Organic LETTERS

Letter

pubs.acs.org/OrgLett

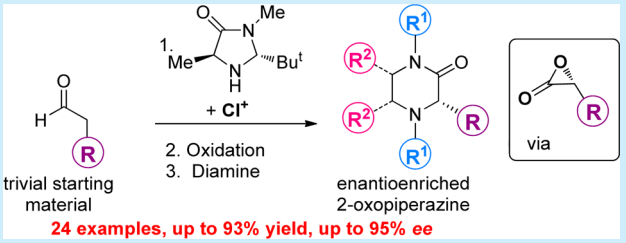
Enantioselective Organocatalytic Synthesis of 2-Oxopiperazines from Aldehydes: Identification of the Elusive Epoxy Lactone Intermediate

Nikolaos Kaplaneris, Constantinos Spyropoulos, Maroula G. Kokotou, and Christoforos G. Kokotos*

Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis, Athens 15771, Greece

Supporting Information

ABSTRACT: An organocatalytic linchpin catalysis approach was envisaged to convert simple aldehydes into enantioenriched 2-oxopiperazines. A four-step reaction sequence (chlorination, oxidation, substitution, and cyclization) was developed and led to different substitution patterns in high yields and selectivities. The reaction mechanism was studied, and the previously elusive epoxy lactone intermediate was identified by HRMS.



The 2-oxopiperazine moiety constitutes a common structural motif in a number of pharmaceuticals and medicinally interesting natural products (Figure 1).[1] It

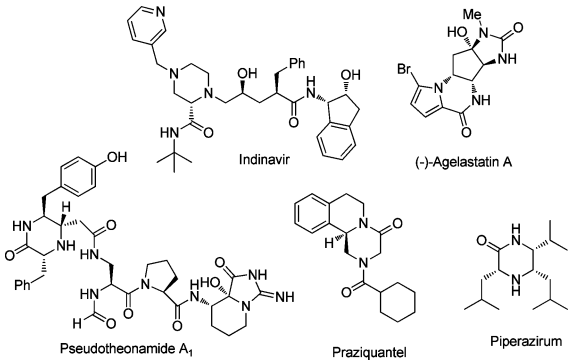


Figure 1. Natural products and pharmaceuticals bearing or derived from the 2-oxopiperzine core.

represents the structural core of several biologically active molecules, such as Leu-enkephalin analogues,[2a] cholecystokinin receptor antagonists,[2b] RGD mimetics,[2c] the neurokinin-2 receptor ligand,[2d] and promising candidates for the treatment of rheumatoid arthritis,[3a] depression,[3b] sexual dysfunction,[3c] and arterial thrombosis.[3d] Representative examples include the HIV protease inhibitor indivanir[4a] and the antischistosomiasis and soil-transmitted helminthiasis drug praziquantel[4b] (Figure 1).

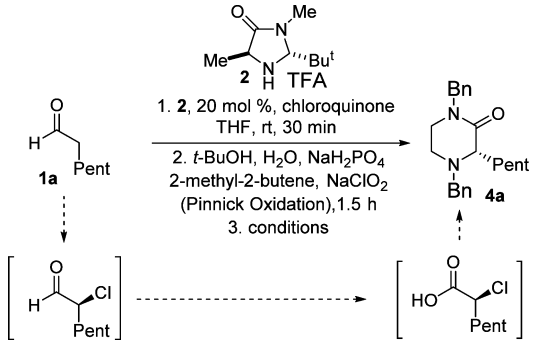
For such an often-occurring moiety, one would expect a plethora of synthetic approaches. Unfortunately, until very recently, only approaches based on chiral pool techniques were available in the arsenal of a synthetic chemist.[5] This daunting challenge was recently addressed with complementary methods based on chiral-auxiliary-promoted dynamic resolutions[6] and multistep metal-catalyzed processes.[7] In 2015, Stoltz and co-workers reported an elegant palladium-catalyzed asymmetric allylic alkylation approach for the synthesis of chiral 2-oxopiperazines.[8]

Having been actively involved in the field of organocatalysis,[9] and in particular in the field of organocatalytic oxidation,[10] and being inspired by MacMillan's enantioselective linchpin SOMO catalysis,[11,12] we introduce herein the use of enamine-promoted linchpin catalysis for the enantioselective synthesis of 2-oxopiperazines[13] along with mechanistic investigations regarding the reaction outcome. A mild organocatalytic α-chlorination of heptanal (**1a**) was coupled with a selective oxidation, leading to chiral α-chloro acids in a single-flask operation. Nucleophilic substitution by *N*,*N*′-dibenzylethylenediamine (**3a**) can give rise to a substituted amino acid derivative that could be cyclized upon reaction conditions affording chiral 2-oxopiperazine **4a** (Table 1). This would summarize a four-step reaction sequence in just one operation, without requiring any intermediate purifications, that affords stereodefined molecules of increased molecular complexity beginning from trivial and cheap starting materials. From the available chlorination protocols,[11,14] a modified procedure utilizing MacMillan's third-generation catalyst **2** in conjunction with chloroquinone as the chlorinating agent[14a] led to a highly enantioselective and fast protocol that can be coupled with Pinnick oxidation to afford α-chloroheptanoic acid almost quantitatively. This chlorination protocol provides high levels of asymmetric induction and avoids postreaction epimerization. Treatment of this acid with diamine **3a** in a pressure vessel at 100 °C for 2 h led to a moderate yield of 2-oxopiperazine **4a** with 93% *ee* (entry 1). Increasing the amount of the diamine had a positive effect on the reaction yield (entry 2). Increasing or decreasing the reaction temperature did not improve the reaction outcome (entries 3 and 4 vs entry 2). It has to be noted that decreasing the reaction temperature led to a slight erosion of the

Received: September 8, 2016
Published: October 28, 2016

DOI: 10.1021/acs.orglett.6b02699
Org. Lett. 2016, 18, 5800−5803

Table 1. Design Plan and Optimization of the Reaction Conditions Leading to Chiral 2-Oxopiperazines[a]



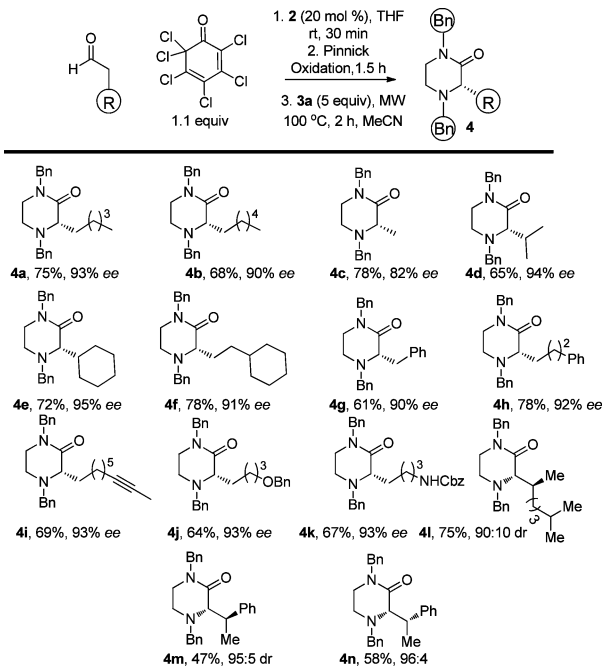
entry	conditions	yield (%)[b]	*ee* (%)[c]
1	$BnNHCH_2CH_2NHBn$ (3 equiv), 100 °C, 2 h	47	93
2	$BnNHCH_2CH_2NHBn$ (5 equiv), 100 °C, 2 h	57	93
3	$BnNHCH_2CH_2NHBn$ (5 equiv), 80 °C, 2 h	54	85
4	$BnNHCH_2CH_2NHBn$ (5 equiv), 120 °C, 2 h	56	92
5	$BnNHCH_2CH_2NHBn$ (5 equiv), 100 °C, MW, 2 h	75	93

[a]Catalyst **2** in THF, chloroquinone (1.1 equiv), heptanal (1 equiv) for 15 min at rt. *t*-BuOH, H_2O, 2-methyl-2-butene, $NaH_2PO_4.H_2O$, and $NaClO_2$ for 90 min at rt. Then MeCN and diamine. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

enantiointegrity of the product, which is due to competing mechanistic pathways, as will be discussed in detail later. Extending the reaction time led to a slight increase in the yield, but prolonging the reaction time (8 or 18 h) allows postepimerization to occur, leading to higher yields but significantly lower *ee*'s. Microwave irradiation constitutes a solution to this problem, since performing the reaction in a microwave reactor (entry 5) afforded the optimum reaction conditions, leading to the isolation of 2-oxopiperazine **4a** in 75% yield with 93% *ee*.

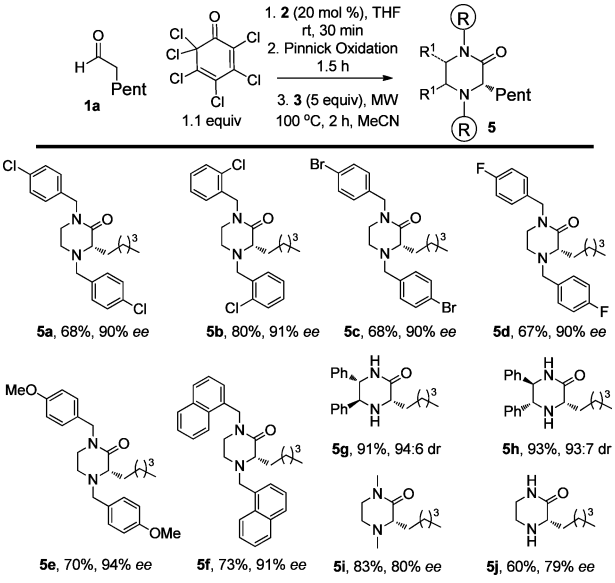
We next explored the scope of the aldehyde component. As highlighted in Scheme 1, a variety of functional groups can be readily tolerated on the aldehyde part. Linear aliphatic aldehydes led to high yields and enantioselectivities (**4a**–**c**), while branched aliphatic aldehydes, which are thought to be more sterically demanding, can also be employed, leading to similar high yields and selectivities (**4d**–**f**). A plethora of functional groups, such as aryl moieties, triple bonds, and protected alcohols and amines, can be employed without loss of reaction efficiency or enantiocontrol (**4g**–**k**). An additional chiral center at the β position of the carbonyl group could be problematic, since additional concerns regarding enamine formation, the geometry of the enamine formed, and whether there is substrate or catalyst control in the protocol would emerge. In these cases, the reaction time for chlorination step had to be increased (from 30 min to 1 h). When an aliphatic side chain was employed, the reaction yield remained high, but unfortunately a slight deterioration of the stereocontrol was observed (**4l**). On the other hand, when (*S*)- or (*R*)-3-phenylbutyraldehyde was employed, excellent enantiocontrol was observed, albeit in moderate yields (**4m**, **4n**). Thus, in the latter cases, the resident stereogenicity does not govern the generation of the stereocenter and the catalyst clearly plays a dominant role in the reaction outcome, demonstrating catalyst-directed induction rather than substrate-enforcing control.

Scheme 1. Enantioselective Synthesis of 2-Oxopiperazines: Aldehyde Substrate Scope



We then diverted our efforts to an exploration of the diamine substrate scope (Scheme 2). The substitution pattern on the aromatic moiety does not affect the reaction outcome (**5a**–**f**). Similarly as before, treatment of the chiral α-chloro acid with either (1*S*,2*S*)- or (1*R*,2*R*)-diphenylethylenediamine led to the incorporation of three chiral centers on the 2-oxopiperazine skeleton with high stereocontrol in excellent yields (**5g**, **5h**). One limitation of the current protocol is that decreased enantioselectivities are observed when diamines that do not possess an aromatic moiety are utilized (**5i**, **5j**).

Scheme 2. Enantioselective Synthesis of 2-Oxopiperazines: Diamine Substrate Scope



In order to determine the absolute configuration of the product, commercially available Boc-Phe-OH (**6**) was con-

DOI: 10.1021/acs.orglett.6b02699
Org. Lett. 2016, 18, 5800–5803