One-Pot Synthesis of Symmetrical and Unsymmetrical Diketopiperazines from Unprotected Amino Acids

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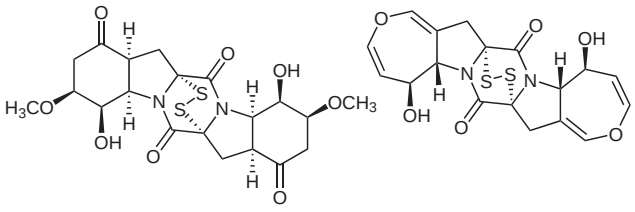
Abstract: An efficient synthesis of symmetrical and unsymmetrical proline-type diketopiperazines using a phosphite-promoted coupling was used to generate diketopiperazines with overall good yields from unprotected amino acids.

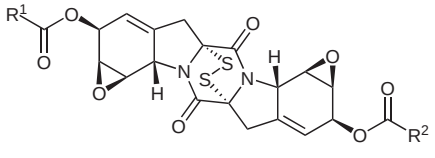
Key words: amino acids, diketopiperazines, thiolation, heterocycles

Amino acids can be found in a great variety and play an important role in nature. One interesting structural motif is the class of the epithiodiketopiperazines, diketopiperazines with a disulfide bridge (Figure 1). In some cases, like silvatin,[1] gliotoxin,[2] gliovictin, sporidesmin,[3] and scabrosinester (**3**),[4–6] total syntheses or studies have already been reported, but the majority of this group is still unexplored.[4,7] Within this group the rostratins **1**, four new marine mycotoxins, have been recently reported by Fenical et al.[8]



rostratin C (**1**)

aranotin (**2**)



	R^1	R^2
3a	CH_3	CH_3
3b	CH_3	C_3H_7
3c	C_3H_7	C_3H_7
3d	CH_3	C_5H_{11}
3e	C_3H_7	C_5H_{11}

scabrosinester (**3**)

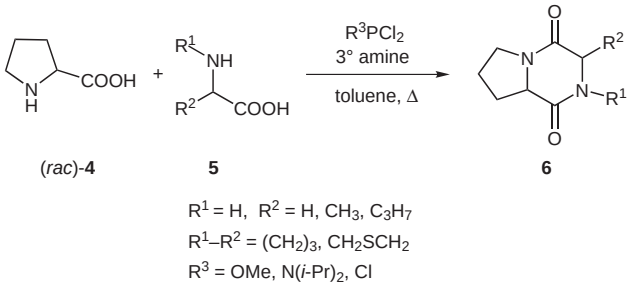
Figure 1 Some naturally occurring symmetrical epithiodiketopiperazines

In order to further investigate the chemistry of these natural products, we started a program to synthesize symmetrical epithiodiketopiperazines. These compounds do not only represent the core of many natural products but have recently attracted attention in conformational studies.[9]

Retrosynthetically, these molecules can be reduced to diketopiperazines and then thiolated as originally devised by Schmidt and co-workers.[10] In this regard, an efficient synthesis of symmetrical diketopiperazines was needed. Although various methods are applicable, we focused on a one-step synthesis from the corresponding free amino acid. Yamamoto et al. reported a straightforward route to the molecules by condensation of amino acids in the presence of a bulky boronic acid.[11]

Although this transformation is suitable for many substrates, we were faced with some problems using more functionalized substrates.

Ugi et al. described the syntheses of symmetrical diketopiperazines from amino acids in the presence of a stoichiometric amount of dichloromethoxyphosphine (Scheme 1).[12] In this manuscript, we extend this method to more functionalized proline derivatives.



Scheme 1 Synthesis of diketopiperazines as reported by Ugi[12]

After some optimization of reaction time and workup, we dimerized a number of proline derivatives to obtain the symmetrical diketopiperazines **8a–d** (Scheme 2). This method is also applicable for hexahydroindolecarboxylic acid (**9**), which gave the dimer **10** in 94% yield. This molecule already contains the complete framework of the rostratins B–D (Figure 1).

Under these conditions, dimerization of the unsaturated analogues indoline-2-carboxylic acid (**11**) and indole-2-carboxylic acid (**13**), afforded the corresponding pentacyclic diketopiperazines in 83% and 57% yield, respectively (Scheme 3).

In all cases, complete retention of the stereochemistry was observed by NMR spectroscopy and it could be unequivocally proven by X-ray crystallography of *cyclo*-Pro-Pro (**8a**, Figure 2).[13]

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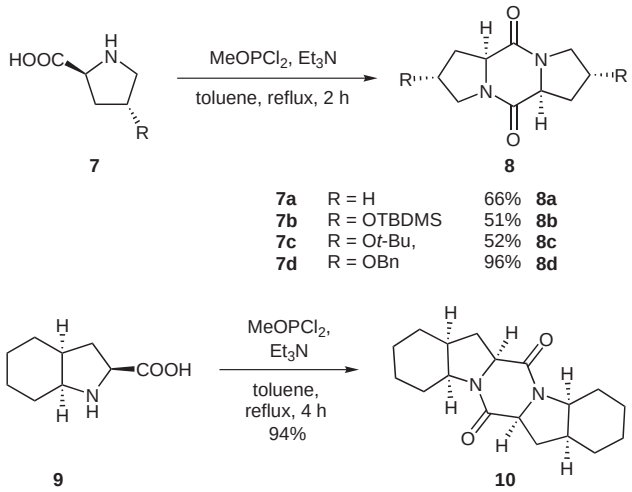


Scheme 2 Synthesis of substituted *cyclo*-Pro-Pro derivatives

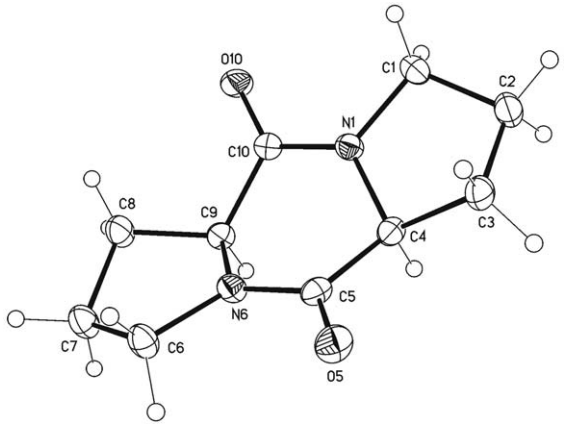
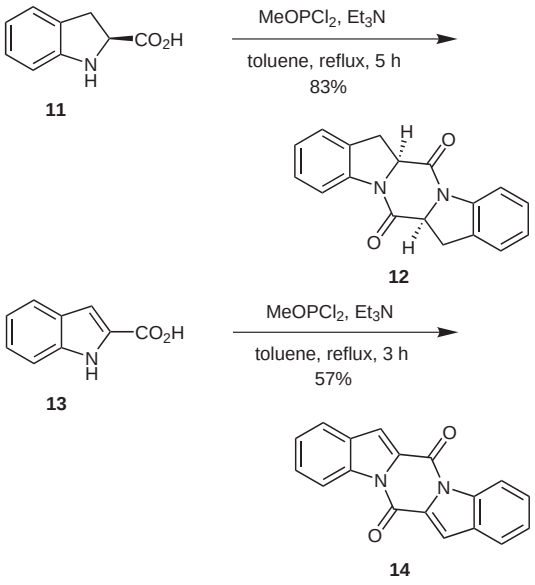


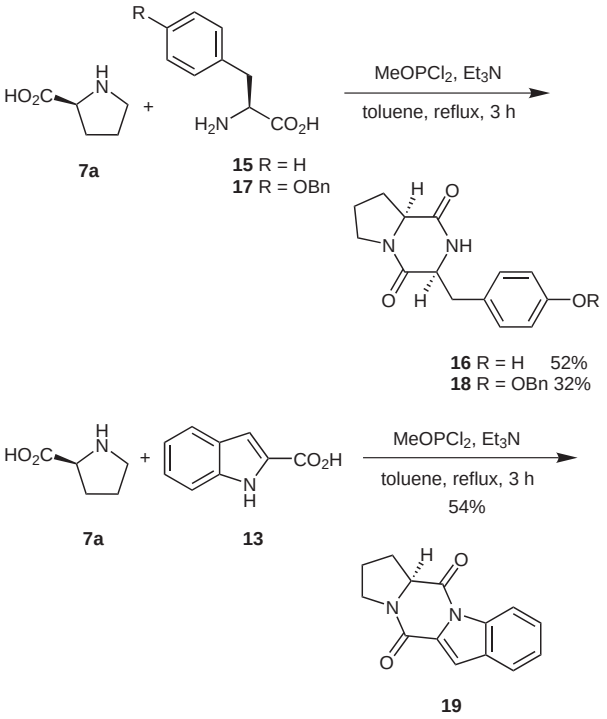
Figure 2 X-ray crystal structure of **8a**



Scheme 3 Preparation of unsaturated diketopiperazines

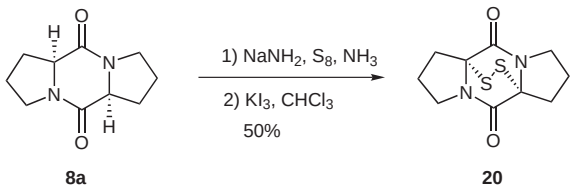
The reaction was also carried out generating the coupling reagent dichloromethoxyphosphine in situ. For that purpose we quenched one equivalent of trichlorophosphine with one equivalent of anhydrous methanol at –10 °C.[14] Dilution with toluene, then addition of an amino acid and a base, gave the diketopiperazines with no significant differences in yields.

Extending this method, we also generated unsymmetrical diketopiperazines in a one-pot reaction. To obtain the cross-coupled substrates, treatment of the first amino acid **7a** with the coupling reagent at elevated temperature was necessary. After subsequent addition of the second amino acid (**13**, **15**, **17**) and heating to reflux, we observed the formation of the unsymmetrical diketopiperazines (**16**, **18**, **19**) in good yields (Scheme 4).



Scheme 4 Preparation of unsymmetrical diketopiperazines

To reach for the above-mentioned higher functionalized epithiodiketopiperazines, we tested some thiolation methods starting with our previous synthesized diketopiperazines (Scheme 5). The method using sodium amide and elemental sulfur in liquid ammonia, developed by Schmidt and co-workers.[10] was found to be the most effective way to introduce the sulfur functionality. Our unsubstituted model system *cyclo*-Pro-Pro (**8a**) could be



Scheme 5 Synthesis of epithiodiketopiperazines

easily thiolated to yield the expected product **20** in 50% yield.

In summary, an efficient method to generate highly functionalized symmetrical and unsymmetrical diketopiperazines in a one-pot reaction has been developed. The scalability, easy workup and good yields are the advantages of this method. Furthermore it was shown that the reaction is free of racemization or inversion and leads reliably and successfully to the expected diketopiperazines. Overall, this one-flask cyclization quickly assembles diketopiperazines, which are common structural features in natural products.

General Method for the Dimerization of α-Amino Acids

The amino acid (4.2 mmol) was dissolved in 30 mL anhyd toluene and Et_3N (16.6 mmol) and methyldichlorophosphite (4.2 mmol) was added via canula under argon. The solution was heated under reflux for 3–6 h. Afterwards, the hot solution was filtered off and the precipitate was washed with hot toluene. The filtrate was evaporated and the resulting crude product was purified by flash column chromatography.

(*S*,*S*)-(6a,7,13a,14)-Tetrahydropyrazino [1,2-*a*:4,5-*a*′]diindol-6-13-dione (12)

R_f = 0.38 (hexanes–EtOAc, 3:1); $[\alpha]_D^{20}$ –2.21 (*c* 1.00, $CHCl_3$); mp 263–268 °C. IR (neat): 3344, 3069, 3050, 2898, 2863, 1793, 1681, 1603, 1483, 1462, 1446, 1410, 1343, 1315, 1245, 1213, 1182, 1156, 1131, 1086, 1018, 996, 928, 867, 849, 776, 756, 713, 647, 563, 528 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.46 (dd, *J* = 9.6, 16.8 Hz, 2 H, 7,14-H), 3.82 (dd, *J* = 9.6, 16.8 Hz, 2 H, 7,14-H), 4.99 (dd, *J* = 9.6, 16.8 Hz, 2 H, 6a,13a-H), 7.13 (dt, *J* = 1.0, 8.0 Hz, 2 H, 1,8-H), 7.29 (t, *J* = 8.0 Hz, 4 H, 3,4,10,11-H), 8.13 (d, *J* = 8.0 Hz, 2 H, 2,9-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0 (s, 2 C, C-7,14), 61.6 (t, 2 C, C-6a,13a), 115.7 (t, 2 C, C-4,11), 125.0 (t, 4 C, C-2,3,9,10), 127.9 (t, 2 C, C-1,8), 129.7 (t, 2 C, C-7a,14a), 140.5 (q, 2 C, C-4a,11a), 164.2 (q, 2 C, *C*O). MS (EI, 70 eV): *m/z* = 290 [M^+]. HRMS: *m/z* calcd for $C_{18}H_{14}N_2O_2$ [M^+]: 290.1055; found: 290.1049. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.45; H, 5.08; N, 9.65.

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