Enantioselective Synthesis of the Elaiophylin Aglycon

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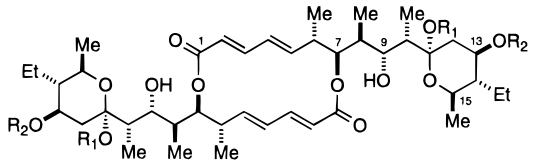
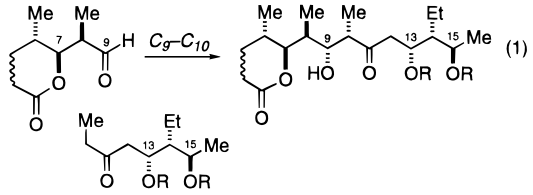
Elaiophylin (**1**) was isolated in 1959 by Arcamone and co-workers from cultures of *Streptomyces melanosporus*.[1] Subsequently, this natural product has also been obtained from other strains of *Streptomyces*.[2] Structure elucidation of **1**, including assignment of absolute stereochemistry, was based on chemical degradation,[3] NMR studies,[4] and ultimately X-ray crystallographic analysis.[5] Isolation and characterization of the elaiophylin aglycon, elaiolide (**2**), was accomplished by Zeeck and Bindseil in 1993 through deglycosylation of **1**.[6]



Elaiophylin (**1**) $R_1 = H$, R_2 = 2-deoxy-L-fucose
Elaiolide (**2**) $R_1 = R_2 = H$
11,13,11′,13′-Tetra-*O*-methylelaiolide (**3**) $R_1 = R_2 = Me$

As a result of its structural complexity and potent biological activity,[7] elaiophylin has been a target of considerable synthetic interest. The first synthesis of elaiophylin was accomplished by Kinoshita and co-workers in 1986.[8] In the previous year, Seebach and co-workers reported the synthesis of an aglycon derivative originally obtained from the acidic methanolysis of elaiophylin,[9] which was later identified as 11,13,11′,13′-tetra-*O*-methylelaiolide (**3**).[6] Several other studies directed toward the synthesis of the elaiophylin framework have also been published.[10,11] The common fragment coupling strategy in the majority of these syntheses has been the double stereodifferentiating aldol bond construction of the C_9-C_{10} bond (eq 1).[11] This aldol assemblage strategy



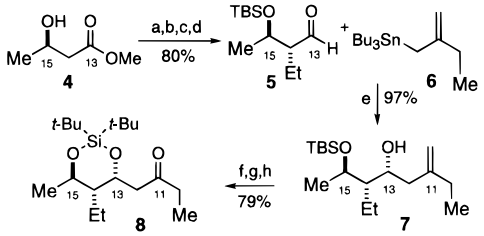
(1)

carries the inherent liability that any lack of selectivity in the aldol process is magnified over two reaction sites, producing a complex mixture of isomers. In both the Kinoshita and Seebach syntheses, this problem resulted in isolation of the desired aldol adduct as the minor product diastereomer in low yield.

Recent studies from this laboratory concerned with the synthesis of bafilomycin A_1 have revealed a strategy for rendering these types of aldol bond constructions highly diastereoselective.[12] In this investigation, it was found that high aldol diastereoselectivity could be obtained by restricting the conformational flexibility of the ketone through the use of a linking cyclic protecting group for the C_{13} and C_{15} hydroxyl groups in conjunction with the use of an electronically altered phenylchloroboryl enolate.[13] An application of this successful strategy to the synthesis of elaiolide (**2**) is described below.

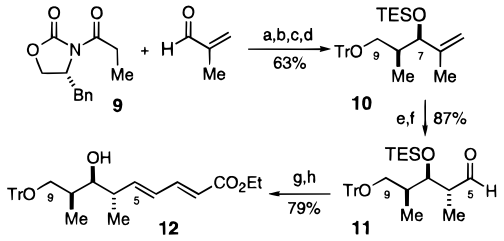
Synthesis of ethyl ketone **8** began with the α-ethylation of **4** according to the Seebach procedure[9a] to afford the

Scheme 1[a]



[a] Key: (a) LDA, THF; EtI, −78 °C; (b) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C; (c) DIBAl-H, CH_2Cl_2, −78 to −40 °C; (d) oxalyl chloride, DMSO, CH_2Cl_2; Et_3N, −78 °C; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (f) TBAF, THF, 25 °C; (g) 2,6-lutidine, $(t\text{-Bu})_2Si(OTf)_2$, CH_2Cl_2, 0 °C; (h) O_3, 3:1 CH_2Cl_2/MeOH, −78 °C; Me_2S.

Scheme 2[a]



[a] Key: (a) *n*-Bu_2BOTf, Et_3N, 0 °C; methacrolein, CH_2Cl_2, −78 °C; H_2O_2; (b) 2,6-lutidine, TESOTf, CH_2Cl_2, 0 °C; (c) $LiBH_4$, Et_2O, H_2O, 25 °C; (d) TrCl, Et_3N, DMAP, CH_2Cl_2; (e) 9-BBN dimer, THF, 0 °C; H_2O_2; (f) oxalyl chloride, DMSO, CH_2Cl_2; Et_3N, −78 °C; (g) LiHMDS, triethyl 4-phosphonocrotonate, THF, −78 °C; **11**; (h) HF·pyr., THF, 0 °C.

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(10) (a) Wakamatsu, T.; Nakamura, H.; Nara, E.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 3895. (b) Wakamatsu, T.; Yamada, S.; Nakamura, H.; Ban, Y. *Heterocycles* **1987**, *25*, 43. (c) Formal total synthesis of elaiophylin: Nakamura, H.; Arata, K., Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2435.
(11) A notable exception is the approach of Ziegler and co-workers, which involves the design of a fully elaborated monomeric fragment suitable for dimerization: Ziegler, F. E.; Tung, J. S. *J. Org. Chem.* **1991**, *56*, 6530.
(12) (a) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871. (b) Calter, M. A. Ph.D. Dissertation, Harvard University, 1993. (c) This same aldol reaction has been subsequently employed by Toshima and co-workers in their synthesis of bafilomycin A_1. Toshima, K.; Yamaguchi, H.; Jyojima, T.; Noguchi, Y.; Nakata, M.; Matsumura, S. *Tetrahedron Lett.* **1996**, *37*, 1073.

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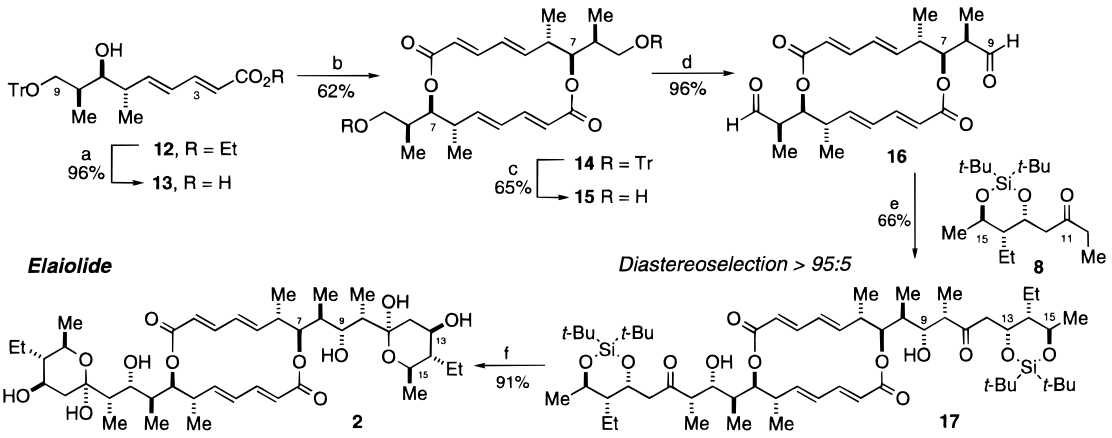
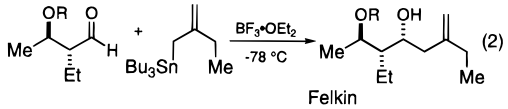
Scheme 3[a]



[a] Key: (a) 1 N KOH, THF, MeOH, 25 °C; (b) 2,4,6-trichlorobenzoyl chloride, toluene, Et_3N; DMAP, 25 °C; (c) CSA, MeOH, THF, 25 °C; (d) oxalyl chloride, DMSO, CH_2Cl_2; Et_3N, −78 °C; (e) $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; (f) HF·pyr, pyridine, THF, H_2O.

desired *anti* diastereomer in 82% yield (Scheme 1). Silylation was followed by reduction with diisobutylaluminum hydride and Swern oxidation to produce aldehyde **5** in excellent overall yield. The requisite ketone was constructed by successive Lewis acid-promoted addition of allylstannane **6**[14] to aldehyde **5**, reconfiguration of oxygen protecting groups, and subsequent ozonolysis of the derived homoallylic alcohol **7** to afford ethyl ketone **8** in 74% overall yield for the four steps.

The diastereoselectivity of the preceding allylstannane addition was found to be sensitive to the nature of the protecting group on the β-oxygen in aldehyde **5** as the data in eq 2 document.[15] The correlation between Felkin



R	Solvent	Felkin selectivity
p-$MeOC_6H_4CH_2$-	CH_2Cl_2	60:40
Et_3Si-	CH_2Cl_2	84:16
Et_3Si-	toluene	79:21
t-$BuMe_2Si$-	CH_2Cl_2	92:8

selectivity and the size of the protecting group can be rationalized by the increase in steric discrimination between the α-ethyl substituent and the α-alkoxyethyl substituent. Use of the *tert*-butyldimethylsilyl protecting group resulted in a 92:8 mixture of diastereomers from which the desired Felkin isomer **7** was isolated in 89% yield.

The synthesis of a monomeric subunit of dialdehyde **16** began with the addition of methacrolein to the boron enolate of carboximide **9**,[16] establishing two of the three requisite stereocenters in good yield (Scheme 2). Silyl protection of the hydroxyl group was followed by consecutive reductive cleavage of the auxiliary and trityl protection to afford the differentially protected diol **10**. Diastereoselective hydroboration[17] of **10** with 9-BBN afforded a single alcohol isomer was oxidized to the aldehyde under Swern conditions. Horner−Wadsworth−Emmons olefination following the Roush procedure[18] provided the requisite dienoate as a 92:8 mixture of *E,E*:*Z,E* isomers[19] from which the major diastereomer was isolated in 85% yield. Selective removal of the silyl protecting group was accomplished with HF·pyridine at 0 °C to reveal alcohol **12** in 93% yield.

At this point, the synthesis intersected with the Seebach route to the dialdehyde fragment. Scheme 3 illustrates the four-step sequence, in which dienoate **12** was converted to dialdehyde **16** according to the published procedure.[9a,20] The cyclodimerization of hydroxy acid **13** was operationally simplified through use of the Yonemitsu modification[21] to Yamaguchi's macrocyclization methodology.

In the crucial aldol coupling, dialdehyde **16** was treated with 3 equiv of the chlorophenylboryl enolate[12,22] of **8** to provide a 66% yield of bis-aldol adduct **17** as the only detectable product isomer.[19] We feel that the enhanced rigidity of the enolate and the modified boron enolate both contribute to the enhanced diastereoselectivity of this reaction. Consecutive deprotection of the di-*tert*-butylsilylene protecting groups and subsequent cyclization to the bis-lactol was accomplished with HF·pyridine containing 1 equiv of water, completing the synthesis of elaiolide (**2**) in 91% yield as a white crystalline solid. All spectral data obtained from the synthetic material was in complete agreement with reported values (^1H NMR, ^{13}C NMR, IR, TLC, $[\alpha]_D$, HRMS).[6]

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Supporting Information Available: Experimental procedures and spectral data for all compounds are provided (30 pages).

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(13) Toshima and co-workers later found that while using the di-*tert*-butylsilylene, enolization with Bu_2BOTf and i-Pr_2NEt provided a 3:1 mixture of isomers, favoring the desired anti-Felkin, syn aldol adduct (see ref 12c).

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(19) Determined by ^1H NMR analysis of the unpurified reaction mixture.

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(22) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729. We have found that optimal enolization conditions involve the addition of $PhBCl_2$ (2.0 equiv) to the ketonic substrate (CH_2Cl_2) followed by the addition of Et*N*(i-Pr)$_2$ (2.8 equiv) and subsequent enolization (30 min, −78 °C; 30 min, 0 °C). Subsequent aldol reactions were performed at −78 °C.