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

Ian Paterson,* Henry-Georges Lombart, and Charlotte Allerton

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

ip100@cus.cam.ac.uk

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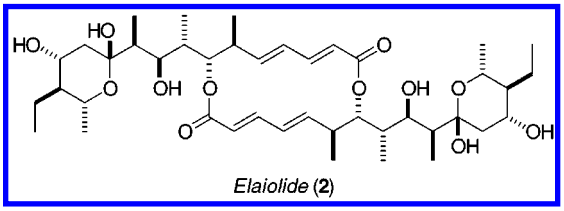
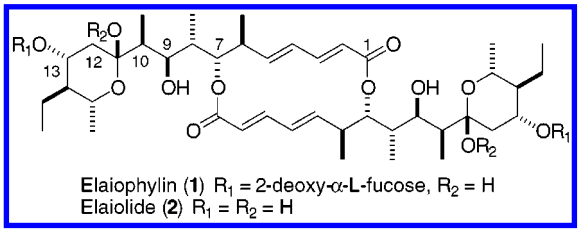
ABSTRACT



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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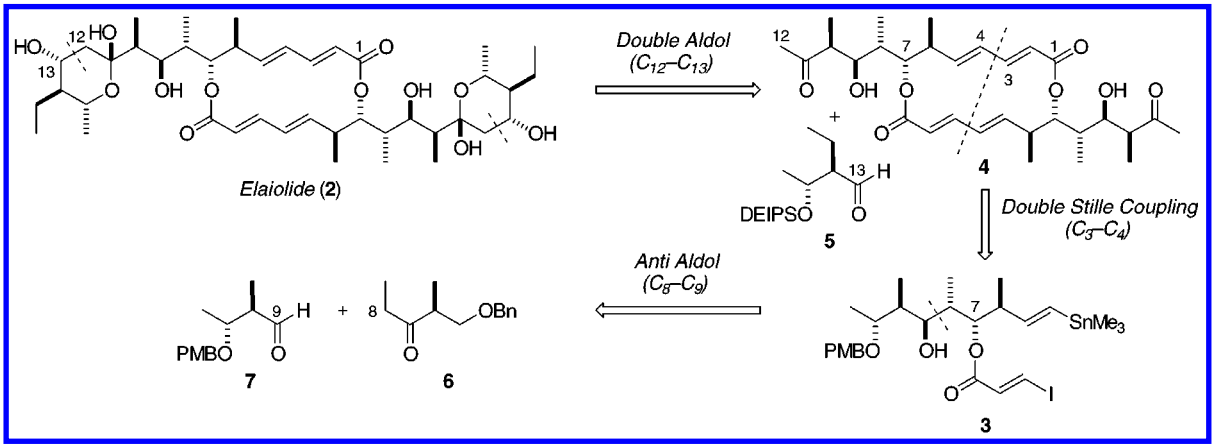
Scheme 1

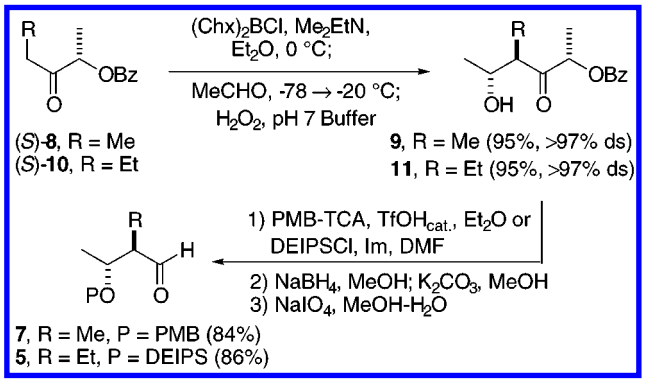


have been synthesized, including a derivative originally obtained from the acidic methanolysis of elaiophylin.[6c,d] Recently, an elegant synthesis of elaiolide (**2**) was reported by Evans and Fitch,[6h] in which a high level of diastereoselectivity was achieved in the C_9-C_{10} aldol coupling step 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.

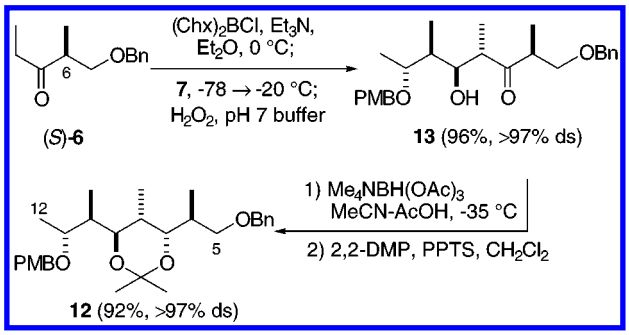
Using our standard conditions, a boron-mediated *anti* aldol reaction between the lactate-derived ethyl ketone (*S*)-**8**[9] and acetaldehyde proceeded with high diastereoselectivity (>97% ds) to give adduct **9** in 95% yield (Scheme 2). The β-hydroxy ketone **9** was then converted into aldehyde **7** 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.

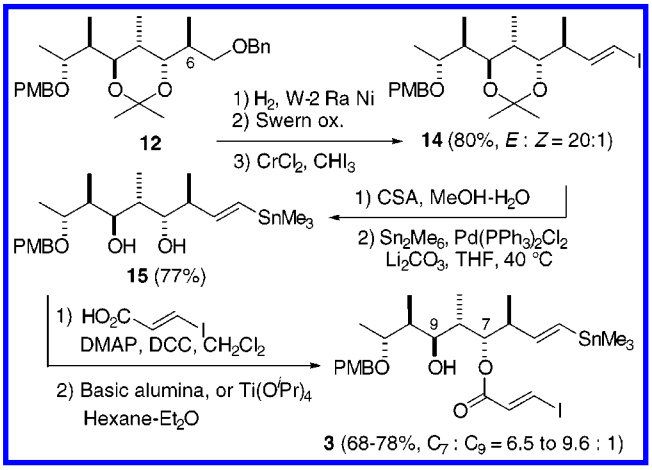
(8) For a model study for this cyclodimerization strategy, see: Paterson, I.; Man, J. *Tetrahedron Lett.* **1997**, *38*, 695.

(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

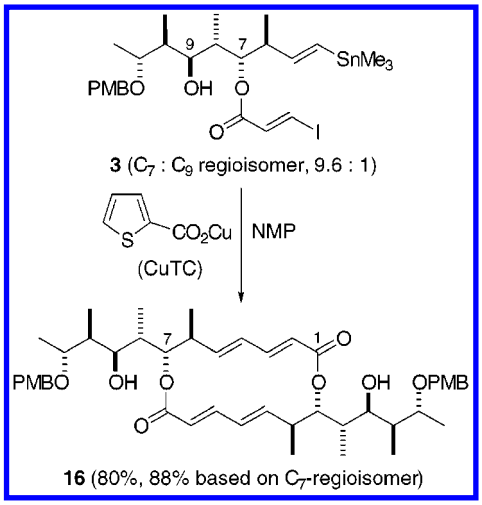


to the (*E*)-alkenyl iodide **14** in 80% overall yield. This was achieved via a three-step sequence of Raney nickel selective deprotection,[13] Swern oxidation,[14] and Takai olefination.[15] The Takai reaction was performed with CHI_3 and $CrCl_2$ in THF−dioxane (1:1) and produced a 20:1 ratio of *E* 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.

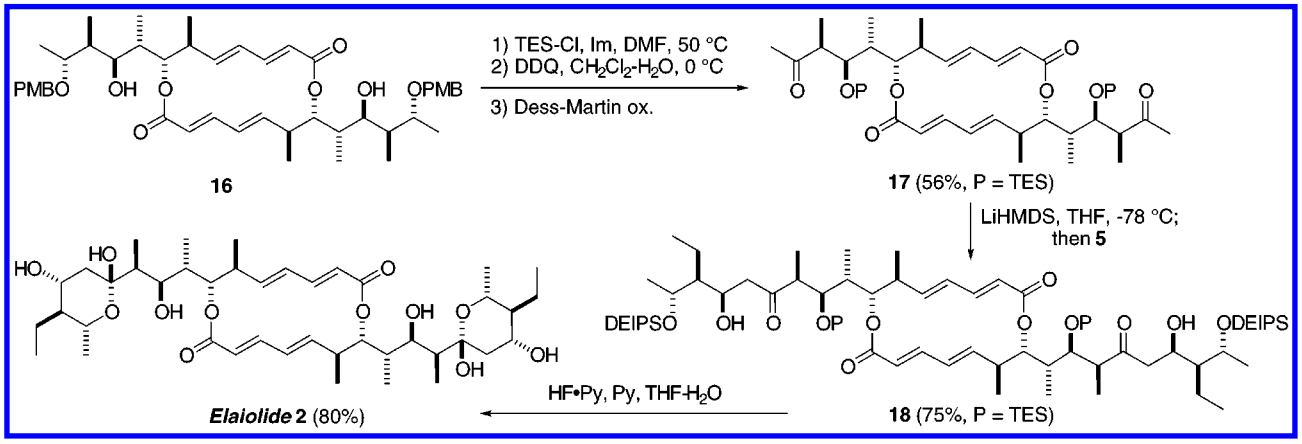
(22) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(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.

Acknowledgment. We thank the EPSRC (Grant No. L41646) and Pfizer Central Research for support and Robert Davies (Cambridge) and Dr. Mark Gardner (Pfizer) for helpful discussions.

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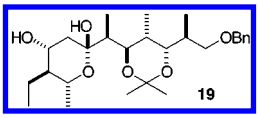
(26) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(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.