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Highly Diastereoselective Desymmetrizations of Cyclo(Pro,Pro): An Enantioselective Strategy toward Phakellstatin and Phakellin

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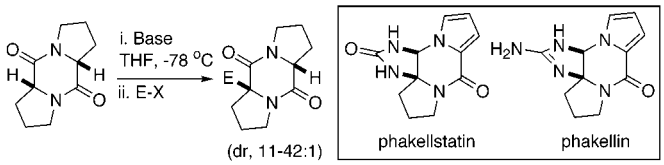
ABSTRACT



Monoenolates of C_2-symmetric, proline-derived piperazine-2,5-diones were generated and trapped with a variety of electrophiles to produce, in a highly diastereoselective fashion, functionalized diketopiperazines (DKPs). These reactions provide the basis for an asymmetric, desymmetrization strategy toward the marine alkaloids phakellstatin and phakellin. The relative stereochemistry of the functionalized DKPs was confirmed by single-crystal X-ray analysis and/or NOE experiments. Bis-functionalization of the DKPs was also found to proceed with high levels of diastereoselectivity.

Marine organisms continue to be a rich source of diverse natural products that show promise for development into pharmaceuticals and tools for biology.[1] The oroidin-derived secondary metabolites are prime examples of the immense and true structural diversity that can only be found in Nature.[2] Although phakellin (**1a**) has not been isolated, the isolation of both mono- and dibromophakellin (**1b** and **1c**)[3] in addition to palau'amine (**3**) suggests that phakellin is also likely a natural product that may be present in only minute quantities. The phakellins (**1a**−**c**) and related phakellstatins (**2a,b**)[4] possess a unique array of functionality including a cyclic guanidine or urea, a pyrrole carboxylic acid, a pyrrolidine, and potentially delicate vicinal diaminal stereocenters. The concise and elegant biomimetic synthesis of racemic dibromophakellin by Büchi stands as a benchmark for synthetic efforts in this area.[5] In connection with our synthetic studies toward the immunosuppressive agent palau'amine (**3**),[6] we became interested in developing strategies for annulation of the phakellin substructure onto a palau'amine spirocyclic core intermediate. In addition, phakellin (**1a**) presented itself as a challenging and attractive synthetic target due to its compact, heteroatom-dense structure and potential antibiotic activity.[7] For these reasons, we initiated a total synthesis of these tetracyclic natural products.[8]Our asymmetric synthetic strategy is premised on the recognition that a diketopiperazine

[†] NSF-REU participant, Summer 2001.

(1) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1−6. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55. (c) Jaspars, M. *Chem. Ind.* **1999**, 51−55.

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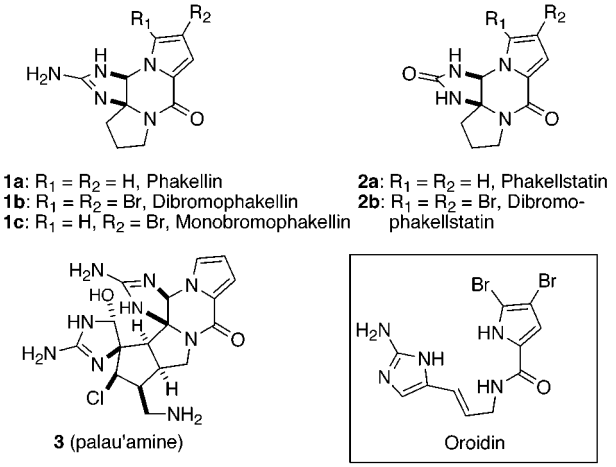
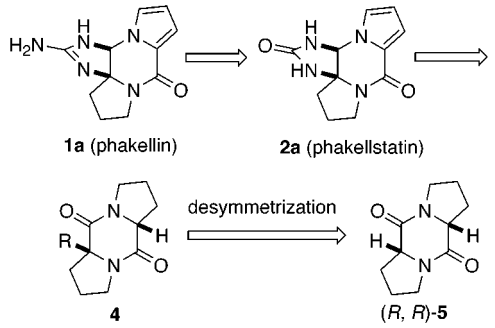


Figure 1. Structures of oroidin and oroidin-derived marine alkaloids.

is embedded in the phakellin/phakellstatin structure (Scheme 1). We, thus, sought to employ D-prolyl-D-proline anhydride

Scheme 1. Retrosynthetic Analysis of Phakellstatin and Phakellin



[(*R*,*R*)-cyclo(Pro,Pro)] (**5**)[9] as an optically active starting material and utilize a diastereoselective desymmetrization process to functionalize this system. Subsequent oxidation to a pyrrole, ring annulation, and guanidinylation would deliver phakellin (**1a**) via phakellstatin (**2a**). While there are reports of electrophilic additions to enolates derived from diketopiperazines,[10,11] there are relatively few examples of functionalization of cyclo(Pro,Pro).[12] At first inspection, electrophilic addition to the enolate of cyclo(Pro,Pro) might be expected to show only low degrees of facial diastereoselectivity as a result of the near planarity of the tricyclic system. Schöllkopf reported high diastereoselectivity for alkylations of amino acid derived bislactim ethers.[13] His rationale for the observed selectivity was based on steric effects due to ring substituents. It has also been suggested that facial selectivity in related alkylations of lactam enolates is directed either by stereoelectronic,[14] torsional effects[15] or by solvation of the enolate counterion.[16] Seebach also suggested the role of adjacent nitrogen and α-carbon pyramidalization on facial selectivity.[14d]

We initiated our desymmetrization studies with the DKP derived from the less expensive (*S*) enantiomer of proline rather than the (*R*) enantiomer as required for the natural product. Low-temperature deprotonation of DKP **5** with 1 equiv of either LDA or KHMDS produced the monoenolate (~90%, as evidenced by quenching with MeOD). Trapping of the monoenolates with a variety of electrophiles occurred with high diastereoselectivity (dr 11−42:1, GC) in all cases studied (Table 1). Unsurprisingly, potassium enolates were found to be slightly more reactive than lithium enolates (entries 2, 6, and 8 versus 3, 5, and 7). Treatment of the potassium enolate of DKP **5** with benzylchloroformate initially gave only a 48% yield of monobenzylester DKP **6c**. This acylation was improved by slow, inverse addition of the enolate to the electrophile, which presumably lowers the possibility of competing deprotonation of the slightly more acidic, monoacylated DKP product **6c**. However, neither inverse addition nor an increase in base employed improved the yields of 3-azido DKP **6a**.

The stereochemical outcome of these electrophilic additions was determined by NOE and/or X-ray analysis. A key NOE was observed for 3-methyl DKP **6d** between the C_6 hydrogen and the methyl group, confirming the *cis* arrangement of these substituents (Figure 2a). Single-crystal X-ray analysis of the crystalline benzyl DKP **6f** confirmed the relative stereochemistry of this alkylated DKP (Figure 2b). The high degree of diastereoselectivity in these electrophilic additions may be attributed to the slightly puckered nature of the tricyclic system, in which the electrophile approaches

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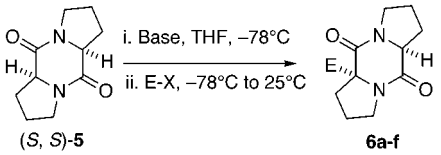
Table 1. Enolization and Diastereoselective, Electrophilic Additions to Cyclo(Pro,Pro)



entry	base	E-X	compd no.	% yield[a]	dr[b]
1	KHMDS[c]	Tris-N_3	**6a**	42 (33)	nd[d]
2	KHMDS[c]	$ClCO_2Me$	**6b**	82 (6)	11:1
3	LDA[e]	$ClCO_2Me$	**6b**	80	nd
4	KHMDS[f]	$ClCO_2Bn$[g]	**6c**	70 (9)	12:1
5	LDA[d]	MeI	**6d**	55	nd
6	KHMDS[c]	MeI	**6d**	65 (19)	27:1
7	LDA[d]	allyl-Br	**6e**	54	nd
8	KHMDS[c]	allyl-Br	**6e**	66 (13)	18:1
9	KHMDS[c]	BnBr	**6f**	75 (6)	42:1

[a] Yields shown are for purified products (SiO_2). Recovered starting material is indicated in parentheses. [b] Determined on crude reaction mixtures using chiral GC (see Supporting Information for details). [c] KHMDS is added to a precooled solution of DKP **5**. [d] nd = not determined. [e] A solution of DKP **5** is added to freshly prepared LDA. [f] A solution of DKP **5** is added to a precooled solution of KHMDS in THF. [g] The enolate is added to a precooled solution of benzyl chloroformate.

the enolate from the sterically less encumbered face. However, this explanation does not adequately rationalize the high diastereoselectivity observed and contributions from stereoelectronic effects cannot be excluded.[14]

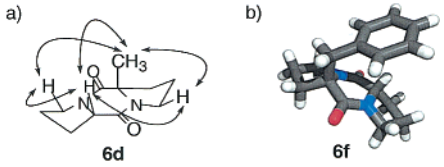


Figure 2. (a) NOEs observed for 3-methyl DKP **6d.** (b) Single-crystal X-ray structure of 3-benzyl DKP **6f** (POVchem rendering).

To determine the *syn* stereochemistry of the monofunctionalized DKP **6a**, the azide moiety was reduced and subsequent guanidinylation by the method of Kim and Qian[18] delivered the di-Boc-protected guanidine **7**. The latter compound exhibited a NOE between the *tert*-butyl of the Boc group when H_5 was irradiated (Scheme 2).

It is known that cyclo(Pro,Pro), unlike other cyclic dipeptides, exists almost exclusively (99.5:0.5) as the *cis* isomer under equilibrating conditions.[13b] Thus, the high diastereomeric ratio of the alkylated and acylated DKPs described above could be the result of a *trans* to *cis* interconversion following the initial electrophilic addition.

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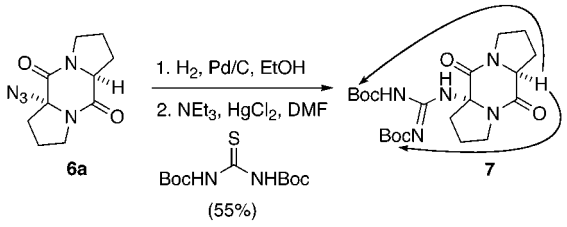
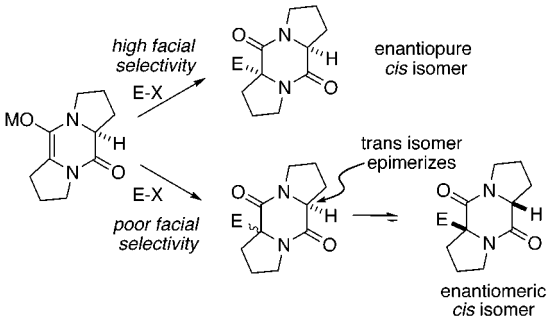
Scheme 2. Functionalization of Azide **6a** (Observed NOEs Indicated by Arrows)



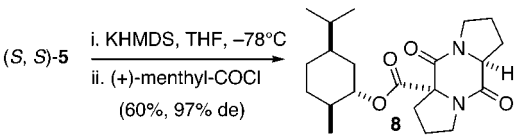
To confirm that this was not occurring, we investigated methods to assay the enantiopurity of the products since equilibration would manifest itself by loss of optical purity (Scheme 3).

Scheme 3. Mechanism for Potential Erosion of Enantiopurity of Monofunctionalized DKPs



Unfortunately, after numerous studies, we were unable to determine the enantiomeric purity of any of the monofunctionalized DKPs or derivatives by use of chiral GC, HPLC, or NMR shift reagents. Thus, we employed the chiral electrophile (+)-menthyl chloroformate, as this would lead to the formation of diastereomers, if indeed epimerization was occurring. Only one diastereomer was formed (97% de) based on comparative GC analysis with a 1:1 diastereomeric mixture obtained from racemic **5** (Scheme 4). This provides

Scheme 4. Diastereoselective Acylation with Menthyl Chloroformate Confirming High Facial Selectivity

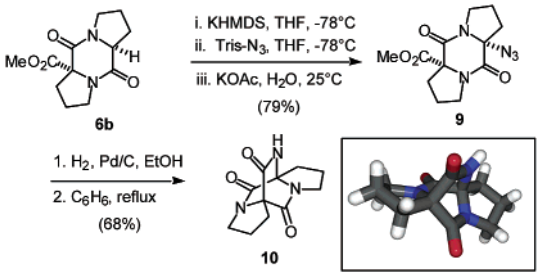


evidence that diastereoselectivity in these alkylations and acylations is solely due to the initial, high facial selectivity during electrophilic additions to the DKP enolates, rather than subsequent epimerization of an initial diastereomeric mixture.

We also studied a bis-functionalization of cyclo(Pro,Pro) **5**. Interestingly, the 3-carbomethoxy DKP **6b** (and also

3-carbobenzyloxy DKP **6c**, not shown) underwent azidation with high diastereoselectivity and in higher yields than the parent DKP **5**. The relative stereochemistry of azide **9** was determined by reduction of the azide group to the free amine, which upon reflux in benzene cyclized to the tetracyclic system **10**. This structure was further confirmed by single crystal X-ray analysis (Scheme 5). This cyclization would

Scheme 5. Diastereoselective Bisfunctionalization of DKP **5** (inset is POV chem rendering of X-ray crystal structure of lactam **10**)



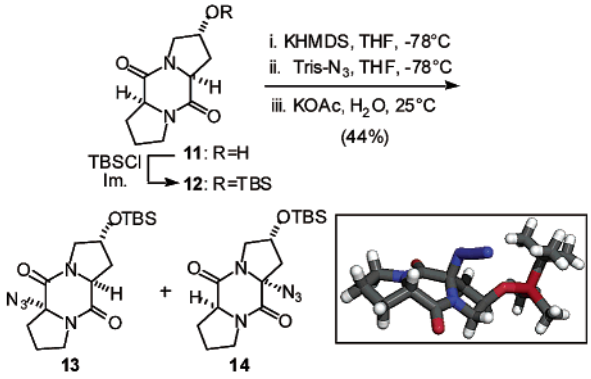
only be possible for a *syn* arrangement of the intermediate amine and ester, which could be attained either by direct azide reduction of the *syn* isomer of **9** or by reduction of the *trans* azide ester followed by reversible ring opening via a presumed imine intermediate. Although it has not been verified which pathway is followed, if a *syn* arrangement of azide and ester is obtained, it is interesting to note that the steric hindrance introduced by the C-3 substituent does not invert the facial selectivity. This is true even when C_3 is substituted with the bulky carbobenzyloxy group, which is presumably folded over the DKP ring system.[19]

When the starting DKP is not C_2-symmetric, i.e., TBS-protected L-prolyl-L-4-hydroxy proline [cyclo(Pro,Hyp), **12**], electrophilic addition yields a 1:1 mixture of regioisomers **13** and **14**, surprisingly with no change in facial selectivity. The structure of DKP **14** was confirmed by single-crystal X-ray crystallography (Scheme 6). Hence, introduction of bulky groups to direct the electrophilic attack of the DKP enolate *does not* invert the facial selectivity, suggesting that other factors are involved in this diastereoselective process.

In conclusion, we have demonstrated that electrophilic additions to proline-derived DKP enolates with both alkyl

(19) It has been demonstrated using NMR and X-ray crystallography that aromatic systems are folded over DKP ring system, see ref 13b. Moreover, the upfield shift of H-6 in benzyl DKP **6f** and carbobenzyloxy DKP **6c** suggests that the aromatic rings are indeed folded over the DKP in solution.

Scheme 6. Functionalization of Unsymmetric DKP **12**[a]



[a] Inset is POV chem rendering of X-ray crystal structure of lactam **14**.

halides and acyl halides proceed with high facial selectivity. The selectivity is presumably due to steric biases inherent to the tricyclic system. However, other factors such as stereoelectronic effects cannot be excluded at this time. Azidation of cyclo(Pro,Pro) and 3-carbomethoxy DKP **6b** as well as derivatization of the azide moiety proceed smoothly. The electrophilic addition of acyl halides to DKP **5** represents the starting point for our total synthesis of phakellstatin and phakellin. Further studies toward this end will be reported in due course.[20]

Acknowledgment. Dedicated to Prof. A. I. Meyers on the occasion of his 70th birthday. We thank the NIH (GM 52964-05), the Robert A. Welch Foundation (A-1280), Zeneca, and Pfizer for support of these investigations. A.T.K. was a Summer 2001 NSF-REU participant (CHE-0071889). D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher-Scholar. We thank Prof. Robert M. Williams (Colorado State) for helpful input. We thank Dr. Joe Reibenspies for X-ray structure determination using instruments obtained with funds from the NSF (CHE-9807975). The NSF (CHE-0077917) also provided funds for purchase of NMR instrumentation.

Supporting Information Available: Selected experimental procedures and characterization data (including ^{1}H and ^{13}C NMR spectra) for compounds **6a**−**f** and **7**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026140Q

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