Asymmetric Synthesis

DOI: 10.1002/anie.200800329

Organocatalytic Asymmetric Synthesis of Versatile γ-Lactams**

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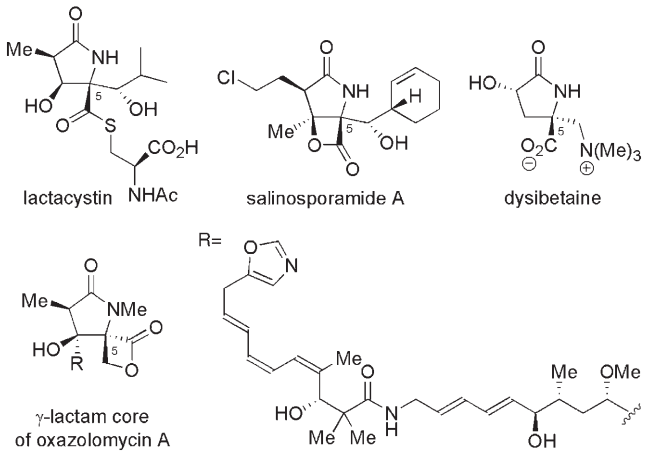
Molecules of natural origin containing a functionalized γ-lactam (pyrrolidin-2-one) ring system with a quaternary stereocenter[1] at C5 hold a prominent position in chemistry and biology. Important examples of these γ-lactams include the proteasome inhibitors lactacystin and salinosporamide A, dysibetaine, and several examples from the oxazolomycin family of antibiotics (Scheme 1).

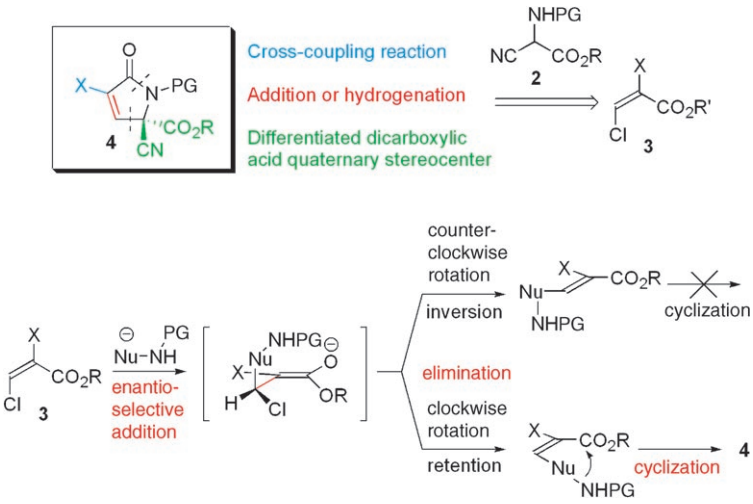
The biological profiles of these molecules, combined with the synthetic challenge of constructing the elaborate heterocyclic core, have resulted in a number of inspiring enantioselective chemical syntheses.[2] Furthermore, recognizing the potential for discovery of novel bioactive small molecules based upon the γ-lactam core structure, several research groups have recently presented interesting multicomponent or cascade approaches towards functionalized γ-lactams.[3] Unfortunately these methods do not offer stereochemical control in an absolute sense. Consequently, we propose that a catalytic enantioselective reaction which may provide access to both enantiomers of a simple structure containing the γ-lactam ring, a C5 quaternary stereocenter, and functionalities to allow the introduction of additional molecular complexity would be an important development. Such a structure could be the starting point, not only for total synthesis, but also for more systematic approaches to the diversification of the γ-lactam core. Application of robust and well-tested methodologies to elaboration of the core structure may eventually result in the discovery of new bioactive compounds.



Scheme 1. γ-Lactam-containing natural products.

Recently, organocatalysis has been the subject of intensive development, with a special focus on methodology.[4] An important step in making organocatalysis a more mature field of research is to demonstrate its potential usefulness for the synthesis of important target structures.[5]

Herein, we demonstrate a novel use of the organocatalytic enantioselective vinylic substitution reaction[6] for the single-step construction of C5 quaternary 3-halo-3-pyrrolin-2-ones **4** (Scheme 2). As will be demonstrated, these structures are predisposed for functionalization and may be regarded as common precursors for a range of more complex structures built around the γ-lactam core.



Scheme 2. Target structure and mechanistic hypothesis. PG = protecting group.

A key to the reaction is the use of the stereochemically well-defined α,β-dihalogenated acrylate ester **3** as the electrophile in the substitution process.[7] Under the control of a chiral phase-transfer catalyst, enantioselective C–C bond formation by the stereospecific substitution of the chlorine atom, with retention of configuration, by a 1,2-dinucleophile such as **2** followed by immediate ring closure results in the selective formation of **4** (Scheme 2).[8] The success of this transformation pays tribute to the stereospecificity[6,9] of the vinylic substitution reaction, as only the products that have

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[**] This work was funded by a grant from The Danish National Research Foundation and the OChemSchool.

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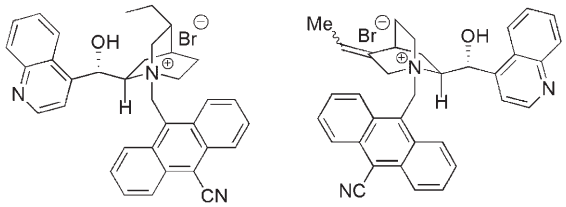
retained their configuration will undergo the desired cyclization.

From initial screening experiments (see the Supporting Information) we identified the dihydrocinchonine-derived phase-transfer catalyst **HCn-1** (Scheme 3) as very active; it delivered, for example, **4a** in about 80% *ee* when the reaction



HCn-1 **isoCd-1**

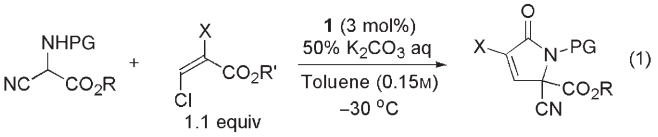
Scheme 3. Structures of the catalysts.

was performed in toluene at −30 °C. Although improvements were possible by performing the reaction at lower temperatures, we found that these conditions resulted in a good compromise between reactivity and selectivity as the products were easily recrystallized in enantiopure form and were obtained in high yields (Table 1).

These considerations led to the reaction conditions shown in Equation (1). The iodo-substituted products **4a–d** (Table 1, entries 1, 3, 5, and 6) were obtained as single enantiomers in 63–73% yield by recrystallization of the crude reaction mixture.

For synthesis of the enantiomeric products, for example, *ent*-**4a** and *ent*-**4b** (Table 1, entries 2 and 4), we employed the isocinchonidine-derived phase-transfer catalyst **isoCd-1**

Table 1: The synthetic scope for the preparation of 3-halo-3-pyrrolin-2-ones **4**.[a]



2 **3a**: X = I, R' = Me; **3c**: X = Cl, R' = Me

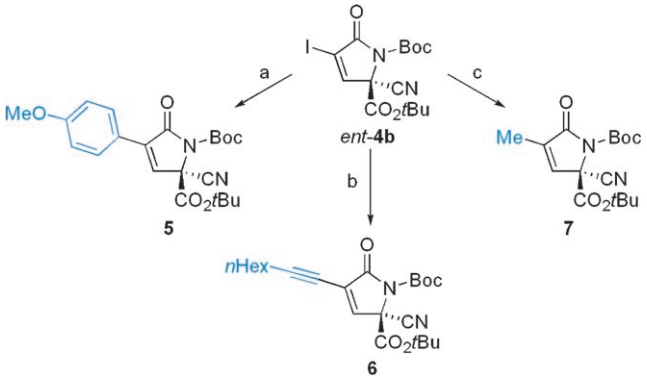
4a: X = I, PG = Boc, R = Et
4b: X = I, PG = Boc, R = *t*Bu
4c: X = I, PG = Troc, R = *t*Bu
4d: X = I, PG = Cbz, R = *t*Bu
4e: X = Cl, PG = Boc, R = *t*Bu

Entry	Catalyst	Acrylate ester	Product	*ee* [%][b] (crude)	Yield [%][c]	*ee* [%][b] (config.)
1	**HCn-1**	**3a**	**4a**	79	73	>99 (*R*)[d]
2[e]	**isoCd-1**	**3a**	*ent*-**4a**	78	68	>99 (*S*)
3	**HCn-1**	**3a**	**4b**	89	71	>99 (*R*)[d]
4[e]	**isoCd-1**	**3a**	*ent*-**4b**	73[f]	62	>99 (*S*)
5	**HCn-1**	**3a**	**4c**	91	63	>99 (*R*)
6	**HCn-1**	**3a**	**4d**	80	64	>99 (*R*)
7	**HCn-1**	**3c**	**4e**	85	90[g]	85 (*R*)

[a] Reactions were performed with 1 mmol of **2**. [b] Determined by HPLC on a chiral stationary phase using a Chiralpak AD column. [c] Yield of isolated product after crystallization. [d] Configuration was determined by X-ray analysis. [e] Toluene/$CHCl_3$ (4:1) as the solvent. [f] See Ref. [10]. [g] Yield of isolated product after chromatography. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Troc = 2,2,2-trichloroethoxycarbonyl.

because of the poor performance of the true quasi-enantiomeric catalyst.[10] The chloro-substituted product **4e** (Table 1, entry 7) was unfortunately not crystalline, but was isolated in 90% yield and with 85% *ee* after column chromatography. X-ray crystallographic analysis of **4a** and **4b** allowed the determination of the absolute stereochemistry.[11]

The optically active γ-lactams **4** were easily modified (Scheme 4). It was possible to introduce different substituents at C3 by standard palladium-catalyzed cross-coupling meth-

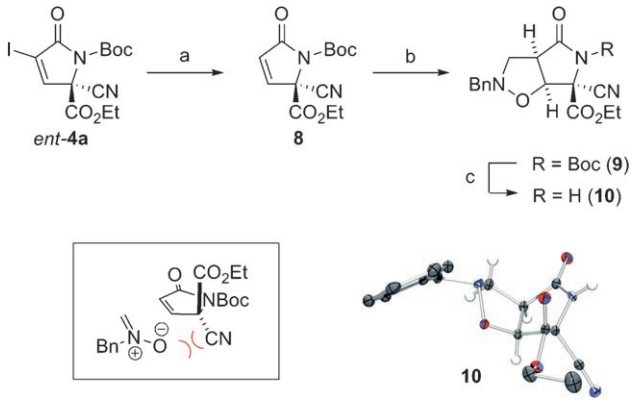


Scheme 4. Different cross-coupling reactions with *ent*-**4b**. Reagents and conditions: a) 10% $[Pd(PPh_3)_4]$, PMP-$B(OH)_2$, toluene, 2 M aq Na_2CO_3, 60 °C, 75 min, 71%; b) 10% $[PdCl_2(PPh_3)_2]$, 15% CuI, 1-octyne, DIPEA, CH_2Cl_2, RT, 40 min, 83%; c) 5% $[PdCl_2(PPh_3)_2]$, $ZnMe_2$, DMF/THF (1:1), RT, 105 min, 86%. DMF = *N*,*N*-dimethylformamide, PMP = *para*-methoxyphenyl, DIPEA = *N*,*N*-diisopropylethylamine.

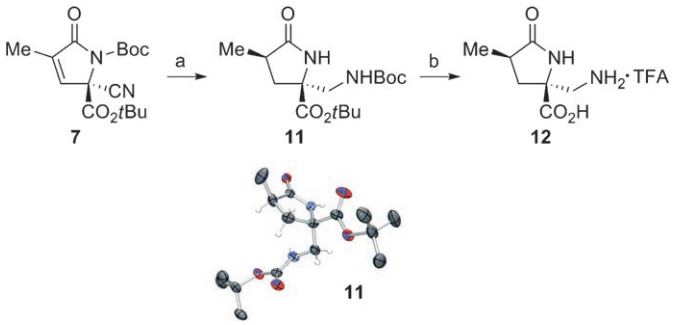
odologies. Suzuki coupling was used to introduce an aryl group (→**5**, 73%), Sonogashira coupling allowed alkynyl substitution (→**6**, 83%), and an alkyl substituent was introduced through Negishi coupling (→**7**, 86%). Notably, many γ-lactam-containing natural products have a C3 methyl group.

The iodine atom of **4** can also be readily removed, as demonstrated for *ent*-**4a** (Scheme 5). The resulting unsubstituted 3-pyrrolin-2-one **8** may be involved in 1,3-dipolar cycloaddition reactions to introduce *syn*-related substituents at the 3- and 4-positions of the γ-lactam. Towards this end, **8** was treated with *N*-benzylnitrone under thermal conditions and cycloadduct **9** (d.r. 4:1) was obtained as the major isomer. As determined by X-ray analysis of the derivative **10**,[11] the ethyl ester group is *syn* to the isoxazolidine ring. For steric reasons the observed selectivity is surprising, but it may be attributed to an unfavorable dipolar interaction between the nitrile group and the nitrone, which thus favors attack at the opposite face of the molecule. Accordingly, this effect is attenuated when the reaction is performed in polar media; in acetonitrile the observed diastereoselectivity is 1:1. Cycloadduct **9** may be a viable precursor to lactacystin or closely related analogues.[12]

Selective hydrogenation from the α face of **7** (Scheme 6) is an efficient method for the introduction of an additional stereogenic center on the γ-lactam ring. In fact, it was possible to carry out this transformation with concomitant hydrogenation of the nitrile and in situ Boc protection. Filtration of



Scheme 5. Iodine atom removal and nitrone 1,3-dipolar cycloaddition. Reagents and conditions: a) Pd/C, quinoline, H_2 (1 bar), NaOAc, MeOH, RT, 2 h, 77–84%; b) BnN(O)CH_2, toluene/*c*-hexane (1:1), RT→40°C, 40 h, 53%; c) 20% $Mg(ClO_4)_2$, CH_2Cl_2, 35°C, 75 min, 100%. Bn = benzyl.



Scheme 6. Diastereoselective hydrogenation and amino acid synthesis. Reagents and conditions: a) 1. H_2 (10 bar), Pd/C, Boc_2O, NEt_3, EtOH/THF (5:3), RT, 16 h; 2. 20% $Mg(ClO_4)_2$, CH_2Cl_2, reflux, 22 h, 82% (over 2 steps); b) TFA/CH_2Cl_2 (1:1), 3.5 h, RT, 86%. TFA = trifluoroacetic acid.

the crude mixture through silica gel and selective removal of the amide Boc group with catalytic $Mg(ClO_4)_2$ afforded **11** as a single stereoisomer in 82% yield. The relative stereochemistry was established by X-ray analysis.[11] Standard deprotection under acidic conditions afforded (*R*)-pyroglutamic acid derivative **12**—a structure also related to the natural product dysibetaine.[13]

In conclusion, we have developed a new organocatalytic vinylic substitution reaction to prepare optically pure halo-substituted pyrrolin-2-ones—compounds that are a flexible starting point for the preparation of structurally diverse optically active γ-lactams. The overall process is very practical, scalable, and chromatography-free. Through a number of transformations we have demonstrated how the products may be modified to yield derivatives of potential biological relevance. Albeit still in its early stage of development, the enantioselective vinylic substitution reaction is emerging as a powerful tool for the expeditious assembly of complex molecules, and the continued advancement and application of this reaction is a prime focus of our current research.

Experimental Section

A precooled (−30°C) solution of 50% aq K_2CO_3 (3.3 mL) was added to a cooled (−30°C) mixture of **2** (1 mmol), **1** (3 mol%, 0.03 mmol), solvent (6.7 mL), and **3** (1.1 mmol). The reaction was vigorously stirred until judged to be complete (as evident by TLC; Et_2O/CH_2Cl_2 3:97) then allowed to warm to room temperature. The mixture was diluted with H_2O (10 mL) and Et_2O (15 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (2×10 mL), and the combined organic extracts were washed successively with H_2O (10 mL) and brine (10 mL). After drying with Na_2SO_4 the mixture was concentrated and the resulting residue was rapidly filtered through a short pad of SiO_2 (3×2 cm) with Et_2O/CH_2Cl_2 (5:95; 100 mL), which upon concentration afforded the crude product as a viscous yellow oil. Evaporation with pentane gave a solid material which was recrystallized from EtOAc/*n*-hexane to afford the enantiopure lactam **4**.

Representative example: (*R*)-1-*tert*-Butyl 2-ethyl 2-cyano-4-iodo-5-oxo-1*H*-pyrrole-1,2(2*H*,5*H*)-dicarboxylate (**4a**) was isolated in 73% yield (>99% *ee*) to give colorless crystals after recrystallization (m.p. 126–128°C). ^{1}H NMR ($CDCl_3$): $\delta = 7.40$ (s, 1H), 4.36 (m, 2H), 1.56 (s, 9H), 1.36 ppm (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta =$ 162.5, 160.9, 146.3, 143.5, 111.4, 99.1, 86.7, 66.2, 65.2, 27.8 (3C), 13.9 ppm. HRMS: *m/z* calcd for $C_{13}H_{15}IN_2NaO_5$ 428.9923; found: 428.9922. The *ee* value was determined by HPLC on a chiral stationary phase using a Chiralpak AD column; eluent: *n*-hexane/*i*PrOH (98:2); flow rate: 1.0 mL min^{-1}; $\tau_{major} = 26.3$ min, $\tau_{minor} =$ 28.3 min. $[\alpha]_D^{RT} = -79.4°$ ($c = 0.56$ g cm^{-3}, CH_2Cl_2, >99% *ee*).

Received: January 22, 2008
Published online: May 14, 2008

Keywords: asymmetric catalysis · cinchona alkaloids · natural products · phase-transfer catalysis · vinylic substitution

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[11] CCDC 675042 (**4a**), 675043 (**4b**), 675044 (**10**), and 675045 (**11**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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