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Stereodivergent synthesis of 2-oxo-oligopyrrolidines by an iterative coupling strategy†

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Natural linear polyamines play diverse roles in physiological processes by interacting with receptors at the cellular level. Herein, we describe the stereodivergent synthesis of oligopyrrolidines, which are conformationally constrained polyamines. We synthesized dimeric and trimeric 2-oxo-oligopyrrolidines using an iterative coupling strategy. The key to our success is an iridium-catalyzed *trans/cis*-selective nucleophilic addition and subsequent *threo/erythro*-stereoselective reduction. The synthesized pyrrolidines show varying cytotoxicities against a human cancer cell line depending on the number of rings and their stereochemistry.

Introduction

Polyamines are organic cations containing a repeating structure of acyclic alkyl amines. Natural polyamines such as putrescine (1), spermidine (2) and spermine (3) exhibit a broad range of physiological functions such as cell replication and the modulation of gene expression (Scheme 1a).¹ Moreover, polyamines have attracted attention as “privileged” templates to induce versatile biological activities (Scheme 1b).² In 1988, the Melchiorre group documented tetraamine disulfide benztramine (4) as an irreversible α -adrenoreceptor antagonist.^{2a} Subsequently, 4 was also found to bind to other receptors such as nicotinic receptors and muscarinic receptors. These studies indicated that synthetic polyamines are attractive candidates in drug discovery. Woster and co-workers reported antibacterial polyamines targeting bacterial membranes.³ Compound 5 exhibits bactericidal activity against various Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) due to electrostatic interaction between the positively charged polyamines and the negatively charged bacterial membrane. Bissati and co-workers reported thiourea-based polyamine 6 as being potent against the malaria parasite.⁴

Cyclic polyamines with stereogenic centers are promising structural motifs for controlling the three-dimensional

arrangements of protonated amine groups, which is crucial for recognizing the target polyanion structures, as seen in DNA and mRNA (Scheme 1c).⁵ In 1997, Ganesh’s group reported the first example using spermine analogues 7 and 8, which have a pyrrolidine backbone. Their synthetic analogues exhibited stronger binding to the DNA triplex than natural spermine.⁶ Müller, Koert and co-workers synthesized the *trans-threo-trans* oligopyrrolidines 9 and 10, which have helical conformations due to the rigid structure of pyrrolidines.⁷ The rate of ssRNA cleavage by oligopyrrolidine 10 was faster than that of natural spermine. Higuchi and colleagues reported pentamine-based inhibitors of lysine-specific demethylase 1 (LSD1) and LSD2 such as 11, which are promising potent anticancer agents.⁸ These pentamines exhibit better LSD1- and 2-inhibitory activities than simple linear polyamines, probably through conformational restriction with the three *trans*-cyclopentane units contained in the six stereogenic centers. They also found that the LSD-inhibitory activities depended on the stereochemistry of each artificial polyamine.

Results and discussion

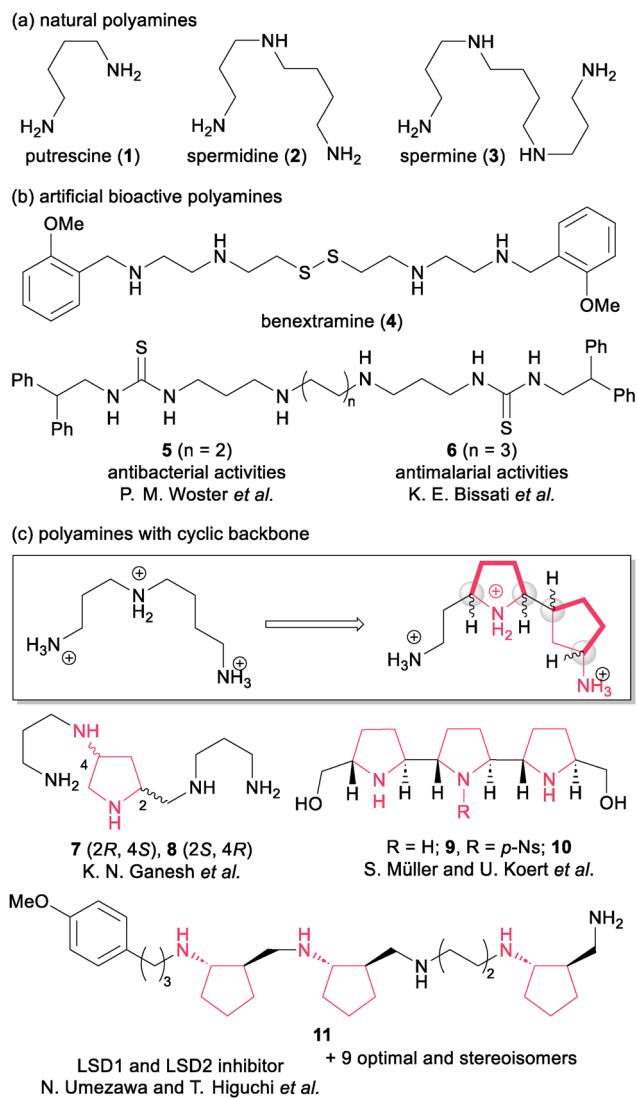
To obtain three-dimensionally constrained polyamines, we took interest in 2-oxo-oligopyrrolidines 12 possessing diverse stereochemistry at C2’–C5 on the cyclic amines (Scheme 2). Casiraghi and coworkers documented pioneering reports on a building-block-based synthesis of 2-oxo-oligopyrrolidines by a coupling reaction using *N*-Boc-lactam 13 and 2-silyloxyprrolide 16 (Scheme 2a).⁹ The method began with LiEt₃BH reduction of *N*-Boc-lactam 13, followed by acid-mediated formation of *N,O*-acetal 14. Addition of TBSOTf to 14 at $-90\text{ }^\circ\text{C}$ formed the

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Scheme 1 Overview of polyamines.

N-acyliminium ion 15, which underwent the vinylogous Mannich reaction^{10,11} with 16 to give *trans*-*erythro* and *cis*-*erythro* 2-oxo-bispyrrolidines 17 α and 17 β . Pd/C-catalyzed hydrogenation of the resulting bispyrrolidines 17 provided 18, which could be converted to oligo-heterocyclic compounds by the same four-step sequence. Their pioneering work successfully demonstrated the utility of the iterative approach. However, some synthetic issues remained unsolved. First, reduction of amide carbonyls required a stoichiometric amount of a strong reductant. Second, transformation of the resulting hemiaminal to *N*,*O*-acetal 14 prior to the vinylogous Mannich reaction was essential to form the unstable *N*-acyliminium ion 15 under acidic conditions. In addition, only two out of the four possible stereoisomers were obtained by their method. To resolve these issues, we envisioned an iterative approach¹² based on *N*-methoxylactams.^{13,14} Our method begins with an iridium-catalyzed reductive vinylogous Mannich reaction between *N*-methoxylactam 19 and 2-silyloxy-

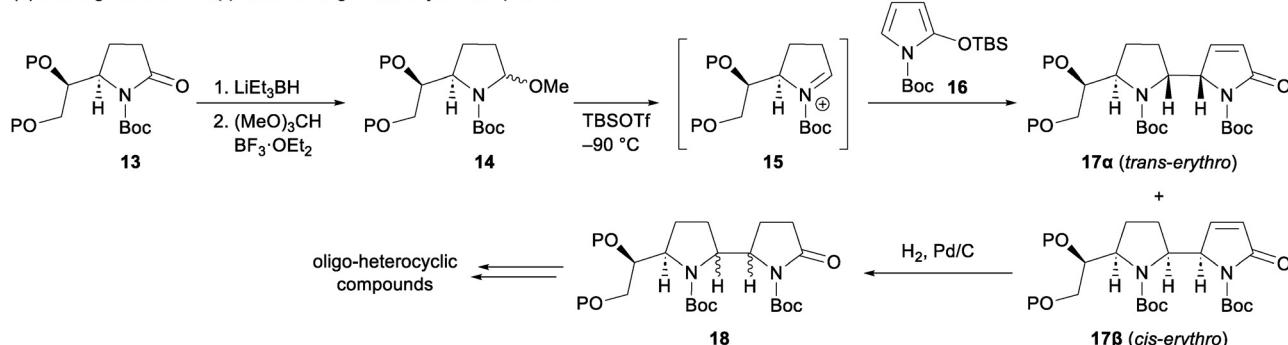
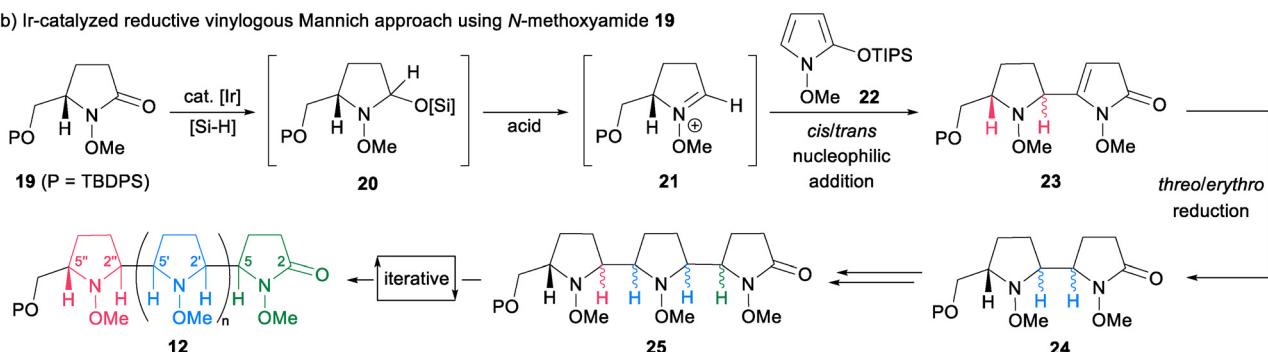
pyrrole 22.^{15,16} Iridium-catalyzed hydrosilylation of 19 would give *N*,*O*-acetal 20. Subsequent addition of an acid to 20 forms the *N*-methoxyiminium ion 21, which could undergo a *cis*/*trans*-selective vinylogous Mannich reaction with 22 to provide enamide 23. We employed *N*-methoxylactams instead of *N*-Boc-lactams due to the following reasons. *N*-Methoxylactams undergo Ir-catalyzed hydrosilylation under mild conditions, while *N*-Boc-lactams do not.¹⁷ Formation of the *N*-methoxyiminium ion 21 is feasible by direct addition of an acid without isolation of *N*,*O*-acetal 20. Thus, a reductive vinylogous Mannich reaction would give enamide 23 in a one-pot process. In addition, *N*-methoxyiminium ions are known to be more electrophilic than *N*-alkyliminium ions such as the *N*-benzyliminium ion, leading to a high yielding vinylogous Mannich reaction.¹⁸ The resulting enamide 23 could be converted to *threo*- or *erythro*-2-oxo-bispyrrolidines 24 by stereoselective reduction. These sequences would enable the stereodivergent synthesis of all four possible diastereomers of 24. The key to success is the development of appropriate reaction conditions to control the *cis*/*trans* configurations on the pyrrolidine ring, and the *threo*/*erythro* configurations on the rotational bond. Ultimately, we found that the stereocontrol of *trans*- or *cis*-selectivity could be achieved using kinetic or thermodynamic conditions, respectively. Subsequent *threo*/*erythro*-selectivity was controlled by the choice of reducing agent. Iterative application of this process enabled the construction of 2-oxo-oligopyrrolidines 12. In this paper, we demonstrate the synthesis of all four possible diastereomers of 2-oxo-bispyrrolidines 24. The method is applicable to the synthesis of 2-oxo-trispyrrolidines 25 *en route* to 2-oxo-oligopyrrolidines 12.

Our stereodivergent nucleophilic addition was evaluated using *N*-methoxylactam 19 and 2-silyloxyprrole 22 (Scheme 3). After extensive screening, *trans*-selective nucleophilic addition under kinetic control was realized as follows. Treatment of a solution of 13 in CHCl₃ with (Me₂HSi)₂O and a catalytic amount of IrCl(CO)(PPh₃)₂ initiated hydrosilylation to generate the *N*-methoxyiminium ion 21. Subsequently, the addition of Sc(OTf)₃ and 2-silyloxyprrole 22 at -60 °C generated the *N*-methoxyiminium ion 26. Aqueous work-up afforded a mixture of four lactams and two enamides 27–30.¹⁹ Successful *trans*-selectivity is dependent on the nature of the solvent used, and CHCl₃ was found to be the best solvent [*trans*-(27 + 28) : *cis*-(29 + 30) = 4 : 1]. Although the vinylogous Mannich reaction produced a mixture of six diastereomers, these diastereomers converged to two enamides 28 and 30 through deprotonation with NaHMDS, and α -selective protonation with AcOH at -78 °C. Thus, the reductive vinylogous Mannich reaction and subsequent α -selective protonation gave enamides 28 and 30 in a *trans*-selective fashion (73% for 2 steps, 28 : 30 = 3.7 : 1).²⁰

With the optimized conditions for the *trans*-selective nucleophilic addition reaction in hand, we examined the *cis*-selective reaction as shown in Scheme 4. After iridium-catalyzed hydrosilylation of 19, the vinylogous Mannich reaction using MeCN as a co-solvent at room temperature was found to



(a) Casiragli's iterative approach for oligo-heterocyclic compounds

(b) Ir-catalyzed reductive vinylogous Mannich approach using *N*-methoxyamide 19

Scheme 2 Iterative synthesis of 2-oxo-oligopyrrolidines 12.

show *cis*-selectivity. The resulting mixture converged to two enamides **30** and **28** by a regioselective deprotonation/protonation sequence (51%, 2 steps, *cis/trans* = 5.7 : 1).²⁰

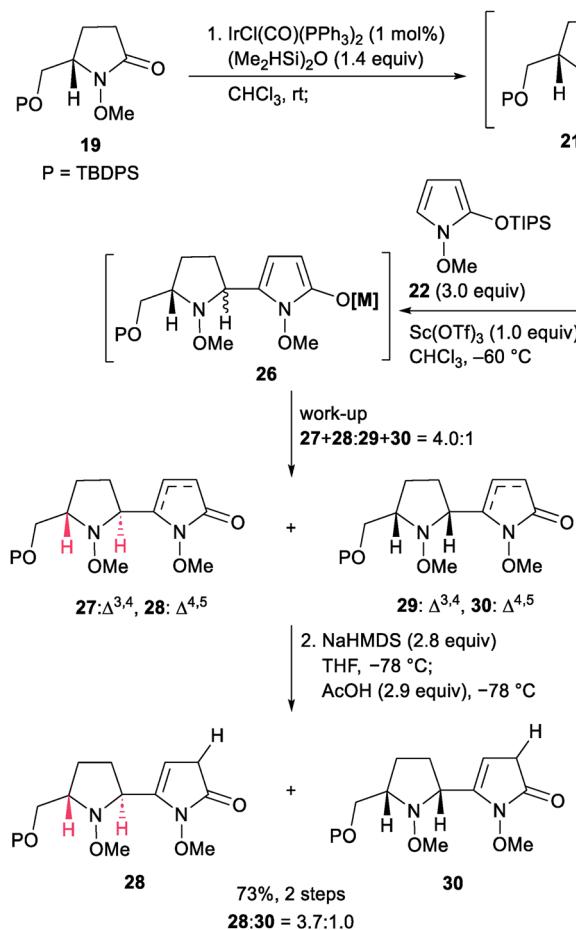
To elucidate the mechanism leading to the *cis*-selectivity, we investigated the effect of reaction temperature (Table 1). After iridium-catalyzed hydrosilylation of **19** in toluene at room temperature, addition of **22** in the presence of 7 mol% of $\text{Sc}(\text{OTf})_3$ at -78°C promoted the vinylogous Mannich reaction. Interestingly, a mixture of four lactams and two enamides **27–30** was obtained with slight *trans*-selectivity [99%, *cis*-(**29** + **30**) : *trans*-(**27** + **28**) = 1 : 1.7] (entry 1). The vinylogous Mannich reaction at room temperature was found to be *cis*-selective [31%, *cis*-(**29** + **30**) : *trans*-(**27** + **28**) = 3.1 : 1], although some decomposition was observed (entry 2). To increase both yield and selectivity, the addition of MeCN was proved to be effective [62%, *cis*-(**29** + **30**) : *trans*-(**27** + **28**) = 5.5 : 1]. These results indicated that the *cis*-selectivity was achieved under thermodynamic conditions.

To clarify the thermodynamic nature, the reversibility of the vinylogous Mannich reaction was further confirmed by a cross-over experiment (Scheme 5). A solution of **27–30** in toluene/MeCN was treated with 1-benzyloxy-2-silyloxyprrole **31** in the presence of a catalytic amount of $\text{Sc}(\text{OTf})_3$. Subsequent isomerization to enamides through the deprotonation/protonation protocol gave enamide **33** [44% (2 steps), *trans* : *cis* = 1 : 2.0], along with a mixture of **28** and **30** [44% (2 steps), **28** : **30** = 1 : 7.0]. These results clearly indicated that enamide **33** was formed by a retro-Mannich/Mannich reaction under equilibrium conditions.

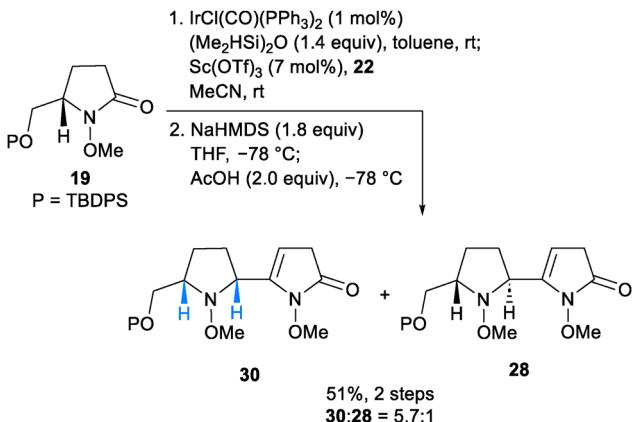
Having established the *cis/trans*-selective vinylogous Mannich reaction, we investigated the stereoselective reduction of *trans*-enamide **28** and *cis*-enamide **30** (Scheme 6). Hydrogenation of *trans*-enamide **28** with $\text{Rh}/\text{Al}_2\text{O}_3$ formed the 2-oxo-bispyrrolidines, favoring *erythro* lactam **34** over *threo* lactam **35** (Scheme 6a, 76%, 34 : 35 = 3.2 : 1).²⁰ In contrast, hydride reduction under acidic conditions reversed this stereoselectivity. Thus, treatment of *trans*-enamide **28** with NaBH_3CN and HCl in the presence of 15-crown-5 gave a mixture of 2-oxo-bispyrrolidines **34** and **35** with *threo* selectivity (78%, 34 : 35 = 1 : 1.8).^{20,21} *cis*-Enamide **30** showed similar stereoselectivity (Scheme 6b). In contrast, $\text{Rh}/\text{Al}_2\text{O}_3$ -catalyzed hydrogenation of *cis*-enamide **30** predominantly provided *threo*-lactam **36** (70%, 36 : 37 = 2.9 : 1),²⁰ and hydride reduction with NaBH_3CN and TFA produced *erythro* lactam **37** as a major product (66%, 36 : 37 = 1 : 2.0). Reduction of *trans*-*erythro* lactam **34** was achieved by hydrosilylation with 1 mol% of $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ and $(\text{Me}_2\text{HSi})_2\text{O}$, followed by the addition of $\text{Sc}(\text{OTf})_3$ to give bispyrrolidine **38**.

We demonstrated the feasibility of iterative assembly of a pyrrolidine unit by investigating the stereoselective synthesis of 2-oxo-trispyrrolidines **41** and **42** (Scheme 7). Under the optimized kinetic conditions for *trans*-selective addition, *trans*-*erythro* lactam **34** was converted to *trans* enamide **39**, along with the formation of minor *cis* enamide **40** (66% (2 steps), 39 : 40 = 4.5 : 1).²⁰ $\text{Rh}/\text{Al}_2\text{O}_3$ -catalyzed hydrogenation promoted *erythro*-selective reduction of enamide **39**, providing *erythro* lactam **41** and *threo* lactam **42** in 75% yield (41 : 42 = 4.9 : 1).²⁰ The lactam carbonyl of 2-oxo-trispyrrolidine **41** was success-





Scheme 3 *trans*-Selective vinylogous Mannich reaction under kinetic conditions.

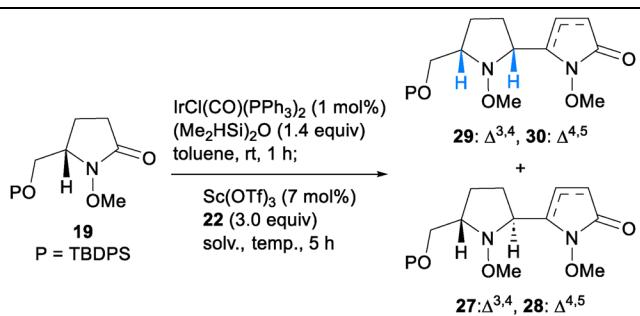


Scheme 4 *cis*-Selective vinylogous Mannich reaction and regio-selective deprotection/protection.

fully reduced by iridium-catalyzed hydrosilylation followed by the addition of $\text{Sc}(\text{OTf})_3$ to give trispyrrolidine 43.

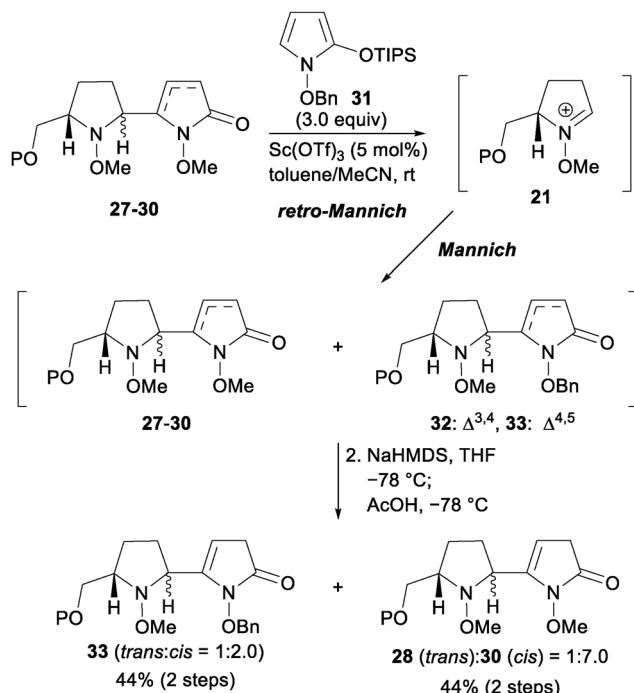
The antiproliferative activity of the series of mono-, bis-, and 2-oxo-trispyrrolidines against Jurkat cells (human T-cell

Table 1 Vinylogous Mannich reaction under thermodynamic conditions^a



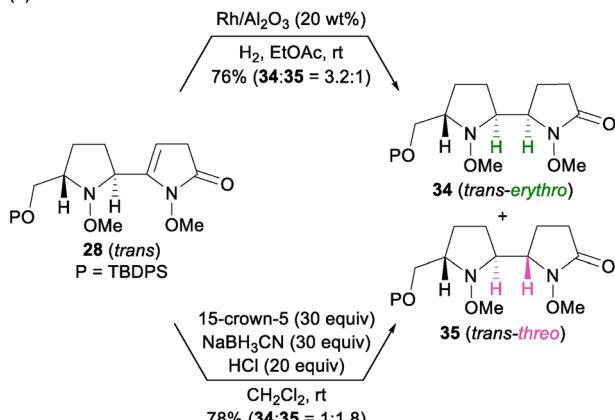
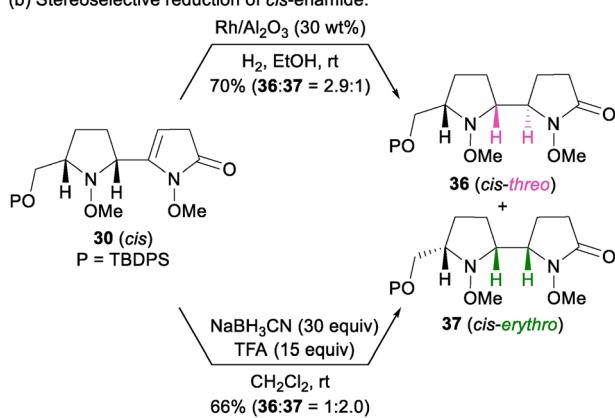
Entry	Temp.	Solv.	<i>cis</i> -(29 + 30) : <i>trans</i> -(27 + 28)	Combined yield (%)
1	-78 °C	None	1 : 1.7	99
2	rt	None	3.1 : 1	31
3	rt	MeCN	5.5 : 1	62

^a Optimal reaction conditions: 19 (1 equiv.), $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (1 mol%), $(\text{Me}_2\text{HSi})_2\text{O}$ (1.4 equiv.), toluene, rt, 1 h; $\text{Sc}(\text{OTf})_3$ (7 mol%), 22 (3.0 equiv.), co-solvent, 5 h.

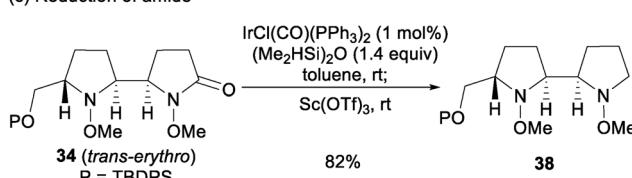


Scheme 5 Crossover experiment.

leukemia cells) is summarized in Table 2. Comparison of the activity of 2-oxo-pyrrolidine 19, 2-oxo-bispyrrolidines 34–37, and 2-oxo-trispyrrolidines 41 and 42 revealed clear relationships between the number of rings and the compound's anti-proliferative activity. 2-Oxo-bispyrrolidines 34–37 were found to be more potent than 2-oxo-pyrrolidine 19, with 2-oxo-trispyrrolidines 42 displaying the strongest activity, approximately 10-fold when compared to monomeric 2-oxo-pyrrolidine 19.

(a) Stereoselective reduction of *trans*-enamide.(b) Stereoselective reduction of *cis*-enamide.

(c) Reduction of amide



Scheme 6 Synthesis of four stereoisomers of 2-oxo-bispyrrolidines.

Table 2 IC₅₀ values of synthetic compounds^a

(a) IC₅₀ values of mono- and 2-oxo-bispyrrolidines in Jurkat cells

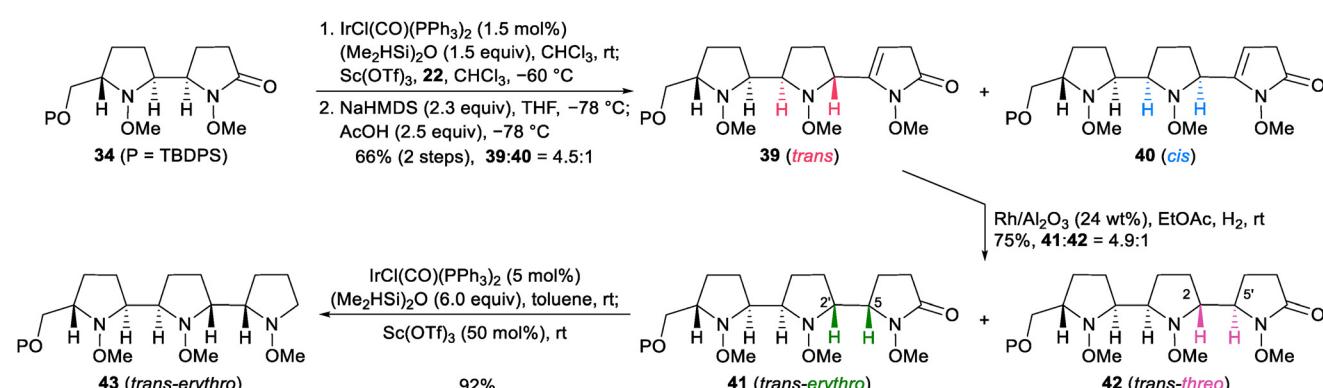
Compounds	IC ₅₀ [μM]	Compounds	IC ₅₀ [μM]
19	22.9	41	15.5
34	14.0	42	2.00
35	5.50	43	44.1
36	10.7		
37	17.0		
38	27.6		

^a The antiproliferative activity against Jurkat cells was evaluated by the standard MTT assay. Cells were treated for 72 h with increasing concentrations of the evaluated compounds.

Stereochemistry played an important role in the antiproliferative activity of the compounds. Of the 2-oxo-bispyrrolidines 34–37, *trans*-*threo* lactam 35 exhibited the highest activity. A similar tendency was observed for the trimeric compounds, although only two diastereomers were tested. Thus, the activity of 2-oxo-trispyrrolidine 42 with a *trans*-*threo* configuration at C2–C5' was 8-fold higher than that of 34 with a *trans*-*erythro* configuration. Interestingly, 2-oxo-oligopyrrolidines 34 and 41 exhibited stronger activity than the corresponding 38 and 43, their fully reduced counterparts.

Conclusion

In conclusion, the results reported here provide an iterative and stereodivergent method to construct 2-oxo-oligopyrrolidines. *trans/cis*-Selectivity in the nucleophilic addition to amide carbonyls was controlled by choosing either kinetic or thermodynamic conditions. Subsequent *erythro/threo*-selective reduction of the enamides was realized by hydrogenation with Rh/Al₂O₃ or hydride reduction with NaBH₃CN. The developed conditions enabled the stereodivergent synthesis of all four possible diastereomers of the 2-oxo-bispyrrolidines. Moreover, the established method was successfully applied to the synthesis of the trimeric derivatives. The antiproliferative activity



Scheme 7 Stereoselective synthesis of 2-oxo-trispyrrolidines 41 and 42.



of the synthetic lactams against human cancer cells revealed the role of the number of rings and their stereochemistry in the cytotoxicity of the compounds. Detailed investigations of the antiproliferative activities and RNA binding assays of compounds are underway.

Author contributions

Conceptualization: Y.S., N.C., T.O., and T.S.; data curation: Y.S., K.T., M.F., and T.M.; formal analysis: M.F., T.M.; funding acquisition: N.C., T.S.; investigation: Y.S., K.T., M.F., S.S., K.S., and T.M.; methodology: Y.S., M.F., T.M.; project administration: T.O., T.S.; resource: S.S., N.C., T.S.; software: N/A; supervision: S.S., N.C., T.O., T.S.; validation: N/A; visualization: Y.S., T.O., T.S.; writing – original draft: Y.S., T.O.; writing – review and editing: S.S., N.C., T.O., T.S.

Conflicts of interest

There are no conflicts to declare.

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- 19 α -Protonation of the oxypyrrrole moiety in compound **19** provides *trans*- or *cis*-enamide (**28** and **30**), and γ -protonation gave two *trans*- or *cis*- α,β -unsaturated compounds each (**27 α** , **29 α** , **29 β** and **29 β**). The details are described in the ESI.†
- 20 These diastereomers were separated by HPLC, see the ESI for details.†
- 21 Their stereochemistry was determined by NOESY measurement of the converted cyclic urea (see the ESI).†

