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α-Vinylic amino acids: occurrence, asymmetric synthesis, and biochemical mechanisms

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α-Vinylic amino acids: occurrence, asymmetric synthesis, and biochemical mechanisms

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Abstract — This report presents an overview of the family of naturally occurring "vinylic" amino acids, namely those that feature a C–C double bond directly attached to the α-carbon, along the side chain. Strategies that have been brought to bear on the stereocontrolled synthesis of these olefinic amino acids are surveyed. The mechanistic diversity by which such "vinylic triggers" can be actuated in a PLP (pyridoxal phosphate) enzyme active site is then highlighted by discussion of vinylglycine (VG), its substituted congeners, particularly AVG [4*E*-(2′-aminoethoxy)vinylglycine], and a naturally occurring VG-progenitor, SMM [(*S*)-methylmethionine].

Contents

1. Introduction

Enzymes that depend on the cofactor, pyridoxal phosphate (PLP),[1] generally serve to transform amino acids. In contrast to the amino acid decarboxylases (e.g., L-DOPA or L-ornithine decarboxylase) and the retroaldolases (e.g., serine hydroxymethyltransferase), most classes of PLP enzymes initiate their chemistry by abstracting the α-proton of the substrate amino acid. These include: (i) transaminases, such as γ-aminobutyrate (GABA) transaminase, that interconvert amino acids and their corresponding α-keto acids; (ii) racemases, such as alanine racemase, a key bacterial cell wall biosynthetic enzyme; (iii) β-eliminase or replacement enzymes, such as cystathionine β-synthase (CBS), a key human transsulfuration enzyme, and (iv) γ-eliminase or replacement enzymes, such as cystathionine γ-lyase (CGL), the next enzyme in this pathway. For the latter enzymatic class, a subsequent β-deprotonation is also necessary. The eliminase or replacement enzymes, then subsequently expel the leaving group attached to the β- or γ-carbon, respectively, using the electron density imported into the PLP π-system from the deprotonation step(s).

As can be seen in Figure 1, α-vinylic amino acids feature a C–C double bond directly attached to the α-carbon atom. If an α-proton is also present, one may regard these as vinylglycine congeners. For such amino acids, removal of the α-proton has the effect of conjugating the otherwise isolated vinyl group with the extended π-system of the cofactor. This can lead to a more reactive intermediate, as will be discussed later. At the outset, it suffices to note the correspondence between the initial step in the mechanism of many PLP enzymes and the initial step in the unmasking of the vinyl group in this class of amino acids.

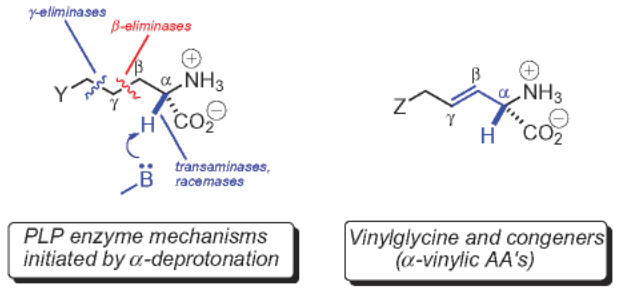


Figure 1. PLP enzymes that α-deprotonate and α-vinylic amino acid structure.

2. Natural occurrence

Perhaps, seeking to capitalize on the latent reactivity of the double bond, in some cases, perhaps benefiting from the "conformational constraint" afforded by the sp^2-alkene geometry, in others, Nature has evolved a class of α-vinylic amino acids—the subject of this Report. Note that the discussion herein will be restricted to the class of vinylic amino acids bearing unsaturation directly attached to the α-center, and also bearing an α-proton. Quaternary α-vinylic amino acids represent both a structurally and functionally distinct amino acid class, as these do not possess an α-proton and, thus target a different set of PLP enzymes (vide supra).[2, 3, 4, 5, 6, & 7]

2.1. Vinylglycine

Among the naturally occurring α-vinylic amino acids, the simplest and probably most widely studied member of the family is α-vinylglycine (VG) itself. The D-antipode is known to be produced by the mushroom, *Rhodophyllus nidorosus*.[8] On the other hand, the antipode, L-VG is generated in a variety of PLP enzyme active sites. For example, L-VG is observed as a mechanistic intermediate to α-ketobutyrate in the reaction catalyzed by cystathionine γ-synthase,[9] and in the conversion of homoserine to threonine by threonine synthetase.[10] L-VG is a substrate for sheep liver threonine deaminase,[11] *E. coli* tryptophan synthetase,[12] rat liver cystathionine γ-lyase and *Salmonella typhimerium* cystathionine γ-synthetase.[13] L-VG also reportedly undergoes deamination and γ-addition by L-methionine γ-lyase.[14 & 15] D-VG is a substrate (processed to α-ketobutyrate and NH_3), but not inhibitor, of ACC deaminase, while L-VG is neither (Fig. 2).[16]

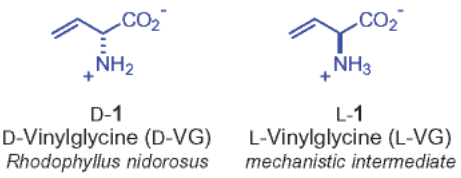


Figure 2. Naturally occurring vinylglycine antipodes.

Perhaps because of its small side chain, the parent member of the family displays a rather broad spectrum of transaminase inhibition. Thus, (dl)-VG inhibits aspartate aminotransferase,[17 & 18] D-amino acid transaminase,[13] and kynurenine aminotransferase,[19] whereas the D-isomer has been specifically shown to inhibit rat hepatic alanine aminotransferase.[18]

Interestingly, it appears that one can also tap into radical based inactivation pathways with VG. Thus, the flavoenzyme L-amino acid oxidase is presumably inactivated by the L-antipode, though, to the best of our knowledge, these studies have only been performed on the racemate.[20] In a complementary study, Vederas and Zabriskie have shown that the tripeptide D-Phe-L-Phe-D-VG inactivates peptide α-hydroxylating enzyme, an enzyme responsible for installing C-terminal carboxamide functionality.[21 & 22] Interestingly, inversion of the stereocenter of the terminal amino acid to L-VG yields a tripeptide that displays only reversible inhibition of the enzyme.

L-VG also irreversibly inactivates the nifS gene product, an enzyme that releases S from L-cysteine for Fe–S cluster biosynthesis.[23] Finally, the best characterization of the mode of inactivation of a PLP enzyme by VG is for the enzyme ACC (1-aminocyclopropane-1-carboxylate) synthase.[24, 25, 26, 27, & 28] This is discussed in considerable detail in Section 4.

2.2. β-Substituted

Three naturally occurring β-substituted vinylglycine analogues are described in the literature (Fig. 3). L-3,4-Didehydrovaline **2** is a constituent of the 13-membered macrocycle phomopsin A, isolated from *Phomopsis leptostromifrmis*.[29 & 30] β-Methylene-L-norvaline **3** has been isolated from both *Lactarius helvus*[31] and *Philadelphus coronarius*.[32] Finally, β-methylene-L-norleucine **4** is found in isolates from *Amanita vaginata*.[33]

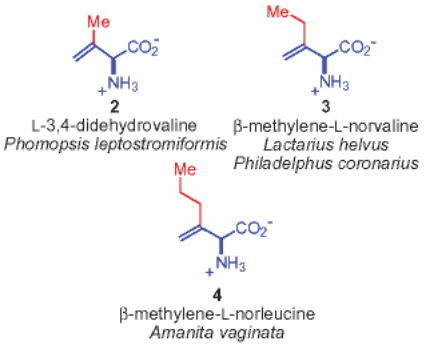


Figure 3. β-Substituted vinylglycines from natural sources.

2.3. γ-Substituted

As is shown in Figure 4, there is a notable spectrum of γ-substituted vinylglycine-based natural products. Several of these have an interesting enol ether substructure that appears to influence the mechanism (vide infra).

2.3.1. MVG

The first vinylic amino acid bearing an enol ether functionality to be characterized was 4*E*-methoxyvinylglycine **5** (MVG), isolated from *Pseudomonas aeruginosa*.[34 and 35] Interestingly, this vinyl ether serves as a substrate of methionine γ-lyase,[15] and both a substrate and an inhibitor of tryptophan synthase.[36 & 12] In pioneering work, Rando showed that **5** inactivates porcine aspartate aminotransferase.[37 & 38] Similar observations were made with the rat enzyme.[18] *E*-MVG has been reported to inhibit porphobilinogen synthase,[39] as well as δ-aminolevulinic acid synthetase and dehydratase from rat tissue.[40] As it turns out, the *Z*-isomer of MVG, though apparently not naturally occurring, is one of the most effective inhibitors of methionine adenosyltransferase.[41 & 42] This is discussed in more detail in Section 4.

2.3.2. AVG

The *E*-isomer of 4-(2′-aminoethoxy)vinylglycine, AVG **6** can be biosynthesized in *Streptomyces*.[43] Like MVG, AVG bears an oxygen at the γ-carbon, and so resembles methionine. However, unlike MVG, AVG has a more extended side chain, terminating is an ammonium group, that is positively charged at physiological pH. This ammonium group is positionally juxtaposed on the cysteine-derived ammonium group of l, L-cystathionine. Whereas *Z*-MVG serves as an apparent L-methionine isostere in the methionine adenosyltransferase active site, unsurprisingly, AVG was found to inhibit cystathionine processing enzymes including cystathionine β-lyase,[44 & 43] and human recombinant cystathionine γ-lyase.[45] AVG also inhibits cystalysin,[46] the enzyme that catalyzes the β-elimination of cysteine to pyruvate, ammonia, and H_2S.

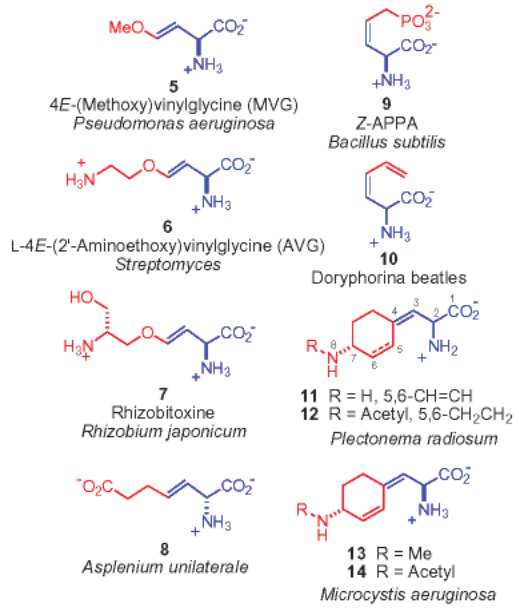


Figure 4. γ-Substituted vinylic amino acids.

Most importantly, the positively charged ammonium group along the methionine-like side chain engenders AVG with a structural similarity to SAM. Indeed, AVG is a well-known inhibitor of 1-aminocyclopropane-1-carboxylate (ACC) synthase, the PLP enzyme that converts SAM into ACC. Since this serves as a key step in plant ethylene biosynthesis, AVG has seen wide application as a fruit ripening inhibitor. The ACC synthase inhibitory behavior of AVG has been characterized with the enzymes from both red tomato and apple.[47, 48, & 49]

2.3.3. Rhizobitoxine

The third and most structurally complex member of the enol ether subfamily of the α-vinylic amino acids is rhizobitoxine **7**. The backbone of this amino acid superimposes upon that of AVG, but a second stereocenter is added precisely where the second stereocenter in cystathionine is located. Only here, a hydroxymethyl group is appended to this stereocenter, in place of the cystathionine carboxylate group, and with the appropriate stereochemistry to mimic this amino acid.

Rhizobitoxine is produced by symbiotic bacteria, such as *Rhizobium japonicum*,[50, 51, & 52] and also by the plant pathogen, *Pseudomonas andropogonis*.[53] Presumably, at least in part because of its close structural resemblance to cystathionine, rhi-

zobitoxine inhibits cystathionine β-lyase, from both *Salmonella typhimurium* and spinach.[50 & 54] Rhizobitoxine also decreases hydrogenase biosynthesis in *Bradyrhizobium japonicum*,[55] by inhibiting depression of the hydrogenase gene. However, as this effect is reversed by the addition of methionine, this may be a downstream consequence of rhizobitoxine's inhibition of methionine biosynthesis at the cystathionine β-lyase stage.

Probably the most important activity of rhizobitoxine resides in its ability, analogous to AVG, to inhibit ACC synthase.[56] This is one of the two important mechanisms by which symbiotic bacteria are known to inhibit ethylene biosynthesis in the roots of their host legumes.[57] The other is through the activity of bacterial SAM deaminase, which rather than inhibit the conversion of SAM to ACC, simply siphons off SAM by oxidative deamination. As the plant hormone, ethylene, is known to inhibit root nodulation, rhizobia have presumably evolved these interesting mechanisms for ethylene biosynthesis inhibition to insure a favorable nodulation environment for their survival. As there are agricultural biotechnological interests in nitrogen fixation, rhizobitoxine and/or the rhizobitoxine biosynthetic machinery may have future applications here.

2.3.4. Other γ-substituted VG analogues

A naturally occurring phosphonate analogue of homoserine phosphate, *Z*-2-amino-5-phosphono-3-pentenoic acid **9** (*Z*-APPA) is a constituent of the dipeptide rhizocticins,[58 & 59] and tripeptide plumbemycins.[60 & 59] One might predict, that the free amino acid, APPA is active against PLP enzymes that normally take L-homoserine phosphate as a substrate. This includes cystathionine γ-synthase (synthesize cystathionine from cysteine and homoserine phosphate) for which *E*-APPA is a tight-binding reversible inhibitor (see Section 4 for further discussion).[61] Threonine synthase is a PLP enzyme that performs a β,γ-phosphate elimination/β-hydration sequence from L-homoserine phosphate. The threonine synthase enzyme from *E. coli* is irreversibly inactivated by both the *E*- and *Z*-isomers of APPA.[62]

E-3,4-Dehydro-2-aminopimelic acid **8** has been isolated from *Aspenium unilaterale*.[63 & 64] *Z*-3,5-Hexadienoic acid **10** (butadienylglycine) is found in the defensive secretions of *Dorypohorina* beetles,[65] *Platyphora kollari* beetles,[66] and in the fruiting bodies of *Clavulinopsis helvola*.[67] Amino acids **11** and **12** were found as amino acid constituents of the dipeptide trypsin inhibitor, radiosumin A, biosynthesized by the cyanobacterium *Plectonema radiosum*.[68 & 69] The two differ only through N-acetylation at the 8-position in compound **12**, and the unsaturation across the 5,6-carbons in compound **11**. The very closely related amino acids, **13** and **14,** are the constituents of a similar dipeptide trypsin inhibitor, later identified in the cyanobacterium *Microcystis aeruginosa*, and named radiosumin B.[70]

2.4. β,γ-Disubstituted

Densely functionalized vinylic amino acids **15** and **16**, differing only in the oxidation state of the β-appendage, were isolated together from the mushroom *Bankera fulgineoalba*.[71] The novel chlorinated glutamate analogue, **17**, is found in isolates of *Streptomyces viridogenes*.[72] The function of these interesting α-vinylic amino acids remains to be elucidated (Fig. 5).

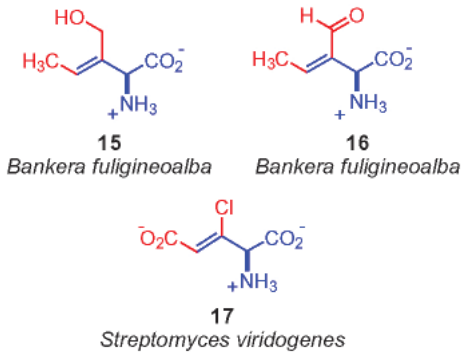


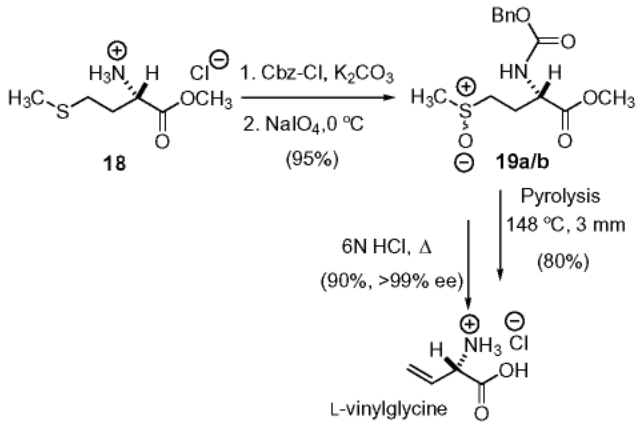
Figure 5. β,γ-Substituted vinylic amino acids.

3. Asymmetric synthesis

Owing to its interesting enzyme-inhibitory activity and its potential as a synthon,[73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, & 90] vinylglycine has attracted the attention of synthetic chemists. Hence, a variety of asymmetric synthetic methodologies to access D- and L-vinylglycine are available in the current literature. A compilation of known stereocontrolled approaches for this important target is presented below.

3.1. Chiron-based entries into vinylglycine

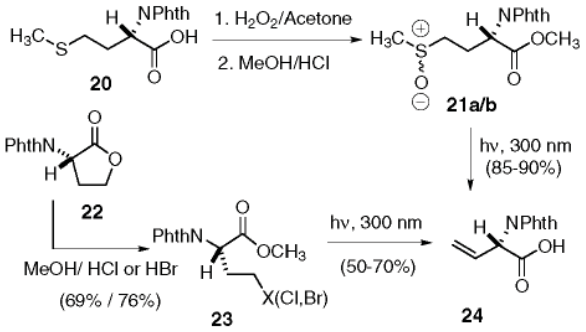
Afzali-Ardakani and Rapoport reported the first synthesis of vinylglycine from L-methionine.[91] In this synthesis, controlled oxidation to the sulfoxide, followed by pyrolysis under Kugelrohr conditions, allowed them to distill over the protected vinylglycine product as it forms. Deprotection produces L-vinylglycine in 99% enantiomeric excess (Scheme 1).



Scheme 1. Rapoport's sulfoxide pyrolysis entry.

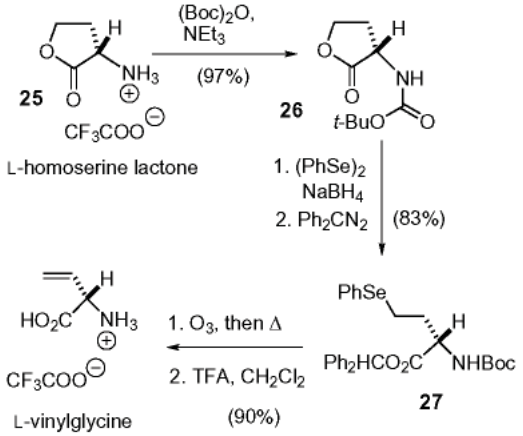
A photofragmentation approach, again starting from L-methionine has been developed by Griesbeck et al.[92 & 93] Irradiation

of the sulfoxide(s) **21a**/**b** at 300 nm in acetonitrile gives methyl *N*-phthaloyL-L-vinylglycinate **24**. This protocol encountered problems due to side reactions when substrate concentrations above 10 mM were used. This limitation was overcome by photolyzing the ring-opened product of L-homoserine lactone with HBr or HCl (Scheme 2).



Scheme 2. Griesbeck's photofragmentation route from L-methionine.

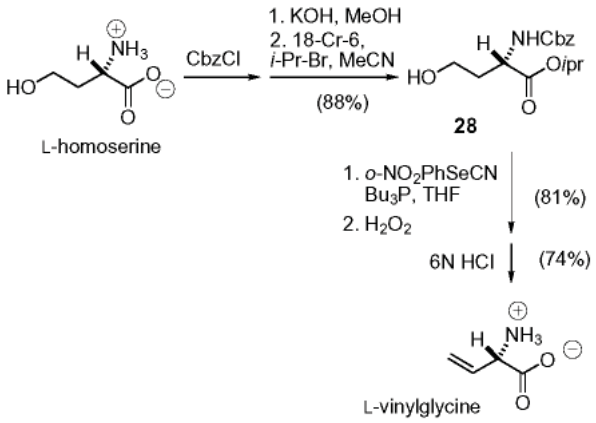
Berkowitz et al. also developed a practical route to L-vinylglycine from homoserine lactone, in this case, via organoselenium chemistry (Scheme 3).[94] Thus, opening of *N*-Boc-protected L-homoserine lactone **26** with phenylselenolate anion occurs exclusively at the softer γ-carbon, allowing for subsequent installation of the double bond via *syn* elimination of the selenoxide.



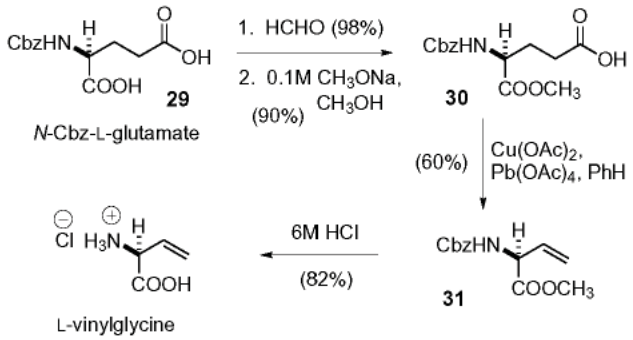
Scheme 3. Berkowitz et al.'s use of phenylselenolate lactone-opening chemistry.

A route developed by Pellicciari et al.,[95] likewise employs L-homoserine as the chiron, and also avails itself of selenoxide elimination chemistry. In this route, however, rather than use nucleophilic lactone opening for the introduction of selenium, a modified Mitsunobu protocol developed by Grieco[96, 97, & 98] was exploited (Scheme 4).

There are two classic vinylglycine syntheses that employ L-glutamate as the chiron. Early on, Hanessian developed an elegant route based upon a Cu(II)/Pb(IV)-mediated oxidative decarboxylation of the γ-carboxylate to introduce the vinyl



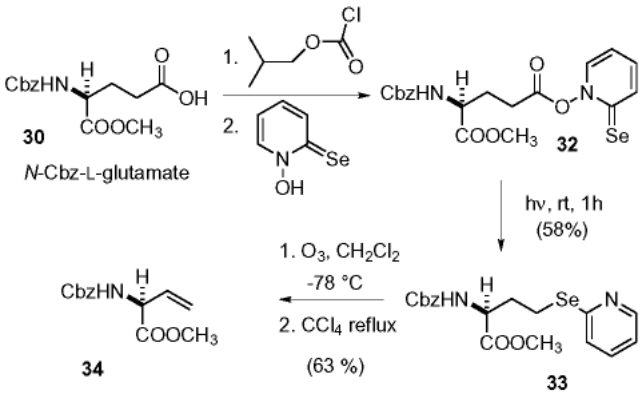
Scheme 4. Arylselenium introduction via the Grieco protocol.



Scheme 5. Hanessian's oxidative decarboxylation of L-glutamate.

group (Scheme 5).[99] Townsend et al. later reported improvements in the procedure, based upon the use of benzyl and benzhydryl esters to facilitate the purification (crystallization), deprotection, and assessment of enantiomeric purity.[84]

A complementary route from L-glutamate exploits the Barton decarboxylation of *N*-hydroxyl-2-chalcogenopyridone esters (Scheme 6).[100] The photochemical decarboxylative rearrangement of ester **32** provides the γ-arylselenide **33** directly. This in-

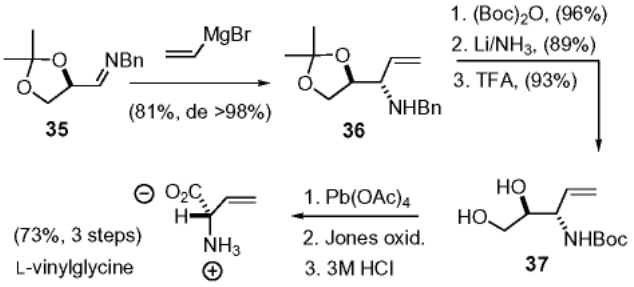


Scheme 6. Decarboxylative introduction of selenium via a Barton ester.

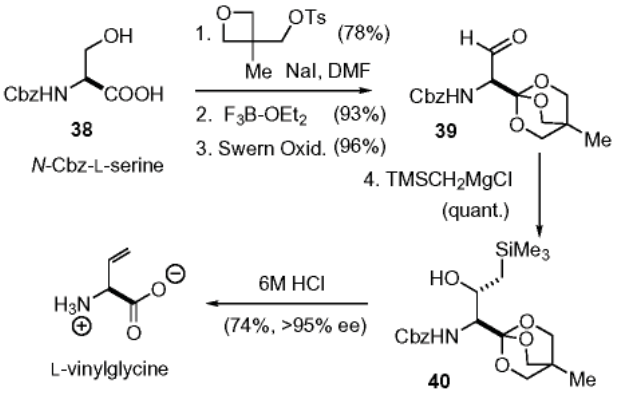
termediate is primed for introduction of the α-vinyl group via oxidative pyrolysis of the pyridyl selenide. One obtains protected L-vinylglycine in acceptable yield and with uncompromised ee.

Diaz-de-Villegas et al.[101] have achieved the synthesis of L-vinylglycine from D-glyceraldehyde. This synthesis utilizes stereochemical communication, wherein the original, chiral pool-derived stereocenter is used to induce stereochemistry in an adjacent center, and is then excised oxidatively in unveiling the α-carboxyl group. A highly diastereoselective vinyl-Grignard addition to *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldimine is the hallmark of this synthesis (Scheme 7). Note that the diastereopreference observed is in accordance with the Felkin-Anh model. However, for such cyclic systems, the authors suggest that other transition state models might also be considered.[102]

L-Serine also serves as a chiral pool precursor to L-vinylglycine, via methylenation protocols, though here extra care must be taken to minimize racemization of the intermediate aldehyde. Thus, Lajoie et al.[103] report that application of the Peterson olefination to a suitably protected L-serinal derivative leads to L-vinylglycine in high ee (Scheme 8). Whereas attempts to induce conversion of the intermediate β-hydroxysilane **40** to the alkene with base failed, acidic conditions not only succeeded, but also permitted concomitant Cbz and OBO orthoester deprotection. Note that other olefination methods examined generally gave a significant degree of racemization. In a similar vein, Beaulieu et al.[104] used methylenation of the Garner aldehyde to access vinylglycine, albeit in modest yields and ee.



Scheme 7. Galvez's Felkin-Anh-vinylation route from D-glyceraldehyde.

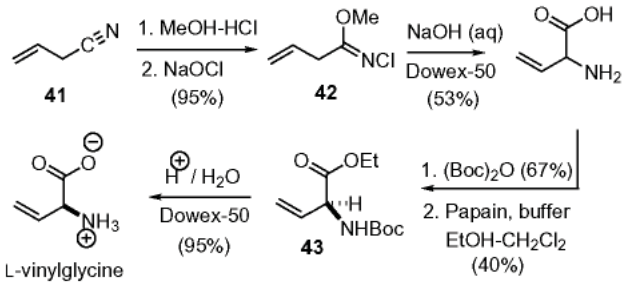


Scheme 8. Lajoie's Peterson olefination route from L-serine.

3.2. Enzymatic kinetic resolutions to VG

In a couple of instances, enzymatic kinetic resolution has been applied to VG targets. Very early on, Helboe et al.[105] subjected (dl)-vinylglycine, obtained via a Strecker synthesis with acrolein, to fermentation with baker's yeast. D-Vinylglycine was obtained in 39% yield and 82% ee.

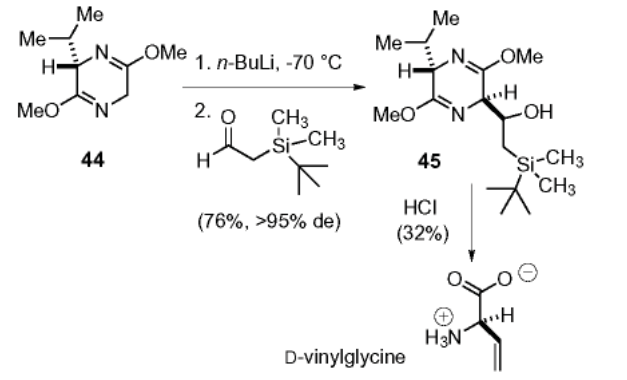
Later, Crout et al.[106] described an interesting route to racemic vinylglycine via Neber rearrangement of *N*-chloroimidate **41**. This was followed by a papain-mediated esterification in a biphasic system to give the individual antipodes (Scheme 9). Two cycles were employed to obtain the remaining D-enantiomer. Precise ee determinations were not reported, but the specific rotations reported compared well with literature values.



Scheme 9. Neber rearrangement/papain-based kinetic resolution.

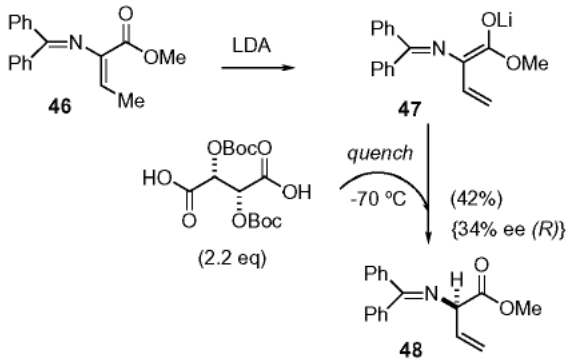
3.3. Chiral auxiliary-based approaches to VG

Schöllkopf[107] demonstrated that his widely employed chiral glycine enolate equivalent could be formally α-vinylated using a vinyl cation equivalent developed by Hudrlik[108] (Scheme 10). During the reaction, the condensation of the lithiated bis-lactim ether **44** (derived from L-valine and glycine) with 2-(*tert*-butyldimethylsilyl)acetaldehyde proceeded in good yield and with excellent cyclic stereocontrol. Subsequent treatment with HCl serves to effect β-elimination of the elements of "HO-SiR_3" and unravel the bis-lactim ether auxiliary, yielding free D-vinylglycine of high enantiomeric purity.



Scheme 10. Schöllkopf's formal vinylation of his chiral glycine enolate.

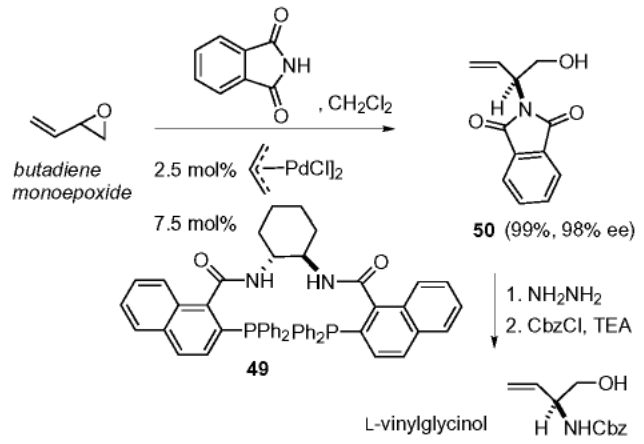
Duhamel et al. examined the possibility of inducing asymmetry from an external chiral acid source, upon enolate quenching. Specifically, the benzophenone imine-protected dehydrobutyrine derivative **46** was deprotonated with LDA to generate an extended dienolate **47**, that was then quenched at −70 °C with (*R*,*R*)-*O*,*O*′-dipivaloyltartaric acid. This kinetic quench produced a 42:58 ratio of α- to γ-protonation, with the former (deconjugation) product showing modest facial selectivity in favor of the D-antipode of vinylglycine (Scheme 11).



Scheme 11. Duhamel's chiral acid dienolate protonation approach.

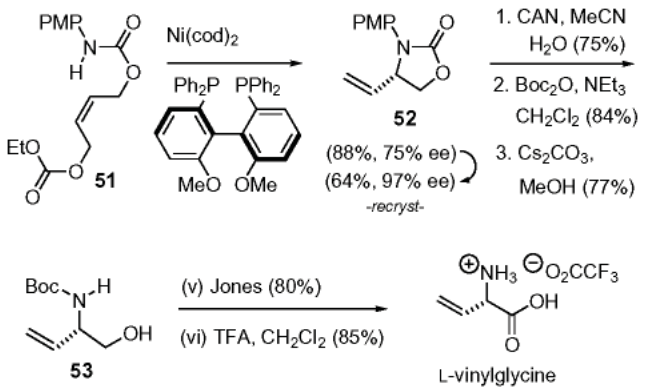
3.4. Catalytic asymmetric syntheses of vinylglycine

Trost et al.[109, 110, & 111] have developed an elegant DYKAT (dynamic kinetic asymmetric transformation) approach to L-vinylglycinol from racemic butadiene monoepoxide (Scheme 12). The approach hinges on a Pd(0)-mediated allylic amination reaction, with ligand **49** serving to provide the chiral scaffold about Pd. Phthalimide is used as *N*-nucleophile and no exogenous base is needed, as relief of ring strain is used to form a formally charge-separated π-allyl-Pd intermediate, bearing a transient alkoxy leaving group. Presumably, this alkoxide is well suited to deprotonate the phthalimide nucleophile and deliver it to the appended π-allyl acceptor. This highly regio- and stereoselective process leads to the formation of (*S*)-2-phthalimido-3-buten-1-ol **50**, which is then transformed to vinylglycinol in two steps.



Scheme 12. Trost's DYKAT asymmetric allylic amination route.

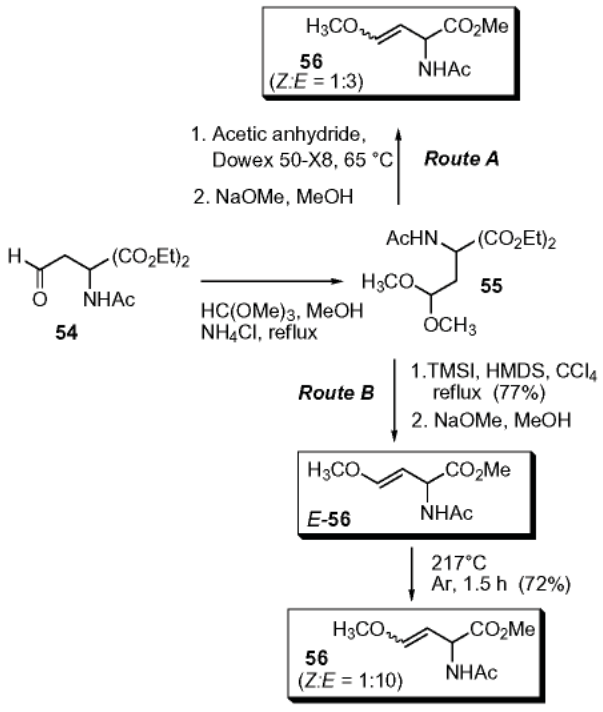
Recently, in the context of an ISES (in situ enzymatic screening) approach to catalyst discovery,[112] our group reported the first examples of asymmetric Ni(0)-mediated allylic amination chemistry.[113 & 114] Here an *N*-protected-4-vinyloxazolin-2-one intermediate was generated via an enantioselective, intramolecular allylic amination with a Ni(0)-BIPHEP catalyst system (Scheme 13). This was then transformed to L-vinylglycine.



Scheme 13. Berkowitz et al.'s Ni(0)-mediated asymmetric allylic amination route.

3.5. Methoxyvinylglycine (MVG)

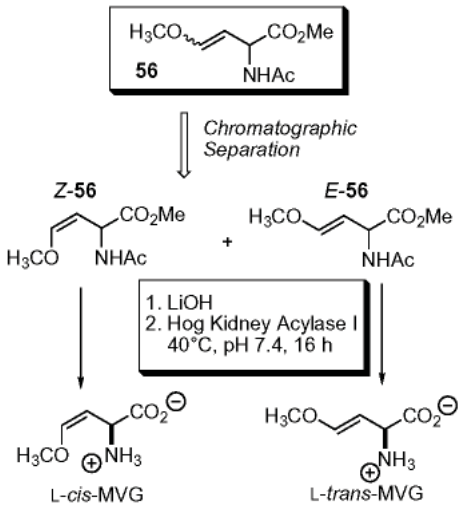
An *N*-acylase mediated resolution of the *Z*- and *E*-isomers of MVG has been reported by Keith et al. (Route A, Scheme 14).[115] Alks[116] introduced the following two modifications: (i) stereose-



Scheme 14. Introducing the enol ether into *E*- and *Z*-MVG.

lective synthesis of *N*-Ac-(dl)-*E*-MVG methyl ester; (ii) thermal isomerization of the *E*- to *Z*-methyl ester (Route B, Scheme 14).

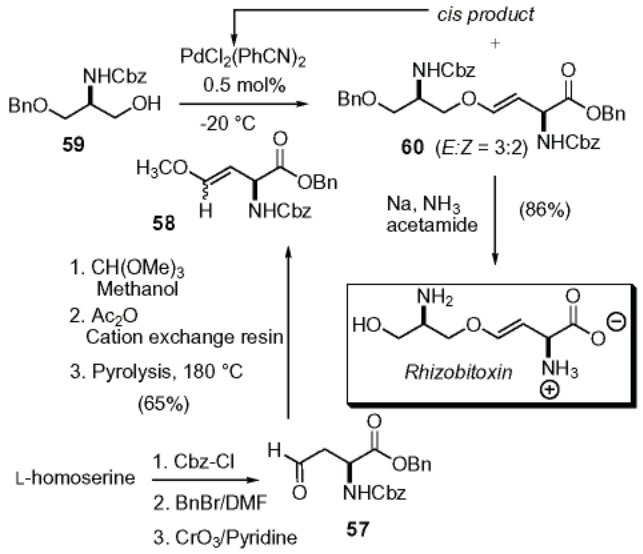
Acylase resolves each geometric isomer of MVG, by selectively deacetylating the L-amide[115] (Scheme 15).



Scheme 15. Enzymatic resolution of *E*- and *Z*-MVG.

3.6. Rhizobitoxine

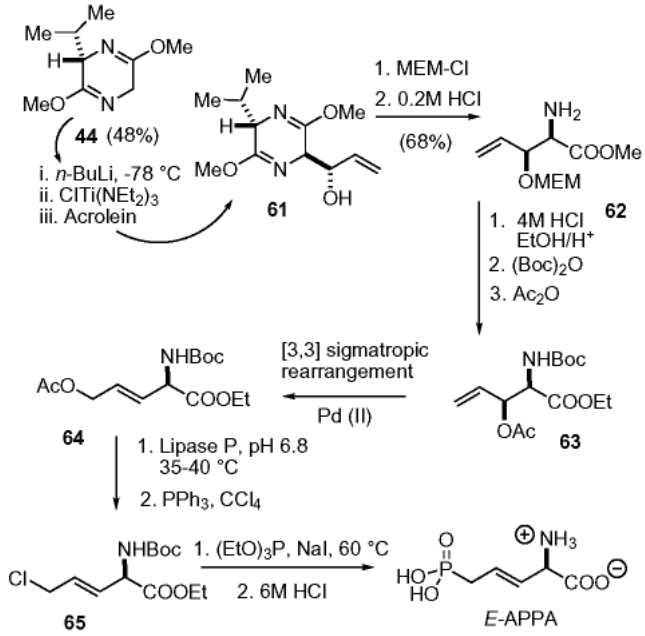
A concise synthesis of L-rhizobitoxine has been reported by Keith et al.[117] (Scheme 16). The key transformation is a palladium(II)-mediated *trans*-vinyl etherification between *N*-Cbz-*O*-benzyl-D-serinol and *N*-Cbz-L-MVG benzyl ester (*E*:*Z* ~ 3:2).



Scheme 16. Keith's route to rhizobitoxine.

3.7. 2-Amino-5-phosphono-4-pentenoic acid (APPA)

Kirihata has reported an asymmetric synthesis of *E*-APPA that strategically resembles Schöllkopf's vinylglcyine synthesis (Scheme 10), in that reaction of an aldehyde with the lithiated chiral bis-lactim ether **44**, sets the α-stereochemistry in both approaches. Here, the use of acrolein results in an allylic center, which can then be coerced to undergo Pd(II)-mediated allylic transposition, albeit in modest yield, to **64**. Subsequent Arbuzov chemistry installs the terminal phosphonate (Scheme 17).



Scheme 17. Kirihata's approach to *E*-APPA.

4. Mechanism

4.1. Vinylic amino acids as conformationally constrained amino acid analogues?

As was mentioned earlier, *Z*-MVG, the geometric isomer of the natural product, inhibits methionine adensyl transferase, the enzyme responsible for the synthesis of SAM [(*S*)-adenosylmethionine] from ATP and L-methionine. The crystal structure of this enzyme in complex with *Z*-MVG reveals the L-methionine binding site.[41 & 42] This may be an example of an α-vinylic amino acid that serves as a good conformationally constrained analogue of the saturated, and hence, inherently more flexible, natural substrate.

Similarly, perhaps *E*-APPA, also the geometric isomer of the natural product, acts as a reversible, tightly bound analogue of homoserine phosphate in the active site of cystathionine γ-synthase (CGS).[61] In this case as well, the X-ray crystal structure of the E–I complex, identified the binding pocket of the phosphate side chain of the natural substrate. This suggests this vinylic amino acid with its *E* double bond configuration mimics L-homoserine phosphate "frozen" in an extended conformation, that is especially productive for binding. The X-ray structure reveals that *E*-APPA interacts with both the α-carboxylate and side chain phosphate binding pockets of CGS, in support of this view.

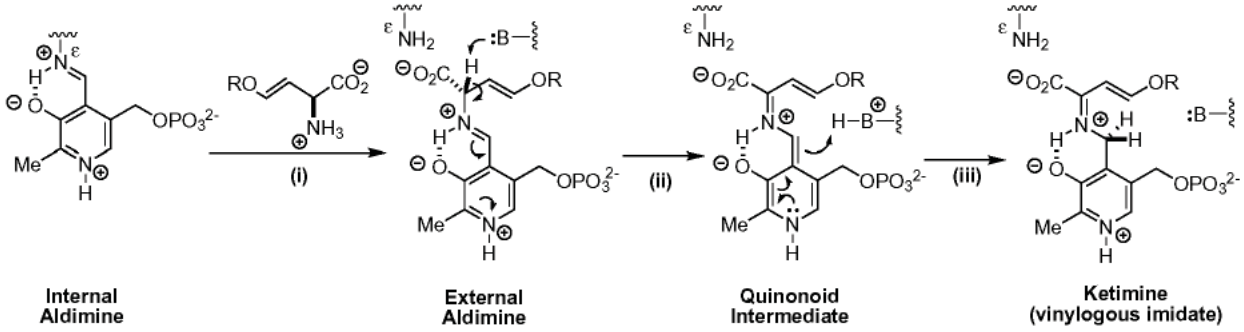
In the sections to follow, we focus on inhibition mechanisms that appear to require enzymatic chemistry beyond the simple initial transimination reaction that is the canonical first step in the binding of an amine substrate or substrate analogue to a PLP enzyme. In this sense, the mechanisms that follow highlight the possibility for *mechanism-based* or *enzyme-activated* inhibition in this class of α-vinylic amino acids.

4.2. Mechanism A—vinylogous imidate formation

The first mechanism that we wish to consider is likely favorable for the subclass of α-vinylic amino acids that features a heteroatom directly attached to the γ-carbon. This is the case for MVG, AVG, and rhizobitoxine (Fig. 4), for which the heteroatom is oxygen (i.e., enol ethers), though the same principle could apply to other heteroatoms. Although Rando first carried out important mechanistic studies on the inhibition of aspartate aminotransferase by MVG many years ago, crystallographic information on the bound states of members of this vinylic amino acid class has only appeared much more recently.

As illustrated in Scheme 18, transimination from the resting state of the PLP enzyme would produce the external aldimine in which the α-vinylic functionality remains isolated from the π-system of the cofactor. As mentioned in the outset of this Report, the first mechanistic step for a PLP dependent transaminase, racemase, or eliminase is α-deprotonation. This produces a quinonoid intermediate in which the vinyl group is now fully conjugated with the PLP system. However, heteroatoms with donating lone pairs oppose one another at the ends of this system. Should protonation at C-4′ ensue, this would have the effect of removing the N-1-lone pair from the system, and this generates a vinylogous imidate. Such a ketimine is expected to benefit from the excellent alkoxy electron donor/iminium electron acceptor juxtaposition at the ends of this five atom π-system. In other words, the π-delocalization energy inherent in the enol ether functionality of the inhibitor would have been significantly enhanced through an enzyme-mediated azaallylic isomerization, leading to this stable bound cofactor adduct.

In fact, three X-ray crystal structures are available for AVG bound in PLP enzyme active sites (Fig. 6): apple ACC synthase (PDB ID: 1M7Y; 1.6 Å),[49] cystalysin (PDB ID: 1C7O; 2.5 Å),[46] and cystathionine β-lyase (PDB ID: 1CL2; 2.2 Å).[44] It should be noted that these enzymes are all eliminases, catalyzing the α,γ-elimination of SAM to ACC, the α,β-elimination of cysteine to pyruvate (eventually) and the α,β-elimination of cystathionine to cysteine, respectively. So, all inherently α-deprotonate their natural substrates.



Scheme 18. Mechanism A: vinylogous imidate formation from γ-alkoxy-α-vinyl amino acids via PLP enzyme-catalyzed azallylic isomerization.

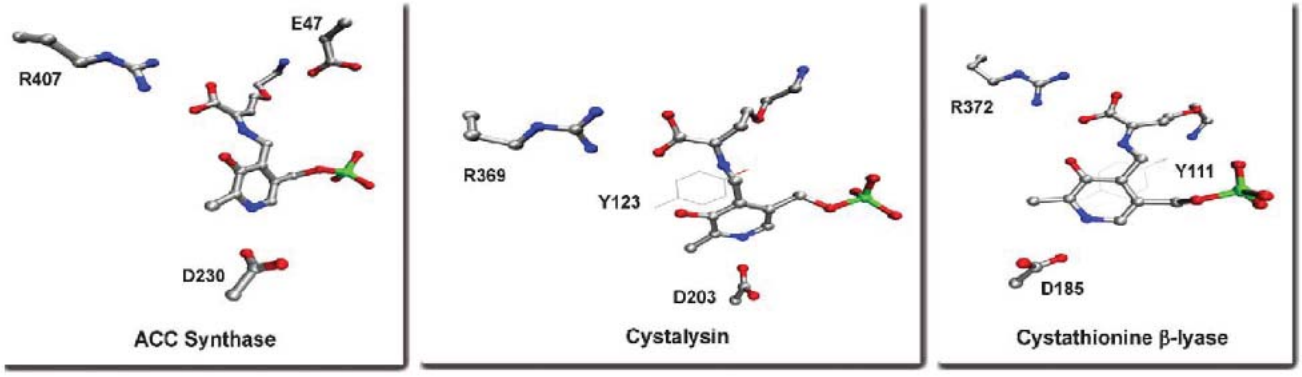


Figure 6. Cofactor-AVG adducts bound in three PLP enzyme active sites (PDB codes: 1M7Y, 1C7O, and 1CL2, respectively).

The ACC synthase structure is the highest resolution of the three and also provides the best evidence for such a bound vinylogous imidate. The dihedral angles across the C_γ–C_β and C_β–C_α bonds are modeled at 177° and −146°, respectively, consistent with such conjugation. Furthermore, the $C_{4'}$–N–C_α–C_β and $C_{4'}$–N–C_α–carboxylate dihedrals are at 7° and −175°, respectively, consistent with azallylic isomerization having occurred in the ACC synthase active site. Deviation from planarity increases across C_β–C_α as one moves from this structure to the CBL structure, but near planarity is retained across C_γ–C_β. The cystalysin structure provides little evidence for such conjugation, but is also the lowest resolution of the three. Furthermore, the uncertainty inherent in E–I X-ray structures of this sort does not allow us to assign the double bond loci with certainty.

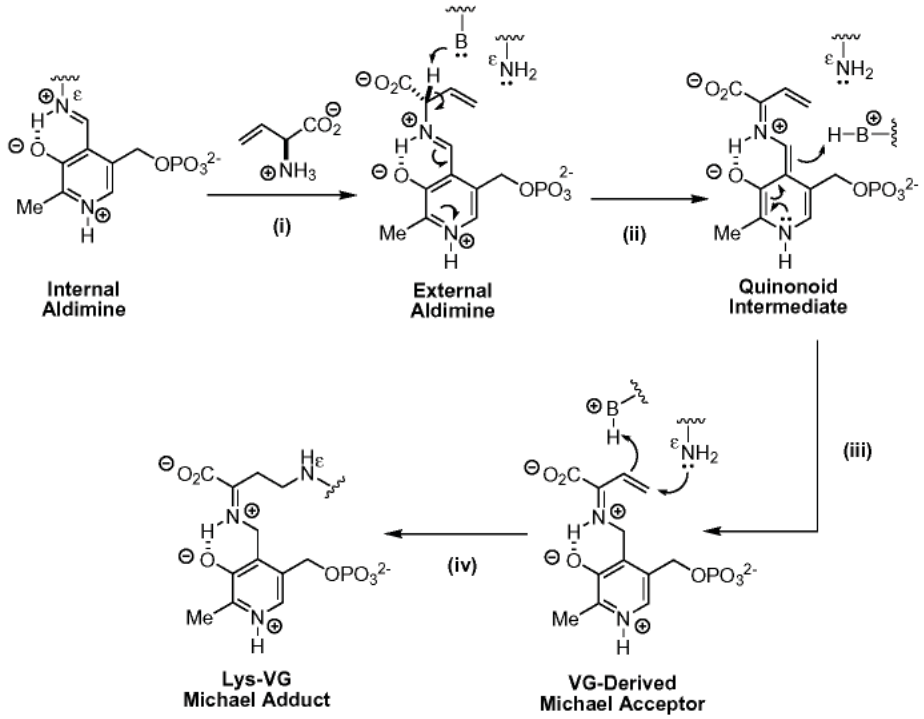
Nonetheless, the notion that γ-alkoxy-α-vinylic amino acids have a preference to form stabilized vinylogous imidate complexes with PLP would appear to be a chemically reasonably postulate, worthy of further scrutiny in investigations of this amino acid subclass. Interestingly, in his early work with MVG, Rando observed a pronounced tendency of that amino acid to undergo azaallylic isomerization, even in Snell-type model reactions with PLP and Al^{3+},[38] consistent with the notion of a thermodynamic driving force toward vinylogous imidate formation in these adducts.

4.3. Mechanism B—Michael addition

Vinylglycine, the parent member of the α-vinyl amino acid family was isolated from a mushroom source in 1974.[8] In the same year, Rando reported on its irreversible inactivation of a PLP enzyme, namely aspartate aminotransferase.[17] As was discussed earlier (Section 2.1), vinylglycine inactivates a number of PLP enzymes, most of which are transaminases. Yet only in the past year has the nature of the covalent adduct formed between vinylglycine and one of its target enzymes lent itself to crystallographic characterization. This feat was accomplished with the enzyme ACC synthase.[24] This enzyme normally engages its natural substrate, SAM in PLP aldimine linkage, followed by α-deprotonation. An unusual expulsion of the γ-leaving group, methylthioadenosine (MTA), is the normal next mechanistic step, leading to the formation of the strained cyclopropane ring of ACC.

As is discussed in greater detail below, L-vinylglycine is both an inhibitor and an abnormal (β,γ-elimination) product of this enzyme. A possible mechanism for the inactivation of ACC synthase with L-vinylglycine is depicted in Scheme 19. The normal first step, α-deprotonation is followed by C-4′-protonation, as in Mechanism A, leading to an α,β-unsaturated iminium ion. This Michael acceptor is then captured by an active site nucleophile. The active site lysine is always a candidate for this role, as it is displaced in the initial transimination step. This lysine residue then presumably remains in the vicinity of the resulting E–S or E–I adduct and of the complexes mechanistically derived therefrom.

The 2005 Grütter/Kirsch crystal structure of ACC synthase inactivated with L-vinylglycine is depicted in Figure 7[24] and reveals that, indeed, the active site lysine has formed a covalent bond with the γ-carbon of the inhibitor, as predicted. The observation of the three dimensional structure of this adduct cements perhaps the most widely accepted mechanism for actuation of the α-vinylic trigger. It also serves to rule out an alternative Michael addition pathway, whereby α-deproton-



Scheme 19. Mechanism B: inactivation of ACC synthase by L-vinylglycine via enzyme-catalyzed azaallyllic isomerization-Michael addition.

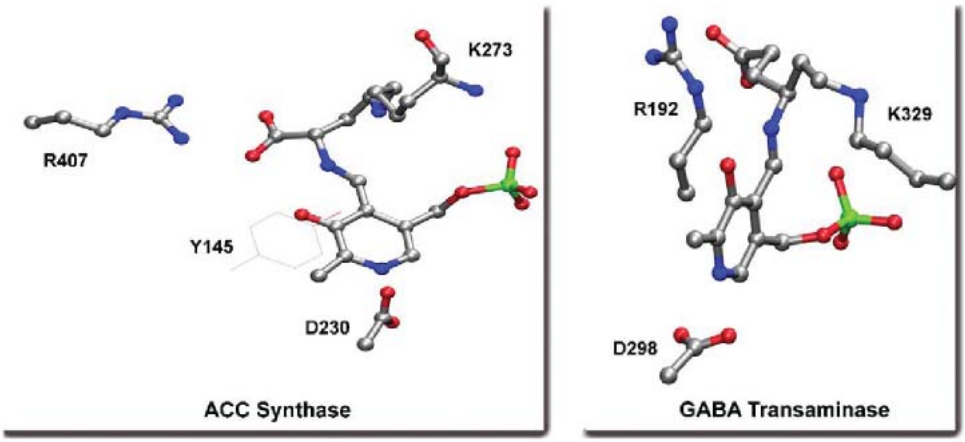


Figure 7. Evidence of Mechanism B for L-vinylglycine with ACC synthase (PDB 1YNU) and for vigabatrin with GABA transaminase (PDB 1YHW).

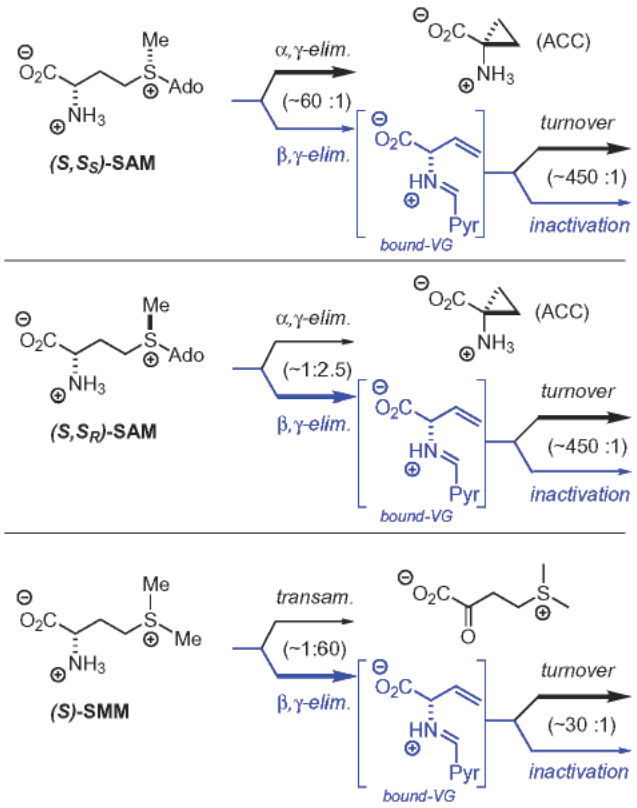
ation would be followed by γ-protonation, leading to an electrophilic β-, rather than γ-carbon.

Finally, the α-vinylic trigger found in the class of amino acids being reviewed here surely served as the inspiration for development of vigabatrin (γ-vinyl-GABA), as a mechanism-based inactivator of GABA transaminase. Vigabatrin was developed by the Marion Merrell Dow group into an anti-epileptic drug of widespread use, particularly in Europe.[118] It is probably fair to say that Vigabatrin was designed to act by a Michael addition mechanism analogous to Mechanism B (Scheme 19). Indeed, elegant mechanistic studies by the groups of Silverman[119] and John[120] pointed to such a mechanism as the primary one through which the drug inactivated its target enzyme, GABA transaminase. Pleasingly, the X-ray crystal structure appeared in 2004,[121] and served to validate this mechanism, again with the active site lysine serving as the Michael nucleophile (Fig. 7).

4.4. SMM: A natural "Pro-Form" of a vinylic amino acid?

The enzyme ACC synthase not only ended up serving as the showcase for the long-suspected Michael addition inactivation pathway of vinylglycine, it has also brought to light a novel mechanism by which Nature may biosynthesize vinylic amino acid progenitors. Namely, through a series of elegant studies from Kirsch et al., it has now been established that even subtle changes in the vicinity of the γ-leaving group of the SAM substrate for ACC synthase can lead to profound changes in mechanistic partitioning in the active site. These findings are illustrated schematically in Scheme 20.

Kirsch first studied the effect of the often ignored sulfur stereocenter in SAM on ACC processing. Natural SAM has the S_S stereochemistry, and undergoes errant β,γ-elimination to vinylglycine only once for every 60 α,γ-eliminations to ACC.[27] On the other hand, inversion of this sulfonium stereocenter alone, retaining the important L-methionine center, results in a partition reversal. β,γ-Elimination now predominates by a 2.5:1 ratio over the usual α,γ-elimination.[26] This is really a remarkable observation, especially when one considers that these two substrates not only share the same α-stereochemistry, but have chemically exactly the same leaving group, MTA.



Scheme 20. Fate of SAM and analogues in the ACC synthase active site.

Perhaps led by this result, Kirsch et al. then decided to examine the behavior of L-(*S*)-methylmethionine (SMM), a ubiquitous component of the tissues of flowering plants; SMM undergoes no α,γ-elimination whatsoever with ACC synthase. Instead, a small amount of transamination to the ketone is observed. Otherwise, one sees almost exclusive conversion of SMM to vinylglyine in this active site.

Furthermore, there is 15-fold greater probability for SMM-derived "vinylglycine" to inactivate, when compared with SAM-derived "vinylglycine." This probably reflects a greater percentage of enamine tautomer (i.e., γ-protonation) in the SAM case, leading to more α-ketobutyrate product, as opposed to C-4′-protonation, which would lead to the inactivating Michael acceptor. These studies raise the intriguing possibility that L-SMM is a natural, masked progenitor of L-vinylglycine, itself a masked enzyme inactivator. Why two layers of unmasking? One possibility lies in the relatively broad spectrum PLP-enzyme inactivation profile of vinylglycine itself. Perhaps Nature has biosynthesized SMM as a way of targeting specific formation of vinylglycine to the ACC active site.

5. Conclusion

The known α-vinylic amino acids comprise of a diverse set of structurally and mechanistically fascinating natural products, many of which act as inhibitors of PLP enzymes, though additional members of the class are surely yet to be discovered. The parent member of the family, vinylglycine, has drawn the most attention, as it is both generated in a number of active sites, and serves as a broad spectrum inactivator. Its covalent mechanism of attachment to ACC synthase via Michael addition was just recently revealed by X-ray crystallography.

From a medicinal chemistry point of view, vinylglycine also served to inspire the development of Vigabatrin, an established drug for the prevention of epileptic seizures, and a possible candidate for future treatment of drug addiction.[122, 123 and 124] Interestingly, X-ray crystallographic studies on its GABA transaminase target now reveal as close a parallel between mechanisms of the designed drug and the natural product as could ever have been imagined.

From a synthetic point of view, vinylglycine has also been at the center of this amino acid class, because of its high value as a chiral synthetic building block toward the synthesis of alkaloids, azasugars, and novel amino acids. This continues to motivate organic chemists to develop asymmetric routes to each antipode of vinylglycine, from chiron based, to chiral auxiliary based, to catalytic asymmetric approaches.

Acknowledgments

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