DOI: 10.1002/ejoc.200600838

Asymmetric Synthesis of Antithrombotic Agents M58163 and M58169: Dynamic Kinetic Resolution in Amide Formation Catalyzed by La-Linked BINOL Complex

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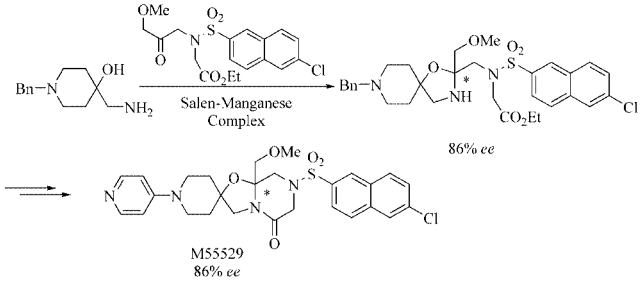
Keywords: Antithrombotic agent / Kinetic resolution / Enantioselectivity / Acetals

The first asymmetric syntheses of antithrombotic agents M58163 and M58169 are reported. Dynamic kinetic resolution is observed in the amide formation step.

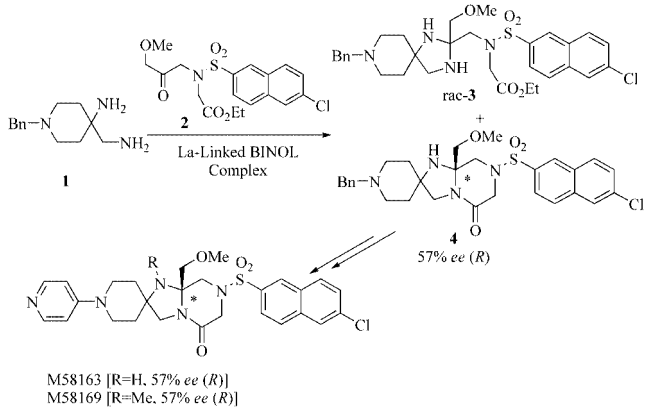
Introduction

Factor Xa (FXa) is a key enzyme that plays an important role in the coagulation cascade. The design of a new drug as a FXa inhibitor has thus been a challenge for the treatment and prevention of thrombosis diseases.[1] During the course of the development of a FXa inhibitor as an antithrombotic agent, we have found unique FXa inhibitor M55529, which contains a cyclic N,O-acetal structure.[2] We have also reported the enantioselective cyclic N,O-acetal formation and the asymmetric synthesis of M55529 with the use of a chiral salen–manganese complex (Scheme 1).[3]



Scheme 1. Enantioselective cyclic N,O-acetal formation and the asymmetric synthesis of antithrombotic agent M55529.

Recently, we reported other oral FXa inhibitors, M58163 and M58169,[4] with the characteristic spiro unit and an imidazopyrazinone as a cyclic N,N-acetal structure instead of the cyclic N,O-acetal moiety of M55529. These compounds show higher FXa inhibitory activity [M58163 (IC_{50}: 0.61 nM), M58169 (IC_{50}: 0.58 nM)] than that of M55529 (IC_{50}: 2.0 nM). Cyclic N,N-acetals have been found in natural products[5] and used as protecting groups for imine compounds,[6] as synthetic intermediates of N-containing heterocyclic compounds,[7] or as chiral synthons prepared from chiral diamines and/or chiral carbonyl compounds.[8] However, enantioselective cyclic N,N-acetal synthesis with the use of achiral substrates has never been reported so far. We report here the first enantioselective formation of cyclic N,N-acetals, and the dynamic kinetic resolution in the subsequent amide formation step leading to the tricyclic key intermediate of M58163 and M58169 (Scheme 2).



Scheme 2.

Results and Discussion

First, a salen–manganese complex, by which the cyclic N,O-acetal of M55529 was enantioselectively formed,[3] was examined for the formation of cyclic N,N-acetal **3** [Equa-

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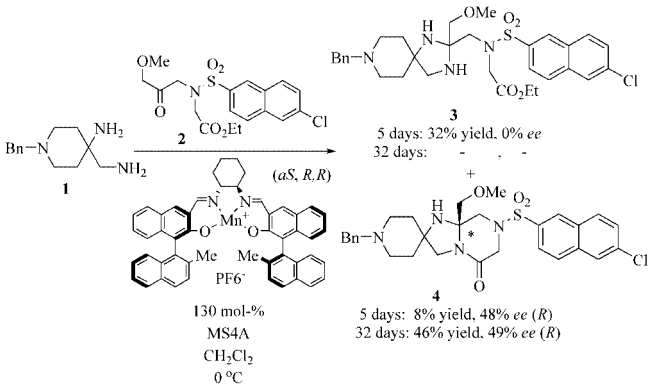
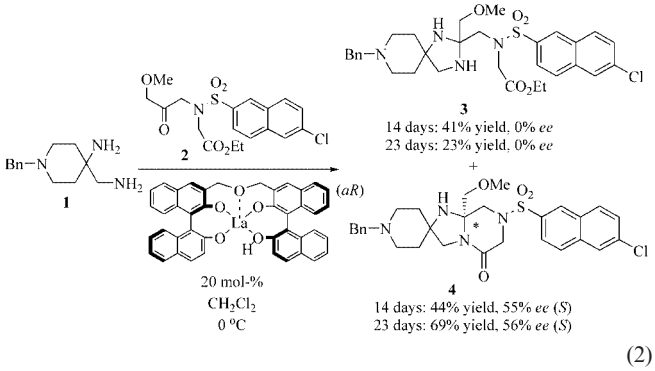
tion (1)]. Desired cyclic N,N-acetal **3** was not obtained enantioselectively (0% *ee*), but surprisingly, enantioenriched tricyclic compound **4** was instead obtained in 48% *ee*. The reaction time was thus prolonged until N,N-acetal **3** disappeared and tricyclic compound **4** was clearly observed on TLC (32 d); compound **4** was obtained in moderate yield (46% yield) and with the same enantioselectivity (49% *ee*). However, the salen–manganese complex could not be used in a catalytic amount because highly basic diamine **1** coordinates with the Lewis acidic salen–manganese complex. In sharp contrast, a chiral base complex may efficiently catalyze the second amide formation step.[3]



(1)

We thus examined a commercially available La-linked BINOL complex.[9] As expected, the reaction proceeded with a catalytic amount of the La-linked BINOL complex and the enantioselectivity increased to 56% *ee* [Equation (2)]. Particularly, tricyclic compound **4** was obtained in 69% yield without reducing the enantioselectivity of the reaction, even after a prolonged reaction time. In this case, racemic N,N-acetal **3** was again obtained.



(2)

These results suggest the following: (1) Because N,N-acetal **3** can easily racemize, **3** was not obtained enantioselectively. (2) Dynamic kinetic resolution should take place in the second amide formation step. We therefore tried to confirm the racemization of both enantiopure N,N-spiroacetals, (+)- and (–)-**3**, which were isolated by chiral HPLC [Daicel CHIRALCEL OJ-H column at 40 °C; flow rate: 0.5 mL/min; hexane/EtOH (diethylamine: 0.1%) = 50:50; (+)-**3**: 10.6 min and (–)-**3**: 16.0 min]. Both enantiomers, (+)- and (–)-**3**, slowly racemized at 0 °C without any catalyst and racemization was faster (within 2 d) with La-linked BINOL catalyst at 0 °C (Figure 1).

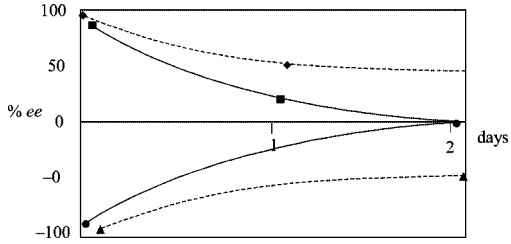


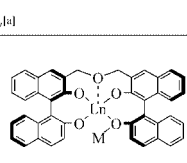
Figure 1. Racemization of (+)-**3**/(–)-**3** with La-linked BINOL. --♦-- (dashed line): (+)-**3**, —■— (line): (+)-3 with La-linked BINOL, --▲-- (dashed line): (–)-**3**, —●— (line): (–)-**3** with La-linked BINOL.

On the basis of these results, this asymmetric induction, which is observed in the second step of amide formation from racemic N,N-acetal **3**, can be a result of dynamic kinetic resolution.[10] The yield of **4** exceeded 50% and racemic **3** was obtained, and both enantiomers of **3** racemized with La-linked BINOL complex at 0 °C within 2 d.

We next tuned the alkaline and central lanthanide metals (Table 1). A change in the alkaline metal in the La-linked BINOL complex from lithium via sodium to potassium resulted in reduction of the chemical yield and enantioselectivity of **4** (Entries 1–3; **4**: 7–24% yield, 15–21% *ee*).[9] When the central lanthanide metals were changed to yttrium and gadolinium instead of lanthanum, the chemical yield and enantioselectivity of **4** slightly decreased (Entries 5 and 6; **4**: 38–44% yield, 51–52% *ee*). Although the ytterbium complex gave a low yield, moderate selectivity was observed (Entry 7; **4**: 11% yield, 40% *ee*). The nonalkaline metal La-linked BINOL complex gave the best yield and selectivity (Entry 4; **4**: 44% yield, 55% *ee*).

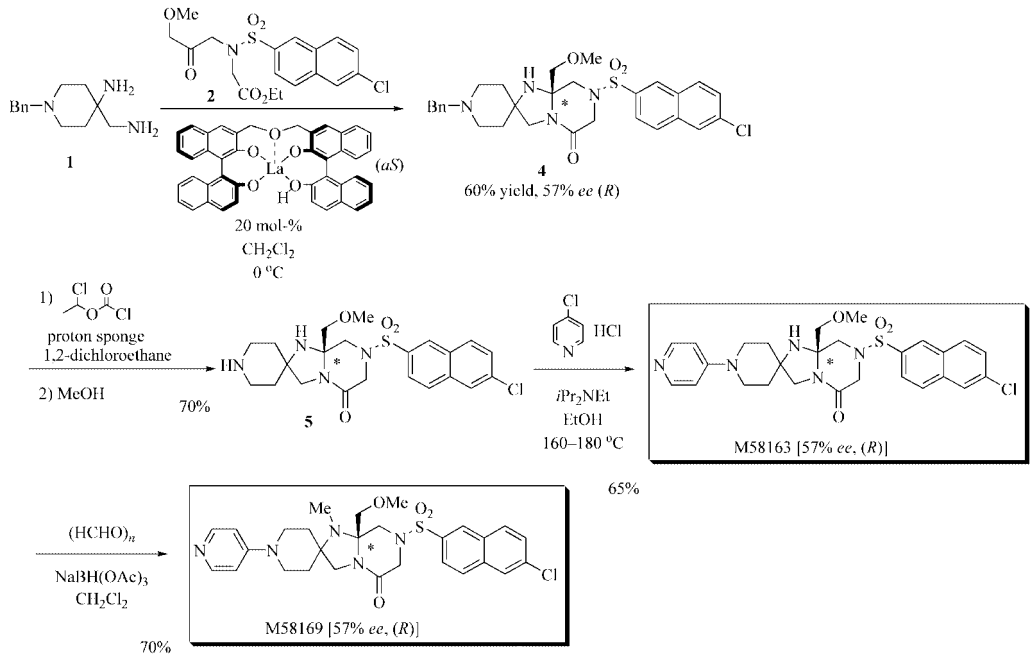
Table 1. Comparison of alkaline metals or of central lanthanide metals.

				3		4	
Entry[a]	M[b]	Ln[b]	Yield [%]	% *ee*[c]	Yield [%]	% *ee*[d]
1	Li	La	26	0	24	21(*S*)
2	Na	La	23	0	14	15(*S*)
3	K	La	16	0	7	19(*S*)
4	**H**	**La**	**41**	**0**	**44**	**55(*S*)**
5	H	Y	34	0	44	52(*S*)
6	H	Gd	53	0	38	51(*S*)
7	H	Yb	30	0	11	40(*S*)



[a] Each reaction was carried out at 0 °C for 14 d. [b] See ref.[9] [c] % *ee* was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL/min; hexane/EtOH (diethylamine: 0.1%) = 50:50; 10.6 and 16.0 min, respectively. [d] % *ee* was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL/min; hexane/EtOH (diethylamine: 0.1%) = 50:50; 20.5 and 46.9 min; The absolute configuration was correlated to M58169, of which the absolute configuration was determined by X-ray crystallography analysis (See ref.[4]).

Finally, target compounds M58163 and M58169 were synthesized (Scheme 3). Because the absolute configuration of M58169 was determined to be (*R*) by X-ray crystallogra-



Scheme 3. Asymmetric synthesis of M58163 and M58169.

phy analysis,[4] commercially available (*aS*)-La-linked BINOL complex was used to obtain (*R*)-**4** [60% yield, 57% *ee* (*R*)]. Compound **4** was deprotected by α-chloroethyl chloroformate in the presence of proton sponge.[11] Deprotected compound **5** was coupled with 4-chloropyridine hydrochloride to afford M58163. Reductive *N*-methylation completed the synthesis of M58169. In this reaction sequence, racemization did not take place; M58163 and M58169 could be obtained in 57% *ee*.[4]

Conclusions

In summary, we have reported not only the asymmetric synthesis of cyclic N,N-acetals but also dynamic kinetic resolution in the second step of the amide formation. We have thus accomplished the asymmetric syntheses of antithrombotic agents M58163 and M58169.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and spectroscopic data of compounds **3**, **4**, **5**, M58163, and M58169.

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Received: September 25, 2006
Published Online: November 21, 2006

