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PAPER

Cyclic dipeptides: catalyst/promoter-free, rapid and environmentally benign cyclization of free amino acids†

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"The best catalyst is no catalyst." With growing public concern over global warming and the amount of greenhouse gases, it is important to reduce the amount of chemicals and eliminate waste, to obtain better results in a simple, selective, safe, and environmentally benign fashion compared to conventional tedious chemical synthesis. Herein, we disclose an environmentally benign, rapid, catalyst/promoter/coupling reagent-free cyclization procedure of free amino acids to furnish exclusively cyclic dipeptides (2,5-diketopiperazines, DKPs) in excellent or even quantitative yield, along with their solid state self-assembling properties. This process is extremely simple and highly efficient with little or no traditional synthetic skills and without any chromatographic purification. Synthesis of structurally diverse DKPs has been achieved with a dramatic decrease in the reaction time, the amount/number of solvents used, a significant increase in the yield and nearly complete elimination of waste. As a result, this is an excellent example for the environmentally benign, clean and green chemistry concept. The most exciting outcome of our investigation is an unusual case of chiral self-recognition encountered upon the cyclization of *rac*-pipecolic acid, which resulted in the formation of the *meso*-product exclusively.

Introduction

Bioactive cyclodipeptides [(termed as 2,5-diketopiperazines (DKPs), 2,5-dioxopiperazines or dipeptide anhydrides)] are ubiquitous in nature, and they represent the simplest and first completely characterized small peptides.[1,2] This class of molecules are potential drug candidates because of their antibacterial,[3] anticancer,[4] herbicidal,[5] and antiviral properties.[6] Recent progress in the field of molecular biology, medicinal chemistry, neuroscience, and nanoscience has uncovered the wide spectrum of biological activities of DKPs, such as inhibitors of topoisomerases,[7] collagenase-1,[8] chitinase,[9] tubulin depolymerization, plasminogen activator inhibitor-1 (PAI-1), and bradykinin antagonists.[10] It has been shown that DKPs are involved in quorum sensing (cell to cell communication in *Vibrio* spp.),[11] neuroprotection,[12] and can be used as blood–brain barrier (BBB) shuttles.[13] Furthermore, the self-assembly of DKPs derived from aromatic amino acids as building blocks for bionanostructures/peptide nanotubes, has recently been reported.[14] Because of their rigidity and restricted conformational freedom, they provide a unique opportunity to design suitable receptors and drug candidates, which can be used as models to shed light on more complex peptides and proteins.[15] The crystalline nature of DKPs has proved to be useful to elucidate the primary structure or analyze the sequence of polypeptides and proteins.[16] This property of DKPs has attracted both experimental and theoretical chemists. Very recently, Buděšínský *et al.* reported combined experimental X-ray studies and computational calculations of cyclopeptides with diverse functionalities.[17] Blanco *et al.* evaluated discrimination in the recognition of self-assembled complexes of DKPs using density functional theory (DFT) calculations.[18] It has been suggested that microbial peptides are derived partly or completely by enzymatic condensation and ring expansion of diketopiperazines.[19] Recent findings using hydrothermal conditions also showed the importance of DKPs towards the origin and evolution of life in primordial earth.[20] A careful analysis of structurally diverse natural products clearly suggests that a number of medicinally important natural products contain DKP moieties embedded with them (Fig. 1).[21]

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† Electronic supplementary information (ESI) available: Supplementary information including experimental procedures along with MW graphs for all the compounds studied, ^{1}H, ^{13}C NMR, ESI-MS data, elemental analysis, melting points, optical rotation, single crystal X-ray data collection procedure, tables containing crystallographic details of (**1**, **9**, **11–13**, bond length, bond angles, dihedral angles and hydrogen bonding interactions), CCDCs 783550–783553 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1gc15043j

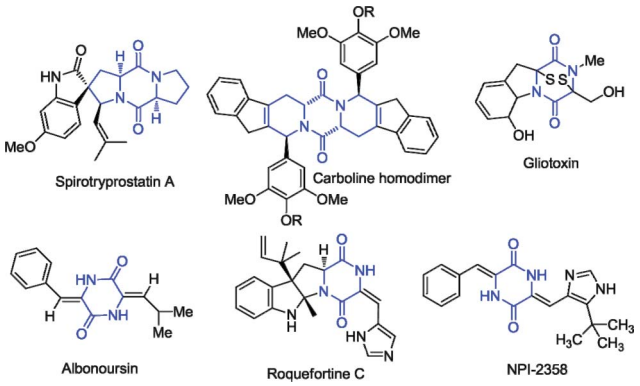


Fig. 1 Representative examples of natural products containing DKP moieties.

It is noteworthy that the cyclization of amino acids leading to DKP formation continue to be major reactions in natural product synthesis, and still the methods suffer from protection/deprotection and the use of a base or an acid and a low yield.[22] There is a steady increase in the isolation of DKPs from natural sources. Studies on DKPs started as early as the 1940s and several synthetic methods have been reported in the literature *via* which both symmetric and unsymmetrical DKPs can be obtained.[2,23] So far there have been no reports on the condensation of free secondary amino acids, such as proline and substituted proline derivatives without using any catalyst or promoter, to yield pure DKPs in quantitative yield.

It is often said that "the best catalyst is no catalyst". Herein, we disclose a rapid catalyst- and promoter-free cyclization/condensation of free amino acids using controlled microwave irradiation, which furnished exclusively DKPs in an excellent yield without involving any chromatographic purification or extraction. The most important and interesting finding in our discovery is that the rapid cyclization of secondary amino acids, such as proline, substituted proline and pipecolic acid derivatives provided a one step synthesis of tri- or pentacyclic DKPs and their structures have been ascertained unambiguously using single crystal X-ray diffraction. One of the most fascinating findings of our investigation is the chiral self-recognition of *rac*-pipecolic acid, which resulted in the optically inactive *meso*-product in spite of several possible products. Specific examples showing a dramatic decrease in the amount/number of solvents, number of steps, reaction time, cost and a significant increase in the yield, the nearly complete elimination of waste and other purification steps compared to that of conventional synthetic methods, are presented. This is one of the excellent examples for the environmentally benign, green, clean and quick chemistry approach to the synthesis of bioactive small molecules without any tedious purification methods. The fundamental concepts of environmentally benign synthesis, the application of this methodology and the solid state self-assembling properties of DKPs are highlighted in this paper.

Results and Discussion

The condensation of a free carboxylic group with an amine (intermolecular) under microwave conditions has been known for some time.[24] While working on this topic, we envisioned that a microwave reaction with simple amino acids without any catalyst, promoter or base would be interesting. We speculated that such a reaction may result in a complex mixture of products. In order to test our hypothesis, glycine was chosen as a model compound in our initial studies. Solution of glycine in water, *N*,*N*-dimethlyformamide (DMF) and solid glycine were subjected to controlled (temperature, pressure and power) microwave (MW) irradiation (ESI†). The reaction mixture in DMF turned into a clear solution after 5 min and transformed from colorless to a pale yellow solution. When the reaction had ceased, a pale yellow precipitate was formed. Analysis of the filtered product revealed the formation of 2,5-diketopiperazine (DKP) **1** (Fig. 2). It is noteworthy that no other side product was obtained and the compound required no chromatographic separation or extraction. The product obtained underwent spontaneous crystallization in D_2O (NMR sample) and the structure was proved unambiguously using single crystal X-ray diffraction (Fig. 4). On the other hand the reaction carried out with water as a solvent turned into a clear solution and unreacted starting material was recovered. However, it was not possible to attain the requisite temperature for the solid alone and as a result, the starting material remained unchanged. Inspired by this observation we decided to use DMF as a solvent and continued our investigation with other optically active amino acids. A series of compounds were screened and, interestingly, all amino acids underwent cyclization and furnished their respective DKP derivatives (Fig. 2). Carrying out a selective reaction when multiple functional groups are present is a challenge. Therefore, in order to test our methodology tyrosine was subjected for MW reaction under similar experimental conditions. After completion of the reaction a brown precipitate was obtained, which after filtration followed by recrystallization from methanol resulted in **6** as a colorless solid. It is noteworthy that the compound **6** and its analogues are reported to bind μ-opioid receptors and are active against tumour cell lines at μM concentration.[25] The above results are highly interesting and resulted in a new direction toward the synthesis of DKPs in a green, clean and rapid approach, which is highly efficient in terms of time, purity, yield and labor. However, the cyclization of secondary amino acids, such as proline, will be even more exciting and the condensation of substituted prolines are equally challenging because of possible side reactions. DKPs derived from proline and substituted prolines are frequently found to be an integral part of many natural products, such as Spirotryoprostratin A (Fig. 1).[26] This prompted us to investigate the cyclization of secondary amino acids. When proline was subjected to the similar reaction conditions, a pale yellow solution was obtained, which upon solvent evaporation followed by addition of acetonitrile, resulted in a colorless crystalline solid. Structural characterization and systematic spectral analysis revealed the formation of racemic DKPs. It is noteworthy that there exist both experimental and theoretical investigations towards understanding the racemization of amino acids under pyrolytic conditions. Extensive mechanistic studies for various amino acids including the racemization of proline and its derivatives under various reaction conditions have been reported in the literature.[27] Such a phenomenon depends on multiple experimental factors. A number of experiments conducted to

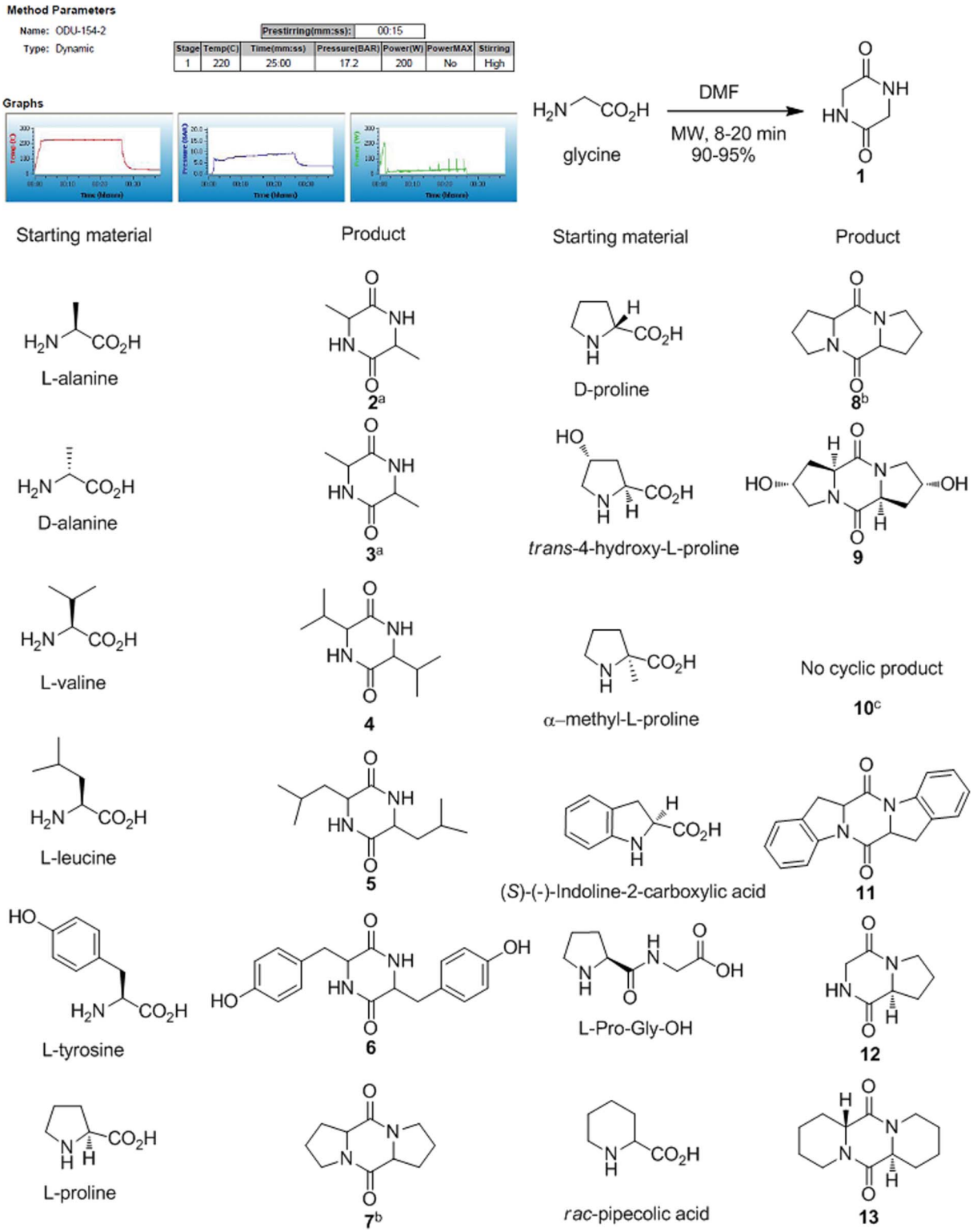


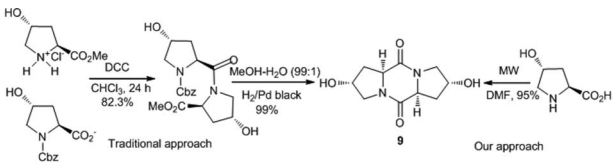
Fig. 2 Representative graphs of the controlled MW reaction of compound **9**; temperature (red); pressure (blue); power (green) and the examples studied. [a]*rac*-mixture **2** = **3**; [b]*rac*-mixture **7** = **8**; [c]starting material remained unreacted.

understand prebiotic chemistry resulted in the formation of racemic products.[20]

Nevertheless, a detailed literature search suggested that compounds like **9** will be of immense interest because of the following reasons; (i) Heath and Northcote reported that the sycamore cell wall was composed of a glycopeptide where the peptide part was a cyclic dimer of 4-hydroxy proline;[28] (ii) this compound was an intermediate in the synthesis of a microtubule inhibitor, where the synthesis involves multiple steps, reagents, protection/deprotection and tedious purifications.[29] Inspired by

these observations we continued our investigation towards the one-step synthesis of a target molecule starting from *trans*-4-hydroxy-L-proline ((2*S*,4*R*)-4-hydroxy proline). To our pleasant surprise the reaction mixture yielded a pale yellow solid upon solvent evaporation and recrystallization in methanol furnished the desired compound **9** in quantitative yield (Fig. 2 and 3). This clearly indicates how one can think beyond the conventional approach.

The synthesis reported earlier[29] (Fig. 3) for the compound **9** utilizes 2 different starting materials (more expensive), more than 6 different solvents (~2.0 L), catalysts, chromatographic purification, a longer reaction time (days) and multiple side/waste products (5), whereas our approach is extremely simple with a relatively cheap starting material and one solvent (0.04 L) with a dramatic decrease in the reaction time (25 min) and only water as a side product at the end of the reaction. The structure of **9** was proved unambiguously using a single crystal X-ray structure for the first time (Fig. 4). The determination of the optical rotation was in agreement with data reported in the literature.[29]



Methods / Details	Conventional method (ref. 27)	Our approach
Starting materials & cost	2 & 92.10 €/5 g	1 & 22.00€/5 g
Reagents/catalysts	2	nil
Solvents	6 ($CHCl_3$, MeOH, Pet.ether, EtOAc, Acetone and H_2O)	1 (*N*,*N*-dimethylformamide)
Amount of solvent used	>2.0 L	0.004 L
Reaction time	2 days	25 min
Side products	dicyclohexyl urea, MeOH, CO_2, PhMe and H_2O	H_2O
Chromatography	yes	no
Yield	82%	>95%

Fig. 3 A comparison of the traditional approach and our approach towards the synthesis of compound **9**.

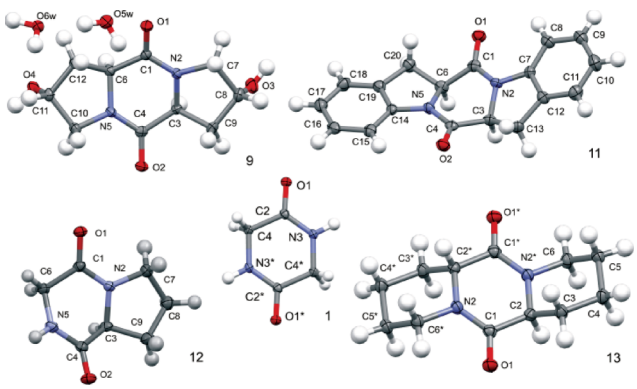


Fig. 4 The molecular structures and labelling schemes of compounds **1**, **9** and **11**–**13**. Symmetry operator for **1** * = $-x + 2, -y, -z + 1$ and **13**: * = $-x, -y + 1, -z + 1$. The hydrogens are numbered according to their host atoms. The thermal ellipsoids are drawn with 50% probability.

The strategy was extended for the construction of a pentacyclic system by taking (*S*)-(−)-indoline-2-carboxylic acid as starting material (Fig. 2). This reaction also furnished compound **11** in quantitative yield, the structure of which has been ascertained unambiguously using single crystal X-ray analysis (Fig. 4). It is noteworthy that there have been several efforts to utilize microwave irradiation for the condensation of amino acids, but the procedure still involves multiple reagents, a promoter, a base, ionic liquids and tedious chromatographic purification.[30] Houston *et al.* reported a series of cyclodipetides as chitinase inhibitors and the authors concluded that the cyclo(Pro-Gly) substructure is enough for binding, allowing modification of the non-proline residue side chain.[9] Inspired by this report, we decided to prepare cyclo(Pro-Gly) as a model compound to test our speculations starting from L-Pro-Gly-OH. Indeed, the reaction mixture turned to a clear colorless solution and upon cooling to room temperature, the crystalline solid was obtained. The spectral characterization and successful single crystal X-ray analysis unambiguously proved the formation of compound **12** (Fig. 4).

Chiral self-recognition

A large number of biochemical reactions in living systems depend on chiral recognition, "a process in which discrimination between enantiomers or enantiotopic ligands achieved by well defined reagents or catalysts (enzymes or synthetic)".[31a] Chiral self-recognition is a process in which a chiral compound reacts preferentially with one of its enantiomers.[31b,c] Complete self-recognition will result in exclusive formation of either a racemic mixture of enantiomeric products or an achiral *meso* product. However, when there is no chiral self-recognition, the reaction products will be a mixture of *rac* : *meso* (1 : 1) products in equal amounts. This is of great importance in organic synthesis and the principle is often compared to that of non-linear effects in asymmetric catalysis. In the course of our investigation towards the synthesis of DKPs derived from pipecolic acid, an unusual case of chiral self-recognition was encountered.

Racemic pipecolic (piperidine-2-carboxylic) acid under MW reaction conditions resulted in a colorless solid. Recrystallization from methanol resulted in quality crystals and X-ray single crystal analysis revealed the formation of the *meso*-product exclusively, showing chiral self-recognition (Fig. 4). Theoretically, a racemic starting material (1 : 1 mixture of L- and D-pipecolic acid) may undergo cyclization and result in the formation of a racemic mixture of DKPs or the *meso* product (Fig. 5). Although the exact reason behind self-recognition in pipecolic acid is not known, we speculate that this may be due to the conformational stability of the DKP or to the more energetically favoured interaction between enantiomers than within one single enantiomer. What is more important to note here is the possible synthetic scheme outlined in Fig. 5b. The synthesis of **13** is possible only using optically pure enantiomers, with two different starting materials and multiple steps and catalysts, and will result in tedious purification and waste. This is one of the most fascinating outcomes of this investigation as it is almost impossible to obtain compound **13** exclusively using routine organic synthetic procedures starting from a racemic mixture.

Single crystal X-ray studies

The understanding and unambiguous determination of the molecular structure of small molecules are of utmost importance

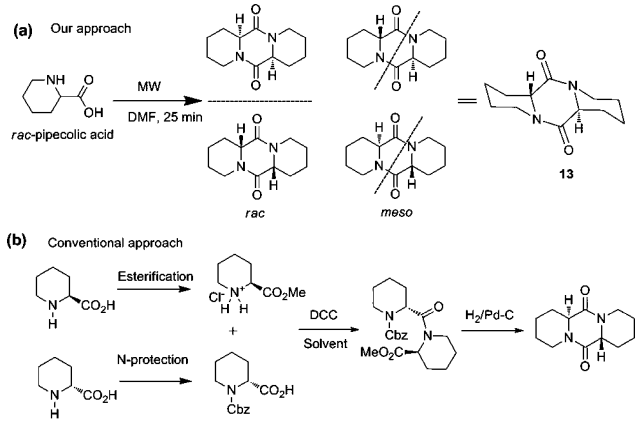


Fig. 5 (a) A reaction scheme showing the possible products from the cyclization of *rac*-pipecolic acid and the selective formation of **13** (dashed lines represent mirror planes); (b) a possible synthetic route to **13** using conventional synthetic methods.

and are equally challenging. Single crystal X-ray structure determination provides a unique opportunity to study and extract useful information on molecular structure in the solid state. Attempts were made to crystallize all the samples, while compounds **1**, **9**, **11–13** underwent crystallization resulting in quality single crystals, the others resulted in amorphous solids and their structures have been characterized by NMR (ESI†). The crystallographic data of compounds **1**, **9**, **11–13**, the selected bond lengths, angles together, dihedral angles and hydrogen bond distances (ESI, Tables S1–S6†) along with the labelling and the molecular structure of the dipeptides (Fig. 4) are presented.

Compound **1** crystallizes in the monoclinic space group $P2_1/c$ (No. 14) having a half molecule in an asymmetric unit (ESI, Fig. S5†), therefore being structurally equivalent to that reported in the literature (CSD: DIKPIP02),[32] although the crystallographic agreement factors (R-values) are clearly better in our case (ESI, Table S4†). The six-membered diketopiperazine is virtually planar, having a dihedral angle of –178.4(1)° for O(1)–C(2)–N(3)–C(4)#1. The molecules form infinite chains parallel to the (101) plane and individual molecules are located on top of each other along the *a*-axis (ESI, Fig. S1†). In these chains, dipeptide molecules are hydrogen bonded to each other *via* O(1) and N(3) (and their symmetry equivalents) atoms showing a d(H···A) distance of 1.958(16) Å. Moreover, the adjacent and top dipeptide chains are connected to each other by weaker hydrogen bonding *via* H(4a)–O(1) and H(4b)–O(1) atoms, having distances of 2.64 and 2.51 Å, respectively. The selected bond distances and angles are collected in Tables S2 and S3 (ESI†). Crystallization of compound **9** in methanol furnished single crystals as its dihydrate in the orthorhombic space group $P2_12_12_1$ (No. 19), having a single molecule in the asymmetric unit with two molecules of water (Fig. 6a). Although the absolute configuration cannot be determined reliably as Mo-radiation has been used in the structure determination without a heavier scatterer (meaningless Flack parameter = –0.1(11)), the structure is expected to be a pure enantiomer of the L-form, clearly suggesting that the enantiomerically pure starting material (4-hydroxy-L-proline) did not undergo any racemization under the reaction conditions. The six-membered diketopiperazine core is slightly folded upwards *via* an axis drawn through carbons C(3) and C(6) forming a shallow boat conformation (dihedral angle N(2)–C(3)–C(4)–N(5) = 28.6°), so that both keto-groups (O(1) and O(2)) are situated above the main plane (*via* atoms C(1)–C(4)–C(8)–C(11)), whereas the H(3) and H(6) hydrogens are located below the plane, as are the hydroxyl groups O(3) and O(4). Dipeptide molecules are ordered in parallel rows along the *b*-axis, forming wavy layers along the *c*-axis at the same time, with every second dipeptide facing up, whereas the other points down. An extensive hydrogen bonding network is present in the crystal lattice, as both the keto- and hydroxyl groups participate in 3-dimensional hydrogen bonding with neighbouring water molecules (Fig. 6a), and due to this conventional hydrogen bonding between adjacent dipeptides cannot be observed, instead only weak interactions occur between the C(3)–H(3)···O(2)#5 and C(7)–H(7A)···O(3)#6 atoms having d(H···A) distances of 2.35 and 2.53 Å, respectively. Moreover water molecules are hydrogen bonded to each other having d(H···A) distances of 1.93(3) Å with a contact angle of 173(3)°, and they act as hydrogen bonding links both between dipeptide molecules situated within a single layer as well as between two dipeptide layers (ESI, Table S6†).

Racemic compound **11** underwent crystallization upon addition of methanol and resulted in the monoclinic space group $P2_1/c$ (No 14) having a single molecule in an asymmetric unit (Fig. 4). In contrast to compound **9**, the dipeptide molecule is now slightly more folded across the axis between the C(3) to C(6) atoms (dihedral angle N(2)–C(3)–C(4)–N(5) = 39.2°) and due to the aromatic ring, the molecule is forced to be nearly planar across the folding axis. The CSD search reveals one entry (COSGEX)[33] having the same molecular composition as **11** but representing the enantiopure L-form that crystallizes in the orthorhombic space group $P2_1P2_1P2_1$ and has nearly the same unit cell volume (1339.1 Å^3) as **11** (1342.7 Å^3). Also the molecular conformations of both the racemic and enantiopure crystal structures are very similar (ESI, Fig. S2†) having only a small conformational difference in the folding axis (*via* C(3) to C(6)). Therefore the enantiopure L-form (COSGEX) has a slightly larger dihedral angle of 42.5° (N(2)–C(3)–C(4)–N(5)). In the case of compound **11**, both enantiomers are packed partially facing each other, forming rows of paired molecules along *a*- and *b*-axes (Fig. 6b). These pairs are packed along the *c*-axis having a nearly 90° horizontal rotation on each pair of facing dipeptides (ESI, Fig. S3†). This enables weak π–π interactions to occur between the aromatic groups of the two overlapping molecules that have ~90° longitudinal rotation in their orientation, as well as between an aromatic group and the six-membered ring of the diketopiperazine core of two facing enantiomers. In the enantiopure structure, the packing scheme is somewhat different as molecules are now packed in rows along the *b*-axis, forming a wavelike formation along the *c*-axis. Moreover, dipeptides are not facing each other while packed along the *a*-axis and having a longitudinal ~90° turn on every second molecule, albeit molecules are also flipped on each rotation. In compound **11** conventional hydrogen bonding cannot be observed in the packing scheme. However, dipeptide molecules are interconnected to each other by weak C–H···O interactions, of which d(H···A) distances vary from 2.38 to 2.58 Å.

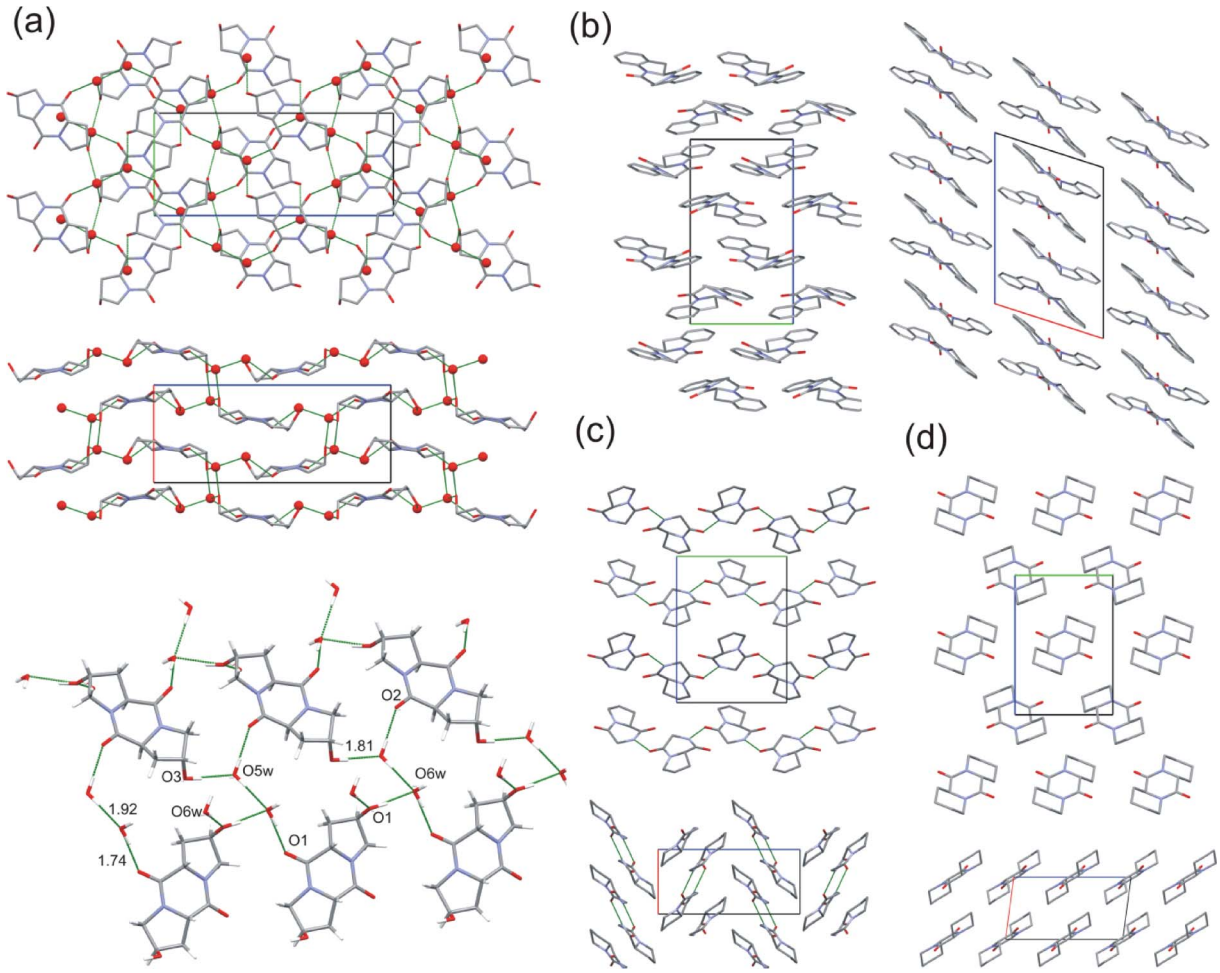


Fig. 6 The molecular packing (a) of **9** along the *a*- (top) and *b*-axis (middle) and the hydrogen bonding scheme (bottom) (some water and dipeptide molecules have been omitted for clarity); (b) the packing of **11** along the *a*- (left) and *b*-axis (right); (c) the packing of **12** along the *a*- (top) and *b*-axis (bottom). The hydrogen bonding between the N(5) and O(1) atoms are shown by dashed green lines; (d) the molecular packing of compound **13** along the *a*- (top) and *b*-axis (bottom) (hydrogen atoms have been omitted for clarity).

Compound **12** crystallizes in the orthorhombic space group $P2_12_12_1$ (No. 19) having also a single molecule in an asymmetric unit. Although the absolute configuration cannot be determined unambiguously, the structure is expected to be the L-form. The structural parameters for the L-form can be found in the CSD (entry code LPROGL03),[34] having nearly equal unit cell volume 740 Å^3 compared to that of **12** (721 Å^3). The molecules are packed in infinite hydrogen bonded parallel zigzag rows along the *b*-axis, and at the same time the chains overlap along the *a*-axis (Fig. 6c). Furthermore, the rows going through the asymmetric unit along the *a*-axis are tilted nearly 90° to each other when viewed along the *b*-axis. The hydrogen bonding occurs only between the H(5) and O(1) atoms of adjacent dipeptides, having a d(H···A) distance of 1.96(2) Å with an angle of 175(3)°. In addition, weak hydrogen bonding C–H···O=C occurs from the H(3) and H6a hydrogens to the O1 and O2 carbonyls, respectively, with distances of about 2.5 Å. The packing scheme of the known L-enantiomer is very similar, as the infinite hydrogen bond networks forming zigzags run along the *b*-axis and having the same contact atoms for hydrogen bonding.

Compound **13** crystallizes in the monoclinic space group $P21/c$ (No. 14), having a half molecule in an asymmetric unit (Fig. 6d). The six-membered diketopiperazine core is virtually planar having dihedral angles of –0.5° and 175° for O(1)–C(1)–C(2)–N(2)#1 and O(1)–C(1)–N(2)–C(6)#1, respectively. In addition, the dipeptide is in a chair-conformation having a dihedral angle of –60.5° for O(1)–C(1)–C(2)–C(3). The molecules are overlapping along the *a*-axis and form rows along the *b*-axis. The dipeptide molecules in every other row are pointing right whereas they point to the left in the other ones (Fig. 6d). The molecules are connected to each other only by weak hydrogen bonds, which are visible between the carbonyl oxygens and the C–H hydrogens, H6a and H6b belonging to the two nearest molecules located on the top and bottom layers (ESI, Fig. S5†) with d(H···A) distances of 2.35 and 2.49 Å, respectively.

Conclusions

In summary, we have shown how free amino acids can be selectively cyclized under microwave conditions to afford cyclodipeptides (2,5-diketopiperazines, DKPs). This process

is extremely simple, environmentally benign and involves no catalysts/promoters or coupling reagents. The entire process involves no chromatographic purification and as a result, the solvent waste is minimal or even completely eliminated. We also demonstrated the potential application of this process for the synthesis of a natural product, which otherwise involves multiple steps and sensitive reaction conditions using traditional synthetic methods. An unusual case of chiral self-recognition was encountered in the case of *rac*-pipecolic acid. We have shown how one can think beyond traditional synthetic methods and we believe that our demonstration will be highly useful for synthetic, bioorganic, medicinal, and materials chemists, and biologists. As there are no catalysts or promoters involved, it will be of great interest to carry out reactions of molecules having a variety of functional groups. Though a few amino acids resulted in racemic DKPs, others yielded enantiomerically pure forms indicating that the process of racemization depends on the stability of amino acids and the reaction conditions. We strongly believe that the application of our method offers a unique opportunity to solve problems in natural product synthesis, chemical biology, and the design of biomaterials.

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