

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 3230

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

Yasuki Soda,^a Kumpei Tatsumi,^a Matteo Forner,^{id} a,b Shunsei Sato,^a Kana Shibuya,^a Tomoe Matagawa,^a Siro Simizu,^a Noritaka Chida,^{id} a Toshitaka Okamura^{id} *^a and Takaaki Sato^{id} *^a

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.

Received 4th March 2024,
Accepted 26th March 2024

DOI: 10.1039/d4ob00350k

rsc.li/obc

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 benextramine (**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

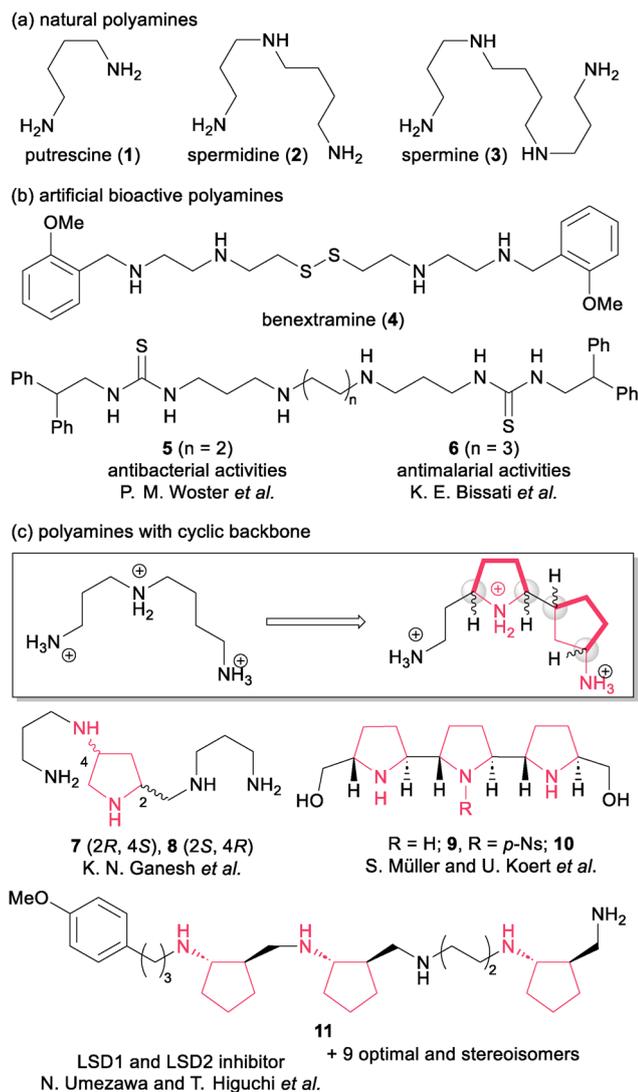
To obtain three-dimensionally constrained polyamines, we took interest in 2-oxo-oligopyrrolidines **12** possessing diverse stereochemistry at C2'–C5 on the cyclic amines (Scheme 2). Casiraghi and coworkers documented pioneering reports on a building-block-based synthesis of 2-oxo-oligopyrrolidines by a coupling reaction using *N*-Boc-lactam **13** and 2-silyloxyppyrrrole **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 °C formed the

^aDepartment of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama, 223-8522, Japan.
E-mail: t-okamura@applic.keio.ac.jp, takaakis@applic.keio.ac.jp

^bDepartment of Pharmaceutical and Pharmacological Sciences, University of Padova, Via Marzolo, 5, 35131 Padova, PD, Italy

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ob00350k>





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-

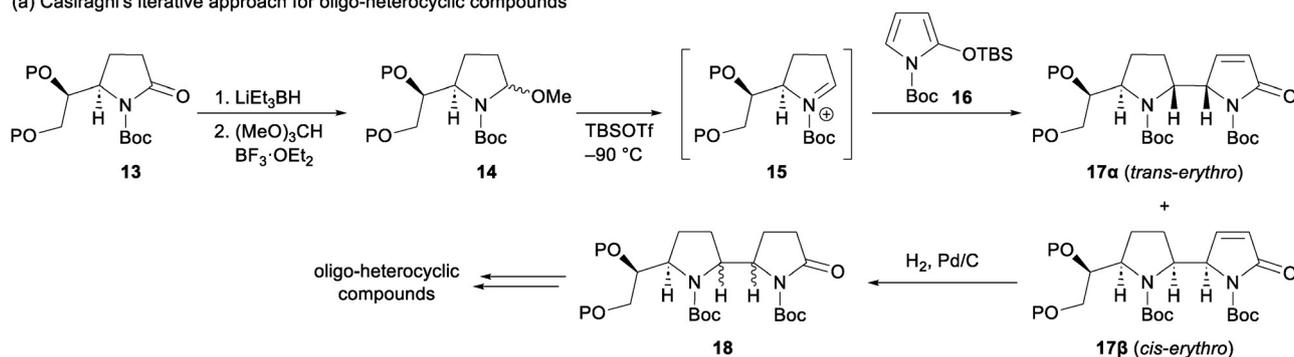
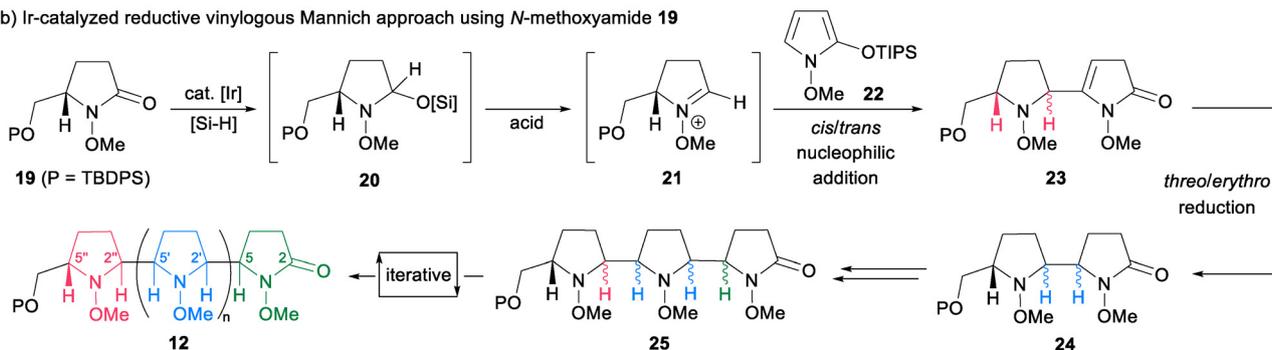
pyrrole **22**.^{15,16} Iridium-catalyzed hydrosilylation of **19** would give *N,O*-acetal **20**. Subsequent addition of an acid to **20** forms the *N*-methoxyiminium ion **21**, which could undergo a *cis/trans*-selective vinylogous Mannich reaction with **22** to provide enamide **23**. We employed *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 stereo-selective reduction. These sequences would enable the stereo-divergent 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-silyloxy-pyrrole **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-silyloxy-pyrrole **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) Casiraghi'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

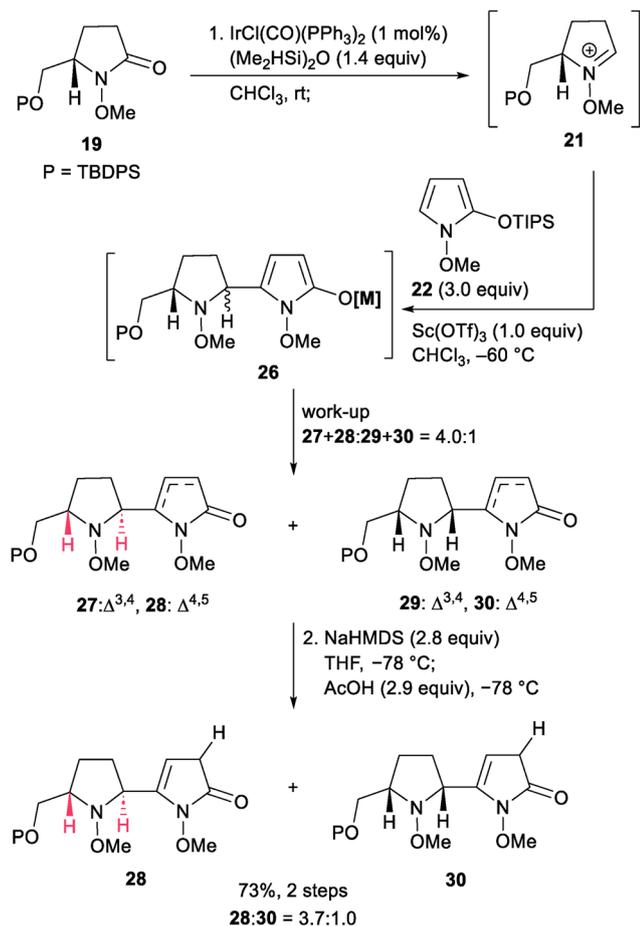
To elucidate the mechanism leading to the *cis*-selectivity, we investigated the effect of reaction temperature (Table 1). After iridium-catalyzed hydrosilylation of **19** in toluene at room temperature, addition of **22** in the presence of 7 mol% of Sc(OTf)₃ at -78 °C promoted the vinylogous Mannich 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-silyloxy-pyrrole **31** in the presence of a catalytic amount of Sc(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.

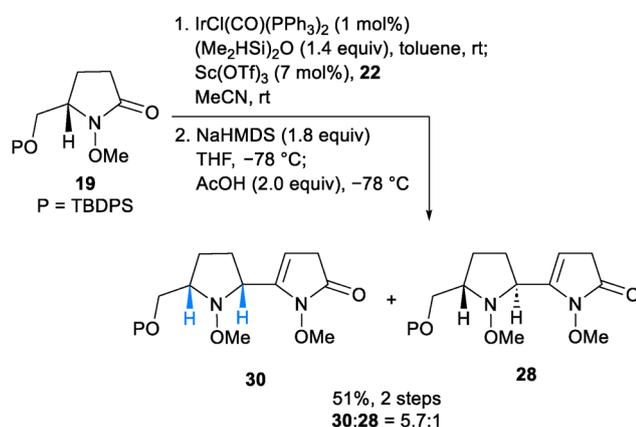
Having established the *cis/trans*-selective vinylogous Mannich reaction, we investigated the stereoselective reduction of *trans*-enamide **28** and *cis*-enamide **30** (Scheme 6). Hydrogenation of *trans*-enamide **28** with Rh/Al₂O₃ formed the 2-oxo-bispyrrolidines, favoring *erythro* lactam **34** 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 NaBH₃CN 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, Rh/Al₂O₃-catalyzed hydrogenation of *cis*-enamide **30** predominantly provided *threo*-lactam **36** (70%, **36** : **37** = 2.9 : 1),²⁰ and hydride reduction with NaBH₃CN 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 IrCl(CO)(PPh₃)₂ and (Me₂HsSi)₂O, followed by the addition of Sc(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 Rh/Al₂O₃-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 deprotonation/protonation.

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

19
P = TBDPS

$\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (1 mol%)
 $(\text{Me}_2\text{HSi})_2\text{O}$ (1.4 equiv)
toluene, rt, 1 h;

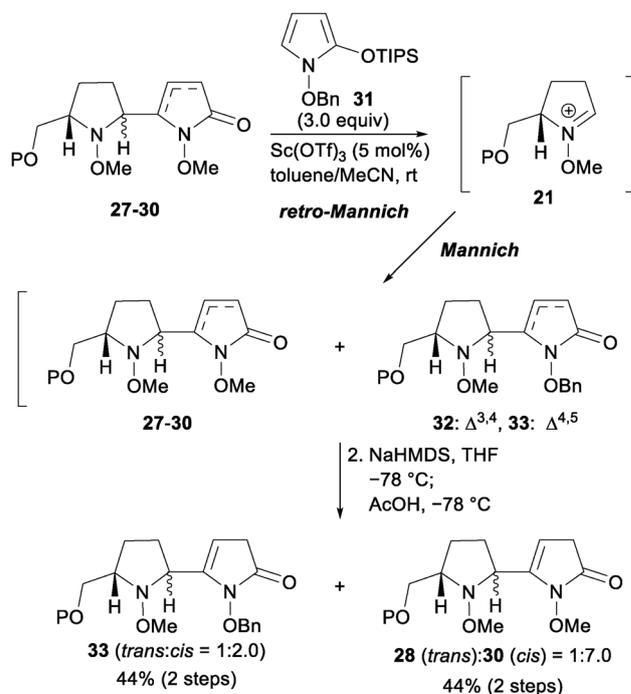
29: $\Delta^{3,4}$, **30**: $\Delta^{4,5}$

$\text{Sc}(\text{OTf})_3$ (7 mol%)
22 (3.0 equiv)
solv., temp., 5 h

27: $\Delta^{3,4}$, **28**: $\Delta^{4,5}$

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

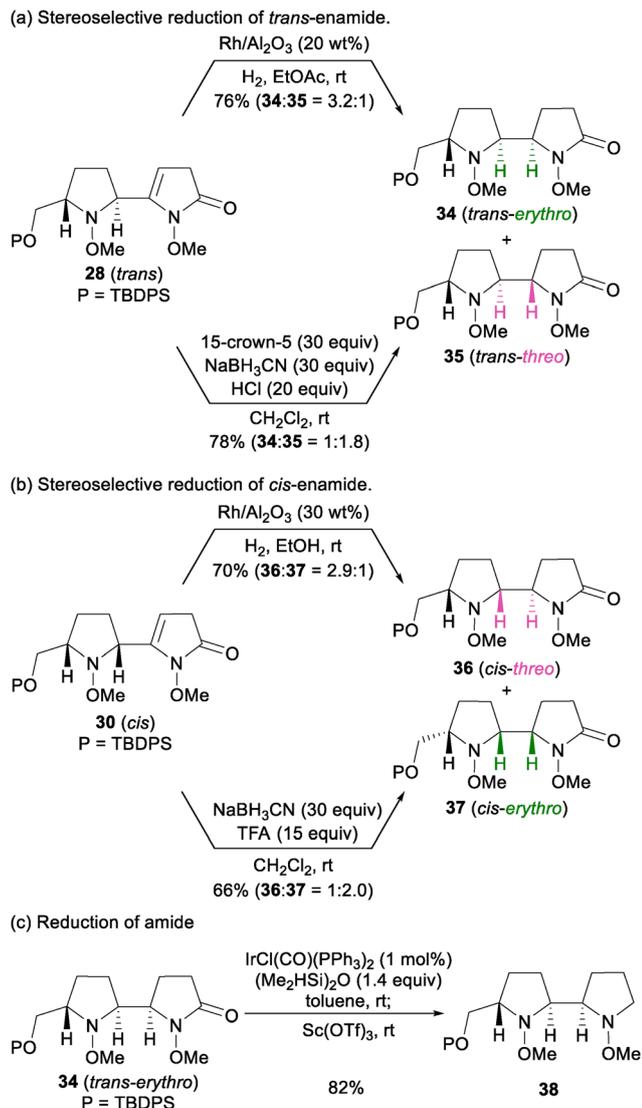
^a Optimal reaction conditions: **19** (1 equiv.), $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (1 mol%), $(\text{Me}_2\text{HSi})_2\text{O}$ (1.4 equiv.), toluene, rt, 1 h; $\text{Sc}(\text{OTf})_3$ (7 mol%), **22** (3.0 equiv.), co-solvent, 5 h.



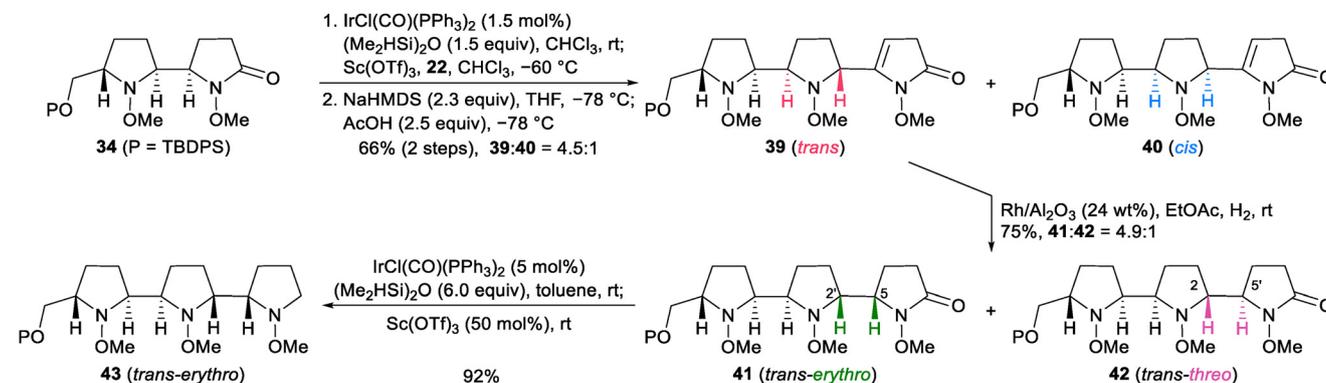
Scheme 5 Crossover experiment.

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 antiproliferative 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**.





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

Scheme 7 Stereoselective synthesis of 2-oxo-trispyrrolidines **41** and **42**.Table 2 IC₅₀ values of synthetic compounds^a

(a) IC ₅₀ values of mono- and 2-oxo-bispyrrolidines in Jurkat cells		(b) IC ₅₀ values of 2-oxo-trispyrrolidines 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-trispyrrolidines **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



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., Su.S., K. S., and T.M.; methodology: Y.S., M.F., T.M.; project administration: T.O., T.S.; resource: Si.S., N.C., T.S.; software: N/A; supervision: Si.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: Si.S., N.C., T.O., T.S.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research (B) from MEXT (22H02084), the Tobe Maki Foundation, the JGC-S Scholarship Foundation, the Kato Memorial Bioscience Foundation, the Sasakawa Scientific Research Grant from The Japan Science Society (2022-0613), and the Amano Institute of Technology Foundation. The financial support of the Yoshida Scholarship Foundation to Y. Soda is gratefully acknowledged.

References

- (a) A. E. Pegg, *IUBMB Life*, 2009, **61**, 880–894; (b) A. E. Pegg, *J. Biol. Chem.*, 2016, **291**, 14904–14912; (c) E. W. Gerner and F. L. Meyskens, *Nat. Rev. Cancer*, 2004, **4**, 781–792; (d) B. Li, J. Liang, H. R. Baniasadi, M. A. Phillips and A. J. Michael, *Proc. Natl. Acad. Sci. U. S. A.*, 2023, **120**, e2214165120; (e) F. Madeo, T. Eisenberg, F. Pietrocola and G. Kroemer, *Science*, 2018, **359**, eaan2788.
- (a) M. L. Bolognesi, A. Minarini, R. Budriesi, S. Cacciaguerra, A. Chiarini, S. Spampinato, V. Tumiatti and C. Melchiorre, *J. Med. Chem.*, 1988, **41**, 4150–4160; (b) C. Melchiorre, M. L. Bolognesi, A. Minarini, M. Rosini and V. Tumiatti, *J. Med. Chem.*, 2010, **53**, 5906–5914.
- B. Wang, B. Pachaiyappan, J. D. Gruber, M. G. Schmidt, Y.-M. Zhang and P. M. Woster, *J. Med. Chem.*, 2016, **59**, 3140–3151.
- K. El Bissati, H. Redel, L.-M. Ting, J. D. Lykins, M. J. McPhillie, R. Upadhyaya, P. M. Woster, N. Yarlett, K. Kim and L. M. Weiss, *Front. Cell. Infect. Microbiol.*, 2019, **9**, 9.
- K. Igarashi and K. Kashiwagi, *Biochem. Biophys. Res. Commun.*, 2000, **271**, 559–564.
- (a) K. G. Rajeev, G. J. Sanjayan and K. N. Ganesh, *J. Org. Chem.*, 1997, **62**, 5169–5173; (b) D. Nagamani and K. N. Ganesh, *Org. Lett.*, 2001, **3**, 103–106.
- H.-D. Arndt, R. Welz, S. Müller, B. Ziemer and U. Koert, *Chem. – Eur. J.*, 2004, **10**, 3945–3962.
- (a) N. Umezawa, K. Tsuji, S. Sato, M. Kikuchi, H. Watanabe, Y. Horai, M. Yamaguchi, Y. Hisamatsu, T. Umehara and T. Higuchi, *RSC Adv.*, 2018, **8**, 36895–36902; (b) Y. Yoshikawa, N. Umezawa, Y. Imamura, T. Kanbe, N. Kato, K. Yoshikawa, T. Imanaka and T. Higuchi, *Angew. Chem., Int. Ed.*, 2013, **52**, 3712–3716; (c) N. Umezawa, Y. Horai, Y. Imamura, M. Kawakubo, M. Nakahira, N. Kato, A. Muramatsu, Y. Yoshikawa, K. Yoshikawa and T. Higuchi, *ChemBioChem*, 2015, **16**, 1811–1819.
- (a) F. Zanardi, L. Battistini, G. Rassu, L. Pinna, M. Mor, N. Culeddu and G. Casiraghi, *J. Org. Chem.*, 1998, **63**, 1368; (b) F. Zanardi, L. Battistini, G. Rassu, L. Auzzas, L. Pinna, L. Marzocchi, D. Acquotti and G. Casiraghi, *J. Org. Chem.*, 2000, **65**, 2048; (c) C. Curti, B. Ranieri, L. Battistini, G. Rassu, V. Zambrano, G. Pelosi, G. Casiraghi and F. Zanardia, *Adv. Synth. Catal.*, 2010, **352**, 2011.
- For selected reviews on the vinylogous Mannich reaction, see: (a) G. Rassu, F. Zanardi, L. Battistini and G. Casiraghi, *Chem. Soc. Rev.*, 2000, **29**, 109–118; (b) S. K. Bur and S. F. Martin, *Tetrahedron*, 2001, **57**, 3221–3242; (c) G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076–3154.
- For selected examples of 2-silyloxyfuran or 2-silyloxypyrrole to construct five-membered iminium ions, see: (a) S. F. Martin and J. W. Corbett, *Synthesis*, 1992, 55–57; (b) ref. 9a; (c) S. F. Martin, K. J. Barr, D. W. Smith and S. K. Bur, *J. Am. Chem. Soc.*, 1999, **121**, 6990–6997; (d) ref. 9b; (e) M. Yoritata, Y. Takahashi, H. Tajima, C. Ogihara, T. Yokoyama, Y. Soda, T. Oishi, T. Sato and N. Chida, *J. Am. Chem. Soc.*, 2017, **139**, 18386–18391.
- For a selected review, see: J. W. Lehmann, D. J. Blair and M. D. Burke, *Nat. Rev. Chem.*, 2018, **2**, 0115.
- For a selected review on pyroglutamic acid as a unique synthon, see: S. K. Panday, J. Prasad and D. K. Dikshit, *Tetrahedron: Asymmetry*, 2009, **20**, 1581–1632.
- For selected examples of enantioselective transformation of amides, see: (a) H. Chen, Z.-Z. Wu, D.-Y. Shao and P.-Q. Huang, *Sci. Adv.*, 2022, **8**, eade3431; (b) F.-F. Xu, J.-Q. Chen, D.-Y. Shao and P.-Q. Huang, *Nat. Commun.*, 2023, **14**, 6251.
- For selected reviews on nucleophilic addition to amides, see: (a) V. Pace, W. Holzer and B. Olofsson, *Adv. Synth. Catal.*, 2014, **356**, 3697–3736; (b) T. Sato, M. Yoritata, H. Tajima and N. Chida, *Org. Biomol. Chem.*, 2018, **16**, 3864–3875; (c) D. Kaiser, A. Bauer, M. Lemmerer and N. Maulide, *Chem. Soc. Rev.*, 2018, **47**, 7899–7925; (d) P.-Q. Huang, *Acta Chim. Sin.*, 2018, **76**, 357–365; (e) D. Matheau-Raven, P. Gabriel, J. A. Leitch, Y. A. Almeahadi, K. Yamazaki and D. J. Dixon, *ACS Catal.*,



- 2020, **10**, 8880–8897; (f) D. Y. Ong, J.-h. Chen and S. Chiba, *Bull. Chem. Soc. Jpn.*, 2020, **93**, 1339–1349.
- 16 For selected pioneering examples of iridium-catalyzed reductive nucleophilic addition to amides, see: (a) P.-Q. Huang, W. Ou and F. Han, *Chem. Commun.*, 2016, **52**, 11967–11970; (b) P. W. Tan, J. Seayad and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2016, **55**, 13436–13440; (c) Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2017, **56**, 3655–3659; (d) L.-G. Xie and D. J. Dixon, *Nat. Commun.*, 2018, **9**, 2841; (e) W. Qu, F. Han, X.-N. Hu, H. Chen and P.-Q. Huang, *Angew. Chem., Int. Ed.*, 2018, **57**, 11354–11358; (f) Z. Li, F. Zhao, W. Ou, P.-Q. Huang and X. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 26604–26609; (g) F. Jiang, F. Zhao, Y. He, X. Luo and X. Wang, *Cell Rep. Phys. Sci.*, 2022, **3**, 100955.
- 17 Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto and H. Nagashima, *Chem. Commun.*, 2009, 1574–1576.
- 18 (a) Y. Kurosaki, K. Shirokane, T. Oishi, T. Sato and N. Chida, *Org. Lett.*, 2012, **14**, 2098–2101; (b) M. Nakajima, Y. Oda, T. Wada, R. Minamikawa, K. Shirokane, T. Sato and N. Chida, *Chem. – Eur. J.*, 2014, **20**, 17565–17571.
- 19 α -Protonation of the oxypyrrole 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).†

