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A Direct Route to Fluostatin C by a Fascinating Diels−Alder Reaction

Maolin Yu[†] and Samuel J. Danishefsky*[,†,‡]

Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, and Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065

Received December 23, 2007; E-mail: s-danishefsky@ski.mskcc.org

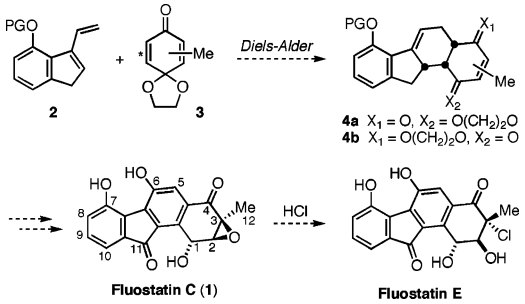
Fluostatin C was isolated from the fermentation broth of *Streptomyces* strain Acta 1383.[1] It is a member of a larger family of fluostatins which exhibit varying degrees of antibiotic and antitumor activity.[2] The fluostatins also bear a structural similarity to the kinamycins, which display related biological profiles.[3,4] At the time we undertook this project, no particular fluostatin had emerged as the clear-cut leading candidate for a total synthesis/diverted total synthesis venture. Thus, we defined as our goal the accomplishment of a concise total synthesis which could be directed to a selection of fluostatins. For purposes of providing focus, our initial foray was directed to fluostatin C (see Scheme 1 for structure **1** and numbering system).

Not the least of our considerations in embarking on this program was the incentive it provided to explore an intriguing possibility, that is, a Diels−Alder reaction between a substituted vinylindene (cf. **2**) as the diene component with a quinoneketal (cf. **3**) as the dienophile. While each of the component subtypes which we were envisioning had been shown to function in nonrelated Diels−Alder contexts, the two component types had not been combined in a single cycloaddition step. In principle, reaction of **2** and **3** in the endo mode could, as suggested in Scheme 1, give rise to either **4a** or **4b**. The endo outcome pictured in Scheme 1 need not be central to reaching **1** since the latter lacks sp^3-based stereopresentation in the ring C area.

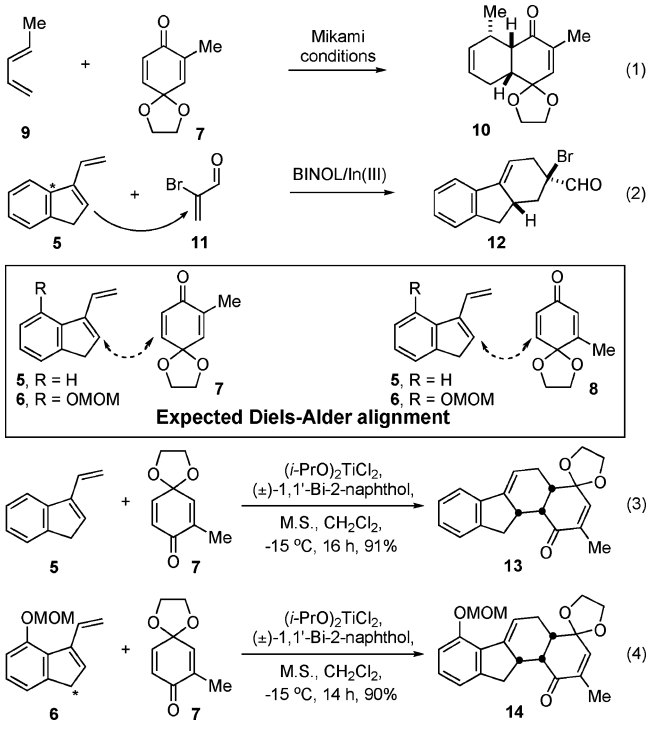
At this stage of our argument, we do not specify the orientational preference for the critical Diels−Alder step. At the chemoselectivity level, we naturally assumed that the active dienophilic double bond within **3** would be the disubstituted site (see asterisks), corresponding eventually to carbons 4a and 11b of the defining target **1**. It was further supposed that either the keto or the ketal functions of a Diels−Alder cycloadduct could be managed such as to emerge as the alcohol function (C_1 of structure **1**) or the keto group (C_4 of structure **1**). Accordingly, our "need to know" the regiochemistry of the alignment *would arise only for the purpose of selecting among the two possible placement sites of the methyl group in 3* (i.e., next to the ketal or next to the ketone).

Viability of the vinylindene-type dienes (cf. **2**) in the projected cycloaddition was another concern. It had been reported that even the parent compound (**5**, Scheme 2) has a pronounced tendency toward polymerization.[5] Conceivably, systems of the type **2** bearing an electron-donating group in the benzo ring (cf. **6**) could be even more vulnerable.[6] The general record of quinoneketals as Diels−Alder dienophiles suggested that they are not particularly reactive under strictly thermal conditions.[7] Fortunately for our plans, Corey and associates had described some studies of the Diels−Alder reaction of quinoneketal **7** under mediation by the Mikami Lewis acid catalytic system.[8] The dienes used by Corey in his demonstrations were well-established in their Diels−Alder "regio" characteristics. Thus, we started by asking whether the Mikami protocols would be applicable to potentially unstable vinylindene (type **2**) dienes, with either quinoneketals **7** or **8**.[9] Of course, while we assumed that either of the regiochemical types of alignments shown below could be managed, such a proposed route to fluostatin C would be badly compromised if a mixture of cycloadducts, resulting from competitive regio-alignments, arose.

Scheme 1. Synthetic Strategy toward Fluostatin C



Scheme 2. Investigations of Diels−Alder Reactions



Below, we describe how the total synthesis of fluostatin C (**1**) was realized. As it turned out, a highly regioselective Diels−Alder reaction of a type **2** diene with a type **3** dienophile under the Mikami−Corey protocols did prevail, thereby enabling a straightforward total synthesis of fluostatin C (**1**) and, shortly thereafter,

[†] Columbia University.
[‡] Sloan-Kettering Institute for Cancer Research.

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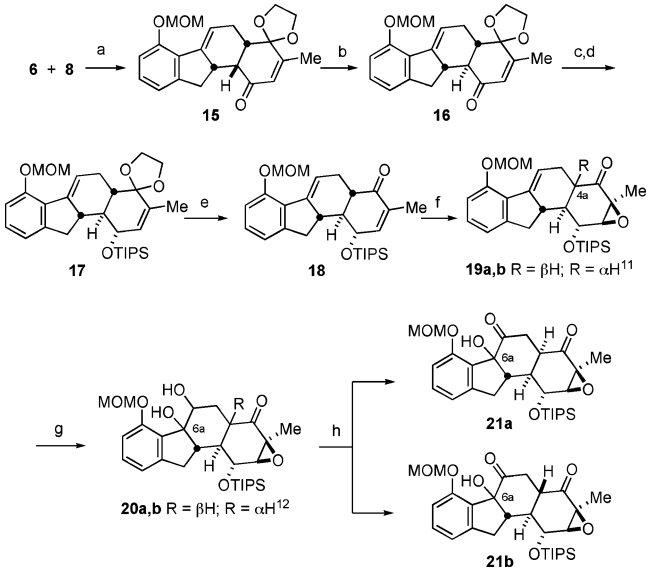
Scheme 3. Synthesis toward Fluostatin C[a]



[a] Key: (a) $(i\text{-PrO})_2TiCl_2$, (*R*)-1,1′-bi-2-naphthol, M.S., CH_2Cl_2, −35 °C, 3 days, 93%, ca. 65% ee; (b) NaOMe, MeOH, 12 h, 92%; (c) superhydride, −78 °C, THF, 30 min, 92%; (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 3 h, 93%; (e) PPTS, acetone, H_2O, reflux, 30 h, 88%; (f) *t*-BuOOH, Triton B, THF, 0 °C, 48 h, 72%; (g) OsO_4, NMO, *t*-BuOH, acetone, H_2O, 0 °C, 12 h, **20a**, ca. 1.5:1, 46%, **20b**, 23%; (h) TPAP, NMO, CH_2Cl_2, rt, 12 h, **21a**, 39%, **21b**, 22%.

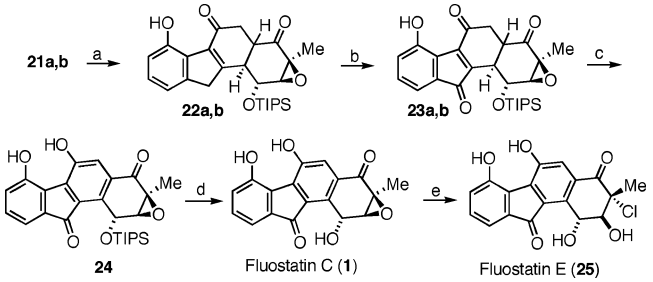
fluostatin E (vide infra). In conjunction with the total synthesis program, further studies of Diels−Alder reactions of type **2** and type **3** systems were undertaken. The findings of these studies are suggestive of an intriguingly subtle balance of forces in controlling the diene−dienophile alignment of the cycloaddition step.

We anticipated that the prevailing regiochemical alignment in the reaction of dienophile **7** with vinylindene-type dienes (see **5** or **6**) would occur as implied in Scheme 2. In formulating this expectation, we took note of the Corey precedent,[8c] wherein **7** and **9**, under the Mikami conditions, cleanly afforded **10**, thereby suggesting that, within **7**, the prevalent directing function is the keto group. We also noted a reported Lewis acid catalyzed Diels−Alder reaction (albeit under guidance by a BINOL/In(III) system) of **5**, with α-bromoacrolein (**11**).[10] This reaction cleanly afforded **12**. We took this result to suggest that the governing group within the diene **5** is the aryl function (see asterisk) attached to carbon 2 of the local 1,3-butadiene moiety. These cases prompted anticipation that cyclocombination of components **5** and **7** would align as suggested (see curved double headed arrows). Remarkably, in practice, this reaction, conducted under the Mikami−Corey protocols, afforded **13**, contrary to the expected alignment. In a similar vein, the Diels−Alder reaction of **6** and **7** cleanly afforded **14**. The structure assignment of the latter was corroborated by X-ray crystallography.

We shall revisit the general "Diels−Alder issues" associated with these cycloadditions. Presently, we focus on how the total synthesis of fluostatin C was accomplished in light of these findings. In line with our plan of synthesis adumbrated above, we next examined the cycloaddition of **6** and **8** under the same Mikami−Corey protocols. Indeed, this reaction afforded a 93% yield of the required **15** (Scheme 3). The structure of **15**, at the time assigned by extensive NMR analysis, was verified by completion of the total synthesis of fluostatin C via this intermediate (vide infra).

The steps in the progression of **15** to fluostatin C started with isomerization of the CD junction from cis to trans.[11] This outcome was accomplished through the agency of sodium methoxide in

Scheme 4. Completion of Syntheses of Fluostatins C and E[a]



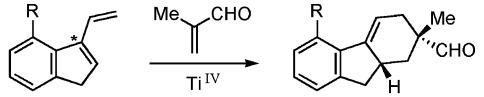
[a] Key: (a) TsOH, benzene, reflux, 2.5 h; (b) SeO_2, dioxane, 90 °C, 2 h; (c) *i*-Pr_2NEt, air, CH_2Cl_2, rt, 2 h, 47% for less polar series, 38% for more polar series, over 3 steps; (d) HF, CH_3CN, rt, 4 days, 85%; (e) 1 N HCl, acetone, rt, 10 min, 90%.

methanol (see **16**).[8c] Reduction of the ketone group with superhydride afforded a 92% yield of the equatorial alcohol which was protected as its triisopropyl silyl derivative (see compound **17**). To complete the setting for nucleophilic epoxidation, compound **17** was treated with PPTS to provide the α,β-unsaturated ketone, **18**. Next, the oxido linkage was introduced in a stereospecific fashion under the conditions shown[12] to afford **19**. During the course of the nucleophilic epoxidation reaction, the trans junction had undergone partial epimerization. Owing to difficulties in separation, the two compounds were submitted concurrently to the next step which involved treatment with osmium tetroxide,[13] as shown. This led to the formation of three products. Apparently, each of the diastereomers of **19** gave rise to a single dihydroxylation product (see **20**). In addition, there was also obtained an over-oxidation product shown as ketone **21** (stereochemistry of tertiary alcohol not formally assigned). Oxidation of the diol mixture with TPAP, as shown, afforded the previously obtained **21a** as well as a new hydroxylketone shown as **21b**. Compounds **20** and **21**, whose relative configurations were not rigorously assigned, were separable and were advanced individually wherein the two arms converged at the stage where the stereochemical distinctions were no longer present in the molecule (see compound **24**; Scheme 4).

The transformations, conducted under the same conditions for both series (i.e., starting with **21a** or **21b**), consisted of (i) dehydration of the C_{6a} alcohol concurrently with deprotection of the C_7 phenolic function (see **22a,b**), (ii) benzylic (and allylic) oxidation (see **23a,b**),[14] and (iii) dehydrogenation−tautomerization with Hünig's base in the presence of air (see convergence product **24**). Cleavage of the TIPS blocking group served to convert **24** to fluostatin C (**1**). It was noted that the NMR spectra of the post-chromatography, fully synthetic fluostatin C were variable and the color of the seemingly pure eluates ranged between orange and purple even following successive attempts at purification. We wondered whether the two phenolic functions at carbons 6 and 7 manifest variable levels (and perhaps sites) of deprotonation with attendant intramolecular stabilization of the monophenoxides through hydrogen bonding. In support of this surmise, it was found that treatment of the fully synthetic fluostatin C (in acetone-d_6) with a trace of trifluoroacetic acid led to a solution with a consistently orange color, which provided reproducible NMR spectra. We received a sample of impure fluostatin C from Professor H.P. Fiedler which was subjected to chromatographic purification. When the stable ^1H spectra of the natural and total synthesis derived fluostatins were measured (in the presence of TFA), they were identical.

Our next goal was the synthesis of fluostatin E (**25**). Treatment of fully synthetic fluostatin C with aqueous HCl afforded the chlorohydrin. In this case, there was no authentic sample of natural

Scheme 5. Diels−Alder Reactions with Methacrolein



5 R = H
6 R = OMOM

26 R = H
27 R = OMOM

product **25** available. However, the very close correspondence in the high-field ^{1}H and ^{13}C NMR of our synthetic material with data tabulated in the published report on fluostatin E, as well as our independent spectral analysis, strongly suggests that the fully synthetic chlorohydrin does indeed correspond to fluostatin E. This finding, perhaps surprising at first glance, is actually precedented.[15]

With the main fluostatin total synthesis goals accomplished, we revisited the remarkable specificities of the regio-alignments which were displayed in the course of this program. Thus, the results in the cycloadditions of **5** with **11** under Lewis acid catalysis (In^{III})[9] suggested that the "2-aryl" group governs the sense of cycloaddition with the classical α,β-unsaturated carbonyl type of dienophile. Moreover, in the Corey example under titanium^{IV} mediation,[8c] the ketonic function of quinoneketal governs the sense of regiochemistry. Thus it seems surprising that vinylindenes **5** as well as **6** line up with **7** such that the 1-methylene group of the local butadiene rather than the 2-aryl appears to be dominant. We wondered whether the apparent anomaly might reflect different directing tendencies of the two different Lewis acid (Ti^{IV} vs In^{III}) systems. However, the cycloadditions of **5** and **6** with methacrolein (Scheme 5) in the context of the Mikami system cleanly afford **26** and **27**, again suggesting orientational control by the 2-aryl function. Yet with each of the dienophilic quinoneketal cases (see **5** + **7**, **6** + **7**, and **6** + **8**), control in the vinylindene seems to be manifested by the 1-methylene group.[16] In principle, it could be argued in the quinoneketals that the governing group on the dienophile is actually the ketal, following the precedent of Gassman with simple α,β-unsaturated ketals.[17] However, the important Corey precedents (see for instance *trans*-piperylene and **7**) teach away from such an interpretation. In summary, dienophiles **5** and **6** behave consistently with well-understood dienes. Similarly, dienes **7** and **8** behave as expected with "standard" dienophiles. Yet the cycloadditions of **5** and **6** with **7** and **8** are anomalous. In essence, the regiopreferences of at least these dienes and dienophiles are not a fixed property of each one component of the cycloaddition but are contingent on one another (i.e., "contextual").

Obviously, there are various ad hoc theories that can be summoned to explain these observations. Still we find the high regiospecificity of each of the seemingly contradicting modalities remarkable. In the future, we hope to sort out the underlying issues of context. It may be that context associated specificities reflect differing steric compatibilities. We hope to explore such issues in the context of a broader computational level exploration. What is clear is the continuing power of well-designed Diels−Alder reactions in enabling well-directed thrusts at complex bioactive targets (cf. **1** and **25**). Apparently, there remain ever more subtle messages to students of the venerable Diels−Alder reaction.

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Supporting Information Available: Experimental procedures, compound characterization data (PDF), and X-ray structure data for compound **14** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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