

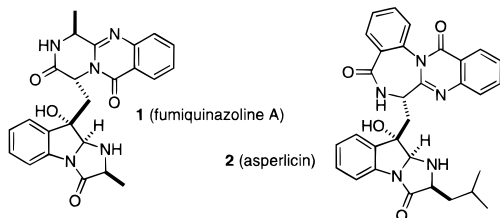
Total Syntheses of (–)-Asperlicin and (–)-Asperlicin C

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We recently reported an efficient synthesis of the tripeptide quinazolinone antibiotic fumiquinazoline G.¹ To extend this synthesis to the structurally more complex tetrapeptide members of this family such as fumiquinazoline A (**1**),^{2–4} we needed to develop a route to the 9-hydroxy-1*H*-imidazo(1,2-*a*)indol-3-one moiety from the indole ring of tryptophan. This ring system also occurs in the potent cholecystokinin antagonist asperlicin (**2**),⁵ but has only been synthesized in the stereochemically and structurally simpler tryptoquivalines by Büchi,⁶ Ban,⁷ and Nakagawa and Hino.⁸ The initial challenge was therefore to develop a practical, stereochemically controlled method to the hydroxy-imidazoindolone moiety **10** from a 3-alkyl indole.



Condensation of 3-methylindoline (**3**)⁹ with *N*-CBZ-*L*-alanine and DCC afforded 90% of the amide, which was oxidized¹⁰ with DDQ in toluene at reflux to provide 90% of acylated indole **4a**. Mercuration¹¹ of **4a** with Hg(OTFA)₂, exchange with KI, and then iodination afforded 82% of iodoindole **5a** and 14% of recovered **4a**. The palladium-catalyzed amidation reaction recently developed by Buchwald (Pd₂(dba)₃, P(*o*-tolyl)₃, K₂CO₃, toluene, 105 °C)¹² provided 83% of **6a** containing the crucial imidazoindolone moiety.

Completion of the model study required the syn addition of H and OH to the double bond of **6a**. Hydroboration failed, so we turned our attention to epoxidation–reduction sequences. Epoxidation of **6a** with *m*-CPBA in MeOH afforded 77% of a mixture of four methoxy alcohols **7a** and **8a**, in which the epoxide

opened by an S_N1 process to give a cationic intermediate analogous to **9** that reacted with MeOH from both faces. Hydroxyl-directed reduction¹³ of this mixture with sodium borohydride in acetic acid gave 80% of a 1.1:1 mixture of alcohols **10a** and **12a** in which an alkoxy borohydride such as **9a** is formed from **7a** and delivers a hydride intramolecularly to give **10a** with H and OH on the same face of the imidazoindolone. Hydrogenolysis over Pd/C in MeOH proceeded quantitatively to give **11a** and **13a**. The structures of **11a** and **13a** were established by NOE studies and confirmed for **11a** by X-ray crystal structure determination.¹⁴ Since the ratio of **10a** to **12a** is determined in the epoxidation step, we investigated other oxidants. Use of 3-*n*-butyl-1,2-benzisothiazole-1,1-dioxide oxide (**26**)¹⁵ followed by reduction gave 60% of a 2.3:1 mixture favoring the desired isomer **10a** while use of dimethyldioxirane¹⁶ afforded 80% of a 1:1.9 mixture favoring the undesired isomer **12a**. More hindered oxaziridines did not epoxidize **6a**. Epoxidations with dioxiranes often give very different stereoselectivity than those with peracids and oxaziridines,^{17a} and calculations indicate transition state geometries for these reactions are quite different.^{17b}

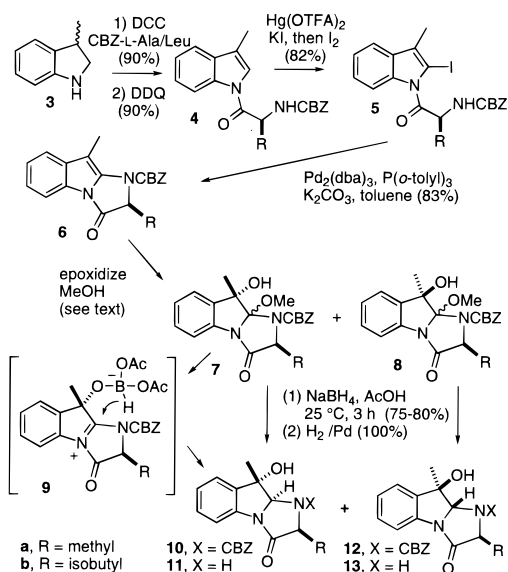
A similar series of reactions with *N*-CBZ-*L*-leucine afforded **6b** with the larger isobutyl side chain of asperlicin. Epoxidation was now more selective for the less hindered α-face, giving **10b** and **12b** as a 3.4:1 mixture with **26**, a 1.7:1 mixture with *m*-CPBA, and a 1:1.4 mixture with dimethyldioxirane. Hydrogenolysis completed the model study, giving **11b** with spectral data very similar to that of asperlicin.

We chose to apply this procedure to the synthesis of asperlicin since the top half of the molecule is more readily accessible than that of fumiquinazoline A. Bock and co-workers reported an efficient synthesis of asperlicin C by reacting **14** with Lawesson's reagent to give a 1:1 mixture of monothioamides which were separated; the desired thioamide was elaborated to **16** in two steps.¹⁸ This synthesis can be improved by using the Eguchi protocol for elaboration of a quinazolin-4-one onto an amide.^{1,19,20} Reaction of **14** with *o*-azidobenzoyl chloride,^{19,21} Et₃N, and DMAP occurred selectively on the more acidic anilide nitrogen, giving exclusively the desired isomer **15** in 83% yield. Reaction of **15** with Bu₃P in benzene at 60 °C formed the aza-Wittig reagent, which cyclized to provide 80% of asperlicin C (**16**) (Scheme 2), with spectra identical with those of the natural product.²²

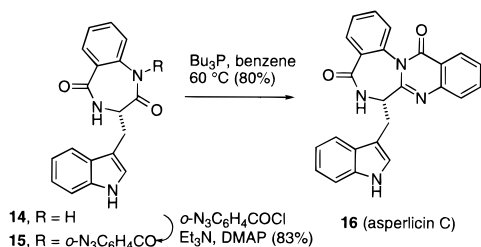
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Scheme 1



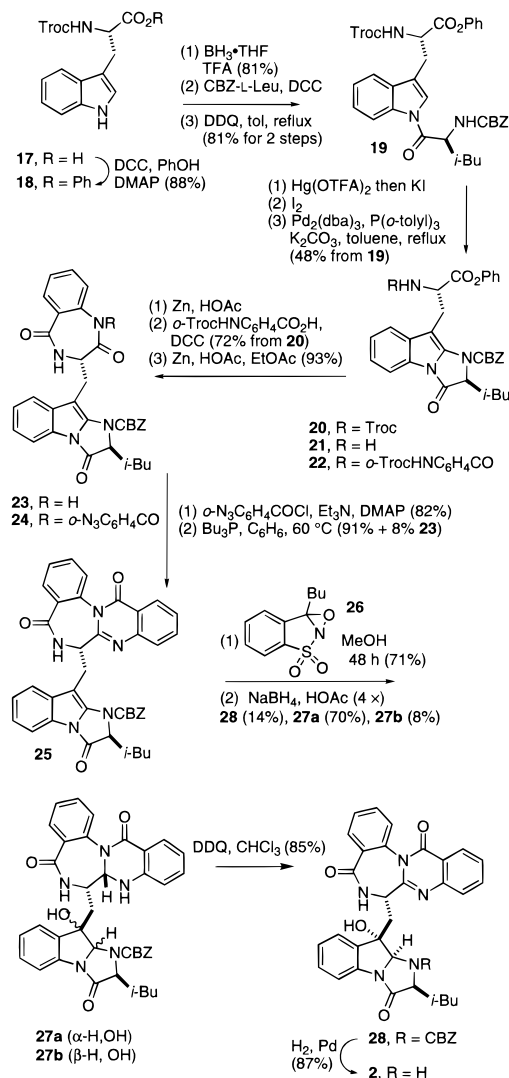
Scheme 2



Application of these sequences to the synthesis of asperlicin required careful consideration of the order of steps to avoid problems with functional group incompatibility. DCC coupling of phenol with *N*_α-(trichloroethoxycarbonyl)-L-tryptophan (**17**)²³ with phenol afforded 88% of phenyl ester **18**. Reduction of the indole with BH₃•THF in TFA²⁴ afforded 81% of the indoline, which was acylated with *N*-CBZ-L-leucine to give 81% of *N*-acylindole **19** after oxidation with DDQ.¹⁰ Iodination¹¹ as described above for **4** followed by the Buchwald palladium-catalyzed condensation¹² afforded 48% of the desired imidazoindolone **20** and 11% recovered **19**. The trichloroethoxycarbonyl (Troc) group was removed with Zn in AcOH to give **21**, which was coupled with *o*-TrocHNC₆H₄CO₂H²³ and DCC to afford 72% of amide **22**. Deprotection of the Troc group with Zn in AcOH and EtOAc gave an amine phenyl ester that spontaneously cyclized to give benzodiazepinedione **23** in 93% yield.

The quinazolinone was now elaborated by the Eguchi protocol;¹⁹ reaction with *o*-N₃C₆H₄COCl, Et₃N, and DMAP afforded 82% of **24**, which was treated with Bu₃P in benzene at 60 °C to provide 91% of **25** and 8% of recovered **23**. We were delighted to find that the epoxidation of **25** with oxaziridine **26**¹⁵ was much more selective than in the model study, giving 71% of an 11:1 mixture favoring the desired α-alcohol. Reduction of this mixture with NaBH₄ in AcOH was slower than that of **7** and **8**; the procedure was repeated 4 to 5 times to remove the methoxy group completely. Competitive reduction of the quinazolinone occurred under these conditions so that we obtained 14% of **28**, 70% of dihydroquinazolinone **27a**, and 8% of **27b**. The unstable dihydroquinazolinones could be easily separated; oxidation of **27a** with DDQ in CHCl₃ at room temperature afforded 85% of **28**.

Scheme 3



Hydrogenolysis of the CBZ group of **28** over Pd/C in MeOH at 1 atm for 15 min gave 87% of asperlicin (**2**) with spectra identical with those of the natural product.²²

We prepared the diastereomer of **25** from *N*-CBZ-D-leucine to examine the factors responsible for the vastly improved stereoselectivity of the epoxidation of **25** as compared to **6b**. Epoxidation of this diastereomer with **26** gave a 5.5:1 mixture of isomers in which the major product is formed from epoxidation on the face opposite the isobutyl group as in **27a**. Since the stereoselectivity of the epoxidation of the diastereomer is better than that of **6b**, but worse than that of **25**, both double asymmetric induction and the steric bulk of the side chain must contribute to the excellent selectivity observed in the epoxidation of **25** with oxaziridine **26**.

In conclusion we have shortened and improved the synthesis of asperlicin C, developed a general route to the hydroxyimidazoindolone ring system, and applied it to the first synthesis of asperlicin, which proceeds efficiently (15 steps, 8% overall yield) and stereospecifically.

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Supporting Information Available: Experimental procedures and X-ray data for **11a** (27 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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