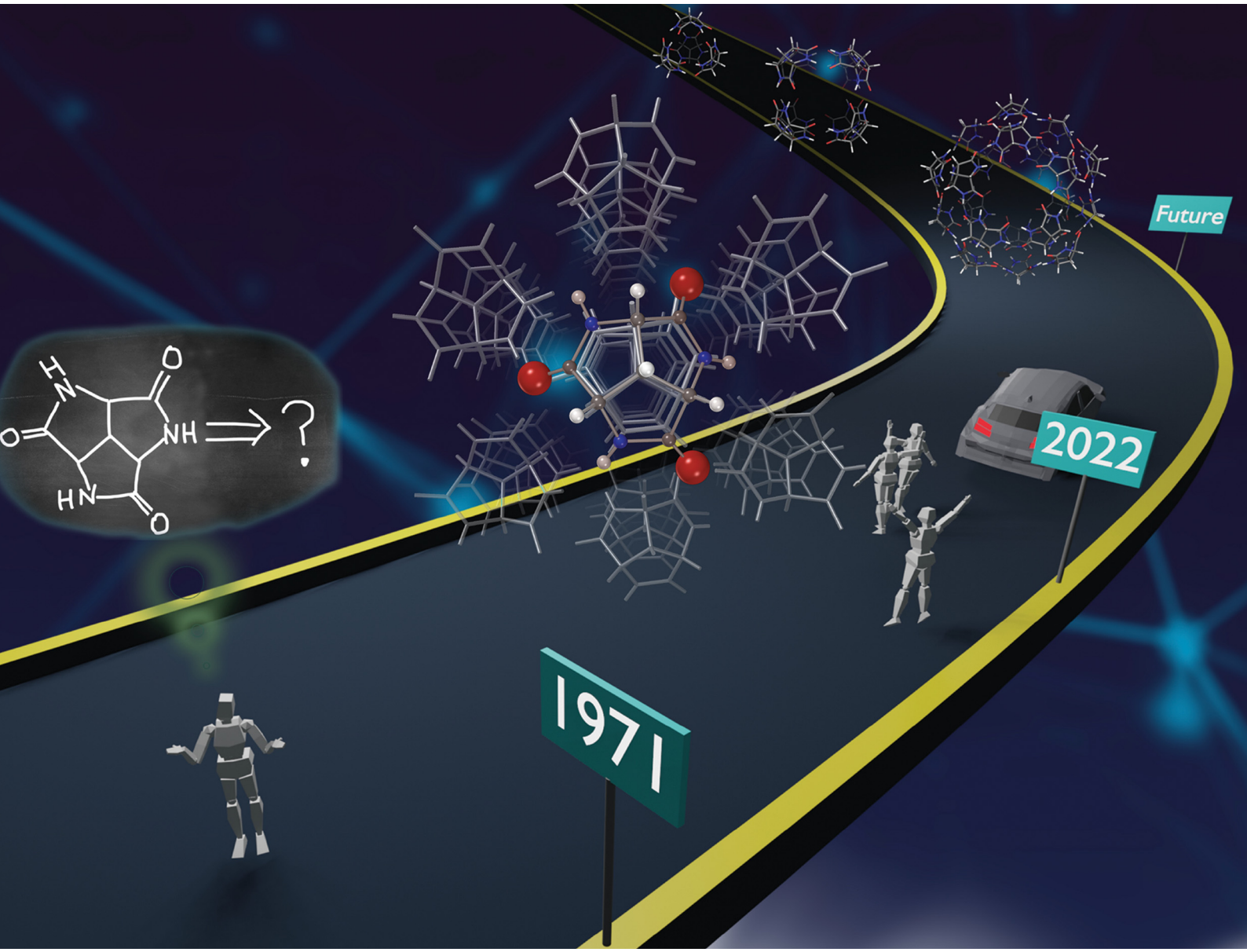
Volume 58
Number 23
21 March 2022
Pages 3707–3836

ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

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ChemComm

ROYAL SOCIETY OF CHEMISTRY

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View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2022, **58**, 3751

Received 18th January 2022,
Accepted 15th February 2022

DOI: 10.1039/d2cc00345g

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The long-awaited synthesis and self-assembly of a small rigid C_3-symmetric trilactam†

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The challenging synthesis of a fused C_3-symmetric trilactam (1) was executed in racemic and enantiomerically pure form. The rigidity, symmetry and high density of hydrogen bonding motifs make 1 an attractive candidate for self-assembly study, which revealed different hydrogen bond patterns in the crystals of *rac*-1-d_3 and (+)-(*SSS*)-1.

As a non-covalent interaction, hydrogen bonding has received a lot of attention from chemists ever since its establishment in the early 1900s.[1–3] Its directionality, predictability and tunability have made the hydrogen bond a powerful and reliable tool to manipulate structures and properties on a supramolecular level. Numerous molecules containing hydrogen bond donors and/or acceptors have been designed and synthesized as building blocks for host–guest chemistry[4] or as supramolecular synthons for crystal engineering.[5–8] One simple motif that is commonly found in these molecules is the amide group.[9–11] Herein we report the first synthesis, characterization, and solid-state self-assembly of a remarkably small molecule containing three amide groups, trilactam **1** (Fig. 1), which was first proposed and modelled as a scaffold for supramolecular structures in 1993[12] and has been the target of synthetic efforts from several research groups at the latest since 1971.[13]

The charm of **1** itself is revealed in many aspects, and one of them is its symmetry. From a purely aesthetic point of view, the structure of **1** possesses an attractive three-fold rotational symmetry which can be found both in Nature and human civilization.[14,15] Furthermore, compound **1** is the smallest possible C_3 symmetric fused trilactam to our best knowledge. Another attractive aspect is its chirality, which makes **1** a potential candidate for chiral recognition and asymmetric catalysis.[14–16] In addition, the high density of amide groups in **1** also contribute to its versatility: The inherent *cis* amide groups provide three pairs of self-complementary hydrogen-bonding motifs within one molecule of **1**. The rigid and planar nature of amides reinforces the molecular rigidity established by the concave tricyclic backbone. All these features make **1** an attractive candidate for hydrogen-bond based self-assembly. Some of the possible assemblies of **1** are modelled, which includes three regular closed-shell polyhedrons and a non-planar hexagonal tiling (Fig. S5, ESI†).[17] The approximate cavity volumes of the three regular polyhedrons vary from 69 Å^3 to 2298 Å^3,[18] which implies its versatility in host–guest chemistry. The hexagonal tiling illustrates the potential application of **1** in surface engineering.[19–21] Moreover, there are several possible intermolecular binding modes (Fig. 2),[17] which further increases the number of possible assemblies.

Historically, synthetic efforts towards *rac*-**1** have been carried out by several research groups following different strategies. One obvious and efficient synthetic strategy is to base the synthesis of *rac*-**1** on its high symmetry. In 1971, Mock reported the synthesis of C_3 symmetric triacetate *rac*-**2** (Fig. 3a).[13] It was later confirmed by Mock that his group initially prepared *rac*-**2** as an intermediate in a planned synthesis of *rac*-**1**, where trisubstitution of *rac*-**2** with azide nucleophile followed by azide reduction and concomitant ring closure of the corresponding tri(α-aminoacetate) would form *rac*-**1**.[22] However, the substitution of *rac*-**2** with sodium azide was found to trigger the elimination of HBr. Later the triacetate *rac*-**3** (Fig. 3b) bearing no hydrogen at the central carbon was synthesized by Branda[23] and Rebek with the expectation that this molecule would

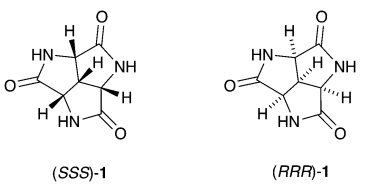

Fig. 1 The structure of the racemic trilactam *rac*-**1**.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d2cc00345g

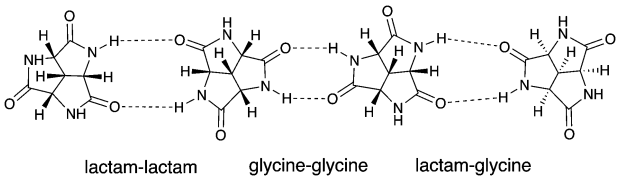


Fig. 2 The three modes for (*SSS*)-**1** to self-assemble *via* hydrogen bonding: lactam–lactam (left), glycine–glycine (middle) and lactam–glycine (right).

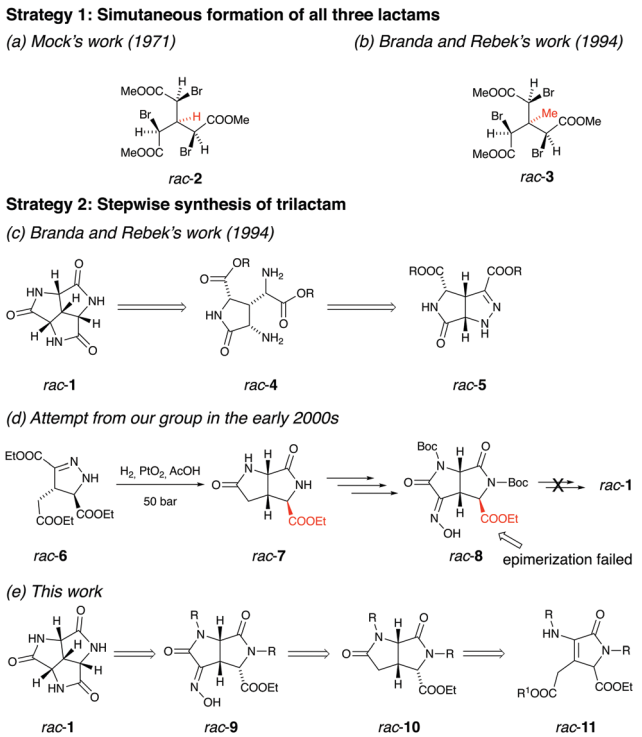


Fig. 3 Synthetic efforts towards *rac*-**1** using different strategies.

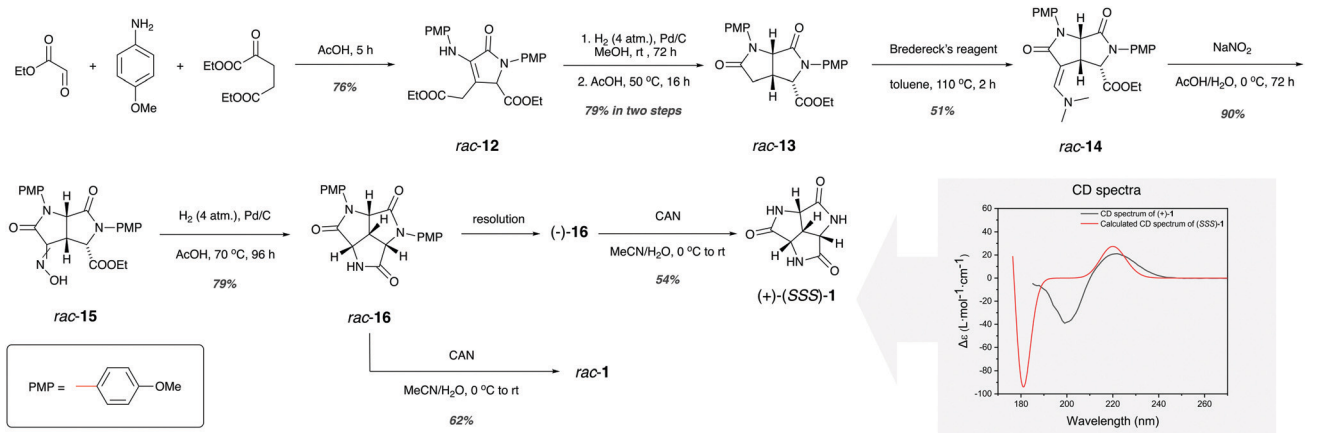
undergo the azide substitution.[17] Unfortunately, the methyl group in *rac*-**3** on the central carbon, although excluding the elimination of HBr, introduced neopentyl systems within the molecule, which hindered the reactivity of the bromides towards S_N2 reactions with azide as a nucleophile.

Since the strategy based on the simultaneous formation of all three lactams failed, Branda and Rebek turned their attention to a stepwise procedure (Fig. 3c).[17] The key intermediate in this route is bicyclic pyrazoline *rac*-**5**, which could afford *rac*-**4** *via* hydrogenation. Several synthetic routes were attempted in an endeavour to obtain *rac*-**5** but turned out to be fruitless.

Unaware of the extensive efforts by Branda and Rebek, we started our journey towards *rac*-**1** in the early 2000s aiming to study its self-assembly. Several different synthetic routes were attempted without succeeding to reach the target molecule. The furthest-reaching route is shown in Fig. 3d. Similar as planned in Branda and Rebek's second route, the reduction of pyrazoline *rac*-**6** followed by the acid-promoted ring-closure gave dilactam *rac*-**7**, which was transformed to oxime *rac*-**8** in several steps. Unfortunately, the obtained stereochemistry of the carboxylic ester in *rac*-**8** prevented the final ring-closure. Epimerization of *rac*-**8** to acquire the correct stereochemistry was attempted with no success.

A turning point appeared in 2018, when we were inspired by a three-component synthesis of highly functionalized 3-pyrrolin-2-ones reported by Palacios in the same year.[24] We recognized that *rac*-**11** could be a suitable synthon for *rac*-**1**. Based on this, we performed a new retrosynthetic analysis (Fig. 3e). The stereoselective hydrogenation of *rac*-**11** followed by the ring-closure would afford dilactam *rac*-**10**, which possesses the correct stereochemistry to allow for the final ring-closure. The installation of the third nitrogen on *rac*-**10** could be performed similarly as from *rac*-**7** to *rac*-**8** (Fig. 3d). The third lactam would be formed by the reduction of oxime *rac*-**9** in acidic condition, followed by deprotection, giving the final trilactam *rac*-**1**.

As presented in Scheme 1, the synthesis of *rac*-**1** started by the three-component synthesis of 3-pyrrolin-2-one *rac*-**12**, where *p*-methoxyphenyl (PMP) groups were installed on the amine and the lactam, respectively. Compared to the phosphoric acids that were used by Palacios in a similar cyclization,[24]



Scheme 1 Synthesis of trilactam *rac*-**1** and (+)-(*SSS*)-**1** and the determination of the absolute configuration of (+)-**1**.

acetic acid was found to give a higher yield by facilitating the intramolecular lactamization. Treatment of *rac*-**12** with pressurized hydrogen over palladium on activated charcoal allowed the stereoselective addition of hydrogen from the less sterically hindered face of the double bond. Further lactamization promoted by acetic acid established the *cis*-fused dilactam *rac*-**13** with the desired stereochemistry of the carboxylic ester (Fig. S2, ESI†). The stepwise reaction was necessary, since direct hydrogenation in acetic acid resulted in a lower yield as well as the epimerization at the α-carbon of the ester group. The attachment of the third nitrogen was accomplished by the α-enamination of *rac*-**13** using Bredereck's reagent.[25] The desired intermediate *rac*-**14** was obtained in almost 1 : 1 ratio together with its epimer. The epimerization could be attributed to the *tert*-butoxy anion generated from Bredereck's reagent during the reaction. Variation of the solvent, temperature and reagent stoichiometry failed to tune the ratio between the two epimers. The reaction of *rac*-**14** with sodium nitrite in cold acetic acid/water mixture provided oxime *rac*-**15** as a mixture of the *E*/*Z* isomers in excellent yield. With everything set for the final lactamization, *rac*-**15** was subjected to another pressurized palladium-catalysed hydrogenation to give diprotected trilactam *rac*-**16**. Even though the ring-closure was accelerated by acetic acid and the increased reaction temperature, it took four days for the reaction to be completed. The removal of the two PMP groups on *rac*-**16** by ceric ammonium nitrate (CAN) was straightforward. However, the purification of the product was a challenge. Bearing three lactam groups within the structure, *rac*-**1** exhibited higher affinity for water than for organic solvents. Therefore, extraction of the reaction crude during work-up with organic solvents did not result in the separation of *rac*-**1** from the excess inorganic components. This issue was later solved by employing ion-exchange chromatography, where the uncharged product had a different retention time than the charged inorganic species. Further separation by HPLC yielded *rac*-**1** as a white solid. Enantiopure **1** was also prepared. The low solubility of *rac*-**1** in most solvents made it difficult to resolve the enantiomers by normal phase chiral chromatography. Instead, the more soluble precursor *rac*-**16** was resolved on a preparative chiral column. Deprotection of (−)-**16** followed by the same purification as for *rac*-**1** resulted in (+)-**1**. The absolute configuration of (+)-**1** was assigned as (+)-(*SSS*)-**1** by comparing the experimental optical rotation and circular dichroism (CD) spectrum with corresponding quantum chemically calculated ones (see Scheme 1 and ESI†).

Preliminary self-assembly studies in solution were carried out with and without guests for both *rac*-**1** and (+)-(*SSS*)-**1**, respectively (see ESI†). However, no indication of host–guest complexation was observed in ^{1}H NMR spectra. This could be attributed to the poor solubility of *rac*-**1** and (+)-(*SSS*)-**1** in less polar solvents such as chloroform and toluene, which can provide a benign environment for hydrogen bonding. For both *rac*-**1** and (+)-(*SSS*)-**1**, the least polar solvent that could give sufficient solubility for NMR study was DMF-d_7, which in general is too polar for hydrogen-bond based self-assembly.

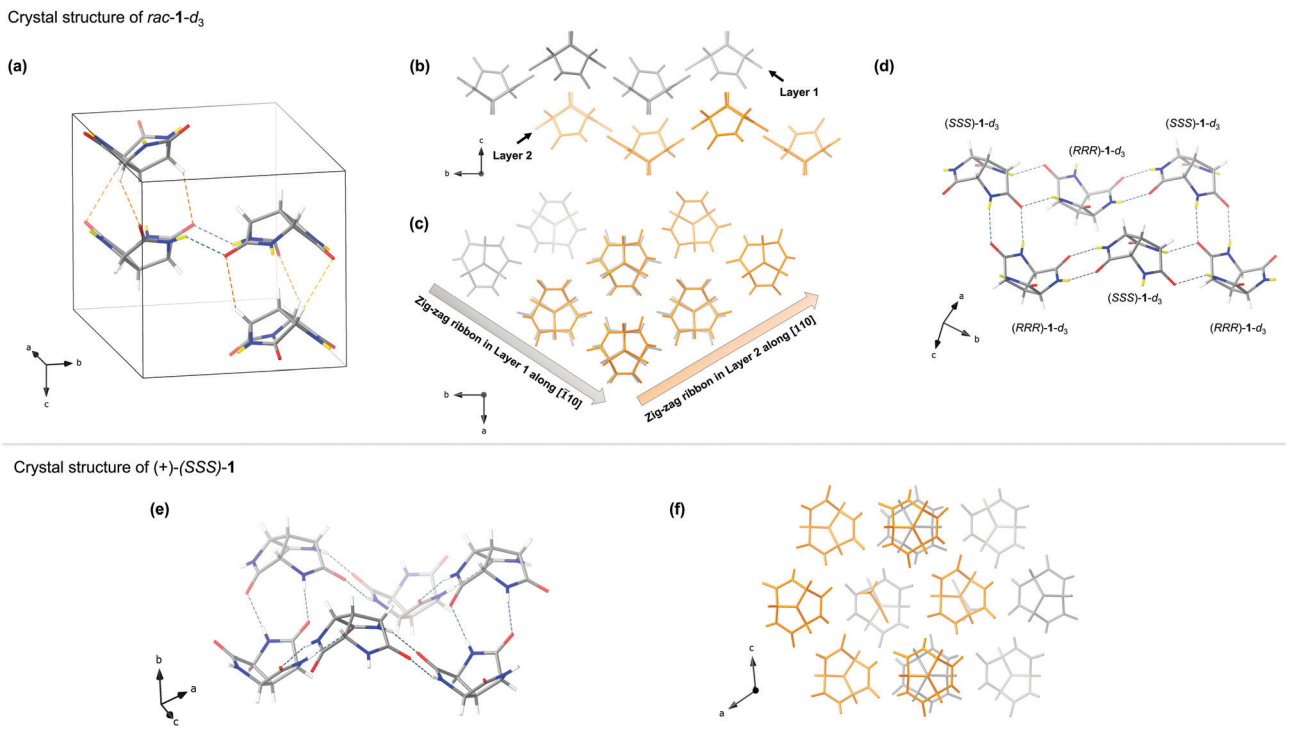


Fig. 4 Crystal structures of *rac*-**1**-d_3 and (+)-(*SSS*)-**1**. The hydrogen bonds are showed as dashed lines. (a) The unit cell of *rac*-**1**-d_3; (b) The packing diagram of *rac*-**1**-d_3 viewing from [100]; (c) The packing diagram of *rac*-**1**-d_3 viewing from [001]; (d) The hexagonal tiling of *rac*-**1**-d_3; (e) The hexagonal tiling of (+)-(*SSS*)-**1**; (f) The packing diagram of (+)-(*SSS*)-**1** viewing from [010]. In (a), (d) and (e), grey = carbon atom; red = oxygen atom; blue = nitrogen atom; white = hydrogen atom; yellow = deuterium atom.

Fortunately, we were more successful with solid-state self-assembly studies. Single crystals of *rac*-**1**-d_3‡ were obtained from deuterium oxide by slow cooling and investigated by X-ray diffraction. As shown in Fig. 4a, the unit cell consists of two opposite-pointing stacks of trilactams. Each stack contains one (*RRR*)-**1**-d_3 and one (*SSS*)-**1**-d_3 that overlay along the *c*-axis *via* three pairs of weak C–H···O hydrogen bonds with the average C(H)···O distance of 3.55 Å. The two stacks are linked by a pair of glycine–glycine hydrogen bonds with the N(D)···O distance of 2.91 Å, which is within the range of typical hydrogen bond length for peptides.[26] Closer inspection of the packing diagram reveals more interesting aspects. Viewing from [100], two layers of parallel zig-zag ribbons along [$\bar{1}$10] and [110] alternately stack along the *c*-axis (Fig. 4b and c). Each ribbon is assembled from alternating (*RRR*)-**1**-d_3 and (*SSS*)-**1**-d_3. Within each ribbon, the interaction between the adjacent trilactam alternates between glycine–glycine hydrogen bonds and lactam–lactam hydrogen bonds. Parallel ribbons of the same layer are cross-linked every other trilactam through another pair of lactam–lactam hydrogen bonds (Fig. 4c). This pattern could also be regarded as alternately stacked infinite layers of non-planar hexagonal tiling where alternating (*RRR*)-**1**-d_3 and (*SSS*)-**1**-d_3 assemble according to an unusual $R_6^4(24)$ graph set (Fig. 4d).[27,28] Given that glycine–glycine interaction tends to give more stable assemblies compared to lactam–lactam interaction,[17] it is interesting to note that in the present case the hexagonal pattern consists of two pairs of lactam–lactam hydrogen bonds and one pair of glycine–glycine hydrogen bonds. The energy demand for the formation of the energetic unfavourable pattern could be compensated by the efficient packing and the C–H···O hydrogen bonds between the layers.

Single crystals of (+)-(*SSS*)-**1**‡ were obtained from a water/acetonitrile mixture by layer diffusion. X-ray diffraction revealed the formation of infinite layers of a more regular hexagonal tiling which can be found in the crystals of similar compounds.[10,17] In each hexagonal unit, six trilactams with alternating orientations are linked through glycine–lactam interaction according to the $R_6^6(27)$ graph set (Fig. 4e).[27,28] The average length of the N(H)···O bonds is 2.87 Å, which is slightly shorter than those in racemic crystals. The layers stack along the *b*-axis in a repeating pattern where over the centre of each hexagonal unit there is a trilactam from the adjacent layer (Fig. 4f). The voids between the layers are occupied by acetonitrile molecules (Fig. 4f).

In summary, 51 years since it was first proposed as a synthetic target, the highly symmetric trilactam **1** was finally synthesized in both racemic and enantiopure form. Solid-state self-assembly of *rac*-**1**-d_3 and (+)-(*SSS*)-**1** were investigated by X-ray diffraction, which revealed two different patterns of hexagonal tiling through intermolecular hydrogen bonding. Further exploration into the self-assembly of *rac*-**1** and (+)-(*SSS*)-**1** in solution was hindered by their limited solubility in less polar aprotic solvents. Nevertheless, the successful synthesis of **1** opens new possibilities in host–guest chemistry, crystal engineering, chiral recognition, asymmetric catalysis as well as surface engineering. To be able to study the self-assembly of the trilactam in non-polar solvents, effort towards lipophilic derivatives of **1** is currently underway in our group.

K. W. thanks the Swedish Research Council (VR) and the Swedish Foundation for Strategic Research (Chemistry for life science program) for financial support. Y. L. acknowledges the Royal Physiographic Society of Lund for financial support and China Scholarship Council for PhD scholarship. We are grateful to Dr. Alexey Polukeev for helping to build the set-up for pressurized hydrogenation.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

‡ Crystal data for *rac*-**1**-d_3: $C_7H_4D_3N_3O_3$, M = 184.17, monoclinic, a = 7.2905(7), b = 11.3194(9), c = 9.0781(10) Å, U = 695.89(13) Å^3, T = 293(2) K, space group $P2_1/c$ (no. 14), Z = 4, 4010 reflections collected, 1622 unique (R_{int} = 0.0249). The final wR_2 was 0.1184 (all data). Crystal data for (+)-(*SSS*)-**1**: [2($C_7H_7N_3O_3$), C_2H_3N], M = 403.36, monoclinic, a = 10.2416(18), b = 9.0837(12), c = 10.5564(16) Å, U = 873.1(3) Å^3, T = 293(2) K, space group $P2_1$ (no. 4), Z = 2, 10598 reflections collected, 10598 unique. The final wR_2 was 0.2876 (all data).

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