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Total Synthesis of Elaiolide Using a Copper(I)-Promoted Stille Cyclodimerization Reaction

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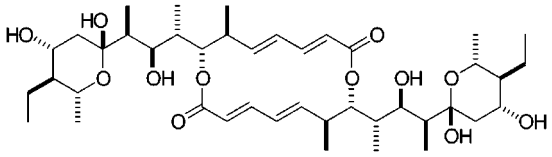
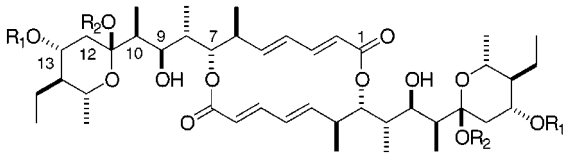
ABSTRACT



Elaiolide (**2**)

The 16-membered macrodiolide elaiolide (2) has been prepared in 20 steps from the ketone (*S*)-8 in 9.3% overall yield with a diastereoselectivity of 76%. Key steps included the copper(I) thiophene-2-carboxylate promoted cyclodimerization of the vinyl stannane 3 to give the C_2-symmetric macrocycle 16 in 80% yield and the two-directional aldol coupling of the macrocyclic diketone 17 with aldehyde 5. Most of the stereocenters in the macrocyclic precursor 3 were constructed using boron aldol methodology developed in this laboratory.

Elaiophylin (**1**), first isolated from cultures of *Streptomyces melanosporus* by Arcamone *et al.*[1a] and shortly thereafter from a related microorganism by Arai,[1b] is a 16-membered macrolide which displays antimicrobial activity against several strains of Gram-positive bacteria.[2a−c] Elaiophylin also has anthelmintic activity against *Trichonomonas vaginalis*,[3a] as well as inhibitory activity against K^+-dependent adenosine triphosphatases.[2d] The C_2-symmetric macrodiolide structure was determined by chemical degradation[3a−c] and spectroscopic methods,[3d] with the full absolute configuration being elucidated by X-ray crystallographic analysis.[3e,f] Elaiophylin belongs to a family of structurally related compounds, all having similar stereochemistry in the secoacid moiety. These include several other 16- and 18-membered monomeric macrolides, in particular the bafilomycins and concanamycins.[4] The elaiophylin aglycon elaiolide (**2**) has been obtained through acidic deglycosylation of **1**.[5]



Elaiophylin (**1**) R_1 = 2-deoxy-α-L-fucose, R_2 = H
Elaiolide (**2**) $R_1 = R_2 = H$

Previous synthetic efforts[6] directed toward elaiophylin (**1**) have constructed the macrodiolide core by a conventional esterification/lactonization strategy. This has generally been followed by a double aldol coupling between a macrocyclic dialdehyde and an ethyl ketone to form the C_9-C_{10} bond, which was employed in the total synthesis by Kinoshita *et al.*[6a,b] In the same manner, various aglycon derivatives[6c−h]

(1) (a) Arcamone, F. M.; Bertazzoli, C.; Ghione, M.; Scotti, T. G. *G. Microbiol*. **1959**, *7*, 207. (b) Azalomycin B, as reported by Arai, is identical with elaiophylin: Arai, M. *J. Antibiot., Ser. A* **1960**, *13*, 46, 51.

(2) (a) Hammann, P.; Kretzschmar, G. *Tetrahedron* **1990**, *46*, 5603. (b) Hammann, P.; Kretzschmar, G.; Seibert, G, *J. Antibiot.* **1990**, *43*, 1431. (c) Liu, C.-M.; Jensen, L.; Westley, J. W.; Siegel, D. *J. Antibiot.* **1993**, *46*, 350. (d) Drose, S.; Bindseil, K. U.; Bowman, E. J.; Siebers, A.; Zeek, A.; Altendorf, K. *Biochemistry* **1993**, *32*, 3902.

(3) (a) Takahashi, S.; Arai, M.; Ohki, E. *Chem. Pharm. Bull.* **1967**, *15*, 1651. (b) Takahashi, S.; Kurabayashi, M.; Ohki, E. *Chem. Pharm. Bull.* **1967**, *15*, 1657. (c) Takahashi, S.; Ohki, E. *Chem. Pharm. Bull.* **1967**, *15*, 1726. (d) Kaiser, H.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 407. (e) Neupert-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 262. (f) Ley, S. V.; Neuhaus, D.; Williams, D. J. *Tetrahedron Lett.* **1982**, *23*, 1207.

(4) Omura, S. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 510−546.

(5) Bindseil, K. U.; Zeeck, A. *J. Org. Chem.* **1993**, *58*, 5487.

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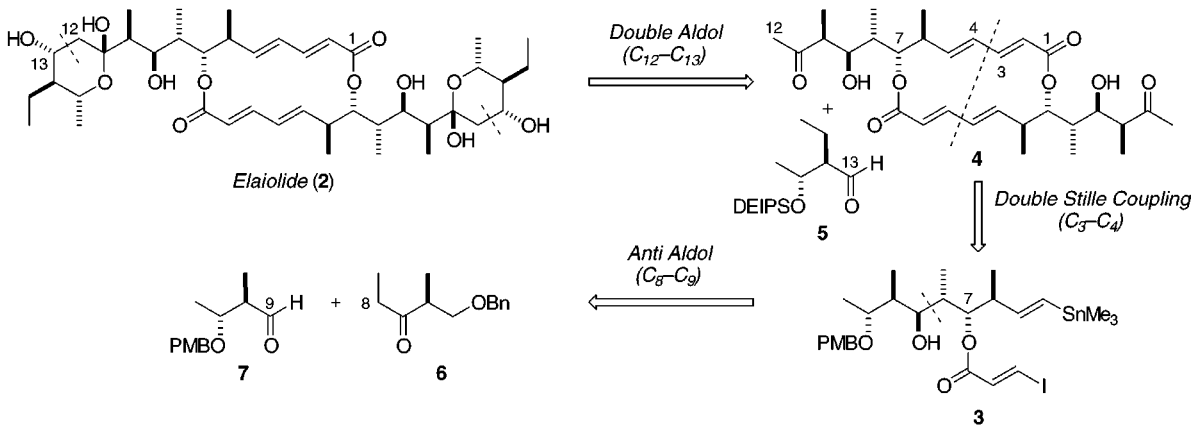
Scheme 1

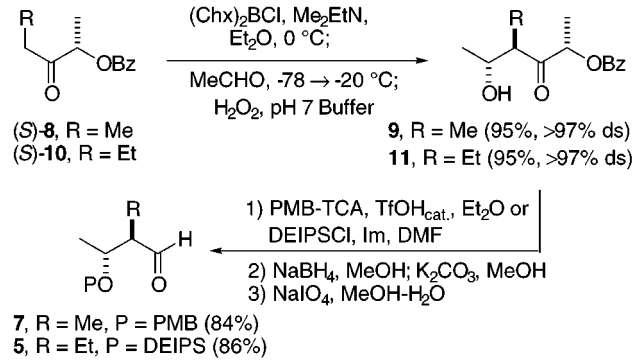


have been synthesized, including a derivative originally obtained from the acidic methanolysis of elaiophylin.[6c,d] Recently, an elegant synthesis of elaiolide (**2**) was reported by Evans and Fitch,[6h] in which a high level of diastereoselectivity was achieved in the C_9-C_{10} aldol coupling step described previously. As part of our studies in macrolide synthesis,[7] we devised an alternative strategy to synthesize elaiolide (**2**) which did not rely on a conventional macrolactonization step to construct the 16-membered ring.

We envisaged[8] a novel cyclodimerization process, involving a Stille cross-coupling reaction of vinylstannane **3**, to form the $C_3-C_4/C_{3'}-C_{4'}$ bonds while simultaneously constructing the macrocyclic core (Scheme 1). A double aldol coupling between the macrocyclic methyl ketone **4** and aldehyde **5** would then be required to form the $C_{12}-C_{13}/C_{12'}-C_{13'}$ bonds. A further aldol disconnection at C_8-C_9 in the monomeric unit **3** leads to ethyl ketone **6** and aldehyde **7**. We now report a novel synthesis of elaiolide based on this cyclodimerization strategy, which further demonstrates the use of our chiral ketone methodology for the controlled introduction of key stereocenters.

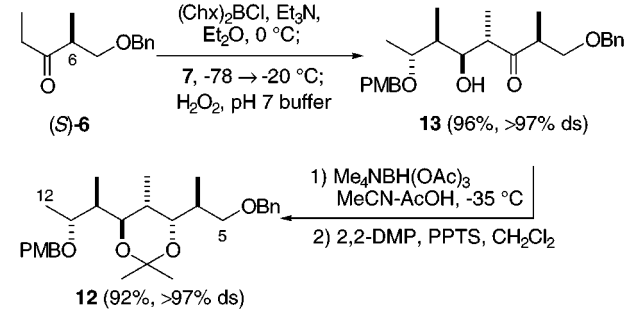
Using our standard conditions, a boron-mediated *anti* aldol reaction between the lactate-derived ethyl ketone (*S*)-**8**[9] and acetaldehyde proceeded with high diastereoselectivity (>97% ds) to give adduct **9** in 95% yield (Scheme 2). The β-hydroxy ketone **9** was then converted into aldehyde **7** in 84% yield, via a three-step sequence of PMB protection, ketone reduction/ester hydrolysis, and finally oxidative cleavage. The aldehyde **5** was prepared from the propyl ketone (*S*)-**10**[9] and acetaldehyde in a similar fashion, where the β-hydroxyl group in intermediate **11** was protected as a diethylisopropylsilyl (DEIPS)[6b] ether, in 86% overall yield.

Scheme 2



As shown in Scheme 3, the C_5-C_{12} fragment **12** of elaiolide was prepared from the ethyl ketone (*S*)-**6**,[10] which has been used extensively as a dipropionate building block for the expedient synthesis of a range of polypropionate natural products.[11] Using our standard conditions,[10] a boron-

Scheme 3



(6) (a) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1986**, *27*, 4741. (b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369. (c) Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Lawson, K.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *J. Am. Chem. Soc.* **1985**, *107*, 5292. (d) Seebach, D.; Chow, H.-F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *Liebigs Ann. Chem.* **1986**, 1281. (e) Wakamatsu, T.; Nakamura, H.; Nara, E.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 3895. (f) Wakamatsu, T.; Yamada, S.; Nakamura, H.; Ban, Y. *Heterocycles* **1987**, *25*, 43. (g) Formal total synthesis of elaiophylin: Nakamura, H.; Arata, K.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2435. (h) Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454. (i) Ziegler, F. E.; Tung, J. S. *J. Org. Chem.* **1991**, *56*, 6530.

(7) For reviews on macrolide synthesis, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (b) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 127−198.

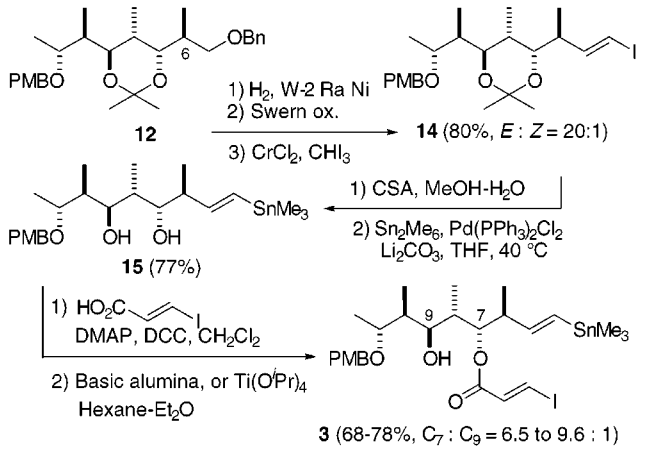
(8) For a model study for this cyclodimerization strategy, see: Paterson, I.; Man, J. *Tetrahedron Lett.* **1997**, *38*, 695.

(9) Paterson, I.; Wallace, D.; Cowden, C. *Synthesis* **1998**, 639.

mediated *anti* aldol reaction between (*S*)-**6** and aldehyde **7** proceeded with high diastereoselectivity (>97% ds) to give adduct **13** in 96% yield. This was followed by an *anti* reduction[12] using tetramethylammonium triacetoxyborohydride, which afforded, after hydroxyl protection, a 92% yield of acetonide **12** with a similar level of diastereoselectivity. In this way, the *anti-syn-anti-syn* C_5-C_{11} stereopentad was efficiently established.

The synthesis of the cyclodimerization substrate **3** (Scheme 4) began with the conversion of the benzyl ether functionality

Scheme 4

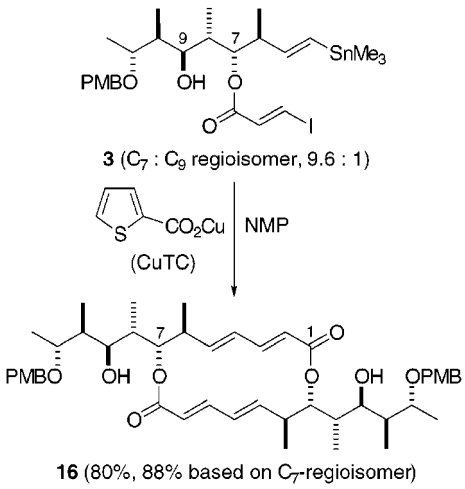


to the (*E*)-alkenyl iodide **14** in 80% overall yield. This was achieved via a three-step sequence of Raney nickel selective deprotection,[13] Swern oxidation,[14] and Takai olefination.[15] The Takai reaction was performed with CHI_3 and $CrCl_2$ in THF−dioxane (1:1) and produced a 20:1 ratio of *E* to *Z* isomers. Acetonide hydrolysis followed by a Pd(0)-catalyzed iodine−tin exchange,[16] using $(Me_3Sn)_2$ in the presence of Li_2CO_3, then gave the desired vinylstannane **15** in 77% yield. Esterification[17,18] of diol **15** with (*E*)-3-iodopropenoic acid,[19] using DCC and DMAP in CH_2Cl_2 at −20 °C, then provided an inseparable 1:5 mixture[20] of **3** and its C_9 regioisomer.[21]

Isomerization of this mixture was achieved under mild conditions using basic alumina or $Ti(O^iPr)_4$[22] to provide the desired C_3 regioisomer **3** in 78% yield (6.5:1) or 68% yield (9.6:1) from **15**, respectively.

In our earlier model study,[8] a Cu(I)-promoted Stille cross-coupling[23] reaction was successfully used to prepare a truncated version of the macrocyclic core of elaiolide (**2**), where the two (*E*)-alkenes precluded cyclization to form an eight-membered ring. The key cyclodimerization reaction was performed on the vinylstannane **3** with copper(I) thiophene-2-carboxylate (CuTC), a new Cu(I) reagent introduced by Allred and Liebeskind[24] to promote rapid Stille cross-coupling reactions under mild conditions in the absence of Pd catalysis. Thus, treatment of a 0.01 M solution of monomer **3**, in *N*-methylpyrrolidinone with CuTC (10 equiv) at room temperature for 15 min, produced the required 16-membered macrocycle **16** as a white crystalline solid in 80% yield (88% based on the C_7 regioisomer), accompanied by traces of other macrocycles (Scheme 5). The reaction led to

Scheme 5



clean formation of **16** without the isolation of the open-chain intermediate, suggesting the occurrence of a rapid Cu(I)-mediated cyclization without competing oligomerization. In contrast, under more concentrated reaction conditions (*c* 0.2 M), the monomer **3** was converted into a mixture of three major macrocycles. Here, the desired dimer **16** was obtained in 42% yield, along with 34% of the C_7 macrotrimer and 13% of the C_9 macrotrimer.[25]

(10) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.

(11) Reviews: (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (b) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821.

(12) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(13) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(14) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(15) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(16) (a) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49. (b) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Org. Chem.* **1996**, *61*, 685. (c) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray. C. K. *J. Org. Chem.* **1986**, *51*, 277.

(17) Steric hindrance at the C_7 position when C_9 is protected prevents direct esterification, and an esterification on the diol **15** is thus required.

(18) (a) Boyce, R. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 3501. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (c) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(19) (*E*)-3-Iodopropenoic acid was prepared via a modification of a procedure described by: Zoller, T.; Ugen, D. *Tetrahedron Lett.* **1998**, *39*, 6719. See the Supporting Information for details.

(20) Determined by 500 MHz ^{1}H NMR of the crude reaction mixture.

(21) Under these kinetic conditions, reaction at the C_9-OH was greatly preferred over that at the presumably more hindered C_7-OH.

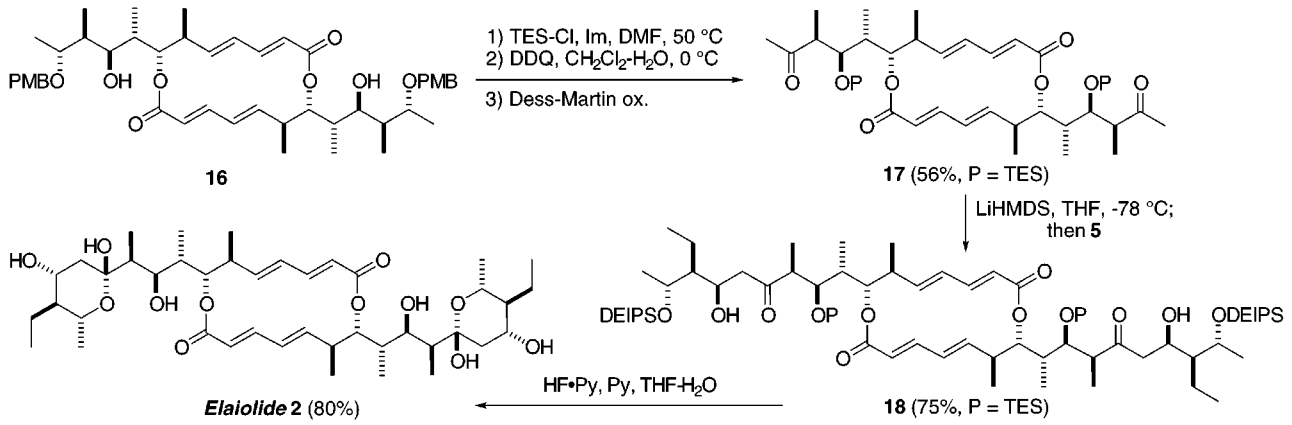
(22) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(23) Reviews: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803. (c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.

(24) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

(25) The structures of these macrocycles were confirmed by FAB MS.

Scheme 6



The macrodiolide **16** was converted into the bis(methyl ketone) **17** by a three-step sequence of TES protection, PMB deprotection, and Dess−Martin oxidation[26] in 56% overall yield (Scheme 6). The final key step of the synthesis of elaiolide required a double aldol coupling between the macrocyclic diketone **17** and the chiral aldehyde **5**. Obtaining a high level of Felkin−Anh selectivity from the aldehyde component in this reaction was crucial in order to set up the 13,14-*syn* relationship.[27] The diketone **17** was enolized with LiHMDS at −78 °C for 1 h, followed by addition of an excess of aldehyde **5**. This led to isolation of the desired adduct **18** in 75% yield along with 15% of a mixture of diastereoisomers. We attribute the good diastereoselectivity of this two directional extension (*ca*. 90% ds for each side) to matching of Felkin−Anh control from the aldehyde with the facial bias of the macrocyclic enolate. Finally, global deprotection[28] using HF·pyridine−THF−H_2O[6h] was accompanied by concomitant cyclization to form the bis(hemiacetal), leading to isolation of elaiolide (**2**) in 80% yield. The ^{1}H NMR data of the product corresponded well with that of material obtained by acid hydrolysis of elaiophylin.[29] All spectral data (^{1}H and ^{13}C NMR, IR, MS, $[\alpha]_D$) obtained from the synthetic material were in agreement with reported values.[5,6h]

In summary, a novel total synthesis of elaiolide (**2**) has been completed using the copper(I)-mediated cyclodimerization, 2 × **3** → **16**. This route demonstrates the power of the Liebeskind modification of the Stille cross-coupling reaction in the synthesis of structurally complex macrocycles.

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Supporting Information Available: Text giving experimental procedures and tables and figures giving complete spectroscopic data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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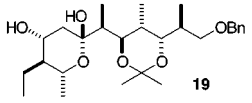
(26) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(27) Originally this aldol was attempted using Mukaiyama conditions, involving treatment of the ketone **17** with TMSCl−Et_3N and LiHMDS to form the silyl enol ether and then addition of **5** and BF_3 etherate. These conditions (Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed.*, in press) provided a 7:1 ratio in favor of the desired aldol in model studies, producing hemiacetal **19** on deprotection. In contrast, with diketone **17** only recovered starting ketone and aldehyde were isolated.



(28) Using TASF, only 35% of elaiolide was obtained, accompanied by an eliminated compound which was also formed in the degradation of elaiophylin: Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, C. D.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

(29) (a) Elaiophylin, kindly provided by Professor S. V. Ley, was degraded according to the procedure described by Zeeck.[5] (b) See the Supporting Information for tabulated ^{1}H and ^{13}C NMR data for elaiolide with comparative data previously reported.