

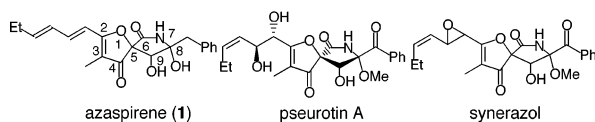
Asymmetric Total Synthesis of (–)-Azaspirene, a Novel Angiogenesis Inhibitor

Yujiro Hayashi,^{*,†} Mitsuru Shoji,[†] Junichiro Yamaguchi,[†] Kenji Sato,[†] Shinpei Yamaguchi,[†] Takasuke Mukaiyama,[†] Ken Sakai,[§] Yukihiko Asami,^{||} Hideaki Kakeya,^{||} and Hiroyuki Osada^{||}

Department of Industrial Chemistry, Faculty of Engineering, and Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan, and Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

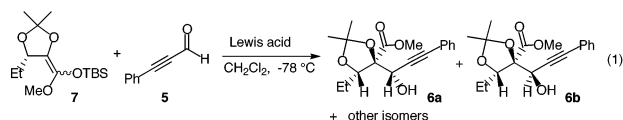
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The inhibition of angiogenesis is a promising method of treating angiogenesis-related diseases such as cancer and rheumatoid arthritis.¹ We have recently completed an asymmetric total synthesis of epoxyquinols A and B,² which we have isolated and identified as novel, unique angiogenesis inhibitors.³ Our continuing search for new angiogenesis inhibitors from natural sources led us to azaspirene (**1**), isolated from the fungus *Neosartorya* sp.⁴ Structurally, azaspirene (**1**) contains a highly oxygenated 1-oxa-7-azaspiro-[4.4]non-2-ene-4,6-dione skeleton with benzyl and hexadiene substituents, and a core structure also found in the pseurotins⁵ and synerazol.⁶ Although several synthetic studies on the pseurotins have been reported,^{5e–h} their total synthesis has not yet been accomplished. Because of its interesting biological properties and rare structure, we have investigated the total synthesis of azaspirene (**1**), aiming to determine its absolute stereochemistry.



Our synthesis (see Scheme 1) started with the Sharpless asymmetric dihydroxylation of methyl 2-pentenoate (**2**) using (DHQD)₂PHAL as the chiral ligand.⁷ This gave (2*R*,3*S*)-diol **3** in 88% yield. This was treated with dimethoxypropane in the presence of a catalytic amount of TsOH·H₂O, to afford acetal **4** in 95% ee⁸ and 79% yield. The next step, an aldol condensation of **4** with phenylpropargyl aldehyde (**5**),⁹ proved troublesome. Although the lithium enolate of **4** reacted with **5** smoothly at –78 °C, all four possible aldol products **6** were obtained with very poor diastereoselectivity (57:20:13:8), albeit in good yield (total 98%). The desired *syn*-aldol **6a** was obtained in only a small amount (13%), while the major isomer was *anti*-aldol **6b** (57%). As screening of solvent, base, and additives did not significantly improve this result, we examined the alternative, Mukaiyama aldol reaction.

After conversion of ester **4** to its ketene silyl acetal **7**,¹⁰ the aldol reaction of this was investigated in the presence of various Lewis acids (eq 1),



* To whom correspondence should be addressed. E-mail: hayashi@ci.kagu.tus.ac.jp.

[†] Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science.

[§] Department of Applied Chemistry, Faculty of Science, Tokyo University of Science.

^{||} Antibiotics Laboratory, RIKEN.

Table 1. Effect of Lewis Acid in Mukaiyama Aldol Reaction of **5** and **7**^a

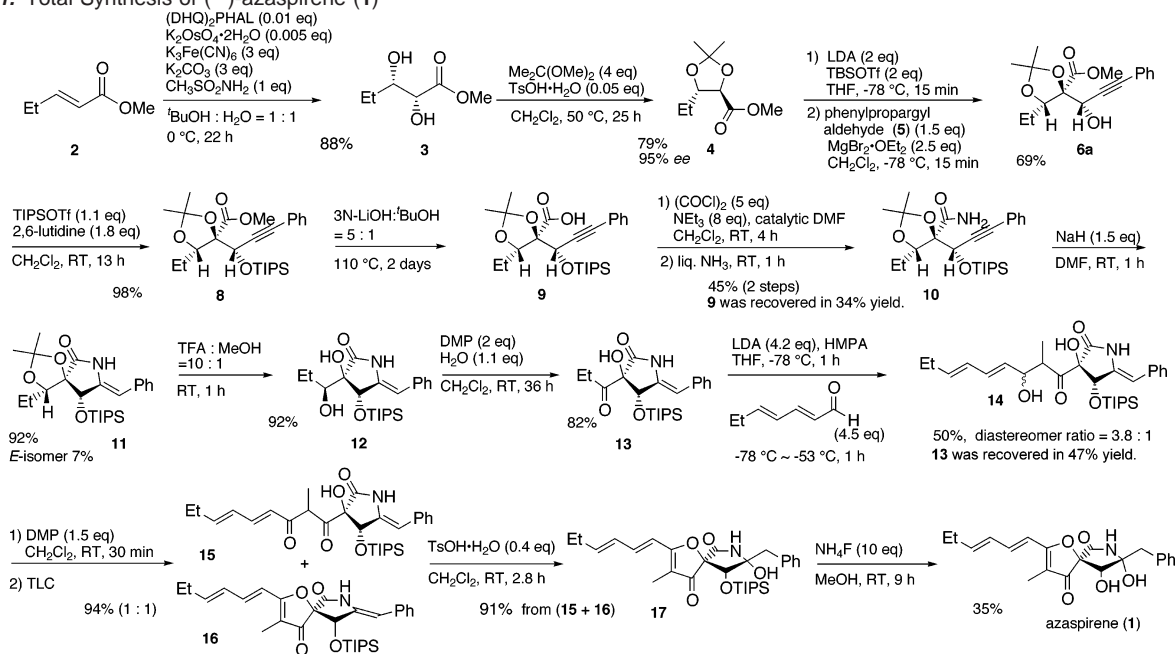
Lewis acid	yield/% ^b	isomer ratio/%		other isomers
		6a	6b	
SnCl ₂	67	61	33	6
BF ₃ ·OEt ₂	41	63	34	3
ZnBr ₂	62	68	31	1
Ti(O- <i>i</i> -Pr)Cl ₃	49	91	9	0
MgBr ₂ ·OEt ₂	72	94	6	0

^a Reaction conditions; **7**:**5**:Lewis acid = 1:1.5:2.5, CH₂Cl₂, –78 °C. ^b Isolated yield based on ester **4**. ^c Isomer ratio was determined by 400 MHz ¹H NMR analysis.

with the results summarized in Table 1. Although the desired *syn*-aldol **6a** was obtained as the major isomer using SnCl₂, BF₃·OEt₂, and ZnBr₂, the diastereoselectivity was insufficient. Ti(O-*i*-Pr)Cl₃¹¹ afforded the desired isomer **6a** with high selectivity but in poor yield. MgBr₂·OEt₂,¹² on the other hand, was found to be a suitable promoter, affording **6a** with both high diastereoselectivity and in good yield, without loss of enantioselectivity as checked by chiral-HPLC analysis.⁸ The stereochemistry of **6a** was established unambiguously by X-ray crystallographic analysis of a crystalline amide,¹³ synthesized by the following sequence: protection of the hydroxy group of **6a** as its benzyl ether, ester hydrolysis, and amide formation. The stereochemistry of **6b** was determined by oxidation of **6a**, followed by reduction, affording **6a** and **6b**.

Protection of **6a** with TIPSOTf and 2,6-lutidine, afforded silyl ether **8** in 98% yield, which was hydrolyzed to provide carboxylic acid **9**. This was next treated with oxalyl chloride and NEt₃, providing the acid chloride, which was reacted with NH₃ to give amide **10** in 45% yield over two steps, along with recovered carboxylic acid **9** in 34% yield. Amide **10** was crystalline, and a single recrystallization gave optically pure compound.⁸ When this amide **10** was reacted with NaH in DMF at room temperature for 1 h, the *Z*-benzylidene γ -lactam **11**¹⁴ and its *E*-isomer¹⁴ were obtained in 92 and 7% yield, respectively.¹⁵ Treatment of **11** with CF₃CO₂H in the presence of MeOH cleaved the acetal, affording diol **12** in 92% yield without affecting the benzylidene moiety. Oxidation of **12** with the Dess–Martin periodinane (DMP)¹⁶ in the presence of water according to Schreiber's modified conditions¹⁷ gave α -hydroxy ketone **13** in 82% yield. Aldol condensation of the lithium enolate of **13** and heptadienal in the presence of HMPA afforded a mixture of diastereomeric aldols **14** in 50% yield. Ketone **13** was recovered in 47% yield, and thus a high conversion yield (94%) had been achieved. It should be noted that it is not necessary to protect the *tert*-alcohol or amide functionality during this aldol reaction. Oxidation of **14** with DMP gave 1,3-diketone **15**,¹⁸ which was partially converted to the azaspiro[4.4]nonenedione bicycle **16** when purified on thin-layer chromatography (**15** + **16**, 94%, **15**:

Scheme 1. Total Synthesis of (–)-azaspirene (1)



16 = 1:1). When a mixture of **15** and **16** was treated with a catalytic amount of TsOH·H₂O for 2.8 h, complete formation of the azaspiro[4.4]nonenedione bicyclic and hydration of the benzylidene group occurred concurrently to afford **17** as a single isomer¹⁹ in 91% yield. Deprotection of the TIPS group with NH₄F in MeOH afforded azaspirene (**1**) in 35% yield. The order of the last two reactions is very important: When the benzylidene derivative **16**²⁰ was first deprotected with NH₄F, and then hydrated with TsOH·H₂O, racemic azaspirene was formed, probably because of a retro-aldol reaction. During the sequence of hydration and deprotection, the presence of an hydroxy group at C8 of the azaspiro[4.4]nonenedione seems to prevent the recemization. Synthetic azaspirene exhibited properties identical to those of the natural product (¹H NMR, ¹³C NMR, IR, mp, *R_f* value, and chiral HPLC analysis). Comparison of the optical rotation (synthetic **1**; [α]_D²⁵ -207 (*c* = 0.13, MeOH), natural **1**¹⁴; [α]_D²⁵ -204.4 (*c* = 0.158, MeOH), established the absolute stereochemistry of the natural product to be (5*S*,8*R*,9*R*).

In summary, the first asymmetric total synthesis of (–)-azaspirene (**1**) has been achieved, and its absolute stereochemistry has been determined. There are several noteworthy features to this total synthesis: The MgBr₂·OEt₂-mediated, diastereoselective Mukaiyama aldol reaction of **5** and **7**, the NaH-promoted intramolecular cyclization of the alkynylamide **10** to form selectively the *Z*-benzylidene γ -lactam **11**, the aldol reaction of **13** containing functionalized γ -lactam moiety without protection of *tert*-alcohol and amide functionalities, and the importance of the order of the last two reactions.

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Supporting Information Available: Detailed experimental procedures, full characterization, copies of ¹H, ¹³C NMR, and IR spectra of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (13) Crystal data: monoclinic, space group *P*2₁, *a* = 11.404(3) Å, *b* = 7.941(2) Å, *c* = 12.843(3) Å, β = 105.643(5)°, *V* = 1120.0(5) Å³, *Z* = 2, *R*₁ = 0.0698 for *I* > 2.0σ(*I*), *wR*₂ = 0.1713 for all data (5002 reflections). The details are supplied as Supporting Information (Figure S1).
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- (18) ¹H and ¹³C NMR analyses show that **15** exists in the 1,3-diketo form rather than the keto–enol form.
- (19) The stereochemistry at C8 was confirmed by NOESY and difference NOE experiments, see Supporting Information.
- (20) **16** was obtained in 94% yield from **15** by repeated treatment with thin-layer chromatography (TLC).

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