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Dehydration reactions in polyfunctional natural products

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Abstract.

In this review, we present state of the art methods for performing dehydration reactions in alcohol substrates to deliver alkene products. The dehydration of alcohols typically proceeds through activation of the alcoholic moiety to a nucleofugal species followed by a subsequent elimination step. While the alcohol is a quintessential functional group, selective adressability of alcohols in complex molecular scaffolds has not been harnessed to allow molecular diversification strategies. We present the perspective of utilizing complex molecular compounds containing alcoholic functionalities to generate novel molecular constructs that impose on chemical space of characterized bioactivity. Nature inspires the direct and selective dehydration of alcohols in complex molecules and demonstrates a potential that has not yet been realized by chemical methodology. We present challenging substrates for direct and selective dehydration reactions and argue that chemical methodology solving the challenges presented will be valued by synthetic and natural product chemists alike.

1 Introduction

The conversion of a hydroxyl group into the corresponding alkene by formal removal of water – dehydration – constitutes one of the most basic transformations in organic synthesis. The importance of dehydration reactions extend from transformations of bulk scale industrial chemicals, such as conversion of 1-butanol to form 1-butene¹ or styrene production from 2-phenyl ethanol,² to the synthesis of precious chemicals. Dehydration reactions comprise several intrinsic selectivity challenges: (a) achieving chemoselectivity for dehydration through elimination, versus other competing reaction pathways, (b) controlling regioselectivity and stereoselectivity with respect to formation of an alkene in substrates with several possible isomeric elimination products and (c) site-selective dehydration in molecules having multiple hydroxyl groups. The latter is of particular relevance to the present review (see Scheme 1A). Many natural products are highly complex and polyfunctional molecules that have evolved characteristics facilitating binding to biological macromolecules. Due to their functional capacity, natural products have been developed as highly successful drugs³ and are used as specific molecular probes⁴ to study the biological function of their respective biomolecular targets.⁵ In both cases, structural modification of natural product compounds is often necessary to increase potency, install reporter groups or to modulate pharmacokinetic properties. The molecular complexity of many natural products, however, makes development of *de novo* synthetic routes, that can support structural diversification, a very challenging undertaking, although notable examples have been reported.^{6–}

⁸ By comparison, a more efficient strategy for diversification involves the direct introduction of functional groups into complex molecules, also known as late-stage functionalization.^{9–12} Although daunting selectivity challenges typically need to be overcome, the direct modification of natural products, peptides or drugs offers access to novel compounds for structure-activity analysis or synthetic utility by further derivatization.^{7,12} Hydroxyl groups are ubiquitous in natural products and their selective functionalization have been subject to significant interest. Interestingly, despite of the development of methods involving reagent control as well as bespoke catalysts,^{11,12} e.g. based on peptides,^{11,13–16} the examples of late-stage dehydrations that have been reported in the literature are few. Surely, there are interesting opportunities within this area, as the development of selective dehydration reactions of complex molecules would be an efficient approach to unique and interesting compounds (relevant, but challenging, dehydration substrates are illustrated in Scheme 1A). As is often the case, we need only look towards Nature's enzymatic transformations for sources of inspiration, for instance in biosyntheses of lantipeptides, such as lacticin 481, in which dehydration occurs at four out of six Ser/Thr-derived alcohol moieties (Scheme 1B).¹⁷ The primary purpose of this review is to provide a concise overview of the current methods used to perform chemical dehydrations and to discuss the potential utility of these methods in high complexity settings. Our examples also include methods/reagents that have so far seen only limited use in synthesis as we believe that 'exotic' examples serve as inspiration for development of novel chemistry. Where appropriate, we integrate our examples with discussions of major biochemical mechanisms for effecting dehydration during natural product biosynthesis. In order to maintain a concise text, we unfortunately had to prioritize among many illustrative examples, and we apologize to authors whose work have not been included.

A

Dehydration of alcohols to alkenes

Challenge

- Chemoselective reactivity favoring elimination
- Controlling regio- and stereochemistry of alkene products
- Site-selectivity of elimination in poly-hydroxylated molecules

Opportunity

- Late-stage molecular diversification
- Direct access to novel and complex derivatives
- Semi-synthetic utility of natural products

B

Lactacin 481 biosynthesis

Scheme 1: A) The challenge to be overcome for selective dehydration of alcoholic compounds to alkene products. The possibilities are clear for late-stage molecular diversification from natural products and drugs to access unique and interesting synthetic derivatives. Somatostatin **(1)**, Zoladex **(2)** and cholic acid **(3)** are polyfunctional molecules that would be amenable for direct modification with availability of chemo- and site-selective dehydration chemistries. B) In the biosynthesis of lactacin 481, site-selective dehydration delivers elimination of 4 out of 7 Ser/Thr moieties to the corresponding dehydroamino acid residues, followed by intramolecular nucleophilic addition from cysteine residues.

2 Chemical methods for dehydration of alcohols

In the following section, we provide a state-of-the-art overview of chemical dehydration methods. Regioselectivity of alkene formation is critical in this regard, with the complication of E/Z-isomerism that may be generated with double-bond formation. Meanwhile, functional group tolerance, chemoselectivity for dehydration of alcohols, and preferences of site-selectivity in

polyol substrates are central aspects that dictate the potential late-stage utility of dehydration methodologies. As mentioned, we emphasize non-canonical examples of dehydration chemistry to provide a broad display of conditions that are relevant for the continued development of dehydration methods.

2.1 Selectivities in olefin formation

The activation of primary alcohols for elimination generates terminal alkenes as the immediate product. For dehydration of secondary and tertiary alcohols, a selection bias occurs as incipient π -bonds may be formed in different directions. The regioselective formation of alkene products from secondary and tertiary alcohols are dictated by the mechanistic pathway of the elimination reaction and the stereo-electronic constitution of the substrate. The prevalence of E_i , E1, E1cB and E2-type reactions have implications for the choice of dehydration methodology. The regioselectivity in double bond formation is a key aspect of synthetic planning in targeted syntheses. Stereospecific or stereoselective elimination allows predictable formation of alkene products, as dictated by relevant transition states mediating elimination.

2.2.1 Acid-mediated elimination

Historically, dehydration chemistries have utilized harsh acidic conditions, to enhance the leaving group capability of the hydroxy-group. Brønsted and Lewis acids both function to facilitate dehydration. An extensive list of reagents such as *p*-toluenesulfonic acid (PTSA), HCl, H₂SO₄, KHSO₄, trifluoroacetic acid (TFA), P₂O₅, BF₃ · OEt, H₃PO₄, and numerous others, have been reported to effect acid-mediated elimination, typically with generation of nascent double bonds being guided by construction of conjugated π -systems. Acid-mediated elimination reactions generally yield products adhering to Saytzeff's rule. A trait of acid-mediated elimination is the occurrence of rearrangements, that modify the skeletal framework of carbocyclic molecules. For instance, a boron trifluoride mediated elimination reaction of labdane-derivative (**4**) has been characterized to effect dehydration followed by cationic rearrangement to relocate the double bond formed from the initial dehydration product, as visualized by the transformations indicated in Scheme 2.¹⁸

Scheme 2: Elimination from a tertiary alcohol substrate (**4**), using Lewis acidic boron trifluoride-etherate. This example illustrates the common reactivities of acid-mediated dehydration in carbocyclic molecules.

The kinetically favored Hoffmann product (**5**) is formed first, through momentary (2 min.) treatment of (**4**) with boron trifluoride at -78°C . Prolonging the reaction time to 20 minutes at the same temperature delivers an isomeric mixture of elimination products - (**6**) and (**7**) - containing either a tri- or tetra-substituted double bond. Finally, treating the substrate alcohol (**4**) with boron trifluoride at 0°C for 4 hours affords the tetrasubstituted olefin (**8**), a scaffold belonging to the halimane compound class, through a stereospecific [1,2]-methyl shift.¹⁹ Mechanistically, these diverse outcomes likely follows from an initial dehydration to (**5**) and subsequent re-complexation of boron trifluoride with the olefin of (**5**) to facilitate formation of the subsequent rearrangement products. This example illustrates the significant complexity of dehydration reactions facilitated by strong Lewis acids where both kinetic and thermodynamic factors impact olefin formation, with prevalence of skeletal rearrangements through formation of cationic intermediates. Dehydration using $\text{BF}_3 \cdot \text{OEt}_2$ has been demonstrated as being a rapid and efficient strategy for dehydration of tertiary alcohols,²⁰ but the harsh reaction conditions are typically incompatible with sensitive functional groups and selective engagement of the alcohol functionality can be very challenging. Further, because of the involvement of full or partial cations as intermediates, acid-mediated dehydrations are not advantageous for primary and secondary alcohols, where the generation of

cationic intermediates are less facile. For acid-mediated dehydrations to become broadly applicable as a late-stage dehydration method, new and milder conditions are necessary.

2.2.2 Acid/base catalysis in biosynthetic dehydrations

The conceptual feasibility of acid-mediated elimination reactions in complex molecular compounds is demonstrated in fundamental aspects of polyketide biosynthesis. Dehydration reactions - mediated by dehydratase enzymes - are part of the pipeline that empowers polyketide natural products to expand into a diverse chemical space of both complexity and molecular function. Biosynthesis of polyketide natural products is performed by large enzymatic assembly lines that control the sequence of reactions by tethering intermediates onto dedicated carrier proteins, post-translationally modified with a phosphopantetheinyl arm. Intermediates are extended with monomers of 2-3 carbons at a time, with three optional enzymatic transformations that change the oxidation state of the previously installed monomer - a ketone reduction, an alcohol dehydration, and a reduction of the resulting α - β unsaturated thioester. These optional steps are hallmark transformations of polyketide biosynthesis and enable the remarkable structural complexity of molecules built from acetyl-CoA, malonyl-CoA, and methylmalonyl-CoA. The typical dehydratase domain is composed of a double-hotdog fold that aligns two catalytically active amino acids – a histidine and an aspartate – to carry out a dehydration using dual general acid-base catalysis, as depicted in Scheme 3.²¹ The orientation ensures a syn-elimination from the D- β -hydroxy group and a the L- α -proton forming a trans- or E- double bond as the product.^{22,23}

Scheme 3: Formation of olefinic dehydration products bonds through stereospecific, catalytic activity of a dehydratase enzyme in iterative polyketide synthesis. ACP designates an acyl carrier protein.

Although *trans* double bonds are more common, *cis* double bonds are also produced through biosynthesis, but these are made from L- β -hydroxy groups.²⁴ As such, dehydrations in iterative polyketide synthesis utilize a genetically encoded molecular architecture to precisely position a dehydration substrate allowing an acid/base enabled push-pull system to facilitate elimination. The encoded substrate recognition and molecular architecture of the dehydratase complex is a

determining benefactor for site selective dehydration reactivity. In comparison, current chemical means of dehydration do not offer equivalent spatial control of acid/base catalysis in facilitation of dehydration, and therefore must rely on reagents with a greater chemical reactivity. The capabilities of dehydratase enzymes, suggests that development of novel bifunctional catalysts might enable site- and stereoselective dehydration in complex molecules.

2.3 Non-canonical enzymatic dehydrations

The versatility of biosynthetic dehydrations, however, extends beyond the canonical transformations described above. Recently, Fiers et al. reported a dehydratase domain from the curacin biosynthesis pathway that can facilitate elimination of two equivalents of water from β,δ -dihydroxy thioester using the same catalytic dyad.²⁵ Other examples of double dehydrations are seen in trans-acyltransferase polyketide synthases where dehydrating bi-modules are responsible for installing an α/β -trans, γ/δ -cis diene in the difficiadin biosynthesis.²⁶ The identification of a predicted protease, PynH, performing dehydration of a serine side-chain to an *exo*-methylene moiety in the biosynthesis of the pyranonigrins has also been reported.²⁷

Scheme 4: A) Sulfene formation from methanesulfonyl chloride (**9**) by dehydrohalogenation generates a highly reactive sulfonylating agent. B) Preparation of 5-phenylbicyclo[2.2.2]oct-5-en-2-one (**13**) through an E2 syn pathway, using unconventional conditions to facilitate elimination. C) Site-selective dehydration of a threonine residue in a bis-alcohol substrate (**14**) in the synthesis of the A-C-D fragment of thiocilline I.

2.4 Sulfonate ester derivatives

The most abundant method for formal dehydration of alcohols to alkenes is effectuated through activation of the alcohol to a sulfonate ester derivative, typically employing an amine base (Et_3N , pyridine, DIPEA) in combination with an appropriate sulfonyl chloride or sulfonic anhydride.²⁸ Mitsunobu-type conditions to activate alcoholic compounds to sulfonate ester derivatives with stereochemical inversion has also been reported.²⁹ Olefin formation from sulfonate ester derivatives may proceed concurrent with activation of the alcoholic substrate or in a stepwise manner following isolation of the sulfonate ester, through extractive work up procedures or chromatography. Notably, methanesulfonyl chloride (**9**) may allow generation of a highly reactive sulfene intermediate (**10**) (see Scheme 4A), whereas sulfonyl chloride reagents without α -protons function by nucleophilic substitution at sulfur.^{30,31} Therefore, the use of sulfene forming reagents such as methanesulfonyl chloride may have functional differences from other synthetic methods that generate sulfonate esters. A number of sulfonyl chloride reagents are commercially available, predominantly in the form of simple aliphatic or aryl sulfonyl chlorides. Being relevant for enantioselective syntheses, both antipodes of camphorsulfonyl chloride may be procured, thus allowing generation of diastereomeric sulfonate esters from racemic alcohol substrates. This may allow separation of diastereoisomeric elimination substrates prior to olefin formation, as induced by base treatment. An anti-periplanar relationship between a sulfonyl ester and a β -positioned hydrogen of sufficient acidity are preferred to facilitate anti-selective elimination in E2 fashion mediated by a non-nucleophilic base (such as DBU, Et_3N , DABCO or similar). The stereochemical requirement for anti-periplanar E2 elimination in a concerted reaction process may e.g. be harnessed to deliver isomerically pure Z-olefins upon dehydration of threonine residues.³² In contrast, geometries that obstruct anti-periplanar E2 elimination may significantly hamper reaction outcomes, for instance, as demonstrated by the elimination of a bicyclic alcohol derivative (**11**) under the requirement of an E2 syn-elimination of the corresponding mesylate derivative (**12**) (see Scheme 4B).³³ Following sampling of various dehydration strategies, highly concentrated reaction conditions using refluxing 2,4,6-collidine as solvent/base, were needed to access to 5-phenylbicyclo[2.2.2]oct-5-en-2-one (**13**) in an efficient process from (**11**). Such forcing conditions, however, do not have general applicability. Varying steric accessibility of substrate alcohols allows for selective functionalization in polyol substrates, and thus site-selective elimination. Such transformations may be achieved using a sulfonylation reagent of controllable reactivity such as tosyl chloride.^{34,35,36} With careful control, more reactive electrophilic reagents may also offer site-selective dehydration as exemplified by the selective generation of an intermediate triflate derivative in a recent route to azamerone.³⁷ Similarly, the preparation of the A-C-D fragment of the thiopeptide thiocilline I (see Scheme 4C), employed a strategic and site-selective dehydration from a threonine residue in (**14**) to engender stereoselective formation of the corresponding Z-configured olefin in (**15**).³⁸ An early experiment afforded the desired dehydration product (**15**) in 56% yield, with the double dehydration product being a major side-product, using standard $\text{Et}_3\text{N}/\text{MsCl}$ conditions. Instead, using methanesulfonyl chloride in pyridine, selective activation of the secondary hydroxy-group of (**14**) in the presence of the tertiary

alcohol was achieved. Subsequent elimination using DBU facilitated stereoselective generation of the Z-olefin product (**15**) in 88% yield. Methanesulfonyl chloride activation of serine and threonine derivatives have been employed strategically in the synthesis of dehydroalanine and dehydrobutyrine building blocks that are characteristic parts of lanthibiotic compounds.³⁹ The use of phenyl triflimide has been reported in dehydration of N-protected β -hydroxy- α -amino esters, although this methodology has seen limited use after the initial report.⁴⁰ While the transformation of alcohol moieties into the corresponding triflate, mesylate, ethylsulfonate or tosylate is a facile process, as discussed above, the nucleofugal predisposition does not automatically favor an elimination reaction, with intra- and intermolecular substitutions being another common application of sulfonate ester derivatives. The E2 reaction pathway is typically enabled by strong base, but careful control of reaction concentration may also be decisive for achieving efficient elimination reactivity. Currently, dehydration through the formation of a sulfonate ester is the preferred/default strategy for transformation of alcohols to olefins. While site-selective dehydration is possible in medium-complexity substrates (e.g. thiocilline I), the reactivity of sulfonyl chlorides and anhydrides offers poor compatibility with nucleophilic functionality, and consequently, this approach has limited utility in most high-complexity settings, such as late-stage functionalization of polyfunctional natural products. From our experience, the choice of sulfonylation conditions used, should be made carefully and consciously, instead of utilizing methanesulfonyl chloride in combination with triethylamine by default. Furthermore, the access to elimination reactivity over cyclodehydration or substitution can be exceptionally challenging to control.

2.5 Martin's sulfurane

The reactivity of a dialkoxydiphenylsulfurane⁴¹ as a dehydrating reagent was identified by J.C. Martin and this reagent, now known as Martin's sulfurane (**18**) (Scheme 6A), was first applied in reactions with simple alcoholic compounds.⁴² A subsequent report evaluated further details of the dehydration reaction.⁴³ Elimination reactions using Martin's sulfurane are practically simple to perform, but require inert conditions to maintain the integrity of the sulfurane, due to its hydrolytic lability. The hygroscopic nature of the reagent means that preparation of a stock solution of Martin's sulfurane in an appropriate anhydrous solvent (such as PhH, PhMe, CH₂Cl₂, CHCl₃) is advised to allow precise dosage of the reagent while limiting hydrolytic decomposition. Martin's sulfurane is distinguished by an inherent oxophilic propensity, that enables direct and selective dehydration of alcohols. Typical conditions employ a small stoichiometric excess of the sulfurane in methylene chloride or chloroform at varying temperatures depending on the reactivity of the substrate. Secondary and tertiary alcohols undergo facile elimination, whereas primary alcohols without acidic β -hydrogens may undergo substitution to generate unsymmetrical ethers through nucleophilic reactivity of the alkoxy-substituent from the native sulfurane.⁴² The elimination has been shown to be guided by an anti-periplanar transition state following a preferential E2-type mechanism in olefin formation for secondary alcohols, while evidence has also been presented that steric factors may dictate elimination through a mechanism

better described by an E1-type reaction.⁴² In short, elimination reactions using Martin's sulfurane operates in a continuum from E1-type (e.g. elimination of *tert*-butanol) to preferential anti-selective E2-type reactivity, which is e.g. observed in peptide-based systems, and the stereoselectivity is best assumed to be substrate dependent. Furthermore, as the transformation of **(16)**, illustrated in Scheme 5 shows, small differences may bias a substrate towards competing (here cyclodehydration) reaction pathways.⁴⁴

Scheme 5: Martins sulfurane delivers both olefin formation and cyclodehydration in a trimeric peptide substrate **(16)**, to showcase the acidity required for facile elimination instead of the competing cyclodehydration reactivity.

When the C-terminal acyl-moiety of an amino acid residue is bound as an amide, the α -proton is significantly less acidic than for the corresponding amino ester derivative. This change in substrate acidity obstructs the elimination pathway. The increased difficulty of dehydration in peptide sub-

Scheme 6: A) Dehydration reactions of the Burgess reagent and Martin's sulfurane towards compounds derived from structural simplification of gracillin A. B) Site-selective dehydration of both *threo*-configured bis-alcohols (**25a**), (**25b**) afforded the *Z*-alkene (**26**) through utility of Martin's sulfurane during synthetic preparation of resormycin. C) Site-selective dehydration of a poly-chlorinated bis-alcohol (**27**) during the total synthesis of the complex chlorosulfolipid mytilipin B.

structures, relative to the elimination in monomeric amino ester substrates is a recurring observation in dehydroamino acid synthesis.

Conformational preferences in peptide-derived structures and relative stereochemistry of substituents also guide reaction pathways in formal dehydrations, but these effects are inherently substrate dependent and not easily delineated. Dehydration using Martin's sulfurane has been adopted into natural product synthesis in a number of instances. In the recent conceptual

demonstration of pharmacophore-directed retrosynthesis applied to gracillin A, dehydration of similar tertiary alcohol variants **(19)**, **(21)**, **(23)**, produced by a synthesis-defining fragment coupling, was required (see Scheme 6A).⁴⁵ Martin's sulfurane proved to selectively produce one regioisomeric alkene in >19:1 regioisomeric ratio to furnish **(20)**, and **(22)**, while selectivity was largely absent utilizing the Burgess reagent with **(23)** as the dehydration substrate. The profound difference in regioselectivity of olefin formation between the Burgess reagent and Martin's sulfurane in these systems is interesting and may follow from a combination of reagent-determined elimination geometries and conformational preferences of the central cyclohexane ring in **(19)**, **(21)** and **(23)**. For instance, the lack of an aligned syn-periplanar relationship between the alcohol and a β -proton may hamper the selective function of the Burgess reagent (see more details about Burgess reagent below). By an equivalent hypothesis, two protons in pseudo-axial positions in **(19)** and **(21)** are aligned in anti-periplanar fashion for reaction with Martin's sulfurane, but the clear favoring of one olefin product (either **(20)** or **(22)**) is not easily rationalized. Martin's sulfurane has been utilized for the stereoselective formation Z- Δ lle containing peptides through an anti-selective E2 dehydration reaction.⁴⁶ In the report from Ma et. al, the mechanistic details of the elimination reaction with Martin's sulfurane was analyzed by computational methods to suggest a highly asynchronous anti-configured transition state, likely with involvement of the (bis-trifluoromethyl)benzyl alkoxide expelled from Martin's sulfurane, by substitution at sulphur. Intriguing solvent effects, resulting in variable ratios of stereoisomeric olefin products, were observed in elimination reactions during Gais and coworkers' studies of total synthesis of (+)-3-oxacarbacyclin.⁴⁷ Martin's sulfurane has been employed successfully to effect regioselective and stereoselective dehydration to olefins as shown above, but selectivity preferences of the reagent in polyol substrates is not well documented, although recent examples have shown that selective dehydrations in complex bis-alcoholic substrates is feasible.^{48–50} In the synthesis of resormycin, the simultaneous dehydration of both *threo*-isomeric benzylic alcohols **(25a)**, **(25b)** converged upon a single Z-configured olefin **(26)**, in a site-selectivity dehydration mediated by Martin's sulfurane (Scheme 6B).⁴⁹ Recently, Martin's sulfurane was employed in site-selective dehydration of a bis-alcohol substrate **(27)** during the total synthesis of the complex chlorosulfolipid mytilipin B, to selectively construct an E-configured olefin **(28)**.⁵⁰ Martin's sulfurane is commercially available or can be prepared following the detailed preparation published.⁵¹ Notably, vicinal diols have been demonstrated to react cleanly into epoxides, through a partial cationic intermediate that is trapped by an appropriately positioned alcohol.⁵² Similar chemistry has been harnessed in complex transformations through elaborate cyclic sulfurane intermediates.⁵³ Collectively, Martin's sulfurane is a reagent that clearly can provide very useful levels of selectivity even amongst hydroxy groups of very similar nature. Although the commercial reagent is nearly exclusively used, it is useful to keep in mind, that several different versions of this reagent has been reported previously and their performance in complex dehydrations remains largely unknown.⁴³

2.6 Burgess reagent

The Burgess reagent (**29**) (see Scheme 7A) is an inner sulfamate salt that functions to eliminate secondary and tertiary alcohols under neutral conditions.⁵⁴ Practical and mild dehydration is characteristic for the Burgess reagent. Mechanistically, the sulfur atom of the sulfamate is attacked by an incoming alcohol in formation of a sulfamate ester salt under expulsion of triethylamine, and this intermediate may undergo stereospecific syn-elimination to furnish an alkene product, usually requiring heat treatment to facilitate elimination. Contrary to Martin's sulfurane, Burgess' reagent generally delivers syn-selective dehydration (i.e. in the generation of **(31)** depicted in Scheme 7A), but the reactivity profile is similar to Martins' sulfurane, in that tertiary alcohols react faster, but olefin formation may offer greater stereoselectivity for secondary alcohols. A protocol for the preparation of the Burgess reagent and an application for urethane synthesis has been published.⁵⁵ In similarity with Martin's sulfurane, Burgess' reagent performs well in elimination reactions that present the retron for aldol-type chemistries. Based on detailed mechanistic studies performed by Burgess, using the sulfamate ester derived from 1,2-diphenylethanol as a model system, a rate-limiting ion-pair formation followed cis- β -proton transfer to the anionic species being expelled in the elimination step was hypothesized. The elimination did not appear to allow interconversion between *erythro*- and *threo*-configured ion pairs in the model system, thus allowing stereoselective formation of either trans- or cis-stilbenes.⁵⁶ Structural manipulations of the Burgess reagent have been made to improve the thermal stability of the reagent, to permit maintained reactivity at elevated temperatures.⁵⁷ Chiral variants of the Burgess reagent also exist and have been utilized for generation of chiral α -amino alcohols in stereoselective fashion.⁵⁸ Burgess' reagent functions to allow cyclodehydration in amide substrates by engaging the nucleophilic reactivity of amides, through oxygen, in formation of heterocyclic ringsystems as given by the transformation from **(32)** to **(33)** (see Scheme 7B) which is a convenient approach to oxazoline derivatives from serine- or threonine-derived precursors.^{59,60}

Scheme 7: Diverse utility of the Burgess reagent **(29)** in various chemical transformations. A) Syn-selective dehydration of an alcohol, as exemplified by the transformation from alcohol **(30)** to olefin **(31)**. B) Cyclodehydration of threonine derivative **(32)** to the corresponding oxazoline **(33)**. C) urethane synthesis to prepare **(36)** from primary alcohol **(34)**, using a modified variant of the Burgess reagent **(35)**.

Cyclodehydration mediated by Burgess' reagent and subsequent hydrolysis allows stereospecific interconversion of threonine and D-allo-threonine through the sequence reported by Wipf.^{61,62}

This method for access to, the less abundant, D-allo-threonine was later utilized to prepare the cyclopeptide lissoclinamide 7.⁶³ Primary alcohols form intermediate sulfamate esters by treatment with Burgess' reagent, but yield carbamate products by substitution (see the transformation from **(34)** to **(36)**, Scheme 7C).⁵⁷ This reactivity allows direct conversion of primary alcohols, to carbamate-protected amines, where the N-protection is decided by the utility of various Burgess-type reagents, such as **(35)**. Dehydration of α -hydroxymethyl tetrahydrofurans, to prepare 2-vinyl-tetrahydrofurans, has been investigated in the search for chemistries that enable synthesis of tetrahydrofuran-containing natural product motifs. An exemplary α -hydroxymethyl tetrahydrofuran **(37)** was employed as a model system for dehydration, attempting to selectively afford the 2-vinyl-tetrahydrofuran motif of **(38)**, over the alternative alkylidene derivative **(39)**. The substrate **(37)** is prepared by oxidative cyclization of geranyl benzoate, followed by benzylation of the resulting secondary alcohol.⁶⁴ Sampling of various classical acidic reagents (H_2SO_4 , KHSO_4 , ZnCl_2 , P_2O_5) was conducted in search of elimination reactivity, but product formation was only observed using refluxing conditions of KHSO_4 (see Table 1), but this reaction was still sluggish and low yielding. Table 1 is adapted from the results published by Gross and Stark.⁶⁵

Entry	Reagent	Eq.	Solvent	Temp.	Time	Yield ((38))	Ratio 38:39
1	KHSO_4	2.0	PhMe	110 °C	96 hrs	25%	-
2	Martin's sulfurane	1.0	CH_2Cl_2	0 °C	15 hrs	51%	-

3	Martin's sulfurane	2.5	CH ₂ Cl ₂	0 °C	15 hrs	55%, 30% (39)	1.8:1 ^a
4	Burgess reagent	3.0	PhMe	110 °C	5 min.	39%	-
5	Burgess reagent	4.0	PhMe	110 °C	20 min.	37%	>20:1 ^b
6	Burgess reagent	2.0	PhMe	110 °C	30 min.	65%	15.1 ^b
7	Burgess reagent	2.5	PhMe	75 °C	20 min.	62%	>2:1 ^b
8	Burgess reagent	2.0	1,4-dioxane	rt	140 min	55%	3:1 ^b
9	Burgess reagent	2.0	1,4-dioxane	μwave, 150 °C	3 min.	68%	9:1 ^b
10	Burgess reagent	2.0	1,4-dioxane	μwave, 150 °C	1 min.	55%	8:1 ^b

Table 1: Dehydration reaction upon α-hydroxymethyl tetrahydrofuran (**37**) using various conditions, leading to an optimal protocol for preparing (**38**) using the Burgess reagent under microwave conditions.^a:Ratio of isolated products. ^b:Ratio determined by GC analysis.

Subsequently, the Burgess reagent and Martin's sulfurane were tested and found to facilitate elimination of (**37**) with improved reaction rates (Table 1, entry 2-4). Utilizing 1.0 equivalent of

Martin's sulfurane in dichloromethane at 0 °C delivered the desired 1,2-disubstituted alkene (**38**) in 51% yield after 15 hours of reaction time, with reisolated 41% of the starting material (**37**). Adjusting the stoichiometry of the sulfurane to 2.5 equivalents delivered full conversion of the starting material (**37**), and produced the desired product (**38**) in 55% yield. However, increased stoichiometry of the sulfurane resulted in generation of the undesired olefin regioisomer (**39**) in 30%, giving below 1.8:1 selectivity for the desired product (Table 1, entry 3). By comparison, the Burgess reagent (3.0 equiv) provided full selectivity for the 2-vinyl-tetrahydrofuran (**38**) but in only 39% yield (Table 1, entry 4). The conditions were then investigated further to potentially increase the yield. Different stoichiometries under refluxing conditions in toluene were sampled and curiously 2.0 equivalents of the Burgess reagent actually provided the best result (Table 1, entry 6). Thus, the regioselectivity of olefin formation was dependent on the stoichiometric excess of the reagent which suggests a complex involvement of the Burgess reagent during the elimination process. The regioselectivity of olefin formation was also found to be solvent dependent, with the best results observed in 1,4-dioxane. As extensive heating had a detrimental effect on the reaction, the dehydration was developed further by using a microwave reactor. The optimal conditions employed 2.0 equivalents of the Burgess reagent heated to 150 °C in a microwave reactor for 3 minutes. These conditions were extrapolated for use in a diverse set of substrates with good to excellent yields of 2-vinyl-tetrahydrofuran derivatives. An excerpt of the dehydration reactions reported, are presented in Scheme 8.

Scheme 8: Dehydration reactions using the Burgess reagent in elimination of tertiary alcohols under microwave conditions.

Examples of unexpected reactivity has been observed in dehydrations with the Burgess reagent, such as ring expansion chemistry of **(48)** or dehydrative cyclization of a hydroxylated N-oxide derivative **(50)** (Scheme 9).^{66,67} More recently, the oxidative potential of the Burgess reagent has been explored through reactivity similar to the Pfitzner-Moffatt conditions and other new uses for the reagent have been demonstrated in formation of cyclic sulfamides and sulfamides from 1,2-substituted amino alcohols or diols.^{68,69} The reagent has also been employed for conversion of Bayliss-Hillman adducts into carbamates.⁷⁰

Scheme 9: Unexpected reaction products in formal dehydrations using the Burgess reagent. A) Rearrangement to a cycloheptatriene derivative (**49**) from a secondary alcohol (**48**) facilitated by the Burgess reagent. B) Intramolecular cyclization of an N-methyl-N-oxide (**50**) to an oxazolidine derivative (**51**), most likely through a dehydration/addition pathway.

Ostensibly, the Burgess reagent enables a palette of interesting chemical transformations that are remarkably diverse. The reagent, however, is susceptible to nucleophilic substitution, meaning that it does not allow tractable dehydration of alcohols in substrates that contain other nucleophilic functionality. This disadvantage of the Burgess reagent follows from the inherent electrophilic reactivity of the sulfamate, and the Burgess reagent has been characterized to react with carboxylic acids,⁷¹ thioureas,⁷² epoxides,⁵⁸ thiols,⁷³ amines⁶⁸ and amides^{74,75} alike. This suggests that the reagent is not a general and chemoselective dehydration agent with potential applicability in very complex molecular scaffolds. The chemistry possible using the Burgess reagent is, however, captivating and the zwitterionic nature of the reagent could perhaps inspire design of new dehydration methods.

2.7 Grieco-Sharpless elimination

An elimination approach investigated in the 1970's both by the laboratories of Grieco and Sharpless, utilizes alkyl aryl selenides as intermediates in the synthesis of olefins. Notably, electron deficient alkyl aryl selenides were found to be suitable precursors for olefin formation.⁷⁶ The alkyl aryl selenide species were demonstrated to be directly accessible from alcoholic compounds using *o*-nitrophenyl selenocyanate (**56**), (see Scheme 10) in combination with a nucleophilic phosphine.

This procedure is now termed the Grieco-Sharpless elimination.⁷⁷ Mechanistically, the generation of an alkyl aryl selenide proceeds through attack of tributylphosphine onto the selenium atom of **(56)** to expel a cyanide equivalent, with generation of a selenylphosphonium species **(52)**. Subsequent attack of an alcohol onto phosphorus generates an oxaphosphonium ion **(54)** and 2-nitrobenzeneselenolate **(53)** using cyanide as a base (see Scheme 10A). These two species, **(53)** and **(54)** then react to form an alkyl aryl selenide and tributylphosphine oxide. The installation of the alkyl aryl selenide likely occurs with inversion. The typical reaction proceeds as a two-step procedure where the intermediate alkyl aryl selenide may be isolated chromatographically or directly treated with an oxidant, typically aqueous hydrogen peroxide, to generate an aryl selenium oxide that allows pericyclic and stereospecific intramolecular syn-elimination in E_i fashion.⁷⁸ The pericyclic E_i elimination mechanism of the Grieco dehydration is the signature characteristic of this dehydration method and the elimination mechanism is related to the Cope elimination, where an N-oxide functions to facilitate concerted and pericyclic syn-elimination. Site-selectivity of the reaction is controlled by the nucleophilic reactivity of alcohols, also in polyol substrates. Therefore, the Grieco dehydration allows selective elimination of the sterically most accessible alcohol, which has been exemplified by the selective dehydration of primary alcohols in the presence of either secondary or tertiary alcohols, or by dehydration of secondary alcohols

in the presence of tertiary alcohols. Representative examples of site-selective dehydration in either bis-alcohol (Scheme 10B) or tris-alcohol substrates (Scheme 10C) are depicted below.^{79,80}

Scheme 10: A) Generation of an oxaphosponium intermediate **(54)** during the Grieco-Sharpless elimination. B) Selective elimination of the primary alcohol **(55)** towards the synthesis of merrilactone A. C) The more accessible primary alcohol was selectively addressed using the Grieco dehydration in the triol-derivative **(59)** in synthetic studies towards synthesis of penitrem E.

Elimination reactions from primary alcohols are the most common application of the Grieco dehydration and benchmark examples may be found in the literature.^{81–85} As the oxaphosponium ions, such as **(54)**, of secondary or tertiary alcohol are sterically less accessible, these

intermediates may complicate construction of the alkyl aryl selenide. In studies geared towards the synthesis of the chartelline C core, elimination of the secondary hydroxyl in **(62)**, was problematic, as all sampled conditions favored substitution over elimination (see Scheme 11A).⁸⁶ Even Martin's sulfurane and Burgess' reagent did not afford elimination reactivity, but again engendered substitution products. Although an arylselenide could be introduced to furnish **(63d)**, the oxidation step returned the starting material alcohol **(62)** without formation of the desired elimination product. Thus, a resonance-stabilized intermediate enabled by the electron-rich imidazole, hindering elimination to the desired alkene, was hypothesized and ultimately circumvented by exchanging the SEM-protecting group on the imidazole-moiety of **(63d)** to an electron withdrawing benzoyl-group. The protecting group manipulation from **(63d)** through **(64)**, allowed subsequent elimination in construction of **(65)** (see Scheme 11B). The peroxides utilized in the oxidation of selenium impact the functional group tolerance of the Grieco dehydration, as these oxidants may cause unwanted reactivity themselves.

Scheme 11: A) Stabilization of a cationic species complicated elimination of the secondary alcohol in **(62)**, during the synthesis of the core structure of chartelline C, and caused the isolation of undesired substitution products **(63a-c)**. B) Switching the electronic induction of the imidazole protecting group allowed facile elimination using the Grieco dehydration to an olefin derivative **(65)**.

Likely being a consequence of the overall predictability and the absence of competing intra- and intermolecular substitution processes, the Grieco dehydration method is predominant for generation of alkenes from primary alcohols in natural product synthesis. The possibility for distinguishing alcohols based on steric congestion is well documented and compelling, but, to our knowledge, the Grieco dehydration has not been reported to differentiate between primary alcohols in polyol compounds. The reagent, perhaps with bespoke modifications, could potentially be used in even more challenging situations.

2.8 CuCl/Carbodiimide conditions

The reactivity of carbodiimide species in combination with copper chloride salts function to deliver O-alkylisourea intermediates for dehydroalanine preparation as was demonstrated by Miller (see Scheme 12). In the initial report, various carbodiimide reagents were demonstrated to allow dehydration of monomeric serine and threonine derivatives, and the presence of a copper additive was found compulsory for dehydration to proceed.⁸⁷ These conditions have seen almost exclusive use in peptide-based structures. The use of water-soluble carbodiimides may ease the purification of the reaction products, by efficiently removing both the copper salt and the urea by-products formed from the carbodiimide by an aqueous wash. The CuCl/carbodiimide dehydration reaction is commonly performed upon monomeric amino acid derivative such as **(66)** before standardized coupling chemistries enables incorporation into more elaborate molecular structures, using dehydroamino acids to rigidify peptide scaffolds or as precursors to cysteine bridges.

Scheme 12: Modular dehydroamino acid building blocks such as **(68)** are conveniently prepared using EDCI/CuCl conditions to allow their incorporation into peptidic compounds following the approach

reported by Miller. The dehydration conditions allow formation of an intermediate O-alkylisourea (**67**), that undergoes subsequent elimination.

Both application of catalytic Cu(I) and Cu(II) sources have been reported. Application of CuCl₂ and EDC was employed at a late stage in the formation AB-dicarba analogs of nisin and allowed simultaneous elimination of the two hydroxy-groups in (**69**), to stereoselectively construct the Z-configured dehydrobutyrine derivative (**70**) (see Scheme 13A).⁸⁸ The use of DBU in generation of (**70**) allowed more expedient elimination from isourea intermediates generated from (**69**), but is generally not required. In the synthesis of macrocyclic precursors of the vioprolides, which are depsipeptidic macrocyclic natural products containing (E)-dehydrobutyrine and thiazoline moieties, the dehydration from threonine derivatives (**71**) and (**74**) was performed using CuCl₂ and EDC to engender (E)-dehydrobutyrine products (**73**) and (**76**) (Scheme 13B).⁸⁹ The converse (Z)-dehydrobutyrines (**72**) and (**75**) were constructed through an intermediate sulfonate ester, or by the action of DAST in pyridine. Notably, the (E)-dehydrobutyrine residue of the vioprolides could not be generated in the macrocyclic structure, perhaps due to steric clash with a proximal proline residue, and the coupling of the pre-installed (E)-dehydroamino acid did not proceed. The CuCl/carbodiimide conditions have been examined for utility in solid phase peptide chemistry to furnish dehydroamino acid containing peptides.^{90,91} The CuCl/carbodiimide conditions offer generation of O-alkylisourea intermediates before elimination of an urea by-product affords the alkene product. The chemical selectivity in activation of the alcohol is different from other dehydration strategies, with the most notable distinction being that the conditions appear to function predictably in peptide substrates with the C-terminal acyl moiety bound as an amide. Therefore, these conditions are appropriate for the direct modification of peptides that bear serine or threonine as dehydroamino acid precursors. The CuCl/carbodiimide conditions typically function without stoichiometric addition of a nitrogenous base, which should render the

Scheme 13: A) Late-stage dehydration of a bis-alcohol (**69**) during synthesis of AB-dicarba analogs of nisin. B) Synthetic preparation of dehydrobutyrine derivatives in synthesis of macrocyclic precursors of the vioprolides was achieved using EDC/CuCl, DAST/pyridine and Et₃N/MsCl reagent combinations. The choice of conditions allowed access to either Z- or E-configured olefin products.

conditions tractable in compounds bearing base-labile functionality. However, the conditions are not applicable in the presence of other functional groups that react with carbodiimide reagents.

2.9 Activation by acylation

Acylation of alcohols allows for the generation of esters that may undergo elimination with release of a carboxylate with concomitant olefin formation. Both acetates and benzoates have been utilized for olefin synthesis though functionalization of alcoholic moieties, typically in the form of electron deficient acyl-moieties. The tunable reactivity in elimination of acetate esters with varying degrees of halogenation has enabled dehydration of alcohols to olefins in two step approaches by esterification followed by base treatment.⁹² Acetyl synthons may be installed using acetyl chlorides or anhydrides in combination with a base, to neutralize the acid generated upon esterification. Like the Burgess reagent and sulfonylation of alcohols, acylation chemistries require preferential nucleophilic reactivity of the alcohol targeted for elimination. In principle, acylation of multiple alcohols in a substrate followed by selective elimination is possible, but quickly becomes a fickle endeavor, that compromises synthetic efficiency. A procedure that utilizes acetate-functionalized alcohols for elimination using DBU in combination with lithium perchlorate

is a generally applicable dehydration method to access dehydroamino acid motifs.⁹³ This approach was e.g. utilized in the first synthesis of the antifungal cyrmenins, that have also been characterized as inhibitors of electron transport in the respiratory chain.⁹⁴ As depicted in Scheme 14, an elimination attempt upon the primary alcohol of **(77)** via the mesylate, delivered only cyclodehydration to an oxazoline derivative **(78)**. Instead, efficient acetylation of the primary alcohol in **(77)** and subsequent elimination furnished (8E,10E)-cyrmenin B₁ **(80)**.⁹⁵

Scheme 14: Elimination through an acetate-derivative **(79)**, followed by treatment with lithium perchlorate and DBU to facilitate elimination.

2.9.1 Oxalyl chloride

In similarity with acetylation chemistries, oxalyl dichloride has been utilized to effect direct elimination, most prominently through the method reported by Ranganathan and coworkers.⁹⁶ Classically, oxalyl chloride functions as a chlorination reagent upon alcohols, and its utility for elimination may be difficult to segregate between a halogenation/dehydrohalogenation or a direct elimination approach. Ranganathan and coworkers suggests collapse of a chloro-oxalate intermediate in olefin formation, meaning that the reaction should proceed without going

through the alkyl chloride. The elimination reaction is selective for serine residues over threonine and does not afford elimination if the acyl-moiety of a serine residue is bound as an amide. The methodology is applicable upon serine-derived amino esters in peptide substrates. The mild conditions are reportedly compatible with methionine, suggesting compatibility with substrates that are cross-linked by disulfides bridges.

2.9.2 Activation by phosgene variants

Dehydration reactions have been explored utilizing structural equivalents of phosgene containing a symmetrically disubstituted carbonyl moiety either as the di-*tert*-butylcarbonate, di-succinimidylcarbonate (DSC) (**86**) or carbonyl di-imidazole in combination with a base. This type of reagent functions by activating an alcohol to a mixed carbonate species that can then undergo elimination. A number of reports display the utility of di-*tert*-butylcarbonate in combination with DMAP to activate serine into a mixed carbonate, followed by treatment with tetramethylguanidine to effect elimination to dehydroalanine containing motifs (see Scheme 15A).^{97–100} The reactivity of carbonyl di-imidazole has been investigated to indicate a requirement of sufficiently acidic protons positioned on the α -carbon of β -hydroxy amino acid residues in dehydration.¹⁰¹ Dehydration of C-terminal serine derivatives with methyl ester protection of the carboxyl moiety afforded the corresponding dehydroalanine residue, whereas serine-containing dipeptides with the C-terminal acyl-moiety bound as an amide did not undergo dehydration. Efficient access to dehydroamino acid derivatives have also been demonstrated by Ramapanicker through anti-selective E2-elimination of serine or threonine-derived carbonate derivatives, such as (**88**), in combination with TBAF (see Scheme 15C).¹⁰² The efficient reactivity of this dehydration method was proposed to exploit the basicity of poorly solvated fluoride ions supplied from TBAF. The results of Ramapanicker and coworkers indicate that the properties of the applied base are critical to enable efficient elimination, and perhaps the combination of basicity and poor nucleophilicity separates the fluoride anion from the nitrogenous bases (such as DBU, DIPEA, triethylamine etc.) typically employed in base-induced eliminations.

Scheme 15: Representative dehydration conditions through transformation of alcohols into mixed carbonate derivatives, followed by base-induced elimination. A) Synthesis of dehydroamino acid derivative (**84**), using Boc_2O followed by treatment with tetramethylguanidine (**83**). B) Generation of the APD-CLD natural product rakicidin A (**87**) using di-succinimidylcarbonate (**86**) and DIPEA. C) Elimination of an ethylcarbonate derivative (**88**) using TBAF.

The report by Ramapanicker and coworkers includes one substrate being a serine residue bound as a C-terminal amide (see Scheme 15C), and it is unclear whether the conditions allow dehydration from carbonate derivatives in more elaborate peptide backbones or if the conditions

have better utility in monomeric amino ester substrates. In similar fashion, di-succinimidyl carbonate in combination with tertiary amine bases has been demonstrated to enable efficient dehydrations of alcohols.^{103–106} In our laboratory's efforts to construct members of the 4-amido-2,4-pentadienoate (APD) bearing cyclolipodepsipeptide (CLD) natural products, such as rakicidin A (**87**) (see Scheme 15B), we have employed the combination of DSC and DIPEA to construct the trademark exocyclic double bond present in these natural products.¹⁰⁶ In the synthesis of rakicidin A, the elimination process requires selectivity between the secondary alcohol of the hydroxy-asparagine motif in the southern part of the molecule and the primary alcohol that must be eliminated to construct the APD-functionality. The elimination process that engenders rakicidin A is low yielding, regardless of dehydration conditions employed, likely a consequence of the poor stability of the natural product. The mixed carbonate activation mode has afforded site-selective dehydration in construction of rakicidin A and remains our conditions of choice in formation of the APD-moiety from the corresponding alcohol. The difficulty of obtaining selective dehydration is apparent from the unintentional dehydration of the hydroxy-asparagine moiety which occurred in preparation of a rakicidin-derived alkyne probe, that was utilized for "click chemistry" purposes.¹⁰⁷ Notably, in other syntheses of APD-CLD natural products, studied by us, as well as others, the final dehydration may be accomplished through sulfonate-ester intermediates.^{108–110}

2.9.3 Dehydrations in lanthipeptide biosynthesis

The synthesis of olefinic compounds relying on initial acylation of alcohols is not only performed by synthetic chemists, but also occurs in the biosynthetic construction of lanthipeptide natural products. Lanthipeptides are members of the ribosomally synthesized and post-translationally modified peptides (RiPPs) where nisin is most prominent example. They are characterized by the presence of lanthionine (Lan) and methyllanthionine (MeLan) – a sulfide crosslink between the sidechain of cysteine and dehydrated serine or threonine. The installation of Lan or MeLan requires several steps: activation of the hydroxyl group, elimination to dehydroalanine or dehydrobutyrine, and cyclization by nucleophilic attack of a cysteine-derived thiol. The activation can happen in two different ways. The first is exemplified in the biosynthesis of nisin, where studies by Otega et al. demonstrated that the dehydrating enzyme NisB recruits glutamyl-tRNA^{Glu} and transfers glutamate to the sidechain alcohol by a transesterification.¹¹¹ This creates a suitable leaving group for the subsequent elimination combined with an extraction of the α -proton. The second option is a phosphorylation. In 2004, Xie et al., showed that LctM required both ATP and Mg²⁺ when installing lanthionines in lactacin 481 biosynthesis (see also Scheme 1B).¹⁷ In a subsequent study, it was shown that LctM can eliminate a phosphorylated threonine in synthetic substrates *in vitro*, providing compelling support for a mechanism that uses ATP to phosphorylate the side chain alcohols and thereby priming them for elimination.¹¹² In RiPP biosynthesis, dehydratase enzymes are characterized by decoupling of enzymatic substrate recognition and dehydratase function. Substrates are recognized through a leader sequence, and subsequently, the dehydratase modifies the core peptide of the RiPP. This makes the dehydration fairly

promiscuous, as most, if not all, serine and threonines in the core peptide are dehydrated. A detailed discussion of the enzymatic mechanisms has been covered previously.¹¹³

2.10 Mitsunobu dehydration

The Mitsunobu reaction utilizes the combination of an alcohol, an acidic nucleophile, a phosphine and an azodicarbonyl derivative (DEAD, DIAD, ADDP etc.) to further substitution of an alcohol moiety with inversion of stereochemistry.^{114,115} The reaction is a powerful tool for stereospecific substitution processes, but side-reactivity observed in substitution reactions, for example in preparation of serine-derived azides, has been observed under the standard displacement conditions.¹¹⁶ The niche application of various reagent combinations and even catalytic Mitsunobu reactions have been reported,^{117–119} but the targeted development of Mitsunobu-type elimination has not been investigated thoroughly. Similar sulfonylation and alkyl halide elimination methods, the Mitsunobu elimination requires the absence of nucleophilic moieties that may interfere with the desired elimination reaction pathway by preference of intra- or intermolecular substitution processes. For instance, the dehydration of β -hydroxy carboxylic acids allows stereoselective synthesis of olefins through dehydrative decarboxylation mediated by triphenylphosphine/DEAD.¹²⁰ This transformation has found application in also more elaborate substrates, as exemplified in Scheme 16, where the dehydrative decarboxylation of β -hydroxycarboxylate (**90**), stereoselectively afforded (**91**) during the synthesis of the proteasome inhibitor TMC-95A.¹²¹

Scheme 16: Grob-type anti-elimination of a β -hydroxy acid derivative prepared from **(90)** by deprotection of the benzyl ester and subsequent anti-selective elimination to afford **(91)**.

Formally, the Mitsunobu reaction always delivers dehydrative transformations, either in intra- or intermolecular fashion, but dehydration of alcohols to alkene products has also been demonstrated. The stereoselective generation of Z-alkene products by anti-selective elimination was a critical requirement in the studies performed by Brückner, that targeted all Z-configured polyunsaturated butenolides towards a strategy for assembly of γ -alkylidenebutenolides, such as the apocarotenoid pigment peridinin.^{122,123} The Mitsunobu-type dehydration was been used to good effect upon allylic alcohols of butenolide derivatives, such as **(92)**, which is presented in Scheme 17, with access to preferential anti-elimination. The elimination of the allylic alcohols in these systems was reportedly functional, when other, perhaps most standard, conditions failed to deliver the desired anti-selective reactivity.

Scheme 17: Anti-selective dehydration using Mitsunobu-type condition allows stereoselective generation of Z-configured butenolides.

Mitsunobu-type conditions were also applied to a number of related substrates in the stereoselective synthesis of the acetylenic sesquiterpenoid freelingyne and other related γ -alkylidenebutenolide compounds.¹²⁴

2.11 Direct eliminations using halogenation reagents

Alkene formation from alcohols may utilize halogenation/elimination sequences as a general approach. Indeed, a diverse manifold of chemistries enable functional group interconversion between alcohols and the corresponding alkyl halides. Subsequent treatment with base is a viable approach to alkene derivatives. We will not review general reaction conditions that enable halogenation from alcohols, followed by base induced elimination, as these methods likely will not allow direct modification of highly complex substrates. Instead, we have opted to limit our discussion of dehydrations using halogenation reagents that allow direct dehydration without going through alkyl halide intermediates, with the exception of methyltriphenoxyposphonium iodide because this reagent offers selective dehydration of secondary alcohols.

2.11.1 Methyltriphenoxyposphonium Iodide

The application of methyltriphenoxyposphonium iodide (**95**) in hexamethylphosphoramide (HMPA), to selectively dehydrate secondary alcohols with predominant formation of the Saytzeff product has been reported.¹²⁵

Scheme 18: Dehydration of *cis*-2-methyl-cyclohexanol (**94**) using methyltriphenoxyposphonium iodide (**95**) in HMPA, preferentially affords the Saytzeff product (**96**) along with trace amounts of the Hoffmann product (**97**).

Iodide-facilitated equilibration towards the thermodynamically favoured alkene product was speculated based on the stereochemistry of the olefin products obtained. Primary alcohols are converted to iodides using methyltriphenoxyposphonium iodide but the relatively mild conditions only allow the subsequent dehydrohalogenation step to proceed efficiently for secondary alcohols. The dehydration of secondary alcohols, was evaluated using an array of alcohol substrates that contained no other heteroatomar functionality. Notably, this method employs stoichiometric quantities of HMPA which is undesirable due to the carcinogenic character of this substance.¹²⁶ The utility of methyltriphenoxyposphonium iodide, without use of HMPA, was demonstrated in a reported synthesis of Δ^6 -estrogens, where dimethylformamide was employed as the solvent in the dehydration reaction. The methyltriphenoxyposphonium iodide approach proved slightly more efficient than Martin's sulfurane in elimination of the secondary, and benzylic, alcohol that was dehydrated in the report.¹²⁷

2.11.2 Thionyl chloride

The dehydration of alcohols using thionyl chloride is a common way to facilitate elimination. Especially tertiary alcohols are amenable to elimination by treatment with thionyl chloride. Thionyl chloride classically affords conversion of an alcohol to the corresponding alkyl chloride, before dehydrohalogenation may take place in olefin formation. While examples of dehydrations are many using thionyl chloride and concurrent dehydration of multiple hydroxy-group has been reported through intermediate chlorination,¹²⁸ site-selective dehydration does not appear feasible using thionyl chloride. The generation of cyclic sulfamidites (**100a-e**) from N-protected β -hydroxy amino esters (**99**) using thionyl chloride allows subsequent elimination using stoichiometric DBU through the method developed by Stohlmeyer, Tanaka and Wandless¹²⁹ during preparation of the tripeptide side-chain of phomopsin A (**98**) (see Scheme 19A).¹³⁰ The cyclic sulfamidite controls the conformation of the elimination substrate while the irreversible nature of the entropically favoured elimination step ensures stereospecific elimination to dehydroamino acid derivatives (**101a-e**). The elimination step occurs in anti-periplanar fashion and allows the predictable generation of Z- or E-alkene products depending of the stereochemistry of the cyclic sulfamidite such as (**100a-e**). The compatibility of the method and

various N-protection groups was evaluated (see Scheme 19B), and stereoselective generation of the Z- Δ lle motif of phomopsin A was also feasible. A one-pot operation to dehydroamino acids was developed and generally afforded slightly better overall yields than the sequential process. However, this method appears to suffer, when the C-terminal acyl-moiety is bound as an amide, likely due to the decrease in acidity of the α -proton of the amino acid derivative. Scheme 19B shows an excerpt of the dehydroamino acids prepared by Stohlmeyer, Tanaka and Wandless.¹²⁹

Scheme 19: A) Chemical structure of phomopsin A (**98**). B) Stereoselective generation of dehydroamino acid building blocks (**101a-e**) through formation of cyclic sulfamidite compounds (**100a-e**).

2.11.3 Phosphoryl chloride

Phosphoryl chloride is another classical chlorination reagent functioning in a manner that is conceptually similar to that of thionyl chloride. For example, a report geared towards the synthesis of difluorinated analogues of shikimic acid, evaluated the regioselective elimination a secondary alcohol derivative (**102**) using Martin's sulfurane, phosphoryl chloride in pyridine, Burgess reagent and DAST (see Scheme 20).¹³¹ The secondary alcohol imposes a selectivity problem in dehydration as double bond formation may occur in either of two directions. Martin's sulfurane was found to selectively induce formation of the desired alkene product (**104**) in a ratio of approximately 30:1. Elimination using triflic anhydride, DAST, phosphoryl chloride and the Burgess reagent were also

evaluated but found to offer modest regioselectivity in olefin formation. These dehydration reactions were sampled and analyzed by ^1H -NMR of the crude reaction mixtures to assess the regioselectivity of olefin formation through integration of the signals observed for the vinylic hydrogens. Subsequently, a preparative scale experiment delivered the desired alkene product (**104**) in a yield of 84% using Martin's sulfurane following chromatography and recrystallization.

Scheme 20: Regiochemical preferences in olefin formation was critical during efforts to generate non-natural analogues of shikimic acid.

A related substrate (**105**), offered similar, and reasonably stereoselective dehydration, using either the Burgess reagent, phosphoryl chloride in pyridine, but resulted in an intriguing loss of selectivity using Martin's sulfurane relative to the selectivity observed using (**102**) as the substrate (see Scheme 21).

Scheme 21: Stereoselective dehydration of secondary alcohol derivative (**105**), applied in the preparation on non-natural analogues of shikimic acid.

The conformational preference of the bicyclic structure in (**102**) may dictate the regioselectivity of olefin formation, and the removal of one conformation-defining substituent can clearly have profound effects upon the stereoselectivity olefin formation by dehydration.

2.11.4 DAST

(diethylamino)sulfur trifluoride (DAST) is a fluorination reagent that has seen extensive use, and additionally, application of DAST in combination with pyridine was reported as a stereoselective method for dehydration of β -hydroxy amino acid derivatives in 1983, and was found to stereoselectively mediate elimination in threonine-derive structures.¹³² The reaction was proposed to occur by substitution at sulfur with expulsion of a fluoride in generation of a ROSF₂NEt₂ species as the enabler of elimination. As such, the elimination approach may occur without generation of an alkyl halide intermediate. In the total synthesis of somamide A,¹³³ which is a (3-amino-6-hydroxy-2-piperidone) containing cyclic depsipeptide, dehydrative elimination of an N-acyl threonine ester (**108**) to the corresponding Z-configured alkene (**109**) was evaluated using respectively, the two-step sulfamidite approach mentioned above, thionyl chloride in combination with triethyl amine, the Burgess reagent, DAST in combination with triethylamine, and Martin's sulfurane (see Scheme 22). Of these methods, DAST/NEt₃ was relatively efficient affording the product in 51% yield but Martin's sulfurane proved superior. The dehydration substrate (**108**) was found to be sensitive towards α -elimination of the O-acylthreonine moiety, which became apparent under treatment with DBU.

Scheme 22: Dehydration conditions tested during the establishment of a synthetic approach to somamide A.

2.12 Npys-derivatives

Our laboratory has explored the reactivity of nitro-pyridinesulfonyl (Npys) activation of alcohols and thiols for elimination reactions that can proceed in a sequential or one-pot operation in synthesis of alkene products.¹³⁴ Npys-chloride was reported as a stable sulfonyl halide and was subjected to development as a cysteine protecting group for solid phase peptide synthesis.¹³⁵ The direct exchange between classical cysteine protecting groups and the Npys-group has been utilized for application in elimination reactions, but the controlled assembly of disulfides in peptidic compounds has also been reported.^{136,137} Npys-Cl is now a commercially available reagent employed strategically in solid-phase peptide synthesis, through the remarkable acid stability of Npys-protected cysteine derivatives. While this reagent is underdeveloped as an activator for dehydration, we speculate that further utility is feasible and warranted by the studies performed to date. The intriguing chemical structure and the redox chemistry that may occur between the nitropyridine and the sulfenate of the Npys-group separates its reactivity from classical reagents for elimination reactions. However, the mechanistic details of Npys-mediated elimination reactions are not clearly elucidated and further studies are required to illuminate the fundamental chemistry of Npys-mediated elimination reactions.

2.13 Asymmetric dehydration for kinetic resolution of β -hydroxy esters

A kinetic resolution approach utilizing organozinc species has been demonstrated to allow enantioselective dehydration. The use of a Reformatsky reagent (**111**) in enantioselective

synthesis of β -hydroxy ester derivatives, such as *R*-(**110**), through activity of a prolinol-derived chiral ligand (**112**), was the stepping-stone for the discovery of a kinetic resolution that furnishes the enantiopure β -hydroxy esters by dehydration.¹³⁸

Scheme 23: Example of a kinetic resolution to furnish enantiopure *R*-(**110**), by selective dehydration of the L-enantiomer of the β -hydroxy ester (**110**) to the corresponding alkene (**113**). The conditions use a Reformatsky-type reagent (**111**) in combination with catalytic quantities of a chiral ligand (**112**).

This chemistry was later utilized in the synthesis of enantioenriched flavane derivatives.¹³⁹ While the asymmetric chemistry clearly exemplifies the stereochemical requirements for facile elimination, and the possibility for reagent-based facilitation of selective dehydration reactions, the kinetic resolution approach clearly provides enantio-enriched β -hydroxy esters as the output is not an expedient output of alkene products that could not have been prepared in other ways. This methodology promises the development of a site-selective dehydration by identifying a system that can recognize one specific alcohol moiety and facilitate its dehydration.

3 Complex polyol compounds – selective dehydration as a key challenge

Synthetic chemists challenge themselves with the controlled construction of complex molecular architectures, and the efficiency of modern total synthesis campaigns are becoming more and more streamlined. Fundamentally, the dehydration of alcohols to alkenes is a functional group interconversion that can, at least in principle, offer complete translation of stereochemical information and therefore has been strategically employed in synthesis design. On the other end of the spectrum, the application of molecular diversification strategies to complex and abundant building blocks, allows access to novel and biologically relevant chemical space, and here the ubiquitous presence of alcohols in many natural products and peptides suggests valuable

application of direct and selective dehydration reactions. The clear message from the dehydration approaches we have reviewed, including the many examples from various target-based syntheses of natural products, is, however, that site-selective dehydration in polyol compounds is by-and-large circumvented. Although there may be compelling reasons for this, it means that there currently is a discrepancy between the methodology available and the interesting opportunities that would follow from efficient site- and stereo-selective dehydration reactions. For instance, dehydroamino acids have been discussed as chemical multitools for late stage diversification strategies,¹⁴⁰ and a recent report demonstrated the divergent functionalization of thioestrepton by site-selective cobalt catalysed amidation of dehydroalanines in this natural product.¹⁴¹ Such chemistry in combination with putative selective chemical dehydration of complex (cyclic) peptides is clearly interesting. While catalytic methods for site-selective modifications of polyols have been demonstrated in high-complexity settings,^{11,12} the expansion of such chemistry to effect dehydration is not trivial. Notably, current dehydration methods are inherently two-step activation/elimination sequences, in contrast with the biosynthetic dehydrations that allow direct elimination of alcohols, in a single, concerted reaction.¹⁴² Furthermore, many complex substrates may demand reaction conditions involving highly polar or protic solvents to maintain solubility. We suggest that the design of new bifunctional catalysts that can emulate the fundamental function of canonical dehydratases, could be a potential path towards the realization of late-stage dehydration methods.

4 Conclusion

In this article, we have surveyed the current toolbox used for performing dehydration of alcohols in natural product syntheses. Of the different methods, Martin's sulfurane is perhaps the most successful reagent in direct chemical dehydration of alcohols, due its stereoselectivity in olefin formation, while generally affording good reaction yields. The application of dehydration reactions for direct functionalization of complex molecular structures, however, remains largely unexploited. Evidently, contemporary methodologies can solve some specific problems of dehydration, but the stage is cleared for reactions that engage alcoholic substrates in selective and predictable fashion to furnish novel alkene-containing chemical entities of functional utility.

5 Conflicts of interest

There are no conflicts to declare.

6 Acknowledgements

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