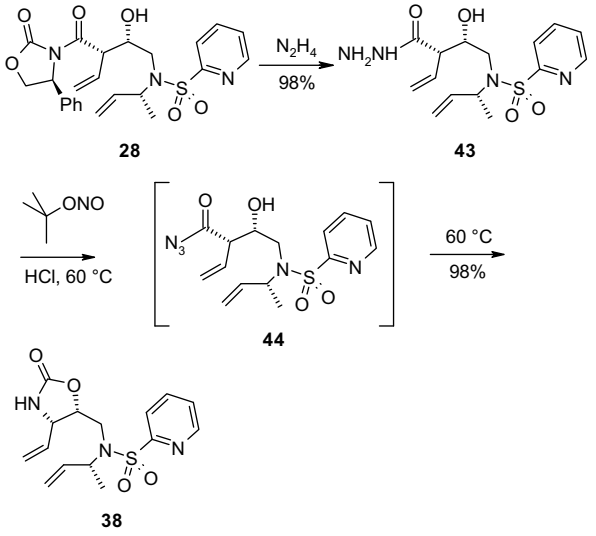
A reasonable way of circumventing the high catalyst loading, therefore, was to carry out the oxazolidinone auxiliary removal and Curtius reaction first, and perform the RCM reaction on carbamate **38** (Scheme 8). Carbamate **38** does not have a chelation pocket and should allow for lower catalyst loading in the RCM. This new sequence also eliminates the safety concern of carrying heavy metals into oxazolidinone removal step and the Curtius reaction. Furthermore, RCM product **39** is expected to be more stable to base and tolerate workup conditions for ruthenium removal.



Scheme 8.

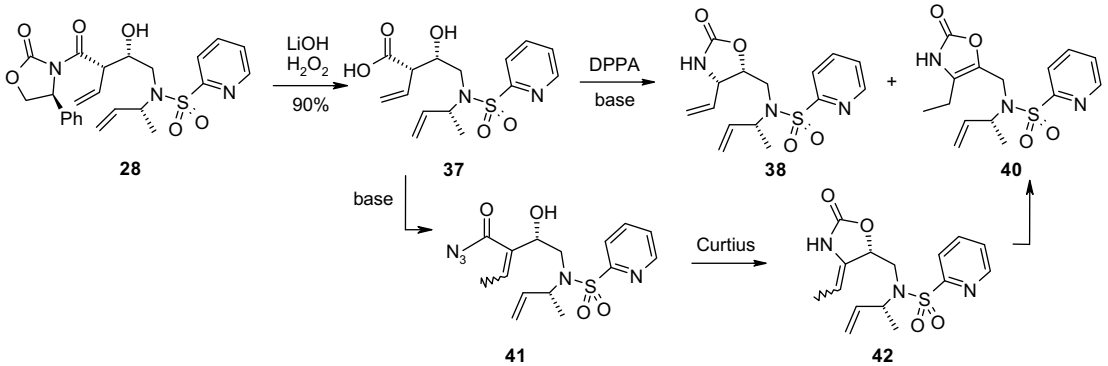
Therefore, aldol product **28** was hydrolyzed to give acid **37**,[21] which was subjected to diphenylphosphoryl azide (DPPA) and base.[22,23] The ensuing Curtius reaction of β,γ-unsaturated acid **37** occurred smoothly, however, isomerization product **40** was observed along with desired product **38** (Scheme 9). Presumably, the removal of oxazolidinone facilitated the migration of the double bond into conjugation under the reaction conditions.[24] Although the amount of **40** could be reduced when hindered bases were used, its formation was never completely suppressed.[25] It became clear that a non-basic method would be needed for the acyl azide formation to prevent double bond migration.

Fortunately, it was found that the oxazolidinone moiety in aldol adduct **28** could be cleaved using hydrazine to give hydrazide **43** (Scheme 10).[26] Treatment of hydrazide **43** with *tert*-butyl nitrite in the presence of HCl readily generated acyl azide **44**, which underwent immediate Curtius rearrangement. The resultant isocyanate was trapped by the neighboring C3 hydroxyl group to provide carbamate **38** in excellent yield. It should be pointed out that this aldol–Curtius sequence could serve as a general method for the synthesis of chiral allylamine derivatives and 4-vinyl oxazolidinones. This extension of the classic Evans aldol methodology has been previously unexplored, presumably due to the high migration propensity of the β,γ-double bond.

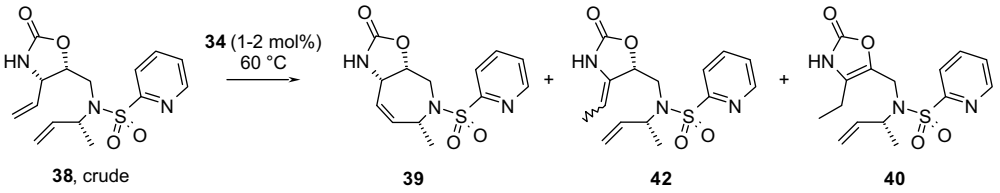


Scheme 10.

Olefin migration in both the starting material and the product was a significant side reaction in the RCM of **38**.[27] The product (**39**) underwent significant double bond migration (20–30%) when the reaction was conducted in refluxing toluene while lower temperature (60 °C) suppressed this side reaction completely. Furthermore, when crude carbamate **38** from the Curtius reaction was used without chromatographic purification, the RCM reaction was extremely capricious, often resulting in unconsumed starting material while producing **40** and **42** as side products from olefin isomerization, especially at higher temperatures (Scheme 11). Although the reaction proceeded in a number of solvents,[28] no single solvent provided the desired ring closing metathesis with a consistent and predictable amount of the isomerization side products. For instance, when the reaction was conducted in THF at 60 °C, the result ranged from 87% conversion with 2% isomerization to 37% conversion with 60% isomerization. Addition of HOAc,[29] styrene or



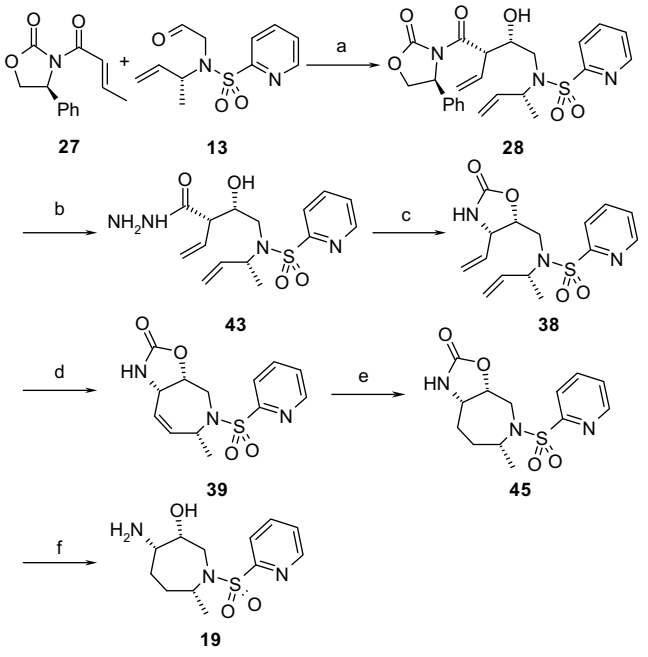
Scheme 9.



Scheme 11.

Cy_3PO[30] to the reaction mixture did not lead to appreciable improvement in the conversion or consistent suppression of olefin migration.

Fortunately, it was found that isolating **38** as its HCl salt from the Curtius reaction greatly improved its purity consistency and afforded a much more robust RCM reaction, allowing for its scale-up. The RCM reaction was performed in EtOAc at 60 °C and the migration side products were observed to be <2%. Upon completion of the reaction, the residual ruthenium was removed by extraction using a basic solution of cysteine.[31,32] Cyclic carbamate **39** was isolated in 90% yield after crystallization and contained only small amounts of residual ruthenium. Hydrogenation and deprotection of the carbamate afforded aminoalcohol **19** as a white crystalline solid in 91% yield. Scheme 12 outlines the finalized sequence for the route to aminoalcohol **19**.

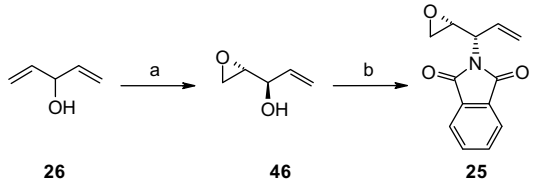


Scheme 12. (a) $TiCl_4$, Hunig's base, NMP, 91%; (b) N_2H_4, quant.; (c) *tert*-butyl nitrite, HCl, isopropanol, 50 °C, 84%; (d) **34** (1 mol %), EtOAc, 60 °C, then cysteine/NaOH, 90%, Ru 148 ppm; (e) DME, Pd/C, H_2; (f) aq NaOH, reflux, 91% over 2 steps, Ru 14 ppm.

2.2.3. Synthesis of aminoalcohol *23*: the Sharpless–RCM route

Epoxide **25**, the key intermediate in the synthesis of *trans* aminoalcohol **23**, was prepared from divinyl carbinol in two steps (Scheme 13). An asymmetric Sharpless epoxidation using diisopropyl tartrate ligand and cumene hydroperoxide as the oxidant provided epoxide **46** in 98% ee and 90% yield.[33] Consistent with literature observations,[34] cumene hydroperoxide provided a higher yield for epoxide **46** relative to *tert*-butyl hydroperoxide. Treatment of **46** with phthalimide under Mitsunobu conditions provided the desired product **25** in 85% yield.

Isolation of the low-melting phthalimidoepoxide **25** (mp= 72.3 °C), however, presented a significant challenge. Although co-



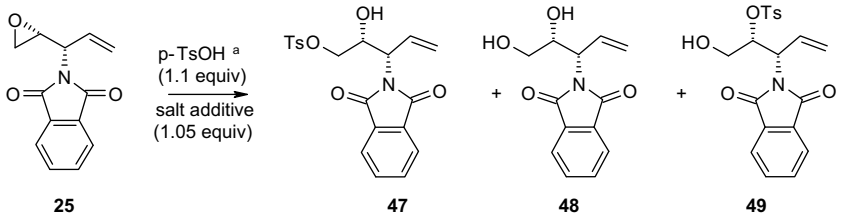
Scheme 13. (a) Ti(O*i*-Pr)$_4$ 10 mol %, (−)-DIPT 13 mol %, CH_2Cl_2, *tert*-butyl hydroperoxide, 1.8 equiv, 75% yield, 97% ee; or cumene hydroperoxide 1.1 equiv, 90% yield, 98% ee; (b) DIAD, 1.3 equiv, PPh_3 1.3 equiv, toluene, 85%.

precipitation of triphenylphosphine oxide and diisopropyl hydrazinedicarboxylate[35] could purge >80% of these by-products, numerous other impurities resulting from both the Sharpless oxidation and the Mitsunobu reaction made the crystallization of **25** extremely difficult. Consequently, batch chromatographic purifications were necessary to afford **25** of suitable purity. While this sequence was successfully used to deliver >200 kg of epoxide **25** (in 60% yield) for early-phase supplies, the chromatographic operations were a significant bottleneck in the overall synthetic route and added significantly to the cost.

In developing this route for use on commercial scale, it was discovered that reaction of epoxide **25** with toluenesulfonate under acidic conditions provided the more crystalline tosylate **47** (mp=129.6 °C).[36] Tosylate **47** could be generated from crude epoxide **25** and crystallized directly from the crude reaction mixtures after the Sharpless and Mitsunobu steps in excellent purity and yield. As shown in Table 2, optimized formation of the desired tosylate **47** was achieved by using anhydrous toluenesulfonate reagents (to minimize the formation of diol **48**). Among the tosylate nucleophiles screened, tetraalkylammonium tosylates (entries 4 and 5) afforded exclusive epoxide opening from the primary carbon, providing the desired product in excellent yield. Epoxide **25** could then be regenerated from **47** in nearly quantitative yield by treatment with DBU in toluene. Incorporation of tosylate **47** provided a more scalable and cost-effective intermediate by eliminating the need for chromatographic purification of epoxide **25**. The process was readily scalable, allowing for the preparation of 850 kg of tosylate **47** in 50% yield from divinyl carbinol.

Generation of requisite RCM precursor **24** was accomplished by coupling epoxide **25** with sulfonamide **4**. Although this type of coupling reaction is well precedented, initial attempts using inorganic carbonates[37] or Triton B failed to give the desired coupling product **24**. In most cases, the epoxide either did not react, or simply decomposed during the reaction, presumably due to its relative instability. Fortunately, it was found that this reaction could be catalyzed by small amounts of organic bases in refluxing IPA (Table 3).[38,39] Among the bases screened, DBU and BTPP proved to be the most efficient in catalyzing this coupling reaction. Good yields were obtained when DBU was used as the catalyst, although a main side pathway appeared to be slow reaction between DBU and epoxide **25** to form an adduct. Thus, the yield was further improved by ~10% when the highly basic yet non-nucleophilic *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP)[40] was used in lieu of DBU as the catalyst (Table 3).

Table 2
Epoxide opening of **25** with toluenesulfonate

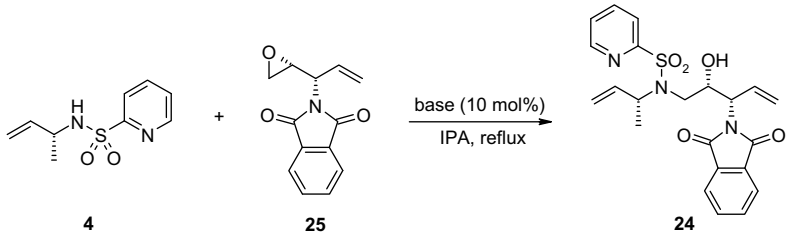


25 **47** **48** **49**

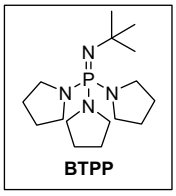
Entry	Salt additives	Solvent	Rxn temp/°C	Diol **48**/%[b]	Isomer **49**/%[b]	Yield of **47**/%
1	—	Toluene	60	15	15	50
2	2,6-Lutidinium OTs hydrate	CH_2Cl_2	40	13	4	64
3	Pyridinium OTs	CH_2Cl_2	40	6	2	70
4	NBu_4OTs	Toluene	60	2	<1	97
5	NEt_4OTs	Toluene	60	2	<1	96

[a] Prepared from TsOH hydrate by azeotropic removal of H_2O.
[b] By area% in HPLC.

Table 3
Organic base-catalyzed epoxide opening of **25** with sulfonamide **4**



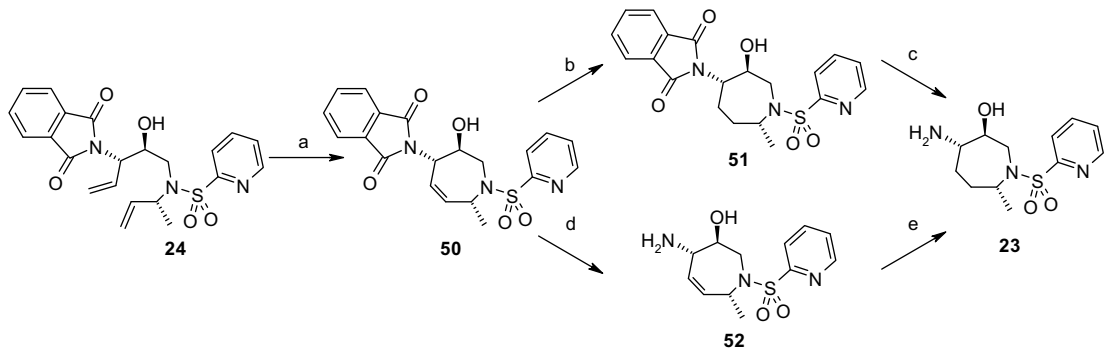
4 **25** **24**



BTPP

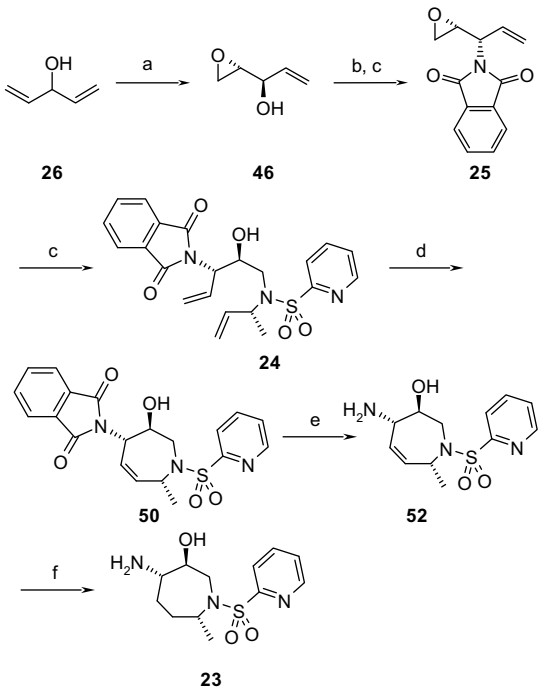
Entry	Base	Yield/%	Entry	Base	Yield/%
1	Et_3N	<5	4	DMAP	63
2	DABCO	<5	5	DBU	73
3	Pyridine	30	6	BTPP	85

Diene **24** proved to be an exceptional substrate for RCM. When it is of high purity, complete conversion could be achieved with 0.1–0.2 mol % of Hoveyda's catalyst **34**.[41] Perhaps due to the steric bulk of the allylic substituents, olefin migration was never observed, even in cases where the diene was of low purity and the reaction did not reach completion. Hoveyda's catalyst **34** was found to be the best catalyst for this RCM reaction. Grubbs 2nd generation catalyst **33** was also effective on small scale, however, the results were not



24 **50** **51** **52** **23**

Scheme 14. (a) **34**, toluene, 96%; (b) 10% Pd/C, 21 dry wt %, H_2 120 psi, 82%; (c) N_2H_4, 93%; (d) NH_2OH, MeOH, 73%; (e) 10% Pd/C, 3 dry wt %, H_2 60 psi, 98%.



Scheme 15. (a) Ti(O*i*-Pr)$_4$, 10 mol %, (−)-DIPT 13 mol %, CH_2Cl_2, cumene hydroperoxide 1.1 equiv, 90%, 98% ee; (b) DIAD, 1.3 equiv, PPh_3, 1.3 equiv, tol, 85%; (c) **4**, BTPP 10 mol %, isopropanol, 73%; (d) **34** (0.5 mol %), toluene, 96%, residual Ru 359 ppm; (e) NH_2OH, MeOH, 73%; (f) 10% Pd/C, H_2, 98%.

consistent upon scale-up and low conversion was often observed even with pure diene **24**.[42] This RCM reaction was most conveniently performed in toluene, in which the product had very low solubility and readily crystallized from the reaction mixture upon formation. This crystallization also effectively purged the residual ruthenium from the isolated product, giving low metal content which was further lowered by downstream processing.

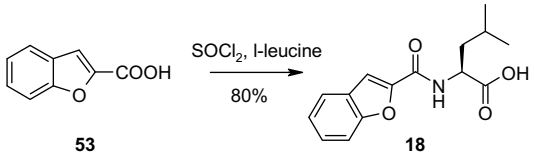
Presumably due to the steric bulk of the phthalimide, RCM product **50** exhibited very low reactivity in the subsequent hydrogenation. Coupled with its low solubility, the hydrogenation of **50** required a high catalyst loading (21% w/w) and relatively high dilution (Scheme 14). Conversely, the hydrogenation of deprotected aminoalcohol **52** was much more facile, requiring significantly lower catalyst loading (~3% w/w) and hydrogen pressure. A plausible explanation is that the hydrogenation of **52** is facilitated by coordination of the C4 amino group to Pd, as it was observed that this hydrogenation was significantly retarded by small amounts of acid.

Scheme 15 summarizes the synthetic route to aminoalcohol **23**.

2.3. Synthesis of the side chain, coupling and oxidation of C3 carbinol

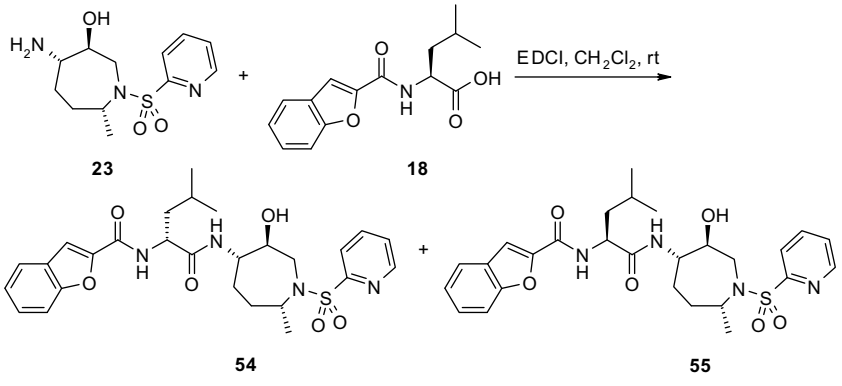
Side chain **18** was prepared from known acid **53**[43] and L-leucine (Scheme 16). This sequence was used to produce >450 kg of **18** in 80% yield.

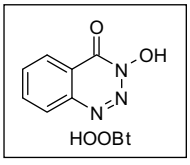
Under most of the conditions tested, the stereocenter on side chain **18** was prone to partial racemization during the coupling with azepane aminoalcohol **23** (Table 4). As much as 10% racemization product



Scheme 16.

Table 4
HOOBt-mediated amide coupling between **23** and **18**





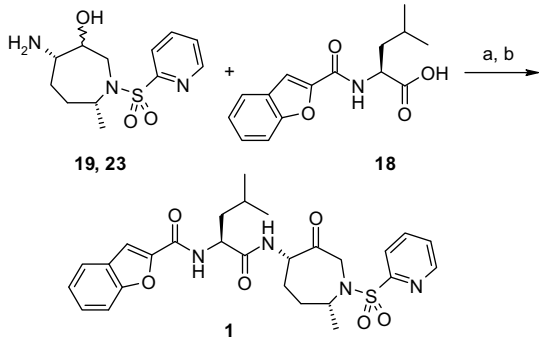
Entry	Additive	Equiv	Racemization/%
1	—	—	10
2	DMAP	1	32
3	HOBt	1	25
4	HOOBt	1	0.8
5	HOOBt	0.01	1.2
6	HOOBt	0.001	5.3
7	HOOBt	0.01[a]	0.4

[a] Reaction at 0 °C.

54 was observed in the reaction mixture when the EDCI-mediated coupling was carried out without any additive, and 32% racemization occurred when DMAP was used as an additive.[44] The formation of this diastereomer was not suppressed by the addition of HOBt (entries 1–3).[45] However, 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HOOBt)[46] proved to be an effective additive in minimizing the racemization. Only a very small amount of HOOBt was needed as the amount of diastereomer **54** only increased slightly when the HOOBt loading was lowered from 1 equivalent to 1 mol % (entries 4 and 5). Even when only 0.1 mol % of HOOBt was used, the amount of racemization was still significantly below that obtained in the blank experiment. Finally, the coupling reaction was carried out with 1 mol % of HOOBt in CH_2Cl_2 at 0 °C (entry 7). The coupling proceeded smoothly, providing the desired product in 86–92% yield with >99% purity.

The oxidation of alcohol **55** to **1** has been extensively studied.[47] After evaluating numerous conditions, it was found that this oxidation was best accomplished using DMSO/Ac_2O[48] or NaOCl with TEMPO as the catalyst.[49] Both methods provided the desired ketone product in good isolated yield (>85%), although the activated DMSO conditions tended to be operationally more convenient and more reproducible.

Although developed using *trans* aminoalcohol **23**, this coupling–oxidation sequence was also applicable to *cis* aminoalcohol **19**. At the same HOOBt loading, the coupling reaction with **19** was slightly slower and gave higher amounts of racemization by-product than that of **23**, but **1** was obtained starting from either aminoalcohol in comparable yield and purity profile, as shown in Scheme 17. Furthermore, the process using **23** was successfully piloted on multi-kilo scale, producing >200 kg of SB-462795 (**1**) which was suitable for clinical studies.



Scheme 17. (a) EDCI, HOOBt, CH_2Cl_2, 0 °C; (b) DMSO, Ac_2O. From **19**: 75% over 2 steps; from **23**: 74% over 2 steps.

3. Summary

In conclusion, two stereoselective synthetic routes to SB-462795, a highly potent cathepsin K inhibitor, have been developed. In the first route, an aldol–Curtius–RCM sequence is used to construct the key azepane moiety. It is highlighted by: (1) a highly efficient aldol reaction involving a crotonate imide using Crimmins modifications; (2) cleavage of the oxazolidinone using hydrazine followed by a Curtius reaction to convert the resultant β,γ-unsaturated carbonyl intermediate into an allylamine derivative without double bond migration; and (3) an efficient RCM reaction that utilized low catalyst loading. The second route, utilizing a Sharpless epoxidation–Mitsunobu sequence to establish the C3/C4 stereocenters, is highlighted by: (1) a selective epoxide opening using TsOH to give the monotosylate of a vicinal diol; (2) an efficient epoxide opening reaction by sulfonamide catalyzed by BTPP; and (3) a remarkably efficient RCM reaction requiring extremely low catalyst loading. Both routes are amenable to large-scale manufacturing, and over 200 kg of SB-462795 has been synthesized via *trans* aminoalcohol **23**. The multi-kilo synthesis also featured one of the first examples of large scale RCM in a pharmaceutical setting.[50]

4. Experimental details

4.1. General

Unless otherwise indicated, all reactions were conducted in glass-lined reactors under a nitrogen atmosphere. Solvents, reagents, allyl sulfonamide **4**, phthalimidoepoxide **25**, tosylate **47** and side chain **18** were obtained from commercial sources and used without further purification.

4.2. *N*-[(1*R*)-1-methyl-2-propen-1-yl]-2-pyridinesulfonamide (4)

ES-MS: *m*/*z* 213 ($M+H^+$). ^1H NMR δ ppm ($CDCl_3$, 400.13 MHz): 8.72 (ddd, *J*=4.7, 1.7, 0.9 Hz, 1H), 8.01 (dt, *J*=7.9, 1.0 Hz, 1H), 7.90 (td, *J*=7.7, 1.8 Hz, 1H), 7.49 (ddd, *J*=7.6, 4.8, 1.2 Hz, 1H), 5.64 (ddd, *J*=17.2, 10.4, 6.0 Hz, 1H), 5.12 (br, 1H), 5.06 (dt, *J*=17.2, 1.2 Hz, 1H), 4.92 (dt, *J*=10.4, 1.1 Hz, 1H), 4.03 (m, 1H), 1.22 (d, *J*=6.8 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 158.0, 149.9, 138.8, 137.9, 126.5, 122.2, 115.0, 52.2, 21.3. Anal. Calcd for $C_9H_{12}N_2O_2S$: C 50.92, H 5.70, N 13.20. Found: C 51.03, H 5.79, N 13.12.

4.3. *N*-(1-Benzofuran-2-ylcarbonyl)-L-leucine (18)

ES-MS: *m*/*z* 276 ($M+H^+$), 298 ($M+Na^+$), 339 ($M+Na^++CH_3CN$). ^1H NMR δ ppm ($CDCl_3$, 400.13 MHz): 7.68 (d, *J*=7.9 Hz, 1H), 7.53 (m, 2H), 7.44 (ddd, *J*=8.5, 7.2, 1.2 Hz, 1H), 7.31 (m, 1H), 7.01 (d, *J*=8.3 Hz, 1H), 4.89 (m, 1H), 1.83 (m, 3H), 1.02 (dd, *J*=6.1, 1.2 Hz, 6H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 176.8, 159.0, 154.8, 147.7, 127.4, 127.2, 123.8, 122.8, 111.8, 111.5, 50.6, 41.4, 24.9, 22.8, 21.8. Anal. Calcd for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09. Found: C 65.55, H 6.24, N 5.04.

4.4. 4,5-Anhydro-1,2,3-trideoxy-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-L-*threo*-pent-1-enitol (25)

ES-MS: *m*/*z*: 230 ($M+H^+$), 252 ($M+Na^+$), 293 ($M+Na^++CH_3CN$). ^1H NMR δ ppm ($CDCl_3$, 400.13 MHz): 7.82 (m, 2H), 7.70 (m, 2H), 6.14 (m, 1H), 5.29 (m, 2H), 4.46 (tm, *J*=7.2 Hz, 1H), 3.68 (m, 1H), 2.92 (ddd, *J*=6.3, 2.4, 2.1 Hz, 1H), 2.76 (m, 1H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 167.6, 134.0, 131.7, 130.9, 123.3, 119.4, 56.2, 50.9, 46.8. Anal. Calcd for $C_{13}H_{11}NO_3$: C 68.12, H 4.84, N 6.11. Found: C 68.19, H 4.76, N 6.11.

4.5. 1,2,3-Trideoxy-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-*O*-[(4-methylphenyl)sulfonyl]-L-*threo*-pent-1-enitol (47)

ES-MS: *m*/*z*: 402 ($M+H^+$), 424 ($M+Na^+$). ^1H NMR δ ppm ($CDCl_3$, 400.13 MHz): 7.70–7.82 (m, 6H), 7.30 (d, *J*=8.0 Hz, 2H), 6.12 (ddd, *J*=17.2, 10.2, 8.0 Hz, 1H), 5.24 (m, 2H), 4.89 (td, *J*=7.8, 0.8 Hz, 1H), 4.44 (dt, *J*=7.8, 4.9 Hz, 1H), 4.08 (d, *J*=4.8 Hz, 2H), 3.25 (br, 1H), 2.40 (s, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 168.4, 145.0, 134.2, 132.2, 131.5, 131.1, 129.8, 127.9, 123.5, 120.4, 70.1, 68.6, 55.8, 21.6. Anal. Calcd for $C_{20}H_{19}NO_6S$: C 59.84, H 4.77, N 3.49. Found: C 59.91, H 4.68, N 3.39.

4.6. *N*-[(1*R*)-1-Methyl-2-propen-1-yl]-*N*-(2-oxoethyl)-2-pyridinesulfonamide (13)

A mixture of **4** (1.0 kg, 4.71 mol), NMP (4 L) and Cs_2CO_3 (2.3 kg, 7.07 mol) was heated to 115 °C under nitrogen. Once the temperature was above 100 °C, bromoacetaldehyde diethyl acetal **12** (1.393 kg, 7.07 mol) was charged via an addition funnel over

approx. 2 h, and the mixture was heated at 115 °C for a total of 17 h. The slurry was cooled to 25 °C and H_2O (6 L) was added in portions over approx. 10 min to control the slightly exothermic quench below 35 °C. The acetal intermediate was extracted into TBME/heptane (1:2 ratio, 5 L×2), and the combined organic extracts were washed with 1 M aq NaOH (2 L). The solution of the diethyl acetal intermediate was distilled under vacuum (approx. 30 mmHg) to remove ~10 L of solvent. THF (2 L×2) was added and subsequently distilled under vacuum to further drive off the extraction solvents. THF (4 L) and 10% v/v H_2SO_4 (4 L) were added and the mixture heated to 60 °C for 2.5 h. The solution was then cooled to <35 °C, toluene (3 L) was charged, and the mixture distilled to remove 5–6 L of solvent (mostly THF). The remaining layers were separated. The aqueous layer was extracted with toluene (3 L). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (1 L) and H_2O (1 L), and more solvent (1.2 L) was removed by vacuum distillation while keeping the internal temperature at 37–42 °C.[51] Toluene was added and removed by vacuum distillation in 2 L portions (total of 5 portions) until NMR analysis showed complete removal of EtOH and THF, and the level of $BrCH_2CHO$ was <1%. A total of 4.14 kg of toluene solution was obtained, which was stored in a freezer. NMR and LC w/w analysis showed the solution contained 20.6 wt % of **13** (3.35 mol, 71%, typically 70–80%). The aldehyde was thermally unstable and was used as a toluene solution directly in the aldol reaction. An analytically pure sample could be obtained by flash column chromatography. ES-MS: *m*/*z*: 255 ($M+H^+$), 277 ($M+Na^+$). ES-HRMS: calcd for $[C_{11}H_{14}N_2O_3S+H]^+$: 255.0803; found: 255.0800. ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 9.58 (t, *J*=1.2 Hz, 1H), 8.63 (dm, *J*=4.8 Hz, 1H), 7.88 (m, 2H), 7.47 (ddd, *J*=6.8, 4.9, 1.6 Hz, 1H), 5.59 (ddd, *J*=17.3, 10.6, 4.7 Hz, 1H), 5.04 (m, 2H), 4.67 (m, 1H), 3.95 (dd, *J*=19.0, 1.3 Hz, 1H), 3.83 (dd, *J*=19.0, 1.4 Hz, 1H), 1.11 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 199.5, 157.6, 150.0, 137.9, 136.4, 126.8, 122.1, 117.7, 54.6, 52.5, 16.6.

4.7. (4*S*)-3-[(2*E*)-2-Butenoyl]-4-phenyl-1,3-oxazolidin-2-one (27)

The synthesis of **27** is based on procedure by Ho and Mathre.[52] LiCl (0.299 kg, 7.05 mol) and Et_3N (0.744 kg, 7.35 mol) were added to (4*S*)-4-phenyl-1,3-oxazolidin-2-one (1.00 kg, 6.13 mol) in THF (10 L). The mixture was stirred for 20 min at 23 °C, then cooled to 15 °C. Crotonic anhydride (0.964 kg, 6.25 mol) was added over approx. 30 min while maintaining the internal temperature below 20 °C. After the addition, the solution was stirred for 1 h at 23 °C. The reaction was quenched with the addition of H_2O (5 L). The organic solvent was removed by vacuum distillation while maintaining the internal temperature between 20–30 °C. Once most of the THF was removed, the oily product converted to a free-flowing solid and was filtered. H_2O (3 L×2) was charged to rinse the reactor and the wet cake. The wet cake was then washed with TBME/heptane at 10 °C (1:1 ratio, 3 L×2). The product was dried in a vacuum oven at 40 °C to afford **27** (1.286 kg, 5.56 mol, 91%, HPLC purity 99.5%). ES-MS: *m*/*z*: 232 ($M+H^+$), 254 ($M+Na^+$), 295 ($M+Na^++CH_3CN$), 485 ($2M+Na^+$). ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 7.26–7.41 (m, 6H), 7.11 (ddd, *J*=15.2, 13.8, 6.8 Hz, 1H), 5.50 (dd, *J*=8.7, 3.8 Hz, 1H), 4.71 (t, *J*=8.8 Hz, 1H), 4.29 (dd, *J*=8.9, 3.9 Hz, 1H), 1.95 (dd, *J*=6.9, 1.6 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 164.3, 153.6, 147.1, 139.0, 129.0, 128.5, 125.8, 121.6, 69.8, 57.6, 18.4. Anal. Calcd for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06. Found: C 67.24, H 5.62, N 5.93.

4.8. *N*-((2*S*,3*S*)-2-Hydroxy-3-{[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]carbonyl}-4-penten-1-yl)-*N*-[(1*R*)-1-methyl-2-propen-1-yl]-2-pyridinesulfonamide (28)

Crotonate imide **27** (234.0 g, 1.01 mol) was dissolved in CH_2Cl_2 (2.3 L) at −10 °C under nitrogen and titanium chloride (200 g, 1.05 mol) was added. The resultant solution was added slowly to a separate vessel charged with diisopropylethlyamine (195 mL, 141.2 g, 1.09 mol) in CH_2Cl_2 (2.3 L) while maintaining the temperature at −5 °C. NMP (199.2 g, 193.1 mL, 2.01 mol) was added and the resulting dark purple mixture was stirred cold for 2 h. A solution of aldehyde **13** in 1:1 DCM/toluene (1.736 kg, 20.6% w/w, 1.41 mol) was charged and the resulting mixture was stirred for 90 min. The mixture was quenched by sequential addition of acetic acid (300 mL), saturated aqueous Rochelle's salt (400 mL), and 4 L of 10% v/v aqueous HCl. The mixture was warmed to 20 °C and the layers separated. The organic layer was washed with 4 L of 10% v/v aqueous HCl, then mixed vigorously with saturated aqueous $NaHSO_3$ at 40 °C until all residual aldehyde **13** was consumed. The layers were separated. The organic layer was concentrated under vacuum and was used in further processing without any purification (total weight: 522.7 g, product **28**: 85% w/w, 0.915 mol, 91% yield). An analytically pure sample could be obtained by flash column chromatography. ES-MS: *m*/*z*: 486 ($M+H^+$), 508 ($M+Na^+$). ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 8.64 (dm, *J*=4.7 Hz, 1H), 8.01 (d, *J*=7.9 Hz, 1H), 7.91 (td, *J*=7.7, 1.5 Hz, 1H), 7.49 (ddd, *J*=7.6, 4.8, 0.7 Hz, 1H), 7.23–7.36 (m, 5H), 5.92 (ddd, *J*=17.3, 10.1, 8.9 Hz, 1H), 5.79 (ddd, *J*=17.5, 10.3, 5.6 Hz, 1H), 5.45 (dd, *J*=8.7, 3.6 Hz, 1H), 5.23 (m, 2H), 5.05 (m, 2H), 4.99 (br, 1H), 4.67 (m, 2H), 4.34 (m, 2H), 4.20 (dd, *J*=8.9, 3.7 Hz, 1H), 3.57 (dd, *J*=15.1, 9.3 Hz, 1H), 3.40 (dd, *J*=15.1, 2.5 Hz, 1H), 1.22 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 171.5, 158.2, 153.2, 149.4, 138.8, 138.4, 137.8, 131.5, 128.9, 128.5, 126.7, 125.6, 122.8, 120.4, 116.8, 69.9, 69.7, 57.5, 55.8, 50.8, 48.8, 17.0. Anal. Calcd for $C_{24}H_{27}N_3O_6S$: C 59.37, H 5.60, N 8.65. Found: C 59.67, H 5.90, N 8.32.

4.9. (4*S*)-3-{[(3*S*,4*S*,7*R*)-3-Hydroxy-7-methyl-1-(2-pyridinylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepin-4-yl]carbonyl}-4-phenyl-1,3-oxazolidin-2-one (30)

In a round bottom flask, aldol product **28** (233 mg, 0.480 mmol, purified by flash column chromatography) was dissolved in toluene (2 mL, pre-degassed), and Hoveyda's catalyst **34** (30.0 mg, 0.048 mmol, 10 mol %) was added. The resultant solution was again degassed and heated to reflux. HPLC analysis of the reaction mixture after 2.5 h showed that diene **28** was consumed. The product was purified by flash column chromatography (170 mg, 0.372 mmol, 78%). ES-MS: *m*/*z*: 458 ($M+H^+$), 480 ($M+Na^+$), 937 ($2M+Na^+$). ES-HRMS: calcd for $[C_{22}H_{23}N_3O_6S+H]^+$: 458.1386; found: 458.1382. ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 8.68 (d, *J*=4.3 Hz, 1H), 8.00 (d, *J*=7.8 Hz, 1H), 7.90 (ddd, *J*=7.7, 7.7, 1.3 Hz, 1H), 7.48 (m, 1H), 7.26–7.39 (m, 5H), 5.47 (m, 3H), 5.13 (m, 1H), 4.96 (m, 1H), 4.74 (t, *J*=8.8 Hz, 1H), 4.60 (m, 1H), 4.24 (dd, *J*=8.9, 3.9 Hz, 1H), 4.15 (dd, *J*=15.5, 6.6 Hz, 1H), 3.29 (br, 1H), 3.23 (dd, *J*=15.5, 7.3 Hz, 1H), 1.09 (d, *J*=7.0 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 173.2, 158.1, 152.8, 149.9, 138.9, 138.1, 133.0, 129.0, 128.5, 126.6, 125.6, 122.4, 122.2, 70.4, 70.0, 57.6, 54.7, 47.5, 45.2, 18.2.

4.10. *N*-[(2*S*,3*S*)-3-(Hydrazinocarbonyl)-2-hydroxy-4-penten-1-yl]-*N*-[(1*R*)-1-methyl-2-propen-1-yl]-2-pyridinesulfonamide (43)

Aldol product **28** (436.7 g, 0.90 mol) was dissolved in THF (1.25 L). The solution was cooled to 0 °C and hydrazine hydrate (55 mL, 56.8 g, 1.13 mol) was added dropwise. After the addition of 10 mL of hydrazine hydrate, the reaction mixture became cloudy. Seed crystals of hydrazide **43** were added and the addition was continued. After 90 min, TBME (2 L) was added and the mixture was stirred at 0 °C for 1 h. The resultant precipitate was collected by filtration, washed with a 1:1 mixture of THF/TBME (2 L), air dried for 1 h, then vacuum dried overnight at 50 °C to give

hydrazide **43** as a white solid (329.2 g, 0.93 mol, quant.). ES-MS: *m*/*z*: 355 ($M+H^+$), 377 ($M+Na^+$). ^{1}H NMR δ ppm (DMSO-d_6, 400.13 MHz): 9.03 (s, 1H), 8.73 (dm, *J*=4.7 Hz, 1H), 8.08 (td, *J*=7.7, 1.7 Hz, 1H), 7.94 (d, *J*=7.9 Hz, 1H), 7.67 (ddd, *J*=7.6, 4.7, 1.0 Hz, 1H), 5.86 (m, 1H), 5.67 (m, 1H), 5.12 (m, 1H), 5.09 (m, 1H), 5.00 (m, 3H), 4.40 (m, 1H), 4.22 (s, 2H), 3.99 (m, 1H), 3.25 (dd, *J*=15.0, 2.4 Hz, 1H), 3.10 (dd, *J*=15.0, 9.2 Hz, 1H), 2.85 (dd, *J*=8.6, 6.4 Hz, 1H), 1.18 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ppm (DMSO-d_6, 100.61 MHz): 170.6, 157.6, 150.2, 138.8, 138.4, 134.7, 127.2, 122.5, 118.0, 116.5, 70.1, 55.3, 53.6, 49.3, 17.7. Anal. Calcd for $C_{15}H_{22}N_4O_4S$: C 50.83, H 6.26, N 15.81. Found: C 50.94, H 6.09, N 15.66.

4.11. *N*-{[(4*S*,5*R*)-4-Ethenyl-2-oxo-1,3-oxazolidin-5-yl]methyl}-*N*-[(1*R*)-1-methyl-2-propen-1-yl]-2-pyridinesulfonamide (38)

To a mixture of hydrazide **43** (521.0 g, 1.47 mol) and 1.3 M HCl in isopropanol (5.2 L) at 50 °C was added a solution of *tert*-butyl nitrite (200 mL, 172.0 g, 1.67 mol) in IPA (1 L) over 2 h. The solution was cooled and concentrated under vacuum. The resulting solid was slurried in isopropyl acetate (1 L), collected by filtration, washed with isopropyl acetate, and dried at ambient temperature under vacuum to give the HCl salt of carbamate **38** as a beige solid (460.3 g, 1.23 mol, 84%). ES-MS: *m*/*z*: 338 ($M+H^+$), 360 ($M+Na^+$). ^{1}H NMR δ ppm (DMSO-d_6, 400.13 MHz): 12.22 (br, 1H), 8.72 (dm, *J*=4.7 Hz, 1H), 8.07 (td, *J*=7.8, 1.7 Hz, 1H), 7.95 (m, 2H), 7.66 (dd, *J*=7.6, 4.7 Hz, 1H), 5.83 (ddd, *J*=17.1, 10.2, 6.9 Hz, 1H), 5.54 (ddd, *J*=17.1, 10.8, 5.3 Hz, 1H), 5.28 (m, 2H), 5.00 (m, 1H), 4.96 (d, *J*=10.2 Hz, 1H), 4.81 (m, 1H), 4.41 (m, 2H), 3.54 (dd, *J*=15.7, 2.0 Hz, 1H), 3.20 (dd, *J*=15.8, 9.9 Hz, 1H), 1.18 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ppm (DMSO-d_6, 100.61 MHz): 157.9, 157.5, 150.4, 138.9, 137.5, 133.5, 127.6, 122.6, 118.9, 117.3, 77.6, 56.2, 55.3, 45.7, 18.0. Anal. Calcd for $C_{15}H_{20}N_3O_4SCl$: C 48.19, H 5.39, N 11.24. Found: C 48.07, 5.38, 11.05.

4.12. General procedure for RCM reaction using crude carbamate diene 38

In a round bottom flask under N_2, crude carbamate diene **38** (free base) from the Curtius reaction and Hoveyda's catalyst **34** (1–2 mol %) were dissolved in degassed solvent (~0.2 M) and the resultant solution was re-degassed. The mixture was heated to 60 °C and the reaction mixture was analyzed using HPLC. Isomerization product **42** was unstable and converted into **40** upon isolation by flash column chromatography.

*4.12.1. N-[(4-Ethyl-2-oxo-2,3-dihydro-1,3-oxazol-5-yl)methyl]-N-[(1R)-1-methyl-2-propen-1-yl]-2-pyridinesulfonamide (**40**)*

ES-MS: *m*/*z*: 338 ($M+H^+$), 360 ($M+Na^+$). ES-HRMS: calcd for $[C_{15}H_{19}N_3O_4S+H]^+$: 338.1175; found: 338.1175. ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 9.72 (s, 1H), 8.66 (d, *J*=4.6 Hz, 1H), 7.84 (m, 2H), 7.44 (dd, *J*=8.8, 4.6 Hz, 1H), 5.80 (m, 1H), 5.11–5.15 (m, 2H), 4.71 (m, 1H), 4.32 (d, *J*=16.4 Hz, 1H), 4.12 (d, *J*=16.4 Hz, 1H), 2.48 (q, *J*=7.6 Hz, 2H), 1.34 (d, *J*=6.9 Hz, 3H), 1.18 (t, *J*=7.6 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 158.5, 156.8, 150.0, 137.8, 137.6, 131.1, 126.6, 126.4, 121.8, 116.8, 55.5, 37.5, 17.4, 16.6, 12.2.

4.13. (3a*R*,6*R*,8a*S*)-6-Methyl-5-(2-pyridinylsulfonyl)-1,3a,4,5,6,8a-hexahydro-2*H*-[1,3]oxazolo[5,4-*c*]azepin-2-one (39)

Carbamate diene **38** (HCl salt, 81.28 g, 0.217 mol) was suspended in 800 mL of EtOAc and Hoveyda's catalyst **34** (1.358 g, 2.16 mmol, 1 mol %) was dissolved in 400 mL of EtOAc. The entire system was degassed and the EtOAc solution of the diene was heated to 60 °C. The EtOAc solution of the catalyst was slowly added to the diene solution over 1.5 h. The reaction mixture was heated at 60 °C for another 1.5 h and HPLC analysis of a reaction sample showed the conversion was complete. Cysteine (13.16 g, 0.109 mol, 0.5 equiv) and NaOH (19.2 g, 0.48 mol, 2.2 equiv) were dissolved in 400 mL of H_2O, and the resultant solution was slowly added to the reaction mixture. A dark mixture formed. The biphasic mixture was stirred at 60 °C overnight and cooled to rt. The dark aqueous layer was separated and discarded. The light-amber organic layer was washed with aqueous NaOH solution (1 N, 400 mL×2) and concentrated to ~100 mL. Heptane (300 mL) was added and the resultant suspension was stirred at rt overnight, filtered and dried at 45 °C under vacuum to provide carbamate **39** (59.74 g, 0.193 mol, 89%, purity by HPLC: 98.8%). ES-MS: *m*/*z*: 310 ($M+H^+$), 332 ($M+Na^+$). ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 8.70 (dm, *J*=4.6 Hz, 1H), 8.00 (d, *J*=7.8 Hz, 1H), 7.92 (td, *J*=7.7, 1.7 Hz, 1H), 7.52 (ddd, *J*=7.6, 4.7, 1.1 Hz, 1H), 6.72 (br, 1H), 5.30 (s, 2H), 5.17 (ddd, *J*=10.8, 8.4, 6.1 Hz, 1H), 4.75 (m, 1H), 4.64 (dd, *J*=8.4, 2.8 Hz, 1H), 4.21 (dd, *J*=14.6, 6.0 Hz, 1H), 3.37 (dd, *J*=14.7, 10.9 Hz, 1H), 1.07 (d, *J*=7.0 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 159.0, 157.8, 150.2, 138.2, 131.2, 127.0, 126.6, 122.4, 77.0, 55.1, 52.9, 42.7, 18.2. Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C 50.48, H 4.89, N 13.58. Found: C 50.05, H 4.79, N 13.25.

4.14. (3a*R*,6*R*,8a*S*)-6-Methyl-5-(2-pyridinylsulfonyl)-octahydro-2*H*-[1,3]oxazolo[5,4-*c*]azepin-2-one (45)

RCM product **39** (39.8 g, 0.129 mol) was dissolved in 400 mL of DME and the resultant mixture was divided in half. Pd/C catalyst (10%, containing 65% H_2O, 4 g) was added to each portion and the resultant mixtures were hydrogenated at rt overnight, one portion under 120 psi and the other under 60 psi of H_2. No significant difference was observed in the reaction profile by HPLC between the two batches. The two portions were recombined, the Pd/C catalyst was removed by filtration and the product was directly used in the next step. An analytically pure sample could be obtained by recrystallization from EtOH/TBME. ES-MS *m*/*z*: 312 ($M+H^+$), 334 ($M+Na^+$). ^{1}H NMR δ ppm ($CDCl_3$, 400.13 MHz): 8.69 (dm, *J*=4.7 Hz, 1H), 7.97 (d, *J*=7.8 Hz, 1H), 7.91 (td, *J*=7.7, 1.7 Hz, 1H), 7.50 (ddd, *J*=7.5, 4.7, 1.2 Hz, 1H), 6.35 (br, 1H), 4.97 (ddd, *J*=11.2, 8.1, 5.5 Hz, 1H), 4.20 (m, 1H), 3.99–4.09 (m, 2H), 3.20 (dd, *J*=15.2, 11.2 Hz, 1H), 1.90 (m, 1H), 1.65–1.75 (m, 3H), 0.98 (d, *J*=6.7 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 159.1, 157.7, 150.0, 138.1, 126.8, 122.3, 76.8, 55.0, 52.4, 41.3, 30.0, 25.0, 17.1. Anal. Calcd for $C_{13}H_{17}N_3O_4S$: C 50.15, H 5.50, N 13.50. Found: C 50.13, H 5.44, N 13.41.

4.15. (3*R*,4*S*,7*R*)-4-Amino-7-methyl-1-(2-pyridinylsulfonyl)-hexahydro-1*H*-azepin-3-ol (19)

The DME solution of the azepane carbamate **45** (0.129 mol) was concentrated to ~200 mL and aqueous NaOH (16.1 g, 0.402 mol, 3.1 equiv, in 400 mL of H_2O) was added. The mixture was heated to reflux for 2.5 h and HPLC analysis of a reaction sample showed the conversion was complete. The organic solvent was removed by distillation. The resultant suspension was cooled to rt overnight. The solid product was collected by filtration, washed with EtOAc (50 mL) and dried at 50 °C under vacuum to give *cis* aminoalcohol **19** (33.68 g, 0.118 mol, 91%, purity by HPLC: 100%). Ru content: 14 ppm. ES-MS *m*/*z*: 286 ($M+H^+$), 308 ($M+Na^+$). ^{1}H NMR δ ppm (DMSO-d_6, 400.13 MHz): 8.73 (dm, *J*=4.7 Hz, 1H), 8.07 (td, *J*=7.7, 1.6 Hz, 1H), 7.95 (d, *J*=7.9 Hz, 1H), 7.66 (ddd, *J*=7.6, 4.7, 0.7 Hz, 1H), 4.94 (d, *J*=2.7 Hz, 1H), 3.88 (ddd, *J*=17.7, 12.1, 6.2 Hz, 1H), 3.50 (m, 1H), 3.39 (m, 1H), 3.19 (m, 1H), 2.98 (br, 1H), 1.87 (ddd, *J*=14.2, 11.2, 11.0 Hz, 1H), 1.52 (m, 2H), 1.32 (br, 2H), 1.24 (m, 1H), 0.86 (d, *J*=6.4 Hz, 3H). ^{13}C NMR δ ppm (DMSO-d_6, 100.61 MHz): 158.6, 150.1, 138.7, 127.1, 121.9, 72.1, 53.2, 50.0, 42.8, 27.2, 26.0, 20.1. Anal. Calcd

for $C_{12}H_{19}N_3O_3S$: C 50.51, H 6.71, N 14.73. Found: C 50.05, H 6.71, N 14.44.

4.16. 1,3,4,5-Tetradeoxy-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[[(1*R*)-1-methyl-2-propen-1-yl](2-pyridinylsulfonyl)amino]-L-*threo*-pent-4-enitol (24) from epoxide 25

To a mixture of allyl sulfonamide **4** (75.0 kg, 353 mol) and epoxide **25** (83.4 kg, 364 mol, 1.03 equiv) in 2-propanol (339 L) was added *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP) (11 kg, 35.2 mol, 10 mol %) at room temperature. The mixture was heated at gentle reflux for 8 h before being cooled to 35 °C. Aqueous citric acid solution (10%, 165 L) was charged to the mixture followed by slow addition of water (488 L) over 30 min, while maintaining the temperature between 35–40 °C. Seed crystals (300 g, 0.4 mol %) were added. The resulting suspension was stirred overnight, cooled to room temperature, and stirred for an additional 1 h at this temperature. The slurry was filtered with centrifuge, washed with cold 50% aqueous IPA (150 L), and dried under vacuum at 35 °C to afford diene **24** (113 kg, 256 mol, 73%) as a white crystalline solid. ES-MS: *m*/*z*: 442 ($M+H^+$), 464 ($M+Na^+$), 905 ($2M+Na^+$). ^{1}H NMR δ ($CDCl_3$, 400.13 MHz): 8.61 (dm, *J*=4.8 Hz, 1H), 8.01 (dm, *J*=7.9 Hz, 1H), 7.92 (td, *J*=7.7, 1.7 Hz, 1H), 7.81 (m, 2H), 7.69 (m, 2H), 7.48 (ddd, *J*=7.6, 4.8, 1.0 Hz, 1H), 6.28 (ddd, *J*=17.2, 10.1, 8.7 Hz, 1H), 5.80 (ddd, *J*=17.4, 10.6, 5.0 Hz, 1H), 5.37 (d, *J*=17.2 Hz, 1H), 5.28 (d, *J*=10.2 Hz, 1H), 5.10 (m, 2H), 4.87 (br, 1H), 4.67 (t, *J*=9.0 Hz, 1H), 4.59 (td, *J*=9.2, 2.6 Hz, 1H), 4.39 (m, 1H), 3.55 (dd, *J*=15.1, 2.6 Hz, 1H), 3.44 (dd, 1H, *J*=15.2, 9.2 Hz), 1.28 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ($CDCl_3$, 100.61 MHz): 168.1, 158.0, 149.5, 138.5, 137.3, 133.8, 132.2, 131.8, 126.8, 123.2, 122.9, 120.8, 117.2, 68.7, 57.6, 55.7, 48.9, 17.6. Anal. Calcd for $C_{22}H_{23}N_3O_5S$: C 59.86, H 5.25, N 9.52. Found: C 59.80, H 5.26, N 9.49.

4.17. 1,3,4,5-Tetradeoxy-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[[(1*R*)-1-methyl-2-propen-1-yl](2-pyridinylsulfonyl)amino]-L-*threo*-pent-4-enitol (24) from tosylate 47

A slurry of tosylate **47** (8.5 kg, 21.2 mol) and toluene (34 L) was heated to 56 °C and DBU (3.3 kg, 21.7 mol) was added via pressure vessel to maintain the temperature between 55–65 °C. The starting material dissolved during the addition and the mixture was aged at this temperature for 60 min. Upon completion of the reaction, the mixture was cooled to 25 °C and 10% w/w aq citric acid (0.42 L water with 45 g citric acid monohydrate) was added. After stirring for 10 min, water (25.5 L) was added, the mixture stirred and the layers allowed to separate. The organic layer was then washed twice with water (8.5 L×2). The solution of crude **25** was then transferred to a second reactor via an inline filter to remove a small layer of film, and the transfer line then rinsed with toluene (8.5 L). To this second reactor was charged **4** (4.5 kg, 21.2 mol) and the solvent partially removed by vacuum distillation to reach 15 L total volume (36.0 L toluene removed). 2-Propanol (25.5 L) was charged and the system vacuum distilled to achieve 15 L total volume (25.5 L removed). 2-Propanol (15.0 L) was added followed by BTPP (0.7 kg, 2.12 mol), and the mixture heated to 80 °C over ~30 min. After aging for 3.5 h, the reaction was complete and heptane was added (17.0 L) while maintaining the temperature ≥60 °C. The temperature was then adjusted to 53 °C and seeds of **24** (4.5 g in 2:1 heptane/2-propanol) were charged to the reactor. The slurry was held at 52 °C for 60 min, then cooled to ~10 °C at 0.5 °C/min. After holding for 30 min, the slurry was isolated by centrifugal filtration, washed with cold heptane/2-propanol (2:1 v/v, 8.5 L×2). The product was dried under vacuum at 45 °C to afford **24** (7.25 kg, 16.4 mol, 78%, HPLC purity >99.9%).

4.18. 2-[(3*S*,4*S*,7*R*)-3-Hydroxy-7-methyl-1-(2-pyridinylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepin-4-yl]-1*H*-isoindole-1,3(2*H*)-dione (50)

A solution of diene **24** (80.0 kg, 181 mol) in toluene (880 L) was degassed. Hoveyda's catalyst **34** (600 g, 0.5 mol %) was added and the mixture was degassed once again. The reaction was then heated to 110 °C and kept for 5 h at this temperature. Upon cooling to 60 °C, 80% tetrakis(hydroxylmethyl)phosphonium chloride (5.8 L) and sodium bicarbonate (2.7 kg) were added. The resulting mixture was stirred at 60 °C for 13 h, and cooled to 40 °C. Water (112 L) and cyclohexane (880 L) were added before further cooling to 20 °C. The slurry was filtered with centrifuge, washed with water (112 L×2) and IPA (56 L×2), then dried under vacuum at 35 °C to afford **50** (71.8 kg, 174 mol, 96%) as a light gray solid. ES-MS: *m*/*z*: 414 ($M+H^+$), 436 ($M+Na^+$), 849 ($2M+Na^+$). ^{1}H NMR δ ($CDCl_3$, 400.13 MHz): 8.86 (dm, *J*=4.8 Hz, 1H), 8.09 (d, *J*=7.8 Hz, 1H), 8.01 (td, *J*=7.7, 1.7 Hz, 1H), 7.81 (m, 2H), 7.70 (m, 2H), 7.64 (ddd, *J*=7.6, 4.8, 1.2 Hz, 1H), 5.58 (ddd, *J*=11.0, 5.1, 2.9 Hz, 1H), 5.22 (m, 2H), 4.84 (br, 1H), 4.68 (m, 1H), 4.46 (dd, *J*=9.7, 4.4 Hz, 1H), 4.29 (d, *J*=16.2 Hz, 1H), 3.91 (dd, *J*=16.2, 4.6 Hz, 1H), 1.36 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ppm ($CDCl_3$, 100.61 MHz): 168.0, 157.2, 150.6, 138.6, 133.8, 131.6, 131.0, 126.8, 126.7, 123.0, 122.3, 71.5, 54.8, 52.8, 48.3, 19.6. Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C 58.10, H 4.63, N 10.16. Found: C 58.01, H 4.59, N 10.05.

4.19. 2-[(3*S*,4*S*,7*R*)-3-Hydroxy-7-methyl-1-(2-pyridinylsulfonyl)hexahydro-1*H*-azepin-4-yl]-1*H*-isoindole-1,3(2*H*)-dione (51)

To a Hastelloy pressure reactor were charged alkene **50** (28.0 kg, 67.7 mol), 10% Pd/C (PMC1625C, 16.1 kg, 63% wet, 20 wt %) and THF (420 L). The mixture was stirred at 35 °C under hydrogen pressure (120 psi) for 4 h. Upon cooling, the mixture was filtered through a pad of Celite, and the reactor and the pad were rinsed with dichloromethane (364 L). The combined filtrate was concentrated under atmospheric pressure to ~140 L. Acetone (280 L) was charged, and the distillation was continued until the volume of the mixture was ~140 L. IPA (28 L) was added. The slurry was heated to reflux for 30 min, cooled to 0 °C, and filtered with centrifuge. The wet cake was washed with IPA (56 L), and dried under vacuum at 35 °C to afford **51** (23.1 kg, 55.6 mol, 82%) as an off-white crystalline solid. ES-MS: *m*/*z*: 416 ($M+H^+$), 438 ($M+Na^+$), 853 ($2M+Na^+$). ^{1}H NMR δ ($CDCl_3$, 400.13 MHz): 8.87 (dm, *J*=4.7 Hz, 1H), 8.06 (d, *J*=7.8 Hz, 1H), 7.98 (td, *J*=7.7, 1.7 Hz, 1H), 7.80 (m, 2H), 7.70 (m, 2H), 7.60 (ddd, *J*=7.6, 4.8, 1.1 Hz, 1H), 4.90 (br s, 1H), 4.34 (m, 1H), 4.24 (m, 3H), 3.75 (dd, *J*=16.6, 3.6 Hz, 1H), 2.48 (m, 1H), 1.57 (m, 3H), 1.23 (d, *J*=6.9 Hz, 3H). ^{13}C NMR δ ($CDCl_3$, 100.61 MHz): 168.2, 157.7, 150.2, 138.6, 133.8, 131.9, 126.8, 123.1, 122.4, 72.0, 57.9, 51.2, 46.4, 34.6, 25.3, 17.6. Anal. Calcd for $C_{20}H_{21}N_3O_5S$: C 57.82, H 5.09, N 10.11. Found: C 57.92, H 5.03, N 10.08.

4.20. (3*S*,4*S*,7*R*)-4-Amino-7-methyl-1-(2-pyridinylsulfonyl)-hexahydro-1*H*-azepin-3-ol (23) from 51

A solution of phthalimide **51** (32.0 kg, 77.2 mol) in 95% EtOH (320 L) was heated to ~55 °C, and hydrazine monohydrate (9.3 L, 193 mol) was added. The reaction mixture was stirred at 75 °C for 1 h before being cooled to 35 °C. The mixture was diluted with CH_2Cl_2 (256 L). The resulting slurry was filtered with centrifuge and the solid was washed with CH_2Cl_2 (128 L). The combined filtrate was concentrated to the minimum stir volume of the vessel. Water (96 L) was added. The mixture was concentrated under vacuum to ~60 L, extracted with CH_2Cl_2 (320 L+96 L) to give aminoalcohol **23** as a CH_2Cl_2 solution (quantitative yield assumed). This solution was used in the next coupling step without further purification. A pure

sample can be obtained by recrystallization from water in 85% yield. ES-MS: *m*/*z*: 286 ($M+H^+$), 571 ($2M+H^+$), 593 ($2M+Na^+$). ^{1}H NMR δ (DMSO-d_6, 400.13 MHz): 8.69 (ddd, *J*=4.7, 1.6, 0.8 Hz, 1H), 8.04 (td, *J*=7.7, 1.8 Hz, 1H), 7.89 (d, *J*=7.9 Hz, 1H), 7.62 (ddd, *J*=7.6, 4.7, 1.1 Hz, 1H), 4.72 (br, 1H), 4.00 (ddd, *J*=14.6, 12.7, 6.4 Hz, 1H), 3.47 (m, 2H), 3.23 (m, 1H), 2.59 (ddd, *J*=7.4, 5.2, 2.8 Hz, 1H), 1.32–1.68 (m, 6H), 1.03 (d, *J*=6.4 Hz, 3H). ^{13}C NMR δ (DMSO-d_6, 100.61 MHz): 158.6, 149.6, 138.4, 126.8, 122.0, 73.9, 54.4, 53.4, 46.0, 28.4, 26.7, 20.2. Anal. Calcd for $C_{12}H_{19}N_3O_3S$: C 50.51, H 6.71, N 14.73. Found: C 50.51, H 6.84, N 14.67.

4.21. (3*S*,4*S*,7*R*)-4-Amino-7-methyl-1-(2-pyridinylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azepin-3-ol (52)

Phthalimide **50** (2.4 kg, 5.8 mol) was added to a solution of hydroxyamine hydrochloride (0.9 kg, 13 mol, 2.2 equiv) in methanol (19.5 L). A methanol solution of NaOMe (25% w/w, 6.4 kg, 30 mol, 5.2 equiv) was slowly added while maintaining the temperature of the reaction mixture between 22 and 27 °C. The reaction mixture was stirred at 28–30 °C for 1.5 h. HPLC analysis of the reaction mixture indicated that the starting material was consumed. Water (9.6 L) was added and the mixture was distilled to ~10 L. The aqueous mixture was extracted by CH_2Cl_2 (24 L+7.2 L), and the combined organic layer was distilled to ~5 L. Isopropanol (4.8 L) was added and the mixture was concentrated to ~5 L. A second portion of isopropanol (2.4 L) was added and the mixture was concentrated to ~6 L. TBME (5 L) was charged to the resultant suspension. The mixture was cooled to 0 °C and stirred at 0 °C for 1 h. The product was collected by centrifuge filtration. The wet cake was washed with TBME (5 L) and dried at 35–45 °C under vacuum. The product was obtained as a white crystalline solid (1.2 kg, 4.2 mol, 73%). ES-MS: *m*/*z*: 284 ($M+H^+$), 306 ($M+Na^+$), 567 ($2M+H^+$), 589 ($2M+Na^+$). ^{1}H NMR δ (DMSO-d_6, 400.13 MHz): 8.73 (dm, *J*=4.7 Hz, 1H), 8.08 (td, *J*=7.8, 1.6 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 1H), 7.66 (ddd, *J*=7.6, 4.7, 0.5 Hz, 1H), 5.31 (m, 2H), 5.14 (br, 1H), 4.67 (q, *J*=6.9 Hz, 1H), 3.64 (dd, *J*=14.6, 4.7 Hz, 1H), 3.50 (dd, *J*=14.6, 5.7 Hz, 1H), 3.30–3.40 (m, 2H), 1.53 (br, 2H), 1.01 (d, *J*=7.1 Hz, 3H). ^{13}C NMR δ ($CDCl_3$, 100.61 MHz): 157.6, 150.1, 138.7, 133.4, 130.8, 127.1, 122.1, 73.7, 53.3, 52.3, 48.5, 18.0. Anal. Calcd for $C_{12}H_{17}N_3O_3S$: C 50.87, H 6.05, N 14.83. Found: C 50.85, H 5.79, N 14.66.

4.22. (3*S*,4*S*,7*R*)-4-Amino-7-methyl-1-(2-pyridinylsulfonyl)-hexahydro-1*H*-azepin-3-ol (23) from 52

To a Hastelloy pressure reactor were charged alkene **52** (1.1 kg, 3.9 mol), 10% Pd/C (JM10R391, 66 g, 50% wet, 3 wt %) and industrial methylated spirits (IMS, 11 L, 94% ethanol, 5% methanol, 1% water). The mixture was stirred at 33–37 °C under hydrogen pressure (60 psi) for 3.5 h. HPLC analysis of the reaction mixture indicated that the starting material was consumed. CH_2Cl_2 (4.4 kg) was charged and the mixture was stirred at 30 °C for 0.5 h. The mixture was filtered through a pad of Celite, and the reactor and the pad were rinsed with CH_2Cl_2 (4.4 kg). The filtrates were combined (total weight: 17.6 kg, containing **23**: 6.2% w/w, ~1.1 kg, 3.8 mol, 98%).

4.23. *N*-[(1*S*)-1-({[(3*S*,4*S*,7*R*)-3-Hydroxy-7-methyl-1-(2-pyridinylsulfonyl)hexahydro-1*H*-azepin-4-yl]-amino}carbonyl)-3-methylbutyl]-1-benzofuran-2-carboxamide (55)

The CH_2Cl_2 solution of aminoalcohol **23** (~114 mol) was distilled to ca. 330 L under atmospheric pressure, and cooled to 20 °C. To the resultant mixture were added side chain **18** (31.4 kg, 114 mol) and 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HOOBt) (200 g, 1.23 mol, 1.1 mol %), and the reaction mixture was cooled to 0 °C. EDCI (24.0 kg, 126 mol) was added, and the reaction mixture was stirred at this temperature for 5 h. Upon the completion of the reaction, it was quenched with 3% aqueous sodium bicarbonate (200 L). The organic layer was washed with water (195 L) and concentrated under vacuum to the minimum stir volume of the vessel. The residue was diluted with toluene (390 L), and the mixture was concentrated to ca. 290 L. Toluene (98 L) was added. The mixture was heated to 90 °C and clear dissolution was observed. The mixture was cooled to 58 °C, seeded (10 g, 0.03 wt %), and held at this temperature for 30 min. TBME (325 L) was charged over 30 min at 52 °C. The mixture was cooled to 15 °C over 1 h, and filtered with centrifuge. The solid product was washed with TBME (195 L), and dried under vacuum at 45 °C to afford coupling product **55** (50.7 kg, 93.4 mol, 82% over two steps) as a white crystalline solid. ES-MS: *m*/*z*: 543 ($M+H^+$), 565 ($M+Na^+$). ^{1}H NMR δ ($CDCl_3$, 300.13 MHz): 8.69 (d, *J*=4.6 Hz, 1H), 8.05 (dt, *J*=7.8, 1.0 Hz, 1H), 7.93 (td, *J*=7.8, 1.6 Hz, 1H), 7.66 (ddd, *J*=7.8, 1.2, 0.7 Hz, 1H), 7.53 (tm, *J*=3.7 Hz, 1H), 7.50 (m, 1H), 7.48 (s, 1H), 7.44 (ddd, *J*=8.4, 7.1, 1.3 Hz, 1H), 7.31 (ddd, *J*=7.9, 7.0, 1.1 Hz, 1H), 7.10 (br, 1H), 6.80 (br, 1H), 4.66 (m, 1H), 4.19 (dd, *J*=16.3, 3.0 Hz, 1H), 3.93 (m, 2H), 3.74 (m, 1H), 3.46 (d, *J*=16.2 Hz, 1H), 1.66–1.87 (m, 6H), 1.40 (m, 1H), 0.97–1.05 (m, 9H). ^{13}C NMR δ ($CDCl_3$, 100.61 MHz): 171.5, 159.0, 158.0, 154.8, 149.6, 147.8, 138.2, 127.2, 127.1, 126.8, 123.7, 122.9, 122.6, 111.8, 110.9, 72.5, 54.8, 52.5, 51.8, 44.6, 41.0, 30.7, 24.7, 24.4, 22.8, 22.0, 18.6. Anal. Calcd for $C_{27}H_{34}N_4O_6S$: C 59.76, H 6.32, N 10.32. Found: C 59.45, H 6.39, N 10.09.

4.24. SB-462795 (1)

To a solution of coupling product **55** (50.7 kg, 93.4 mol) in DMSO (507 L) was added acetic anhydride (26.5 L, 280 mol, 3 equiv) at room temperature, and the resulting solution was stirred at 50–55 °C for 3 h. Upon the completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (507 L), and washed with water (304 L×3). The organic layer was concentrated under vacuum to ~150 L, warmed to 55 °C, and filtered through an in-line filter. The reactor and the filter were rinsed with ethyl acetate (51 L), and the combined product solution was diluted with TBME (507 L). The mixture was heated to 55 °C. Seeds of **1** (50 g, 0.1 wt %) were added as a TBME slurry. The mixture was stirred at this temperature for 1 h, diluted further with warm TBME (507 L), then cooled to −10 °C at a rate of 0.5 °C/min. It was filtered with centrifuge, washed with cold TBME (253 L), and the solid was spun dry under nitrogen to give **1**/TBME complex (69.8 kg). The TBME solvate was slurried in heptane (760 L), and the mixture was heated at 80 °C for 3 h before cooling to 20 °C over 2 h. The solid was isolated with centrifuge, washed with heptane (760 L), and dried under vacuum at 40 °C to afford SB-462795 (43.1 kg, 79.7 mol, 85%) as a white crystalline solid. ES-MS: *m*/*z*: 541 ($M+H^+$), 563 ($M+Na^+$). ^{1}H NMR δ ($CDCl_3$, 300.13 MHz): 8.71 (m, 1H), 7.99 (d, *J*=7.9 Hz, 1H), 7.92 (tm, *J*=7.7 Hz, 1H), 7.66 (dm, *J*=7.8 Hz, 1H), 7.50 (m, 3H), 7.42 (tm, *J*=7.7 Hz, 1H), 7.28 (m, 1H), 7.15 (br, 1H), 7.02 (br, 1H), 5.12 (m, 1H), 4.77 (m, 2H), 4.41 (m, 1H), 3.86 (dd, *J*=19.4, 2.2 Hz, 1H), 2.15 (m, 2H), 1.74 (m, 3H), 1.45–1.62 (m, 2H), 0.94–1.00 (m, 9H). ^{13}C NMR δ ($CDCl_3$, 100.61 MHz): 206.2, 170.7, 158.5, 157.5, 154.7, 150.2, 148.0, 138.1, 127.3, 127.0, 126.9, 123.6, 122.6, 122.2, 111.8, 110.8, 57.1, 52.1, 52.0, 51.4, 41.8, 33.2, 27.0, 24.7, 22.8, 22.0, 15.4. Anal. Calcd for $C_{27}H_{32}N_4O_6S$: C 59.98, H 5.97, N 10.36. Found: C 59.86, H 6.03, N 10.27.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.022.

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