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# An Asymmetric Organocatalysis Approach to the Prenylated Alkaloid Family

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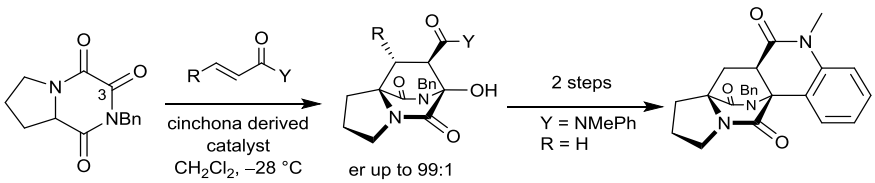
*Supporting Information Placeholder*




**ABSTRACT:** Michael addition of a proline-derived triketopiperazine (TKP) to β-substituted enones and acrylamides, mediated by a cinchona alkaloid catalyst, delivers products possessing a bicyclo[2.2.2]diazaoctane structure in high yield and enantiomeric ratio (er). Further modification of the amide products towards polycyclic scaffolds resembling members of the prenylated alkaloid family is also demonstrated.

Members of the prenylated indole alkaloid family, possessing a bicyclo[2.2.2]diazaoctane core structure, remain the subject of intense research interest in respect of their synthesis, biosynthesis, and diverse biological activities.[1] These compounds, which have been isolated from both marine and terrestrial fungal sources, feature complex polycyclic architectures with multiple functionalities and stereogenic centres, e.g. **1**–**4**. Paraherquamide A (**1**) is a venerable example, which succumbed to synthesis by the Williams group, who have spearheaded research in this area.[2] The arrival of stephacidins A and B in 2002 triggered widespread interest, due to both the molecular complexity of stephacidin B (**2**) (itself a dimer of another compound, avrainvillamide), and its potent activity against testosterone-dependent prostate LNCaP cells ($IC_{50}$ = 60 nm).[3] Notable syntheses of these compounds by the groups of Myers, Baran and Williams,[4-6] spurred further activity.[7]

Taichunamides (e.g **3**), peniciherquamides (e.g **4**) are representative of more recently isolated examples, which also include mangrovamides, penioxalamine A, and waikialoid A, as well as novel paraherquamide and notoamide variants.[8]

The reported activities of these compounds are as varied as the structures themselves and include tumour cell cytotoxicity, anti-hepatitis C virus activity, and potential neuroprotective action. A further intriguing aspect of this natural product family is their stereochemical diversity, with either C-6 stereochemistry being evident, and some members having been isolated in either *enantiomeric* series.[9]

The principle access to these compounds involves either a biomimetic intramolecular hetero-Diels-Alder reaction or stepwise elaboration of alkylated prolines obtained using the Seebach 'self-regeneration of stereocentres' method.[10] Both approaches have limitations and a definitive access to the bicyclo[2.2.2]diazaoctane structures with control of absolute and relative stereochemistry remains elusive.[11,12]

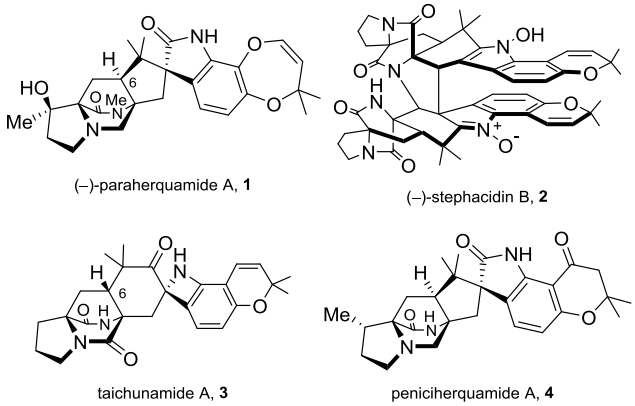



Figure 1. Structures of prenylated indole alkaloids

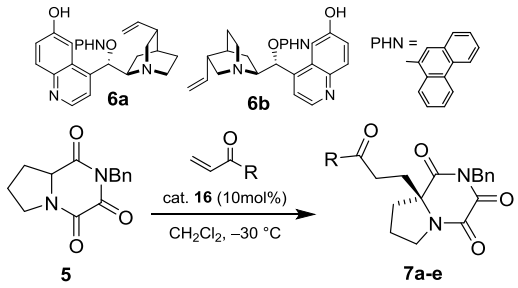
Against this backdrop, a new catalytic approach, providing access to this type of alkaloid structure, *in either enantiomeric series*, and with high levels of control, would be very valuable. Herein we report one such solution, which relies upon our recently described method for activation of amino acid systems towards organocatalysed Michael addition by formation of a derived triketopiperazine (TKP).[13]

Engagement of a proline derived TKP (e.g. **5** below) in a chiral catalyst-driven Michael addition process could result in a kinetic resolution if the TKP were to be configurationally stable, or a stereochemical convergence through dynamic kinetic resolution if the TKP proved to be configurationally labile under the reaction conditions.[14] To probe which of these situations would prevail we initiated our study by synthesis of TKP **5** in three steps from Boc-*L*-proline, using an established approach, (see ESI for details).

TKP isolated from the key ring forming reaction, involving oxalyl diimidazole proved to be racemic, and despite strenuous efforts, it has not been possible to isolate non-racemic samples of **5**, a result which attests to the activating effect of the TKP ring towards enolization.

Preliminary screening of Michael additions of TKP **5** to methyl vinyl ketone (MVK), mediated by typical cinchona alkaloid derived catalysts, identified the *O*-phenanthryl (PHN) system **6** as the most promising (Table 1).[15] Interesting levels of selectivity were seen using catalyst **6a**, with a number of enone acceptors and also an unsaturated *N*-acyl oxazolidinone, giving products **7** in up to 94:6 er. In the case of MVK we also established that the pseudoenantiomeric catalyst **6b** gave the enantiomeric product (Entry 2).

**Table 1. Michael additions of TKP 5.**




| Entry | Cat. | R | Time[a] | 7[b] [%] | er[c] |
|---|---|---|---|---|---|
| **1** | **6a** | Me | 22 | **7a** 93 | 10:90 |
| **2** | **6b** | Me | 30 | **7a** 81 | 78:22[d] |
| **3** | **6a** | Et | 25 | **7b** 75 | 13:87 |
| **4** | **6a** | Ph | 20 | **7c** 88 | 6:94 |
| **5** | **6a** | H | 24 | **7d** 64[e] | 21:79 |
| **6** | **6a** |  | 48 | **7e** 98 | 15:85 |

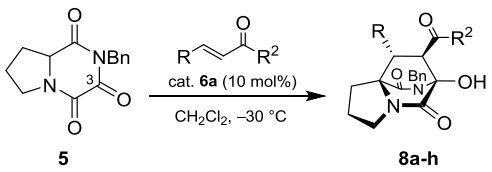
a Hours. b Isolated yield after chromatography. c Determined by HPLC analysis. d enantiomeric product to one shown. e Isolated yield of derived acetal product over two steps (see ESI).

When we explored the enone acceptor class in more detail it was a surprise to find *in-situ* ring-closure had occurred to give products **8** (Table 2). Previously this reactivity had only been observed with alternative Michael acceptors. [13]

Entry 1 details the remarkable outcome of TKP reaction with chalcone, using catalyst **6a**, tricyclic hydroxy-DKP **8a** being isolated as a single diastereoisomer, possessing four contiguous stereocenters, and in 96% yield and 99:1 er. Comparison of this result with the similarly selective enantiocomplementary version in Entry 2 underlines the power of this approach for asymmetric synthesis of either enantiomeric series, and confirms the operation of a highly efficient dynamic kinetic resolution.

To further explore this mode of reaction, a number of additional β-substituted enones were reacted with TKP **5** (Entries 3-8). Ring closure was found to occur in all cases and excellent levels of asymmetric induction were obtained, with er ≥ 94:6. Interestingly, *N*-cinnamoyl oxazolidinone was also found to undergo addition–ring-closure, to provide adduct **8h** in good yield and with excellent selectivity (Entry 9).

**Table 2. Michael additions of TKP 5 to β-substituted Michael acceptors.**




| Entry | R | $R^2$ | Time[a] | 8[b] [%] | er[c] |
|---|---|---|---|---|---|
| **1** | Ph | Ph | 18 | **8a** 96 | 99:1 |
| **2** | Ph | Ph | 18 | **8a** 85 | 1:99[d] |
| **3** | Ph | *o*-$C_6H_4Br$ | 27 | **8b** 75 | 97:3 |
| **4** | *p*-$C_6H_4F$ | Ph | 20 | **8c** 95 | 94:6 |
| **5** | *p*-$C_6H_4OMe$ | Ph | 22 | **8d** 70 | 99:1 |
| **6** | Ph | Me | 21 | **8e** 98 | 98:2 |
| **7** | Me | Ph | 22 | **8f** 99 | 99:1 |
| **8** | Me | Et | 24 | **8g** 96 | 99:1 |
| **9** | Ph |  | 24 | **8h** 81 | 97:3 |

[a] Hours. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis. [d] Enantiomeric structure to that shown (cat **6b**).

Ring closure in these systems may be promoted by a 'buttressing' effect, akin to a Thorpe-Ingold effect, with the β-substituent causing the intermediate enolate to be in closer proximity to the electrophilic TKP C=O function at C-3. Orientation of the intermediate ketone enolate to minimise interactions with the β-substituent and with the TKP *N*-benzyl substituent, results in the formation of a single diastereoisomer. Notably, this is the same relative configuration seen in the majority of the natural product series – i.e. C-6 in Figure 1.

Crystallisation of adduct **8a**, allowed the absolute and relative configuration to be determined by X-ray crystallography (Figure 2).[16] The sense of initial asymmetric Michael addition matches that seen in our previous work and is in agreement with the stereochemical model originally proposed by Deng.[22]

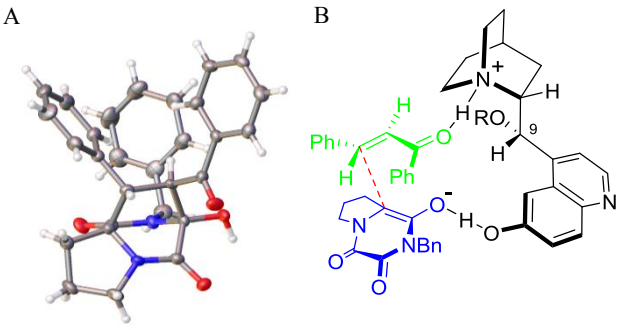


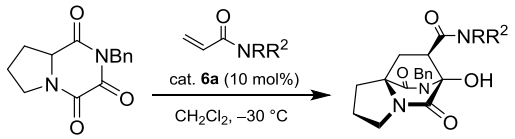

Figure 2. (A) The structure of one of the two crystallographically independent molecules of **8a**, with ellipsoids drawn at the 50% probability level;[16] (B) Model for **6a** catalysed Michael addition of **5** to chalcone.

Figure 3(B) shows an alternative speculative picture based upon a modification of recently disclosed calculations by the Houk group.[18] The proposed model shows activation of the

acceptor by the quinuclidinium ion, whilst the TKP enolate is orientated by association with the phenolic group on the quinoline. In this novel model variant the ether group at the C-9 position is not actively involved in hydrogen bonding.

In subsequent screening of alternative Michael acceptors that might also provide direct access to the chiral bicyclo[2.2.2]diazaoctane, but without the need for a β-substituent, we identified unsubstituted acrylamides as systems that deliver exceptional results (Table 3). Amides **9**, having a wide variety of nitrogen substituents, were isolated as single diastereoisomers and with excellent levels of enantioselectivity, (er ≥ 97:3).

**Table 3. Michael reaction of TKP 5 with α,β-unsaturated amides.**




**5** **9a-i**

| Entry | R | $R^2$ | Time[a] | 9[b] [%] | er[c] |
|---|---|---|---|---|---|
| **1** | H | Ph | 20 | **9a** 72 | 97:3 |
| **2** | H | Bn | 48 | **9b** 64 | 99:1 |
| **3** | Me | Ph | 64 | **9c** 83 | 99:1 |
| **4** | Me | Me | 48 | **9d** 81 | 99:1 |
| **5** | Ph | Ph | 22 | **9e** 80[d] | 96:4 |
| **6** | Me | OMe | 42 | **9f** 98 | 98:2[e] |
| **7** | Piperidine | | 20 | **9g** 80 | 99:1 |
| **8** | Morpholine | | 44 | **9h** 98 | 99:1 |
| **9** | Indoline | | 40 | **9i** 95[d] | 98:2 |

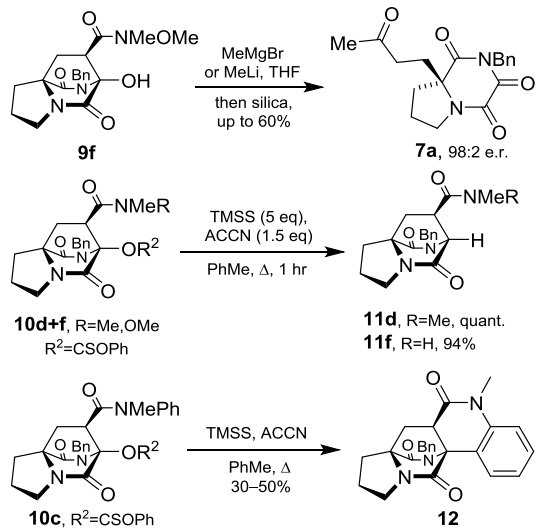
[a] Hours. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis. [d] *ca.* 5-10% of the corresponding amide epimer in the crude reaction mixtures. [e] HPLC run on **7a** (MeMgBr addition).

That amides should perform so well here was unexpected and to our knowledge, these are the first enantioselective Michael additions to aliphatic acrylamides using a cinchona alkaloid catalyst, as well as the first Michael additions to acrylamides using an amidic donor.[19–22]

Interestingly, treatment of Weinreb amide product **9f** with excess MeMgBr or MeLi afforded the *bridge-opened* ketone **7a** (Scheme 1). The er of **7a** obtained this way was considerably higher (98:2) than that obtained from the direct MVK addition approach, and establishes **9f** as a useful stepping stone to 'open' TKP adducts **7** via apparent addition–ring-opening.

Although the products obtained in Table 3 possess the characteristic tricyclic core common in the prenylated indole alkaloid family, the bridgehead hydroxyl group, which forms part of a hemiaminal type function, renders these products somewhat reactive. We were keen to demonstrate that this bridgehead function could be either removed, or engaged in useful C–C bond formation to generate novel scaffolds more closely resembling the natural alkaloids. To this end we chose to explore bridgehead radical chemistry with selected amides **9**.[23] Initial conversion of Michael adducts **9c**, **9d** and **9f** into the corresponding thiocarbonates **10** was achieved using *O*-phenyl chlorothionoformate (see ESI for details).

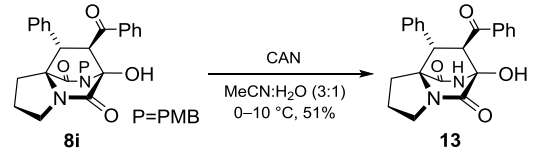
**Scheme 1. Transformations of Michael adduct 9.**




When thiocarbonate **10d** was heated with tristrimethylsilylsilane (TTMS) and 1,1′-azobis(cyclohexane-carbonitrile) (ACCN) in toluene under reflux, quantitative reduction of the bridgehead position was observed, leading to **11d**. Analogous reduction of Weinreb amide **9f**, via **10f**, also proceeded in excellent yield, although with unexpected concomitant amide deoxygenation, giving *secondary* amide **11f** (Scheme 1).

The pentacyclic lactam **12** was generated cleanly, albeit in moderate yield, starting with **10c**, resulting from intramolecular radical addition and re-aromatisation. Such polycyclic scaffolds are obvious mimics of the natural products and may well possess interesting biological activities.

**Scheme 2. Deprotection of PMB adduct 8i.**




Attempts to address the issue of protecting group removal using an *N*-*p*-methoxybenzyl (PMB) series showed that Michael addition chemistry can be applied without erosion in selectivity. Despite well-documented difficulties in the removal of the PMB group from this type of structure, we have found that oxidative conditions readily generate the desired deprotected bridged DKP **13** (Scheme 2).[24]

In conclusion, we have shown that the proline derived TKP motif can allow access to a number of highly enantioenriched hydroxy DKPs, that share key similarities to a number of the prenylated indole alkaloids. A number of Michael acceptors have been shown to undergo addition, including unsubstituted acrylamides. Either enantiomeric series can be accessed by switching between pseudoenantiomeric cinchona alkaloid derivatives, starting from a racemic starting TKP, demonstrating that a highly effective dynamic kinetic resolution is operative. Further reduction and cyclisation of the hydroxy-DKPs at the bridgehead position has also been demonstrated. Extension of this approach to enable synthesis of more complex examples, including natural products, is under way.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, and spectra data for new compounds and HPLC traces (PDF). Single-crystal X-ray data for **8a** (CIF).

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### Notes

The authors declare no competing financial interest.

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