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

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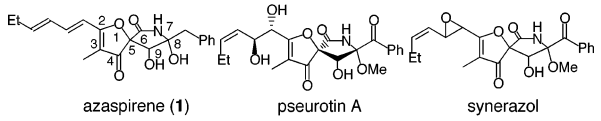
The inhibition of angiogenesis is a promising method of treating angiogenesis-related diseases such as cancer and rheumatoid arthritis.[1] We have recently completed an asymmetric total synthesis of epoxyquinols A and B,[2] which we have isolated and identified as novel, unique angiogenesis inhibitors.[3] 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 pseurotins[5] 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 $(DHQ)_2PHAL$ 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 $TsOH\cdot H_2O$, to afford acetal **4** in 95% ee[8] 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),

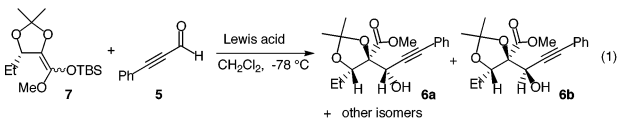


Table 1. Effect of Lewis Acid in Mukaiyama Aldol Reaction of **5** and **7**[a]

Lewis acid	yield/%[b]	isomer ratio[c]/% **6a**	**6b**	other isomers
$SnCl_2$	67	61	33	6
$BF_3\cdot OEt_2$	41	63	34	3
$ZnBr_2$	62	68	31	1
$Ti(O\text{-}i\text{-}Pr)Cl_3$	49	91	9	0
$MgBr_2\cdot OEt_2$	72	94	6	0

[a] Reaction conditions; **7**:**5**:Lewis acid = 1:1.5:2.5, CH_2Cl_2, −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 $SnCl_2$, $BF_3\cdot OEt_2$, and $ZnBr_2$, the diastereoselectivity was insufficient. $Ti(O\text{-}i\text{-}Pr)Cl_3$ [11] afforded the desired isomer **6a** with high selectivity but in poor yield. $MgBr_2\cdot OEt_2$,[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 NEt_3, providing the acid chloride, which was reacted with NH_3 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*-isomer[14] were obtained in 92 and 7% yield, respectively.[15] Treatment of **11** with CF_3CO_2H 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 conditions[17] 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**:

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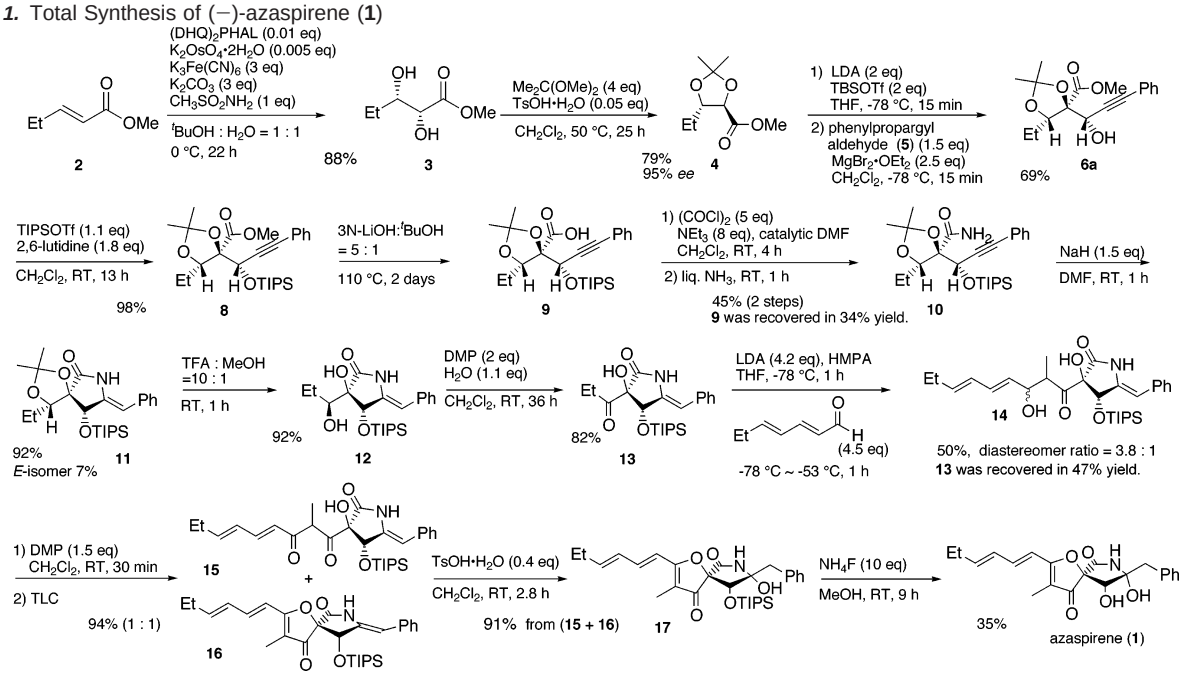
Scheme 1. Total Synthesis of (−)-azaspirene (**1**)



16 = 1:1). When a mixture of **15** and **16** was treated with a catalytic amount of TsOH·H_2O for 2.8 h, complete formation of the azaspiro-[4.4]nonenedione bicycle and hydration of the benzylidene group occurred concurrently to afford **17** as a single isomer[19] in 91% yield. Deprotection of the TIPS group with NH_4F 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 NH_4F, and then hydrated with TsOH·H_2O, 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 (^{1}H NMR, ^{13}C NMR, IR, mp, R_f value, and chiral HPLC analysis). Comparison of the optical rotation (synthetic **1**; $[\alpha]^{27}_D$ −207 (c = 0.13, MeOH), natural **1**[4]; $[\alpha]^{25}_D$ −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 $MgBr_2$·OEt_2-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.

Acknowledgment. This work was partially supported by the Sumitomo Foundation.

Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^{1}H, ^{13}C 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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(8) For the determination of ee, see the Supporting Information.

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(10) Ketene silyl acetal **7** was obtained as a single isomer, the geometry of which has not been determined.

(11) In the elegant total syntheses of zaragozic acid and cinatrins by Evans et al., Ti(O-*i*-Pr)Cl_3 is an effective Lewis acid in Mukaiyama aldol reaction of a silylketene acetal derived from di-*tert*-butyl-(2*S*,3*S*)-1,4-dioxaspiro-[4.4]nonane-2,3-dicarboxylate. Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111; Evans, D. A.; Trotter, B. W.; Barrow, J. C. *Tetrahedron* **1997**, *53*, 8779.

(12) For recent elegant use of $MgBr_2$·OEt_2 as an effective Lewis acid, see: (a) Fujisawa, H.; Sasaki, Y.; Mukaiyama, T. *Chem. Lett.* **2001**, 190. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (c) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984.

(13) Crystal data: monoclinic, space group $P2_1$, a = 11.404(3) Å, b = 7.941-(2) Å, c = 12.843(3) Å, β = 105.643(5)°, V = 1120.0(5) Å^3, Z = 2, R1 = 0.0698 for $I > 2.0\sigma(I)$, wR2 = 0.1713 for all data (5002 reflections). The details are supplied as Supporting Information (Figure S1).

(14) The geometry of the olefins was determined by NOESY experiment.

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(18) ^{1}H and ^{13}C 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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