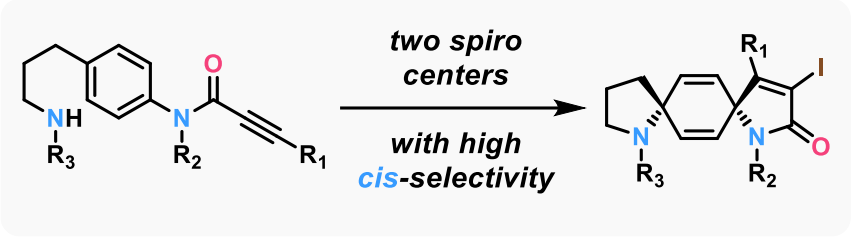
Cis-selective double spirocyclization via dearomatization and isomerization under thermodynamic control

Hiromasa Yokoe*, Akiko Kiriyama, Miho Shimoda, Satoru Nakajima, Yuna Hashizume, Yuto Endo, Ryoko Iwamoto, Masayoshi Tsubuki, Naoki Kanoh*

School of Pharmacy and Pharmaceutical Sciences and Institute of Medicinal Chemistry, Hoshi University, Shinagawa-ku, Tokyo, Japan



ABSTRACT: Spiro compounds have been considered key scaffolds for pharmaceutical applications. Although many synthetic methods exist for monospirocycles, fewer approaches are known for dispirocycles. Here, we report a highly *cis*-selective method for constructing a 5/6/5-dispirocyclic structure containing pyrrolidine and γ-lactam rings with various substituents from a series of *N*-arylpropiolamides. The high *cis*-selectivity would result from isomerization under thermodynamic control. *Cis*- and *trans*-diastereomers can be in equilibrium, favoring *cis*-adducts.

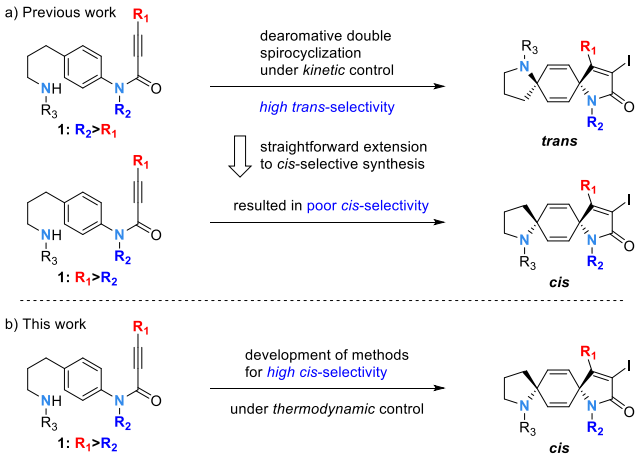
Spirocyclic structures, which are widely found in bioactive natural products and therapeutic drugs, have recently been recognized as an important class of structural motifs that can improve clinical success in drug discovery and development.[1-3] The distinctive three-dimensionality and conformational rigidity of the spirocycles embedded in the potential drug candidates can enhance the drug-likeness of the candidates, restricting the molecular conformation and the spatial arrangement of functional groups, and thereby facilitating interaction between the candidates and target biological molecules.[4] These structures have thus attracted much attention for pharmaceutical applications.

Continuous efforts have been made to develop efficient methods for the construction of the spirocyclic structures.[5] In particular, a strategy of spirocyclization through dearomatization, *ipso*-cyclization,[6] has attracted much attention, providing these structures in short steps from easily available compounds.[7] Although there has been significant progress in the synthesis of *mono*spirocycles with this direct strategy, the availability of *di*spirocyclic counterparts is relatively limited despite the high demand for a wide variety of spirocyclic structures.[7j,k,8] To expand the diversity of the spiro compounds currently available, there is an urgent need to develop efficient synthetic methods to realize previously unexplored spirocyclic structures.

Previously, we reported diastereoselective double spirocyclization of *N*-arylpropiolamide **1** through a dearomatization initiated by electrophilic activation of the alkyne (Scheme 1a).[7k] Higher *trans*-selectivity was observed when bulkier substituents R_2 and a small R_1 were employed. However, a straightforward extension of this strategy to *cis*-selective synthesis gave unsatisfactory results. The combination of a small R_2 and a bulky R_1 under the developed reaction conditions resulted in poor diastereoselectivity.

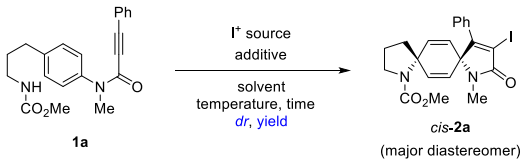
Here, we report highly *cis*-selective dearomative double spirocyclization (Scheme 1b). We established two methods, Methods A and B, for the diastereoselective synthesis of a 5/6/5-dispircyclic framework containing pyrrolidine[9] and γ-lactam[10] rings with various substituents from a series of *N*-arylpropiolamides.

Scheme 1. Diastereoselective double spirocyclization through dearomatization



We selected **1a** as a substrate for developing and optimizing the reaction conditions (Table 1). Entry 1 is the previously reported result in which treatment of **1a** with *N*-iodosuccinimide (NIS) as an I^+ source and AgTFA in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent gave *cis*-**2a** in 56% yield with a low *cis*:*trans* diastereomeric ratio (dr) of 60:40.[7k] We initiated this investigation by examining I^+ sources. Molecular iodine required a prolonged reaction time, and the dr was not improved (entry 2). When iodine chloride (ICl) was used in CH_2Cl_2 from –78°C to room temperature (rt), the reaction was completed in one hour albeit with low selectivity and 60:40 dr (entry 3). Next, the solvent effect was examined. Switching CH_2Cl_2 to MeCN dramatically improved the selectivity, and the reaction of **1a** with ICl in MeCN solvent from –40 °C to rt occurred with >95:5 dr, and the desired *cis*-**2a** was isolated in 80% yield (entry 4). Lowering the reaction temperature further provided a better result. With a reaction in EtCN solvent from –78 ºC to rt, *cis*-**2a** was obtained in 90% yield with >95:5 dr, and we set these as the optimal conditions for Method A (entry 5). Furthermore, two additional experiments in entries 6 and 7 provided key insights into the mechanism for the diastereoselective outcome. Keeping the reaction temperature at –78 °C (entry 6) or adding Na_2CO_3 base (entry 7) afforded a mixture of *cis*- and *trans*-**2a** with low diastereoselectivity. These results suggested that the higher temperature and acidic conditions were necessary for higher diastereoselectivity.

Table 1. Optimization of the Reaction Conditions

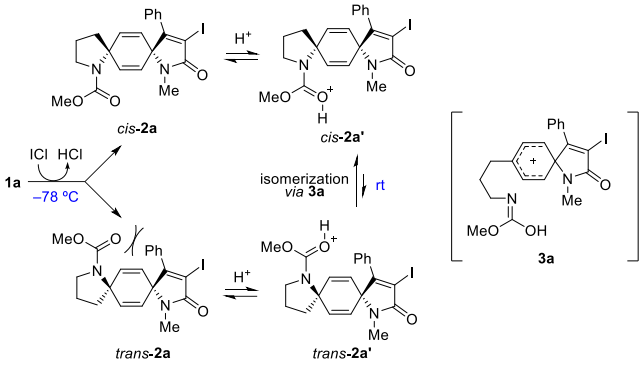


entry	I^+ source	additive	solvent	temperature	time (h)	*dr*[a]	yield (%)[b]
1	NIS (1.1 equiv)	AgTFA (0.1 equiv)	HFIP	0 ºC	24	60:40	56
2	I_2 (2.0 equiv)	$NaHCO_3$ (2.0 equiv)	CH_2Cl_2	rt	68	64:36	46
3	ICl (1.5 equiv)	–	CH_2Cl_2	–78 ºC~rt	1	60:40	42
4	ICl (1.5 equiv)	–	MeCN	–45 ºC~rt	1	>95: 5	80
5	ICl (1.5 equiv)	–	EtCN	–78 ºC~rt	1	>95: 5	95
6	ICl (2.2 equiv)	–	EtCN	–78 ºC	1	62:38	49
7	ICl (1.5 equiv)	Na_2CO_3 (1.5 equiv)	EtCN	–78 ºC~rt	3	58:42	53

[a]The diastereomeric ratio (*cis*:*trans*) was determined by ^{1}H NMR analysis of crude material; [b]Isolated yield of *cis*-**2a**.

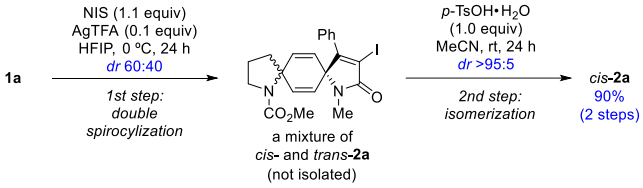
We proposed a possible mechanism for the diastereoselective outcome in Scheme 2. At low temperature of –78ºC, the reaction of **1a** with ICl would afford a mixture of *cis*- and *trans*-**2a** involving HCl release. The mixture would be converted into *cis*-**2a** upon warming to rt. *Cis*- and *trans*-**2a** could be in equilibrium through their protonated forms *cis*-**2a'**, *trans*-**2a'**, and cyclohexadienyl cation **3a**. The equilibrium favors *cis*-**2a** presumably because *trans*-**2a** is less thermodynamically stable due to the steric repulsion between the methoxycarbonyl and the phenyl groups.

Scheme 2. Possible mechanism for the diastereoselective outcome.



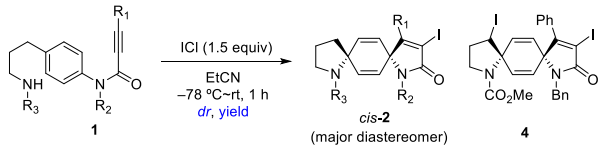
These findings allowed us to establish an alternative two-step procedure consisting of the double spirocyclization step and the following isomerization step (Scheme 3). A crude mixture of diastereomers with 60:40 dr synthesized by NIS/AgTFA/HFIP was treated with *p*-TsOH•H_2O in MeCN to force the isomerization. This procedure provided the desired *cis*-**2a** in 90% yield in two steps with >95:5 dr, and we set this as Method B. For the first step, we selected NIS/AgTFA/HFIP rather than ICl/EtCN since the latter conditions were not suitable for some substrates (vide infra).

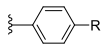
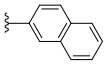
Scheme 3. Alternative procedure for the *cis*-selective double spirocyclization in two steps [Method B].



With the *cis*-selective double spirocyclization established, we next explored the scope and limitations of substrates with Method A (Table 2). The modification of the R_1 substituent was first studied with the same R_2 and R_3 for **1a**. In entries 1–5, variations of substitution at the *para*-position of the phenyl ring were explored. While substrates with the methyl and the methoxy groups, and the chlorine atom gave *cis*-**2b**, *cis*-**2c**, and *cis*-**2d** in high yields, electron-deficient substituents such as the trifluoromethyl and the nitro groups afforded *cis*-**2e** and *cis*-**2f** in lower yields. Moreover, the *ortho*-methoxy group afforded *cis*-**2g** in 90% yield (entry 6). In entries 7 and 8, the 2-naphthyl and the 3-benzothiophene rings were tolerated, and *cis*-**2h** and *cis*-**2i** were obtained in high yields. In all cases, *cis*-**2b**–**i** were formed with high diastereoselectivity of >95:5, and iodination on the aromatic ring core was not observed. Next, in entry 9, the benzyl group for R_2 was employed with the same R_1 and R_3 for **1a**. However, the reaction was complicated, and many products were observed in the crude ^{1}H NMR. Isolable products were *cis*-**2j** in 16% yield and diiodide **4** in 4% yield. In entry 10, the methanesulfonyl group for R_3 was tested with the same R_1 and R_2 for **1a**. However, many byproducts were formed and they prevented the isolation of *cis*-**2k** in its pure form.

Table 2. Scope and limitations of *cis*-selective double spirocyclization with iodine chloride [Method A]

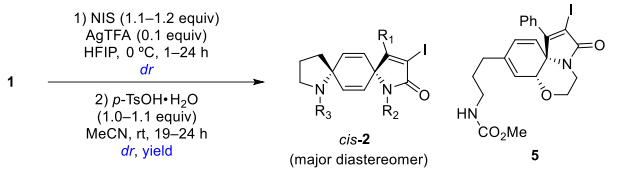


entry	1	R_1	R_2	R_3	dr[a]	yield (%)[b]
1	b	 R = Me	Me	CO_2Me	>95: 5	95
2[c]	c	R = OMe	Me	CO_2Me	>95: 5	85
3[c]	d	R = Cl	Me	CO_2Me	>95: 5	80
4[c]	e	R = CF_3	Me	CO_2Me	>95: 5	57
5[d]	f	R = NO_2	Me	CO_2Me	>95: 5	68
6	g		Me	CO_2Me	>95: 5	90
7	h		Me	CO_2Me	>95: 5	91
8	i		Me	CO_2Me	>95: 5	89
9[c]	j	Ph	Bn	CO_2Me	–	16[e]
10	k	Ph	Me	SO_2Me	–	–[f]

[a]The diastereomeric ratio (*cis*:*trans*) was determined by ^{1}H NMR analysis of crude material; [b]Isolated yield of *cis*-**2**; [c]1.0 equiv of ICl was used; [d]2.2 equiv of ICl was used; [e]**4** was also isolated in 4% yield; [f]Many byproducts were formed.

The scope and limitations of Method B are summarized in Table 3. In entry 1, **1j**, which failed with Method A, was tested. In the double spirocyclization step, **1j** gave almost equal amounts of *cis*- and *trans*-**2j** with a 52:48 dr. Then this crude mixture was applied to the isomerization step. Treatment with one equivalent of *p*-TsOH•H_2O in MeCN gave *cis*-**2j** in 86% yield for two steps with >95:5 dr. During the two steps, byproduct **4** was not observed. Method B seemed to be mild enough for exploring other functional groups on R_2. We then found that ester **1l** (entry 2) and ketone **1m** (entry 3) provided the desired dispiro compounds in high yield with high dr. In entry 4, the reaction with **1n** having the hydroxy group provided oxatricycle **5** as a major product in the first step with a small amount of *cis*- and *trans*-**2n**. After the second step, this mixture was smoothly converted into *cis*-**2n** in 92% yield with dr >95:5, and **5** was not detected. In entry 5, the propargyl group was tested, and the electrophilic activation of the alkyne of propiolamide occurred chemoselectively, providing *cis*-**2o** in high yield with high dr. The reaction was performed at rt without AgTFA because only unreacted **1o** was recovered for the reaction at 0 °C with AgTFA. The silver salt would be deactivated by coordinating with the two alkynyl groups to form a tight complex. In entry 6, the nitrile group was also available for the reaction. Two equivalents of the acid were needed to complete the isomerization. We assume that this result can be attributed to the destabilization of the cationic intermediate **3p** by the highly electron-withdrawing nature of the cyanomethyl substituent,[11] therefore the stronger acidic conditions were required to accelerate the reaction. Next, R_3 substituents were explored in entries 7–11. In addition to phenyl carbamate, relatively acid-labile benzyl carbamate[12] was tolerated and afforded *cis*-**2q** and *cis*-**2r** in high yields with >95:5 dr (entries 7, 8). Dispiro compounds having methanesulfonamide *cis*-**2k**, which was not obtained with Method A, could be synthesized in 81% yield with >95:5 dr (entries 9). Substrate **1s** with the *p*-toluenesulfonyl group was also obtained with high efficiency (entry 10). For *cis*- and *trans*-**2t** having acetamide, the *cis*:*trans* ratio was nearly unchanged after the second step, resulting in the low yield of *cis*-**2t** (entry 11). The reactivity toward acid-mediated isomerization seems to depend on the nature of R_3 substituents. Presumably, the weaker leaving group ability of the acetamide moiety[13] would be insufficient for the generation of the cationic intermediate under these conditions.

Table 3. Alternative milder reaction conditions for the *cis*-selective double spirocyclization in two steps [Method B]



entry	1	R_1	R_2	R_3	dr[a] 1st step	dr[a] 2nd step	yield[b]
1	j	Ph	Bn	CO_2Me	52:48	>95: 5	86
2	l	Ph		CO_2Me	58:42	>95: 5	85
3	m	Ph		CO_2Me	75:25	>95: 5	83
4	n	Ph		CO_2Me	–[c]	>95: 5	92
5[d]	o	Ph		CO_2Me	72:28	>95: 5	85
6[e]	p	Ph		CO_2Me	53:47	>95: 5	82
7	q	Ph	Me	CO_2Bn	56:44	>95: 5	90
8	r	Ph	Me	CO_2Ph	55:45	>95: 5	86
9	k	Ph	Me	SO_2Me	90:10	>95: 5	81
10	s	Ph	Me	SO_2(*p*-tol)	77:23	94: 6	76
11	t	Ph	Me	COMe	72:28	74:26	29[f]

[a]The diastereomeric ratio (*cis*:*trans*) determined by ^{1}H NMR of crude material; [b]Isolated yield of *cis*-**2** for 2 steps; [c]**5** was observed as a major product in the first step; [d]The reaction was run without AgTFA at rt; [e]2.0 equiv of *p*-TsOH•H_2O was used; [f]NMR yield.

In summary, we have developed two new methods (Method A and Method B) for highly *cis*-selective double spirocyclization through dearomatization and isomerization. The key to success was the development of the Method A with a simple operation and short reaction time, the discovery of the equilibrium between *cis*- and *trans*-dispiro adducts in favoring thermodynamically more stable *cis*-diastereomer under acidic conditions, and the development of Method B with a wider functional group tolerance and substrate scope. With these methods, we have constructed a 5/6/5-dispirocyclic ring system with pyrrolidine and γ-lactam moieties with various substituents in high yield and high dr. The methods developed here would be applied to more complex dispirocyclic molecules.

AUTHOR INFORMATION

Corresponding Authors

Hiromasa Yokoe − School of Pharmacy and Pharmaceutical Sciences and Institute of Medicinal Chemistry, Hoshi University, Shinagawa-ku, Tokyo, Japan; orcid.org/0000-0002-3326-7938; Email: h-yokoe@hohsi.ac.jp

Naoki Kanoh − School of Pharmacy and Pharmaceutical Sciences and Institute of Medicinal Chemistry, Hoshi University, Shinagawa-ku, Tokyo, Japan; orcid.org/0000-0002-4382-3725; Email: n-kanoh@hohsi.ac.jp

ACKNOWLEDGMENT

This work was supported by a JSPS KAKENHI Grant (no. 19K06982). We thank Central Glass Co., Ltd. for the generous gift of HFIP.

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