Ribosomal Synthesis of Ketone-containing Peptide Backbone via O to C Acyl Shift

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Abstract: Despite tremendous efforts to engineer translational machinery, replacing the encoded peptide backbone with new-to-Nature structures remains a significant and largely unmet challenge. C, H, O, and N are the elements of life, and yet ribosomes are only capable of forming C–N bonds as amides, C–O bonds as esters, and C–S bonds as thioesters; there is no current strategy to form C–C bonds as ketones embedded in the backbone of ribosomal products. We discovered that peptides containing a dehydrolactic acid motif rapidly isomerize to generate a backbone-embedded α,γ-diketoamide via a spontaneous formal O to C acyl shift. The dehydrolactic acid motif can be introduced into peptides ribosomally or via solid-phase synthesis using α-hydroxy phenylselenocysteine followed by oxidation. Subsequent incubation at physiological pH produces an α,γ-diketoamide that can be diversified using a variety of nucleophiles, including hydrazines and hydroxylamines to form pyrazoles and oximes, respectively. All of these groups remain embedded directly within the polypeptide backbone. This general strategy, predicated on an intricate cascade of acyl rearrangements, provides the first example of a C–C bond forming reaction to take place within the peptide backbone, as well as the first ribosomal strategy for generating protein-like materials with diverse, backbone-embedded heterocycles. The genetically encoded, new-to-nature biopolymers produced should accelerate the discovery of genetically encoded molecules whose properties better resemble those of bioactive natural products.

Ribosomes have evolved over billions of years to catalyze a single reaction: the formation of an amide bond between two α-amino acids. Recent work has shown that in addition to canonical and non-canonical α-amino acids (*1*, *2*), under cellular conditions ribosomes also promote reactions of α-hydroxy acids (*3*, *4*) as well as certain β^2-hydroxy (*5*) and β^3-amino acids (*6*). Under optimized in vitro conditions and using chemically pre-acylated tRNAs, ribosomes also support reactions of α-thio acids (*7*) and a variety of non-α-amino acids, including N-terminal aramids and 1,3-dicarbonyls (*8*, *9*), α-aminoxy and α-hydrazino acids (*10*), and cyclic β-amino acids (*11*). Despite these advances, there are no reports of a ribosomal product containing a newly formed backbone C–C bond as a ketone, due largely to the challenges of generating and maintaining a carbon nucleophile in water (Fig. 1A). Additional carbons can be inserted into the polypeptide backbone via "extension," either by acyl shifts or isoaspartate formation, but the products are amides (Fig. 1B). Enzymes can install backbone ketones by excision via recognition of an 11-amino acid tag (*12*, *13*) or biosynthetically to the termini of peptides (*14–18*) (Fig. 1B). However, none of these given examples install a ketone internally and without a requisite recognition sequence. Herein, we report the discovery of a reaction cascade that edits the peptide backbone through C–C bond formation, yielding a versatile α,γ-diketone, the fundamental element of polyketide natural products, which can be derivatized to form myriad acyclic and cyclic backbone products. The precursor for this reaction cascade can be incorporated into peptides directly by the ribosome or by chemical synthesis. Oxidation followed by incubation in physiological buffer rapidly isomerizes the monomer into the α,γ-diketoamide. Moreover, and in a manner reflective of classic dicarbonyl chemistry (*19*, *20*), the newly formed α,γ-diketoamide can be diversified to embed substituted pyrazoles and oximes within the polypeptide backbone, generating ribosomal products whose structures begin to capture the diversity of synthetic materials.

DHL rearrangements form a new C–C bond in a model tripeptide

As part of ongoing work to expand the chemistry of polypeptide backbones (*5*, *6*, *21*, *22*), we explored the reactivity of dehydrolactic acid (DHL). DHL is the ester analog of dehydroalanine (DHA) (*23*, *24*), a species that may be generated within a polypeptide either biosynthetically (*25*, *26*), or synthetically via oxidation of a selenocysteine analog (*23*) or β-elimination of serine or cysteine heteroatoms (*28–30*). While DHA reacts readily in an intermolecular fashion at the electrophilic β-carbon (*23*, *31*) (Fig. 1C), we were surprised to discover that DHL reacts preferentially in an intramolecular fashion to form an α,γ-diketoamide. The result is a formal transposition of the β-carbon and the α-oxygen, as well as the formation of a new C–C bond (Fig. 1D).

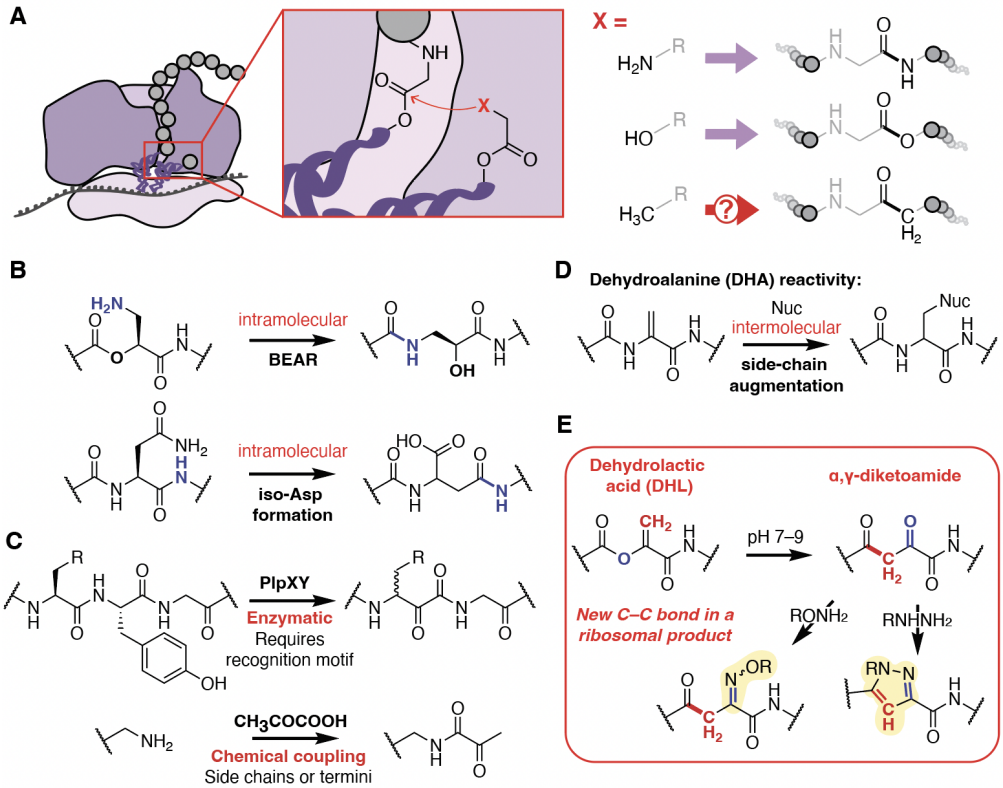

Figure 1. Dehydrolactic acid rearrangement provides a strategy to form C–C bonds as ketones in ribosomal products. (A) Known and unknown reactions promoted within the ribosome active site, the peptidyl transferase center (PTC). Amines are excellent and canonical nucleophiles for peptide bond formation, and alcohols also react within the PTC. While carbanions can act as nucleophiles, they are difficult to generate and control at neutral pH. As a result, C–C bonds have yet to be formed directly within the PTC. (B) Backbone extension acyl rearrangements (BEAR) and isoaspartate formation elongate the peptide backbone to generate β^2- or β^3-peptides, respectively. (C) Established strategies to install ketones in polypeptides. The enzyme PlpXY excises a tyramine motif to leave behind an internal α-ketoamide, although the required 11-amino acid sequence tag can pose limitations. Ketones can also be coupled directly to side-chains or termini of synthetic peptides. (D) Dehydroalanine (DHA) has been utilized for the post-translational installation of diverse side chains. (E) DHL resembles DHA but contains an enol ester once introduced into a polypeptide. Unlike DHA, DHL reacts preferentially in an intramolecular fashion to form an α,γ-diketoamide product embedded within the polypeptide backbone. The α,γ-diketoamide can be diversified using hydrazines to form pyrazoles and hydrazones and with hydroxylamines to form oximes.

The unprecedented DHL rearrangement to form a new C–C bond was first observed in the context of a model tripeptide. DHL was installed using an α-L-hydroxy-phenylselenocysteine (HO-SecPh) (**1**) precursor, which was synthesized via a known epoxide ring-opening reaction (*32*) followed by hydrolysis, and introduced into tripeptide **2**. Treatment of tripeptide **2** with H_2O_2 in MeOH for 1 h afforded DHL-peptide **3**, which was purified to homogeneity using RP-HPLC and characterized

by NMR and LC-HRMS (Fig. 2A–B, fig. S1). The Heteronuclear Multiple Bond Correlation (HMBC) spectrum of **3** shows correlation between the Ala side-chain methyl protons and the ester carbonyl (171 ppm), as well as between the benzyl protons and the amide carbonyl (162 ppm) (Fig. 2C, fig. S2). Although purified DHL-peptide **3** was stable in MeOH, the addition of tetramethyl guanidinium (TMG) base for 15 min at RT led to the appearance of several chromatographically distinct species that possessed the same mass as DHL-peptide **3** when analyzed by LC-HRMS. These isobaric species also arose from treatment of DHL-peptide **3** with 50 mM NaP_i at pH 8 and persisted for at least 8 h (Fig. 2D, fig. S1). When isolated, each peak re-equilibrated into the same set of multiple peaks, suggesting that base treatment of DHL-peptide **3** resulted in a set of at least three interconverting isomers.

Although the isomers of DHL-peptide **3** formed in base could not be isolated, they could be partially characterized by NMR. The HMBC spectrum of purified DHL-peptide **3** in 50% 50 mM NaPi pH 8 in methanol-d_4 contains the same benzyl proton–amide carbonyl cross-peak as purified **3** in methanol-d_4 (167 ppm) (Fig. 2E, fig. S2). However, the cross peak corresponding to the Ala methyl protons shifted downfield on the ^{13}C channel to an apparent ketone region (197 ppm). A singlet methine peak also emerges at 5.9 ppm, suggesting the presence of enol **3'** (fig. S3–4) (*33*).

We confirmed the structure of α,γ-diketoamide isomer **3'** by characterizing its conversion into pyrazole **3a.** DHL-peptide **3** was treated first with 50 mM NaP_i at pH 7 for 1 h at RT and then with excess hydrazine at pH 6, as appropriate for a classic Knorr pyrazole synthesis (Fig. 2F (*20*). Within minutes after the addition of hydrazine, the chromatographically distinct but unisolable peaks that are evident in Fig. 3C coalesced into a single chromatographic peak with a mass that corresponded to pyrazole **3a** (Fig. 2G). Full characterization of the product by NMR confirmed the structure of the pyrazole, further elucidating that intermediate **3'** is a α,γ-diketoamide (Fig. 2H).

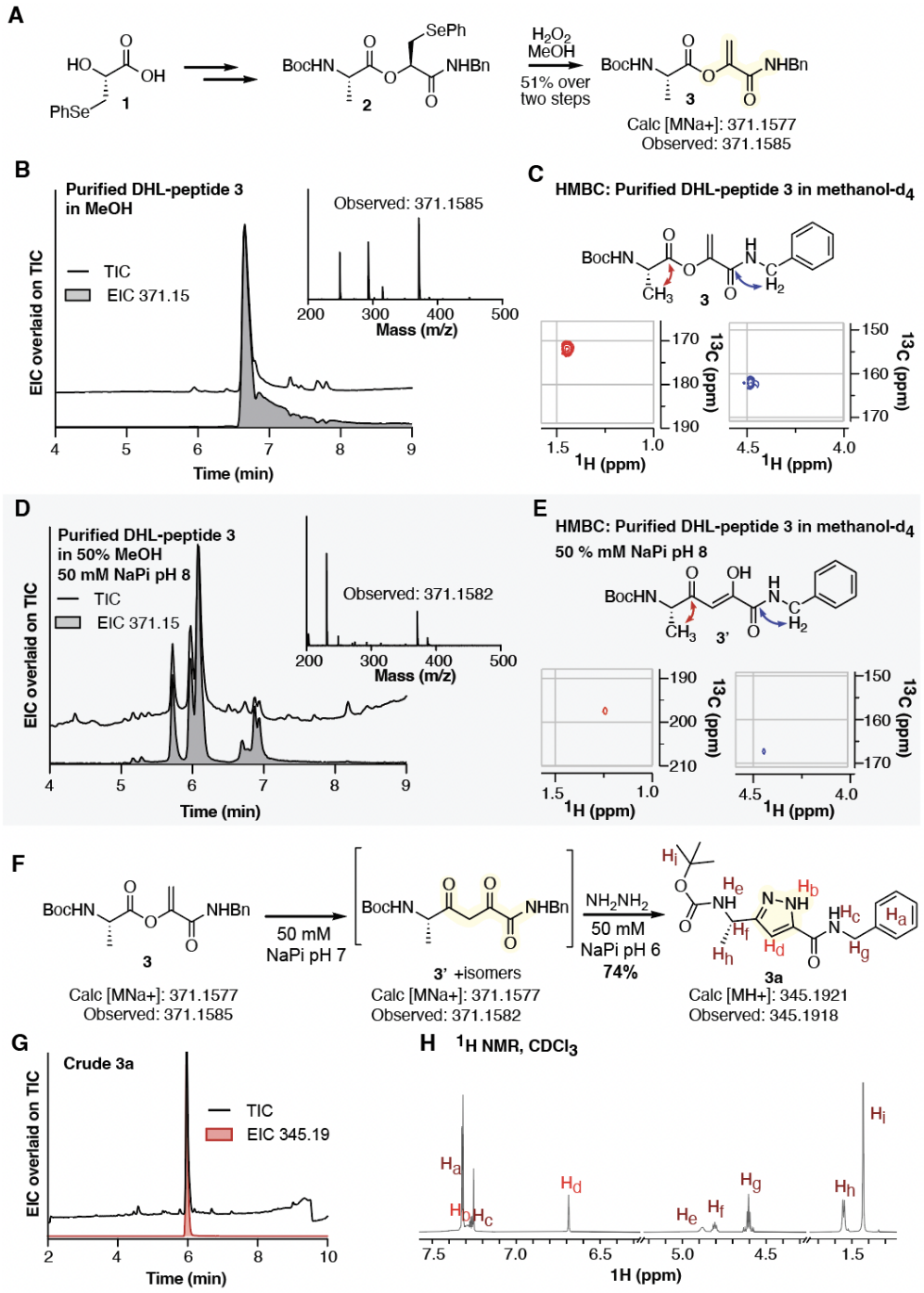

Figure 2. DHL-peptide 3 isomerizes into an α,γ-diketoamide at pH 7. (A) Scheme illustrating the structure of the DHL precursor HO-SecPh (**1**), its incorporation into tripeptide **2,** and oxidation to produce DHL-peptide **3**. (B) LC-HRMS chromatogram and spectrum of DHL-peptide **3**, which is stable in methanol. (C) Two sections of the HMBC NMR spectrum of DHL-peptide **3** in methanol-d_4, showing correlation of the methyl protons with the ester carbonyl (left), and the benzyl protons with the amide carbonyl (right). (D) LC-HRMS chromatogram and spectrum of DHL-peptide **3** following 4 h incubation in 50 mM NaP_i at pH 8. (E) Two sections of the HMBC NMR spectrum of DHL-peptide **3** in 50% methanol-d_4 and 50 mM NaPi pH 8, showing correlation

of the methyl protons with the newly formed ketone carbonyl (left), and the benzyl protons with the amide carbonyl (right). (F) Incubation of DHL-peptide **3** in 50 mM NaP_i at pH 7 followed by 20 mM hydrazine in 50 mM NaP_i at pH 6 generates a product containing a backbone pyrazole, **3a**. (G) LC-HRMS of crude **3a** showing the EIC overlaid on the TIC following reaction in (D). (H) ^1H NMR confirms the structure of purified pyrazole-peptide **3a**.

Computational studies support a dual acyl-shift cascade pathway for C–C bond formation

Acyl shifts are known to alter the peptide backbone. Intramolecular acyl shifts occur spontaneously and rapidly in the context of the native chemical ligation (NCL) (*34*) or during the final step of intein splicing (*35*). Recent work has shown that β-amine nucleophiles generated in proximity to a reactive acyl group promote O to N acyl shifts that establish β^2-peptide linkages within proteins in cells (*22*). In these cases, the acyl shifts utilize a side chain nucleophile and generate a thermodynamically stabilized amide product. Although pseudo-intramolecular decarboxylative Claisen reactions generate new C–C bonds via S to C acyl shifts during polyketide biosynthesis, in this case the carbon nucleophile is generated enzymatically and transiently while held in proximity to the electrophile (*38*). Intramolecular Claisen-type rearrangements and O to C acyl shifts to form C–C bonds have precedent in chemical synthesis (*39*, *40*), but to our knowledge, there is no reported example of an acyl shift that generates a new C–C bond in a peptide backbone.

While O to C acyl shifts have precedent, the observed transformation of DHL proposed above does not. The DHL rearrangement pathway we envision is outlined in Fig. 3A. We suspect that the amide nitrogen initiates isomerization by reacting with the backbone ester, as seen during the rapid formation of succinimides during isoaspartate and aspartimide formation (*36*, *37*). This reaction step could also proceed through imidate tautomer **5**, although a direct addition of the nitrogen to the ester carbonyl cannot be ruled out. Following addition, cyclic intermediate **6** could ring-open to form transient intermediate **7**, which would be in equilibrium with its stable tautomer, **8**. Attack of the enol carbon of **7** on the proximal carbonyl of the acyl-imide would yield compound **9**, thus forging the key C–C bond of the rearrangement. This step is reminiscent of intramolecular Claisen rearrangements of allylic alcohols that are used to produce γ,δ-unsaturated esters stereoselectively (*40*), or the O to C acyl shift employed in the synthesis of benzofurans (*39*). A second ring opening step forms the diketone species **10**, which tautomerizes to the low energy diketoamide (**11**) and enol (**12**). DFT calculations support that the intermediates on this pathway are energetically accessible, and predict an overall enthalpic change of –7.6 kcal/mol for the full transformation (Fig. 3, fig. S5).

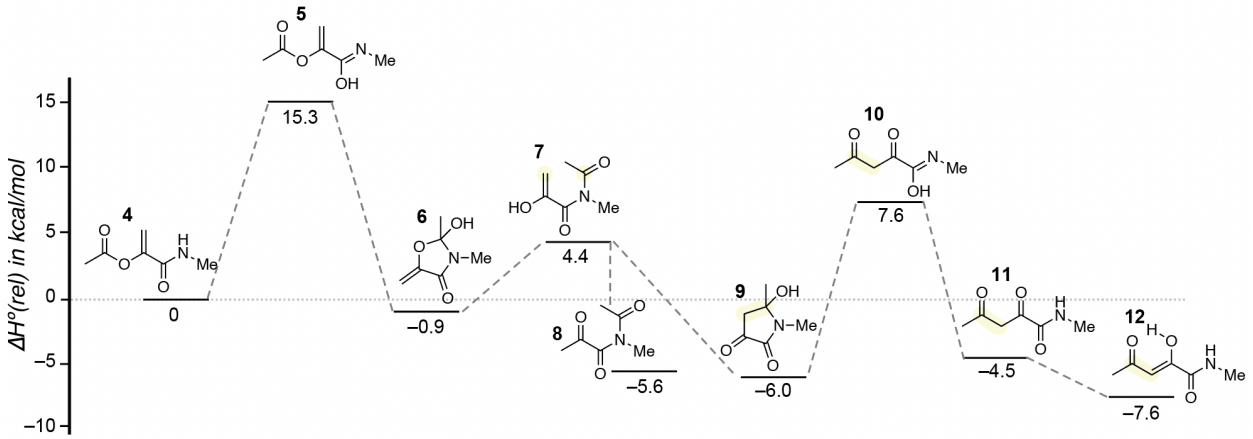

Figure 3. DFT studies suggest that dehydrolactic acid isomerizes via an overall O to C acyl shift. Shown is an energy landscape illustrating the relative calculated enthalpies ($\Delta H^{o}_{(rel)}$) of intermediates along the proposed pathway between DHL **4** and enol **12**. The proposed pathway begins with intramolecular cyclization of DHL tautomer **5** to form succinimide **6**. Release of the ester bond in the tetrahedral intermediate generates the crucial enol-containing intermediate **7**, which can tautomerize into unproductive intermediate **8** or cyclize with the acetamide carbonyl to generate the new C–C bond in **9**. A final ring opening installs the second keto group in **11**, and subsequent tautomerization ultimately leads to low-energy enol **12**. For all species, geometry optimization and frequency calculations were performed at the B3LYP-D4/6-31G** level with an implicit CPCM solvation model. Final electronic energy calculations were performed using ωB97M-V/def2-TZVPPD with a CPCM solvation model.

DHL rearrangements are efficient in tripeptides

Next we explored whether the two-step O to C rearrangement to generate a reactive α,γ-diketoamide would proceed in diverse α-amino acid contexts. We synthesized five analogs of tripeptide **2** in which the N-terminal Boc-Ala was replaced by either Boc-Gly (**13**), Boc-Pro (**14**) Boc-Glu(OtBu) (**15**), Boc-Phe (**16**), or Boc-Val (**17**) (Fig. 4A). Treatment of each tripeptide with H_2O_2 in MeOH afforded the corresponding DHL-peptides **18–22** within an hour as determined by LC-HRMS. The new DHL-peptides (**18–22**) were purified by RP-HPLC and their structures were confirmed by NMR. Each DHL-peptide was incubated at pH 7 for 1 h and then combined at pH 6 with (**a**) hydrazine or (**b**) *O*-methyl hydroxylamine (Fig. 4B). Reactions were incubated for 6 h at RT and analyzed by LC-HRMS.

All DHL-peptides were transformed into pyrazoles and oximes under these conditions. Pyrazole formation was quantitative for DHL-peptides containing an N-terminal Ala, Gly, and Glu(OtBu) residue, while reactions of DHL-peptides containing an N-terminal Pro, Phe, or Val contained a small amount of residual DHL-peptide as determined by LC-HRMS (fig. S6–S7). These observations suggest that rearrangement is most efficient with reduced steric hindrance near the ester carbonyl. Example chromatograms are shown for pyrazole-peptides **18a**, **20a**, and **22a**, and oxime-peptides **19b**, **18b**, and **21b** (Fig. 4C). We observed little double addition of hydroxylamines

to the model tripeptides, although we suspect that oxime formation can occur on either ketone, and that each oxime can exist as the *E* or *Z* isomer, as indicated by the multiple chromatographic peaks observed for the product.

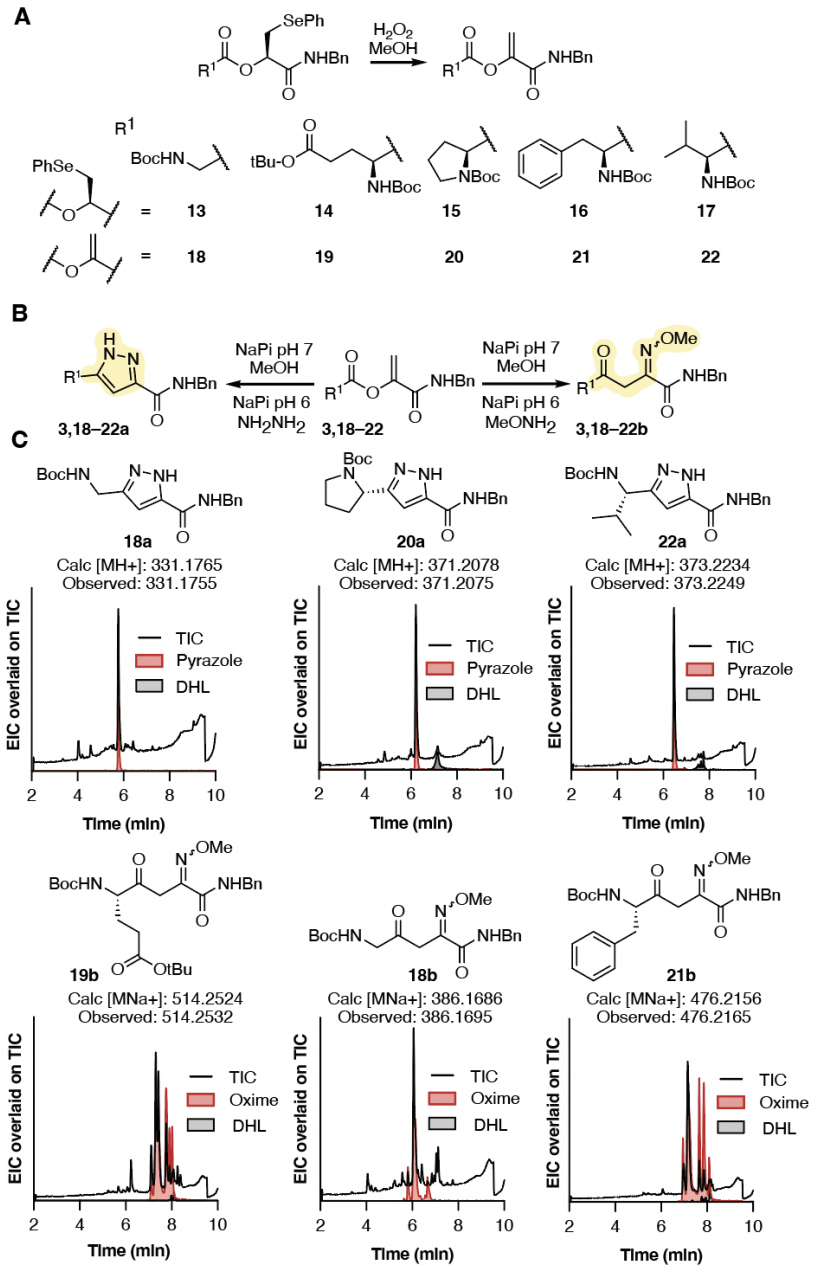

Figure 4. DHL rearrangements proceed in multiple contexts and the α,γ-diketoamide products react with α-nucleophiles. (A) Six additional tripeptides **13-17** containing the DHL precursor HO-SecPh were prepared and oxidized to generate DHL-peptides **18–22**. (B) DHL-containing tripeptides first isomerized in buffer at pH 7 were subsequently reacted with either hydrazine to form pyrazoles or *O*-methyl hydroxylamine to form oximes. (C) LC-HRMS chromatograms showing the EIC (red) corresponding to pyrazole-peptides **18a**, **20a**, and **22a** (top)

and oxime-peptides **19b**, **18b**, and **21b** (bottom), and residual DHL (gray) overlaid on the total ion chromatogram (TIC).

DHL-rearrangements edit the backbones of multiple peptides prepared on the solid phase

The α,γ-diketoamide functional group provides a new strategy for peptide diversification because of the ease with which it can be orthogonally labeled and diversified into drug-like motifs. Incorporation of ketones into polypeptides (>5 amino acids) is challenging on the solid phase, and is often limited to reactions of side chains or the N- or C termini (*15–17*). Peptides containing an internal HO-SecPh monomer could be synthesized on the solid phase and subsequently reacted with a diverse panel of α-nucleophiles to generate substituted pyrazole- and oxime-peptides. We used a depsi-dipeptide block containing HO-SecPh (**1**) preceded by Gly (**S5**) or Ala (**S6**) to prepare a series of hexa- or heptapeptides with a variety of natural side chains (SM section 2). Following resin cleavage, deprotection, and purification, these peptides were treated with H_2O_2 to generate DHL-peptides **23–26** (Fig. 5A, SM section 2). Although oxidative elimination to generate peptides **23–26** proceeded slowly in water (>1 h), the reaction was accelerated in aprotic solvents such as acetonitrile (fig. S8–S10) (*41*). DHL-peptides **23–26** formed within 1 h in MeCN and H_2O_2 and were dried via lyophilization. All peptides were characterized by LC-HRMS, and DHL-peptides **23** and **26** and their precursors were also characterized by NMR (SM Section 3).

DHL peptides **23–26** were then isomerized in 50 mM NaP_i at pH 7–9 for varying times and derivatized with a variety of substituted hydrazines and hydroxylamines (**a–i**) (Fig. 5B). We first investigated the isomerization of DHL-peptides **23–26** in pH 7, 8, or 9 buffer. Samples were incubated between 15 min and 4 h before dilution in pH 6 NaP_i containing excess hydrazine. While higher pH enhanced the rate of isomerization, the majority of the sequences isomerized fully within 1 h at pH 8 and were converted to the corresponding pyrazole-peptide within 15 min (fig. S11–S12). The exception was Pro-containing DHL-peptide **26**, which required a 4 h incubation in NaP_i at pH 9 and then excess hydrazine in NaP_i at pH 6 for 1 h to convert fully into pyrazole peptide **26a** (fig. S13).

DHL peptides **23–26** could also be diversified with α-nucleophiles other than hydrazine. The highest yielding reactions occurred with electron-rich substituted hydrazines, such as 2-hydrazine-benzoic acid (**g**) and 2-fluoro-benzyl hydrazine (**h**), while reactions with the electron-poor 4-cyano-phenyl hydrazine (**d**) proceeded in lower yield. *O*-benzyl hydroxylamine (**f**) and *O*-methyl hydroxylamine (**b**) also efficiently formed their respective oximes. Finally, the thalidomide hydrazine (**i**), an analog of a known binder to the E3 ligase CBRN, also led to majority substituted pyrazole formation in the case of peptides **23i** and **26i**. Example chromatograms illustrating reactions to generate thalidomide-peptide **23i**, oxime **23e**, pyrazole-peptide **25a**, fluoro-benzyl pyrazole-peptide **24h**, phenyl-pyrazole **26c**, and benzoic acid-pyrazole **26g** are shown in Fig. 5C, with the remainder shown in the supplemental materials (fig. S14–S17). Pyrazole-peptides **23h**, **25g**, and **26g** were purified by RP-HPLC and again characterized by LC-HRMS (fig. S18). These

labeling reactions demonstrate the ease with which DHL-peptides prepared via SPPS can be diversified into a wide array of heterocyclic or bioconjugated materials.

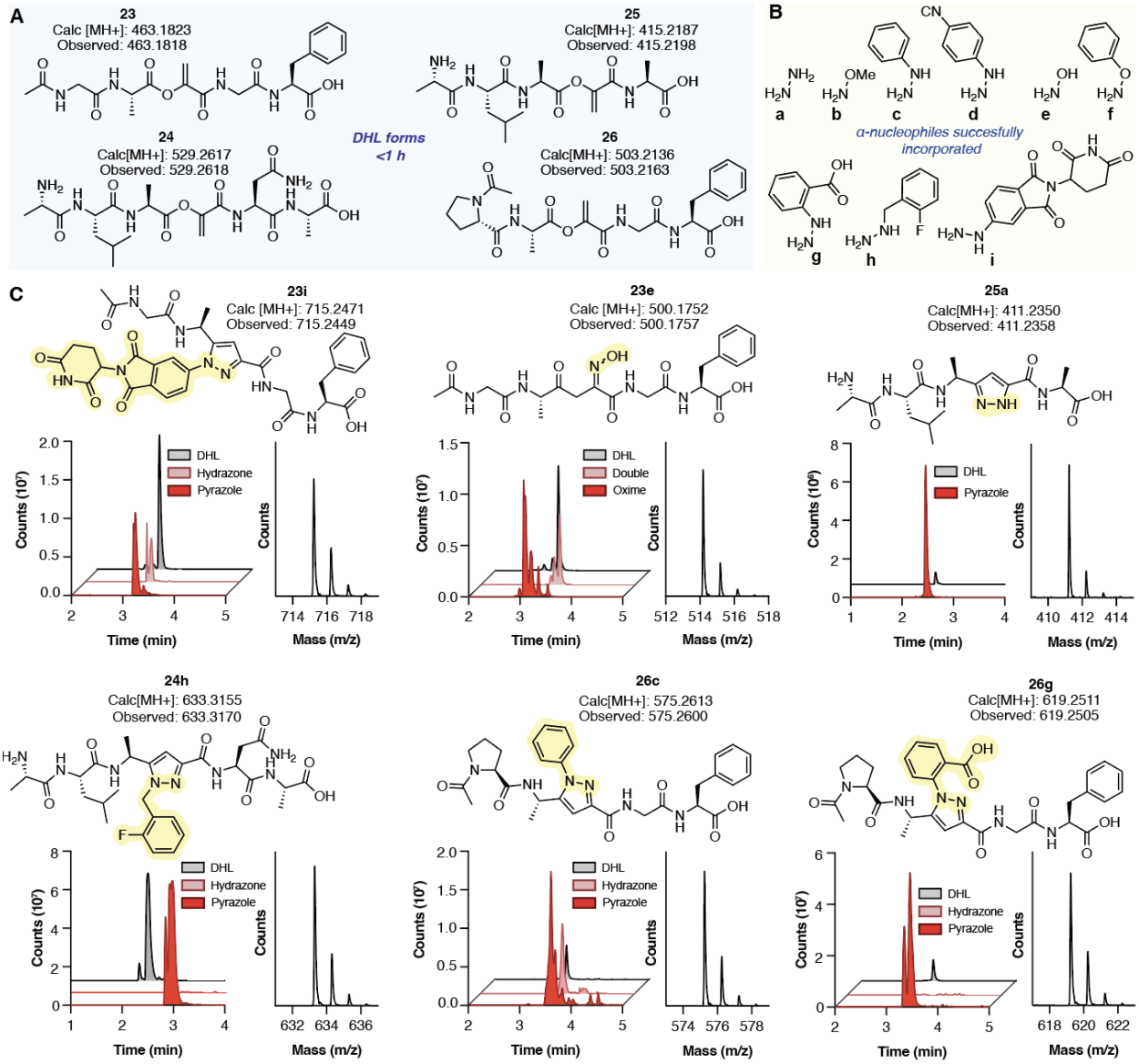

Figure 5. DHL-containing peptides prepared via solid-phase peptide synthesis can be diversified into oximes and pyrazoles following an O to C acyl shift. (A) Structures of DHL-peptides **23–26**. (B) Structures of α-nucleophiles **a–i** used to make pyrazole- and oxime-peptides. (C) Structures of pyrazole- and oxime-peptides and corresponding EICs and mass spectra from LC-HRMS following reactions with the α-nucleophiles, including thalidomide-peptide **23i**, oxime **23e**, pyrazole-peptide **25a**, fluoro-benzyl pyrazole-peptide **24h**, phenyl-pyrazole **26c**, and benzoic acid-pyrazole **26g.**

DHL-rearrangements edit the polypeptide backbones of ribosomally synthesized peptides

Encouraged by the reactivity described above, we sought to establish conditions needed to support DHL rearrangements and modifications of genetically encoded polypeptides prepared by in vitro translation. We evaluated several synthetase/tRNA pairs to generate an appropriate acyl-tRNA, including PhSeRS-K4, which was engineered to incorporate SecPh (*41*). We found the highest activity using FRS1, an analog of *M. alvus* PylRS that acylates $tRNA^{Pyl}$ with several α-hydroxy phenylalanine derivatives (*21*, *43*). FRS1 acylated $tRNA^{Pyl}_{Val}$ with HO-SecPh (**1**) within 4 h at 37 °C to produce a mixture of mono- and diacylated $tRNA^{Pyl}_{Val}$ products in 76% yield, confirmed by triplicate experiments (Fig. 6A). The acylated $tRNA^{Pyl}_{Val}$ products were added to a commercial *in vitro* translation system composed of purified components (PureExpress, NEB) (*44*) lacking Met and Val, along with cDNA encoding MALAVNA **(S11)**, with Val as the recoded position (Fig. 6B, fig. S19). After 2 h at 37 ºC, the peptide products were isolated and desalted; LC-HRMS revealed efficient biosynthesis of peptide **27** (Fig. 6C, fig. S19). We found desalting to be necessary before DHL formation, likely due to excess reducing agent in the PureExpress translation mixture.

The ribosomal product **27** was then oxidized, isomerized, and subjected to Knorr pyrazole synthesis. The desalted translation mixture containing **27** was first treated with 100 mM H_2O_2 in MeCN for 9 h, and the emergence of DHL peptide **24** was detected by LC-HRMS (Fig. 6D). The peptide was then lyophilized to remove the oxidant and reconstituted in 50 mM NaP_i at pH 8 to isomerize for 2 h. Subsequent addition of 20 mM hydrazine in 50 mM NaP_i at pH 6 afforded pyrazole-peptide **24a** (Fig. 6E, fig. S20). DHL-peptide **24** was also diversified with 2-fluorobenzyl hydrazine, resulting in substituted pyrazole-peptide **24g** (Fig. 6F, fig. S20).

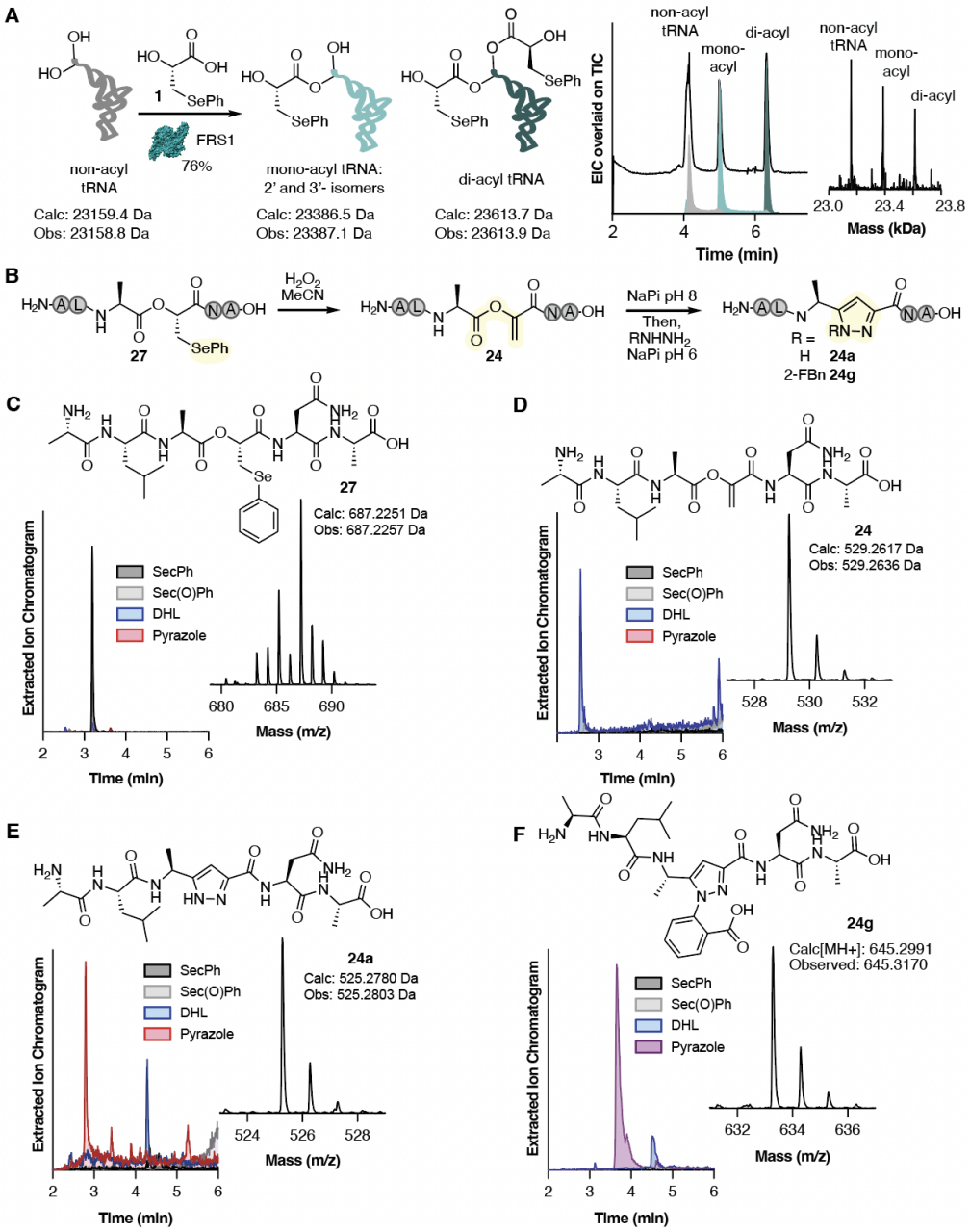

Figure 6. Genetic encoding of HO-SecPh-peptide and transformation into pyrazole-peptide. (A) Scheme illustrating the acylation of $tRNA^{Pyl}_{Val}$ with HO-SecPh **1** using the *M. alvus* PylRS variant FRS1. Shown is the LC-MS total ion chromatogram (TIC) of the product mixture overlayed with the extracted ion chromatograms (EIC) corresponding to unreacted $tRNA^{Pyl}_{Val}$ (non-acyl tRNA), mono-acylated $tRNA^{Pyl}_{Val}$ (mono-acyl) and diacylated $tRNA^{Pyl}_{Val}$ (di-acyl) following incubation with HO-SecPh **1** and FRS1. This mixture was added to an in vitro translation reaction along with cDNA coding for peptide MALAVNA **(S11)**, WT translation machinery, and the amino acids Ala, Leu, and Asn to generate HO-SecPh-containing peptide **25**. (B) Scheme illustrating the oxidation of HO-SecPh-containing peptide **25** into DHL-peptide **24** and its diversification into pyrazole **24a** and **24g**. (C–F) Structures, extracted mass chromatograms, and mass spectra of (C)

IVT-generated HO-SecPh-containing peptide **27**; (D) DHL-peptide **24**; (E) pyrazole **24a;** and (F) 2-fluorobenzoic acid pyrazole-peptide **24g**.

Discussion

While much of the 10^7-fold improvement in peptide bond formation arises from induced proximity (*45*), ribosomal catalysis has thus far been limited to O, N, and S nucleophiles to form carbon-heteroatom bonds. C–C bonds have yet to be formed within the PTC because of the challenges associated with controlling the reactivity of a carbanion in water. The DHL rearrangement reported herein overcomes this limitation by revealing the carbon nucleophile only as a reactive intermediate and in proximity to an equally reactive carbonyl. The result is a new C-C bond in the form of a versatile α,γ-diketone replete in polyketide natural product precursors. While γ-diketones can be generated biosynthetically using mixed multi-enzyme cascades, here we show that similar products can be genetically encoded using the ribosome. Like a polyketide, the α,γ-diketoamide produced by DHL rearrangement can be subsequently diversified to generate genetically encoded materials with diverse and valuable heterocycles embedded within the peptide backbone.

We envision the incorporation of DHL will significantly impact the ability to install non-peptidic elements into genetically encoded peptides or proteins, in vitro or in cells. This advancement provides otherwise non-existent opportunities to expand protein and polypeptide structure and function. For example, cyclic peptides are emerging as powerful therapeutic candidates, but often suffer from proteolysis and poor cell permeability due to solvent-exposed amide protons (*46*) and backbone N-methylation is a hallmark of bioactive cyclic peptides and natural products (*47*). Unnatural peptide backbones, such as additional methylenes or heterocycles, can enhance membrane permeability while adding chemical diversity (*48*, *49*). While recent years have seen notable advances in the ribosomal synthesis of multiple types of amide bonds, still no general strategy exists to embed genetically encoded C–C bonds as ketones internally within the polypeptide backbone. We anticipate that the ease of incorporating DHL into synthetic and ribosomal peptides will inspire further transformations that allow for post-translational polypeptide backbone editing, even in the cellular context.

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from all authors. **Competing interests:** C.K.S. and A.S. have submitted a patent application related to this work. **Data availability:** Experimental procedures, spectroscopic and chromatographic data, NMR spectra, and computational data are available in the supplementary materials. Additional data in this study are available from the authors upon request.

Supplementary Materials

Materials and Methods
References
SM section 1: supplementary figures
SM section 2: supplementary tables
SM section 3: NMR spectra
SM section 4: LC-HRMS Chromatograms
Data File 1: Coordinates for Optimized Structures Used in Computations