Total Synthesis of (−)-Ebelactone A and B[1]

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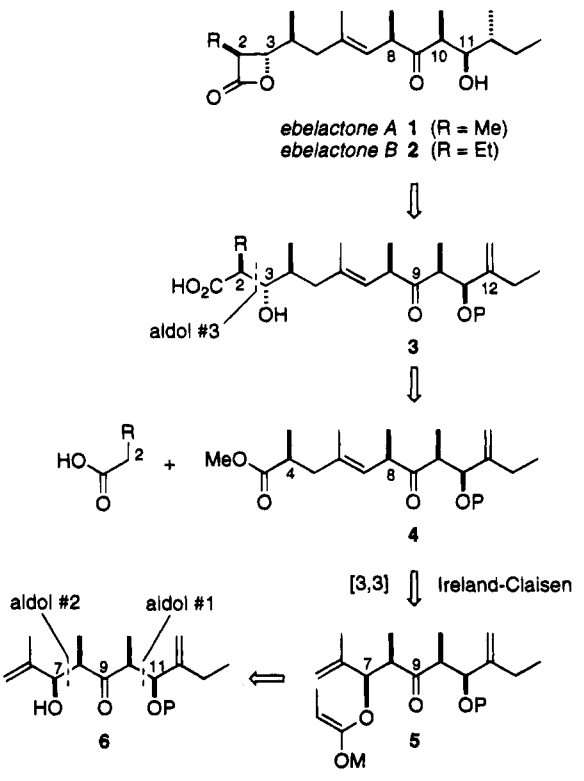
The β-lactone enzyme inhibitors (−)-ebelactone A (**1**) and (−)-ebelactone B (**2**) have been prepared in 12 steps from diethyl ketone (4 and 3% overall yield, respectively). The synthetic strategy adopted for the ebelactones demonstrates the use of reagent- and substrate-derived stereocontrol and requires the minimal use of protecting groups. The stereocenters at C_2, C_3, C_8, C_{10}, and C_{11} were constructed using boron aldol methodology. An asymmetric *syn* aldol addition of diethyl ketone to 2-ethylacrolein gave adduct **8** in 86% ee, followed by a diastereoselective *syn* aldol reaction to give **11**. Subsequently, an Ireland–Claisen rearrangement was used to relay 1,2-*syn* into 1,5-*syn* relative stereochemistry, as in **12** → **14**. In the *anti* aldol construction of the C_2–C_3 bond, the use of either a propionate or butyrate thioester enolate allowed for a divergent approach from aldehyde **17** to both (−)-ebelactone A and B. Several novel analogues of ebelactone A and B were also prepared with inverted stereochemistry at C_2, C_3, or C_{12}.

Introduction

The ebelactones are a small group of β-lactone enzyme inhibitors, isolated from a cultured strain of soil actinomycetes (MG7-G1 related to *Streptomyces aburaviensis*) by the Umezawa group in 1980.[3] The structure of ebelactone A was determined by X-ray crystallography to be as shown in **1** (Scheme 1),[3c] while ebelactone B was proposed from spectroscopic comparisons to be the one-carbon homologue **2**. The ebelactones show structural characteristics in common with the macrolide antibiotics,[4] and biosynthetic studies using [1-^{13}C]-labeled acetate, propionate, and butyrate precursors indicate that they are likewise of polyketide origin.[5]

The β-lactone class of natural products displays a wide range of biological properties,[6–8] which has stimulated considerable interest in their chemistry and synthesis.[9–11] The ebelactones act as potent inhibitors of esterases, lipases, and *N*-formylmethionine aminopeptidases located on the cellular membrane of various kinds of animal cells, and they have been shown to produce enhanced immune responses.[3a] They are also reported to inhibit cutinases produced by fungal pathogens[8] and may have a use as plant protectants.

Scheme 1



The ebelactones present a considerable synthetic challenge, requiring the construction of seven stereocenters and a trisubstituted alkene along a hydrocarbon back-

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(3) (a) Umezawa, H.; Takaaki, A.; Uotani, K.; Hamada, M.; Takeuchi, T.; Takahashi, S. *J. Antibiot.* **1980**, *33*, 1594. (b) Uotani, K.; Naganawa, H.; Kondo, S.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1495. (c) Uotani, K. Ph.D. Thesis, Institute of Microbial Chemistry, Tokyo, Japan.

(4) For a review of macrolide antibiotics, see: *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984.

(5) Uotani, K.; Naganawa, H.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1670.

(6) Esterase and lipase inhibitors. (a) Esterastin: Kondo, S.; Uotani, K.; Miyamoto, M.; Hazato, T.; Naganawa, N.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 797. (b) Valilactone: Kitahara, M.; Asano, M.; Naganawa, H.; Maeda, K.; Hamada, M.; Aoyagi, T.; Umezawa, H.; Iitaka, Y.; Nakamura, H. *J. Antibiot.* **1987**, *40*, 1647. (c) Lipstatin: Wiebel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081. (d) L-659,699: Greenspan, M. D.; Yudkovitz, J. B.; Lo, C.-Y. L.; Chen, J. S.; Alberts, A. W.; Hunt, V. M.; Chang, M. N.; Yang, S. S.; Thompson, K. L.; Chiang, Y.-C. P.; Chabala, J. C.; Monaghan, R. L.; Schwartz, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7488.

(7) Antibiotics and antibacterials. (a) Obafluorin: Wells, J. S.; Trejo, W. H.; Principe, P. A.; Sykes, R. B. *J. Antibiot.* **1984**, *37*, 802. (b) Oxazolomycin: Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073.

(8) Köller, W.; Trail, F.; Parker, D. M. *J. Antibiot.* **1990**, *43*, 734.

(9) For general reviews of the chemistry and synthesis of β-lactones, see: (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441. (b) Searles, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, Chapter 5.13. (c) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 2.2.2.

(10) Paterson, I.; Hulme, A. N. *Tetrahedron Lett.* **1990**, *31*, 7513.

(11) For an interesting synthetic approach to ebelactone A using silicon chemistry, see: Fleming, I. *Pure Appl. Chem.* **1990**, *62*, 1879.

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bone. Furthermore, they possess a potentially acid/base enolizable ketone and a sensitive β-lactone ring. In considering synthetic approaches to the ebelactones,[10,11] we wished to develop a short and flexible route, minimizing the use of protecting groups and oxidation state manipulations, which would also allow for the preparation of novel analogues. We have previously reported the first total synthesis of (±)-ebelactone A,[10] relying on a versatile aldol/Claisen rearrangement strategy. By an extension of this approach, we now describe the first total synthesis of both (−)-ebelactone A and (−)-ebelactone B and detail the synthetic challenges provided by this complex group of β-lactones.

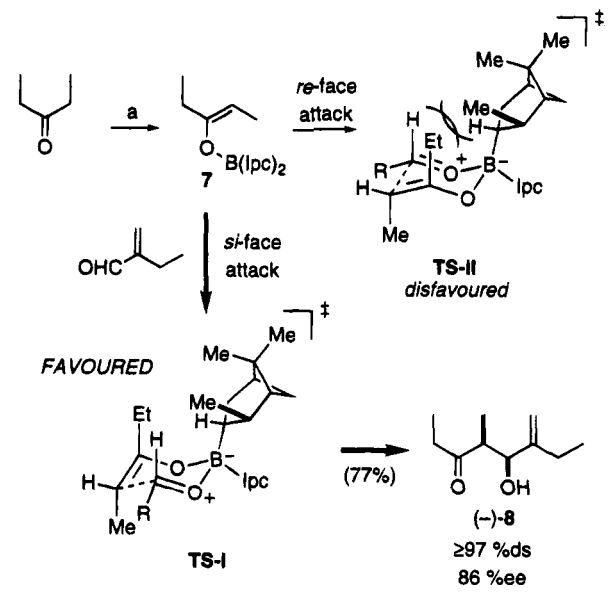
Synthetic Planning

A retrosynthetic analysis for the ebelactones based on aldol/Ireland−Claisen rearrangement chemistry is outlined in Scheme 1. This strategy relies on the rapid and efficient construction of stereocenters at C_2, C_3, C_8, C_{10}, and C_{11}, using aldol methodology,[12] and the final introduction of the C_{12} stereocenter by a hydroxyl-directed hydrogenation. We chose to introduce the sensitive β-lactone ring at the end of the synthesis by closure of the β-hydroxy acids **3** (R = Me for ebelactone A, R = Et for ebelactone B), which should, in turn, be available by an appropriate *anti* aldol reaction with the aldehyde derived from ester **4**. Recognition of the key 1,5-relationship of stereocenters at C_4 and C_8 in **4**, together with the *E*-trisubstituted alkene, suggested an Ireland−Claisen rearrangement[13] on **5**. This would serve to relay 1,2-*syn* into 1,5-*syn* relative stereochemistry[14] and ideally might be performed without protecting the C_9 ketone group. The precursor required for this key [3,3]-rearrangement was the β-hydroxy ketone **6**, which should be available by a tandem aldol coupling of diethyl ketone with two simple enals, 2-ethylacrolein and methacrolein.

Results and Discussion

Synthesis of the C_3−C_{14} Aldehyde 17. From our earlier work on the synthesis of the C_{19}−C_{27} subunit of the ansa chain of rifamycin S,[15] it was expected that the required stereotetrad **6** should be accessible with the correct *all-syn* stereochemistry by boron enolate methodology. This strategy proved highly successful in our earlier racemic synthesis of ebelactone A, where sequential aldol reactions of diethyl ketone with 2-ethylacrolein and methacrolein were performed using *Z*-enol dialkyl borinates with >95% diastereoselectivity in each step.[10] The asymmetric synthesis of the ebelactones now required the use of a chiral enol borinate to set up the absolute, as well as relative, stereochemistry in this first aldol reaction. We chose to make use of our method for enantioselective *syn* aldol reactions of ethyl ketones with aldehydes based on enol diisopinocampheyl borinates[16] (Scheme 2).

Scheme 2[a]



[a] Reagents: (a) (−)-(Ipc)$_2$BOTf, ^{i}Pr$_2$NEt, CH_2Cl_2, −78 °C, 4 h; 2-ethylacrolein, −78 → −20 °C, 17 h; MeOH/pH 7 buffer, H_2O_2, 20 °C, 3 h.

Enolization of diethyl ketone with the chiral boron reagent (−)-diisopinocampheylboron triflate ((−)-Ipc$_2$BOTf)[17] and ^{i}Pr$_2$NEt in CH_2Cl_2 gave the corresponding *Z*-enol diisopinocampheyl borinate **7**, which on addition to 2-ethylacrolein led to a 77% yield of the *syn* aldol adduct **8** with >97% diastereoselectivity. The enantiomeric excess of this β-hydroxy ketone was determined as 86% ee by ^{1}H NMR analysis of the derived MTPA (Mosher) ester,[18] as well as by ^{1}H NMR chiral shift experiments using Eu(hfc)$_3$. By analogy with many other examples,[16] including our asymmetric synthesis of the C_{19}−C_{27} subunit of rifamycin S,[15b] the absolute stereochemistry of β-hydroxy ketone **8** was assigned as 3*S*,4*S*. A rationale for the reagent-induced π-facial selectivity of ketone-derived *Z*-enol diisopinocampheyl borinates has been previously provided by computational studies using aldol transition state modeling.[19] These calculations suggest that transition state **TS-I** is favored over **TS-II**, largely because it minimizes steric interactions between the methyl group of the pseudoaxial Ipc ligand and the ethyl group of the enolate.

The adduct **8** was now made ready for a second aldol reaction on the other side of the carbonyl group (Scheme 3). Protection of the secondary hydroxyl as its *tert*-butyldimethylsilyl (TBS) ether, using *tert*-butyldimeth-

(12) For reviews of the aldol reaction, see: (a) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, p 111. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Wiley-Interscience: New York, 1982; Vol. 13, p 1. (d) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2.

(13) For a recent review of the Ireland−Claisen reaction, see: Pereira, S.; Srebnik, M. *Aldrichim. Acta* **1993**, *26*, 17.

(14) For other examples of this strategy, see: (a) Heathcock, C. H.; Radel, P. A. *J. Org. Chem.* **1986**, *51*, 4322. (b) Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922. (c) Reference 29.

(15) (a) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229. (b) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293.

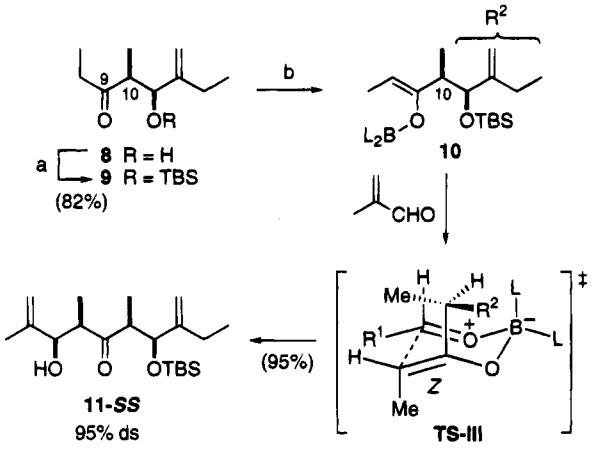
(16) (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (b) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (c) Paterson, I. *Chem. Ind. (London)* **1988**, 390. (d) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (e) Paterson, I.; Lister, M. A.; Ryan, G. R. *Tetrahedron Lett.* **1991**, *32*, 1749. (f) Paterson, I.; Lister, M. A.; Norcross, R. D. *Tetrahedron Lett.* **1992**, *33*, 1767. (g) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821.

(17) Prepared in two steps from (+)-α-pinene. See ref 16d.

(18) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(19) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471.

Scheme 3[a]



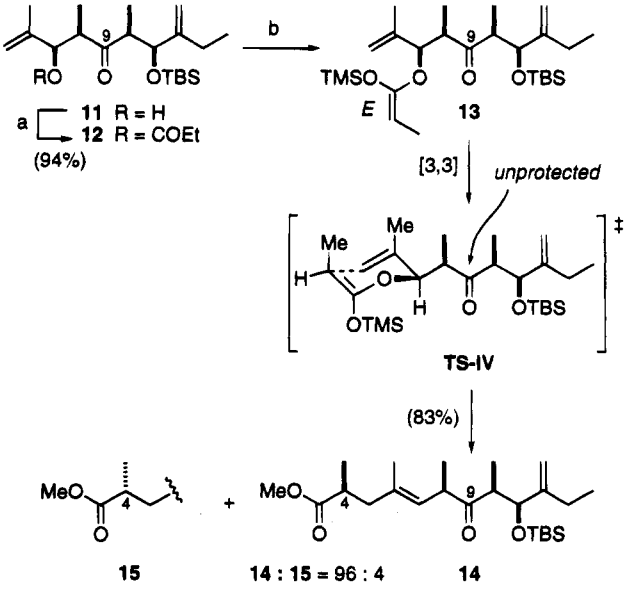
[a] Reagents: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; (b) 9-BBNOTf, Et_3N, CH_2Cl_2, −78 °C, 4 h; $H_2C{=}C(Me)CHO$, −78 → −20 °C, 16 h; H_2O_2, MeOH/pH 7 buffer, 20 °C, 1 h.

ylsilyl triflate and 2,6-lutidine at −78 °C, provided **9** in 82% yield. Enolization of **9** with 9-borabicyclo[3.3.1]nonyl triflate and Et_3N gave the *Z*-enol borinate **10**, which reacted with methacrolein to give the *all-syn* adduct **11-*SS***[20] in excellent yield (83%). This was produced with a high level of substrate-induced diastereoselectivity, resulting from preferred attack on the *re*-face of the aldehyde.[21] The product ratio ***SS*:*SA*:*AS*** was determined as 95:2.5:2.5 by HPLC analysis of the crude product mixture.[22] The reaction stereocontrol results from the preferred chair transition state **TS-III**, which is supported by calculations using our aldol force field.[19]

We planned to leave the C_9 ketone functionality unprotected during the rest of the synthesis, which exposed us to potential problems from α-epimerization and dehydration as well as nucleophilic attack. The sensitivity of this system to epimerization was apparent from our initial attempts to prepare the propionate ester from β-hydroxy ketone **11** (Scheme 4). Reaction with propionyl chloride, under a range of basic conditions,[14b] led to significant α-epimerization next to the ketone and low yields of the desired product. However, treatment with propionic anhydride and Et_3N, in the presence of catalytic quantities of DMAP,[23] gave an excellent yield of the desired propionate ester **12** (94%). Under these mild conditions, a dramatic reduction in the extent of epimerization was seen and minor products (≤5%) were readily separable by flash chromatography.

Although the Ireland−Claisen reaction has been widely used in synthesis,[13] there is apparently no precedent for its use in the presence of an unprotected ketone carbonyl group. Our synthetic strategy for the ebelactones relied on the rapid *in situ* trapping of the kinetically formed (less hindered) ester enolate in **13**, in the presence of the ketone at C_9 (Scheme 4). A modification of the *in situ*

Scheme 4[a]



[a] Reagents: (a) $(EtCO)_2O$, Et_3N, DMAP (catalyst), CH_2Cl_2, 0 → 20 °C, 2 h; (b) TMSCl, Et_3N, LDA, THF, −78 °C, 1 h; 20 → 60 °C, 4 h; H_3O^+; CH_2N_2, Et_2O, 0 °C.

trapping conditions employed by Corey and Gross[24] for the enolization of diethyl ketone was used. A solution of LDA (1.6 equiv) was added to the ester **12** in THF, containing premixed[25] trimethylsilyl chloride (5 equiv) and Et_3N (4.5 equiv) at −78 °C. The resulting *E*-silyl ketene acetal **13** was warmed to 20 °C for 2 h, and then to 60 °C for 2 h, to allow the [3,3]-rearrangement to take place *via* the preferred chairlike transition state **TS-IV**.[13,26] The crude rearrangement product was vigorously stirred with dilute acid (HCl, 1 N aqueous), to ensure complete hydrolysis of the silyl ester, and was isolated as its methyl ester by reaction of the crude acid with diazomethane (Et_2O, 0 °C). This procedure routinely gave the Ireland−Claisen rearrangement product **14** in high yield (79−83%). The diastereoselectivity of this reaction was determined as 96:4 by HPLC separation of the products **14** and **15**,[27] indicating highly *E*-selective silyl ketene acetal formation.

Under these carefully defined reaction conditions, this critical Ireland−Claisen rearrangement could be performed without interference from the C_9 ketone group.[28] The X-ray structure of (−)-ebelactone A[3c] and molecular modeling studies show a preferred local conformation around the C_9 ketone where *syn* pentane interactions are

(20) In our nomenclature system for aldol diastereomers (ref 15a) such as **11-*SS***, the first descriptor (***S*** for *syn*, ***A*** for *anti*) refers to the relative stereochemistry of the aldol bond construction and the second descriptor defines the relative stereochemistry of the two methyl substituents flanking the carbonyl group.

(21) The minor diastereomer **11-*SA*** results from reaction of the *Z*-enol borinate on the *si*-face of the aldehyde, while **11-*AS*** probably results from a small amount of the *E*-enol borinate.

(22) Mosher ester analysis performed on **11-*SS*** showed the material was still of 86% ee.

(23) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

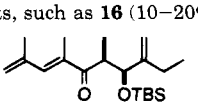
(24) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(25) A clear reagent solution was prepared by mixing trimethylsilyl chloride and Et_3N in a centrifuge tube under argon, followed by removal of the precipitated $Et_3N{\cdot}HCl$ by centrifugation.

(26) (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. (b) Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572.

(27) The spectroscopic data for (±)-**15**, independently synthesized from propionate ester **12-*AS*** (*cf.* ref 29), was in agreement with that obtained for the minor diastereomer of this reaction. The minor 1,5-*anti* product is presumably derived from the Claisen [3,3]-rearrangement of a trace of *Z*-silyl ketene acetal.

(28) The Ireland−Claisen rearrangement reaction was found to be particularly dilution-dependent; initial concentrations of LDA in the reaction mixture greater than 15 mM in THF gave rise to unwanted elimination side products, such as **16** (10−20%).



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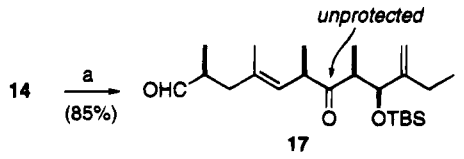
Scheme 5[a]



[a] Reagents: (a) DIBAL-H (1.4 equiv), Et_2O, −98 °C.

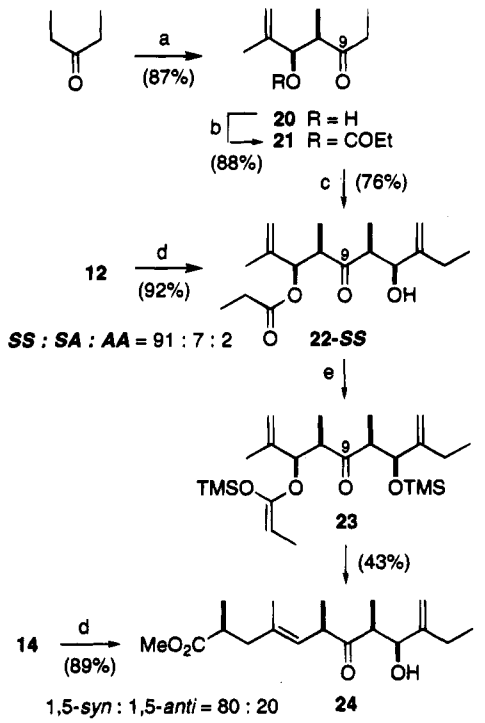
avoided between the α- and α′-substituents. A similar conformation about the C_9 carbonyl group in **12** ensures that the flanking methyl groups effectively shield it from reaction. We have also demonstrated that double Ireland−Claisen rearrangements can be successfully performed on diester derivatives of **12** (*i.e.* TBS replaced by another ester group), permitting the stereocontrolled, two-directional construction of long-chain polypropionate skeletons.[29]

The introduction of an aldehyde at the C_3 position, for subsequent coupling in an *anti* aldol reaction, was now required (Scheme 5). Direct conversion of a methyl ester to an aldehyde by reduction with DIBAL-H is reasonably routine. However, its use in this more sensitive system, where chemoselective reduction of the methyl ester was required to take place in the presence of the C_9 ketone, was more speculative. Gratifyingly, reaction with DIBAL-H (1.4 equiv) in ether at −98 °C was found to give the keto aldehyde **17** in good yield (85%).[30,31] Again, the hindered nature of the C_9 ketone is probably responsible for this selectivity.

An Abortive Approach to a C_3−C_{14} Aldehyde Avoiding Protecting Group Chemistry. In view of our success in avoiding protection of the C_9 ketone, we also examined a more daring approach, avoiding the use of protecting groups altogether. This alternative approach to the synthesis of the ebelactones relied on the reversal of the order of addition of the two aldehydes to diethyl ketone (*cf.* **6** in Scheme 1; aldol #1 and #2 transposed). The feasibility of this revised route was examined in the racemic series (Scheme 6).

The reaction of diethyl ketone with methacrolein *via* the *Z*-enol di-*n*-butyl borinate gave the *syn* aldol adduct **20** in good yield (87%).[15,32] This could be protected as its propionate ester using the conditions previously developed ($(EtCO)_2O$, Et_3N, catalyst DMAP) to give **21** in 88% yield. Enolization of **21** using 9-borabicyclo[3.3.1]-nonyl triflate and $^iPr_2NEt$ in ether gave the *Z*-enol borinate, which reacted with 2-ethylacrolein to give the

Scheme 6[a]



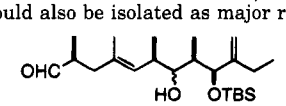
[a] Reagents: (a) $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 4 h; $H_2C{=}C(Me)CHO$, −78 → −4 °C, 16 h; MeOH/pH 7 buffer, H_2O_2, 20 °C, 3 h; (b) $(EtCO)_2O$, Et_3N, CH_2Cl_2, DMAP (catalyst), 20 °C, 3 h; (c) 9-BBNOTf, Et_3N, −78 °C, 3 h; 2-ethylacrolein, −78 → −20 °C, 16 h; MeOH/pH 7 buffer, H_2O_2, 20 °C, 3 h; (d) HF (40% aq), MeCN, 20 °C, 3 h; (e) TMSCl, Et_3N, LDA, THF, −78 °C, 1 h; 20 → 60 °C, 4 h; CH_2N_2, Et_2O, 0 °C.

all-syn adduct **22-*SS*** as the major product (76% overall yield, ratio ***SS*:*SA*:*AS*** = 91:7:2 by HPLC separation).[33] For the Ireland−Claisen reaction of **22-*SS*** *via* the ketene silyl acetal **23**, the temporary *in situ* protection of the free hydroxyl at C_{11} as its trimethylsilyl ether was envisaged. Unfortunately, the yield of rearrangement product **24** isolated from this reaction was poor (43%) and the diastereoselectivity low (80:20 ratio for 1,5-*syn*:1,5-*anti*),[34] precluding further investigation of this route. The stereochemistry of the major product **24** was confirmed by desilylation of **14** (HF, MeCN) to give an 89% yield of the same β-hydroxy ketone. After this brief diversion, we returned to the original approach using a *tert*-butyldimethylsilyl ether to protect the C_{11} hydroxyl group.

The C_2−C_3 Bond Construction. While the asymmetric *syn* aldol reactions of chiral *Z*-enolates have been well developed, such that there are few synthetic problems that cannot be surmounted by the use of a chiral auxiliary, a chiral reagent, or the carefully designed use of substrate control, the corresponding *anti* aldol reactions of *E*-enolates are much less well-resolved.[12] To complete our synthesis of the ebelactones, the *anti* aldol reaction of the *E*-enolate of a propionate, or butyrate unit, with aldehyde **17** was required. Relative to the existing

(29) Paterson, I.; Hulme, A. N.; Wallace, D. J. *Tetrahedron Lett.* **1991**, *32*, 7601.

(30) This reaction was found to be extremely dependent upon the quality of DIBAL-H reagent (Aldrich). With inferior reagent, under the same reaction conditions, both hydroxy aldehyde **18** and diol **19** could also be isolated as major reaction products.



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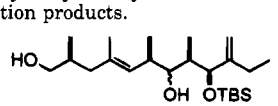

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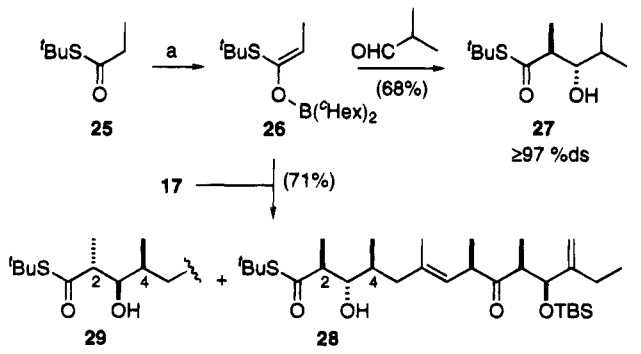
(31) The chemoselectivity of several other reducing agents was also examined. Of particular interest was the production of diol **19**, which might then be oxidized to keto aldehyde **17**. However, the TBS protecting group was found to be labile under many of these over-reduction conditions. Although the stereochemistry of the ketone reduction was not actually determined, selectivities of >10:1 were observed using $LiAlH_4$ (Et_2O, −78 °C). For related reductions, see: Bloch, R.; Gilbert, L.; Girad, C. *Tetrahedron Lett.* **1988**, *29*, 1021.

(32) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(33) Confirmation of the stereochemistry of the major product was obtained by silyl deprotection of the previously prepared stereotetrad **12-*SS*** (HF, MeCN) which gave a 92% yield of a product which was spectroscopically identical to **22-*SS***.

(34) A small amount of a C-silylated byproduct was also isolated (~10%).

Scheme 7[a]



[a] Reagents: (a) $^cHex_2BCl$, Et_3N, pentane, 0 °C, 2 h; RCHO, −78 → −20 °C, 14−16 h; H_2O_2, MeOH/pH 7 buffer, 20 °C, 1 h.

stereocenter at C_4, an anti-Felkin sense[35] of addition was also demanded.

As in our earlier work,[10] the thioester **25**[36] was used as an achiral propionate equivalent[37] for the C_2-C_3 bond formation in ebelactone A (Scheme 7). The *E*(O)-enol dicyclohexyl borinate **26** of thioester **25** could be cleanly generated by the Brown protocol[38] using $^cHex_2BCl$ and Et_3N in ether or pentane. Reaction of **26** with isobutyraldehyde gave the *anti* aldol adduct **27** with a high level of diastereoselectivity (≥97%). In a similar fashion, the addition of **26** to aldehyde **17** in pentane gave the required 3,4-*anti* adduct **28**, together with the 3,4-*syn* isomer **29**, in a roughly equimolar ratio (≤5% *syn* aldol adducts were formed).

The diastereoselectivity of the aldol reactions of α-methyl chiral aldehydes with the enol borinates of ethyl ketones has been examined in detail.[39] The dominant element of stereocontrol, determining aldehyde facial selectivity, is the minimization of gauche pentane interactions in competing chairlike transition states. The low level of intrinsic π-facial selectivity for *E*-enol borinate addition to aldehyde **17** suggested that both **TS-V** and **TS-VI** (R^2 = Me) were equally favorable (Figure 1).

At this stage, comparison of the ^1H NMR spectroscopic data for the two *anti* aldol products with that of the ebelactone A degradation product **30**, reported by Umezawa *et al.*[3b] (Scheme 8), allowed for the tentative assignment of the anti-Felkin product on the basis of the homology between the C_1-C_{10} regions. This was reinforced by conversion of thioester **28** to the corresponding methyl ester **31**, which had ^1H NMR spectroscopic data for the C_1-C_9 region very similar to that reported for **30**.[3b]

This same methodology was then applied to the *anti* aldol required for the synthesis of (−)-ebelactone B

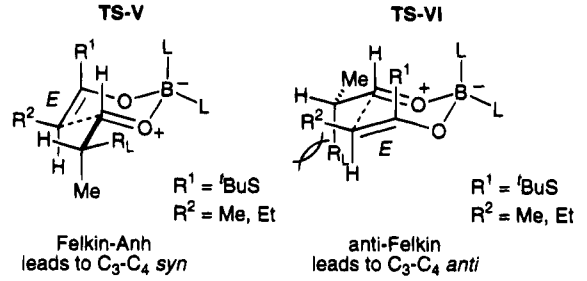
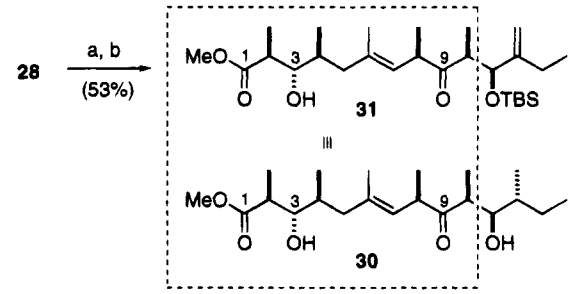


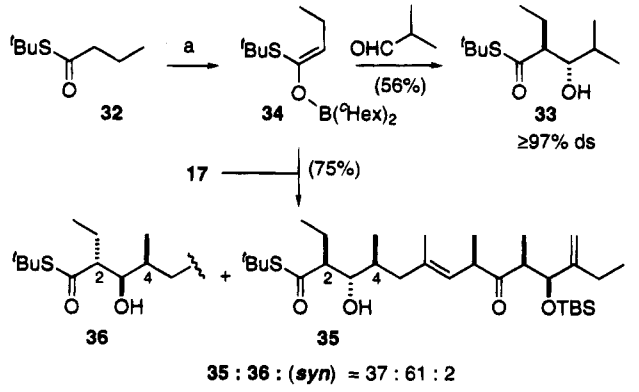
Figure 1.

Scheme 8[a]



[a] Reagents: (a) LiOH, THF/H_2O, 20 °C, 66 h; (b) CH_2N_2, Et_2O, 0 °C.

Scheme 9[a]



[a] Reagents: (a) $(^cHex)_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; RCHO, −78 → 0 °C, 5−16 h; H_2O_2, MeOH/pH 7 buffer, 20 °C, 1 h.

(Scheme 9). Using $^cHex_2BCl$ and Et_3N in ether, enolization of the butyrate thioester **32**[36] and addition to isobutyraldehyde gave the *anti* aldol adduct **33** with a high degree of diastereoselectivity (≥97%). Similarly, reaction of the *E*(O)-enol borinate **34** with aldehyde **17** resulted in a 75% yield of aldol adducts **35** and **36**. However, the Felkin selectivity of the α-chiral aldehyde was increased over its propionate counterpart, leading to the production of a 37:61 mixture of *anti* aldol products (with 2% *syn* isomers). The formation of β-hydroxy thioester **36** (the undesired Felkin adduct) was now favored due to increased gauche pentane interactions destabilizing **TS-VI** relative to **TS-V** (R^2 = Et) in Figure 1.

Since the π-facial selectivity exerted by α-chiral aldehyde **17** in its reaction with the *E*(O)-enol borinates of both propionate and butyrate units was low, the use of double asymmetric induction[40] to improve the diastereo-

(35) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (c) Anh, N. T.; Thanh, B. T. *Nouv. J. Chim.* **1986**, *10*, 681.

(36) The thioesters **25** (81%) and **32** (80%) were prepared from ^{t}BuSH and the appropriate acid chloride (Et_3N, Et_2O, 20 °C, 45 h).

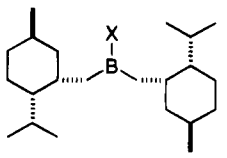
(37) For other examples of the use of thioesters as propionate equivalents, see: (a) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (b) Short, R. P.; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841. (c) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (d) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, 2225. (e) Reetz, M. T.; Rivadeneira, E.; Niemeyer, C. *Tetrahedron Lett.* **1990**, *31*, 3863. (f) Reetz, M. T. *Pure Appl. Chem.* **1988**, *60*, 1607. (g) Corey, E. J.; Lee, D.-H. *Tetrahedron Lett.* **1993**, *34*, 1737 and references cited therein.

(38) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

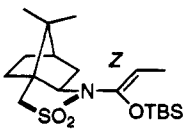
(39) (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Comotti, A.; Bernardi, A.; Gennari, C.; Vieth, S.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439.

(40) For a review of double asymmetric induction, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

selectivity in favor of the desired anti-Felkin product was investigated. Two approaches were employed: (i) the use of some novel chiral boron reagents developed in collaboration with the Gennari group[41] for asymmetric *anti* aldol reactions and (ii) the use of an Oppolzer[42] or Evans[43] chiral auxiliary attached to the enolate. The (−)-menthone-derived reagent $[(Menth)CH_2]_2BCl$ (**37**) has been introduced for asymmetric *anti* aldol reactions of acyclic ketones.[41a] However, its application to the aldol reaction of thioester **25** with isobutyraldehyde proved unsuccessful.[44] We thus turned our attention to the use of an enolate incorporating a suitable chiral auxiliary. Oppolzer *et al.* have reported on the highly diastereoselective formation of *anti* aldol adducts *via* a Lewis acid-mediated addition of silyl enolate **38** with aldehydes.[42] Unfortunately, when this reaction was performed with **17**, the sensitive aldehyde was found to be destroyed by the reaction conditions ($TiCl_4$).[45]



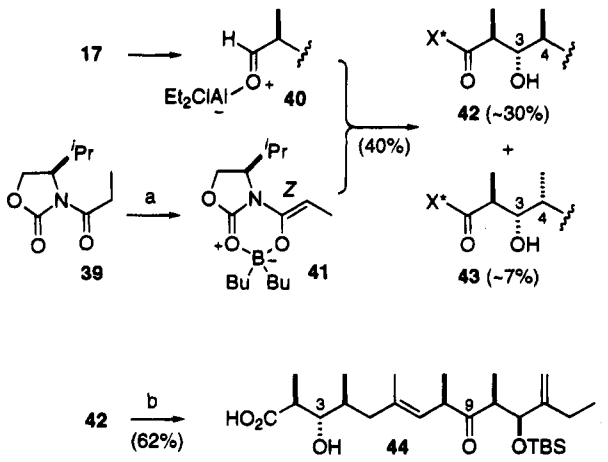
37
X = Cl, Br



38

We next examined the use of Heathcock's variant of the Evans aldol reaction, where *anti* aldol products are favored by the use of the boron enolate from imide **39** and precomplexation of the aldehyde with Et_2AlCl (Scheme 10).[46] Aldehyde **17** was shown to be stable to the presence of Et_2AlCl in CH_2Cl_2 at low temperatures (−78 °C) for several hours. Reaction of aldehyde **17** (86% ee) precomplexed to Et_2AlCl (**40**) with *Z*-enol borinate **41** resulted in a modest overall yield of aldol products (40%). At least four diastereomeric aldol products were formed, with the desired *anti* aldol adduct **42** present in ~30% yield. Correlation of **42**, with material from the *anti* aldol reaction of thioester **25**, was achieved by conversion of the former into carboxylic acid **44** (LiOOH, THF/H_2O, 20 °C, 2 h, 62%). The only other diastereomer to be isolated in sufficient quantity to be characterized was tentatively assigned, on the basis of its ^1H NMR spectrum, as the *anti* aldol adduct **43**.[47]

Scheme 10[a]



[a] Reagents: (a) $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 30 min; **17** (premixed with Et_2AlCl (2 equiv) at −78 °C for 5 min), −78 °C, 4 h; H_2O_2, MeOH, 20 °C, 1 h; (b) LiOOH, THF/H_2O (3:1), 20 °C, 2 h.

In this open transition state situation, Lewis acid-mediated nucleophilic additions to α-chiral aldehydes show an increased diastereofacial preference in favor of Felkin–Anh products.[48] In the case of aldehyde **17**, this means that the π-facial selectivity exerted by the chiral enolate must now overturn an increased aldehyde facial selectivity, in favor of the Felkin–Anh product, to provide the anti-Felkin aldol adduct. The moderate level of selectivity attained using the Heathcock protocol is therefore expected in this mismatched situation.

A *syn* aldol approach to the synthesis of the ebelactones was also investigated. This alternative synthetic strategy requires inversion at the C_3 stereocenter during β-lactone formation. The Evans auxiliary associated with imide **45** was selected for π-facial control in the construction of the *syn* β-hydroxy acid **46**. The *Z*-enol borinate **47**, generated in CH_2Cl_2 using $^nBu_2BOTf$ and $^iPr_2NEt$,[43a] was reacted with aldehyde **17** (86% ee). A kinetic preference for the anti-Felkin product **49** (derived from reaction of *ent*-**17**) was observed, with moderate selectivity for the 2,3-*syn*-3,4-*syn* aldol adduct **48** (77:19:4 ratio for **48**:**49**:**50**, combined yield 52%)[49] and recovery of some unreacted aldehyde (25%) (Scheme 11).

In summary, a sampling of available methods failed to find a chiral reagent or auxiliary-based enolate system which resulted in a substantial improvement over the use of the simple *E*-enol dicyclohexyl borinate of the thioesters **25** and **32**. These shortcomings have served as a stimulus for the recent development of new methodology for the asymmetric synthesis of *anti* aldol products within our laboratory.[50]

Completion of the Synthesis of (−)-Ebelactone A and B. While the hydrolysis of the simple thioester **27** could be carried out using either $Hg(OCOCF_3)_2$[51] or

(41) (a) Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1992**, *57*, 5173. (b) Bernardi, A.; Comotti, A.; Gennari, C.; Hewkin, C. T.; Goodman, J. M.; Schlapbach, A.; Paterson, I. *Tetrahedron* **1994**, *50*, 1227.

(42) (a) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767. (b) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61.

(43) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Review: Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.

(44) Recent studies by the Gennari group have shown that the enolization of thioesters with the bromoborane corresponding to **37** is more successful. However, the resultant chiral *E*(O)-enol borinate appears to have limited utility in overturning the Felkin selectivity from α-chiral aldehydes: (a) Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1618. (b) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron Lett.* **1994**, *35*, 4623.

(45) The only isolable product from this reaction was epimerized, deprotected aldehyde (30–55%). In comparison, the *anti* aldol reaction of **38** with isobutyraldehyde was repeated with a yield and diastereoselectivity comparable to that reported by the Oppolzer group (ref 42b).

(46) (a) Heathcock, C. H.; Walker, M. A. *J. Org. Chem.* **1991**, *56*, 5747. (b) Da, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.

(47) Diastereomer **43** is the product of Felkin–Anh attack on the minor enantiomer of aldehyde **17**.

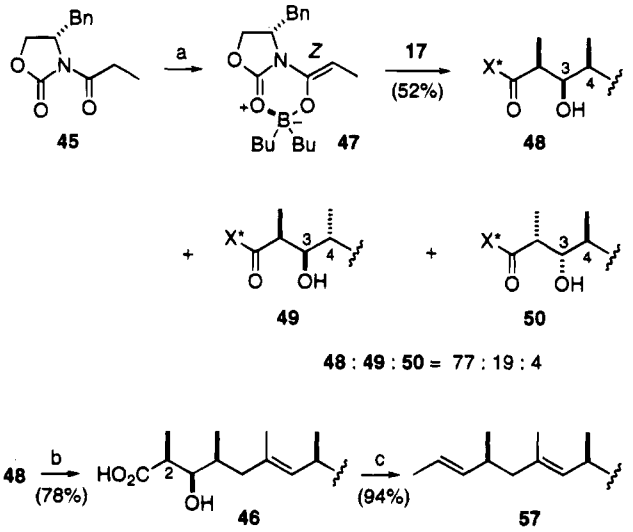
(48) (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819. (c) Review: Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99.

(49) Diastereomer **50** is the product of anti-Felkin attack of the *Z*-enol borinate on the major enantiomer of aldehyde **17**.

(50) For recent developments in *anti* aldol methodology within this group, see: (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (b) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087. (c) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9477.

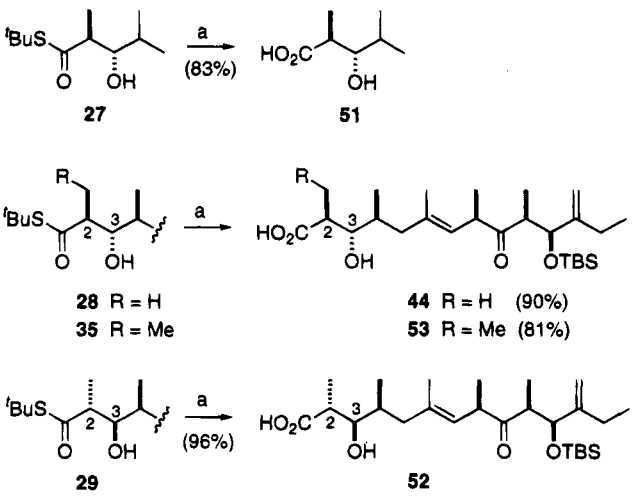
(51) (a) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. (b) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756. (c) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

Scheme 11[a]



[a] Reagents: (a) $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 30 min; **17**, −78 °C, 6 h; H_2O_2, MeOH, 20 °C, 1 h; (b) LiOOH, THF, 20 °C, 30 min; (c) PPh_3, DEAD, 0 °C, 2 h.

Scheme 12[a]

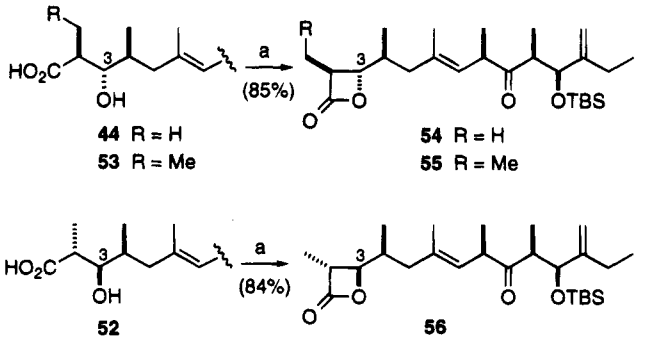


[a] Reagents: (a) LiOOH, THF/H_2O (3:1), 20 °C, 16 h.

lithium hydroxide[52] to give the β-hydroxy acid **51**[53] (96 and 73% yield, respectively), both these conditions were found to be too harsh for **28** (Scheme 12). However, the use of lithium hydroperoxide[54] (THF/H_2O, 20 °C) with thioester **28** resulted in a high yield (90%) of the desired carboxylic acid **44**. Similar results were obtained for the thioesters **29** and **35**, where the corresponding carboxylic acids **52** and **53** were isolated in 96 and 81% yield, respectively.

The complex nature of the C_1-C_{14} backbone of the ebelactones means that β-lactone formation presents a greater synthetic challenge here than in other β-lactone natural products.[55] The application of a modification of the conditions of Adam *et al.* ($PhSO_2Cl$, pyridine, −20 °C, 16 h)[56] proved to be extremely successful in the synthesis of the *trans* β-lactones **54**, **55**, and **56** (Scheme

Scheme 13[a]



[a] Reagents: (a) $PhSO_2Cl$, pyridine, −20 °C, 38 h.

13). In particular, it was found that increasing the number of equivalents of freshly distilled $PhSO_2Cl$ (2 → 6 equiv), by portionwise addition, gave a corresponding increase in the yield of cyclized product. Similarly, increasing the length of reaction time to 38 h, while maintaining a relatively low reaction temperature (−20 °C), also resulted in a greater conversion of the β-hydroxy acids. With these optimized conditions, consistently high yields (≥84%) of β-lactones were obtained.

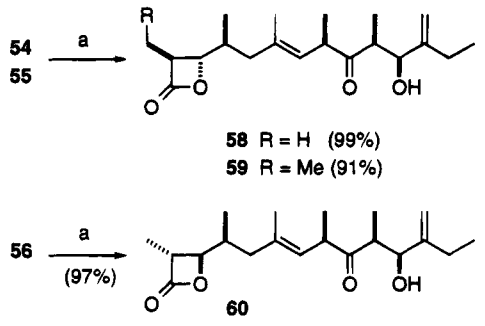
Hydrolysis of imide **48** was also achieved using Evans conditions[54] (LiOOH, THF/H_2O, 20 °C, 30 min), to give the *syn* β-hydroxy acid **46** in 78% yield (Scheme 11). To access ebelactone A, this required β-lactone formation with concomitant inversion at C_3. The application of Mitsunobu-type conditions (Ph_3P, DEAD, THF or toluene, 0 °C, 2 h)[57] to this acid resulted in the isolation of the elimination product **57** in excellent yield (94%). This suggested that activation of the secondary hydroxyl through formation of a zwitterion was relatively facile but that steric crowding of the activated group made the elimination of CO_2, with concomitant *E*-double bond formation, considerably more favorable than β-lactone formation. Similar eliminative processes in the presence of Ph_3P and DEAD have been reported as a means of selective double bond generation from β-hydroxy carboxylic acids.[58]

To complete the synthesis of the ebelactones, we needed to deprotect the *tert*-butyldimethylsilyl ether and selectively hydrogenate the alkene at C_{12} in the advanced intermediates **54**−**56**. The desilylation of **54** (HF, 40% aq, MeCN, 20 °C, 1 h) proceeded cleanly to give an excellent yield (99%) of the desired allylic alcohol **58** (Scheme 14). Analysis of the 400 MHz ^1H NMR spectrum

(52) Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 190.
(53) Chamberlain, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247.
(54) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

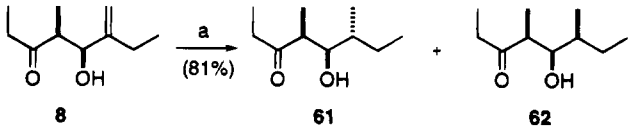
(55) For some recent syntheses of β-lactone natural products, see the following. (a) Valilactone: Bates, R. W.; Fernández-Moro, R.; Ley, S. V. *Tetrahedron* **1991**, *23*, 2651. (b) Tetrahydrolipstatin: (i) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1990**, *25*, 3645 and references cited therein. (ii) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 781. (c) L-659,699: Chiang, Y.-C. P.; Yang, S. S.; Heck, J. V.; Chabala, J. C.; Chang, M. N. *J. Org. Chem.* **1989**, *54*, 5708. (d) Obafluorin: Lowe, C.; Pu, Y.; Vederas, J. C. *J. Org. Chem.* **1992**, *57*, 10. (e) Anisatin: Niwa, H.; Nisiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Mori, T.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001.
(56) Adam, W.; Baeza, J.; Liu, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 2000.
(57) (a) For a review of the Mitsunobu reaction, see: Mitsunobu, O. *Synthesis* **1981**, 1. (b) For an example of this strategy, see: Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649 and references cited therein.
(58) (a) Mulzer, J.; Pointner, A.; Chucholowski, A.; Brüntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52 and references cited therein. (b) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176. (c) For examples of decarboxylation in the cyclization reactions of β-alkyl β-hydroxy amino acids, see: Pu, Y.; Martin, F. M.; Vederas, J. C. *J. Org. Chem.* **1991**, *56*, 1280.

Scheme 14[a]



[a] Reagents: (a) HF (40% aq), MeCN, 20 °C, 1 h.

Scheme 15[a]



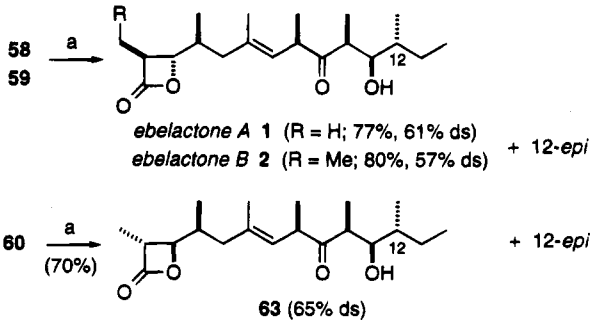
[a] Reagents: (a) $(Ph_3P)_3RhCl$ (10 mol %), PhH, H_2 (1 atm), 20 °C, 3 h.

showed that there was no scrambling of stereochemistry about the β-lactone ring or epimerization α to the ketone at C_9. These conditions were similarly found to be effective in the deprotections, **55** → **59** (91%) and **56** → **60** (97%).

We planned to introduce the final stereocenter at C_{12} *via* a hydroxyl-directed, homogeneous hydrogenation reaction.[59] The hydrogenation of acyclic allylic alcohols using Wilkinson's catalyst ($(Ph_3P)_3RhCl$) can give high levels of stereoselectivity in favor of the *anti* reduction product.[60,61] Reduction of aldol adduct **8** proved to be an excellent model for the reduction of the C_{12} double bond in **58**. Under the conditions of Tatsuta and Kinoshita *et al.* ($(Ph_3P)_3RhCl$ (10 mol %), PhH, H_2 (1 atm), 20 °C, 3 h),[60a] a good overall yield of the saturated products **61** and **62** was obtained (81%). HPLC separation and 250 MHz ^1H NMR analysis indicated a 71:29 mixture of diastereomers in favor of the desired *anti* isomer **61** (Scheme 15).[62-65]

A small scale reduction of the ebelactone A precursor **58** (Scheme 16) required the presence of a greater

Scheme 16[a]



[a] Reagents: (a) $(Ph_3P)_3RhCl$ (50 mol %), PhH, H_2 (1 atm), 20 °C, 15 h.

concentration of catalyst (50 mol %) to ensure completion, which was of particular importance since ebelactone A (**1**) and its synthetic precursor **58** were found to be inseparable by chromatography. The overall yield of reduced products, obtained after HPLC separation, was good (77%) with moderate selectivity in favor of ebelactone A (61:39 ratio for **1**:12-*epi*-**1**). The trisubstituted double bond at C_6 remained untouched by these conditions. The synthetic sample of (−)-ebelactone A had spectroscopic data (400 MHz ^1H NMR, ^{13}C NMR, IR, MS) identical to those recorded for an authentic sample.[66] The mp and specific rotation were also in agreement with the literature data (81−83 °C, *cf.* lit.[3b] 86 °C; $[\alpha]^{20}_D = -166$ (*c* 0.3, MeOH) for 86% ee, *cf.* lit.[3b] $[\alpha]^{20}_D = -221$ (*c* 1.0, MeOH)). Similar results were obtained in the reduction of **60** (70% overall yield, 65:35 ratio *anti:syn*), giving preferentially 2,3-bis-*epi*-ebelactone A (**63**), and **59** (80% overall yield, 57:43 ratio *anti:syn*) to give ebelactone B (**2**). Again the spectroscopic data (400 MHz ^1H NMR, ^{13}C NMR, IR, MS) recorded for the synthetic sample of (−)-ebelactone B (**2**) were identical to those of an authentic sample.[66] The mp and specific rotation were also in agreement with the literature data (70−72 °C, *cf.* lit.[3b] 77 °C; $[\alpha]^{20}_D = -158$ (*c* 0.4, MeOH), *cf.* lit.[3b] $[\alpha]^{20}_D = -203$ (*c* 1.0, MeOH)). This completed asymmetric synthesis of ebelactone A and B served to confirm the absolute configuration (2*S*,3*S*,4*S*,8*R*,10*S*,11*R*,12*R*).

Conclusions

The β-lactone enzyme inhibitors (−)-ebelactone A (**1**) and (−)-ebelactone B (**2**) have each been prepared in 12 steps from diethyl ketone (4 and 3% overall yield, respectively) using a series of three boron enolate aldol reactions, coupled with a remarkable Ireland ester enolate Claisen rearrangement. The use of (−)-diisopinocampheylboron triflate reagent in the initial *syn* aldol reaction allowed for the generation of material of 86% ee. Despite intense investigation into the use of double asymmetric induction to improve the diastereoselectivity of the third aldol reaction, the methodology previously developed in the synthesis of (±)-ebelactone A[10] was found to be the most efficient. These studies demonstrated the limitations of existing asymmetric *anti* aldol methodology, particularly in overriding the inherent face selectivity of highly sensitive chiral aldehydes.

Experimental Section

General. See the supplementary material for details of instrumentation, purification of reagents and solvents, and chromatography. All nonaqueous reactions were performed

(59) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

(60) (a) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749. (b) Nakata, M.; Enari, H.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3283. (c) Nakata, M.; Toshima, K.; Kai, T.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3457. (d) Nakata, M.; Akiyama, N.; Kamata, J.-I.; Kojima, K.; Masuda, H.; Kinoshita, M.; Tatsuta, K. *Tetrahedron* **1990**, *46*, 4629.

(61) Nakata, M.; Arai, M.; Tomooka, K.; Oshawa, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618 and references cited therein.

(62) Attempted reduction of the *tert*-butyldimethylsilyl allylic ether **9**, under the same reaction conditions, only gave recovered starting material (85%). Thus, the importance of the directing hydroxyl group and the unhindered nature of the double bond in **8** was demonstrated.

(63) The effect of increased H_2 pressure in the $(Ph_3P)_3RhCl$-catalyzed hydrogenation reaction was investigated using allylic alcohol **8**. However, the ratio of *anti:syn* reduced products (**61**:**62**) obtained at 48 atm H_2 was 70:30, thus, exhibiting no better selectivity than seen previously. Reduction of the model compound **8** with the cationic rhodium complex [Rh(NBD)(DIPHOS-4)]OTf (refs 64 and 65) was also tried in a range of solvent systems, resulting in both olefin isomerization and nonselective reduction of the double bond.

(64) Brown, J. M.; Naik, R. *J. Chem. Soc., Chem. Commun.* **1982**, 348.

(65) We are grateful to Dr. J. M. Brown (Oxford University) for a sample of this catalyst.

(66) Authentic samples of both (−)-ebelactone A and (−)-ebelactone B were purchased from Sigma Chemical Co. Ltd.

under an atmosphere of argon using an oven-dried apparatus and employing standard Schlenk techniques for handling air-sensitive materials.

(3S,4S)-2-Ethyl-3-hydroxy-4-methyl-1-hepten-5-one (8). To a cooled (−78 °C) stirred solution of (−)-Ipc$_2$BOTf (7.0 mL, 10.5 mmol, ~1.5 M in hexane)[17] in CH_2Cl_2 (20 mL) was added dropwise diisopropylethylamine (4.9 mL, 28 mmol), followed by 3-pentanone (0.74 mL, 7.0 mmol). The pale yellow color of the triflate solution disappeared upon addition of the amine base. The reaction mixture was stirred for 4 h at −78 °C and warmed to 0 °C for 30 min to ensure complete enolization. The solution was recooled to −78 °C, and freshly distilled 2-ethylacrolein was then added (3.4 mL, 35 mmol). The reaction mixture was stirred for a further 1 h at −78 °C before being transferred to the freezer (−20 °C) for 16 h. The pale yellow mixture was partitioned between pH 7 buffer solution (40 mL) and CH_2Cl_2 (35 mL, then 2 × 50 mL), and the combined organic extracts were washed with brine (40 mL, saturated), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was resuspended in a methanol−pH 7 buffer solution mixture (5:1, 18 mL overall) and cooled to 0 °C, and hydrogen peroxide (5 mL, 30% aqueous) was added dropwise. The reaction mixture was stirred for 3 h at 0 °C, until complete as followed by TLC. The disappearance of a HiR_f spot (R_f (CH_2Cl_2) = 0.80) corresponding to the oxidation of the boron aldolate was followed. The mixture was quenched with water (40 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with sodium bicarbonate solution (40 mL, saturated) and brine (40 mL, saturated), dried ($MgSO_4$), and concentrated *in vacuo* to give crude aldol product. Separation of the aldol product from IpcOH was achieved by flash chromatography (30% EtOAc in hexane) and subsequent HPLC (30% EtOAc in hexane) of mixed fractions to give a colorless oil **8** (0.91 g, 77%). Analysis of the 400 MHz ^{1}H NMR showed the presence of a single diastereomer, the *syn* aldol product. Mosher ester formation[18] and chiral shift ^{1}H NMR studies performed in $CDCl_3$ at 250 MHz using tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium-(III), Eu(hfc)$_3$, indicated 86% ee: R_f (30% EtOAc in hexane) 0.44; HPLC t_R (30% EtOAc in hexane) 13.5 min; $[\alpha]^{20}_D = -37.7$ (*c* 2.5, $CHCl_3$); IR ν_{max} (liquid film) 3450, 3080, 1700, 1645 cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.10 (1H, m), 4.94 (1H, m), 4.42 (1H, br d, J = 2.6 Hz), 2.84 (1H, br s), 2.70 (1H, qd, J = 7.2, 3.3 Hz), 2.58−2.43 (2H, m), 2.01−1.89 (2H, m), 1.05 (3H, t, J = 7.4 Hz), 1.05 (3H, d, J = 7.2 Hz), 1.04 (3H, t, J = 7.1 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 216.1, 149.7, 109.4, 73.2, 47.9, 34.9, 25.4, 12.1, 9.7, 7.6; HRMS (CI, NH_3) $[M + H]^+$ found 171.1385, $C_{10}H_{19}O_2$ requires 171.1385; HRMS *m*/*z* (relative intensity) 171 ($[M + H]^+$, 91), 153 (52), 86 (100), 57 (100). Anal. Found: C, 70.65; H, 10.93. $C_{10}H_{18}O_2$ requires: C, 70.55; H, 10.66.

(3S,4S)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-4-methyl-1-hepten-5-one (9). To a cooled (−78 °C) stirred solution of alcohol **8** (571 mg, 3.36 mmol) in CH_2Cl_2 (15 mL) was added 2,6-lutidine (0.94 mL, 8.06 mmol). *tert*-Butyldimethylsilyl triflate (0.71 mL, 3.09 mmol) was added, and the reaction mixture was stirred for 1 h at −78 °C, until complete as followed by TLC. The reaction mixture was quenched with ammonium chloride solution (30 mL, saturated) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with pH 7 buffer solution (2 × 10 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. Any traces of TBS-protected IpcOH were successfully removed by flash chromatography (CH_2Cl_2) to give a colorless oil **9** (0.78 g, 82%): R_f (CH_2Cl_2) 0.63, 0.39 (5% Et_2O in hexane); $[\alpha]^{20}_D = -10.5$ (*c* 2.3, $CHCl_3$); IR ν_{max} (liquid film) 3100, 1710, 1650, 1260 cm^{-1}; ^{1}H NMR δ (250 MHz, $CDCl_3$) 4.93 (1H, br s), 4.82 (1H, m), 4.26 (1H, d, J = 6.8 Hz), 2.67 (1H, qd ≡ qn, J = 6.8 Hz), 2.40 (2H, q, J = 7.4 Hz), 2.12−1.90 (2H, m), 1.07 (3H, d, J = 6.8 Hz), 1.03 (3H, t, J = 7.4 Hz), 0.97 (3H, t, J = 7.3 Hz), 0.87 (9H, s), 0.00 (3H, s), −0.04 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.7, 151.2, 110.4, 77.7, 51.0, 35.7, 25.8, 23.3, 18.1, 12.3, 11.8, 7.4, −4.6, −5.2; HRMS (CI, NH_3) $[M + H]^+$ found 285.2250, $C_{16}H_{33}O_2Si$ requires 285.2250; HRMS *m*/*z* (relative intensity) 285 ($[M + H]^+$, 93), 227 (34), 199 (100), 189 (8), 171 (6), 153 (100), 132 (27). Anal. Found: C, 67.42; H, 11.31. $C_{16}H_{32}O_2Si$ requires: C, 67.55; H, 11.34.

(3S,4S,6R,7R)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-7-hydroxy-4,6,8-trimethyl-1,8-nonadien-5-one (11-*SS*). To a cooled (−78 °C) stirred solution of 9-borabicyclo[3.3.1]nonyl triflate (10.4 mL, 5.2 mmol, 0.5 M in hexanes) in CH_2Cl_2 (10 mL) was first added triethylamine (0.84 mL, 6.0 mmol) and then a solution of ethyl ketone **9** (568 mg, 2.0 mmol) in CH_2Cl_2 (2 mL, +2 mL washings). The reaction mixture was stirred at −78 °C for 4 h and then at 0 °C for a further 30 min before being recooled to −78 °C, and freshly distilled methacrolein (0.83 mL, 10.0 mmol) was added. The reaction mixture was stirred for a further 1 h at −78 °C before being transferred to the refrigerator (−4 °C) for 16 h. The reaction mixture was partitioned between pH 7 buffer (20 mL) and CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were washed with brine (20 mL, saturated), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was redissolved in a methanol−pH 7 buffer mixture (5:1, 6 mL overall) and cooled to 0 °C, and hydrogen peroxide (3 mL, 30% aqueous) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, and then it was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with sodium bicarbonate solution (20 mL, saturated) and brine (20 mL, saturated), dried ($MgSO_4$), and concentrated *in vacuo* to give crude aldol product. Flash chromatography (CH_2Cl_2) gave a colorless oil **11** (587 mg, 83%). HPLC separation (10% EtOAc in hexane) and subsequent analysis of the 250 MHz ^{1}H NMR spectra showed a ratio of 95:2.5:2.5 for *SS*:*AA*:*SA* aldol products. Major diastereomer: R_f (CH_2Cl_2) 0.30; HPLC t_R (10% EtOAc in hexane) 13.0 min; $[\alpha]^{20}_D$ +50.5 (*c* 5.5, $CHCl_3$); IR ν_{max} (liquid film) 3500, 3100, 1700, 1650, 1260 cm^{-1}; ^{1}H NMR δ (250 MHz, $CDCl_3$) 5.08 (1H, br s), 4.92 (1H, m), 4.90 (1H, br s), 4.82 (1H, m), 4.29 (1H, br s), 4.16 (1H, d, J = 8.0 Hz), 3.34 (1H, d, J = 2.0 Hz), 3.00 (1H, dq, J = 8.0, 6.8 Hz), 2.62 (1H, qd, J = 7.3, 1.7 Hz), 2.24−1.94 (2H, m), 1.62 (3H, s), 1.12 (3H, d, J = 6.8 Hz), 1.05 (3H, t, J = 7.4 Hz), 1.01 (3H, d, J = 7.3 Hz), 0.88 (9H, s), 0.05 (3H, s), −0.02 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 219.1, 151.5, 142.9, 111.4, 110.6, 78.8, 72.2, 50.7, 48.1, 25.7, 22.6, 19.7, 18.1, 14.1, 11.5, 8.3, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 355.2668, $C_{20}H_{39}O_3Si$ requires 355.2668; HRMS *m*/*z* (relative intensity) 355 ($[M + H]^+$, 5), 285 (53), 270 (8), 227 (13), 199 (100), 153 (59). Anal. Found: C, 67.48; H, 10.81. $C_{20}H_{38}O_3Si$ requires: C, 67.74; H, 10.80.

(3S,4S,6R,7R)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-4,6,8-trimethyl-7-(propanoyloxy)-1,8-nonadien-5-one (12). To a stirred solution of alcohol **11-*SS*** (637 mg, 1.80 mmol) and DMAP (catalyst) in CH_2Cl_2 (15 mL) was added Et_3N (0.50 mL, 3.60 mmol). The reaction mixture was cooled to 0 °C, and propionic anhydride (0.46 mL, 3.60 mmol) was added. The reaction mixture was stirred at 20 °C for 2 h, until complete as followed by TLC. The reaction mixture was then quenched with sodium bicarbonate solution (25 mL, saturated) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with hydrochloric acid (20 mL, 1 N aqueous), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (CH_2Cl_2) gave a colorless oil **12** (690 mg, 94%): R_f (CH_2Cl_2) 0.53; $[\alpha]^{20}_D$ −3.8 (*c* 2.4, $CHCl_3$); IR ν_{max} (liquid film) 3100, 1745, 1710, 1650, 1260 cm^{-1}; ^{1}H NMR δ (250 MHz, $CDCl_3$) 5.38 (1H, d, J = 4.4 Hz), 4.91 (1H, br s), 4.87 (1H, br s), 4.84 (1H, m), 4.78 (1H, m), 4.27 (1H, d, J = 7.0 Hz), 2.84 (1H, dq ≡ qn, J = 7.0 Hz), 2.77 (1H, qd, J = 7.1, 4.4 Hz), 2.31 (2H, br q, J = 7.4 Hz), 2.15−1.85 (2H, m), 1.68 (3H, s), 1.12 (3H, d, J = 7.0 Hz), 1.11 (3H, t, J = 7.4 Hz), 1.09 (3H, d, J = 7.1 Hz), 1.01 (3H, t, J = 7.4 Hz), 0.85 (9H, s), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 212.5, 173.0, 151.2, 141.6, 112.6, 110.6, 77.3, 74.5, 49.6, 47.2, 27.6, 25.8, 22.9, 19.5, 18.1, 13.4, 11.6, 10.5, 9.0, −4.6, −5.2; HRMS (CI, NH_3) $[M + H]^+$ found 411.2931, $C_{23}H_{43}O_4Si$ requires 411.2931; HRMS *m*/*z* (relative intensity) 411 ($[M + H]^+$, 17), 337 (25), 279 (23), 255 (18), 199 (100), 183 (36). Anal. Found: C, 67.43; H, 10.39. $C_{23}H_{42}O_4Si$ requires: C, 67.27; H, 10.31.

Methyl (2S,4E,6R,8S,9S)-9-[(*tert*-Butyldimethylsilyl)oxy]-10-ethyl-2,4,6,8-tetramethyl-7-oxo-4,10-undecadienoate (14). To a cooled (−78 °C) stirred solution of propi-

onate ester **12** (403 mg, 0.98 mmol) in THF (20 mL) was added a freshly prepared 1:1 v/v mixture of trimethylsilyl chloride: triethylamine (1.24 mL, 4.91 mmol TMSCl), followed by cooled (−78 °C) lithium diisopropylamide (2.74 mL, 1.37 mmol, 0.5 M in THF). The reaction mixture was stirred at −78 °C for 90 min, then warmed to 20 °C for a further 2 h, and finally diluted with THF (5 mL), heated to reflux, and stirred for 4 h. The solution was diluted with ether (25 mL) and washed with hydrochloric acid (2 × 20 mL, 1 N aqueous). In order to ensure the complete hydrolysis of the silyl ester, it was found to be necessary to partially concentrate the organics and stir them vigorously with hydrochloric acid (20 mL, 1 N aqueous) at 20 °C for 2 h. The organics were then washed with brine (25 mL, saturated), dried ($MgSO_4$), and concentrated *in vacuo* to give a viscous oil which was resuspended in ether (~5 mL) and cooled to 0 °C. This mixture was then treated cautiously with a stock solution of diazomethane (~0.3 M in Et_2O), which was added dropwise until the reaction was complete as followed by TLC. The resulting oil was purified by flash column chromatography (CH_2Cl_2) to give a small amount of starting material **12** (24 mg, 6% recovery) and a colorless oil (308 mg, 74% (79% conversion)). HPLC separation (5% EtOAc in hexane) showed a diastereomeric ratio of 1,5-*syn*:1,5-*anti* products **14**:**15** of 96:4. Major diastereomer: R_f (CH_2Cl_2) 0.44; HPLC t_R (5% EtOAc in hexane) 17.3 min; $[\alpha]^{20}_D$ −89.7 (*c* 2.9, $CHCl_3$); IR ν_{max} (liquid film) 3080, 1735, 1705, 1650, 1255 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.03 (1H, d, J = 9.8 Hz), 4.90 (1H, br s), 4.76 (1H, br s), 4.29 (1H, d, J = 8.1 Hz), 3.66 (3H, s), 3.40 (1H, dq, J = 9.8, 6.9 Hz), 2.83 (1H, dq, J = 8.1, 7.0 Hz), 2.60 (1H, ddq ≡ dqn, J = 8.5, 6.8 Hz), 2.40 (1H, dd, J = 13.7, 6.8 Hz), 2.14−2.04 (1H, m), 2.02 (1H, dd, J = 13.7, 8.5 Hz), 1.94−1.84 (1H, m), 1.65 (3H, s), 1.09 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.05 (3H, d, J = 6.8 Hz), 1.00 (3H, t, J = 7.4 Hz), 0.87 (9H, s), 0.04 (3H, s), −0.03 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.7, 176.8, 151.3, 134.4, 126.4, 110.7, 77.5, 51.6, 49.8, 45.8, 43.4, 37.5, 25.8, 22.5, 19.5, 18.1, 16.6, 16.3, 16.1, 11.5, −4.5, −5.1; HRMS (CI, NH_3) [M + H]$^+$ found 425.3087, $C_{24}H_{45}O_4Si$ requires 425.3087; HRMS *m*/*z* (relative intensity) 442 ([M + NH_4]$^+$, 2), 425 ([M + H]$^+$, 31), 339 (9), 293 (100), 199 (68), 169 (40), 132 (14). Anal. Found: C, 67.91; H, 10.65. $C_{24}H_{44}O_4Si$ requires: C, 67.88; H, 10.44.

(2*S*,4*E*,6*R*,8*S*,9*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-10-ethyl-2,4,6,8-tetramethyl-7-oxo-4,10-undecadienal (17). To a cooled (−98 °C) stirred solution of methyl ester **14** (270 mg, 0.64 mmol) in ether (13 mL) was added *via* cannula a cooled (−78 °C) solution of DIBAL-H (0.89 mL, 0.89 mmol, 1.0 M solution in hexanes) in ether (7.0 mL). The reaction mixture was stirred for 20 min, until there was no further change as followed by TLC. The reaction mixture was quenched at −98 °C with methanol (5 mL) and then allowed to warm to 20 °C while MeOH (5 mL) and then ammonium chloride solution (10 mL, saturated) were added. The reaction mixture was then partitioned between ammonium chloride solution (25 mL, saturated) and ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered through Celite in an attempt to remove some of the aluminium salts, and concentrated *in vacuo*. Flash chromatography (CH_2Cl_2) of the resultant oil allowed for the isolation of some unreacted methyl ester **14** (20.1 mg, 8% recovery), the aldehyde **17** as a colorless oil (197 mg, 79% (85% conversion)), and a trace of over-reduction products **18** and **19** (8.2 mg, ~3%). The aldehyde was found to be stable and could be stored in the freezer (−20 °C) for several weeks without decomposition: R_f (CH_2Cl_2) 0.33, (10% EtOAc in hexane) 0.35; $[\alpha]^{20}_D$ −103.0 (*c* 1.1, $CHCl_3$); IR ν_{max} (liquid film) 3100, 2720, 1735, 1720, 1650, 1255 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 9.61 (1H, d, J = 1.7 Hz), 5.05 (1H, br d, J = 9.8 Hz), 4.88 (1H, br s), 4.74 (1H, m), 4.26 (1H, d, J = 8.0 Hz), 3.41 (1H, dq, J = 9.8, 6.9 Hz), 2.82 (1H, dq, J = 8.0, 7.0 Hz), 2.53−2.43 (1H, m), 2.43 (1H, dd, J = 13.2, 5.7 Hz), 2.14−2.00 (1H, m), 1.92 (1H, dd, J = 13.2, 8.4 Hz), 1.97−1.82 (1H, m), 1.64 (3H, s), 1.08 (3H, d, J = 7.0 Hz), 1.03 (3H, d, J = 6.9 Hz), 1.00 (3H, d, J = 6.8 Hz), 0.99 (3H, t, J = 7.5 Hz), 0.86 (9H, s), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.5, 204.5, 151.3, 133.6, 126.8, 110.7, 77.5, 50.0, 45.8, 44.2, 40.3, 25.8, 22.5, 18.2, 16.7, 16.1, 14.2, 12.8, 11.5, −4.6, −5.1; HRMS (CI, NH_3) [M + H]$^+$ found 395.2981, $C_{23}H_{43}O_3Si$ requires 395.2981; HRMS *m*/*z* (relative intensity) 395 ([M + H]$^+$, 14), 263 (93), 199 (100). Anal. Found: C, 70.05; H, 10.80. $C_{23}H_{42}O_3Si$ requires: C, 70.00; H, 10.73.

***tert*-Butyl (2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenethioate (28).** To a cooled (0 °C) stirred solution of dicyclohexylchloroborane (0.82 mL, 3.8 mmol) in ether (1.0 mL) was added triethylamine (0.64 mL, 4.6 mmol) and then thioester **25** (0.88 mL, 5.7 mmol). The reaction mixture was stirred at 0 °C for 2 h and then cooled to −78 °C, and a solution of the aldehyde **17** (99.7 mg, 0.25 mmol) in ether (1 mL, +0.5 mL washings) was added *via* cannula. The reaction mixture was stirred for 2 h at −78 °C and then transferred to the refrigerator (−4 °C) for 12 h. The aldol products were oxidized and isolated as described for aldol adduct **11**. Flash chromatography (10% EtOAc in hexane) allowed for isolation of the diastereomers, which were separated by HPLC (5% EtOAc in hexane) to give the colorless oils **28** (42.4 mg) and **29** (50.4 mg) and a trace of the *syn* aldol adducts (3.7 mg), *i.e.* 71% overall yield in a 44:52:4 ratio **28**:**29**:*syn*. anti-Felkin adduct: R_f (CH_2Cl_2) 0.19; HPLC t_R (5% EtOAc in hexane) 25 min; $[\alpha]^{20}_D$ −63.0 (*c* 0.5, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 1715, 1665, 1650 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 4.94 (1H, d, J = 9.8 Hz), 4.88 (1H, br s), 4.74 (1H, br s), 4.29 (1H, d, J = 8.1 Hz), 3.41 (1H, dq, J = 9.8, 6.9 Hz), 3.29 (1H, ddd ≡ dt, J = 8.6, 4.9 Hz), 2.83 (1H, dq, J = 8.1, 6.9 Hz), 2.79 (1H, qd, J = 7.1, 4.9 Hz), 2.70 (1H, d, J = 8.6 Hz), 2.41 (1H, br d, J = 11.5 Hz), 2.11−2.01 (1H, m), 1.92−1.82 (1H, m), 1.73−1.66 (1H, m), 1.65 (1H, d, J = 11.5 Hz), 1.61 (3H, s), 1.45 (9H, s), 1.26 (3H, d, J = 7.1 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.04 (3H, d, J = 6.9 Hz), 0.98 (3H, t, J = 7.4 Hz), 0.86 (9H, s), 0.81 (3H, d, J = 6.2 Hz), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.8, 206.1, 151.4, 135.9, 125.8, 110.6, 79.0, 77.5, 50.0, 49.8, 48.5, 45.9, 41.9, 34.9, 29.6, 25.8, 22.4, 18.2, 16.6, 16.3, 16.0, 15.8, 14.4, 11.5, −4.6, −5.1; HRMS (CI, NH_3) [M + H]$^+$ found 541.3745, $C_{30}H_{57}O_4SSi$ requires 541.3747; HRMS *m*/*z* (relative intensity) 541 ([M + H]$^+$, 8), 451 (6), 409 (65), 319 (36), 263 (27), 199 (100). Anal. Found: C, 66.46; H, 10.50; S, 5.96. $C_{30}H_{56}O_4SSi$ requires: C, 66.61; H, 10.43; S, 5.93.

***tert*-Butyl (2*R*,3*R*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenethioate (29).** Felkin-Anh adduct: R_f (CH_2Cl_2) 0.16; HPLC t_R (5% EtOAc in hexane) 27 min; $[\alpha]^{20}_D$ −85.6 (*c* 2.1, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 1710, 1660 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.00 (1H, d, J = 9.8 Hz), 4.91 (1H, br s), 4.75 (1H, br s), 4.28 (1H, d, J = 8.1 Hz), 3.46 (1H, ddd ≡ td, J = 7.1, 4.3 Hz), 3.39 (1H, dq, J = 9.8, 6.9 Hz), 2.84 (1H, dq, J = 8.1, 6.9 Hz), 2.79 (1H, dq ≡ qn, J = 7.1 Hz), 2.43 (1H, d, J = 7.2 Hz), 2.13 (1H, dd, J = 13.3, 5.0 Hz), 2.12−2.04 (1H, m), 1.94−1.85 (1H, m), 1.84 (1H, dd, J = 13.3, 9.7 Hz), 1.77−1.70 (1H, m), 1.62 (3H, s), 1.45 (9H, s), 1.16 (3H, d, J = 7.1 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.05 (3H, d, J = 6.9 Hz), 1.00 (3H, t, J = 7.4 Hz), 0.86 (9H, s), 0.79 (3H, d, J = 6.6 Hz), 0.03 (3H, s), −0.04 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.0, 205.3, 151.3, 135.4, 125.9, 110.7, 77.6, 76.8, 51.3, 49.7, 48.3, 45.9, 44.1, 33.6, 29.7, 25.8, 22.4, 18.2, 16.6, 16.1, 15.7, 14.4, 12.6, 11.5, −4.6, −5.1; HRMS (CI, NH_3) [M + H]$^+$ found 541.3745, $C_{30}H_{57}O_4SSi$ requires 541.3747; HRMS *m*/*z* (relative intensity) 541 ([M + H]$^+$, 8), 451 (6), 409 (65), 319 (58), 263 (31), 199 (100). Anal. Found: C, 66.40; H, 10.47; S, 6.14. $C_{30}H_{56}O_4SSi$ requires: C, 66.61; H, 10.43; S, 5.93.

***tert*-Butyl (2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-3-hydroxy-4,6,8,10-tetramethyl-12-methylene-9-oxo-6-tetradecenethioate (35).** To a cooled (0 °C) stirred solution of dicyclohexylchloroborane (0.82 mL, 3.8 mmol) in ether (1.0 mL) was added triethylamine (0.64 mL, 4.6 mmol) and then thioester **32** (0.94 mL, 5.7 mmol). The reaction mixture was stirred at 0 °C for 2 h and then cooled to −78 °C, and a solution of the aldehyde **17** (89.4 mg, 0.23 mmol) in ether (1 mL, +0.5 mL washings) was added *via* cannula. The reaction mixture was stirred for 5 h at −78 °C and then transferred to the refrigerator (−4 °C) for 16 h. The aldol products were oxidized and isolated as described for aldol adduct **11**. Flash chromatography (10% EtOAc in hexane)

allowed for isolation of the diastereomers, which were separated by HPLC (8% EtOAc in hexane) to give the colorless oils **35** (34.8 mg) and **36** (58.3 mg) and a trace of the *syn* aldol adducts (1.6 mg), *i.e.* 75% overall yield in a 37:61:2 ratio **35**:**36**:*syn*. anti-Felkin adduct: R_f (10% EtOAc in hexane) 0.24; HPLC t_R (8% EtOAc in hexane) 12.5 min; $[\alpha]^{20}_D$ −64.5 (*c* 0.7, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 3085, 1705, 1650 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 4.93 (1H, d, J = 9.8 Hz), 4.88 (1H, br s), 4.74 (1H, br s), 4.29 (1H, d, J = 8.1 Hz), 3.42 (1H, dq, J = 9.8, 6.9 Hz), 3.27 (1H, ddd ≡ dt, J = 8.4, 3.8 Hz), 2.83 (1H, dq, J = 8.1, 6.9 Hz), 2.82 (1H, d, J = 8.4 Hz), 2.61 (1H, ddd, J = 8.4, 6.3, 3.8 Hz), 2.51 (1H, br d, J = 11.8 Hz), 2.10−2.03 (1H, m), 1.91−1.83 (1H, m), 1.88−1.79 (1H, m), 1.70−1.59 (3H, m), 1.60 (3H, s), 1.49 (9H, s), 1.08 (3H, d, J = 6.9 Hz), 1.03 (3H, d, J = 6.9 Hz), 0.97 (3H, t, J = 7.4 Hz), 0.96 (3H, t, J = 7.4 Hz), 0.86 (9H, s), 0.79 (3H, d, J = 6.3 Hz), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.8, 206.0, 151.4, 136.1, 125.8, 110.6, 77.7, 77.5, 56.9, 49.8, 48.8, 45.9, 42.6, 35.5, 29.6, 25.8, 24.2, 22.4, 18.2, 16.6, 16.0, 15.7, 14.4, 11.9, 11.5, −4.6, −5.1; HRMS (EI) $[M + H]^+$ found 555.3939, $C_{31}H_{59}O_4SSi$ requires 555.3903; HRMS *m*/*z* (relative intensity) 555 ($[M + H]^+$, 2), 536 (2), 497 (7), 468 (10), 413 (15), 255 (40), 225 (13), 199 (100). Anal. Found: C, 66.97; H, 10.62; S, 5.98. $C_{31}H_{58}O_4SSi$ requires: C, 67.10; H, 10.53; S, 5.78.

***tert*-Butyl (2*R*,3*R*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-3-hydroxy-4,6,8,10-tetramethyl-12-methylene-9-oxo-6-tetradecenethioate (36).** Felkin-Anh adduct: R_f (10% EtOAc in hexane) 0.22; HPLC t_R (8% EtOAc in hexane) 14.0 min; $[\alpha]^{20}_D$ −75.6 (*c* 0.7, $CHCl_3$); IR ν_{max} (liquid film) 3500, 3080, 1720, 1680, 1660 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 4.96 (1H, d, J = 9.8 Hz), 4.90 (1H, br s), 4.75 (1H, br s), 4.28 (1H, d, J = 8.1 Hz), 3.45−3.40 (1H, m), 3.39 (1H, dq, J = 9.8, 6.9 Hz), 2.84 (1H, dq, J = 8.1, 6.9 Hz), 2.56 (1H, ddd ≡ dt, J = 8.8, 5.6 Hz), 2.51 (1H, br s), 2.18 (1H, dd, J = 11.7, 3.3 Hz), 2.13−2.03 (1H, m), 1.94−1.84 (1H, m), 1.79−1.66 (3H, m), 1.63−1.56 (1H, m), 1.61 (3H, s), 1.46 (9H, s), 1.08 (3H, d, J = 6.9 Hz), 1.04 (3H, d, J = 6.9 Hz), 0.99 (3H, t, J = 7.4 Hz), 0.94 (3H, t, J = 7.5 Hz), 0.86 (9H, s), 0.80 (3H, d, J = 6.3 Hz), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.9, 205.1, 151.3, 135.4, 125.9, 110.7, 77.6, 76.2, 58.0, 49.7, 48.6, 45.8, 43.9, 34.4, 29.6, 25.8, 23.7, 22.4, 18.2, 16.6, 16.1, 14.3, 13.4, 11.7, 11.5, −4.6, −5.1; HRMS (EI) $[M]^+$ found 554.3828, $C_{31}H_{58}O_4SSi$ requires 554.3825; HRMS *m*/*z* (relative intensity) 554 ($[M]^+$, 2), 497 (6), 468 (2), 413 (20), 255 (30), 209 (48), 199 (70). Anal. Found: C, 66.88; H, 10.56; S, 5.61. $C_{31}H_{58}O_4SSi$ requires: C, 67.10; H, 10.53; S, 5.78.

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenoic Acid (44). To a cooled (0 °C) stirred solution of the thioester **28** (45.5 mg, 0.084 mmol) in THF:water (3:1, 2 mL overall) were added hydrogen peroxide (57 μL, 0.51 mmol, 30% aqueous) and lithium hydroxide monohydrate (7.1 mg, 0.17 mmol). The reaction mixture was stirred at 20 °C for 16 h and then quenched with sodium metabisulfite solution (2 mL, 1 N aqueous). The reaction mixture was diluted with water (10 mL), acidified to pH 1−2 (HCl, 1 N aqueous), and then extracted with ether (3 × 15 mL). The combined organic extracts were washed with pH 7 buffer solution (25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a viscous oil which was purified by flash chromatography (30% Et_2O in CH_2Cl_2, +1% AcOH) to give acid **44** (35.5 mg, 90%): R_f (30% Et_2O in CH_2Cl_2, +1% AcOH) 0.48; $[\alpha]^{20}_D$ −62.6 (*c* 0.5, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 3300−2800, 1705, 1645 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.00 (1H, d, J = 9.7 Hz), 4.87 (1H, br s), 4.74 (1H, m), 4.25 (1H, d, J = 8.2 Hz), 3.43 (1H, dd ≡ t, J = 5.3 Hz), 3.38 (1H, dq, J = 9.7, 6.9 Hz), 2.88 (1H, dq, J = 8.2, 6.9 Hz), 2.75 (1H, qd, J = 7.2, 5.3 Hz), 2.30 (1H, br d, J = 8.9 Hz), 2.14−2.01 (1H, m), 1.96−1.84 (1H, m), 1.86−1.72 (2H, m), 1.60 (3H, s), 1.31 (3H, d, J = 7.2 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 0.99 (3H, t, J = 7.4 Hz), 0.86 (9H, s), 0.84 (3H, d, J = 6.3 Hz), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.4, 180.2, 151.2, 136.3, 125.9, 110.8, 78.1, 77.8, 49.6, 46.1, 42.6, 42.1, 34.5, 25.8, 22.3, 18.2, 16.6, 16.2, 16.1, 15.1, 14.5, 11.5, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 469.3352, $C_{26}H_{49}O_5Si$ requires 469.3349; HRMS *m*/*z* (relative intensity) 469 ($[M + H]^+$, 5), 451 (11), 385 (13), 337 (32), 253 (12), 199 (100), 171 (21). Anal. Found: C, 66.76; H, 10.19. $C_{26}H_{48}O_5Si$ requires: C, 66.62; H, 10.32.

(2*R*,3*R*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenoic Acid (52). The procedure described for **44** was followed with thioester **29** (37.5 mg, 0.069 mmol), to which was added hydrogen peroxide (47 μL, 0.42 mmol, 30% aqueous) and lithium hydroxide monohydrate (5.8 mg, 0.14 mmol). Isolation gave a viscous oil which was purified by flash chromatography (30% Et_2O in CH_2Cl_2, +1% AcOH) to give acid **52** (31.3 mg, 96%): R_f (30% Et_2O in CH_2Cl_2, +1% AcOH) 0.46; $[\alpha]^{20}_D$ −50.5 (*c* 1.7, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 3300−2800, 1705, 1645 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 5.40 (1H, br s), 5.06 (1H, d, J = 9.8 Hz), 4.88 (1H, br s), 4.74 (1H, m), 4.24 (1H, d, J = 8.2 Hz), 3.53 (1H, dd, J = 8.1, 3.2 Hz), 3.36 (1H, dq, J = 9.8, 6.9 Hz), 2.88 (1H, dq, J = 8.2, 6.9 Hz), 2.63 (1H, dq, J = 8.1, 7.2 Hz), 2.16−2.05 (2H, m), 1.99−1.85 (2H, m), 1.83−1.75 (1H, m), 1.60 (3H, s), 1.31 (3H, d, J = 7.2 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.00 (3H, t, J = 7.4 Hz), 0.86 (9H, s), 0.81 (3H, d, J = 6.6 Hz), 0.03 (3H, s), −0.04 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.7, 180.7, 151.3, 135.1, 126.1, 110.7, 77.9, 75.2, 49.8, 46.0, 44.2, 43.1, 32.6, 25.8, 22.4, 18.2, 16.7, 16.1, 14.4, 14.2, 12.0, 11.5, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 469.3349, $C_{26}H_{49}O_5Si$ requires 469.3349; HRMS *m*/*z* (relative intensity) 469 ($[M + H]^+$, 5), 451 (12), 385 (15), 337 (83), 319 (12), 253 (17), 199 (100), 171 (27). Anal. Found: C, 66.49; H, 10.45. $C_{26}H_{48}O_5Si$ requires: C, 66.62; H, 10.32.

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-3-hydroxy-4,6,8,10-tetramethyl-12-methylene-9-oxo-6-tetradecenoic Acid (53). The procedure described for **44** was followed with thioester **35** (20.0 mg, 0.036 mmol), to which were added hydrogen peroxide (25 μL, 0.22 mmol, 30% aqueous) and lithium hydroxide monohydrate (3.0 mg, 0.072 mmol). After a further 15 h, hydrogen peroxide (25 μL, 0.22 mmol, 30% aqueous) and lithium hydroxide monohydrate (3.0 mg, 0.072 mmol) were added and the reaction mixture was stirred at 20 °C for a total of 18 h. Isolation gave a viscous oil which was purified by flash chromatography (30% Et_2O in CH_2Cl_2, +1% AcOH) to give acid **53** (14.1 mg, 81%): R_f (50% Et_2O in CH_2Cl_2, +1% AcOH) 0.57; $[\alpha]^{20}_D$ −58.3 (*c* 1.3, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 3300−2800, 1745, 1705, 1645 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.00 (1H, d, J = 9.4 Hz), 4.87 (1H, br s), 4.75 (1H, m), 4.25 (1H, d, J = 8.2 Hz), 3.40 (1H, dd, J = 6.7, 3.7 Hz), 3.36 (1H, dq, J = 9.4, 6.9 Hz), 2.89 (1H, dq, J = 8.2, 6.9 Hz), 2.59−2.54 (1H, m), 2.36 (1H, dd ≡ q, J = 9.2 Hz), 2.14−2.04 (1H, m), 1.95−1.84 (1H, m), 1.89−1.67 (4H, m), 1.60 (3H, m), 1.09 (6H, d, J = 6.9 Hz), 1.00 (6H, t, J = 7.4 Hz), 0.86 (9H, s), 0.82 (3H, d, J = 6.0 Hz), 0.03 (3H, s), −0.04 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.5, 179.6, 151.2, 136.4, 125.8, 110.8, 77.8, 76.6, 49.7, 49.4, 46.1, 43.4, 35.2, 25.8, 23.3, 22.3, 18.2, 16.7, 16.2, 16.0, 14.5, 11.8, 11.5, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 483.3506, $C_{27}H_{51}O_5Si$ requires 483.3506; HRMS *m*/*z* (relative intensity) 483 ($[M + H]^+$, 9), 465 (18), 399 (23), 351 (67), 333 (11), 267 (18), 199 (100), 185 (21). Anal. Found: C, 66.99; H, 10.60. $C_{27}H_{50}O_5Si$ requires: C, 67.17; H, 10.44.

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenoic 1,3-Lactone (54). To a cooled (0 °C) stirred solution of acid **44** (13.5 mg, 0.029 mmol) in pyridine (0.5 mL) was added freshly distilled benzenesulfonyl chloride (15 μL, 0.12 mmol), and the reaction mixture was stirred at 0 °C for 5 min. The reaction mixture was placed in the freezer (−20 °C) for 17 h, and then further benzenesulfonyl chloride (7.5 μL, 0.06 mmol) was added at 0 °C. The reaction mixture was stirred for 10 min and then returned to the freezer (−20 °C) for a further 21 h. The reaction mixture was partitioned between water (5 mL) and ether (3 × 8 mL), and the combined organic extracts were washed with brine (15 mL, saturated), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (CH_2Cl_2) gave β-lactone **54** (11.0 mg, 85%) as a colorless oil: R_f (CH_2Cl_2) 0.49; $[\alpha]^{20}_D$ −110 (*c* 0.7, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3085, 1820, 1705, 1645 cm^{-1}; ^1H NMR δ

(400 MHz, $CDCl_3$) 5.01 (1H, d, J = 9.7 Hz), 4.87 (1H, br s), 4.73 (1H, m), 4.26 (1H, d, J = 8.1 Hz), 3.85 (1H, dd, J = 8.6, 4.0 Hz), 3.41 (1H, dq, J = 9.7, 6.9 Hz), 3.25 (1H, qd, J = 7.5, 4.0 Hz), 2.83 (1H, dq, J = 8.1, 6.9 Hz), 2.32 (1H, dd, J = 13.2, 4.0 Hz), 2.12−2.02 (1H, m), 1.98−1.89 (1H, m), 1.91−1.81 (1H, m), 1.71 (1H, dd, J = 13.2, 10.2 Hz), 1.63 (3H, s), 1.37 (3H, d, J = 7.5 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.04 (3H, d, J = 6.9 Hz), 0.97 (3H, t, J = 7.4 Hz), 0.85 (9H, s), 0.80 (3H, d, J = 6.8 Hz), 0.01 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.7, 171.8, 151.3, 133.9, 126.7, 110.6, 82.7, 77.6, 49.9, 48.9, 45.8, 42.7, 35.3, 25.8, 22.4, 18.1, 16.8, 16.0, 14.3, 13.1, 12.8, 11.5, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 451.3244, $C_{26}H_{47}O_4Si$ requires 451.3244; HRMS m/z (relative intensity) 468 ($[M + NH_4]^+$, 7), 451 ($[M + H]^+$, 24), 367 (8), 319 (100), 199 (21). Anal. Found: C, 69.22; H, 10.33. $C_{26}H_{46}O_4Si$ requires: C, 69.28; H, 10.29.

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-3-hydroxy-4,6,8,10-tetramethyl-12-methylene-9-oxo-6-tetradecenoic 1,3-Lactone (55). The procedure described for **54** was followed with acid **53** (24.2 mg, 0.050 mmol), to which were added benzenesulfonyl chloride (39 μL, 0.30 mmol). Flash chromatography (CH_2Cl_2) gave β-lactone **55** (19.8 mg, 85%) as a colorless oil: R_f (CH_2Cl_2) 0.57; $[\alpha]^{20}_D$ −113 (c 0.8, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3085, 1820, 1710, 1645 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.01 (1H, d, J = 9.8 Hz), 4.88 (1H, br s), 4.74 (1H, m), 4.27 (1H, d, J = 8.1 Hz), 3.91 (1H, dd, J = 8.6, 3.9 Hz), 3.44 (1H, dq, J = 9.8, 6.9 Hz), 3.19 (1H, ddd, J = 8.1, 6.7, 3.9 Hz), 2.85 (1H, dq, J = 8.1, 6.9 Hz), 2.36 (1H, dd, J = 13.0, 3.6 Hz), 2.14−2.04 (1H, m), 1.98−1.88 (1H, m), 1.95−1.84 (1H, m), 1.89−1.64 (3H, m), 1.63 (3H, s), 1.08 (3H, d, J = 6.9 Hz), 1.05 (3H, d, J = 6.9 Hz), 1.03 (3H, t, J = 7.6 Hz), 0.98 (3H, t, J = 7.4 Hz), 0.86 (9H, s), 0.80 (3H, d, J = 6.8 Hz), 0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.7, 171.3, 151.3, 134.1, 126.7, 110.6, 81.1, 77.5, 55.7, 50.0, 45.8, 42.7, 35.3, 25.8, 22.4, 21.3, 18.2, 16.7, 16.0, 14.3, 13.2, 11.5, 11.4, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 465.3400, $C_{27}H_{49}O_4Si$ requires 465.3400; HRMS m/z (relative intensity) 465 ($[M + H]^+$, 8), 381 (5), 333 (100), 199 (52), 139 (25). Anal. Found: C, 69.92; H, 10.58. $C_{27}H_{48}O_4Si$ requires: C, 69.78; H, 10.41.

(2*R*,3*R*,4*S*,6*E*,8*R*,10*S*,11*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenoic 1,3-Lactone (56). The procedure described for **54** was followed with acid **52** (27.1 mg, 0.058 mmol), to which was added benzenesulfonyl chloride (43 μL, 0.34 mmol). Flash chromatography (CH_2Cl_2) gave β-lactone **56** (21.9 mg, 84%) as a colorless oil: R_f (CH_2Cl_2) 0.48; $[\alpha]^{20}_D$ −69.4 (c 0.8, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3085, 1820, 1710, 1645 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.05 (1H, d, J = 9.7 Hz), 4.87 (1H, br s), 4.73 (1H, m), 4.25 (1H, d, J = 8.0 Hz), 3.89 (1H, dd, J = 7.8, 4.0 Hz), 3.39 (1H, dq, J = 9.7, 6.9 Hz), 3.25 (1H, qd, J = 7.5, 4.0 Hz), 2.83 (1H, dq, J = 8.0, 6.9 Hz), 2.12−2.04 (1H, m), 2.05 (1H, dd, J = 13.2, 4.5 Hz), 1.98−1.85 (1H, m), 1.93−1.81 (1H, m), 1.72 (1H, dd, J = 13.2, 10.3 Hz), 1.62 (3H, s), 1.36 (3H, d, J = 7.5 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.05 (3H, d, J = 6.9 Hz), 0.97 (3H, t, J = 7.4 Hz), 0.90 (3H, d, J = 6.5 Hz), 0.85 (9H, s), 0.01 (3H, s), −0.06 (3H, s); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 213.5, 171.8, 151.3, 133.4, 127.0, 110.6, 83.3, 77.6, 49.9, 48.8, 45.9, 41.5, 35.2, 25.8, 22.4, 18.1, 16.8, 16.1, 14.5, 14.3, 12.8, 11.5, −4.6, −5.1; HRMS (CI, NH_3) $[M + H]^+$ found 451.3244, $C_{26}H_{47}O_4Si$ requires 451.3244; HRMS m/z (relative intensity) 468 ($[M + NH_4]^+$, 4), 451 ($[M + H]^+$, 22), 367 (8), 319 (100), 199 (23). Anal. Found: C, 69.20; H, 10.18. $C_{26}H_{46}O_4Si$ requires: C, 69.28; H, 10.29.

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-3,11-Dihydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenoic 1,3-Lactone (58). To a stirred solution of the silyl-protected β-lactone **54** (21.8 mg, 0.048 mmol) in acetonitrile (0.8 mL) was added hydrofluoric acid (200 μL; 40% aqueous). The reaction mixture was stirred at 20 °C for 1 h, until complete as followed by TLC. Solid sodium bicarbonate was added cautiously until effervescence stopped. The reaction mixture was then washed through a short plug of $MgSO_4$ with ether and concentrated *in vacuo*. Flash chromatography (10% Et_2O in CH_2Cl_2) gave alcohol **58** (16.3 mg, 99%) as a colorless oil: R_f (10% Et_2O in CH_2Cl_2) 0.42; $[\alpha]^{20}_D$ −210 (c 1.0, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3500, 1820, 1695, 1650 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.11 (1H, br s), 5.03 (1H, d, J = 9.8 Hz), 4.93 (1H, m), 4.33 (1H, br s), 3.84 (1H, dd, J = 8.7, 4.1 Hz), 3.58 (1H, dq, J = 9.8, 6.7 Hz), 3.26 (1H, qd, J = 7.5, 4.1 Hz), 3.10 (1H, br s), 2.81 (1H, qd, J = 7.1, 2.9 Hz), 2.35 (1H, dd, J = 13.2, 4.1 Hz), 2.00−1.92 (1H, m), 1.96−1.79 (2H, m), 1.79 (1H, dd, J = 13.2, 9.8 Hz), 1.69 (3H, s), 1.37 (3H, d, J = 7.5 Hz), 1.10 (3H, d, J = 6.7 Hz), 1.03 (3H, d, J = 7.1 Hz), 1.02 (3H, t, J = 7.3 Hz), 0.80 (3H, d, J = 6.7 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 216.9, 171.7, 149.1, 135.5, 126.3, 109.5, 82.9, 72.8, 49.2, 46.0, 45.3, 42.9, 35.4, 25.5, 16.3 (2 C's), 13.4, 12.8, 12.1, 9.8; HRMS (CI, NH_3) $[M + H]^+$ found 337.2379, $C_{20}H_{33}O_4$ requires 337.2379; HRMS m/z (relative intensity) 337 ($[M + H]^+$, 2), 319 (13), 270 (22), 253 (100), 197 (27).

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*S*)-2-Ethyl-3,11-dihydroxy-4,6,8,10-tetramethyl-12-methylene-9-oxo-6-tetradecenoic 1,3-Lactone (59). The procedure described for **58** was followed with silyl-protected β-lactone **55** (19.5 mg, 0.042 mmol) to give alcohol **59** (13.4 mg, 91%) as a colorless oil: R_f (10% Et_2O in CH_2Cl_2) 0.49; $[\alpha]^{20}_D$ −192 (c 1.1, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3520, 1820, 1695, 1650 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.12 (1H, m), 5.03 (1H, d, J = 9.8 Hz), 4.93 (1H, m), 4.33 (1H, br s), 3.90 (1H, dd, J = 8.8, 3.9 Hz), 3.58 (1H, dq, J = 9.8, 6.7 Hz), 3.18 (1H, ddd, J = 8.2, 6.7, 3.9 Hz), 3.11 (1H, d, J = 2.3 Hz), 2.82 (1H, qd, J = 7.1, 2.9 Hz), 2.38 (1H, dd, J = 13.0, 3.8 Hz), 1.98−1.71 (6H, m), 1.70 (3H, s), 1.11 (3H, d, J = 6.7 Hz), 1.04 (3H, d, J = 7.1 Hz), 1.03 (3H, t, J = 7.4 Hz), 1.03 (3H, t, J = 7.4 Hz), 0.83 (3H, d, J = 6.8 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 217.0, 171.2, 149.1, 135.6, 126.3, 109.5, 81.1, 72.8, 55.9, 45.9, 45.4, 42.8, 35.4, 25.5, 21.3, 16.3 (2 C's), 13.6, 12.1, 11.4, 9.8; HRMS (CI, NH_3) $[M + H]^+$ found 351.2535, $C_{21}H_{35}O_4$ requires 351.2535; HRMS m/z (relative intensity) 368 ($[M + NH_4]^+$, 9), 351 ($[M + H]^+$, 22), 333 (79), 284 (31), 267 (100), 197 (29).

(2*R*,3*R*,4*S*,6*E*,8*R*,10*S*,11*S*)-3,11-Dihydroxy-2,4,6,8,10-pentamethyl-12-methylene-9-oxo-6-tetradecenoic 1,3-Lactone (60). The procedure described for **58** was followed with silyl-protected β-lactone **56** (27.5 mg, 0.061 mmol) to give alcohol **60** (19.9 mg, 97%) as a colorless oil: R_f (10% Et_2O in CH_2Cl_2) 0.45; $[\alpha]^{20}_D$ −143 (c 1.1, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3515, 1820, 1695, 1650 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.11 (1H, br s), 5.08 (1H, d, J = 9.8 Hz), 4.93 (1H, m), 4.33 (1H, br s), 3.91 (1H, dd, J = 7.5, 4.1 Hz), 3.57 (1H, dq, J = 9.8, 6.7 Hz), 3.27 (1H, qd, J = 7.6, 4.1 Hz), 3.06 (1H, br s), 2.80 (1H, qd, J = 7.2, 3.0 Hz), 2.11 (1H, dd, J = 13.0, 4.0 Hz), 2.00−1.93 (1H, m), 1.99−1.81 (2H, m), 1.78 (1H, dd, J = 13.0, 10.2 Hz), 1.70 (3H, s), 1.36 (3H, d, J = 7.6 Hz), 1.12 (3H, d, J = 6.7 Hz), 1.03 (3H, d, J = 7.2 Hz), 1.03 (3H, t, J = 7.4 Hz), 0.92 (3H, d, J = 6.6 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 216.7, 171.6, 149.0, 134.8, 126.7, 109.5, 83.0, 72.9, 48.6, 46.0, 45.3, 41.4, 35.0, 25.4, 16.5, 16.3, 14.4, 12.8, 12.1, 9.8; HRMS (CI, NH_3) $[M + H]^+$ found 337.2379, $C_{20}H_{33}O_4$ requires 337.2379; HRMS m/z (relative intensity) 354 ($[M + NH_4]^+$, 11), 337 ($[M + H]^+$, 10), 319 (56), 270 (39), 253 (100), 235 (21), 197 (28).

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*R*,12*R*)-3,11-Dihydroxy-2,4,6,8,10,12-hexamethyl-9-oxo-6-tetradecenoic 1,3-Lactone (Ebelactone A (1)). The allylic alcohol **58** (9.3 mg, 0.028 mmol) and Wilkinson's catalyst, $Rh(PPh_3)_3Cl$ (12.8 mg, 0.014 mmol), were dissolved in benzene (1.0 mL), and the resultant mixture was stirred until homogeneous and pale brown in color. The solution was thoroughly degassed by the freeze−thaw techniques. The flask was then flushed with hydrogen (H_2-filled double balloon) and the reaction mixture stirred at 20 °C for 15 h, prior to removal of the solvent *in vacuo*. Flash chromatography (10% Et_2O in CH_2Cl_2) allowed for the isolation of the reduction products. HPLC separation (35% EtOAc in hexane) gave the *anti* (4.4 mg) and *syn* (2.8 mg) reduced products (77% overall yield, 61:39 ratio *anti:syn*). Trituration of the major product with hexane resulted in the formation of colorless needles.

Major diastereomer 1: mp 81−83 °C (lit.[3b] mp 86 °C); R_f (40% EtOAc in hexane) 0.41; HPLC t_R (35% EtOAc in hexane) 14.0 min; $[\alpha]^{20}_D$ −166 (c 0.3, MeOH), [lit.[3b] −221 (c 1.0, MeOH)]; IR ν_{max} (solution cell, $CHCl_3$) 3520, 1820, 1700 cm^{-1}; ^1H NMR

δ (400 MHz, $CDCl_3$) 5.02 (1H, d, J = 9.8 Hz), 3.86 (1H, dd, J = 8.7, 4.0 Hz), 3.58 (1H, dq, J = 9.8, 6.7 Hz), 3.49 (1H, ddd ≡ dt, J = 8.9, 2.3 Hz), 3.27 (1H, qd, J = 7.5, 4.0 Hz), 3.09 (1H, d, J = 2.3 Hz), 2.84 (1H, qd, J = 7.3, 2.3 Hz), 2.35 (1H, dd, J = 13.2, 4.1 Hz), 2.03–1.91 (1H, m), 1.79 (1H, dd, J = 13.2, 9.8 Hz), 1.78–1.72 (1H, m), 1.72 (3H, s), 1.47–1.40 (1H, m), 1.39 (3H, d, J = 7.5 Hz), 1.18–1.08 (1H, m), 1.12 (3H, d, J = 6.7 Hz), 1.10 (3H, d, J = 7.3 Hz), 0.87 (3H, t, J = 7.3 Hz), 0.85 (3H, d, J = 6.6 Hz), 0.77 (3H, d, J = 6.8 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 217.7, 171.7, 135.5, 126.4, 82.9, 74.4, 49.2, 45.3, 44.9, 42.7, 36.5, 35.5, 24.9, 16.4, 16.3, 14.8, 13.5, 12.8, 10.8, 9.3; HRMS (CI, NH_3) $[M + H]^+$ found 339.2534, $C_{20}H_{35}O_4$ requires 339.2535; HRMS m/z (relative intensity) 356 ($[M + NH_4]^+$, 8), 339 ($[M + H]^+$, 13), 321 (19), 270 (100), 253 (100), 235 (16), 209 (37), 197 (32).

Minor diastereomer (*epi*-C_{12} ebelactone A): R_f (40% EtOAc in hexane) 0.36; HPLC t_R (35% EtOAc in hexane) 16.3 min; $[\alpha]^{20}_D$ −238 (*c* 0.3, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3520, 1820, 1700 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.01 (1H, d, J = 9.8 Hz), 3.85 (1H, dd, J = 8.7, 4.1 Hz), 3.57 (1H, dq, J = 9.8, 6.7 Hz), 3.59–3.53 (1H, m), 3.27 (1H, qd, J = 7.5, 4.1 Hz), 2.86 (1H, qd, J = 7.1, 4.1 Hz), 2.69 (1H, br s), 2.36 (1H, dd, J = 13.2, 3.9 Hz), 2.01–1.93 (1H, m), 1.78 (1H, dd, J = 13.2, 10.0 Hz), 1.71 (3H, s), 1.44–1.32 (2H, m), 1.38 (3H, d, J = 7.5 Hz), 1.12–1.04 (1H, m), 1.11 (3H, d, J = 7.1 Hz), 1.10 (3H, d, J = 6.7 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.86 (3H, t, J = 7.4 Hz), 0.84 (3H, d, J = 6.7 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 216.9, 171.7, 135.4, 126.5, 82.9, 74.4, 49.2, 45.7, 45.4, 42.8, 36.7, 35.4, 25.6, 16.4, 16.3, 14.3, 13.4, 12.8, 10.9, 10.8; HRMS (CI, NH_3) $[M + H]^+$ found 339.2534, $C_{20}H_{35}O_4$ requires 339.2535; HRMS m/z (relative intensity) 356 ($[M + NH_4]^+$, 7), 339 ($[M + H]^+$, 20), 321 (100), 270 (35), 253 (96), 209 (8), 197 (7).

(2*S*,3*S*,4*S*,6*E*,8*R*,10*S*,11*R*,12*R*)-2-Ethyl-3,11-dihydroxy-4,6,8,10,12-pentamethyl-9-oxo-6-tetradecenoic 1,3-Lactone (Ebelactone B (2)). The procedure described for **1** was followed with allylic alcohol **59** (5.2 mg, 0.015 mmol) and Wilkinson's catalyst (6.9 mg, 0.007 mmol) dissolved in benzene (1.0 mL). The reaction mixture was stirred at 20 °C for 15 h. Flash chromatography (10% Et_2O in CH_2Cl_2) allowed for the isolation of the reduction products. HPLC separation (35% EtOAc in hexane) gave the *anti* (2.4 mg) and *syn* (1.8 mg) reduced products (80% overall yield, 57:43 ratio *anti:syn*). Trituration of the major product with hexane (a few drops) resulted in the formation of colorless needles.

Major diastereomer 2: mp 70–72 °C (lit.[3b] mp 77 °C); R_f (40% EtOAc in hexane) 0.50; HPLC t_R (35% EtOAc in hexane) 12.8 min; $[\alpha]^{20}_D$ −158 (*c* 0.4, MeOH), [lit.[3b] −203 (*c* 1, MeOH)]; IR ν_{max} (solution cell, $CHCl_3$) 3520, 1820, 1700 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 5.01 (1H, d, J = 9.9 Hz), 3.90 (1H, dd, J = 8.6, 3.9 Hz), 3.58 (1H, dq, J = 9.9, 6.7 Hz), 3.49 (1H, ddd ≡ dt, J = 8.7, 2.4 Hz), 3.18 (1H, ddd, J = 8.1, 6.8, 3.9 Hz), 3.08 (1H, d, J = 2.4 Hz), 2.83 (1H, qd, J = 7.3, 2.4 Hz), 2.37 (1H, dd, J = 13.0, 3.7 Hz), 2.01–1.93 (1H, m), 1.89–1.71 (4H, m), 1.71 (3H, s), 1.47–1.35 (1H, m), 1.14–1.04 (1H, m), 1.11 (3H, d, J = 6.7 Hz), 1.09 (3H, d, J = 7.3 Hz), 1.04 (3H, t, J = 7.4 Hz), 0.87 (3H, t, J = 7.4 Hz), 0.83 (3H, d, J = 6.7 Hz), 0.76 (3H, d, J = 6.8 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 217.7, 171.2, 135.5, 126.3, 81.1, 74.4, 55.9, 45.3, 45.0, 42.8, 36.5, 35.4, 24.9, 21.3, 16.4, 16.3, 14.8, 13.6, 11.4, 10.8, 9.3; HRMS (CI, NH_3) $[M + H]^+$ found 353.2690, $C_{21}H_{37}O_4$ requires 353.2692; HRMS m/z (relative intensity) 353 ($[M + H]^+$, 3), 335 (6), 284 (41), 267 (100), 249 (7), 223 (12), 197 (18).

Minor diastereomer (*epi*-C_{12} ebelactone B): R_f (40% EtOAc in hexane) 0.43; HPLC t_R (35% EtOAc in hexane) 14.5 min; $[\alpha]^{20}_D$ −217 (*c* 0.2, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3600, 1820, 1700 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.00 (1H, d, J = 9.9 Hz), 3.90 (1H, dd, J = 8.8, 4.0 Hz), 3.57 (1H, dq, J = 9.9, 6.7 Hz), 3.59–3.54 (1H, m), 3.18 (1H, ddd, J = 8.1, 6.8, 4.0 Hz), 2.85 (1H, qd, J = 7.2, 4.0 Hz), 2.69 (1H, br s), 2.38 (1H, dd, J = 13.2, 3.7 Hz), 1.98–1.91 (1H, m), 1.89–1.72 (3H, m), 1.71 (3H, s), 1.45–1.31 (2H, m), 1.10–1.02 (1H, m), 1.11 (3H, d, J = 7.2 Hz), 1.10 (3H, d, J = 6.7 Hz), 1.04 (3H, t, J = 7.5 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.86 (3H, t, J = 7.4 Hz), 0.83 (3H, d, J = 6.7 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 216.9, 171.2, 135.5, 126.4, 81.1, 74.5, 56.0, 45.6, 45.4, 42.8, 36.6, 35.4, 29.7, 25.6, 21.3, 16.3, 14.3, 13.6, 11.4, 10.9, 10.8; HRMS (CI, NH_3) $[M + H]^+$ found 353.2700, $C_{21}H_{37}O_4$ requires 353.2692; HRMS m/z (relative intensity) 353 ($[M + H]^+$, 4), 335 (14), 284 (42), 267 (100), 249 (4), 223 (10), 197 (17).

(2*R*,3*R*,4*S*,6*E*,8*R*,10*S*,11*R*,12*R*)-3,11-Dihydroxy-2,4,6,8,-10,12-hexamethyl-9-oxo-6-tetradecenoic 1,3-Lactone (bis-*epi*-Ebelactone A (63)). The procedure described for **1** was followed with allylic alcohol **60** (16.3 mg, 0.049 mmol) and Wilkinson's catalyst (9.0 mg, 0.010 mmol) dissolved in benzene (0.5 mL). Flash chromatography (10% Et_2O in CH_2Cl_2) allowed for the isolation of the reduction products. HPLC separation (40% EtOAc in hexane) gave the *anti* (7.5 mg) and *syn* (4.0 mg) reduced products (70% overall yield, 65:35 ratio *anti:syn*).

Major diastereomer 63: R_f (10% Et_2O in CH_2Cl_2) 0.44; HPLC t_R (40% EtOAc in hexane) 13.0 min; $[\alpha]^{20}_D$ −163 (*c* 0.7, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3520, 1820, 1700 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.06 (1H, d, J = 9.6 Hz), 3.91 (1H, dd, J = 7.6, 4.1 Hz), 3.57 (1H, dq, J = 9.6, 6.7 Hz), 3.49 (1H, ddd ≡ dt, J = 8.8, 2.4 Hz), 3.27 (1H, qd, J = 7.6, 4.1 Hz), 3.03 (1H, d, J = 2.4 Hz), 2.83 (1H, qd, J = 7.2, 2.4 Hz), 2.11 (1H, dd, J = 13.0, 3.9 Hz), 2.01–1.92 (1H, m), 1.79 (1H, dd, J = 13.0, 10.1 Hz), 1.79–1.70 (1H, m), 1.71 (3H, s), 1.46–1.40 (1H, m), 1.37 (3H, d, J = 7.6 Hz), 1.15–1.04 (1H, m), 1.12 (3H, d, J = 6.7 Hz), 1.09 (3H, d, J = 7.2 Hz), 0.93 (3H, d, J = 6.6 Hz), 0.87 (3H, t, J = 7.4 Hz), 0.76 (3H, d, J = 6.8 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 217.5, 171.7, 134.8, 126.7, 83.1, 74.4, 48.7, 45.3, 45.0, 41.4, 36.5, 35.0, 24.6, 16.5, 16.4, 14.8, 14.5, 12.9, 10.8, 9.3; HRMS (CI, NH_3) $[M + H]^+$ found 339.2534, $C_{20}H_{35}O_4$ requires 339.2535; HRMS m/z (relative intensity) 356 ($[M + NH_4]^+$, 12), 339 ($[M + H]^+$, 15), 321 (21), 270 (49), 253 (100), 209 (10), 197 (5).

Minor diastereomer: R_f (10% Et_2O in CH_2Cl_2) 0.37; HPLC t_R (40% EtOAc in hexane) 15.5 min; $[\alpha]^{20}_D$ −172 (*c* 0.4, $CHCl_3$); IR ν_{max} (solution cell, $CHCl_3$) 3600, 1820, 1700 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 5.05 (1H, d, J = 9.7 Hz), 3.92 (1H, dd, J = 7.6, 4.1 Hz), 3.57 (1H, dq, J = 9.7, 6.7 Hz), 3.58–3.55 (1H, m), 3.28 (1H, qd, J = 7.6, 4.1 Hz), 2.85 (1H, qd, J = 7.2, 4.1 Hz), 2.66 (1H, br s), 2.10 (1H, dd, J = 13.0, 4.1 Hz), 2.00–1.93 (1H, m), 1.78 (1H, dd, J = 13.0, 10.3 Hz), 1.71 (3H, s), 1.44–1.34 (1H, m), 1.37 (3H, d, J = 7.6 Hz), 1.38–1.31 (1H, m), 1.12–1.04 (1H, m), 1.12 (3H, d, J = 6.7 Hz), 1.11 (3H, d, J = 7.2 Hz), 0.93 (3H, d, J = 7.0 Hz), 0.91 (3H, d, J = 7.2 Hz), 0.86 (3H, t, J = 7.2 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 216.7, 171.7, 134.8, 126.8, 83.1, 74.5, 48.7, 45.7, 45.4, 41.4, 36.7, 35.1, 25.7, 16.5, 16.4, 14.4, 14.3, 12.9, 11.0, 10.9; HRMS (CI, NH_3) $[M + H]^+$ found 339.2535, $C_{20}H_{35}O_4$ requires 339.2535; HRMS m/z (relative intensity) 356 ($[M + NH_4]^+$, 24), 339 ($[M + H]^+$, 26), 321 (36), 270 (16), 253 (100), 209 (6), 197 (5).

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Supplementary Material Available: Details of the experimental procedures for the preparation of compounds **21**, **22**, **24**, **25**, **27**, **32**, **33**, **42**, **46**, **48**, **51**, **57**, and **61**; spectroscopic data for minor diasteromers produced in the aldol and Ireland–Claisen reactions; tables of comparison of the ^1H and ^{13}C NMR data with the literature data[3b] and reassignment of data on the basis of HETCOR experiments; ^1H and ^{13}C NMR spectra for compounds **1**, **2**, and **63** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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