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2,5-*cis*-2,3,5-Trisubstituted tetrahydrofurans from the diastereomixture of 2,4-disubstituted 1,3-dioxepins *via* stereomutation†

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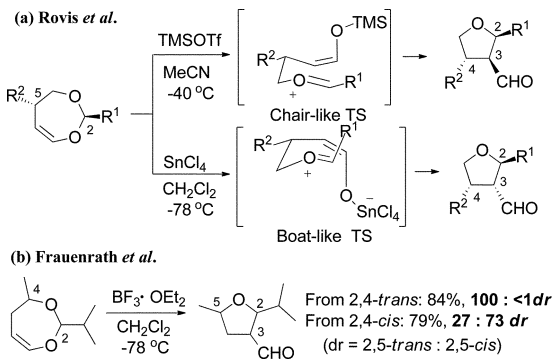
A diastereoselective ring contraction of the diastereomixture of 2,4-disubstituted 1,3-dioxepins to 2,5-*cis*-2,3,5-trisubstituted tetrahydrofurans was achieved using TfOH in DMF. The reaction appears to proceed *via* a chair-like transition state, in which stereomutation of the oxocarbenium occurred, followed by an aldol-type cyclization.

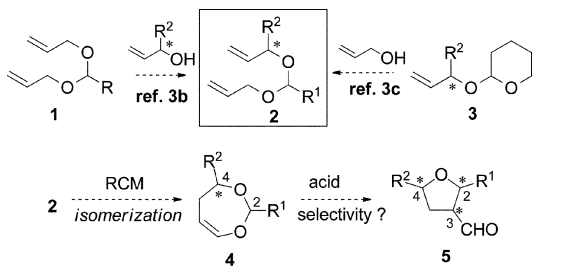
Stereoselective approaches to substituted tetrahydrofurans (THFs) continue to attract much attention due to their appearance in many biologically important compounds, and a number of methods have already been developed.[1] Recently, the acid-mediated ring contraction of 1,3-dioxepins has been reported to be a potential method to prepare stereocontrolled substituted THF derivatives.[2]

Rovis and co-workers reported a ring contraction reaction of the *trans*-2,5-disubstituted 1,3-dioxepins (Scheme 1a).[2d,e] They succeeded in selectively preparing two diastereomers of the 2,3,4-trisubstituted THFs by changing the reaction conditions; TMSOTf/MeCN afforded the 2,3-*cis*/3,4-*trans* isomer whereas $SnCl_4/CH_2Cl_2$ provided the 2,3-*trans*/3,4-*cis* isomer. On the other hand, Frauenrath and co-workers studied the $BF_3{\cdot}OEt_2$-mediated ring contraction of the 2,4-disubstituted 1,3-dioxepins to 2,3,5-trisubstituted THFs (Scheme 1b).[2c] They showed that the relative stereochemical relationship between the 2,5-positions of the produced 2,3,5-trisubstituted THFs depended on the stereochemistry of the starting materials; the 2,4-*trans* isomer gave the 2,5-*trans* isomer as a major product whereas the 2,4-*cis* isomer gave the 2,5-*cis* isomer. We have recently reported the mild and efficient preparation of mixed acetals using TESOTf–2,4,6-collidine combination conditions.[3] This method can enable the rapid preparation of various types of 2,4-disubstituted 1,3-dioxepins as well as the facile incorporation of chirality into their molecules using optically active allyl alcohols.[3b,c] We then intended to apply the method for the preparation of 2,3,5-trisubstituted THFs (Scheme 2). We report here that the mixture of *cis*- and *trans*-isomer of 2,4-disubstituted 1,3-dioxepins **4**, derived from **2**, could be converted to 2,5-*cis*-2,3,5-trisubstituted THFs **5** with high selectivity by the ring contraction reaction independent of the 1,3-dioxepin's stereochemistry.

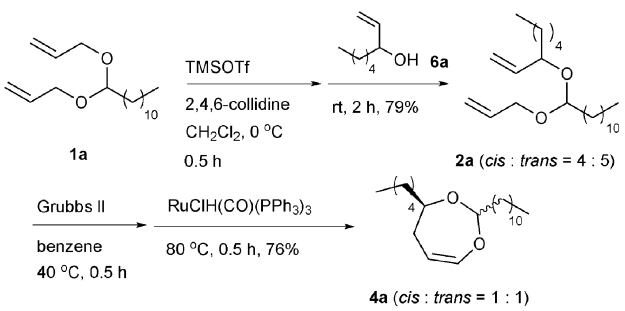
To study the diastereoselectivity of the acid-mediated ring contraction of the 2,4-disubstituted 1,3-dioxepin, we initially attempted to prepare the model 1,3-dioxepin **4a** based on our strategy (Scheme 3).



Scheme 1 Acid-mediated ring contraction of 1,3-dioxepines to substituted THFs.



Scheme 2 Our strategy toward optically active THF derivatives.



Scheme 3 Preparation of model 1,3-dioxepin **4a**.

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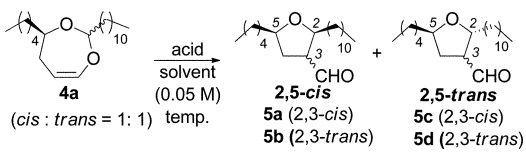
Treatment of the diallyl acetal **1a** using the TMSOTf–2,4,6-collidine combination conditions[3b,4] and subsequent addition of 1-octen-3-ol (**6a**) successfully afforded the mixed allyl acetal **2a** in 79% yield (dr = 4 : 5). The RCM of the mixed allyl acetal **2a** and the following olefin isomerization process were accomplished in a one-pot operation[5] using Grubbs' 2nd catalyst and $RuClH(CO)(PPh_3)_3$ to give the desired model 1,3-dioxepin **4a** in 76% yield as a 1 : 1 mixture of diastereomers.

We then examined the reaction of the 1,3-dioxepin **4a** under various conditions to evaluate the diastereoselectivity (Table 1). Our initial trial under Frauenrath's conditions resulted in a low diastereoselectivity (entry 1). Instead of CH_2Cl_2, the use of the more polar MeCN increased the 2,5-*cis* selectivity (entry 2). We considered that MeCN had a positive effect on the selectivity, so several Lewis acids or Brønsted acids were evaluated in MeCN (entries 3–6). However, no improvement in the selectivity was observed in each case. To our surprise, $BF_3{\cdot}OEt_2$ in the more polar DMF afforded THF in 92% yield with a high 2,5-*cis*-selectivity along with preferential generation of the all-*cis*-2,3,5-trisubstituted THF **5a** (entry 7). TfOH produced a higher selectivity in a shorter reaction time than $BF_3{\cdot}OEt_2$ (entry 8). Decreasing the amount of TfOH[6] to 0.5 equiv. slightly enhanced the 2,5-*cis*-selectivity with a longer reaction time (entry 9). The weaker acid (±)-CSA slightly decreased the 2,5-*cis*-selectivity (entry 10). TfOH in other polar solvents,[7] such as THF or $MeNO_2$, gave high yields, but low selectivities (entries 11 and 12).

Table 1 Evaluations of stereoselectivity in acid-mediated rearrangement of 1,3-dioxepin **4a**



2,5-*cis*
5a (2,3-*cis*)
5b (2,3-*trans*)

2,5-*trans*
5c (2,3-*cis*)
5d (2,3-*trans*)

Entry	Acid (equiv.)	Solvent	Temp. Time	Yield (%)[a] **5a** : **5b** : **5c** : **5d**[b]
1	$BF_3{\cdot}Et_2O$ (0.1)	CH_2Cl_2	−78 to 0 °C 7 h	97 37 : 22 : 15 : 26
2	$BF_3{\cdot}Et_2O$ (0.1)	MeCN	−40 to 0 °C 3 h	98 68 : 9 : 12 : 11
3	TMSOTf(0.1)	MeCN	−40 °C 2 h	Quant. 67 : 9 : 12 : 12
4	TBSOTf (0.1)	MeCN	−40 °C 3 h	95 67 : 10 : 11 : 12
5	TfOH (0.1)	MeCN	−40 °C 2 h	90 68 : 9 : 11 : 12
6	(±)-CSA (0.1)	MeCN	−40 to 0 °C 4 h	92 61 : 13 : 15 : 12
7	$BF_3{\cdot}Et_2O$ (1.0)	DMF	−60 °C to rt, 24 h	92 85 : 8 : 4 : 3
8	TfOH (1.0)	DMF	0 °C to rt 4 h	88 88 : 7 : 3 : 2
9	**TfOH (0.5)**	**DMF**	**0 °C to rt 13 h**	**89 88 : 8 : 3 : 1**
10	(±)-CSA (0.5)	DMF	0 °C to rt 24 h	84 83 : 10 : 5 : 2
11	TfOH (0.5)	THF	0 °C to rt 10 min	94 51 : 15 : 19 : 15
12	TfOH (0.5)	$MeNO_2$	0 °C to rt 10 min	93 54 : 14 : 17 : 15

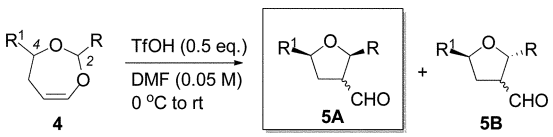
[a] Isolated yields. [b] Ratio based on ^1H NMR spectra.

Thus TfOH (0.5 equiv.) in DMF was chosen for further investigations.

We next explored the substituent effect on the diastereoselectivity (Table 2). A substituent at the 2-position of 1,3-dioxepin was first studied (entries 2–4). 1,3-Dioxepin **4b** bearing a cyclohexyl group afforded the product **5bA** in 88% yield in 4 h (entry 2). The reaction time became short with a slight decrease in the 2,5-*cis*-selectivity compared to **4a** (entry 1). The phenyl group accelerated the reaction along with a high yield and selectivity (entry 3). The cinnamyl group further accelerated the reaction, however, the 2,5-*cis*-selectivity decreased (entry 4). A substituent at the C4-position of 1,3-dioxepin was examined in the following entries (entries 5 and 6). The sterically-hindered isopropyl group made the reaction fast, but the selectivity was moderate (entry 5). The phenyl group made the reaction slow with a very high selectivity (entry 6). The substituent effect is not clear, but the longer reaction time had a tendency to produce a higher selectivity.

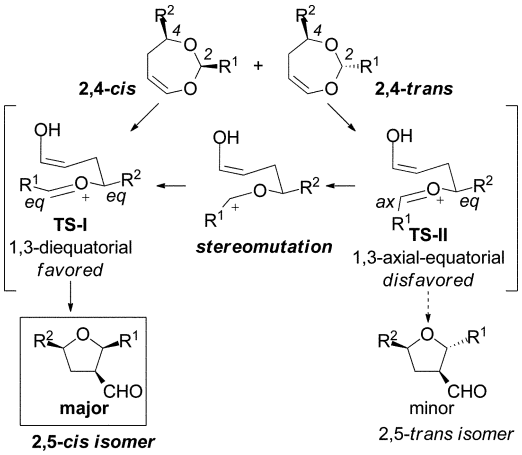
Based on these experimental results, a plausible reaction mechanism is illustrated in Scheme 4. The acid-catalyzed acetal bond cleavage of 1,3-dioxepin may cause the generation of oxocarbenium ion intermediates. 2,4-*cis*-1,3-Dioxepin forms a six-membered chair-like transition state, **TS-I**, in which the geometry of the oxocarbenium ion is *E* and two substituents have

Table 2 Scope of acid-mediated rearrangement of 1,3-dioxepins



Entry	Substrate (*cis* : *trans*)[b]	Time	Product	Yield (%)[a] (**A** : **B**)[b]
1	**4a** (1 : 1)	13 h	**5aA**	89 (96 : 4)
2	**4b** (1 : 1)	4 h	**5bA**	88 (93 : 7)
3	**4c** (2 : 1)	1.5 h	**5cA**	95 (95 : 5)
4	**4d** (5 : 3)	15 min	**5dA**	94 (91 : 9)
5	**4e** (5 : 6)	6 h	**5eA**	85 (92 : 8)
6	**4f** (1 : 1)	26 h	**5fA**	82 (98 : 2)

[a] Isolated yields. [b] Ratio based on ^1H NMR spectra.



Scheme 4 Plausible reaction mechanism.

a 1,3-diequatorial relationship. The intramolecular aldol-type cyclization then occurs to give 2,5-*cis*-THF. On the other hand, the transition state, **TS-II**, from 2,4-*trans*-1,3-dioxepin is relatively unfavorable due to the 1,3-axial-equatorial disposition of the two substituents. Therefore, stereomutation of the geometry of the oxocarbenium ion from *Z* to *E* occurs to give a favorable chair-like transition state. It is also known that the *E* configurations are energetically more preferable than the *Z* configurations in mono-substituted oxocarbenium ions.[8] In addition, the more polar solvent stabilizes the oxocarbenium ion, thus lowering the oxocarbenium ion rotation barrier.[9] Conformational control in the transition state may also assist in the rotation process.

For further application of this reaction, we synthesized a fragment of (−)-amphidinolide K,[10,11] which was isolated from the Okinawan flatworm *Amphiscolops* sp[12] containing a 2,5-*cis*-2,3,5-trisubstituted THF framework in its structure. Synthesis of the (−)-amphidinolide K fragment began with the mixed acetalization of **7** prepared by THF-protection of the known (*R*)-1-(benzyloxy)but-3-en-2-ol.[13] Desilylation afforded the alcohol **8** in 86% yield over two steps. Benzoyl protection followed by the RCM-isomerization sequential protocol resulted in 1,3-dioxepin **10** (dr = 1 : 1) in 57% yield over three steps. The key ring contraction gave the (−)-amphidinolide K fragment **11** in 55% yield with over a 30 : 1 ratio of the 2,5-*cis* to *trans* isomers (Scheme 5).

In summary, we have developed a novel diastereoselective ring contraction of 2,4-disubstituted 1,3-dioxepins for the stereocontrolled construction of 2,5-*cis*-2,3,5-trisubstituted THFs. In these reactions, the stereochemical outcome at the 2-position of the THFs does not depend on the stereochemistry of the starting material and 2,5-*cis*-THF is always preferred. The reactions are effective for the synthesis of a wide range of 2,5-*cis*-2,3,5-trisubstituted THFs. The synthetic application of this reaction was demonstrated in the synthesis of the THF fragment of (−)-amphidinolide K. Studies related to the construction of complex oxacycles are currently underway.

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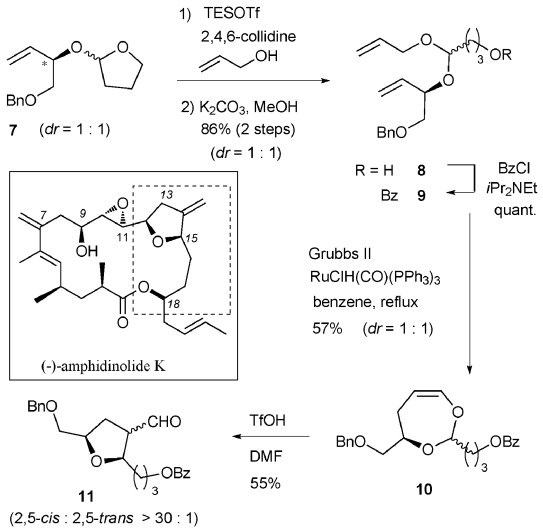

Scheme 5 Application to synthesis of the THF fragment of (−)-amphidinolide K.

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