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COMMUNICATION

Thiolation of symmetrical and unsymmetrical diketopiperazines†

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The introduction of sulfur units into a variety of symmetrical and unsymmetrical diketopiperazines (DKPs) is described. We investigated different thiolation methods utilizing several bases and electrophilic sulfur reagents, leading to monomethylthio-, bis(methylthio)-, and epithio-DKPs. Their formation proceeded diastereoselectively, facilitating the application in total syntheses of many thiodiketopiperazine (TDKP) natural products. Furthermore, possible side reactions as well as mechanistic studies and stereochemical structural assignments of the obtained products are given.

Introduction

The smallest cyclic peptides built by amino acids are the so called diketopiperazines (DKPs). In recent research, DKPs and higher functionalized analogs – the thiodiketopiperazines (TDKPs) – have become attractive due to their versatile biological activity (Fig. 1).[1] Nevertheless, only a few examples of total syntheses of the large family of (T)DKP mycotoxins exist in the literature. Especially the introduction of the sulfur bridge remains a challenge.[2]

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† Electronic supplementary information (ESI) available: Experimental and spectral data for all new compounds. CCDC reference numbers 846902 (**1**{**bb**}), 852473 (**3**{**aa**}), 846903 (**4**{**bb**}), 852472 (**3**{**bb**}), 852474 (**4**{**cc**} and **17**) and 846901 (**14**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06663g

However, there has been progress in the synthesis of complex *epi*(poly)-TDKP natural products during the last few years. Movassaghi *et al.* published an approach to access the dimeric cytotoxic metabolite (+)-11,11′-dideoxyverticillin A (**1**)[3] and (+)-chaetocin A (**2**) as well as the epipoly-TDKPs (+)-chaetocin C (**3**) and (+)-12,12′-dideoxychetracin A (**4**).[4] Their method for the thiolation of the DKP core is based on the postulated biosynthesis[5] of gliotoxin[6] which comprises the formation of acylimmonium ions through dehydration. Following a similar approach, Sodeoka *et al.* were able to synthesize (+)-chaetocin A (**2**), too.[7] Syntheses of the mycotoxins gliocladine C,[8] epicoccin G (**5**), 8,8′-*epi-ent*-rostratin B (**6**)[9] and reported progress toward the preparation of synthetic fragments of challenging TDKPs[10] can be found in the literature as well. The epicoccins M–P (**7–10**) have been isolated from *Epicoccum nigrum* recently.[11] They possess an unusual unsymmetrical sulfur substitution pattern which has not been addressed in total syntheses so far.

Despite the variety and importance of TDKP natural products, to the best of our knowledge, no general method for the introduction of the sulfur bridge has been published to date. Most of the examples above use techniques that seem to be working because of the specific properties and requirements of the individual structures. Therefore, we were looking for a versatile procedure that allows the facile conversion of DKPs to TDKPs in a convenient way.

Results and discussion

The starting materials for the herein reported transformations, symmetrical and unsymmetrical DKPs **1**{**xy**}, could be easily synthesized from commercially available amino acids (**a–e**) using

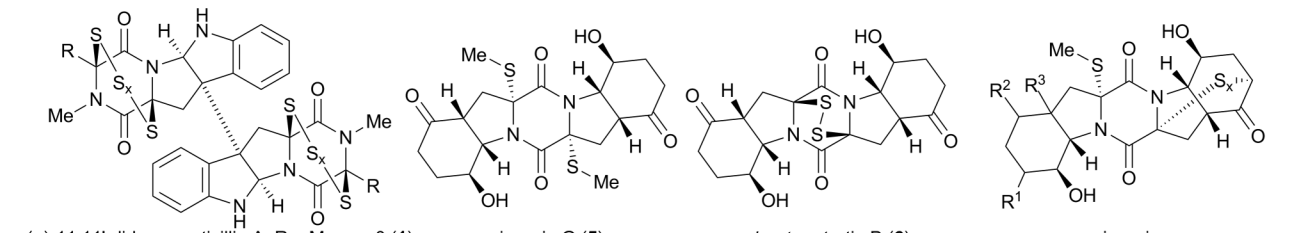
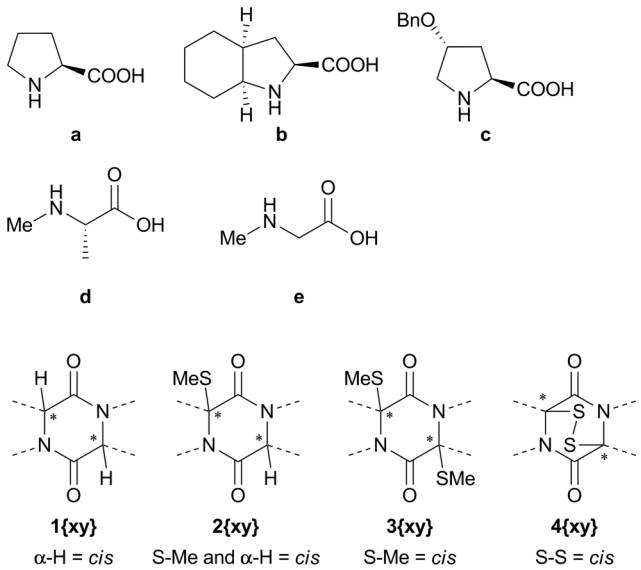


Fig. 1 Examples of *epi*(poly)thiodiketopiperazine natural products.

Table 1 Synthesis of monomethylthio- (**2**{**xy**}), bis(methylthio)- (**3**{**xy**}) and epithio- (**4**{**xy**}) DKPs from symmetrical and unsymmetrical DKPs **1**{**xy**}



Entry	Starting material	Conditions[a]	Isolated yield (%) **2**{**xy**}	**3**{**xy**}	**4**{**xy**}
1	**1**{**aa**}	A	17		
2	**1**{**aa**}	B		52	
3	**1**{**aa**}	C			traces
4	**1**{**bb**}	A	50		
5	**1**{**bb**}	B	50	30	
6	**1**{**bb**}	C			32
7	**1**{**cc**}	B		23	
8	**1**{**cc**}	C			42
9	**1**{**dd**}	B		41	
10	**1**{**dd**}	C			31
11	**1**{**ee**}	B		traces	
12	**1**{**ee**}	C			traces
13	**1**{**ab**}	A	**16**/*epi*-**16** (see Scheme 3)		
14	**1**{**ab**}	B		21	
15	**1**{**ab**}	C			16

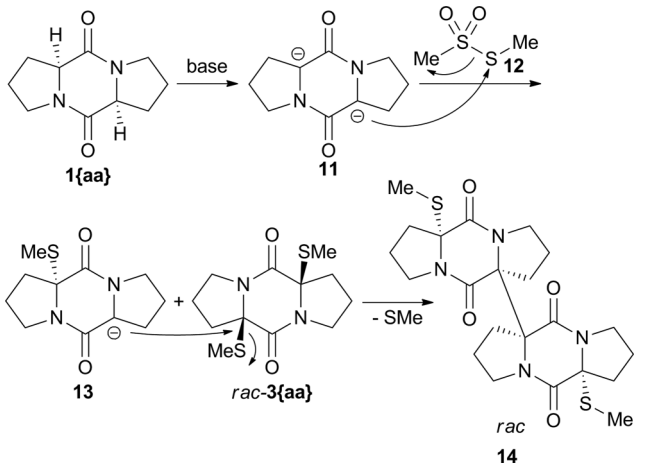
[a] A: NaHMDS, THF, −78 °C, 1 h; then $MeSO_2SMe$ (**12**), THF, −78 °C to r.t., 2 h; B: NaHMDS, S_8, THF, r.t.; then **1**{**xy**}; then NaHMDS, r.t., 30 min; then $NaBH_4$, THF/MeOH (1 : 1), 0 °C to r.t., 45 min; then MeI, r.t., 15 h; C: NaHMDS, S_8, THF, r.t.; then **1**{**xy**}; then NaHMDS, r.t., 30 min; then $NaBH_4$, THF/MeOH (1 : 1), 0 °C to r.t., 45 min; then KI_3, r.t., 10 min.

our previously published one-pot procedure.[12] The figure in Table 1 gives an overview of the amino acid monomers as well as a general structure of the possible starting materials **1**{**xy**} and products **2**–**4**{**xy**} described in this article. In our first experiments, we deprotonated *cyclo*-proline-proline **1**{**aa**} with LDA as a base. This led to the formation of dianion **11** (Scheme 1) as proved by a quench with D_2O followed by work-up and NMR as well as mass spectroscopy experiments. Addition of electrophilic sulfur reagent **12** did not furnish desired bis(methylthio) product **3**{**aa**} (Scheme 2).

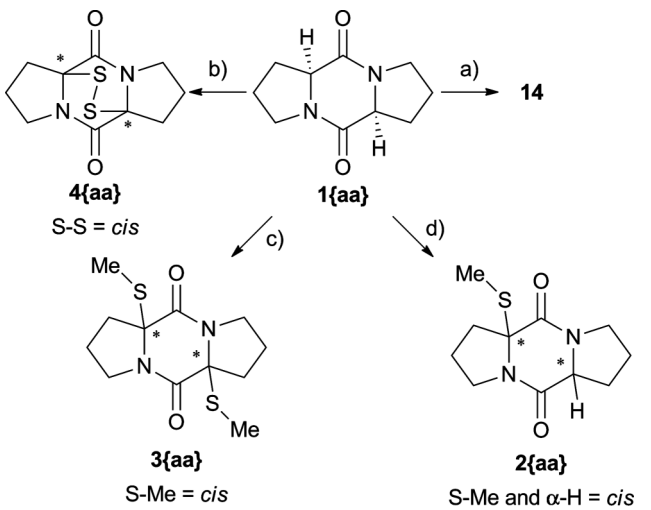
We only observed formation of dimeric product **14** whose structure could be unequivocally proven by X-ray crystallography (Fig. 2).‡ The surprisingly long C–C bond (161 pm) between the two DKP rings is noteworthy. Schmidt *et al.* already postulated this structure as a side product in their thiolation experiments[13] which we were now able to confirm. We postulate that dimerization occurs as shown in Scheme 1. Dianion **11** subsequently reacts with **12** in a substitution reaction. Thus, mono- and bis(methylthio)-derivatives **13** and *rac*-**3**{**aa**} are present in the reaction mixture at the same time. Monoanion **13** can attack derivative *rac*-**3**{**aa**} due to the now positively charged α-carbon atom. This C-C-bond formation furnishes observed DKP dimer **14** as one diastereoisomer in a racemic mixture.

In the further course of our work we varied base (LDA, KHMDS, NaHMDS, LiHMDS, LDEA, LDA + *n*-BuLi, LDA + DMPU), solvent, temperature and sulfur reagent (Me-SS-Me, Me-SO_2S-Me (**12**), PMB-SS-PMB, tolyl-SO_2S-PMB, tolyl-SO_2S-butyl, Ph-SO_2S-Ph, tetramethylthiuram disulfide) to introduce one or more thio units to the DKP core.

With both DKP **1**{**aa**} and DKP **1**{**bb**}, we were able to obtain monomethylthio derivatives **2**{**aa**} and **2**{**bb**} (Scheme 2, Table 1, Entry 1,4) using NaHMDS as a base and *S*-methyl methanesulfonothioate (**12**) as the electrophilic sulfur reagent. This method depicts the first approach toward natural products bearing only one thiomethyl substituent, *e.g.* epicoccins M–P (**7**–**10**).



Scheme 1 Proposed mechanism for deprotonation of DKP **1**{**aa**} with base, followed by thiolation with *S*-methyl methanesulfonothioate (**12**) and formation of dimeric compound **14**.



Scheme 2 Synthesis of thiolated derivatives **2**–**4**{**aa**} and **14** of *cyclo*-proline-proline **1**{**aa**}. Reagents and conditions: (a) LDA, THF, −78 °C, 3 h; then $MeSO_2SMe$, THF, −78 °C to r.t., 71%; (b) NaHMDS, S_8, THF, r.t.; then **1**{**aa**}; then NaHMDS, r.t., 30 min; then $NaBH_4$, THF/MeOH (1 : 1), 0 °C to r.t., 45 min; then KI_3, r.t., 10 min, traces; (c) NaHMDS, S_8, THF, r.t.; then **1**{**aa**}; then NaHMDS, r.t., 30 min; then $NaBH_4$, THF/MeOH (1 : 1), 0 °C to r.t., 45 min; then MeI, r.t., 15 h, 52%; (d) NaHMDS, THF, −78 °C, 1 h; then $MeSO_2SMe$, THF, −78 °C to r.t., 2 h, 17%.

When DKP **1**{**ab**} was treated with NaHMDS followed by the addition of *S*-methyl methanesulfonothioate (**12**) (Table 1, Entry 13), we isolated dehydro-DKP **16** and its epimer *epi*-**16** in a 2 : 1 ratio in overall 87% yield. A proposed mechanism for its formation is shown in Scheme 3.

Initially, the anion of monomethyl derivative **15** is built through deprotonation followed by addition of a methylthio unit. In the presence of an excess of base, this group can be eliminated. Reprotonation occurs in a 2 : 1 favor of one side of the molecule to give the unsaturated species **16** and *epi*-**16**. The dehydro-DKP structural motif can be found in several natural products, *e.g.* spirotryprostatin B[14] and drimentin B.[15] After optimization, the described one-step elimination reaction could be used for their

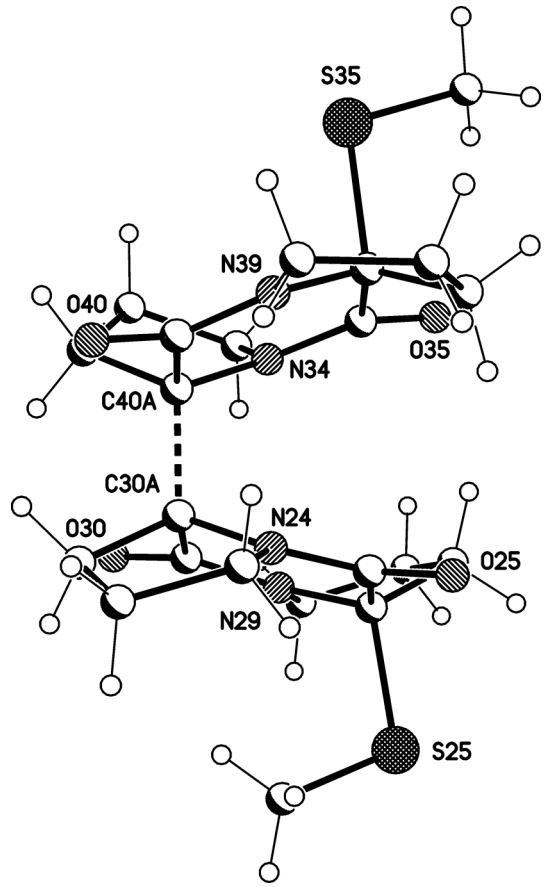
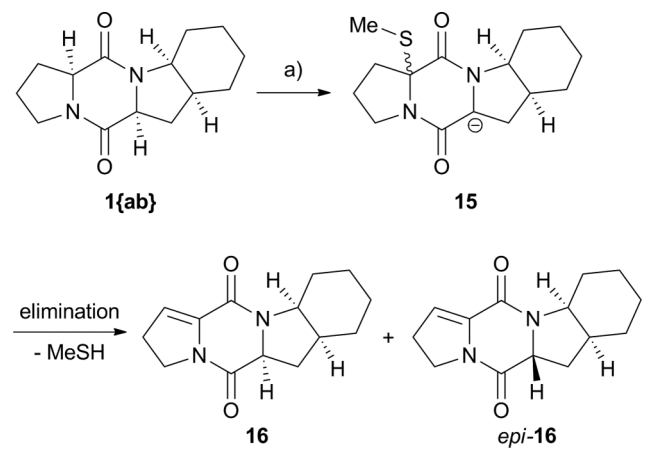


Fig. 2 Crystal structure of dimeric compound **14**. One of the crystallographic independent molecules is shown. The dotted line shows the long C–C bond between the two DKP rings.



Scheme 3 Formation of dehydro-DKP **16** and *epi*-**16**. Reagents and conditions: (a) NaHMDS, THF, −78 °C, 3 h; then $MeSO_2SMe$, THF, −78 °C to r.t., 87%.

total syntheses. It would be an improvement to the non-selective or multi-step procedures that can be found in the literature.[16]

During the course of our work,[12a,17] Nicolaou *et al.* came up with their method using molecular sulfur and NaHMDS[9] based on the pioneering sulfenylation work by Schmidt *et al.*[13] The latter were the first ones to deprotonate a diketopiperazine followed by addition of molecular sulfur to obtain epithio-DKPs. By changing

the non-practicable use of sodium in liquid ammonia to NaHMDS as a base, we, as well as the group of Nicolaou, were able to improve Schmidt's method. We found that applying these revised reaction conditions to our substrates yielded all monomethylthio- (**2**{**xy**}), bis(methylthio)- (**3**{**xy**}) and epithio- (**4**{**xy**}) DKPs depending on the various reaction conditions. The results comparing the different methods with a range of different DKPs **1**{**xy**} are summarized in Table 1.

We were able to synthesize a variety of thiolated DKPs which were all obtained as single diastereoisomers. Upscaling (2 g scale) the reaction of DKP **1**{**aa**} to give TDKP **3**{**aa**} still gave a comparable yield of 39%.

Both sulfur electrophiles were found to attack the molecule from the same side, as all symmetrical bis(methylthio)-DKPs (**3**{**xy**}) only showed one signal in both ^{1}H and ^{13}C NMR for the two methyl groups. Stereochemistry of the thiolated species was assigned using NOE correlations (Fig. 4) as well as X-ray crystallography. The structure of **3**{**aa**} was found to be racemic in its crystal (Fig. 3).

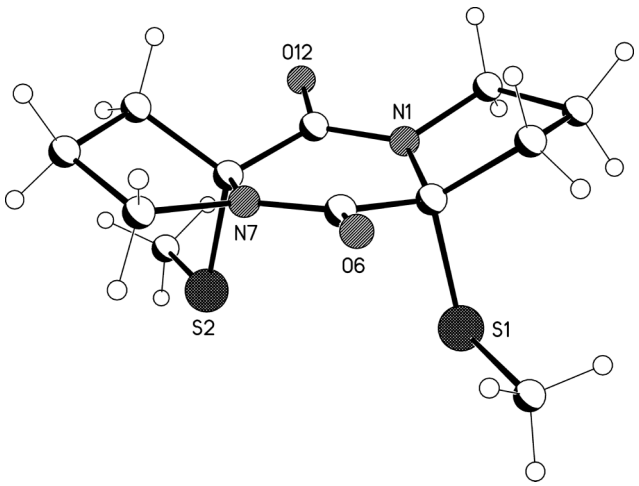


Fig. 3 Crystal structure of bis(methylthio)-DKP **3**{**aa**}. The relative *R*,*R* configuration is shown.

Since the molecule showed optical rotation, no complete racemization had occurred, but the formation of one enantiomer was favored. Apparently, partial racemization occurs during deprotonation as the starting material **1**{**aa**} is an enantiomerically pure compound. The shape of the molecule, as seen in the crystal structure of **1**{**aa**},[12b] has presumably no strongly favored side for an electrophilic attack. This observation is in accordance to the proposed mechanism – comprising a dianion – for the formation of dimer **14** (Scheme 1). The structures of **2**{**bb**}, **3**{**bb**}, **3**{**cc**}, **4**{**bb**}, **4**{**cc**}, **3**{**ab**} and **4**{**ab**} could be assigned as enantiomerically pure. The 4a*S*,14a*S* configuration of **2**{**bb**} and **3**{**bb**} cannot be changed during the reaction. Due to the NOE correlations between these protons and the protons of the methylthio group, the stereogenic center at position 13a (and 6a for **3**{**bb**}) has to have *R* configuration. Furthermore, we were able to confirm the structure of compound **3**{**bb**} by X-ray crystallography (Fig. 4). Since the 2*R* configuration in **3**{**cc**} cannot be altered, a 5a*R*,10a*R* structure must be on hand here. The structure of the corresponding epidithio-DKP, **4**{**cc**}, could be proven by crystal structure analysis (Fig. 5). The structure co-crystallized in a 2 : 1 ratio together with the epitrithio-DKP **17**,

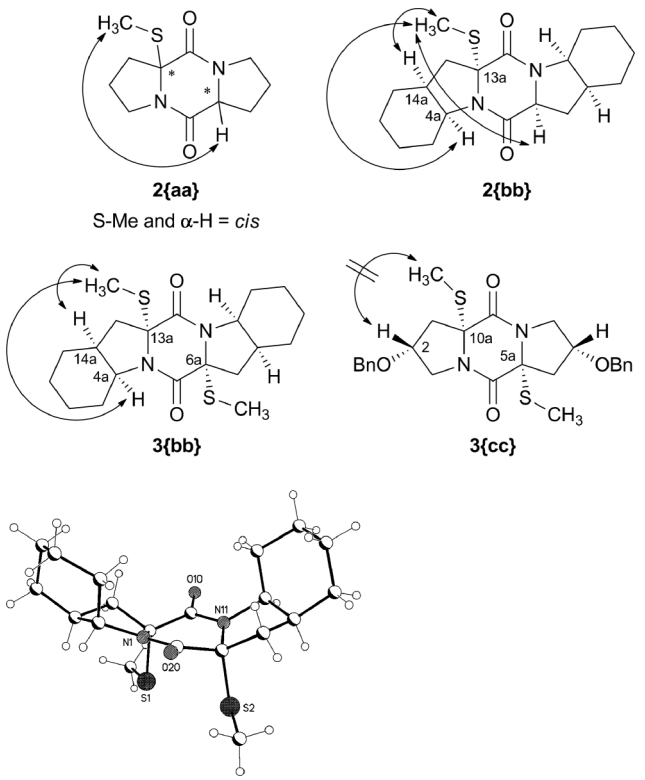


Fig. 4 NOE correlations (arrows) for compounds **2**{**aa**}, **2**{**bb**}, **3**{**bb**} and **3**{**cc**} and crystal structure of compound **3**{**bb**}.

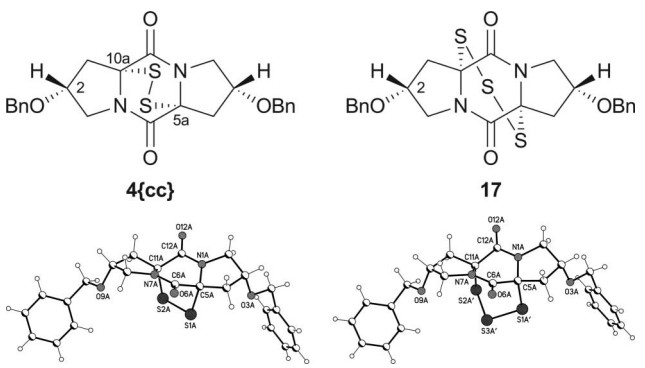


Fig. 5 Structures and crystal structures of epidithio-DKP **4**{**cc**} and epitrithio-DKP **17**.

which is another interesting natural product motif.[18] With this example, we were able to show that the presented method tolerates protected hydroxyl functional groups without epimerization. The unsymmetrical thiolated species **3**{**ab**} and **4**{**ab**} were obtained as single diastereomers confirming that thiolation had occurred in an enantioselective procedure. This supports the applicability of the selective thiolation procedure for unsymmetrical DKPs such as **1**{**ab**}.

Fig. 6 shows a Least Square Fit of the crystal structures of DKP **1**{**bb**} and epithio-DKP **4**{**bb**}. Almost no change in the geometry of starting material and product has occurred during the thiolation reaction. The rigid scaffold of the pentacyclic DKP **1**{**bb**} might be the reason why only one thiolated stereoisomer is formed. Due to the curved shape of **1**{**bb**}, the attack of the sulfur from the convex side of the molecule is strongly favored. The substitution

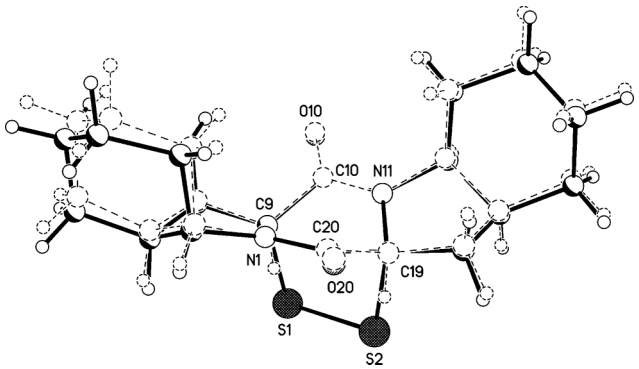
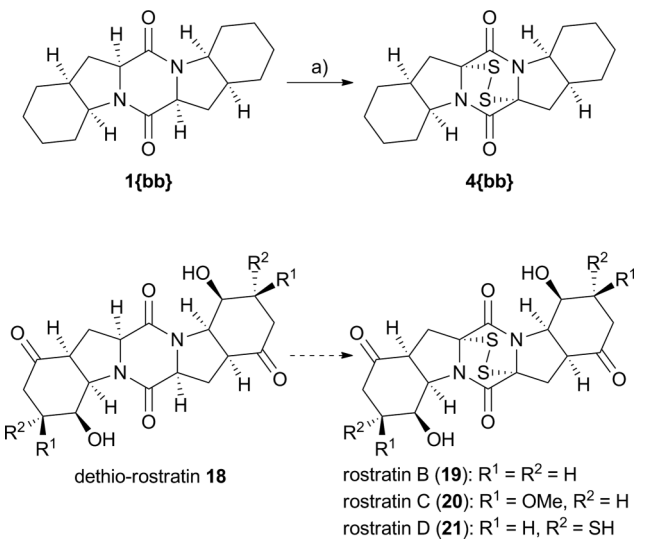


Fig. 6 Least Square Fit of the crystal structures of DKP **1**{**bb**} and epithio-DKP **4**{**bb**}.

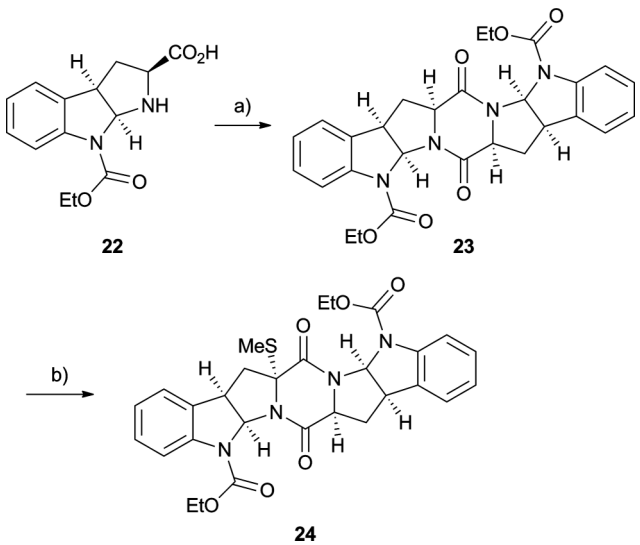
of the hydrogen atoms under retention of the configuration implies the occurrence of free anions since a concerted mechanism would lead to inversion at the α-carbon atoms.

The obtained enantiomeric purity of thiolated species **4**{**bb**} in comparison to racemically built structure **3**{**aa**} shows that the method reported is suitable for the stereoselective synthesis of complex thiolated molecules. DKP **1**{**bb**} represents the scaffold of dethio-rostratin **18** (Scheme 4). The presented method should therefore be applicable for the enantioselective total synthesis of rostratins B–D (**19–21**).[19]



Scheme 4 Enantioselective synthesis of epidithio-DKP **4**{**bb**} and its potential application to the total synthesis of rostratins B–D (**19–21**). (a) NaHMDS, S_8, THF, r.t.; then **1**{**bb**}; then NaHMDS, r.t., 30 min; then $NaBH_4$, THF/MeOH (1 : 1), 0 °C to r.t., 45 min; then KI_3, r.t., 10 min.

If the DKP scaffold of the starting material is bearing small and non-rigid substituents as in the case of **1**{**aa**}, no enantioselectivity can be observed. Due to that fact, the thiolated species **2**{**aa**}, **3**{**dd**} and **4**{**dd**} were presumably obtained as scalemic mixtures of the two possible *cis*-configurated enantiomers, too. Nevertheless, with all DKPs, diastereoselectivity is obtained as both sulfur atoms attack each molecule from the same side. As most of the TDKP natural products have fully substituted structures anyway (see Fig. 1), the method reported could be used for their enantioselective total syntheses. In these cases, the introduction of the sulfur occurs under retention of the configuration at the α-carbon atom of the DKP ring as proved with various examples. When we treated the complex DKP **23** with NaHMDS and molecular sulfur, we observed the formation of monomethylthio-DKP **24** (Scheme 5).



Scheme 5 Formation and thiolation of DKP **23**. (a) $MeOPCl_2$, NEt_3, 1,3-dimethylimidazolium dimethylphosphate, toluene, 30 °C, overnight; then MW, 145 °C, 1 h, 32%; (b) NaHMDS, S_8, THF, r.t.; then **23**; then NaHMDS, r.t., 30 min; then $NaBH_4$, THF/MeOH (1 : 1), 0 °C to r.t., 45 min; then MeI, r.t., 15 h, 23%.

DKP **23** was obtained through dimerization of amino acid **22**, which was prepared in 4 steps according to the literature.[20] Its thiolation result proves the compatibility of the presented method with pyrroloindole units which can be found in many natural products.[21] It can furthermore be seen as another example for the selective preparation of monomethylthio-DKPs.

Conclusions

We were able to synthesize a range of different thiodiketopiperazines (TDKPs) from diketopiperazines (DKPs), which themselves were accessible in one step from commercially available amino acids. The thiolation reactions proceeded with high diastereoselectivity (stereochemistry and structural properties were confirmed by NOESY experiments and/or X-Ray crystallography) and could be carried out on both milligram and gram scales. The substitution pattern of the products obtained depended on the applied reaction conditions, which consisted of treatment with a base and an electrophilic sulfur reagent, such as sulfonothioates or S_8. Hereby, various TDKPs bearing one or two methylthio substituents as well as disulfide bridges could be obtained. The herein proposed mechanism for thiolation – implying the formation of a dianion – was supported by deuteration experiments and determination of the stereochemistry of the products obtained. Furthermore, the formation of a dimeric DKP with a notable structure was observed. We were also able to obtain a dehydro-DKP in a single step procedure, which is another structural motif found in several natural products. In conclusion, we proved that

the selection of the used thiolation methods is applicable to numerous DKPs, as exemplified by a variety of symmetrical, unsymmetrical and unsubstituted as well as functionalized DKPs, which can be mono- to heptacyclic. Because we were able to mono-, bis- and epithiolate DKPs bearing very different structural, electronic, stereochemical and steric properties, we anticipate transferring these results to the thiolation of other DKPs leading to highly biologically active natural products. Investigations toward the total synthesis of potent TDKPs are currently carried out in our group.

Acknowledgements

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Notes and references

‡ *Crystal structure determinations.* The single-crystal X-ray diffraction study was carried out on a Bruker-Nonius Kappa-CCD diffractometer or a Bruker-Nonius APEXII diffractometer at 123(2) K using Mo-Kα radiation (λ = 0.71073 Å). Direct Methods (SHELXS-97)[22] were used for structure solution and refinement was carried out using SHELXL-97[22] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O) free). A semi-empirical absorption correction was applied for **4**{**bb**}. Due to the bad quality of the data caused by the size and shape of the crystal for **3**{**bb**} general ISOR restrains were applied. In **4**{**cc**} **and 17** the two solvent molecules are disordered. Two of the three crystallographic independent molecules are ordered showing the structure **4**{**cc**}. The third molecule is disordered showing the structure of **4**{**cc**} and **17** in the ratio 0.69 : 0.31.

The absolute structure of **1**{**bb**} could neither be determined reliably by refinement of Flack's *x*-parameter (x = –3(3)),[23] nor by using Bayesian statistics on Bijvoet differences (y = 0.3(14)).[24] The enantiomer has been assigned by reference to an unchanging chiral center in the synthetic procedure. The absolute structure of **3**{**bb**}, **4**{**bb**} and (**4**{**cc**} **and 17**) could be determined (x = 0.07(6), y = 0.05(3) (**4**{**bb**}), x = 0.0(2), y = 0.03(1) (**3**{**bb**}), x = 0.03(7), y = 0.047(13) ({**4**{**cc**} **and 17**)).

1{**bb**}: colorless, $C_{18}H_{26}N_2O_2$, M = 302.41, crystal size 0.24 × 0.06 × 0.02 mm, orthorhombic, space group $P2_12_12_1$ (no. 19): a = 6.430(1) Å, b = 11.207(2) Å, c = 21.269(3) Å, V = 1532.7(4) Å^3, Z = 4, ρ(calc) = 1.311 Mg m^{-3}, F(000) = 656, μ = 0.085 mm^{-1}, 15375 reflections ($2\theta_{max}$ = 50°), 2697 unique [R_{int} = 0.141], 199 parameters, $R1$ ($I > 2\sigma(I)$) = 0.078, w$R2$ (all data) = 0.148, GOF = 1.04, largest diff. peak and hole 0.249/–0.280 e Å^{-3}.

3{**aa**}: colorless, $C_{12}H_{18}N_2O_2S_2$, M = 286.40, crystal size 0.32 × 0.04 × 0.04 mm, monoclinic, space group $P2_1/c$ (no. 14): a = 17.1844(13) Å, b = 7.3729(5) Å, c = 10.8107(8) Å, β = 105.732(3)°, V = 1318.39(17) Å^3, Z = 4, ρ(calc) = 1.443 Mg m^{-3}, F(000) = 608, μ = 0.400 mm^{-1}, 6338 reflections ($2\theta_{max}$ = 55°), 2966 unique [R_{int} = 0.032], 165 parameters, $R1$ ($I > 2\sigma(I)$) = 0.048, w$R2$ (all data) = 0.105, GOF = 1.14, largest diff. peak and hole 0.394/–0.288 e Å^{-3}.

3{**bb**}: yellow, $C_{20}H_{30}N_2O_2S_2$, M = 394.58, crystal size 0.15 × 0.02 × 0.02 mm, triclinic, space group $P\bar{1}$ (no. 1): a = 9.1262(9) Å, b = 9.6454(10) Å, c = 11.5103(9) Å, α = 91.426(5)°, β = 101.320(6)°, γ = 91.777(5)°, V = 992.52(16) Å^3, Z = 2, ρ(calc) = 1.320 Mg m^{-3}, F(000) = 424, μ = 0.286 mm^{-1}, 5890 reflections ($2\theta_{max}$ = 50°), 4287 unique [R_{int} = 0.060], 473 parameters, 315 restraint, $R1$ ($I > 2\sigma(I)$) = 0.101, w$R2$ (all data) = 0.226, GOF = 1.17, largest diff. peak and hole 0.665/–0.447 e Å^{-3}.

4{**bb**}: yellow, $C_{18}H_{24}N_2O_2S_2$, M = 364.51, crystal size 0.30 × 0.20 × 0.05 mm, orthorhombic, space group $P2_12_12_1$ (no. 19): a = 6.4416(6) Å, b = 10.8045(5) Å, c = 24.6270(20) Å, V = 1714.0(2) Å^3, Z = 4, ρ(calc) = 1.413 Mg m^{-3}, F(000) = 776, μ = 0.324 mm^{-1}, 12711 reflections ($2\theta_{max}$ = 55°), 3924 unique [R_{int} = 0.035], 217 parameters, $R1$ ($I > 2\sigma(I)$) = 0.035, w$R2$ (all data) = 0.075, GOF = 1.07, largest diff. peak and hole 0.253/–0.199 e Å^{-3}.

4{**cc**} **and 17**: yellow, $C_{74}H_{74}CL_6N_6O_{12}S_{6.31}$ (2.69$C_{24}H_{24}N_2O_4S_2$–0.31 $C_{24}H_{24}N_2O_4S_3$–2$CHCl_3$), M = 1654.39 (formula weight of the asymmetric unit), crystal size 0.36 × 0.12 × 0.06 mm, monoclinic, space group $P2_1$ (no. 4): a = 11.4283(1) Å, b = 17.1077(2) Å, c = 19.3984(2) Å, β = 92.773(1)°, V = 3788.18(7) Å^3, Z = 2, ρ(calc) = 1.450 Mg m^{-3}, F(000) = 1718, μ = 0.466 mm^{-1}, 51084 reflections ($2\theta_{max}$ = 55°), 17215 unique [R_{int} = 0.042], 924 parameters, 220 restraint, $R1$ ($I > 2\sigma(I)$) = 0.076, w$R2$ (all data) = 0.186, GOF = 1.03, largest diff. peak and hole 1.816 (in solvent $CHCl_3$)/–1.324 e Å^{-3}.

14: yellow, $C_{22}H_{30}N_4O_4S_2$–1/8H_2O, M = 480.88, crystal size 0.40 × 0.20 × 0.10 mm, triclinic, space group $P\bar{1}$ (no. 2): a = 9.648(1) Å, b = 14.822(2) Å, c = 16.441(3) Å, α = 104.68(1)°, β = 103.17(1)°, γ = 91.75(1)°, V = 2204.8(6) Å^3, Z = 4, ρ(calc) = 1.449 Mg m^{-3}, F(000) = 1021, μ = 0.281 mm^{-1}, 15993 reflections ($2\theta_{max}$ = 50°), 7743 unique [R_{int} = 0.048], 591 parameters, 3 restraint, $R1$ ($I > 2\sigma(I)$) = 0.058, w$R2$ (all data) = 0.146, GOF = 1.01, largest diff. peak and hole 0.503/–0.399 e Å^{-3}.

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