Diketomorpholines: Synthetic Accessibility and Utilization
Lan Phuong Vu and Michael Gütschow*

ABSTRACT: Diketomorpholines (DKMs; morpholine-2,5-diones) possess a six-membered ring with a lactone and lactam moiety and belong to the family of cyclodepsipeptides. In this review, the synthetic accessibility of DKMs is summarized and their utilization, in particular, for ring-opening polymerization reactions, is highlighted. The occurrence of the DKM scaffold in natural products encompasses small monocyclic compounds but also complex, polycyclic representatives with a fused DKM ring.

1. INTRODUCTION
Diketomorpholines (DKMs; morpholine-2,5-diones) constitute derivatives of the heterocyclic structure 1 (Figure 1).

Figure 1. General structures of diketomorpholines (1), diketopiperazines (2), and substituted glycolides (3).

DKMs bear one lactam and one lactone moiety, which occur each two-fold in highly abundant diketopiperazines 2 and glycolides 3, respectively (Figure 1). With the lactam and lactone group in the same six-membered ring, DKMs can be regarded as the simplest members of the large family of cyclodepsipeptides and are also referred to as cyclodepsidipeptides.1 In this review, a comprehensive overview on the synthetic access to DKMs is given, and some remarkable applications and the occurrence of the DKM scaffold in natural products are described.

2. SOLUTION-PHASE SYNTHESSES
In the following, recent and representative examples showing the synthetic access to DKMs will be summarized (Schemes 1 and 2). In both schemes, only one possible configuration for the two chiral carbons is shown. However, not only the depicted (3S,6S)-configured products have been prepared by the different outlined methods, but also diastereomers with other defined configurations, racemic products, as well as achiral compounds 1 and 10, in which R1 and R2 are hydrogens. Further protocols employed for DKM synthesis are summarized elsewhere.1

DKMs are available through cyclative lactonizations (Scheme 1). For the ring-closure reactions, precursors 4–9 have been utilized, all of which already contain a central amide bond. In the resulting product structures 1 and 10, it appears as an unsubstituted or substituted lactam moiety, respectively. The formation of the lactone bond from free acids 4 or 5 was accomplished either by proton-catalyzed condensations or in the presence of coupling reagents or under Mitsunobu conditions. Acid- or base-promoted conversions of the esters 6 or 7 produced products 1 and 10 in the course of interesterifications. Furthermore, halogen-substituted educts 8 or 9 were employed for lactone generation under basic conditions. In some cases, ester progenitor compounds were saponified to the corresponding acids 8 or 9 prior to the cyclocondensation.

As a second opportunity, educts 11 and 12 with a preformed central ester group have been subjected to lactamization, leading to cyclized products 1 and 10 (Scheme 2). The conversions include the successful application of the Mukaiyama reagent. Typically, the terminal amino group was deprotected before the cyclization occurred.

Macrocyclic analogues of DKMs have been prepared from lactams bearing an ε-hydroxyacyl residue at the cyclic nitrogen atom. Attack of the terminal oxygen at the ring carbonyl led to side-chain insertion to bicyclic cyclols, and the subsequent ring expansion gave monocyclic products which represent macrocyclic counterparts of DKMs 1.14

Recently, in a study on macrocycl-o-oligomerizations, it was observed that the tetradepsipeptide 13 underwent an intramolecular attack of the carboxylate at the central ester, leading to an anhydride isomer 14, followed by fragmentation due to

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the nucleophilic attack of the alcoholic group and generation of the protected compound.

Scheme 4 shows ester-based prodrugs (17) of glucagon-like peptide 1 (GLP) in its biologically active form GLP(7−36) and fused to peptide CEX, a nine-amino-acid C-terminal extension. The N-terminal phenylalanine was replaced with phenyllactic acid, and the prodrugs dissociate under physiological conditions through formation of DKMs and liberate the active peptide.

3. SOLID-PHASE SYNTHESES

DKMs are accessible through various polymer-supported methods. Cyclization of resin-bound bromides 19 (Scheme 5) was induced by treatment with TFA, initially leading to cleavage from the Wang resin, followed by ring closure to DKMs (R1 = H or alkyl, R2 = alkyl). A resin which consisted of polyethylene glycol attached to cross-linked polystyrene through an ether linkage was employed for DKM synthesis. Here, the resin-bound structure 20 (R1 = alkyl, R2 = alkyl) was assembled by Ugi reaction, and the NR2 portion of the products corresponded to the structure of amino acid amides with R2 = CH(alkyl)CONH(cyclohexyl).

DKM precursors were coupled to the polymer matrix via a photolabile 5-bromo-7-nitroindoline moiety, and alanine, leucine, and phenylalanine-based DKMs 22 were produced in the course of an intramolecular photoinduced cyclorelease (Scheme 6).
The resin-bound structure 23 was produced by loading tert-butyl serine, deprotection, alkylation with bromoketones, and acylation (Scheme 7). TFA-mediated liberation from the solid support triggered a cyclization to the 3,4-dihydro-2H-1,4-oxazine scaffold, followed by base-catalyzed lactonization to the fused second ring. At prolonged reaction time, eliminative cleavage occurred and monocyclic DKMs 25 were formed, for example, from 24. An analogous protocol could be used for the solid-phase-supported generation of tricyclic DKMs (Scheme 8).

Scheme 7. Formation of Bi- and Monocyclic DKMs

An N-terminal degradation of peptoid oligomers through sequential cleavage of N-substituted glycine units was accomplished on a solid phase. The protocol relied on the treatment of resin-bound bromoacetylated peptoids 31 with silver perchlorate, leading to an intramolecular lactonization, releasing the terminal residue as part of an N-substituted DKM 34, and resulting in the truncated peptoid 33 (Scheme 9).

Scheme 8. Formation of Tricyclic DKMs

An N-terminal degradation of peptoid oligomers through sequential cleavage of N-substituted glycine units was accomplished on a solid phase. The protocol relied on the treatment of resin-bound bromoacetylated peptoids 31 with silver perchlorate, leading to an intramolecular lactonization, releasing the terminal residue as part of an N-substituted DKM 34, and resulting in the truncated peptoid 33 (Scheme 9).

Scheme 9. Iterative Peptoid Sequencing through DKM Liberation

An N-terminal degradation of peptoid oligomers through sequential cleavage of N-substituted glycine units was accomplished on a solid phase. The protocol relied on the treatment of resin-bound bromoacetylated peptoids 31 with silver perchlorate, leading to an intramolecular lactonization, releasing the terminal residue as part of an N-substituted DKM 34, and resulting in the truncated peptoid 33 (Scheme 9).

Scheme 10. Ammonolysis of DKMs to Diamides and Acyl Transfer to Imides

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Scheme 11. Polydepsipeptide Ring-Opening Reaction

The chemical reactivity of DKMs has mainly been explored to perform ring-opening polymerization reactions (see below). In a model transformation, N-substituted, racemic DKMs 35 were treated with ethanolic ammonia to undergo ring opening to diamides 36 (Scheme 10). The second step leading to intermediates 37 occurred slower and involved the intramolecular participation of the primary carboxamide moiety. The imides 37 were susceptible to subsequent conversions with nucleophiles. The regioselective course of the ring opening of 35 reflected the expected higher electrophilic reactivity of the lactone group compared to that of the lactam group in DKMs. The cleavage of a defined DKM with a functionalized benzylamine was utilized for the preparation of a thrombin inhibitor.

Overall, the synthetic potential of DKMs to generate defined low-molecular weight compounds with tailored properties has not yet been fully exploited. In contrast, DKMs have been frequently utilized as monomers for polymerization reactions. Polydepsipeptides are alternating copolymers of an α-amino and an α-hydroxy acid. They are valued for their nontoxic properties and their degradability and are suitable for numerous applications, such as tissue engineering and drug delivery. Compared to polypeptides, polydepsipeptides do not necessarily require enzymes for their degradation because of the hydrolytic susceptibility of the ester groups. The presence of the carboxamide portions in polydepsipeptides allows for strong intramolecular hydrogen bond interactions, in contrast to polyesters. These hydrogen bonds influence their mechanical and thermal properties, which can be fine-tuned by variations of the amino acid moieties. In particular, telechelic oligodepsipeptides, capable of entering into further polymerization or other reactions through their reactive terminal groups, serve as valuable building blocks for biomedical applications.

Polydepsipeptides (38) are generally accessibly by employing DKMs (1) in ring-opening polymerization reactions (Scheme 11). Several attempts have been made to control copolymer compositions, molecular weights, crystallinity, and degradability by using different polymerization conditions.

As a catalyst, stannous octoate (tin(II) 2-ethylhexanoate, Sn(Oct)2) has frequently been used. Following the “coordination—insertion” mechanism, a tin alkoxide is formed from Sn(Oct)2 and a hydroxyl group of the initiator molecule, the carbonyl oxygen coordinates the metal center, followed by the nucleophilic attack of the alkoxide ligand and subsequent
lactone bond cleavage, thus generating an analogous, active species.\textsuperscript{25} 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was a particularly active catalyst for the generation of polymers 38 (R\textsubscript{1} = H, R\textsubscript{2} = H or alkyl) from corresponding DKMs 1 using benzyl alcohol as an initiator.\textsuperscript{7} Several bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were investigated in polymerizations of methionine-derived DKMs 1 (R\textsubscript{1} = H or alkyl, R\textsubscript{2} = CH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{3}).\textsuperscript{8} The resulting poly(ester amides) 39 were applicable for postpolymerization modifications via “methionine click” chemistry.\textsuperscript{39}

DKMs could be copolymerized with substituted glycolides (3, Figure 1) or lactones such as ε-caprolactone to achieve copolymers with tailored properties.\textsuperscript{10,23} A detailed description has been provided elsewhere.\textsuperscript{23} Instead of Sn(Oct)\textsubscript{2} as the catalyst and ethylene glycol as the initiator,\textsuperscript{23} a single Sn(IV) organotin compound could perform both tasks. 2,2-Dibutyl-1,3,2-dioxastannolane, prepared from dibutyltin oxide and benzyl alcohol as an initiator,\textsuperscript{7} several bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were investigated in polymerizations of methionine-derived DKMs 1 (R\textsubscript{1} = H or alkyl, R\textsubscript{2} = CH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{3}).\textsuperscript{8} The resulting poly(ester amides) 39 were applicable for postpolymerization modifications via “methionine click” chemistry.\textsuperscript{39}

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**Scheme 11. Ring-Opening Polymerization to Produce Polydepsipeptides from DKMs**

Reagents and conditions: (a) Sn(Oct)\textsubscript{2}, ethylene glycol, 140 °C; \textsuperscript{23} or BnOH, TBD or DBU, THF or CHCl\textsubscript{3};\textsuperscript{28} 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was a particularly active catalyst for the generation of polymers 38 (R\textsubscript{1} = H, R\textsubscript{2} = H or alkyl) from corresponding DKMs 1 using benzyl alcohol as an initiator.\textsuperscript{7} Several bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were investigated in polymerizations of methionine-derived DKMs 1 (R\textsubscript{1} = H or alkyl, R\textsubscript{2} = CH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{3}).\textsuperscript{8} The resulting poly(ester amides) 39 were applicable for postpolymerization modifications via “methionine click” chemistry.\textsuperscript{39}

**Scheme 12. Generation of Block Polymers by Ring-Opening Polymerization Reactions of DKMs**

Reagents and conditions: (a) Sn(Oct)\textsubscript{2}, ethylene glycol, 140 °C;\textsuperscript{23} or BnOH, TBD or DBU, THF or CHCl\textsubscript{3};\textsuperscript{28} 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was a particularly active catalyst for the generation of polymers 38 (R\textsubscript{1} = H, R\textsubscript{2} = H or alkyl) from corresponding DKMs 1 using benzyl alcohol as an initiator.\textsuperscript{7} Several bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were investigated in polymerizations of methionine-derived DKMs 1 (R\textsubscript{1} = H or alkyl, R\textsubscript{2} = CH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{3}).\textsuperscript{8} The resulting poly(ester amides) 39 were applicable for postpolymerization modifications via “methionine click” chemistry.\textsuperscript{39}

**Scheme 13. DKM 61 as an Intermediate in a Proposed Pathway to Trimeric Prebiotic Compounds**

5. NATURAL PRODUCTS

Monocyclic DKMs have been reported as natural products. Examples are shown in Figure 2. Enniatins are mixtures of cyclic hexadepsipeptides found in Fusarium fungi. Enniatin B forms an 18-membered ring composed of three alternating N-methyl-(S)-valine and (R)-2-hydroxy-3-methylbutanoic acid building blocks. The DKM congeners 42–44, supposed side products of the nonribosomal enniatin B biosynthesis, were isolated from Fusarium sporotrichioides (Figure 2).\textsuperscript{12} DKM 42, which contained the two enniatin B building blocks, was present in prevailing amounts in the broth and mycelium of Fusarium sporotrichioides, whereas the production of 43 and 44 was presumably due to low substrate specificity of the enniatin synthetase for (S)-amino acids.\textsuperscript{12} Compound 42 exhibited inhibitory properties against xanthine oxidase and anti-inflammatory activity in human peripheral blood mononuclear cells.\textsuperscript{26} Aliphatic DKM derivatives such as 42 and 43 have been evaluated with respect to their antimicrobial, antioxidant, immunomodulatory, and antiproliferative activities.\textsuperscript{1,26}

Bassiatin (45) was isolated from the cultured broth of the entomopathogenic sac fungus Beauveria bassiana, in addition to depsipeptides of a higher oligomerization state such as the cyclic hexadepsipeptide beavercin.\textsuperscript{27} Bassiatin possessed insecticidal activities against Bemisia tabaci, a white insect, and important agricultural pest, in contact and feeding assays. Bassiatin inhibited the ADP-induced platelet aggregation.\textsuperscript{27} A diastereomer (46) from the sac fungus Isaria japonica induced apoptotic cell death in human leukemia cells in the micromolar range.\textsuperscript{27} DKM 47 was identified as a constituent of the traditional Chinese medicine Bombyx batryticatus, the dried dead larva of silkworms after infection by Beauveria bassiana.\textsuperscript{27} DKM 48 was isolated from the sea hare Bursatella leachi.\textsuperscript{27} Other DKMs bearing N-benzyl substituents have been synthesized and investigated as inhibitors of glucosidases, as summarized elsewhere.\textsuperscript{1}

**Figure 2.** Monocyclic DKMs from natural sources.
The greater propensity of proline and N-methyl-substituted amino acids to adopt a cis conformation and the consequent preferred DKM cyclization might account for the more frequent appearance of bicyclic DKMs such as 61 (Scheme 13) and N-methyl-substituted DKMs such as 42–48 (Figure 2).

DKMs are structures of naturally occurring polycyclic indole alkaloids. Respective natural products mainly contain a diketopiperazine ring fused to the terminal five-membered ring of the pyrroldinoindoline system. However, there are also natural products in which a DKM unit replaced the diketopiperazine core. Such tetracyclic compounds (49–58) are depicted in Figure 3. Mollenines A (49) and B (50) were isolated from the sclerotoid ascostromata of Eupenicillium molle. The total synthesis of 49 was realized either by the preparation of a prenylated pyrroldinoindoline ester from tryptophan and the final connection with leucic acid or by a one-pot reaction of the DKM composed of tryptophan and leucic acid with a vinyl cyclopropane reagent. Mollenine A one-pot reaction of the DKM composed of tryptophan and the preparation of a prenylated pyrrolidinoindoline ester from leucic acid followed by lactonization. Recently, similar DKM natural products, such as deacetyl-javanicunine A (54), javanicunine C (53), and javanicunine D (55), were identified from a Penicillium species.

The DKM alkaloids PF1233 B, also referred to as shornephenine A (56) and 9-deoxy-PF1233 A (57) and B (58), were identified from marine-sediment-derived Aspergillus species. Methanolation of 56 occurred at the lactone moiety and led to the opening of the DKM cycle. The total synthesis of 57 and 58 was accomplished via an epoxidation of the intermediate DKM containing a tryptophan and leucic acid moiety. Subsequent intramolecular epoxide opening led to the tetracyclic scaffold. PF1233 B (56) was reported as a noncytotoxic inhibitor of F-glycoprotein transporters, key mediators of drug efflux in multi-drug-resistant human cancer cells. Clonorosin A (59) with the DKM ring fused to a tetracyclic isoindolo[4,5,6-cdf]indole system was isolated from the soil-derived fungus Clonostachys rosea. It showed activity against Fusarium oxysporum, an ascomycete fungus which is pathogenic to plants.

Further DKM alkaloids such as acu-dioxomorpholines from the fungus Aspergillus aculeatus were identified using a fungal artificial chromosome and metabolomic scoring platform. Due to this technology, the DKM biosynthetic pathway was elucidated, and nonribosomal peptide synthetase gene clusters responsible for the production of DKM alkaloids were characterized.

6. CONCLUSIONS

Despite the striking simplicity of the diketomorpholine structure, this chemotype has received less general attention than expected. This review highlights the various synthetic routes to DKMs and their chemical reactivity, in particular, in the application of ring-opening reagents leading to tailored polymers. Furthermore, compounds bearing the DKM scaffold are represented among natural products, particularly fungal metabolites. Naturally occurring DKMs comprise small, monocylic compounds but also complex alkaloids with a fused DKM substructure. Obviously, the class of DKMs still has not been fully explored and gives space for further research and application. Hence, this review might encourage scientists to increasingly take account of several aspects of diketomorpholine synthetic and natural product chemistry for their own research.

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Notes
The authors declare no competing financial interest.

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Michael Gütschow studied Biochemistry at the University of Leipzig, Germany, and received his Ph.D. in Pharmaceutical Chemistry. He was a Scientific Assistant at the Department of Biosciences at the University of Leipzig and a Postdoctoral researcher at the Georgia Institute of Technology, Atlanta, Georgia, USA. In 1998, he received his Habilitation at the University of Leipzig in the field of Pharmaceutical Chemistry. Since 2001, he is Professor for Pharmaceutical Chemistry at the University of Bonn. His research interests include (i) design of inhibitors and activity-based probes for cysteine and serine proteases, (ii) synthesis of bioactive heterocycles,
(iii) peptidic and peptidomimetic drugs, (iv) development of PROTACs, and (v) biochemistry of enzyme-drug interactions. He published more than 280 publications to the scientific topics mentioned.

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