Total Synthesis

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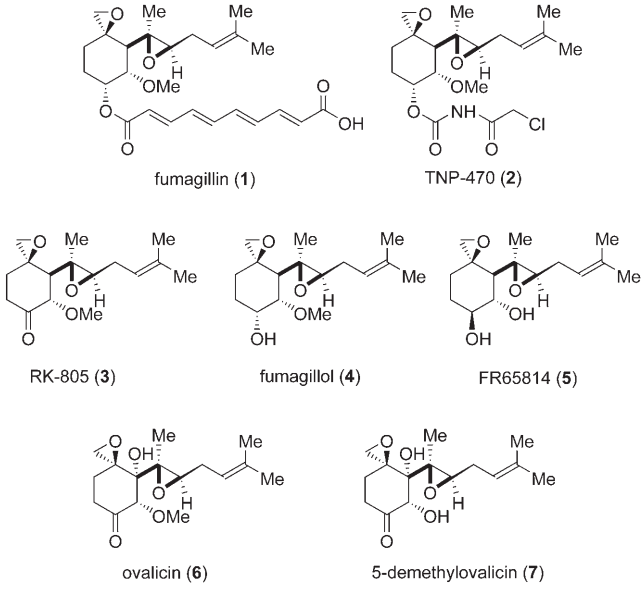
Concise Enantio- and Diastereoselective Total Syntheses of Fumagillol, RK-805, FR65814, Ovalicin, and 5-Demethylovalicin**

*Junichiro Yamaguchi, Maya Toyoshima, Mitsuru Shoji, Hideaki Kakeya, Hiroyuki Osada, and Yujiro Hayashi**

The inhibition of angiogenesis is a promising method of treating diseases in which this process is involved, such as cancer and rheumatoid arthritis.[1] During our continuing research on angiogenesis inhibitors, we have identified and synthesized several novel compounds with such activity, including epoxyquinols A and B,[2] and azaspirene.[3] Recently, we also isolated RK-805 (**3**) from the fungus *Neosartorya* sp.[4] RK-805 is structurally similar to fumagillin (**1**)[5] and TNP-470 (**2**),[6] a synthetic derivative of fumagillin, which are both inhibitors of angiogenesis. Ovalicin (**6**)[7] is another inhibitor



[*] J. Yamaguchi, M. Toyoshima, Dr. M. Shoji, Prof. Dr. Y. Hayashi
Department of Industrial Chemistry
Faculty of Engineering
Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Fax: (+81) 3-5261-4631
E-mail: hayashi@ci.kagu.tus.ac.jp
Dr. H. Kakeya, Prof. Dr. H. Osada
Antibiotics Laboratory
Discovery Research Institute, RIKEN
Wako, Saitama 351-0198 (Japan)

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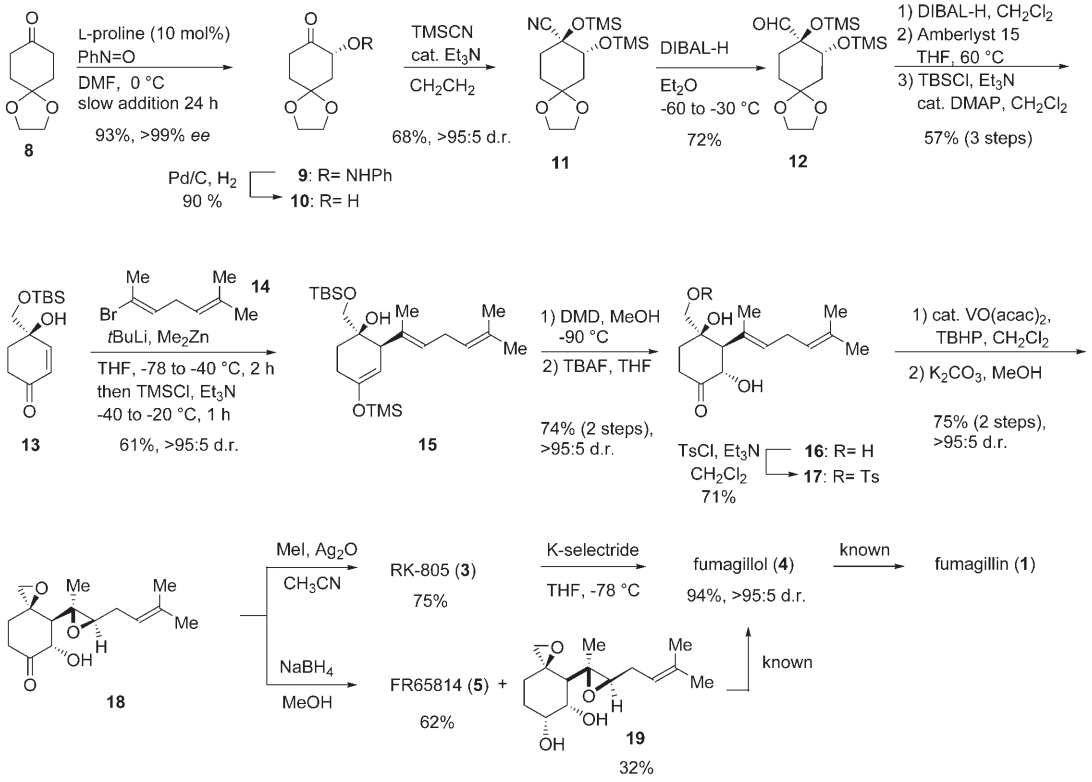
of angiogenesis and is more stable than fumagillin and TNP-470, while 5-demethylovalicin (**7**)[8] was isolated recently and found to be as potent an angiogenesis inhibitor as ovalicin. While these natural products are anti-angiogenesis agents, FR65814 (**5**),[9] which has a similar structure, displays completely different biological activity and is an immunosuppressant.

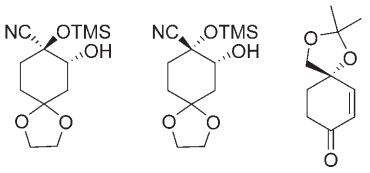
Systematic comparison of the biological properties of these natural products and their derivatives is highly desirable.[10] These compounds comprise a cyclohexane framework, two epoxides, and five or six contiguous stereogenic centers, three or four of which are situated on the cyclohexane ring. As a result of their unique structure and important biological properties, they have proved attractive synthetic targets. Four racemic syntheses[11] including Corey's first excellent total syntheses of fumagillin (**1**)[11a] and ovalicin (**6**) have been reported.[11b] The optically active compounds have been prepared from a chiral pool, starting from quinic acid[12] and quebrachitol[13] for ovalicin, glycidol[14] for fumagillin, allose[15] and mannitol[16] for fumagillin, and glucose[17] for FR65814, while diastereoselective syntheses of fumagillin using chiral auxiliaries have been reported by Sorensen[18] and Eustache[19] and their respective co-workers. However, only one catalytic asymmetric synthesis has been reported for any of these compounds, namely, Corey's synthesis of ovalicin (**6**)[20] through substrate-enhanced asymmetric dihydroxylation. Moreover, there is no single, flexible method to access both families. Herein, we disclose the concise, flexible, and highly diastereoselective asymmetric, catalytic total syntheses of compounds of both families, including RK-805 (**3**), fumagillol (**4**), FR65814 (**5**), ovalicin (**6**), and 5-demethylovalicin (**7**) using our recently developed proline-mediated α-aminoxylation of carbonyl compounds[21] as a key step.

Synthesis of the fumagillin family started from 1,4-cyclohexanedione monoethylene ketal (**8**; Scheme 1). α-Aminoxylation of **8** (1.2 equiv) using 10 mol% of L-proline with slow addition of nitrosobenzene (1.0 equiv) over 24 h proceeded efficiently at 0°C to afford nearly optically pure *R*-α-aminoxylated cyclohexanone **9** (>99% *ee*) in 93% yield, in a reaction that can be scaled up to 25 g of **8** without compromising the yield or enantioselectivity.[21b,c] Reductive cleavage of the N–O bond was performed under an atmosphere of H_2 in the presence of Pd/C[21e] for 3 h in THF (90%). Diastereoselective construction of the epoxide moiety from the ketone carbonyl was found to be troublesome because of easy racemization and low selectivity: Racemic epoxide was obtained, albeit in good yield, when **10** was treated at room temperature with a sulfur ylide such as dimethylsulfonium methylide.[22] The epoxide was generated with low diastereoselectivity (2.5:1–3.4:1) by conventional two-step procedures such as vinylidene formation with $Ph_3P{=}CH_2$ and successive epoxidation with either TBHP in the presence of VO(acac)$_2$[23] at room temperature or MCPBA at 0°C. After some experimentation, it was found that cyano bis(trimethyl-



Scheme 1. Total syntheses of fumagillol (**4**), RK-805 (**3**), FR65814 (**5**), and the formal total synthesis of fumagillin (**1**). DMF = *N*,*N*-dimethylformamide; TMS = trimethylsilyl; DIBAL-H = diisobutylaluminum hydride; TBS = *tert*-butyldimethylsilyl; DMAP = 4-(dimethylamino)pyridine; DMD = dimethyldioxirane; TBAF = tetra-*n*-butylammonium fluoride; Ts = *p*-toluenesulfonyl; acac = acetylacetonate; TBHP = *tert*-butylhydroperoxide; selectride = tri-*sec*-butylborohydride.

silyl) ether **11** could be obtained with high diastereoselectivity in moderate yield, although the diastereoselectivity of the initial cyanation was low. When hydroxy ketone **10** was treated with TMSCN (2.5 equiv) in the presence of Et_3N (0.1 equiv)[24] at 0 °C, cyano mono(trimethylsilyl) ethers **20** and **21** were obtained in low diastereoselectivity (3.5:1) after



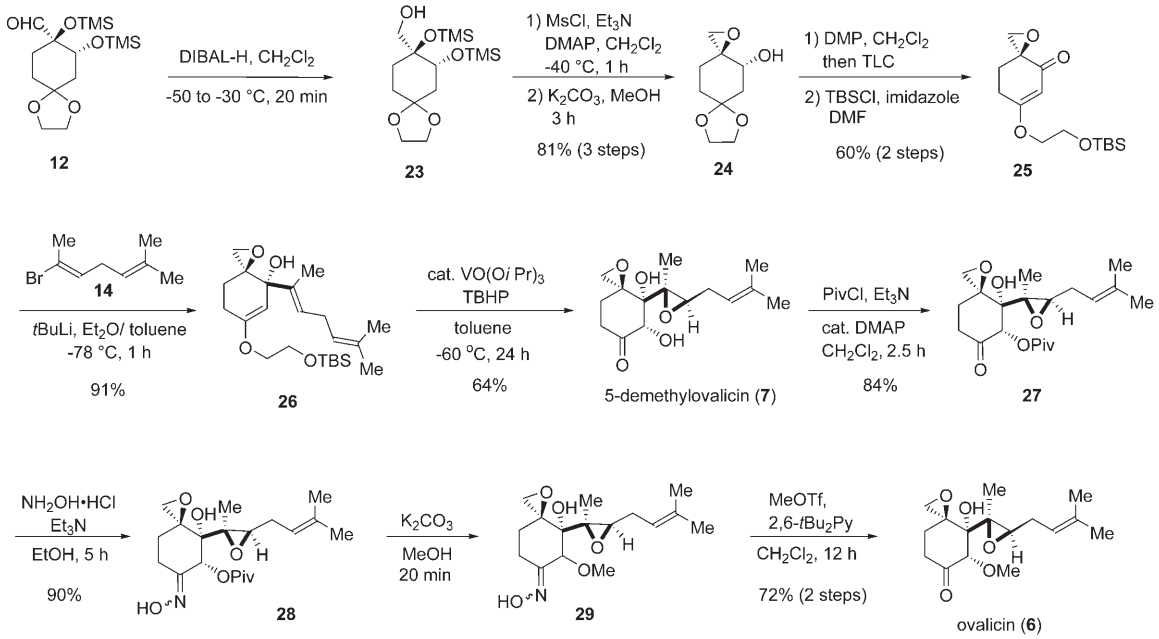
20 **21** **22**

0.5 h. After 2.5 h, however, bis(trimethylsiloxy) cyanocyclohexane **11** was obtained with high diastereoselectivity (> 95:5) in 68 % yield along with cyano mono(trimethylsilyl) ether **21** in 20 % yield because of kinetic discrimination between the diastereomers during the formation of the second TMS ether. The two-step transformation of the cyanide to the alcohol was cleanly performed by repeated reductions with DIBAL-H. Acid treatment with Amberlyst in THF/H_2O at 60 °C for 2 days led to removal of all the protecting groups, with concomitant dehydration affording a cyclohexenone diol. Selective protection of the primary alcohol with TBSCl using Et_3N at room temperature for 12 h afforded TBS ether **13** in 57 % yield over three steps. The optical purity (> 99 % *ee*) of **13** was checked by chiral HPLC analysis of its acetate, which indicated that no racemization had occurred during these transformations. The absolute stereochemistry was confirmed by the conversion of **13** into the enantiomer of Taber's intermediate **22**.[14]

The next task was diastereoselective introduction of the side chain which was also found to be troublesome. The choice of protecting group for the cyclohexenone and the metal cation of the nucleophile are both important for achieving the desired conjugate addition: The tertiary alcohol should be free,[25] and vinyl zincate was found to be the reagent of choice.[26] Thus, α,β-enone **13** reacted with vinyl zincate prepared from **14**[27] at −78 °C to afford the Michael addition product, which was trapped with TMSCl as its trimethylsilyl enol ether **15**. This ether was obtained in 61 % yield as a single isomer, in which the side chain had been introduced stereoselectively from the same side as the hydroxy group. Protection of the tertiary alcohol or use of divinyl cuprate instead of vinyl zincate led to unsatisfactory results. Epoxidation[28] of the silyl enol ether with dimethyldioxirane (DMD) at low temperature (−90 °C) in acetone proceeded diastereoselectively without oxidation of the other trisubstituted double bonds and α-hydroxy cyclohexanone **16** was obtained after treatment with TBAF as a single isomer in 74 % yield over two steps. Though the reaction sequence of conjugate addition, silyl trapping, and Rubottom oxidation was also employed in Taber's synthesis of fumagillin to install a side chain and the hydroxy group at the C5 position, the stereochemistry of the conjugate addition was completely different.[14] Taber et al. reported that intermediate **22** containing an acetal group reacted stereoselectively with a divinyl cuprate derivative in the undesired fashion, that is, *anti* to the oxygen atom of the spirocyclic ether, necessitating several additional steps to correct the stereochemistry. In our synthesis, direct introduction of the side chain with the correct stereochemistry by exploiting the free hydroxy group in combination with a zincate makes the total synthesis efficient and straightforward.

During epoxidation at the side chain, the order of the next two procedures was very important to obtain high diastereoselectivity (Scheme 1). The diastereoselectivity of epoxidation of dihydroxy tosylate **17** with TBHP in the presence of $VO(acac)_2$[23] was excellent, and bis(epoxide) **18** was obtained as a single isomer after treatment with K_2CO_3 in MeOH, whereas reversal of the order of reaction led to low diastereoselectivity (2:1).[29] Formation of the methyl ether with MeI and Ag_2O in CH_3CN gave RK-805, which was stereoselectively reduced with K-selectride at −78 °C to give fumagillol as a single isomer in good yield. The conversion of fumagillol into fumagillin in a single step is known,[11a,14] thus, the formal total synthesis of fumagillin was also accomplished. When **18** was reduced with $NaBH_4$ in MeOH at −50 °C to −10 °C, FR65814 was obtained predominantly in 62 % yield along with **19** in 32 % yield. The conversion of **19** into fumagillol in a single step is known.[11c,18]

Next, the syntheses of 5-demethylovalicin and ovalicin were examined (Scheme 2). The intermediate **12** used in our synthesis of the fumagillin family was employed here also, first to generate the epoxide **24**. Oxidation of **24** with the Dess–Martin periodinane (DMP),[30] followed by acid treatment with thin layer chromatography (TLC) to generate a 3-(2-hydroxyethyloxy)cyclohex-2-enone derivative, and treatment with TBSCl afforded cyclohexenone **25**. The side chain was introduced in a highly diastereoselective manner by using a vinyllithium reagent.[20] As the side chain, the 6-methylhepta-2,5-dien-2-yl substituent was found to be unstable, easy to isomerize, and prone to decomposition, thus its epoxidation had to be carried out immediately.[31] Though conventional epoxidation with $VO(acac)_2$ and TBHP,[23] or *m*-chloroperbenzoic acid gave a complex mixture owing to the instability of the side chain, and the other double bond of the side chain was selectively epoxidized with DMD, $VO(OiPr)_3$[32] was found to be an efficient catalyst, promoting the epoxidation of both the silyl enol ether and the desired side chain alkene at low temperature (−60 °C) to afford 5-demethylovalicin (**7**) as a single isomer with the creation of three chiral centers. The last task necessary to convert 5-demethylovalicin into ovalicin (**6**) was transformation of the alcohol to its methyl ether. Although conventional reagents[33] such as NaH and MeI, Ag_2O and MeI, or MeOTf and 2,6-di-*tert*-butylpyridine, failed, a modification of Corey's method[11b] through the corresponding oxime gave ovalicin stereoselectively. Thus, protection of the alcohol as an ester, formation of the oxime, treatment with base in MeOH, and conversion of the oxime into a ketone gave ovalicin (**6**) as a single isomer, with the ovalicin intermediates **28** and **29** each obtained also as single isomers.[34] Note that oxime **29** was converted into ovalicin (**6**) in good yield without affecting the two epoxides or the trisubstituted alkene under alkylation conditions, when this conversion is usually performed under



Scheme 2. Total syntheses of ovalicin (**6**) and 5-demethylovalicin (**7**). Ms = methanesulfonyl; DMP = Dess–Martin periodinane; Piv = pivaloyl; OTf = trifluoromethanesulfonate, Py = pyridine.

oxidative, reductive, or acid-hydrolysis conditions.[33] Though the synthetic scheme from **25** is similar to that in Corey's elegant synthesis,[11b] in which introduction of the side chain followed by various functional group manipulations are key transformations, there is an important difference; namely, the effective epoxidation catalyst ($VO(OiPr)_3$), which allows diastereoselective double epoxidation without affecting the labile side chain, saves a couple of steps and improves the efficiency of the synthesis.

The ^1H and ^{13}C NMR spectra, IR spectra, and optical rotations of the synthetic samples of **3**,[4] **4**,[14] **5**,[9] **6**,[13b,35] and **7**[8] are in complete agreement with those previously reported.

In summary, the concise enantio- and diastereoselective total syntheses of fumagillol, RK-805, FR65814, 5-demethylovalicin, and ovalicin in 11–15 steps from commercially available compounds have been demonstrated. These are some of the shortest syntheses reported for these chiral natural products and demonstrate clearly the power of the proline-mediated asymmetric catalytic α-aminoxylation. The initial aminoxylation reaction controls both the absolute and the relative stereochemistry of the subsequently generated stereogenic centers, which are formed by the following transformations: 1) a highly diastereoselective formation of bis(trimethylsilyl ether) cyanide **11** involving kinetic discrimination; 2) a diastereoselective Michael reaction by the use of vinyl zincate (**13**→**15**); 3) a stereoselective double epoxidation catalyzed by $VO(OiPr)_3$ at low temperature (**26**→**7**); and 4) an alkylative deprotection of an oxime (**29**→**6**). Corey's asymmetric total synthesis of ovalicin (**6**)[20] using asymmetric dihydroxylation is a landmark chiral synthesis of a member of the fumagillin and ovalicin families. The present route using an α-aminoxylation catalyzed by inexpensive proline is as efficient as Corey's synthesis;[20] it allows the synthesis to be performed on a large scale and allows easy derivatization, as well as being the first strategy applied to both fumagillin and ovalicin families, thus demonstrating the flexibility of the present synthetic method.

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