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Asymmetric Synthesis of Antithrombotic Agent M55529: The First Enantioselective Cyclic *N*,*O*-Acetal Formation

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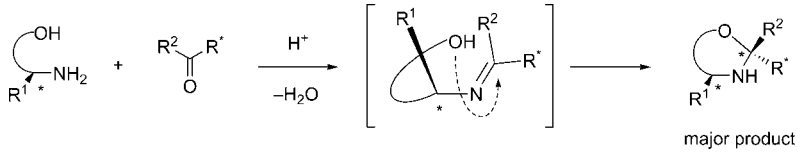
Keywords: Antithrombotic agent / M55529 / Cyclic *N*,*O*-acetal / Enantioselective acetal formation

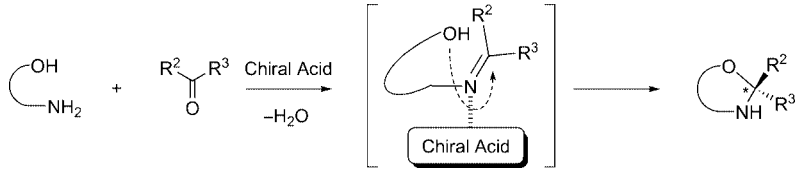
The first asymmetric synthesis of antithrombotic agent M55529 is reported, wherein the first enantioselective cyclic *N*,*O*-acetal formation is clarified.

Introduction

Cyclic *N*,*O*-acetals have often been found in natural products such as alkaloids.[1] However, they have mainly been used as protecting groups for carbonyl compounds,[2] as latent imines for stereoselective addition reactions,[3] and as synthetic intermediates for *N*-containing heterocyclic compounds.[4] Since the carbon center of the N–C–O acetal can be stereogenic depending on its substituents, the carbon-centered chirality of cyclic *N*,*O*-acetals has been controlled diastereoselectively in the preparation step from chiral amino alcohols and/or chiral carbonyl compounds (Scheme 1).[3,4] In contrast, the chiral *N*,*O*-acetal can, in principle, be synthesized enantioselectively from a prochiral carbonyl compound and an achiral amino alcohol. In the first step, the imine is formed in the presence of a chiral acid, and then the chiral cyclic *N*,*O*-acetal can be formed by intramolecular nucleophilic attack of the achiral imino alcohol toward the enantioface of the imine by the chiral acid (Scheme 2). However, the chiral-acid-promoted enantioselective cyclic *N*,*O*-acetal synthesis with achiral substrates has never been reported so far. We report here on enantioselective cyclic *N*,*O*-acetal formation in the context of the asymmetric synthesis of antithrombotic agent **M55529**.



Scheme 1. Diastereoselective cyclic *N*,*O*-acetal formation.



Scheme 2. Enantioselective cyclic *N*,*O*-acetal formation.

Results and Discussion

Since factor Xa is a key enzyme and plays an important role in the coagulation cascade, it has been a promising target for the design of new drugs, with potential for the treatment and prevention of thrombosis diseases.[5] Our oral antithrombotic agent **M55529** is a highly active inhibitor against factor Xa.[5] **M55529** has the characteristic features of a spiro unit and a oxazolopyrazinone as the cyclic *N*,*O*-

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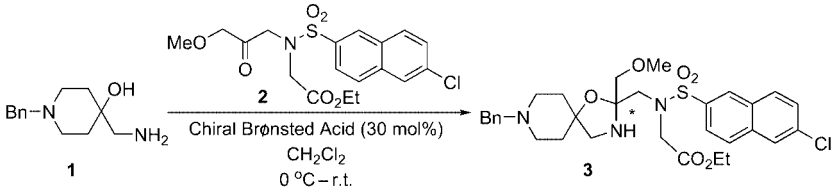
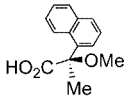
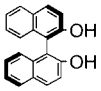
Table 1. Enantioselective cyclic *N*,*O*-acetal formation with chiral Brønsted acids.



Entry	Chiral Brønsted Acid		cpK_a [a]	Time [d]	Yield [%]	3 % *ee*[b]
1	AcOH		4.66	0.5	78	–
2[c]		(*R*)	2.88	10	57	24 (+)
3[c]		(*S*)		10	45	24 (–)
4		(*aR*)	9.08	3	66	15 (+)
5		(*aS*)		3	72	11 (–)

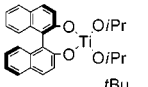
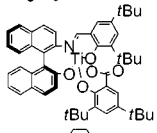
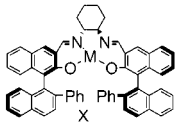
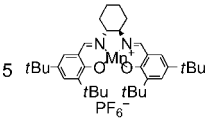
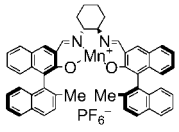
[a] The cpK_a value was calculated by Pallas 3.0 (see ref.[11]). [b] % *ee* was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL/min; MeOH (diethylamine: 0.1%); 16.8 and 21.5 min; (+) and (–) refer to the signs of optical rotation of the first and second eluted product **3**, respectively. [c] Entries 2 and 3 were carried out at 0 °C.

acetal skeleton. The (–)-form of this cyclic *N*,*O*-acetal **M55529** shows a higher inhibitory activity against factor Xa (2 nM) than the (+)-form (129 nM).

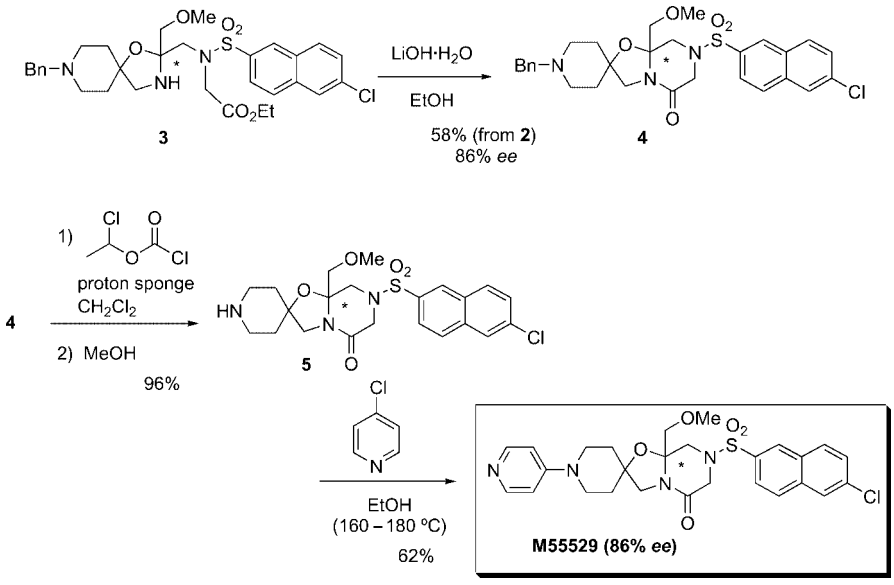
For the asymmetric synthesis of **M55529**, the cyclic *N*,*O*-acetal formation was first attempted in the presence of a chiral Brønsted acid. Typical examples of the enantioselective formation of cyclic *N*,*O*-acetal with chiral Brønsted acids are summarized in Table 1. Among the chiral Brønsted acids examined, (*R*)- or (*S*)-2-methoxy-2-(1-naphthyl)propionic acid[6] produced the chiral cyclic *N*,*O*-acetal with the highest enantioselectivity, though still in a low level, in moderate yields (Entries 2 and 3, 24% *ee*, 45–57%).

On the basis of the results with the chiral Brønsted acids, the use of chiral Lewis acids was examined. Typical examples of the enantioselective formation of cyclic *N*,*O*-acetal with chiral Lewis acids are summarized in Table 2. Unfortunately, BINOL-[7] and NOBIN-derived[8] Ti complexes and the salen-Ti complex[9] gave only low yields of the cyclic *N*,*O*-acetal along with low levels of enantioselectivity (Entries 1, 2, and 3). However, salen-manganese complexes[9,10] afforded moderate to high enantiomeric excesses up to 76% though in low yields (up to 28%) [Entries 4, 5, and 6]. The reason for the low chemical yields is apparent in view of the fact that a strongly bound complex (R_f = 0.5 on TLC; CH_2Cl_2/MeOH 9:1) was formed between the manganese complex and the cyclic *N*,*O*-acetal product **3**. In order to separate product **3** from the manganese complex, further addition of several bases was examined, such as triethylamine, *N*,*N*-dimethylaminopyridine, sodium hydrogen carbonate, potassium carbonate, and so forth, which have higher pK_a values (cpK_a > 8; cpK_a indicates calculated pK_a by Pallas 3.0) than that of the product **3** (cpK_a 5–8).[11] The

Table 2. Enantioselective *N*,*O*-acetal formation with chiral Lewis acids.

Entry	Chiral LA[a]		Time [d]	Yield [%]	3 % *ee*
1		(*aR*)	3	0	–
2		(*aS*)	5	8	20 (+)
3		M = Ti, X = 2Cl$^-$ (*aR*,*RR*)	4	0	–
4		M = Mn, X = PF_6^- (*aR*,*RR*)	3	12	54 (–)
5		(*RR*)	3	14	7 (+)
6		(*aS*,*R*)	5	28	76 (–)
7[b]		(*aS*,*RR*)	3	**80**[c]	**86 (–)**[c]

[a] Each reaction was carried out from 0 °C to room temperature with a chiral Lewis acid complex (1.1 equiv.). MS 4A was used as desiccant. [b] 1.3 equiv. of the chiral Lewis acid was used. [c] iPr$_2$NEt was added to the reaction mixture at the end of the reaction. Exact yield and *ee* were determined after cyclization to compound **4** with LiOH·H_2O (see Scheme 3).



Scheme 3. Asymmetric synthesis of **M55529**.

use of diisopropylethylamine was found to lead to the best result for the isolation of product **3** in 80% yield, along with an increased level of enantiomeric excess of up to 86% (Entry 7).

With this success in isolating product **3** in a good yield and high enantiomeric excess (86%), several conditions for amide formation were further investigated for completion of bicyclization to give oxazolopyrazinone **4** without racemization [58% isolated yield (from **2**), 86% *ee*].

After chromatographic separation by using silica gel, compound **4** was deprotected by α-chloroethyl chloroformate in the presence of proton sponge®. Finally, compound **5** was coupled with 4-chloropyridine to complete the synthesis of **M55529**. In this reaction sequence, racemization did not take place, and **M55529** was obtained in 86% *ee*.[5] Thus, we succeeded in the asymmetric synthesis of **M55529** (Scheme 3).

Conclusions

In summary, we have reported on the first enantioselective cyclic *N*,*O*-acetal formation and, therefore, accomplished the asymmetric synthesis of the antithrombotic agent **M55529** using the chiral salen-manganese complex as a chiral Lewis acid.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and spectroscopic data for compounds **3**, **4**, **5**, and **M55529**.

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