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Synthesis of Proline-Based Diketopiperazine Scaffolds

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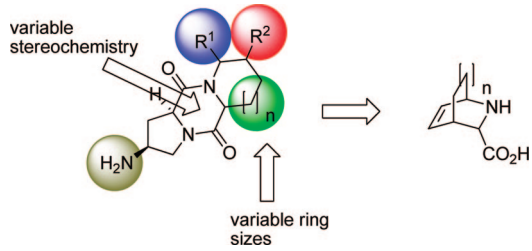

A number of natural products with interesting biological properties are based on a diketopiperazine scaffold. In this context, we have developed a diversity oriented and efficient synthetic strategy to highly functionalized proline-based diketopiperazines. In this paper we describe the stereoselective synthesis of various scaffolds resembling abundant natural product core structures. These scaffolds can be conjugated to a solid phase and are thus platforms for the construction of small compound libraries and the synthesis of natural products with diketopiperazine cores.

Introduction

Small molecules are the key to understanding and modulating protein function as well as developing new therapies and diagnostics.[1] The prerequirements of biological relevance to be met by such molecules are fulfilled by natural product-derived compound collections.[2−5]

Among small heterocyclic molecules, diketopiperazines (DKPs) have attracted considerable attention in recent years[6] and among these, proline (or pipecolic acid) and tryptophan-derived structures with a bicyclo[2.2.x]diazaalkane core constitute a particularly interesting class of natural products.[7−9] Various biological activities, ranging from antihelmintic properties to anti cancer activity, have been assigned to members of this family.[10−17]

As depicted in Figure 1, a common motif of these compounds is a proline-derived DKP-backbone with an annelated ring system derived from a prenylated tryptophan. This tricyclic scaffold forms the core of many natural product families like the cyclotryprostatines, fumitremorgines and spirotryprostatines and is thus an extremely interesting synthetic target for the assembly of natural product-like libraries of high pharmaceutical potential.

In our attempts to find new cancer-specific small molecules for the development of diagnostic tools,[18] we became interested in proline-derived diketopiperazines, because some members have been reported to exert cancer-specific biological effects.[11,15,16] A number of excellent syntheses of different members of this natural product family have been reported and reviewed.[19−23] Most strategies follow a biomimetic approach using indole

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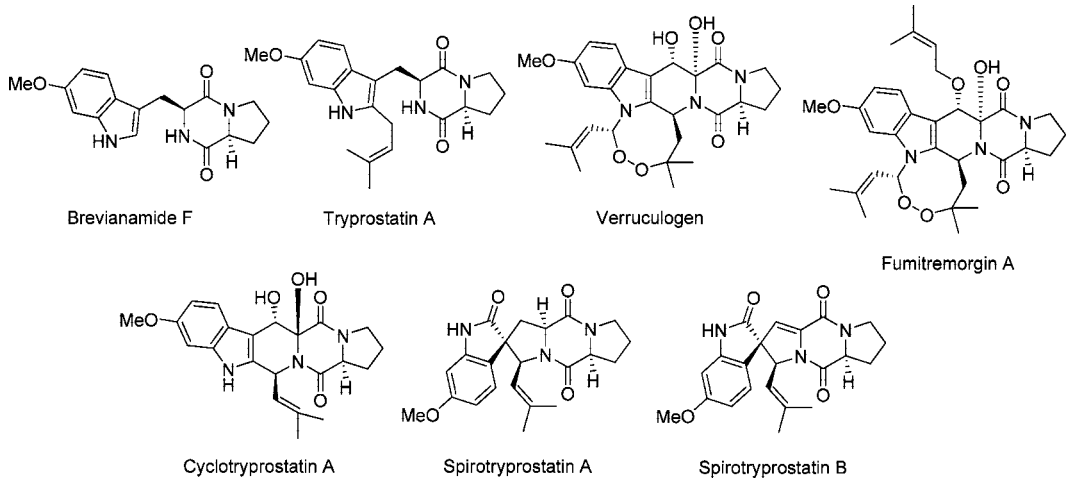
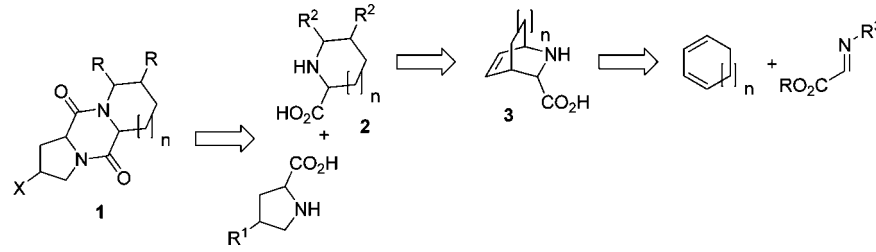


FIGURE 1. Examples for fungal metabolites based on proline-derived DKP scaffolds.

SCHEME 1. Diels-Alder Approach to Proline-Based Diketopiperazine Scaffolds



derivatives as precursor for the assembly of the eastern part of the tricyclic scaffold. However, notable exceptions of this general strategy are known[24] and among these a recently reported protocol by Bräse and co-workers deserves special credits because it provides an easy and quite general excess to various diketopiperazine scaffolds.[25]

Besides their relevance as scaffolds for natural products, conformationally constrained proline-based diketopiperazines play an important role in peptide chemistry as a backbone for artificial peptide receptors[26] and as chiral auxiliaries.[27−29]

In this context, we present a synthetic concept for the tricyclic core of proline-derived DKPs using a Diels−Alder strategy for the assembly of the key fragment **1** (Scheme 1). This concept was pioneered by the Steglich group in a peptide context[30] and was later extended by our group and Arakawas group to the synthesis of cyclic amino acids[31−34] and peptide mimetics.[35−37]

The route that is outlined in Scheme 1 allows us to vary the ring size, stereochemistry and substitution pattern of scaffold **1**. In addition, conjugation sites X for the attachment of scaffolds **1** to a solid phase can be introduced by using hydroxyproline as a precursor (R^1 = OH in Scheme 1). Key intermediates are azabicycloalkenes **3** which can be synthesized easily via enantioselective or diastereoselective protocols as both *endo* and *exo* isomers.[38−41] These strained bicyclic heterocycles are known to be excellent synthetic intermediates useful for the introduction of unnatural amino acids into peptides and diketopiperazines,[30] preparation of peptidomimetics,[42] amino acid derivatives,[33] and various other nitrogen heterocycles (for a review see Maison[33]).

Results and Discussion

We started our synthesis from azabicycloalkene **4** (Scheme 2), which can be prepared stereoselectively on large scale (50 g and more) in a one-pot procedure from cyclopentadiene and an imine that is generated *in situ* from *tert*-butyl glyoxylate and (*R*)-methylbenzylamine.[43] After bis-hydroxylation, the chiral auxiliary is cleaved under hydrogenolytic conditions giving

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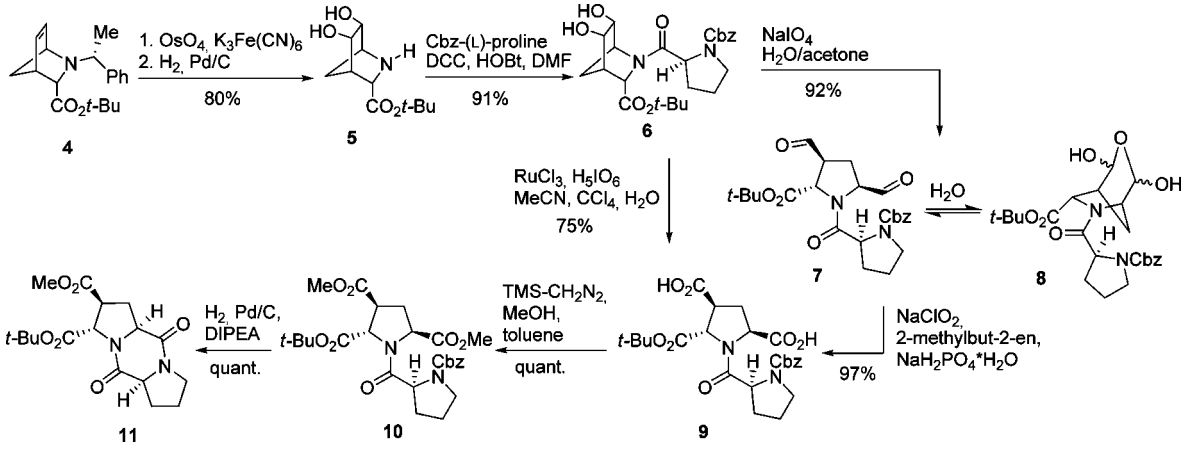
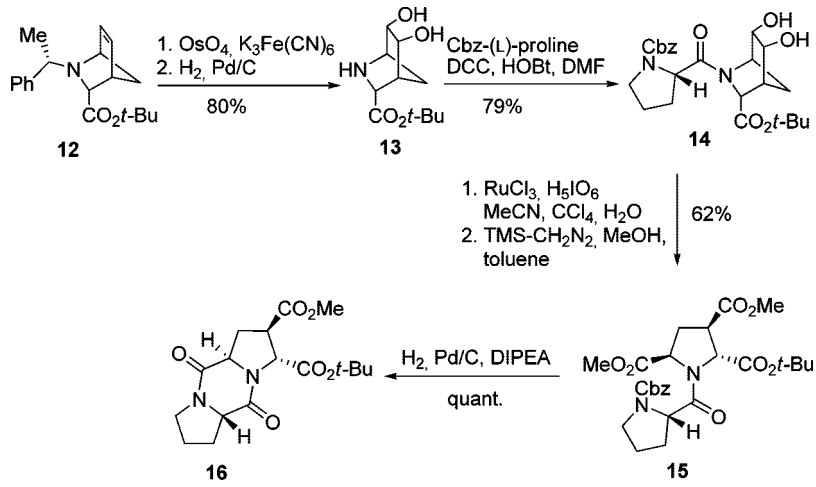
SCHEME 2. Synthesis of Proline-Derived Diketopiperazine 11



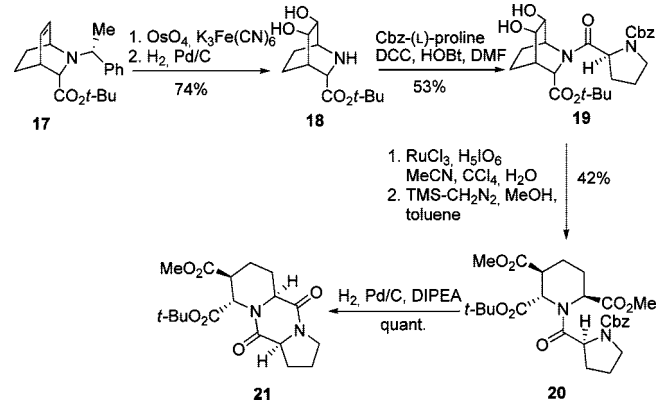
SCHEME 3. Synthesis of Diketopiperazine 16



aminodiol **5**. For large scale applications, the bis-hydroxylation to **5** can also be performed with $KMnO_4$, if reaction conditions are controlled carefully.[43] It should be noted, that azabicycloalkene **4** and aminodiol **5** are both colorless solids, which are easy to purify by crystallization from either hexane or a hexane/ethyl acetate mixture, respectively. Peptide coupling to aminodiol **5** with Cbz-protected proline was accomplished with DCC/HOBt to give the dipeptide **6** in good yield. The following oxidative cleavage of the glycol moiety in **6** was realized via a two-step sequence of periodate cleavage and subsequent chlorite oxidation of the intermediate bis-aldehyde **7** or via a one pot procedure with $RuCl_3/H_5IO_6$. Both procedures work well with the former giving a slightly higher yield of dicarboxylic acid **9**. It is interesting to note that the bis-aldehyde **7** is in equilibrium with the bicyclic hemiacetal **8**, which is the major species observed by NMR in $CDCl_3$. After quantitative esterification of dicarboxylic acid **9** to ester **10**, the Cbz group was cleaved hydrogenolytically under basic conditions followed by intramolecular lactam formation to give diketopiperazine scaffold **11** in excellent 65% yield over seven steps.

Following this general route, we have prepared three enantiomerically pure diketopiperazines **11** (Scheme 2), **16** (Scheme 3) and **21** (Scheme 4) with different ring sizes and stereochemistry. The yields of scaffolds **11**, **16** and **21** are all acceptable with pipecolic acid-derived scaffolds like **21** giving slightly lower yields. This is due to less effective peptide couplings to azabicyclooctanes like **18** compared to azabicycloheptanes like **5** or **13**. This parallels observations that substituted proline derivatives are more easily coupled at their *N*-terminus than the corresponding pipecolic acid derivatives.[31]

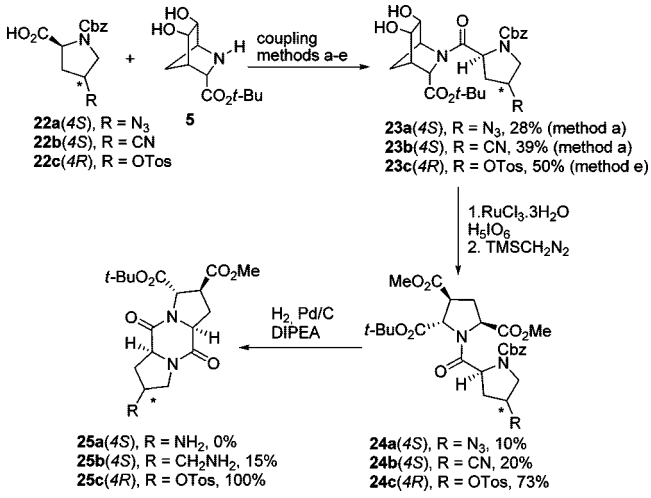
SCHEME 4. Synthesis of Diketopiperazine 21



Stereochemical integrity of the compounds was established by 2D-NOESY NMR and X-ray analysis for scaffolds **11** and **16**, indicating no epimerization of any intermediate in the sequence.

For the design of small compound libraries for screening, the attachment of the scaffolds to a solid phase is desirable. In this context, the careful choice of a suitable anchor group is important, because the nature of this group is essential for the

SCHEME 5. Synthesis of Functionalized Diketopiperazines 25 for Attachment to a Solid Phase[a]



[a] Reagents and conditions: (a) DCC/HOBt; (b) HBTU/DIPEA; (c) HATU/DMAP; (d) PCl_5/DIPEA; (e) pentafluorophenyl trifluoroacetate. Yields for dipeptides **23** are selected examples. For all yields see Supporting Information

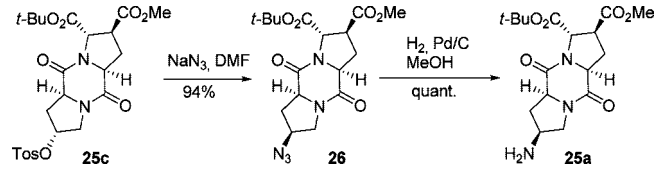
modularity of small molecules for application in our cancer targeting concept.[18,44] We chose a primary amine as an anchor group, because it is compatible with the standard conjugation techniques that are routinely used for the attachment of effector molecules to generate cancer-specific diagnostic tools.

The amino functionality can be conjugated to our scaffold at different stages of the synthesis using derivatives of hydroxyproline **22a**−**c** as precursors (Scheme 5). All three hydroxyproline derivatives can be prepared by literature procedures in large quantities.[45,46] However, the application of azide- or cyanide-substituted proline-derivatives **22a** and **22b** turned out to be low yielding as the substituted dipeptides **23a** and **23b** showed only low stability to oxidative conditions and gave both unacceptable yields for the final hydrogenation to the free amines **25a** and **25b**. In consequence, we followed an alternative route in which the tosyl group of hydroxyproline **22c** was converted to the azide/cyanide at a later stage of the synthesis depicted in Scheme 5. In this case all reactions proceeded smoothly as expected and DKP **25c** was obtained in 30% overall yield for the four-step sequence.

For the peptide coupling with the tosylated proline **22c**, a variety of generally efficient coupling procedures (a−e) were tried as depicted in Scheme 5. DCC/HOBt-coupling as well as HATU and HBTU scored repeatedly 40% yield and less. Application of a proline acid chloride (method d in Scheme 5) led to epimerized dipeptides **23**. The best yields for dipeptides **23** gave method (e) in Scheme 5 that has been used for similar coupling reactions by the Wennemers group.[26]

The substitution of tosylate **25c** with sodium azide gave **26** in quantitative yield without detectable side reactions (Scheme 6). Reduction of the azide in **26** with H_2, Pd/C gave amine **25a**, again in quantitative yield.

SCHEME 6. Synthesis of Amino-Substituted Diketopiperazine 25a



Conclusions

A number of different proline-derived diketopiperazine scaffolds have been synthesized in enantiomerically pure form. The synthetic route to these scaffolds was characterized by high variability with respect to stereochemistry, ring size and substitution pattern of the target compounds. It can be performed on multigram scale as the starting azabicycloalkenes are readily available by Diels−Alder reaction. Amino-substituted DKPs like **25a** are a good platform for the development of small natural product-like DKP collections using solid phase chemistry as they can be attached to a solid phase using the amine as an anchor group.

Experimental Section

Dipeptide 23c. A solution of **22c**[45] (7.5 g, 18.0 mmol) in DMF (40 mL) was treated with pentafluorophenyltrifluoroacetate[47] (5.8 g, 21 mmol) and dry pyridine (1.6 g, 20.0 mmol) for 12 h at rt. EtOAc (100 mL) was added and the organic phase was washed with sat. $NaHCO_3$, 1 M HCl and sat. NaCl, dried with Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The resulting crude oil (hydroxyproline-pfp-ester) was used without further purification in the coupling step.

A solution of azabicycloalkane **5**[43] (4.4 g, 19.2 mmol) in DMF (40 mL) was stirred overnight with hydroxyproline-pfp-ester (13.5 g, 23.06 mmol). EtOAc (100 mL) was added and the organic phase was washed with each 50 mL sat. $NaHCO_3$, 1 M HCl and sat. NaCl, dried with Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Flash chromatography gave dipeptide **23c** (6.34 g, 10.1 mmol; 52%) as a colorless foam. ^{1}H NMR ($CDCl_3$, 500 MHz, mixture of rotamers): δ = 7.77−7.80 (m, 2H), 7.27−7.39 (m, 7H), 4.87−5.11 (m, 3H), 4.67 (t, J = 7.7 Hz, 0.65H), 4.55 (t, J = 7.9 Hz, 0.35H), 4.21 (d, 0.65H, J = 5.4 Hz), 3.99 (br, 0.65H), 3.94 (d, J = 5.5 Hz, 0.35H), 3.67 − 3.84 (m, 2.35H), 3.50 (s, 0.35H), 3.16 (br, 0.65H), 2.39−2.58 (m, 5H), 2.15−2.23 (m, 2H), 1.90 (d, J = 10.8 Hz, 0.65H), 1.80 (d, J = 11.2 Hz, 0.65H), 1.70−1.77 (m, 0.7H), 1.42 (s, 5.85H), 1.41 (s, 3.15H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of rotamers): δ = 169.4, 169.1, 168.4, 168.3, 154.5, 154.0, 145.5, 145.4, 136.0, 136.0, 133.3, 133.2, 132.4, 131.0, 130.3, 130.2, 130.0, 129.1, 128.9, 128.7, 128.6, 128.6, 128.3, 128.2, 128.2, 127.9, 82.0, 81.9, 79.8, 79.1, 72.4, 72.2, 71.9, 71.9, 68.0, 67.5, 60.6, 60.3, 60.2, 56.4, 56.1, 53.1, 52.8, 46.7, 46.5, 37.3, 36.3, 29.8, 29.1, 28.1, 21.8, 21.8 ppm; HRMS (ES): calcd: 653.2139 [$C_{31}H_{38}N_2O_{10}S$ + Na^+]; found: 653.2153. $[\alpha]_D^{20}$ = −49.3 (c 0.7, $CHCl_3$). Elemental analysis: calcd C 59.03%, H 6.07%, N 4.44%; found C 59.37%, H 6.02%, N 4.65%.

Triester 24c. Diol **23c** (6.3 g, 10.1 mmol) was dissolved in a 2:1:1 mixture of H_2O/MeCN/CCl_4. 4.1 equiv. H_5IO_6 and a catalytic amount of $RuCl_3.3H_2O$ was added. The mixture was stirred at rt until the TLC showed complete conversion (12 h). CH_2Cl_2 and H_2O were added and the phases were separated. The aqueous layer was extracted three times with each 100 mL CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the crude product was used without further purification in the next step. The crude dicarboxylic acid was dissolved in MeOH/Toluene 1:4 and $TMSCH_2N_2$ in Et_2O was

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added dropwise until TLC showed complete conversion. Excessive $TMSCH_2N_2$ was quenched by careful addition of 10% HOAc in H_2O. Flash chromatography (EtOAc/PE 1:1) gave the title compound as a colorless foam (4.75 g, 7.4 mmol; 73%). ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers): δ = 7.74−7.78 (m, 2H), 7.27−7.34 (m, 7H), 4.92−5.11 (m, 4H), 4.34−4.69 (m, 2H), 3.60−3.75 (m, 8H), 2.96−3.25 (m, 1H), 2.47−2.81 (m, 3H), 2.44 (s, 1.5H), 2.41 (s, 1.5H), 2.26−2.35 (m, 1H), 1.38−1.51 (m, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of rotamers): δ = 171.1, 170.9, 170.8, 170.7, 170.6, 170.5, 170.5, 170.4, 170.2, 169.8, 169.7, 168.9, 168.9, 154.3, 154.2, 145.4, 145.3, 136.8, 136.7, 136.6, 136.4, 133.5, 133.4, 130.3, 130.2, 128.7, 128.6, 128.6, 128.5, 128.5, 128.3, 128.3, 128.2, 128.1, 128.1, 84.1, 83.5, 82.6, 82.4, 67.4, 67.3, 67.2, 63.9, 63.2, 63.1, 61.9, 58.8, 58.7, 58.6, 58.3, 57.2, 57.0, 56.8, 56.7, 56.5, 53.0, 52.9, 52.7, 52.6, 52.5, 52.4, 52.3, 52.2, 47.9, 47.8, 45.0, 44.8, 36.7, 36.6, 35.6, 35.4, 32.1, 32.0, 29.6, 29.4, 28.0, 28.0, 21.8, 21.8 ppm. HRMS (ES): calcd: 711.2194 [$C_{33}H_{40}N_2O_{12}S + Na^+$]; found: 711.2201. $[\alpha]_D^{20}$ = −22.7 (c 3.2, MeOH). Elemental analysis: calcd C 57.55%, H 5.85%, N 4.07%; found C 57.55%, H 5.96%, N 3.79%.

Diketopiperazine 25c. Triester **24c** (2.95 g, 4.28 mmol) was dissolved in abs. MeOH and stirred for 12 h with 1 equiv. DIPEA and a catalytic amount of 10% Pd/C under a hydrogen atmosphere. The solution was filtered over diatomite and the solvent removed *in vacuo* to give the title compound (2.21 g, 4.24 mmol; 100%) as a colorless foam. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77−7.79 (m, 2H), 7.36−7.38 (m, 2H), 5.15−5.16 (m, 1H), 4.67 (d, J = 6.4 Hz, 1H), 4.51 (dd, J = 6.8 Hz, 11.2 Hz, 1H), 4.68 (dd, J = 8.4 Hz, 8.4 Hz, 1H), 3.71 (s, 5H), 3.14 (ddd, 1H, J = 6.4 Hz, 7.6 Hz, 8.5 Hz), 2.44−2.62 (m, 3H), 2.47 (s, 3H), 2.18−2.25 (m, 1H), 1.49 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 169.1, 165.3, 165.0, 145.7, 133.5, 130.4, 127.9, 83.1, 78.3, 61.8, 60.5, 58.5, 52.8, 52.1, 45.7, 35.0, 31.1, 28., 21.9 ppm. HRMS (ES): calcd: 545.1564 [$C_{24}H_{30}N_2O_9S + Na^+$]; found: 545.1577. $[\alpha]_D^{20}$ = −44.8 (c 1.0, $CHCl_3$). Elemental analysis: calcd C 55.16%, H 5.79%, N 5.36%; found C 55.14%, H 5.93%, N 5.62%.

Diketopiperazine 26. To a suspension of tosylated diketopiperazine **25c** (1.0 g, 1.9 mmol) in DMF (40 mL), NaN_3 (0.5 g, 7.7 mmol) was added and the reaction was heated to 55 °C until TLC showed complete consumption of the starting material. Then the mixture was poured on ice and the aqueous layer was extracted with EtOAc three times. The solvent was evaporated to give the title compound (0.7 g, 1.8 mmol, 94%) as a colorless solid. The product was used without further purification in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.73 (d, J = 6.4 Hz, 1H), 4.46 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 4.36 (dd, J = 6.4 Hz, 8.4 Hz, 1H), 4.20 (m, 1H), 3.78 (dd, J = 12.8 Hz, 3.2 Hz, 1H), 3.73 (s, 3H), 3.51 (dd, J = 5.6 Hz, 12.4 Hz, 1H), 3.15 (ddd, J = 6.4 Hz, 8.2 Hz, 8.1 Hz, 1H), 2.62−2.66 (m, 1H), 2.59 (t, J = 8.1 Hz, 2H), 2.50 (ddd, J = 5.7 Hz, 8.8 Hz, 13.9 Hz, 1H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.4, 169.1, 165.7, 165.1, 83.0, 61.9, 60.2, 58.5, 58.2, 52.8, 50.7, 45.9, 32.7, 31.0, 28.0 ppm. HRMS (ES): calcd [$C_{17}H_{23}N_5O_6 + Na^+$]: 416.1541; found: 416.1527. $[\alpha]_D^{20}$ = −15.1 (c 2.7, $CHCl_3$); Elemental analysis: calcd C 51.90%, H 5.89%, N 17.80%; found C 51.55%, H 5.62%, N 17.98%.

Diketopiperazine 25a. Azide **26** (0.55 g, 1.39 mmol) was hydrogenolysed using 10 mol % Pd/C in methanol to give the title compound (0.48 g, 1.30 mmol, 94%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.70 (d, J = 6.5 Hz, 1H), 4.44 (t, J = 8.0 Hz, 1H), 4.32 (t, J = 7.8 Hz, 1H), 3.73 (s, 3H), 3.58 (dd, J = 11.6 Hz, 6.4 Hz, 1H), 3.47 (dd, J = 11.6 Hz, 5.6 Hz, 1H), 3.14 (m, 1H), 3.10 − 3.16 (m, 1H), 2.52 − 2.63 (m, 2H), 2.47 (ddd, J = 6.1 Hz, 7.8 Hz, 13.4 Hz, 1H), 2.16 (ddd, J = 6.4 Hz, 7.4 Hz, 13.6 Hz, 1H), 1.75 (br, 2H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.6, 169.2, 165.9, 165.6, 82.9, 61.9, 60.3, 59.4, 57.6, 52.7, 50.8, 45.9, 33.7, 31.2, 28.0 ppm. HRMS (ES): calcd: 390.1636 [$C_{17}H_{25}N_3O_6 + Na^+$]; found: 390.1661. $[\alpha]_D^{20}$ = −69.0 (c 1.0, $CHCl_3$). Elemental analysis: calcd C 55.58%, H 6.86%, N 11.44%; found C 55.76%, H 6.80%, N 11.64%.

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Supporting Information Available: Detailed experimental procedures and copies of NMR-spectra for new compounds as well as crystallographic data for compounds **11** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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