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Review

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Allylic Amines as Key Building Blocks in the Synthesis of (*E*)-Alkene Peptide Isosteres

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ABSTRACT: Nucleophilic imine additions with vinyl organometallics have developed into efficient, high-yielding, and robust methodologies to generate structurally diverse allylic amines. We have used the hydrozirconation/transmetalation/imine addition protocol in the synthesis of allylic amine intermediates for peptide bond isosteres, phosphatase inhibitors, and mitochondria-targeted peptide mimetics. The gramicidin S-derived XJB-5-131 and JP4-039 and their analogues have been prepared on up to 160-g scale for preclinical studies. These (*E*)-alkene peptide isosteres adopt type II′ β-turn secondary structures and display impressive biological properties including selective reactions with reactive oxygen species (ROS) and prevention of apoptosis.

INTRODUCTION

Allylic Amines. Analogous to allylic alcohols, allylic amines represent useful functionalized three-carbon building blocks for the synthesis of heterocycles and bioactive amines. In addition to oxygenations and aminations, metathesis reactions of allylic amines have been used to generate more complex derivatives (Figure 1). Several protocols are available for the synthesis of α-

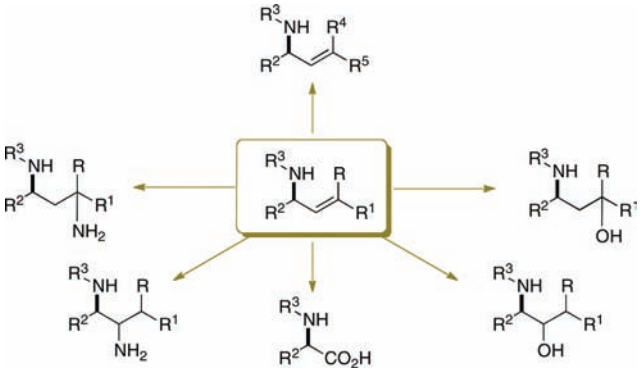
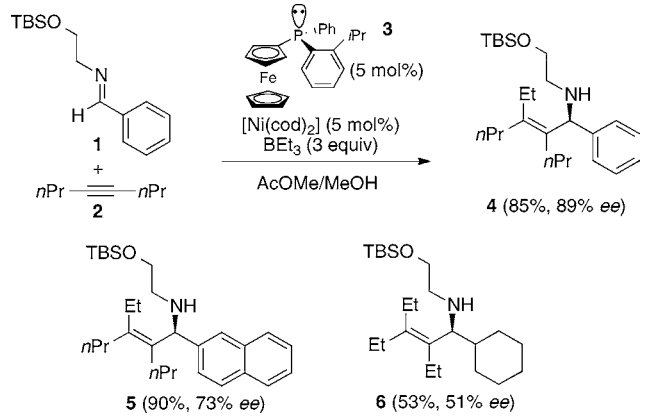


Figure 1. Representative synthetic transformations of allylic amine building blocks.

chiral allylic amines,[1] including the rearrangement of allylic trichloroacetimidates,[1b] Ni(0)-mediated allylic amination,[1c] C,H-bond activation, and C−C bond-forming hydrogenation.[1k] Currently, nucleophilic additions to imines represent the most versatile strategy to prepare chiral allylic amines.[1d−k] In addition to the direct addition of vinyl organometallic species,[1g−i] the reductive coupling of alkynes[1d−f] and the acylvinyl anion addition[1j] provide diastereo- and/or enantiomerically enriched products.

Jamison and co-workers developed an enantioselective synthesis of tetrasubstituted allylic amines by intermolecular coupling of a disubstituted alkyne, an imine, and triethylborane (Scheme 1).[1e] The conversion was catalyzed by a chiral [Ni(cod)$_2$]/ferrocenyl phosphane complex (**3**) (cod = cyclooctadiene). A (*tert*-butyl-dimethylsilyloxy)ethyl group was used to enhance reactivity and selectivity in the reaction of the

Scheme 1. Ni-catalyzed intermolecular coupling to prepare enantiomerically enriched allylic amines[1e]



achiral imine (**1**), and this auxiliary group could be removed from products **4**−**6** via a two-step protocol without decrease in enantiomeric excess.

The Krische group was able to form allylic amines via an asymmetric iridium-catalyzed C−C bond-forming hydrogenation process related to hydroformylation reactions (Scheme 2). Hydrogenation of internal alkyne **8** in the presence of either aryl or alkyl aldimines such as **7** and chiral catalyst **9** resulted in the enantiomerically enriched trisubstituted allylic sulfonylamine **10**. The regioselectivity of the reaction with unsymmetrically substituted internal alkynes was also high.

The reaction of α-hydroxypropargylsilanes with chiral sulfinylimines to form trisubstituted allylic amines was applied by the Scheidt group (Scheme 3).[1j] Brook rearrangement of the α-hydroxypropargylsilane **13** to form the lithium allenolate was achieved with *n*-BuLi. The α-acylvinyl anion equivalent reacted with sulfinylimine (*R*)-**14** to give the β-substituted *aza*-Morita−Baylis−Hillman product **15** in good yield and diastereoselectivity. The (*Z*)-alkene was the preferred product in all cases.

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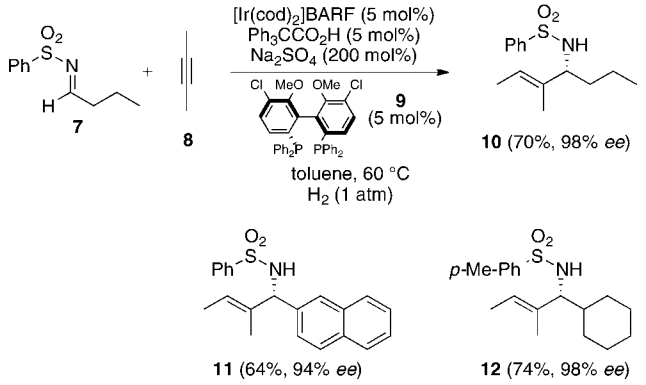
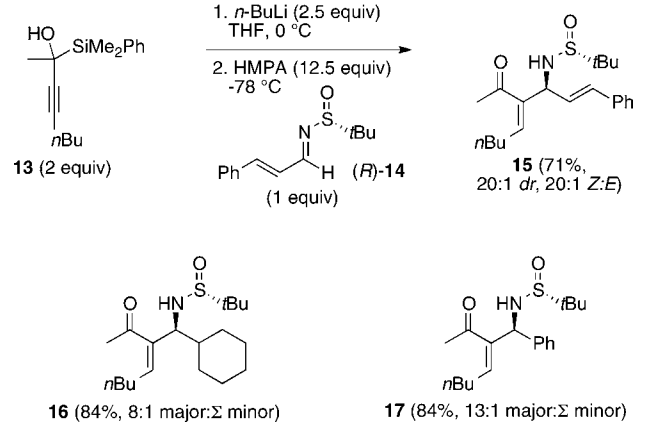
Scheme 2. Reductive coupling of alkynes with *N*-arylsulfonyl imines[1f]

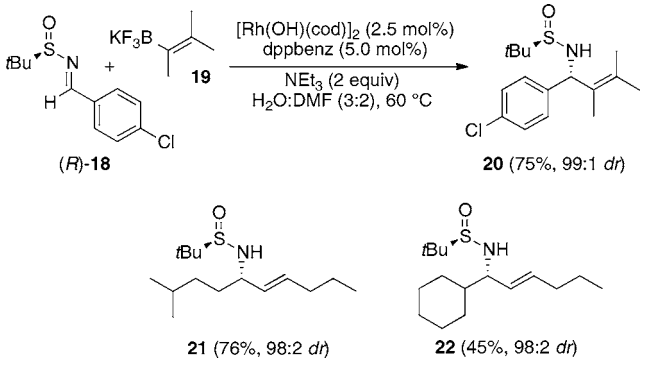


Scheme 3. α-Acylvinyl anion addition to imines (major:$\sum$minor refers to the ratio of the major product as drawn to the sum of all minor products)[1j]



Chiral sulfinyl imines were also utilized by Ellman and co-workers to form di-, tri-, or tetrasubstituted allylic amines (Scheme 4).[1i] The sulfinyl amine (*R*)-**18** was coupled with

Scheme 4. Rh(I)-catalyzed addition of alkenyl trifluoroborates to *N*-*tert*-butylsulfinylimines[1i]



potassium trifluoroborates **19** via Rh(I)-catalysis. Air-stable $[Rh(OH)(cod)]_2$ along with 1,2-bis-(diphenylphosphino)-benzene (dppbenz) gave the best yield and diastereoselectivity of the allylic sulfinylimines **20**–**22**.

In the development of the hydrozirconation/transmetalation/imine addition protocol for the asymmetric synthesis of (*E*)-allylic amines, our group was able to take advantage of the ease of access to functionalized alkyne starting materials. Furthermore, the carboalumination/water-accelerated imine addition chemistry allowed for the preparation of terminally disubstituted allylic amines.[2] Figure 2 provides an overview of the products available with these methodologies.

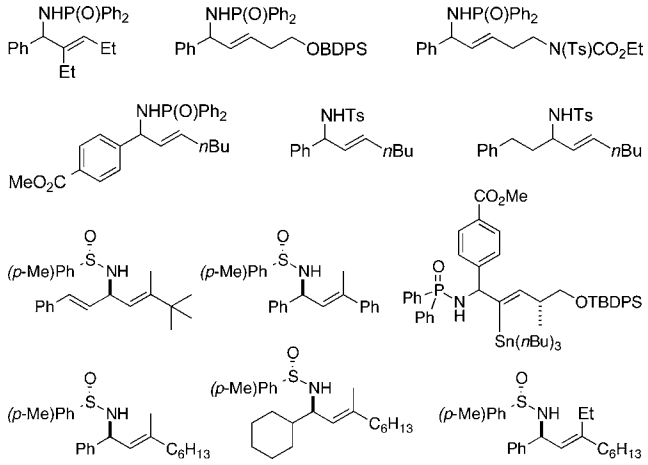


Figure 2. Representative allylic amine building blocks obtained with alkyne hydro(carbo)metalation/imine addition methods.

Peptide Isosteres. The use of peptides as pharmaceuticals is of considerable interest since oligo- and polypeptides are natural ligands for receptors and enzymes. However, peptide-based orally administered drug formulations are still rare and tend to exhibit poor absorption and cell permeability as well as low bioavailability. The undesirable pharmacokinetic (PK) properties of peptides as well as their propensity for rapid in vivo degradation by peptidases have encouraged the pursuit of peptide mimetics as alternative therapeutic agents. Peptide isosteres contain a nonhydrolyzable group in place of the amide bond. In order for a rational design of these compounds to be effective, they must be able to adopt secondary structures typical for native peptides.[3] Among others, methylene amine,[4] ketomethylene,[5] hydroxyethylamine,[6] hydroxymethylene and -ethylene,[7] dihydroxyethylene,[8] cyclopropylalkylamine,[9] methyl- and (trifluoromethyl)alkenes,[10] and β-amino acids[11] have been used for this purpose. Our group has studied (*E*)-alkenes[9b,10b,12] as peptide bond replacements (Figure 3),[3b,13]

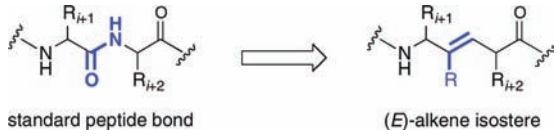


Figure 3. Structure of (*E*)-alkene peptide isosteres as peptide bond replacements.

and the synthesis and applications of these isosteres as mitochondrial targeting compounds[14] is a major focus of our program.

Mitochondrial Targeting Agents. The cyclodecapeptide antibiotic gramicidin S displays significant resistance to peptide-cleaving proteases (Figure 4).[15] It has been shown to interact with microbial membrane lipids, and this interaction as well as its general biological profile are correlated to its secondary structure composed of an amphipathic antiparallel β-sheet and two type II′ β-turns. Our group has studied the conformational

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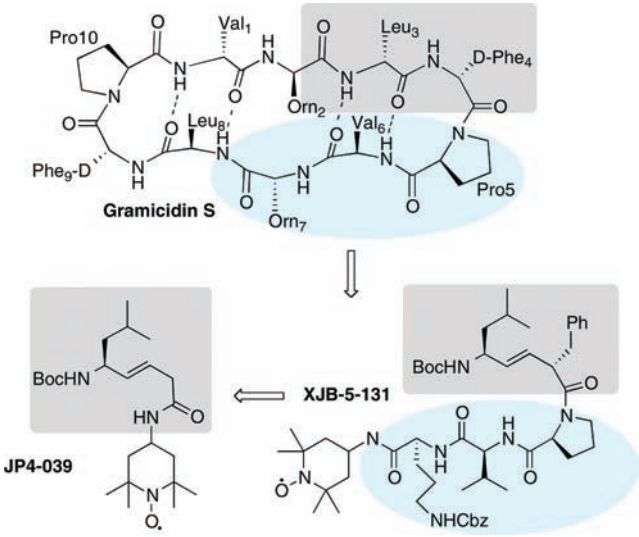


Figure 4. Mitochondrial targeting agents based on the antibiotic gramicidin S.

and biological effects of isosteric substitutions with both di- and trisubstituted alkenes in the gramicidin S backbone.[13,16]

The design of the mitochondrial targeting agents XJB-5-131 and JP4-039 was inspired by the microbial membrane affinity of gramicidin S and guided by its characteristic secondary structural features. Replacement of an internal amide bond with an (*E*)-alkene moiety was envisioned to increase both the rigidity of the peptide mimetic as well as enhance its membrane permeability by removing a polar hydrogen bond donor/acceptor function. XJB-5-131, a first-generation analogue of gramicidin S, retained the Leu-^{D}Phe-Pro-Val-Orn segment of the parent structure to fully encompass the II′ β-turn motif.[9a] A 4-amino-TEMPO (4-AT) "pay load" was added at the C-terminus to serve as a scavenger of reactive oxygen species (ROS) formed in mitochondria. The structurally simplified JP4-039 possesses an alkene dipeptide isostere segment comprising leucine and glycine residues. XJB-5-131 and JP4-039 were found to be enriched in mitochondria by factors of 600 and 30, respectively, over their cytosolic concentrations.[14c,17]

We attribute the ability of these peptide mimetics to cross cellular membranes and concentrate in mitochondria to their β-turn preference as well as their affinity for the mitochondrial lipid, cardiolipin.[14c,17] For example, the X-ray analysis of JP4-039 displays a type II′ β-turn (Figure 5). The distance in the $i\rightarrow i+3$ intramolecular H-bond between the carbonyl of the Boc

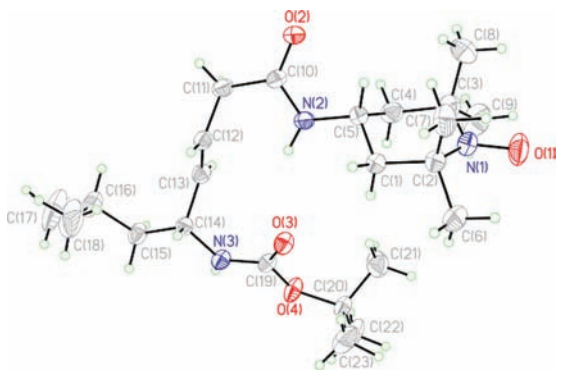


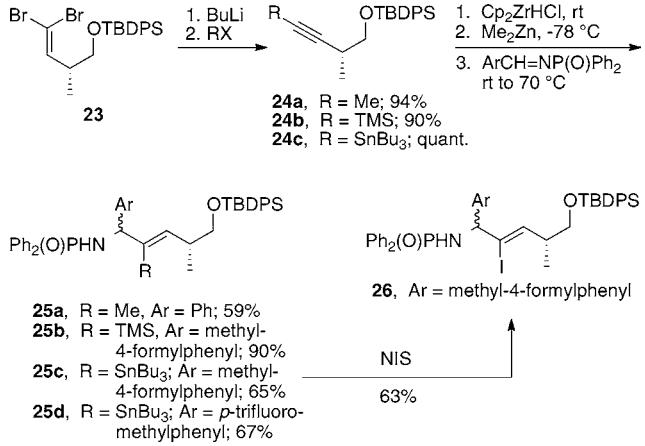
Figure 5. Crystal structure of JP4-039 reveals a type II′ β-turn.

group and the nitrogen of 4-AT measures 3.30 Å. Similarly, a CD-analysis of XJB-5-131 and X-ray analyses of related biologically active peptide mimetics confirm the presence of analogous β-turns.

METHODOLOGIES AND SYNTHETIC APPLICATIONS

Imine Additions. Early studies toward the synthesis of allylic amines in our group explored nucleophilic additions of vinyl zinc reagents to *N*,*N*-diphenylphosphinoylimines. Differentially substituted internal alkynes were synthesized by reaction of dibromoalkene **23** with butyllithium followed by quenching with electrophiles (see Scheme 5). Methyl, trimethylsilyl, and tributylstannyl alkynes **24a–c** were then

Scheme 5. Hydrozirconation/transmetalation/imine addition approach to trisubstituted allylic amines[9b,12b]



subjected to hydrozirconation[2d,18] with zirconocene hydrochloride,[19] followed by transmetalation with dimethylzinc. Addition of phosphinoylimines to the reaction mixture gave alkenes **25a–d** as a 1:1 mixture of diastereomers, which were easily separable by chromatography on SiO_2.[9b,12b] The vinyl stannane **25c** was iodinated with *N*-iodosuccinimide to provide iodoalkene **26**. These intermediates could then be reacted under various cross-coupling conditions to generate a diverse set of allylic phosphinoylamines. For example, Stille cross-coupling of vinyl stannane **25c** under microwave conditions led to the trisubstituted aryl- and heteroarylalkenes **27–29** in good yields (Scheme 6).[9b]

Vinyl iodide **26** was used to synthesize phenyl- and trifluoromethyl-substituted allylic amines **30** and **33**, respectively. Negishi cross-coupling of **26** with phenylzinc bromide provided an 86% yield of **30** (Scheme 7). Alternatively, cross-coupling could be postponed until further elaboration of the *C*- and *N*-terminal functions. The phosphinoyl and silyl groups of **26** were removed with HCl(g), and the amine was acylated with CbzCl (Cbz = carboxybenzyl) to give carbamate **31**. Two-step oxidation of the primary alcohol to the acid followed by coupling to 2-naphthylamine provided **32**, which was converted with methyl fluorosulfonyldifluoroacetate[20] and copper thiophene carboxylate to the chromatographically separable trifluoromethyl alkenes **33a** and **33b**.

Our group also developed an accelerated carboalumination of alkynes in the presence of catalytic Cp_2ZrCl_2 and stoichiometric H_2O.[21] The intermediate vinyl alanes reacted with enantiomerically enriched sulfinyl imines to provide chiral allylic amines.[2a]

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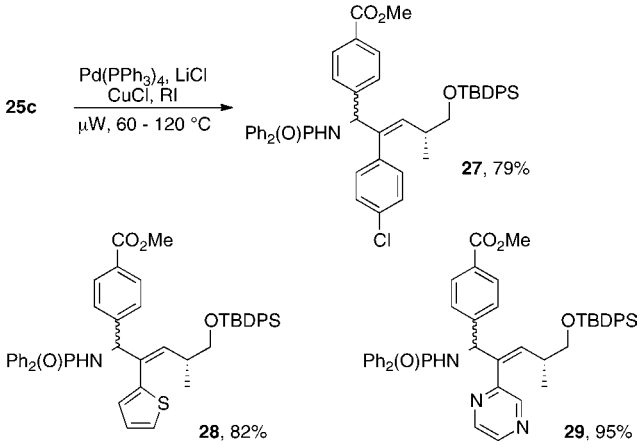
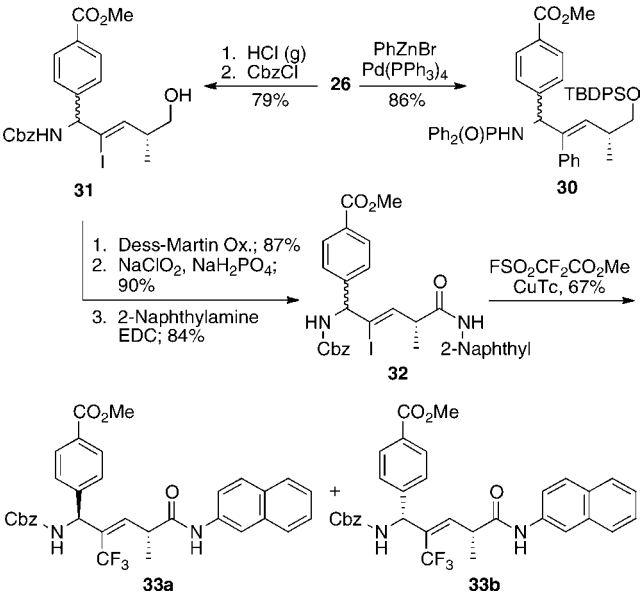
Scheme 6. Microwave-accelerated Stille cross-couplings of 25c[9b]



Scheme 7. Pd-catalyzed arylation of iodoalkene 26 and trifluoromethylation of iodoalkene 32[9b]

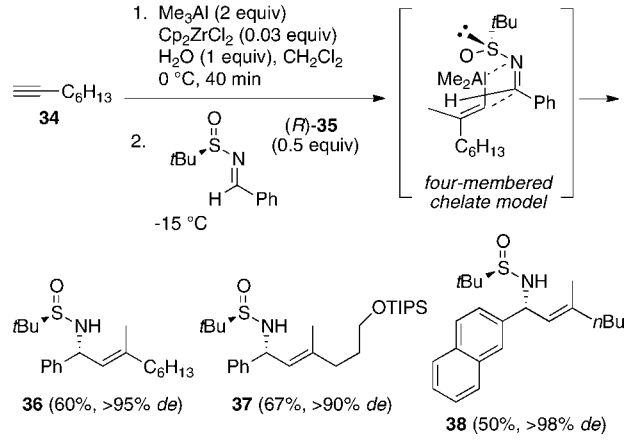


For example, the vinyl alane formed from terminal alkyne **34** converted sulfinyl imine (*R*)-**35** to the trisubstituted (*E*)-alkene **36** in good yield and >95% de (Scheme 8). The diastereoselectivity could be explained by a four-membered Felkin-Anh-type transition state model.[1h,22] This methodology was extended to the synthesis of cyclopropyl alkylamines.[23] Furthermore, allylic amines could be obtained via a dimethylzinc-mediated addition of alkenyl zirconocenes to imino esters[24] and by hydrozirconation followed by transmetalation to aluminum and addition to sulfinyl imines.[2c]

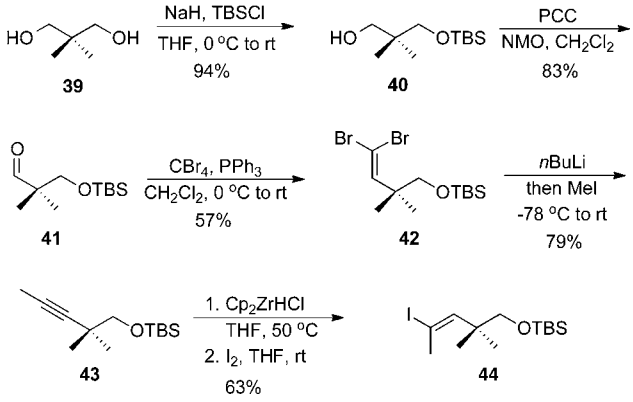
PEPTIDE MIMETICS BASED ON ALLYLIC AMINES

Synthesis of a Cdc25 Inhibitor. The imine addition methodology was optimized and applied to the synthesis of new (*E*)-alkene dipeptide isosteres. Our target design was based on the crystal structure of an active site peptide inhibitor of the dual-specificity phosphatase Cdc25.[25] Monosilylation of the commercially available diol **39** followed by oxidation gave aldehyde **41** (Scheme 9). A Corey–Fuchs[26] reaction provided dibromoalkene **42** which was treated with *n*-BuLi to form

Scheme 8. Alkyne carboalumination/sulfinyl imine addition as a stereoselective entry to (*E*)-allylic amines[2a]



Scheme 9. Synthesis of (*E*)-iodoalkene 44 by hydrozirconation of internal alkyne 43



alkyne **43** after quenching with MeI. Hydrozirconation[2d,18] and iodination of the internal alkyne led to the iodoalkene **44**, which could be used as a common intermediate in the formation of other trisubstituted alkene peptide isosteres.

Building block **44** was used to synthesize intermediate **50** in the synthesis of isostere **57**. Iodine–lithium exchange of **44**, followed by transmetalation to magnesium[1h] and addition to sulfinyl imine (*R*)-**45** gave **46** as a 2.5:1 mixture of diastereomers (Scheme 10). Protecting group removal, *tert*-butyl carbamate formation, and oxidation of the primary alcohol led to acid **47**. Acylation of amine **48** provided the trisubstituted alkene **49**, and saponification, peptide coupling, and removal of the Boc group led to the advanced intermediate **50**.

The crystal structure of tetrapeptide mimetic **49** displayed a type II′ β-turn with prototypical dihedral angles (Figure 6). Interestingly, this compound crystallized in the chiral space group $P\bar{6}s1$ and formed an infinite one-dimensional hydrogen-bonded chain along the *z*-axis. The molecules assemble in a three-fold axis around long channels, which are filled with disordered solvent molecules (Figure 7). The diameter of the channel in the rhombi measures ~5.5 Å, and the sides have a length of ~9 Å.

To complete the synthesis of **57**, phenylalanine sulfonic acid derivative **54** was prepared by reaction of commercially available aldehyde **51** with Wittig reagent **52** and tetramethylguanidine (TMG) to give alkene **53**. Stereoselective

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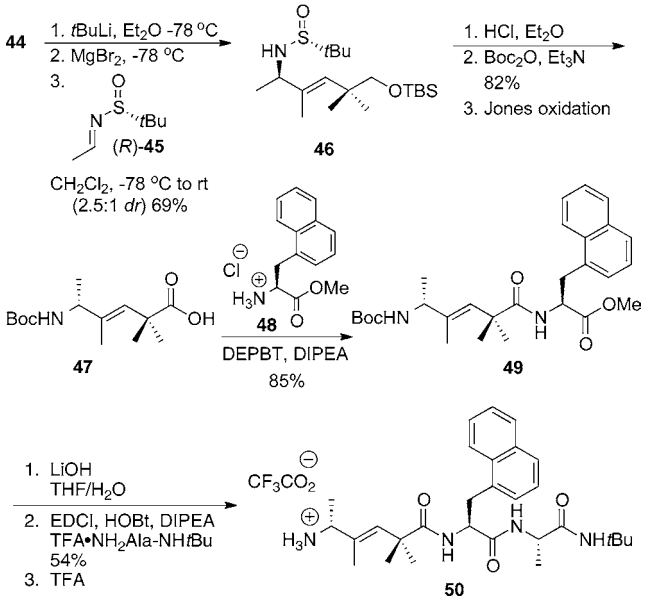
Scheme 10. Synthesis of allylic amine 50



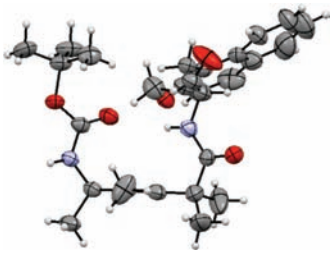


Figure 6. Crystal structure of **49**.

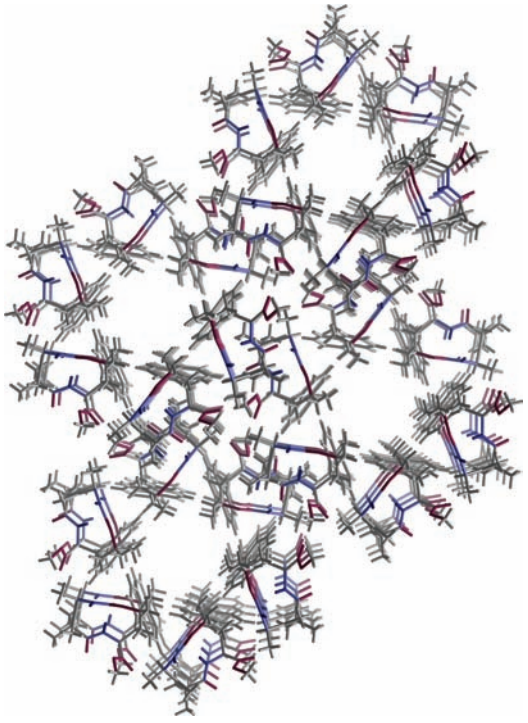
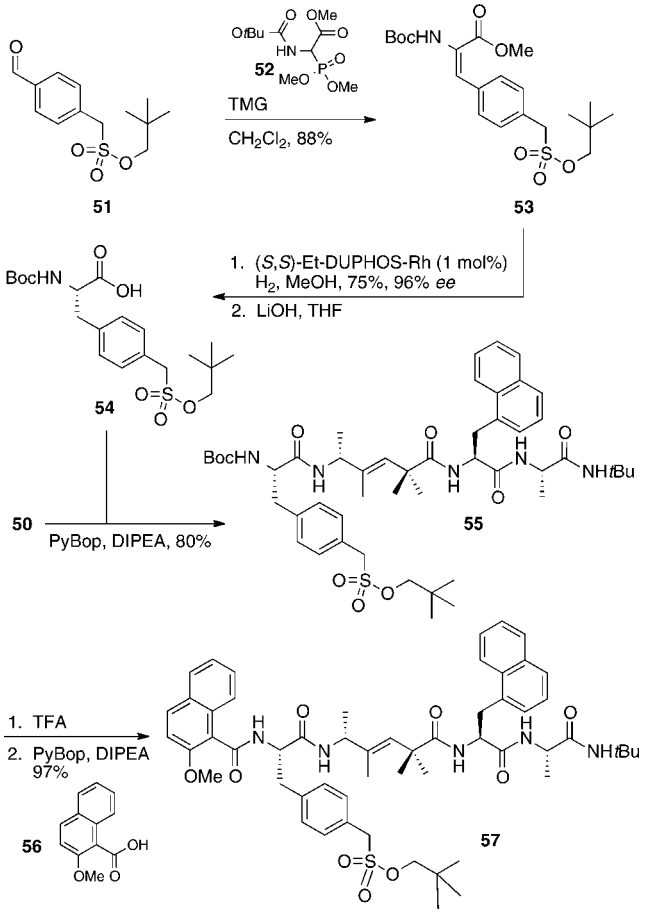


Figure 7. Crystal packing of **49** showing four solvent channels.

reduction of **53** and saponification provided acid **54**. This acid was then coupled to amine **50** to provide **55**. Removal of the Boc protecting group and subsequent coupling to carboxylic acid **56** gave **57**, the protected trisubstituted alkene peptide isostere analogue of a known[25a] peptidic Cdc25 phosphatase inhibitor.

Scheme 11. Completion of the synthesis of the protected alkene peptide isostere 57



Synthesis of Mitochondrial Targeting Agents. Both XJB-5-131 and JP4-039 adopt type II′ β-turn structures suitable for membrane passage. Because the trisubstituted alkene **49** was also shown to adopt this β-turn, an analogue of JP4-039 with a trisubstituted alkene was synthesized from iodoalkene **44** (Scheme 12). Lithium−halogen exchange of **44** followed by transmetalation with cerium(III) and addition to sulfinyl amine (*S*)-**58** provided allylic amine **59** in good yield as a 5:1 mixture of diastereomers that were separable by chromatography on SiO_2. Deprotection of **59** followed by Boc-protection of the free amine gave **60**. The primary alcohol was then oxidized to the acid and coupled to 4-AT to yield **61**.

Significantly, the hydrozirconation/transmetalation/imine addition proved to be a robust method for the scaleup of (*E*)-alkene gramicidin S analogues.[27] The synthesis of (*S*)-**65** began with the silylation of homopropargyl alcohol **62** (Scheme 13). Hydrozirconation of this alkyne on >150-g scale with Cp_2ZrHCl,[19] transmetalation with trimethylaluminum, and addition to sulfinyl imine (*R*)-**58**[28] provided the highly diastereomerically enriched allylic sulfinyl amine (>20:1 de by ^1H NMR analysis of the crude reaction mixture). The commercial availability of the hydrozirconating agent

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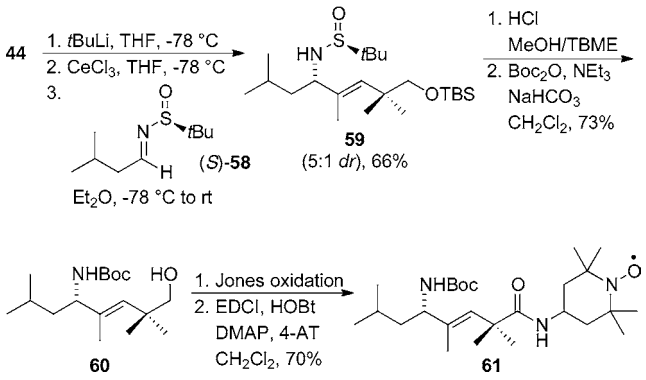
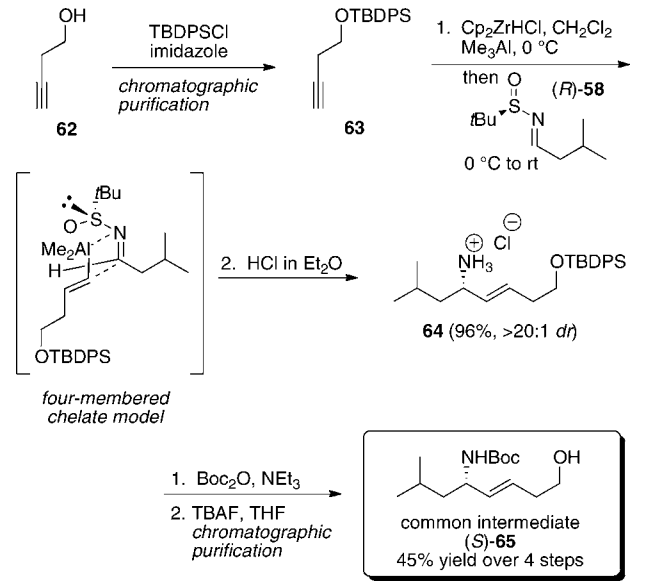
Scheme 12. Synthesis of trisubstituted (*E*)-alkene peptide isostere 61 designed for mitochondrial targeting and scavenging of ROS



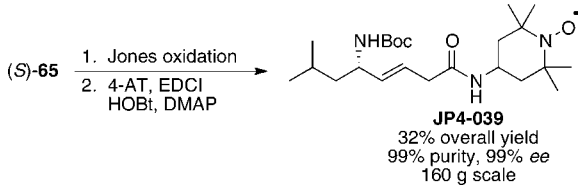
Scheme 13. Large-scale synthesis of allylic amine intermediate (*S*)-65[27]



Cp_2ZrHCl is limited, but the corresponding dichloride Cp_2ZrCl_2 can be obtained in bulk quantities and was converted by LAH reduction in ether to the hydrochloride. Removal of the sulfinyl group led to amine salt **64** in 96% yield. This amine was then Boc-protected, and the silyl group was removed to reveal the homoallylic alcohol (*S*)-**65** in 45% overall yield. (*S*)-**65** was further used as a key intermediate to synthesize several simplified gramicidin S analogues, including XJB-5-131 and JP4-039.

Completion of the synthesis of JP4-039 from (*S*)-**65** was accomplished in just two additional steps (Scheme 14). Jones

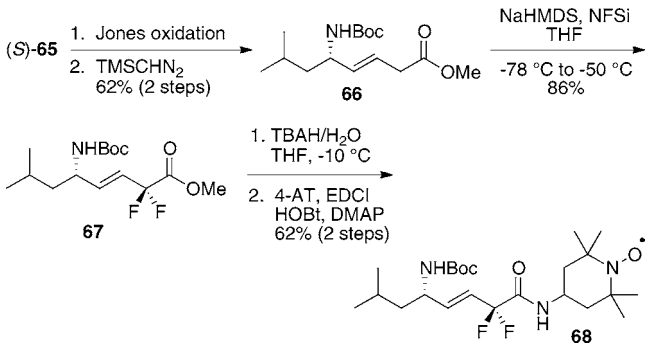
Scheme 14. Completion of the enantioselective synthesis of JP4-039 from carbamate (*S*)-65[27]



oxidation of the primary alcohol followed by coupling to 4-AT gave the mitochondrial targeting agent in 33% overall yield from commercially available **62** in 99% purity and 99% ee. This synthetic sequence was completed on 160-g scale.

Gratifyingly, alkene peptide isosteres such as JP4-039 can demonstrate acceptable metabolic stabilities. In C57BL/6NHsd female mice, the half-life of JP4-039 was found to be 5.0 min in the blood, 10 min in the lungs, and 60 min in the liver, heart, and intestine. A difluorinated analogue **68** was designed to further increase the pharmacokinetic properties of JP4-039 (Scheme 15). The synthesis of **68** originated from the common

Scheme 15. Stereoselective synthesis of the di-fluorinated analogue 68 from (*S*)-65[27]



intermediate (*S*)-**65**. Jones oxidation followed by esterification with TMS-diazomethane gave methyl ester **66**. Fluorination of **66** with *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSi) provided difluorinated ester **67**. Saponification and subsequent coupling to 4-AT led to difluoro-JP4-039 (**68**). Metabolic stabilities in pooled male mouse liver microsomes (MMLM) revealed that **68** was indeed more stable than the parent compounds, XJB-5-131 and JP4-039. Specifically, 13% and 15% of XJB-5-131 and JP4-039, respectively, were detected by LCMS after 60 min in the presence of NADPH, with 98% and 93%, respectively, remaining in the absence of NADPH. Conversely, 27% of **68** was found after 60 min in the presence of NADPH, and 91% in its absence, demonstrating a roughly 2-fold improvement in stability of the fluorinated analogue in the presence of activated cytochrome P450 isoforms.

The straightforward access to (*S*)-**65** also allowed for a large-scale synthesis of XJB-5-131,[29] representing a notable improvement over the first-generation route.[9a] XJB-5-131 was obtained in 34% overall yield in a total of 12 steps for the longest linear sequence from commercially available starting materials (Scheme 16). Specifically, Jones oxidation of (*S*)-**65**, mixed anhydride formation with pivaloyl chloride, and condensation with benzyl oxazolidinone gave imide **70**. The benzyl side chain in **71** was installed in >20:1 dr using an Evans asymmetric alkylation. Cleavage of the chiral auxiliary followed by coupling with tripeptide H-Pro-Val-Orn(Cbz)-OMe provided ester **72**. Saponification and coupling with 4-AT completed the synthesis. This sequence allowed for the preparation of a ~2-g batch of XJB-5-131 as a single detectable stereoisomer. In addition to the improved scalability of this route, its efficiency vs the earlier process was enhanced by the enantioselective approach to allylic amine **70**, the use of a Jones oxidation for the one-step conversion of the alcohol to the acid, and the introduction of the benzyl side chain in the late-stage intermediate **70**.

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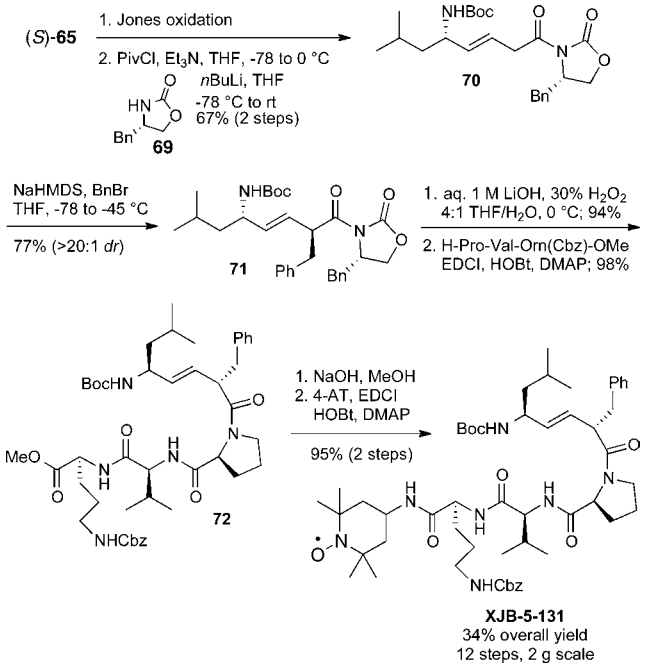
Scheme 16. Second-generation synthesis of XJB-5-131 from (*S*)-65[29]



PERTINENT BIOLOGICAL ASSAYS

The ability of XJB-5-131 and JP4-039 to accumulate in mitochondria,[14c,17] where they scavenge ROS and prevent hydroperoxidation of cardiolipin by cycling between nitroxide redox states, augurs well for their application in the treatment of a number of mitochondria-related diseases as well as for radiation countermeasures (Table 1).[30,31]

Treatment with XJB-5-131 in rats subjected to lethal hemorrhagic shock prolonged survival even without resuscitation and injection with asanguinous fluids or blood.[32] Both XJB-5-131[33] and JP4-039[34] demonstrated radioprotective properties in cells and in mice. Radioprotectants could prove useful in preventing radiation damage side effects in individuals undergoing cancer radiation therapy, for example. Furthermore, JP4-039 was shown to be a mitigator[35] when it was administered to female C57Bl/6HNsd mice 24 h after the radiation event. These mice were found to have reduced peripheral blood lymphocytes, neutrophils, and bone marrow cellularity, demonstrating that JP4-039 was effective at mitigating hematopoietic syndrome.[36] These and other potential therapeutic effects of these agents are currently under further investigation in a range of in vitro and in vivo systems.

CONCLUSIONS

The mitochondrial targeting agents JP4-039 and XJB-5-131 are examples of rationally designed, functional (*E*)-alkene peptide isosteres. The preparations and evaluations of these compounds were contingent on a robust synthetic access to allylic amine building blocks. The stereoselective synthesis of these compounds and other alkene peptide isosteres is concise, high yielding, and scalable to at least a 0.5-kg level based on the hydro(carbo)metalation/transmetalation/imine addition methodologies developed in our laboratory. Specialized organometallic reagents, such as Cp_2ZrCl_2 and trimethylaluminum can be purchased on a multikilogram or even multiton scale. As it is the case for many new methodologies, however, applications at that scale will likely require extensive further optimizations by process chemists. For example, environmental impact, heavy metal usage, toxicity hazard, and cost of organometallic reagents, cryogenics, and chromatographic purifications will have to be resolved. Nonetheless, we hope that new synthetic methods such as the hydro(carbo)metalation/transmetalation/imine addition will inspire the design of structurally novel drug candidates and accelerate their move into phase I studies.

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ABBREVIATIONS

4-AT: 4-amino TEMPO; BARF: $[B[3,5\text{-}(CF_3)_2C_6H_3]_4]$; Cbz: carboxybenzyl; cod: cyclooctadiene; DEPBT: 3-(diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one; DMAP: 4-dimethylaminopyridine; DIPEA: *N*,*N*-diisopropylethylamine; dppbenz: 1,2-bis(diphenylphosphino)benzene; EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; HOBt: hydroxybenzotriazole; NFSi: *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide; NMO: *N*-methylmorpholine *N*-oxide; PCC: pyridinium chlorochromate; PyBop: benzotriazol-1-yl-oxytripyrrolidino-

Table 1. Overview of ongoing biological studies with XJB-5-131 and JP4-039[a]

biological test	results with XJB-5-131	results with JP4-039
lethal hemorrhagic shock	significant prolonged survival in rats[32]	n.d.
radiation protection	n.d.	accelerated bone wound healing in irradiated mice;[34b] increased survival in mice with esophagitis[34a]
radiation mitigation	n.d.	accelerated bone wound healing in irradiated mice;[34b] reduction in damage to irradiated 32Dcl cells at 24 h[35]
hyperoxic acute lung injury	prevents CL oxidation; decreased apoptosis in concentration-dependent manner[37]	n.d.
acute brain injury	reduced neuronal death in vitro and in vivo; reduced behavioral deficits in rats[38]	n.d.

[a]MPEC: mouse pulmonary endothelial cells; CL: cardiolipin; n.d.: not determined.

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phosphonium hexafluorophosphate; ROS: reactive oxygen species; TBS: *tert*-butyldimethylsilyl; TMG: tetramethylguanidine

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