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# Synthesis of Functionalized, Unsymmetrical 1,3,4,6-Tetrasubstituted 2,5-Diketopiperazines

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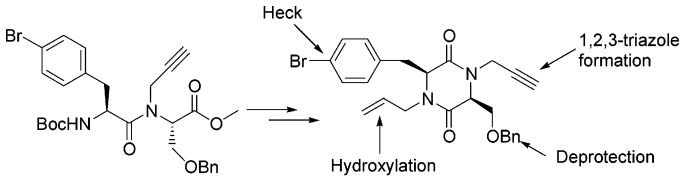


A general and efficient method for the synthesis of unsymmetrical 1,3,4,6-tetrasubstituted 2,5-diketopiperazines (DKPs) is described. Cyclization of *N*-amide alkylated dipeptide methyl esters, followed by alkylation, furnished the corresponding tetrasubstituted DKPs in good overall yields. The influence of steric hindrance in the alkylation reactions appeared to be of lesser importance as long as reactive alkylating agents were used. Furthermore, we have demonstrated the use of tetrasubstituted DKPs as a scaffold for further chemical manipulations to produce novel DKPs with desired properties.

## Introduction

The 2,5-diketopiperazine (DKP) motif is common in many natural products and in pharmacologically active compounds exhibiting a wide range of biological activities, e.g., antibiotic,[1] antifungal,[2] and anticancer[3] effects. 2,5-Diketopiperazines are also considered to be privileged structures for drug development.[4] 3,6-Disubstituted 2,5-diketopiperazines are rigid structures with the side chains in the 3- and 6-positions arranged in a well-defined spatial manner. Additional specific substitutions on the lactam nitrogen atoms of the DKPs would make the ring system a potentially useful scaffold.

There are many reports in the literature on 1,3,4,6-tetrasubstituted 2,5-diketopiperazines.[5] However, most of these derivatives are symmetric; i.e., two of the substituents on opposite sides of the ring are identical,[6] and only a few of the unsymmetrical tetrasubstituted derivatives contain substituents with functional groups which can be further modified.[7] Some of the 1,3,4,6-tetrasubstituted DKPs found in nature have chemically very complex substituents but are still symmetrically substituted.[8] The direct cyclization of a linear substituted dipeptide[9] or the four-component Ugi reaction[7,10] are the most common synthetic procedures for this type of compound.

The present study concerns the synthesis of tetrasubstituted DKPs. By introduction of the appropriate substituents in defined positions, the DKPs can be used as scaffolds for further functionalization in a regioselective manner. As an illustration, this strategy will be used for the preparation of potential-turn mimetics of biologically active peptides.

In the first instance, a general and robust method for the synthesis of a series of tetrasubstituted DKPs is needed. The objective is to define the optimal reaction protocol for the introduction of different substituents and to investigate the possibility of further modification of these substituents regioselectively.

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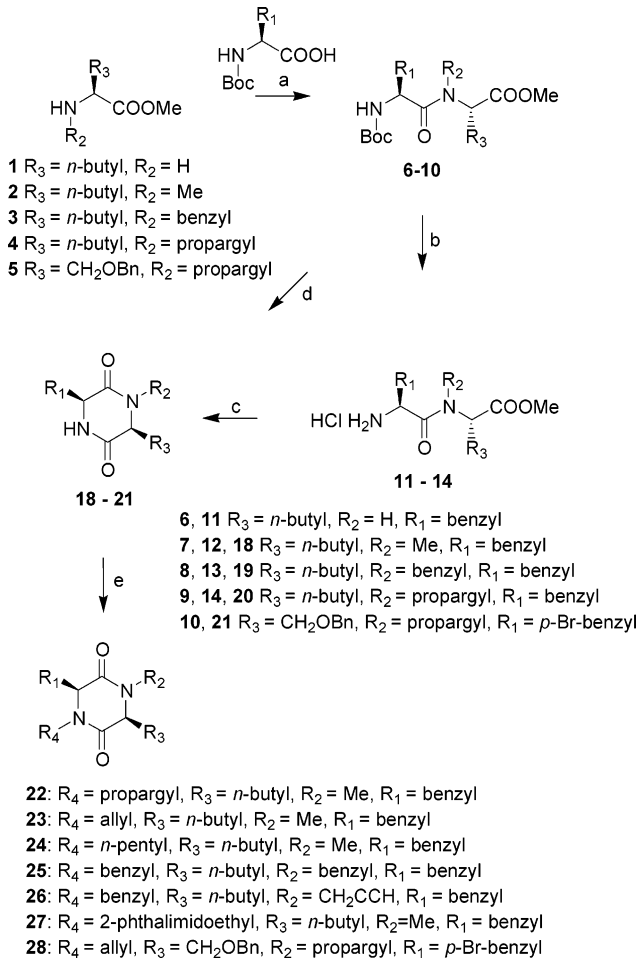
**SCHEME 1** [a]



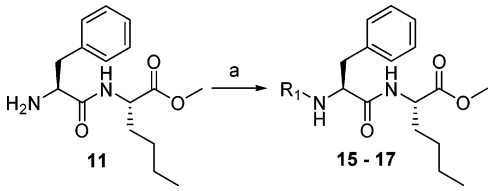

[a] Reagents and conditions: (a) EDC/NMM, $CH_2Cl_2$; (b) HCl(g)/$CH_3OH$; (c) $H_2O$, 200 °C, 10 min, microwave (MW) heating; (d) $Et_3N$, $H_2O$, 140 °C, 10 min, MW heating; (e) BEMP, $R_4-Br$, $CH_2Cl_2$ for 24 h at rt or DMF for 30 min at 60 °C with the use of MW heating. In case of low yield $Bu_4NI$ was added, and the reaction was heated for 3 h at 60 °C with the use of MW heating.

## Results and Discussion

**General.** The synthetic procedure to obtain tetrasubstituted DKPs involved the cyclization of *N*-terminally or *N*-amide alkylated dipeptides (Scheme 1). The fourth substituent was introduced via *N*-alkylation in the final step in the synthesis. We have previously shown that the solution-phase synthesis of 2,5-diketopiperazines using microwave-assisted heating proceeded in high yields independent of the amino acid sequence.[11] In the current work, three amino acids (Phe, Nle, and Ser) were used to study the influence of steric hindrance in the cyclization of the alkylated dipeptides and in the alkylation of the trisubstituted 2,5-DKPs. In addition, one compound (**28**), containing four substituents which could be further chemically modified, was synthesized in order to study the regioselective manipulation of such tetrasubstituted DKPs.

**Synthesis of *N*-Alkylated Amino Acids 1−5.**[12] The *N*-alkylated amino acids were synthesized using alkyl bromides and amino acid methyl esters as shown in Scheme 1. The yields were generally good (74−89%). Reductive amination can also be performed with the use of the appropriate aldehydes, but this reaction gave more complex mixtures with subsequent purification problems.

**TABLE 1. Isolated Yields for the Reductive Amination of 11 to Form 15−17**[a,b]




| compound | $R_1$ | yield (%) |
|---|---|---|
| **15** | benzyl | 88 |
| **16** | *trans*-3-phenyl-2-propenyl | 70 |
| **17** | 3-cyclohexenylmethyl | 60 |

[a] Reaction conditions: $R_1$-CHO, acetic acid, $NaBH(OAc)_3$, 1,2-dichloroethane. [b] For the synthesis of **11,** see ref 11.

**Synthesis of Amide Alkylated Dipeptides 7−10.** The peptide coupling reactions gave generally good yields of *N*-alkylated dipeptides (52−88%); however, the synthesis of **8** (Boc-Phe-*N*-benzyl-NleOMe) proved to be difficult. Despite the use of a range of different coupling reagents such as PyAOP, PyBOP, PyBroP, HOAt, TBTU, HATU, and EDC,[13] only low yields of product were obtained despite successful reports in the literature.[5] A slightly higher yield (54%) was obtained when using 2.0 equiv of *N*-benzylated NleOMe (**3**) with EDC/HOAt as coupling reagents.[5] Fortunately, unreacted **3** could be recovered after flash chromatography.

**Synthesis of *N*-Terminally Alkylated Dipeptides 15−17.** The reductive amination of **11** (Phe-NleOMe•HCl) gave moderate to good yields (60−88%) of the *N*-terminally alkylated dipeptides **15**−**17** (Table 1). Care was taken to ensure full conversion to the imines by the addition of 1.0 equiv of acetic acid. Once the imine was formed, the reduction proceeded smoothly with the use of sodium triacetoxyborohydride as the reducing agent. Compound **11** was synthesized as previously described.[11]

**Cyclization of *N*-Amide Alkylated Dipeptides to Trisubstituted DKPs 18−21.** Two different methods for cyclization to trisubstituted DKPs were tested: either direct cyclization of the Boc-protected dipeptide methyl esters at 200 °C[14] or

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(13) PyAOP ((7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate); PyBOP ((benzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate); PyBroP (bromotripyrrolidino-phosphonium hexafluorophosphate); HOAt (1-hydroxy-7-azabenzotriazole); TBTU (*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate); HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate); EDC (*N*-(3-dimethyl-aminopropyl)-*N*′-ethylcarbodiimide); BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine).

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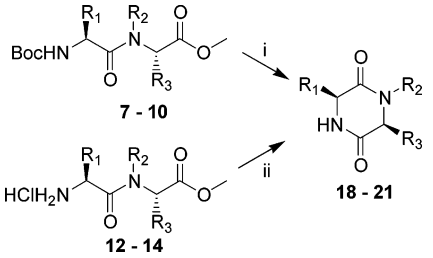
**TABLE 2. Isolated Yields of DKPs Using Two Different Cyclization Methods**[a]




| DKP | starting material | $R_1$ | $R_2$ | $R_3$ | yield (%) |
|---|---|---|---|---|---|
| **18** | **7** | benzyl | methyl | *n*-butyl | 70 |
| **19** | **8** | benzyl | benzyl | *n*-butyl | 40 |
| **20** | **9** | benzyl | propargyl | *n*-butyl | 62 |
| **21** | **10** | *p*-Br-Bn | propargyl | $CH_2OBn$ | 78 |
| **18** | **12** | benzyl | methyl | *n*-butyl | 73 |
| **19** | **13** | benzyl | benzyl | *n*-butyl | 40 |
| **20** | **14** | benzyl | propargyl | *n*-butyl | 72 |

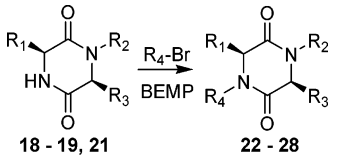
[a] Reaction conditions: 50 mg of each starting material in water (4 mL) was used for the cyclization reactions. When the use of the hydrochloride salt of the dipeptide methyl ester took place, triethylamine (2.0 equiv) was added to the reaction. (i) The reaction was run at 200 °C for 10 min with the use of MW heating. (ii) The reaction was run at 140 °C for 10 min (MW heating) in the presence of 2.0 equiv of triethylamine.

cyclization of the hydrochloride salts of the Boc-deprotected dipeptide methyl esters at 140 °C in the presence of 2.0 equiv of triethylamine (Table 2). Both methods used microwave-assisted heating with water as solvent. No significant difference in yields between the two methods was found. The small difference in yield obtained in the synthesis **20** from **9** or **14** (Table 2) could be explained by the fact that **20** prepared from **9** required column chromatography in order to separate unreacted dipeptide from the target DKP, whereas **14** could easily be separated from **20** by filtration. Probably due to steric interactions in the cyclization, compound **19** was formed in low yields (40%) with both cyclization procedures. Compounds **18** and **20,** however, were formed in moderate to good yields (62−73%). Compound **10** was cyclized with the Boc-group still attached, thus minimizing the number of reaction steps. However, in the cyclization of **10**, which is a solid, care had to be taken not to heat the reaction mixture too fast, in order to avoid decomposition of the dipeptide. Therefore, the reaction vessel was heated to 200 °C during a period of 3 min.

**Cyclization of the Terminally *N*-Substituted Compounds 15−17.** Attempts to cyclize the N-alkylated dipeptides **15**−**17** (Table 3) were performed using water as solvent and microwave-assisted heating ranging from 140 °C for 10 min to 200 °C for 10 h. Unfortunately none of the desired products could be isolated from the reactions; only unreacted starting material could be detected in $^1$H-NMR spectra. The starting material was found to be heat-stable, as no trace of decomposition could be detected in $^1$H-NMR spectra. Apparently, the nucleophilicity and steric hindrance of the *N*-terminal nitrogen are important for efficient cyclization, and unless small *N*-alkyl groups are to be introduced, it is preferred to do the cyclization on the *N*-alkylated amides instead.

**Alkylation on the Lactam Nitrogen of the DKPs.** The most common method for the alkylation of lactam nitrogens of DKPs is based on the use of sodium hydride base.[15] However, in our hands the use of sodium hydride proved unsuccessful, whereas when the use of the stronger, polymer-supported base BEMP[13] (PS-BEMP) was employed, the alkylation reactions proceeded

**TABLE 3. Isolated Yields Obtained in the *N*-alkylation Reactions of DKPs 18, 19, and 21**




| compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | yield (%) |
|---|---|---|---|---|---|
| **22** | benzyl | methyl | *n*-butyl | propargyl | 77[a] |
| **23** | benzyl | methyl | *n*-butyl | allyl | 72[a] |
| **24** | benzyl | methyl | *n*-butyl | *n*-pentyl | 81[b] |
| **25** | benzyl | methyl | *n*-butyl | benzyl | 74[c] |
| **26** | benzyl | benzyl | *n*-butyl | benzyl | 83[c] |
| **27** | benzyl | methyl | *n*-butyl | 2-phthalimido-ethyl | 52[b] |
| **28** | *p*-Br-Bn | propargyl | $CH_2OBn$ | allyl | 94[c] |

[a] The reaction was run at rt for 24 h in $CH_2Cl_2$. [b] MW heating at 60 °C for 3 h in DMF in the presence of $Bu_4NI$. [c] MW heating at 60 °C for 30 min in DMF.

smoothly as shown in Table 3. The alkylation of **18** with propargyl or allyl bromide proceeded at room temperature, giving **22** and **23** in good yields (77 and 72%, respectively). Attempts to alkylate **18** using *n*-pentyl or benzyl bromides to obtain **24** and **25** using PS-BEMP at room temperature failed, and no products could be isolated. However, with microwave heating at 60 °C in DMF for 3 h the compounds were isolated in 31 and 74% yields, respectively.[16] Compound **25** could also be formed in similar yield when heated for only 30 min at 60 °C. In reactions requiring microwave heating, BEMP was used instead of PS-BEMP since the polymer-based base had a tendency to stick to the glass walls of the reaction vessel. Compound **19** was benzylated with benzyl bromide and BEMP with the use of microwave heating for 30 min at 60 °C, affording **26** in 83% yield.

The yield of **24** was only 31% even with the use of microwave-assisted heating for 3 h. Steric hindrance cannot explain the low yield, as the benzyl group in **26** can be expected to be as sterically demanding as the pentyl group in **24**. Instead, the low yield of **24** is probably due to the lower reactivity of pentyl bromide in comparison with that of allyl, propargyl, and benzyl bromide. However, when pentyl bromide was exchanged for the corresponding iodide with the use of 1.0 equiv of tetrabutylammonium iodide, the yield increased from 31 to 81%.[17] The low-yielding alkylation of **18** with *N*-(2-bromoethyl)phthalimide is probably due to a combination of steric hindrance and low reactivity of the alkylating agent. Even with the use of 1.0 equiv of tetrabutylammonium iodide, the yield of **27** was only 52%.

Apparently, efficient alkylation of the DKPs is restricted to reactive alkyl bromides. Then, the reaction time could be reduced from 3 h to 30 min with the use of microwave-assisted heating, affording higher yields of product due to easier workup as a result of less-complex reaction mixtures.

**A. Further Modifications of Substituents in DKP 28.** The different substituents introduced in the tetrasubstituted DKP **28**

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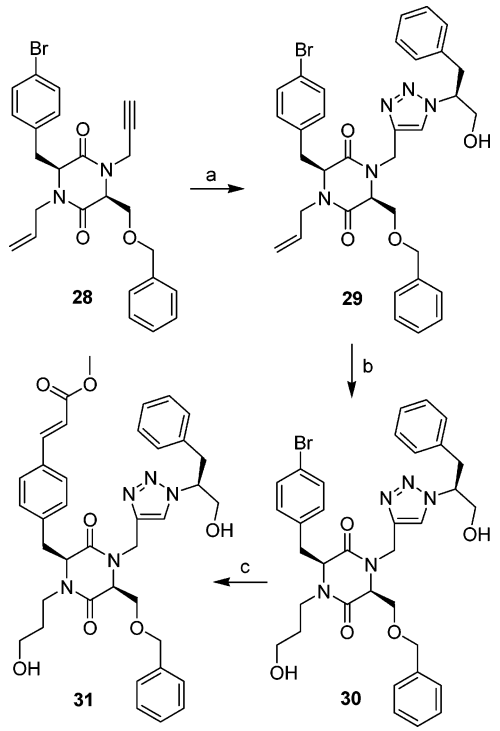
**SCHEME 2. Synthesis of Functionalized, Unsymmetrically 1,3,4,6-Tetrasubstituted 2,5-Diketopiperazines**[a]




[a] Reagents and conditions: (a) *N*-Azide-L-phenylalaninol, $Cu^{II}SO_4$, sodium ascorbate/$CH_2Cl_2$:$H_2O$ (1:1), rt, 20 h; (b1) $BH_3$·THF/THF, −40 °C, 4 h; (b2) $H_2O_2$/NaOH, 0 °C, 2 h; (c) $Pd^{II}(OAc)_2$, tri(o-tolyl)phosphine, $Et_3N$, methyl acrylate/DMF, 150 °C, 30 min, MW heating.

could be functionalized in different ways (Scheme 2). This provides opportunities for using **28** as a scaffold for the synthesis of series of novel DKPs.

**A1. 1,2,3-Triazole Formation from the Propargyl Group.** It was possible to convert the propargyl group in **28** into a 1,4-substituted triazole derivative (**29**) in high yield (95%) using an azide obtained from phenylalaninol.[18] It is expected that the use of different azides would provide easy access to a wide range of new chemical entities.

**A2. Hydroboration of the Allyl Group.** The allyl group was oxidized to the primary alcohol (**30**) by hydroboration of **29** using borane in THF. The subsequent removal of the borane was achieved with the use of hydrogen peroxide in the presence of sodium hydroxide. The reaction was first run at room temperature, resulting in a complex reaction mixture according to TLC. When cooling of the solution of **29** in THF to −40 °C was done before addition of the borane and cooling to 0 °C was done before the oxidation step, the reaction proceeded smoothly, providing **30** in good yield (81%).

**A3. Heck Reaction on the Aryl Bromide.** The final modification involved a Pd-mediated coupling of methyl acrylate with the bromide-substituted benzyl group. The reaction was run using standard Heck conditions (palladium diacetate (10%), tri(*o*-tolyl)phosphine (20%), triethylamine (2.0 equiv)), and the product (**31**) was obtained in good yield (83%).

## Conclusion

A general and efficient method for the synthesis of unsymmetrical DKPs has been developed. Cyclization of *N*-amide alkylated dipeptide methyl esters, followed by alkylation with the use of an alkyl halide in the presence of a sterically hindered strong organic base (BEMP) furnished the corresponding tetrasubstituted DKPs in good overall yields. The influence of the steric hindrance in the alkylation reactions appeared to be of lesser importance as long as reactive alkyl bromides were used. However, cyclization of *N*-alkylated dipeptide methyl esters, using microwave-assisted heating in water failed, thus indicating the importance of the nucleophilic strength of the *N*-terminal nitrogen for efficient cyclization.

Furthermore, we have demonstrated that a 1,3,4,6-tetrasubstituted 2,5-diketopiperazine is a useful scaffold. High regioselectivity in functionalization reactions could be obtained by using orthogonal chemical reactions on a tetrasubstituted DKP. This strategy will allow the synthesis of novel DKPs with desired properties and is currently being explored in our laboratory for the development of $\beta$-turn mimetics.

## Experimental Section

Compounds **2** and **11** were synthesized as described in ref 11.

**Representative Example of Cyclization of Amide Alkylated Dipeptides to Trisubstituted 2,5-DKPs: *c*(L-Phenylalanyl-*N*-propargyl-L-norleucinyl) (20).** A solution of **9** (50 mg, 0.14 mmol) in water (4 mL) was heated at 200 °C for 10 min in a microwave cavity. The crude product was purified by flash chromatography using EtOAc/hexane (3:2) as eluent to give pure **20** as white crystals (26 mg; 62%). Mp: 117−119 °C. $[\alpha]_D$: −122.6° (*c* 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.34−7.24 (m, 5H), 6.44 (s, 1H), 4.73 (dd, $J$ = 17.6, 2.6 Hz, 1H), 4.30−4.24 (m, 1H), 4.22 (dd, $J$ = 6.6, 3.3 Hz, 1H), 3.80 (dd, $J$ = 17.6, 2.6 Hz, 1H), 3.33 (dd, $J$ = 13.7, 3.8 Hz, 1H), 2.98 (dd, $J$ = 13.9, 8.8 Hz, 1H), 2.29 (t, $J$ = 2.6 Hz, 1H), 1.85−1.76 (m, 1H), 1.52−1.43 (m, 1H), 1.32−1.07 (m, 4H), 0.87 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 167.3, 165.0, 135.6, 129.9, 129.1, 127.6, 76.9, 73.6, 58.9, 56.8, 41.4, 33.7, 31.2, 26.6, 22.4, 14.0. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.3; H, 7.6; N, 9.6.

**Representative Example of *N*-Alkylations of Trisubstituted DKPs Using BEMP as Base: *c*(*N*-pentyl-L-phenylalanyl-*N*-methyl-L-norleucinyl) (24).** Compound **18** (50 mg, 0.18 mmol) was dissolved in DMF (4 mL) and BEMP (0.10 mL, 0.36 mmol), 1-bromopentane (33 $\mu$L, 0.27 mmol) and tetrabutylammonium iodide (99.7 mg, 0.27 mmol) were added, and the mixture was heated at 60 °C for 3 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography using EtOAc/hexane (3:2) as eluent to give pure **24** as a colorless oil (48 mg, 81%). $[\alpha]_D$: −42° (*c* 0.3, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.41−7.08 (m, 5H), 4.26−4.16 (m, 1H), 3.87−3.83 (m, 1H), 3.77−3.73 (m, 1H), 3.58−3.53 (m, 1H), 2.99−2.89 (m, 1H), 2.88 (s, 3H), 2.87−2.70 (m, 1H), 1.97−1.87 (m, 1H), 1.86−1.75 (m, 1H), 1.60−1.45 (m, 2H), 1.39−1.05 (m, 8H), 0.91−0.75 (m, 6H). $^{13}$C NMR ($CDCl_3$): $\delta$ 165.8, 165.2, 136.1, 129.7, 128.8, 126.9, 62.1, 60.6, 47.2, 37.8, 32.5, 32.4, 32.0, 31.5, 22.1, 21.3, 14.0, 13.9. Anal. Calcd for $C_{21}H_{32}N_2O_2$: C, 73.22; H, 9.36; N, 8.13. Found C, 73.4; H, 9.6; N, 7.9.

**Synthesis and Further Modifications of Substituents in DKP 28. *c*(*N*-Allyl-4-bromo-L-phenylalanyl-*N*-propargyl-*O*-benzyl-L-serinyl) (28).** Compound **21** (0.10 g, 0.23 mmol) was dissolved in DMF (4 mL) and BEMP (0.31 mL, 0.45 mmol), and allyl bromide (30 $\mu$L, 0.35 mmol) was added. The mixture was heated in the microwave at 60 °C for 30 min. The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography using EtOAc/hexane (3:2) as the eluent to give pure **28** as white crystals (0.10 g, 94%). Mp: 103−105 °C. $[\alpha]_D$: −87.3° (*c* 2, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.38−7.25 (m, 7H),

(18) Fan, Q.-H.; Ni, N.-T.; Li, Q.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2006**, *8*, 1007−1009.

6.90 (d, $J$ = 8.4 Hz, 2H), 5.62 (dddd, $J$ = 17.4, 9.9, 4.7, 0.8 Hz, 1H), 5.18 (dd, $J$ = 10.1, 0.9 Hz, 1H), 5.01 (dd, $J$ = 17.0, 1.7 Hz, 1H), 4.63−4.59 (m, 1H), 4.63 (dd, $J$ = 17.6, 2.6 Hz, 1H), 4.47 (d, $J$ = 12.1 Hz, 1H), 4.38 (d, $J$ = 12.1 Hz, 1H), 4.38−4.36 (m, 1H), 4.20 (t, $J$ = 5.9 Hz, 1H), 3.88 (dd, $J$ = 17.6, 2.6 Hz, 1H), 3.69 (dd, $J$ = 9.9, 2.6 Hz, 1H), 3.12 (dd, $J$ = 9.9, 2.6 Hz, 1H), 3.13−3.10 (m, 2H), 3.01 (dd, $J$ = 15.2, 7.9 Hz, 1H), 2.26 (t, $J$ = 2.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 165.5, 164.2, 137.1, 135.9, 132.0, 131.9, 131.5, 131.2, 128.7, 128.2, 128.1, 121.3, 119.6, 77.5, 73.5, 73.3, 69.9, 60.3, 60.2, 47.3, 39.3, 34.2. Anal. Calcd for $C_{25}H_{25}BrN_2O_3$: C, 62.38; H, 5.23; N, 5.82. Found C, 62.2; H, 5.4; N, 5.9.

**(3*S*,6*S*)-1-Allyl-3-(benzyloxymethyl)-6-(4-bromobenzyl)-4-[((1-(1*S*)-1-hydroxy-3-phenyl-prop-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl]piperazine-2,5-dione (29).** Compound **28** (0.35 g, 0.73 mmol) and (*S*)-2-azido-3-phenyl-propan-1-ol[18] (0.13 g, 0.73 mmol) were dissolved in $CH_2Cl_2$ (1 mL) and a premixed solution of sodium ascorbate (73 $\mu$L, 73 $\mu$mol) (1.0 M in $H_2O$), copper(II) sulfate pentahydrate (0.73 mL, 7.3 $\mu$mol) (10 mM in $H_2O$) was added, and the mixture was stirred vigorously for 20 h at rt. The reaction mixture was concentrated in vacuo and purified by flash chromatography using $CH_2Cl_2$/$CH_3OH$ (8:1) as eluent to give pure **29** as a white fluffy powder (0.46 g, 95%). $[\alpha]_D$: −109° (*c* 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.42 (s, 1H), 7.32 (d, $J$ = 8.4 Hz, 2H), 7.26 (d, $J$ = 7.0 Hz, 2H), 7.25−7.17 (m, 2H), 7.16 (d, $J$ = 7.0 Hz, 2H), 7.13 (d, $J$ = 7.0 Hz, 2H), 6.98 (d, $J$ = 7.0 Hz, 2H), 6.82 (d, $J$ = 8.4 Hz, 2H), 5.54 (dddd, $J$ = 17.4, 9.9, 4.7, 0.8 Hz, 1H), 5.10 (d, $J$ = 10.3 Hz, 1H), 4.92 (d, $J$ = 17.2 Hz, 1H), 4.84 (d, $J$ = 15.0 Hz, 1H), 4.69−4.59 (m, 1H), 4.46 (dd, $J$ = 15.2, 4.6 Hz, 1H), 4.32 (q, $J$ = 21.6, 11.3 Hz, 2H), 4.26 (d, $J$ = 15.0 Hz, 1H), 4.11−4.07 (m, 2H), 4.00 (t, $J$ = 5.5 Hz, 1H), 3.95−3.87 (m, 1H), 3.76 (dd, $J$ = 9.9, 2.6 Hz, 1H), 3.34 (dd, $J$ = 9.9, 2.6 Hz, 1H), 3.21−3.03 (m, 4H), 3.00 (dd, $J$ = 15.9, 7.0 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 166.0, 164.5, 141.7, 137.1, 136.6, 136.2, 131.7, 131.4, 131.3, 129.0, 128.8, 128.6, 128.3, 128.2, 124.3, 121.1, 119.3, 73.5, 69.6, 65.2, 63.5, 61.0, 60.6, 47.4, 39.8, 39.7, 37.8. Anal. Calcd for $C_{34}H_{36}BrN_5O_4$: C, 62.01; H, 5.51; N, 10.63. Found C, 62.1; H, 5.6; N, 10.7.

**(3*S*,6*S*)-3-(Benzyloxymethyl)-6-(4-bromobenzyl)-4-[((1-(1*S*)-1-hydroxy-3-phenyl-prop-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl]-1-(3-hydroxypropyl)piperazine-2,5-dione (30).** Compound **29** (0.10 g, 0.15 mmol) was dissolved in THF (2 mL) and cooled to −40 °C followed by addition of $BH_3$·THF complex (0.38 mL, 0.38 mmol) (1 M in THF). After 2 h the reaction was allowed to reach rt over a period of 3 h. After 12 h the reaction mixture was cooled to 0 °C whereupon NaOH (2 mL, 6 mmol) (3 M aq) and $H_2O_2$ (2 mL, 18 mmol) (30% w/w in $H_2O$) were added. The reaction was stirred for 2 h whereupon the mixture was extracted with EtOAc, dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography using $CH_2Cl_2$/$CH_3OH$ (8:1) as the eluent to give pure **30** as a colorless oil (82 mg, 81%). $[\alpha]_D$: −54.8° (*c* 2, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.37−6.90 (m, 15H), 4.79 (d, $J$ = 14.6 Hz, 1H), 4.65 (s, 1H), 4.55 (t, $J$ = 11.0 Hz, 1H), 4.23 (q, $J$ = 20.5, 12.1 Hz, 2H), 4.13 (d, $J$ = 14.6 Hz, 1H), 4.02−3.92 (m, 4H), 3.63 (t, $J$ = 5.9 Hz, 1H), 3.58−3.50 (m, 1H), 3.22−3.06 (m, 4H), 3.00−2.88 (m, 2H), 2.33−2.27 (m, 1H), 2.19 (dd, $J$ = 12.1, 3.6 Hz, 1H), 1.75−1.55 (m, 2H), 1.13 (dd, $J$ = 23.1, 6.2 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 169.3, 169.0, 147.2, 146.1, 142.8, 136.7, 132.2, 131.1, 129.1, 128.8, 128.7, 128.5, 127.8, 127.2, 124.5, 120.3, 73.3, 70.0, 67.2, 63.7, 61.6, 55.0, 52.3, 47.7, 41.55, 37.8, 35.4, 28.8. Anal. Calcd for $C_{34}H_{38}BrN_5O_5$: C, 60.36; H, 5.66; N, 10.35. Found C, 60.3; H, 5.6; N, 10.3.

**(3*S*,6*S*)-3-(Benzyloxymethyl)-4-[((1-(1*S*)-1-hydroxy-3-phenyl-prop-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl]-1-(3-hydroxypropyl)-6-(4-(2-methoxycarbonyletenyl)benzyl)piperazine-2,5-dione (31).** Compound **30** (48 mg, 71 $\mu$mol), palladium(II) acetate (1.6 mg, 7.1 $\mu$mol), tri(*o*-tolyl)phosphine (4.0 mg, 14 $\mu$mol), triethylamine (20 $\mu$L, 1.4 mmol), and methyl acrylate (13 $\mu$L, 1.4 mmol) were dissolved in DMF (3 mL) and heated in a microwave at 150 °C for 30 min. The reaction mixture was filtered through Celite with EtOAc and concentrated in vacuo. The crude product was purified by flash chromatography using $CH_2Cl_2$/$CH_3OH$ (8:1) as the eluent to give pure **31** as a colorless oil (40 mg, 83%). $[\alpha]_D$: −65.6° (*c* 1, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.62 (d, $J$ = 16.1 Hz, 1H), 7.40−6.90 (m, 15H), 6.35 (d, $J$ = 16.1 Hz, 1H), 4.81 (d, $J$ = 15.0 Hz, 1H), 4.68−4.62 (m, 1H), 4.54 (t, $J$ = 11.0 Hz, 1H), 4.23 (d, $J$ = 6.6 Hz, 2H), 4.13 (d, $J$ = 15.0 Hz, 1H), 4.02−3.93 (m, 4H), 3.78 (s, 3H), 3.63 (t, $J$ = 5.9 Hz, 1H), 3.58−3.50 (m, 1H), 3.22−3.06 (m, 4H), 3.00−2.88 (m, 2H), 2.33−2.27 (m, 1H), 2.22−2.15 (m, 1H), 1.74−1.56 (m, 2H), 1.12 (dd, $J$ = 23.1, 6.2 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 169.5, 169.4, 167.6, 144.7, 141.1, 138.3, 138.0, 136.7, 136.6, 132.1, 131.1, 129.0, 128.9, 128.8, 128.5, 127.8, 127.6, 127.1, 123.8, 117.3, 73.5, 73.3, 69.9, 63.7, 61.6, 54.9, 51.8, 48.3, 41.5, 37.8, 35.4, 31.5. Anal. Calcd for $C_{38}H_{43}N_5O_7$: C, 66.94; H, 6.36; N, 10.27. Found C, 66.8; H, 6.35; N, 10.4.

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**Supporting Information Available:** Compound characterization data for compounds **1**, **3**−**10**, **12**−**19**, **21**−**23,** and **25**−**27**; NMR spectra of compounds **28**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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