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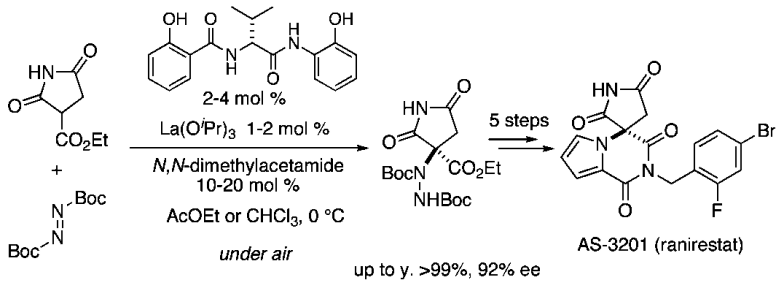

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En Route to an Efficient Catalytic Asymmetric Synthesis of AS-3201

Tomoyuki Mashiko,[†] Keiichi Hara,[†] Daisuke Tanaka,[§] Yuji Fujiwara,[¶] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†]

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, Chemistry Research Laboratories, Dainippon Sumitomo Pharma Company, Ltd., 33-94, Enoki, Suita, Osaka 564-0053, Japan, and Chemical Synthesis Laboratories, Technology Research & Development Center, Dainippon Sumitomo Pharma Company, Ltd., 3-1-98, Kasugade Naka, Konohana-ku, Osaka 554-0022, Japan

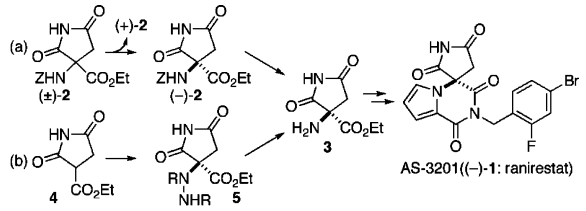
Received July 14, 2007; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Although cellular glucose is mainly metabolized in vivo by the glycolytic pathway, a small amount of non-phosphorylated glucose enters into the polyol pathway, an alternative route of glucose metabolism.[1] The rate-determining step of the polyol pathway is the reduction of glucose to sorbitol catalyzed by aldose reductase.[2] Under hyperglycemic conditions, the increased flux of glucose is metabolized in the polyol pathway,[2,3] inducing various metabolic imbalances such as the accumulation of sorbitol and excessive consumption of NADPH associated with the enhanced activity of aldose reductase.[4,5] Such metabolic disturbances eventually result in the onset and progression of diabetic complications such as neuropathy and vascular disorders.[6] In this context, the development of an aldose reductase inhibitor is of tremendous clinical importance as diabetic disorders are a major health concern throughout the world.[7,8]

Whereas almost all the other candidate aldose reductase inhibitors have been withdrawn in the course of clinical development, AS-3201 ((−)-**1**: ranirestat) was identified as a structurally novel spirosuccinimide-type aldose reductase inhibitor with remarkable efficacy and safety.[8] (−)-**1** is orally available and under clinical development (phase III in the United States and Canada) for the potential treatment of diabetic complications by Dainippon Sumitomo Pharma Co Ltd. (−)-**1** has attracted particular attention because there are no therapeutics for the treatment of diabetic complications.[8] Currently, asymmetric synthesis of (−)-**1** relies on the optical resolution of succinimide (±)-**2** with cinchonidine (Scheme 1a).[8a] Although two cycles of recrystallization with cinchonidine give optically pure (−)-**2**, the overall efficiency is low and cinchonidine recycling is costly and time-consuming. Therefore, the development of an efficient catalytic asymmetric synthesis of (−)-**1** is a formidable task for future therapeutic development and efficient commercial production. To this end, we focused on the catalytic asymmetric amination of succinimide **4** with azodicarboxylate to afford **5**, which can be readily transformed into the key intermediate **3** (Scheme 1b).[8a] Herein, we report an efficient asymmetric synthesis of (−)-**1** using a catalytic asymmetric amination of **4** with a newly developed lanthanum−amide complex.

We initially evaluated known catalysts for the catalytic asymmetric amination of β-ketoesters in the reaction with succinimide **4**. Although the amination of β-ketoesters with azodicarboxylates was reported more than 80 years ago,[9] its enantioselective variant was not explored until recently. The catalytic asymmetric amination of β-ketoesters has quickly emerged and gained popularity as a useful technology for introducing an amine functionality next to a carbonyl carbon.[10,11] On the basis of affordability and availability for large-scale synthesis, we selected representative catalysts and attempted the catalytic asymmetric amination of **4** with di-*tert*-butyl azodicarboxylate. None of the catalysts, however, including cinchona alkaloids (10−22% ee),[10c] Takemoto's urea-type catalyst

Scheme 1. Approach to Asymmetric Synthesis of AS-3201 ((−)-**1**)



(30% ee),[10g] Cu-Box (14% ee),[10a] and La-PyBox (13% ee),[10j] afforded the desired amination product **5** (R = Boc) with satisfactory enantioselectivity, although excellent chemical yields were generally obtained. This was likely due to the unique chemical properties of succinimide substrate **4**, which exhibits multiple coordination modes.

We then turned our attention to the development of a new catalyst for a catalytic asymmetric amination applicable to a highly coordinative substrate such as **4**. We focused on a combination of lanthanides and amide ligands, where a lanthanide metal would be surrounded by amide ligands to avoid unfavorable coordination of **4** owing to the highly coordinative nature of the amide functionality.[12] We hopefully anticipated that the high coordination number of lanthanide would allow for the additional coordination of **4** in a specific coordination mode. After extensive investigation, an amide ligand (*S*)-**7**, derived from L-valine through a chromatography-free process,[13] emerged as a promising ligand for the amination of **4**. The catalytic asymmetric amination of **4** with Ln/(*S*)-**7** complex, prepared from Ln(O^iPr)$_3$ and (*S*)-**7** in a ratio of 1:2, is summarized in Table 1. Among the lanthanides tested, the La/(*S*)-**7** complex performed best, affording (+)-**6** in 66% yield and 43% ee in THF at −40 °C with 10 mol % of catalyst. Reaction in ethyl acetate or chloroform improved the enantioselectivity to 76 or 57% ee, respectively. Decreasing the catalyst loading to 1 mol % gave the better enantioselectivity, whereas the reaction time became longer.[14]

To gain insight into the structure of the La/(*S*)-**7** complex to further improve the amination reaction, we next performed ESI-QFT (quadrupole Fourier transform) MS[15] analysis of the complex.[16] Unexpectedly, the catalyst afforded prominent peaks corresponding to La/(*S*)-**7** = 4/4, 4/5 complexes, suggesting that a highly coordinated macromolecular assembly was formed. Speculating that only a partial structure of the assembly is responsible for the observed enantioselectivity, coordinative additives to fragment the assembly were then investigated in the amination of **4** (Table 2). Although the addition of phenols and acids proved to be ineffective, catalytic use of *N*,*N*-dimethylacetamide (DMA) enhanced the reaction rate with similar to better enantioselectivity (entries 1 vs 2 and 4 vs 5).[17] Based on the fact that the reaction in DMF solvent resulted in significantly decreased enantioselectivity (Table 1), we assumed that amide functionality strongly coordinated to La. A catalytic amount of amide additive would work to partially fragment the oligomeric La/(*S*)-**7** complex into favorable small units, increasing the apparent concentration of the catalytically active component to accelerate the reaction, albeit excess amide compound

[†] The University of Tokyo.
[¶] Chemistry Research Laboratories, Dainippon Sumitomo Pharma Company, Ltd.
[§] Technology Research & Development Center, Dainippon Sumitomo Pharma Company, Ltd.

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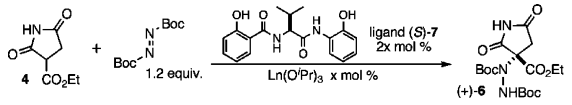
Table 1. Catalytic Asymmetric Amination with Ln/(*S*)-**7** Complex[a]



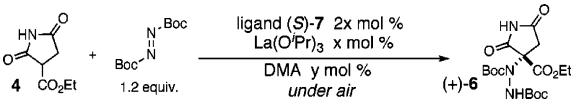
Lanthanide Screening ($x = 10$)[b]		
La: y. 66%, 43% ee	Nd: y. 15%, 16% ee	Sm: y. 21%, 0% ee
Gd: y. 11%, 28% ee	Dy: y. 8%, −5% ee	Er: y. 88%, 3% ee

Solvent Screening ($x = 10$)[c]		
THF: y. 66%, 43% ee	DMF: y. 85%, 7% ee	ether: y. 64%, 46% ee
toluene: y. 31%, 31% ee	$CHCl_3$: y. 96%, 57% ee	AcOEt: y. 86%, 76% ee

Catalyst Loading[d]	
in AcOEt	in $CHCl_3$
$x = 10$, −40 °C: y. 86%, 76% ee, 24 h	$x = 10$, −40 °C: y. 96%, 57% ee, 24 h
$x = 1$, −40 °C: y. 96%, 89% ee, 57 h[14]	$x = 1$, −40 °C: y. 99%, 68% ee, 32 h[14]

[a] Determined by ^{1}H NMR analysis. [b] In THF at −40 °C for 24 h. [c] Ln = La, at −40 °C for 24 h. [d] Ln = La.

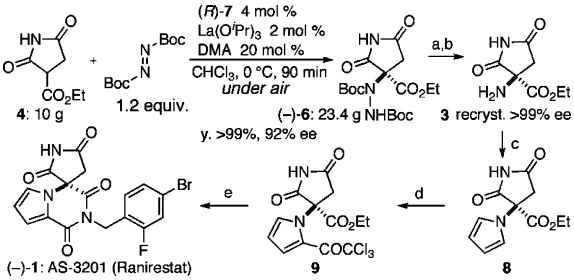
Table 2. Catalytic Asymmetric Amination with La/(*S*)-**7** Complex with DMA[a]



entry	*x*	*y*	solvent	temp (°C)	time (h)	yield[b] (%)	ee (%)
1[c]	1	0	AcOEt	−40	57	96	89
2	1	10	AcOEt	−40	29	>99	87
3	1	10	AcOEt	0	4	99	89
4[c]	1	0	$CHCl_3$	−40	32	>99	68
5	1	10	$CHCl_3$	−40	20	>99	76
6	1	10	$CHCl_3$	0	3	>99	82
7	2	20	$CHCl_3$	0	0.5	99	90
8[d]	0.5	5	$CHCl_3$	0	9	>99	74

[a] 0.4 mmol scale. [b] Determined by ^{1}H NMR analysis. [c] Reaction under Ar. [d] 0.8 mmol scale.

Scheme 2. Catalytic Asymmetric Synthesis of AS-3201 ((−)-**1**)[a]



[a] Key: (a) HCl (g), toluene, 0 °C, 99%; (b) Raney-Ni, H_2, EtOH, rt, recrystallization, 66%; (c) 2,5-dihydroxytetrahydrofuran, THF−H_2O, 40 °C, 85%; (d) CCl_3COCl, 80 °C, 90%; (e) 4-bromo-2-fluorobenzylamine, DMF, rt, 71%.

would substantially disrupt the asymmetric environment. Higher reaction temperature had a beneficial effect on the enantioselectivity, affording **6** in higher enantiomeric excess in either ethyl acetate or chloroform (entries 2 vs 3 and 5 vs 6).[18] The highest enantiomeric excess (90% ee) was observed in chloroform with 2 mol % of catalyst (entry 7). The reaction is not sensitive to oxygen, and laboratory scale experiments have been performed under air.

With the efficient catalytic asymmetric amination protocol of **4** in hand, we attempted the asymmetric synthesis of (−)-**1** (Scheme 2): 10 g of succinimide **4** was subjected to catalytic asymmetric amination with 2 mol % of La/(*R*)-**7** complex at 0 °C to give 23.4 g of (−)-**6** in >99% yield and 92% ee. Boc groups were quantitatively removed by treatment with HCl in toluene at 0 °C. N−N bond cleavage proceeded smoothly with Raney nickel, and the following recrystallization gave **3** in optically pure form. **3** was subjected to modified Clauson−Kaas pyrrole synthesis to give **8** in 85% yield.[19] Installation of a trichloroacetyl group and subsequent treatment with 4-bromo-2-fluorobenzylamine gave rise to a pyrrolopyrazine core, affording (−)-**1**.[20]

In summary, we achieved a catalytic asymmetric synthesis of (−)-**1** via catalytic asymmetric amination promoted by a newly developed La/amide (*R*)-**7** complex. Ligand **7** was synthesized from inexpensive starting materials without chromatographic purification.[16] A novel combination of Ln/amide will provide for a new type of chemistry as the La/**7** complex is effective for the asymmetric amination of **4**, unlike other catalyst types. The amination product was successfully transformed into (−)-**1** on a multigram scale. We anticipate that this route may be useful for enhancing the prospective future supply of (−)-**1**, a highly potent aldose reductase inhibitor under development for the treatment of diabetic complications.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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