JOC*Article*

Permanganate Oxidation of 1,5,9-Trienes: Stereoselective Synthesis of Tetrahydrofuran-Containing Fragments

Richard C. D. Brown,*,† Carole J. Bataille,† Robert M. Hughes,† Anne Kenney,† and Tim J. Luker‡

Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK, and AstraZeneca R&D Charnwood, Medicinal Chemistry, Bakewell Road, Loughborough, Leics LE11 5RH, UK

rcb1@soton.ac.uk

Received August 7, 2002

Permanganate oxidation of farnesoate esters **12a**−**d** afforded perhydro-2,2′-bifuranyl compounds **16a**−**d**, with control of relative stereochemistry at four new stereocenters. Subsequent oxidative cleavage of **16a**−**d** then provided tetrahydrofuran-containing fragments **17a**−**d**, one of them **17b** possessing the same relative stereochemistry present in the C13−C21 portion of the polyether antibiotic semduramycin (**1**). Control of the absolute stereochemistry was achieved through the use of the Oppolzer sultam chiral auxiliary. The requisite starting trienes were prepared stereoselectively in just three steps from geranyl chloride or neryl chloride, providing a short and versatile route to polyether fragments.

Introduction

cis-2,5-Disubstituted tetrahydrofurans are present in a large number of biologically active molecules including many polyether antibiotics and *Annonaceous* acetogenins (see Figure 1 for selected examples).[1−3] Of the approaches available for the synthesis of 2,5-disubstituted tetrahydrofurans, the oxidative cyclization of 1,5-dienes stands out as one of the most attractive in terms of level of structural complexity introduced in a single reaction,[4−8] and recently the development of an asymmetric phase-transfer-catalyzed variant of the reaction has been realized.[7] We have previously reported that the permanganate oxidation of 1,5,9-trienes **3** provided a very short route to perhydro-2,2′-bifuranyl systems **4** (Scheme 1),[8] which are suitable intermediates for further elaboration to acetogenins or polyether antibiotics.[6d−e] Here we provide a full account of some of these earlier studies, along with further results from the permanganate oxidation of other isomeric farnesoate derivatives.

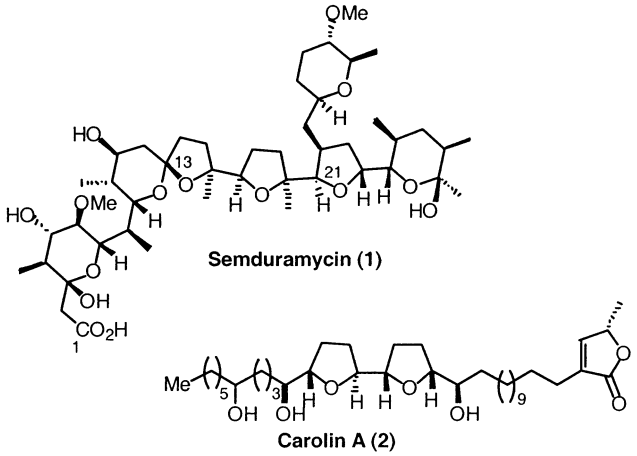


FIGURE 1. Structures of some biologically active tetrahydrofuran-containing compounds.

Results and Discussion

At first inspection, the oxidative cyclization of a 1,5,9-triene apparently presents a problem of regioselectivity

† Department of Chemistry, University of Southampton.
‡ AstraZeneca R&D Charnwood.

(1) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, 165−181.

(2) Fernandez, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235−246.

(3) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540.

(4) For reviews on the synthesis of cyclic ethers see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362. (b) Harmange, J. C.; Figadere, B. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1711−1754. (c) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175−4200.

(5) For studies on the permanganate-mediated oxidative cyclization of 1,5-dienes see: (a) Kötz, A.; Steche, T. *J. Prakt. Chem.* **1924**, *107*, 193. (b) Klein, E.; Rojahn, W. *Tetrahedron* **1979**, *21*, 2353−2358. (c) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396−4397. (d) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. M. *J. Chem. Soc., Chem. Commun.* **1979**, 918−919. (e) Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1981**, *103*, 940−941.

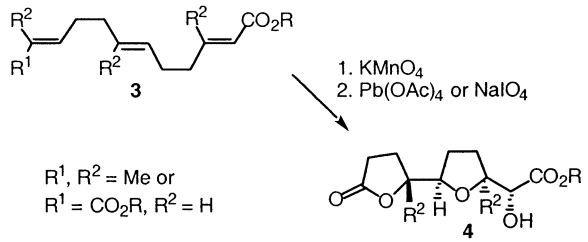
(6) For earlier applications of the permanganate-promoted oxidative cyclization of 1,5-dienes to the synthesis of fragments of polyether antibiotics monensin, ionomycin, and salinomycin see: (a) Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, *21*, 3531−3534. (b) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731−734. (c) Walba, D. M.; Przybyla, C. A.; Walker, C. B. J. *J. Am. Chem. Soc.* **1990**, *112*, 5624−5625. (d) Brown, R. C. D.; Kocienski, P. J. *Syn. Lett.* **1994**, 415−417. (e) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9−39. (f) Cecil, A. R. L.; Brown, R. C. D. *Org. Lett.* **2002**, *4*, 3715−3718.

(7) For asymmetric oxidative cyclization reactions using $KMnO_4$ see refs 6c−f and: Brown, R. C. D.; Keily, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496−4498

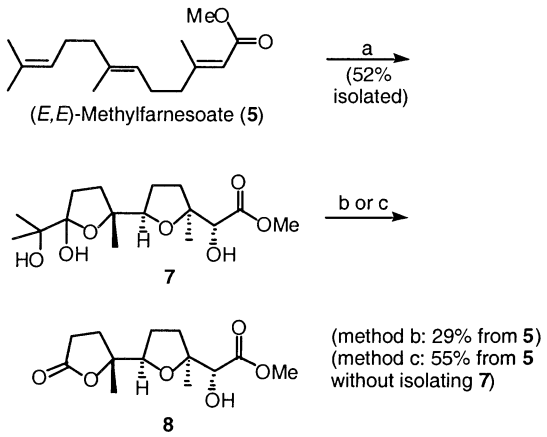
(8) For a preliminary communication of this work see: Brown, R. C. D.; Hughes, R. M.; Keily, J.; Kenney, A. *Chem. Commun.* **2000**, 1735−1736.

10.1021/jo026295b CCC: $22.00
Published on Web 10/22/2002

SCHEME 1. Oxidation of 1,5,9-Trienes



SCHEME 2[a]

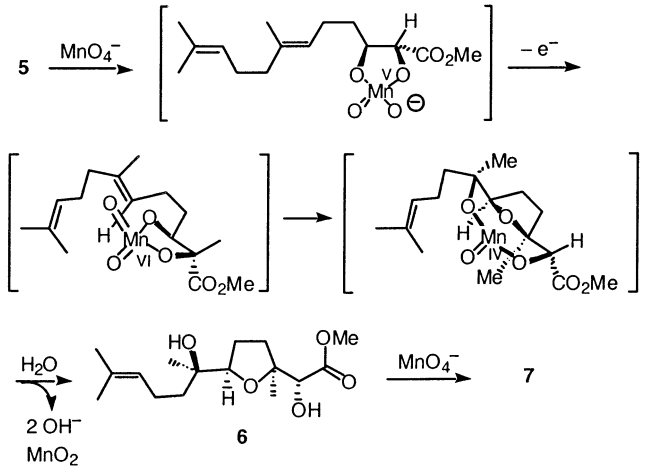


[a] Reagents and conditions: (a) $KMnO_4$ (3 equiv), AcOH (4 equiv), pH 6.2 buffer, acetone−H_2O, −20 °C; (b) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2; (c) $NaIO_4/SiO_2$, CH_2Cl_2.

in terms of directing the initial site of attack of the metal-oxo reagent to one of the three double bonds. However, electronic effects have been shown to significantly affect the rate of olefin oxidation by permanganate,[9] and could be used to direct the initial oxidation to a particular double bond. Our first experiments involved the oxidation of *E,E*-methyl farnesoate (**5**) using 3 equiv of $KMnO_4$ (Scheme 2),[10] anticipating that the enoate double bond would be oxidized most rapidly. Gratifyingly, the desired product **7** was obtained as a mixture of epimers at the hemiacetal position. Ultimately we were able to confirm the stereochemical course of the oxidative cyclization from an X-ray structure of the major epimeric lactol **7** (α-hydroxy), which crystallized from Et_2O−hexane.[11]

The results above are consistent with an initial more rapid attack of permanganate on the electron-deficient C2−C3 olefin to give a Mn^V diester, which has been proposed to undergo oxidation to a Mn^{VI} diester prior to cyclization onto the C6−C7 double bond and hydrolysis to afford **6** (Scheme 3).[5d] The remaining double bond present in **6** is oxidized more slowly to an α-ketol. Additional support for this pathway came from the isolation of the partially oxidized intermediate **6** from reactions carried out with reduced quantities of permanganate.

SCHEME 3. Proposed Reaction Pathway for the Oxidation of *E,E*-Methyl Farnesoate (5) with $KMnO_4$



Careful cleavage of the lactols **7** using $Pb(OAc)_4$ afforded the desired lactone **8** in reasonable overall yield (29% from **5**), although it was subsequently found that cleavage of the crude mixture containing lactols **7** using the $NaIO_4/SiO_2$ reagent provided a milder, more convenient, and higher yielding means of achieving the same transformation (55% from **5**).[12] Thus application of the oxidative cyclization−cleavage sequence to appropriate trienes provides a short and efficient approach to THF-diols with control of four new stereocenters. Additionally, the strategy allows for the selective protection of one of the two hydroxyl groups flanking the THF ring.

To demonstrate the versatility and convenience of the triene oxidation method as a stereocontrolled route to polyether fragments, we decided to prepare and oxidize the four stereoisomers of ethyl farnesoate **12a**−**d**. The requisite trienes **12a**,**b** were synthesized using a slight modification of methodology developed by Weiler et al.,[13] with the central double bond stereochemistry originating from geraniol or nerol and that of the enoate olefin secured by stereoselective enol phosphate generation followed by alkylation using organocuprates (Schemes 4 and 5).

Accordingly, the dianion of ethyl acetoacetate was alkylated with neryl chloride to afford *β*-ketoester **10** (Scheme 4).[14] It is worth noting that allylic chlorides are sufficiently reactive to alkylate the dianion when the olefin is trisubstituted, and are much more stable and convenient to handle than the corresponding bromides. The *β*-ketoester **10** underwent stereoselective enol phosphate formation with LiHMDS/$(EtO)_2POCl$ to provide the 2-(*Z*)-enol phosphate from which traces of the minor 2-(*E*)-stereoisomer were removed by column chromatography. Substitution of the enol phosphate occurred ste-

(9) For studies detailing electronic effects on the rates of oxidation reactions using MnO_4^- see: (a) Lee, D. G.; Brown, K. C.; Karaman, H. *Can. J. Chem.* **1986**, *64*, 1054. (b) Lee, D. G.; Brown, K. C. *J. Am. Chem. Soc.* **1982**, *104*, 5076−5081. (c) Henbest, H. B.; Jackson, W. R.; Robb, B. C. G. *J. Chem. Soc. (B)* **1966**, 803−807.

(10) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616−5617.

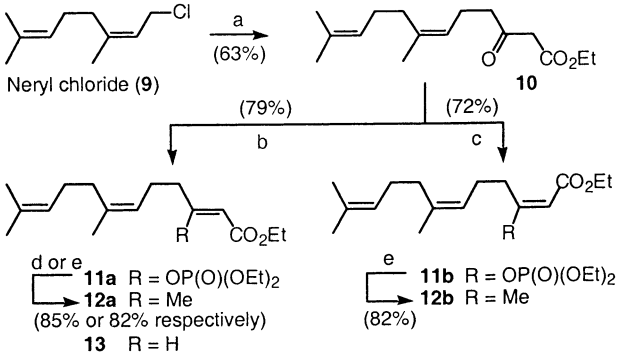
(11) For details of the X-ray structure determination see: Light, M. E.; Hursthouse, M. B. *Acta Crystallogr.* **2000**, *C46*, e483.

(12) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.

(13) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431−1441.

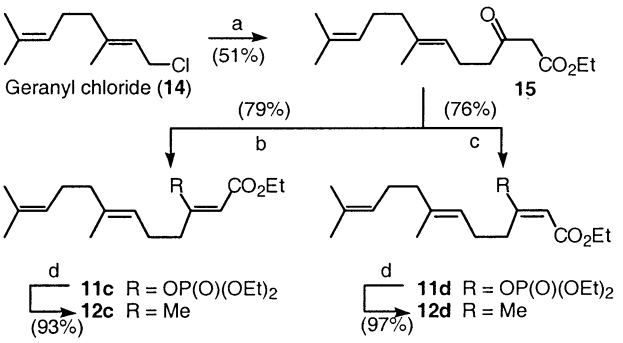
(14) During the course of our investigations the synthesis of all four isomers of ethyl farnesoate was published using a closely related strategy: In this work, alkylation of the dianion of ethyl acetoacetate was achieved using neryl bromide. We found that unless extreme care was exercised during the preparation of neryl bromide (and related allylic bromides), significant isomerization of the C6−C7 olefin to the terminal position occurred. Xie, H.; Shao, Y.; Becker, J. M.; Naider, F.; Gibbs, R. A. *J. Org. Chem.* **2000**, *65*, 8552−8563.

SCHEME 4[a]



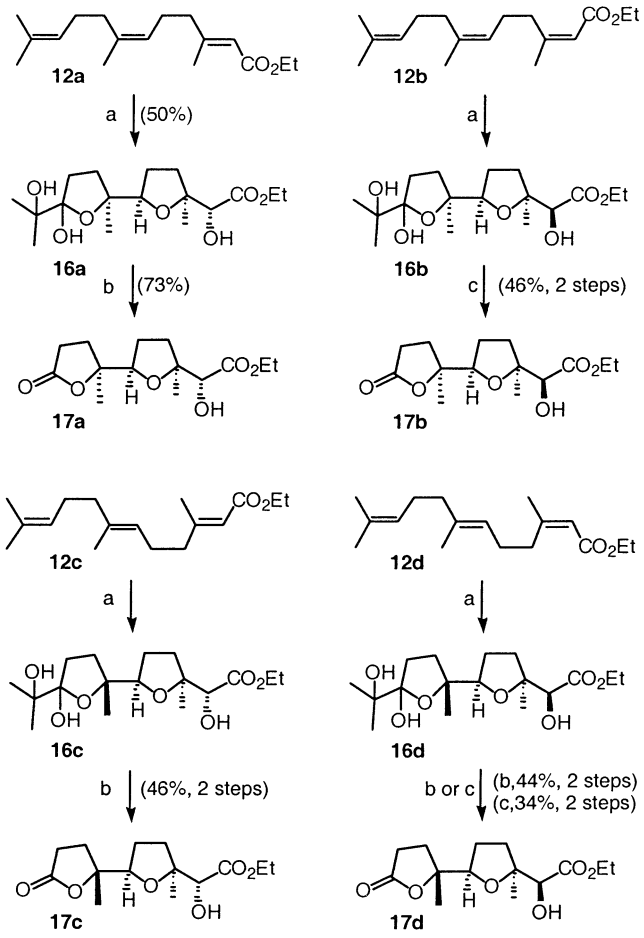
[a] Reagents and conditions: (a) ethyl acetoacetate, NaH (1 equiv.), *n*-BuLi (1 equiv), THF; (b) LiHMDS, THF then $(EtO)_2POCl$; (c) Et_3N, DMPU, $(EtO)_2POCl$; (d) MeLi in Et_2O (2 equiv), CuI, Et_2O, −78 to −50 °C; (e) MeLi in Et_2O (1 equiv), CuI then MeMgCl, −30 °C.

SCHEME 5[a]



[a] Reagents and conditions: (a) ethyl acetoacetate, NaH (1 equiv), *n*-BuLi (1 equiv); (b) LiHMDS, THF then $(EtO)_2POCl$; (c) Et_3N, DMPU, $(EtO)_2POCl$; (d) MeLi in Et_2O (1 equiv), CuI then MeMgCl, −60 °C.

SCHEME 6[a]



[a] Reagents and conditions: (a) $KMnO_4$ (3 equiv), AcOH (4 equiv.), pH 6.2 buffer, acetone−H_2O, −20 °C; (b) $Pb(OAc)_4$, CH_2Cl_2, Na_2CO_3; (c) $NaIO_4$-SiO_2, CH_2Cl_2.

reoselctively either using Me_2CuLi in Et_2O or MeCu/MeMgCl to afford (2*E*)-trienoate **12a** (2*E*:2*Z*, 65:1 by GC analysis).[13] Surprisingly, when the reaction was conducted using commercial MeLi supplied in THF/cumene rather than Et_2O, the desired product was contaminated with an inseparable byproduct **13** in a ratio of 4.5:1 (**12a**:**13**, estimated from the ^1H NMR spectrum).

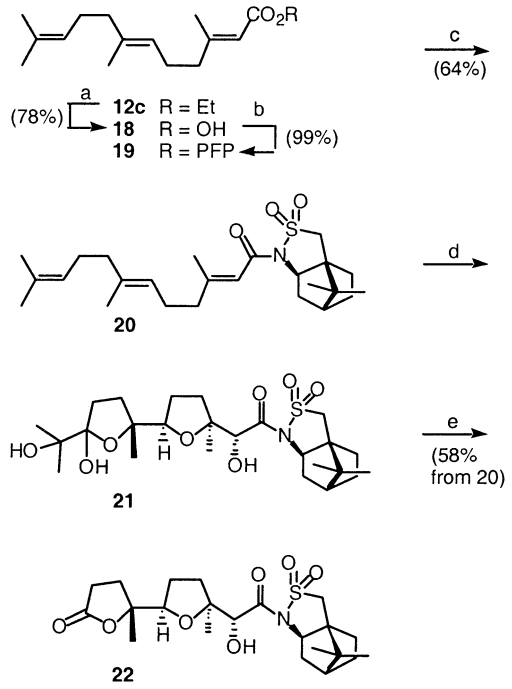
The synthesis of the corresponding 2(*Z*),6(*Z*)-trienoate **12b** was carried out along similar lines (Scheme 4), with the exception that the enolization was performed in DMPU with Et_3N as the base to afford the *E*-enol phosphate **11b** (crude isomer ratio >49:1 by NMR). The desired triene **12b** was obtained stereoselectively from **11b** using the reagent $Me_2CuLiMgCl$, as the analogous reaction using dimethyllithium cuprate afforded a 1:1 mixture of enoate isomers **12a** and **12b** in this case.[15] The two remaining triene isomers **12c** (2*Z*:2*E*, >99:1 by GC) and **12d** (2*E*:2*Z*, >99:1 by GC) were prepared in the same way, starting with geranyl chloride and using $Me_2CuLiMgCl$ (Scheme 5).

Permanganate oxidation of the four individual trienes afforded the expected lactol products **16a**−**d**, which were converted directly to the corresponding lactones **17a**−**d** as described above using $NaIO_4$−SiO_2 or $Pb(OAc)_4$ (Scheme 6). Single anomers of the lactols **16a**−**d** predominated in $CDCl_3$ solution, although this was of little consequence due to the destruction of the anomeric position in the subsequent oxidative cleavage reaction. The stereochemistry of the products **16/17a**−**d** was assigned on the basis of literature precedent,[5c,d] our earlier studies (X-ray structure of lactol **7**),[11] and an X-ray structure obtained from compound **17d**.[16] One of the lactone products **17b** has the same relative stereochemistry present within numerous polyether antibiotics including semduramycin (**1**), and lactone **17d** correlates to the C13−C22 portion of the antibiotic CP-54883.[1]

Finally, to demonstrate that the overall approach could provide enantiomerically enriched polyether fragments, the camphorsultam auxiliary was introduced into one of the trienoates (Scheme 7).[6c−e] Hydrolysis of the unsaturated ester **12c** and activation of the resulting acid **18** produced the pentafluorophenyl ester **19**, which underwent substitution with lithiated (2*R*)-10,2-camphorsultam to afford **20**. Oxidation of the resulting triene **20** proceeded with a high level of diastereoselectivity (we were unable to detect the minor diastereoisomer in the crude ^1H NMR spectrum of **22**) returning the THF lactone **22** in satisfactory yield after cleavage of the lactol

(15) Alderdice, M.; Spino, C.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1643−1646.
(16) Coles, S. J.; Hursthouse, M. B. Personal communication.

SCHEME 7[a]



[a] Reagents and conditions: (a) NaOH, $NaHCO_3$, THF−H_2O; (b) DCC, C_6F_5OH, EtOAc; (c) (2*R*)-10,2-camphorsultam, NaH, THF; (d) $KMnO_4$ (3 equiv), AcOH (4 equiv), pH 6.2 buffer, acetone−H_2O, −20 °C; (e) $NaIO_4$−SiO_2, CH_2Cl_2.

21. Oppolzer provided a model to account for the facial selectivity observed for the dihydroxylation reactions of enoyl camphor sultams with OsO_4,[17] and the same model predicts the observed selectivity for the $KMnO_4$ oxidation of similar substrates.[6c−f] Fortuitously, **22** gave crystals suitable for X-ray structural determination, thus allowing confirmation of the predicted stereochemical outcome from the oxidation of **20**.[18] Chemoselective reduction of the *N*-acylsultam group present in a very closely related lactone has been demonstrated, illustrating the utility of structures such as **22** in the synthesis of complex natural products such as polyether ionophores.[6e]

In summary, we have described a short, efficient, and stereoselective synthesis of perhydro-2,2′-bifuranyl systems from readily accessible trienoates **12a**−**d** using oxidative cyclization methodology. The THF-containing products **17a**−**d** and **22** represent useful intermediates for further elaboration toward biologically active natural products such as polyether antibiotics or novel synthetic ionophores.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR were recorded on 300- or 400-MHz spectrometers (300 or 400 MHz, ^1H NMR, respectively, and 75 or 100 MHz, ^{13}C NMR, respectively) in deuteriochloroform ($CDCl_3$) with chloroform (δ 7.27 ppm ^1H, δ 77.5 ppm ^{13}C) as the internal standard unless stated otherwise. Infrared (IR) spectra were reported as wavenumbers (cm^{-1}). Melting points were obtained in open capillary tubes and are uncorrected. All nonaqueous reactions were carried out under an inert atmosphere, in oven-dried glassware. The solvents THF (from Na/benzophenone) and CH_2Cl_2 (from CaH_2) were distilled before use,: and where appropriate, other reagents and solvents were purified by standard techniques.[19] TLC was performed on aluminum-precoated plates of silica gel 60 with an F_{254} indicator; the chromatograms were visualized under UV light and/or by staining with phosphomolybdic acid (20% solution in ethanol). Flash column chromatography was performed with 40−63 μm silica gel (Merck).

Ethyl (6*Z*)-7,11-Dimethyl-3-oxo-6,10-dodecadienoate (10). To an ice-cooled suspension of sodium hydride (2.79 g of a 60% dispersion in mineral oil, 69.65 mmol) in dry THF (25 mL) was added dropwise ethyl acetoacetate (8.81 mL, 69.55 mmol). After 10 min *n*-BuLi (27.86 mL of a 2.5 M solution in hexanes, 69.65 mmol) was added and the mixture was stirred for a further 10 min. A solution of neryl chloride (**9**, 12 g, 69.50 mmol) in dry THF (20 mL) was added to the reaction and the mixture was allowed to warm to room temperature. After 30 min a solution of HCl (70 mL of 3.4 M aq) and Et_2O (50 mL) were added. The organic layer was separated, re-extracting the aqueous phase with Et_2O. The organic layers were combined, washed with water until neutral, dried ($MgSO_4$), filtered, and concentrated in vacuo to give an orange oil. Purification on SiO_2 eluting with Et_2O:hexane (3:97) gave the title compound as a pale yellow oil (11.66 g, 43.8 mmol, 63%). Spectroscopic data were in agreement with the literature.[14]

Ethyl (6*E*)-7,11-Dimethyl-3-oxo-6,10-dodecadienoate (15). Following the procedure described for the synthesis of compound **10**, geranyl chloride (**14**, 4.0 g, 23.15 mmol) was converted to the title compound **15**, which was obtained as a pale yellow oil (3.12 g, 11.7 mmol, 51%). Spectroscopic data were in agreement with the literature.[19]

General Procedure for the Preparation of *Z*-Enol Phosphates: Ethyl (2*Z*,6*Z*)-3-[(Diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (11a). To an ice-cooled solution of LiHMDS (7.56 mL of a 1.0 M solution in THF, 7.56 mmol) in dry Et_2O (20 mL) was added a solution of β-keto ester **10** (2.0 g, 7.51 mmol) in Et_2O (40 mL). After 15 min $(EtO)_2POCl$ (1.09 mL, 7.56 mmol) was added and the resulting solution was stirred at room temperature for 3.5 h. The reaction was quenched with NH_4Cl (saturated aq) and the organic layer was separated then washed with $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a dark orange/brown oil. Purification on SiO_2 (3 × 12 cm) eluting with Et_2O:hexane (3:97 then 5:95, 1:9) afforded **11a** as a yellow oil (2.39 g, 5.93 mmol, 79%). IR ν_{max} (neat) 1729, 1661, 1285 cm^{-1}; ^1H NMR (400 MHz) δ 5.32 (1H, s), 5.05 (2H, t, J = 6.3 Hz), 4.23 (4H, quintet, J = 7.2 Hz), 4.14 (2H, q, J = 7.1 Hz), 2.40 (2H, t, J = 7.4 Hz), 2.24 (2H, q, J = 7.4 Hz), 2.03−1.96 (4H, m), 1.65 (6H, s), 1.57 (3H, s), 1.33 (6H, t, J = 7.0 Hz), 1.23 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz) 163.9, 161.5, 137.1, 131.8, 124.2, 122.7, 105.4, 64.8 (d, J = 6.1 Hz), 60.0, 35.5, 32.0, 26.6, 25.8, 24.8, 23.4, 17.7, 16.1 (d, J = 7.0 Hz), 14.3; ^{31}P NMR (121 MHz) −8.07 ($P^{(V)}$).

General Procedure for the Preparation of *E*-Enol Phosphates: Ethyl (2*E*,6*Z*)-3-[(Diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (11b). To an ice-cooled solution of DMAP (102 mg, 0.84 mmol) and Et_3N (1.2 mL, 8.4 mmol) in DMPU (15 mL) was added a solution of β-keto ester **10** (2.00 g, 7.5 mmol) in DMPU (9.0 mL). After 50 min the mixture was cooled to −20 °C and $(EtO)_2POCl$ (1.3 mL, 8.4 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. The mixture was diluted with Et_2O and acidified with 2 N HCl. The aqueous layer was extracted with Et_2O and the organic layers combined, washed with saturated $CuSO_4$ solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting rusty orange oil (crude ratio 2*E*:2*Z* > 49:1 by ^1H NMR) was purified on SiO_2 (250 g) eluting with Et_2O:hexane (1:4 then

(17) Oppolzer, W.; Barras, J.-P. *Helv. Chim. Acta* **1987**, *70*, 1666−1675.

(18) Horton, P. N.; Hursthouse, M. B. Personal communication.

(19) Perrin, D. D.; Armarego, W. L. F. *Purification of laboratory chemicals*, 3rd ed; Butterworth-Heinemann Ltd.: Oxford, UK, 1994.

1:1) to give **11b** as a pale yellow oil (2.15 g, 5.34 mmol, 71%). IR ν_{max} (neat) 1716, 1644, 1281, 1030 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.82 (1H, d, J = 1.5 Hz), 5.15 (1H, dt, J = 1.5, 7.0 Hz), 5.12−5.04 (1H, m), 4.17 (4H, quintet, J = 7.4 Hz), 4.12 (2H, q, J = 7.1 Hz), 2.79 (2H, dt, J = 1.5, 7.7 Hz), 2.25 (2H, q, J = 7.6 Hz), 1.98−2.10 (4H, m), 1.66 (6H, s), 1.58 (3H, s), 1.35 (6H, dt, J = 1.5, 7.4 Hz), 1.24 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz) 166.3, 166.2, 136.7, 131.7, 124.3, 123.4, 105.5, 64.8 (d, J = 5.6 Hz), 60.2, 32.2, 32.0, 26.7, 25.8, 25.4, 23.5, 17.7, 16.1 (d, J = 6.7 Hz), 14.3; MS (ES) m/z (rel intensity) 425.3 (38, [M + Na]$^+$), 420.3 (100, [M + NH$_4$]$^+$), 403.3 (32, [M + H]$^+$); HRMS (ES) Calcd for $C_{20}H_{36}PO_6$ 403.2244, found 403.2242 (42, [M + H]$^+$).

Ethyl (2*Z*,6*E*)-3-[(Diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (11c). Following the general procedure for the preparation of *Z*-enol phosphate **11a**, β-keto ester **15** (1 g, 3.75 mmol) afforded **11c** as a yellow oil (1.20 g, 2.97 mmol, 79%). Characterization data can be found in the Supporting Information.

Ethyl (2*E*,6*E*)-3-[(Diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (11d). Following the general procedure for the preparation of *E*-enol phosphates, β-keto ester **15** (2.00 g, 7.51 mmol) afforded **11d** as a very pale yellow oil (2.30 g, 5.71 mmol, 76%). Characterization data can be found in the Supporting Information.

General Procedure for the Alkylation Substitution of Enol Phosphates Using CuMe−MeMgCl: Ethyl (2*E*,6*Z*)-3,7,11-Trimethyl-2,6,10-dodecatrienoate (12a). To a suspension of CuI (211 mg, 1.11 mmol) in THF (10 mL) at 0 °C was added dropwise MeLi (0.70 mL of a 1.6 M solution in Et$_2$O, 1.11 mmol). The orange mixture was stirred at 0 °C for 10 min, before being cooled to −30 °C. MeMgCl (0.61 mL of a 3 M solution in THF, 1.85 mmol) was added dropwise maintaining the temperature below −25 °C. After 20 min the resulting light brown suspension was treated with a solution of enol phosphate **11a** (150 mg, 0.373 mmol) in THF (10 mL), and the mixture was stirred at −30 °C for 3 h, then quenched by pouring quickly onto ice-cold NH$_4$Cl (saturated aq). The organic layer was diluted with Et$_2$O and washed with NH$_4$Cl (saturated aq) until no longer blue. The organic layer was washed with brine, dried (MgSO$_4$), filtered, and concentrated in vacuo to give a yellow/orange oil. Purification on SiO$_2$ (2.5 × 8 cm) eluting with Et$_2$O:hexane (2:98 then 3:97) afforded **12a** as a pale yellow oil (80 mg, 0.303 mmol, 81%). ^{1}H NMR data were consistent with the literature;[14] additional data are provided. IR ν_{max} (neat) 1718, 1653 cm^{-1}; ^{13}C NMR (100 MHz) 167.0, 159.9, 136.4, 131.8, 124.3, 123.8, 115.7, 59.6, 41.4, 30.4, 26.7, 26.0, 25.9, 23.5, 19.0, 17.8, 14.5; MS (CI) m/z (rel intensity) 265 (48 [M + H]$^+$), 191 (100).

Ethyl (2*Z*,6*Z*)-3,7,11-Trimethyl-2,6,10-dodecatrienoate (12b). Following the general procedure for the preparation of **12a**, enol phosphate **11b** (800 mg, 1.99 mmol) afforded **12b** as a pale yellow oil (434 mg, 1.64 mmol, 82%). ^{1}H NMR data were in agreement with the literature;[14] additional data are provided in the Supporting Information.

Ethyl (2*E*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrienoate (12c). Following the general procedure for the preparation of **12a**, enol phosphate **11c** (690 mg, 1.7 mmol) afforded **12c** as a colorless oil (420 mg, 1.59 mmol, 93%). Spectroscopic data were in agreement with that reported in the literature.[19]

Ethyl (2*Z*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrienoate (12d). Following the general procedure for the preparation of **12a**, enol phosphate **11d** (660 mg, 1.64 mmol) afforded **12d** as a colorless oil (420 mg, 1.59 mmol, 97%). ^{1}H NMR data were in agreement with the literature;[20] additional data are provided in the Supporting Information.

Methyl (2*R)-2-Hydroxy-2-[(2*R**,2′*R**,5*S**)-5′-hydroxy-5′-(1-hydroxy-1-methylethyl)-5,2′-dimethyloctahydro[2,2′]-bifuranyl-5-yl]ethanoate (7).** Following the general procedure described below for the KMnO$_4$ oxidation of trienoate **12a**, methyl (*E*,*E*)farnesoate (**5**) (500 mg, 2.00 mmol) afforded the crude title lactol **7** as an oily solid. Purification on SiO$_2$ eluting with Et$_2$O gave the title lactol **7** as a colorless solid (360 mg, 1.04 mmol, 52%). An X-ray quality crystal of the α-epimer of hemiacetal **7** was obtained by recrystallization from Et$_2$O−hexane.[11] Signals reported for major epimer: mp 80−83 °C (Et$_2$O−hexane); IR ν_{max} (neat) 3693, 1738 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.50 (1H, br), 4.01 (1H, s), 3.94 (1H, dd, J = 5.8, 10.0 Hz), 3.77 (3H, s), 2.28−2.53 (3H, m), 2.00−2.20 (1H, m), 1.89−1.95 (1H, m), 1.86 (1H, ddd, J = 1.3, 7.3, 12.3 Hz), 1.79 (1H, ddd, J = 8.3, 10.5, 12.3 Hz), 1.63 (1H, ddd, J = 1.5, 8.0, 12.0 Hz), 1.31 (3H, s), 1.29 (3H, s), 1.23 (3H, s), 1.12 (3H, s); ^{13}C NMR (100 MHz) 173.9, 109.6, 84.8, 84.1, 83.2, 77.1, 73.1, 52.0, 36.8, 32.3, 31.7, 27.6, 24.3, 24.0, 23.9, 23.7; MS (ES) m/z (rel intensity) 355.4 (100, [M + Na$^+$]), 350.5 (20, [M + NH$_4^+$]), 332.4 (4, [M$^+$]).

Methyl (2*R)-2-Hydroxy-2-[(2*R**,2′*R**,5*S**)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl)ethanoate (8).** Following the general procedure described below for the Pb(OAc)$_4$ cleavage of **17a**, lactol **7** (210 mg, 0.63 mmol) afforded the title lactone **8** as a colorless oil (95 mg, 0.347 mmol, 55%). IR ν_{max} (neat) 3420, 1760, 1737 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.02 (1H, d, J = 8.4 Hz), 3.93 (1H, dd, J = 6.7, 8.6 Hz), 3.78 (3H, s), 2.99 (1H, d, J = 8.4 Hz), 2.82 (1H, apparent ddd, J = 8.3, 10.6, 17.8 Hz), 2.38−2.55 (2H, m), 2.33 (1H, ddd, J = 4.8, 9.0, 17.1 Hz), 1.88−2.11 (3H, m), 1.69 (1H, dt, J = 8.5, 12.5 Hz), 1.37 (3H, s), 1.25 (3H, s); ^{13}C NMR (100 MHz) 178.0, 172.6, 85.7, 85.1, 84.7, 76.6, 52.4, 35.3, 32.2, 29.6, 27.0, 24.4, 23.0; MS (ES) m/z (rel intensity) 295.4 (100, [M + Na$^+$]), 273.2 (67, [M + H$^+$]); HRMS (CI) calcd for $C_{13}H_{20}O_6Na$: 295.1155, found 295.1152 (7, [M + Na]$^+$).

Alternative Preparation of Lactone 8. Following the general procedure described below for the KMnO$_4$ oxidation of trienoate **12a**, (*E*,*E*)-methylfarnesoate (**5**, 15 mg, 0.060 mmol) afforded the crude lactol **7** as an oily solid (25 mg crude), which was used without purification in the next reaction. Following the procedure described below for the NaIO$_4$−SiO$_2$ cleavage of **16b**, the crude lactol **7** (25 mg) afforded the title lactone **8** as a colorless oil (9 mg, 0.033 mmol, 55% from **5**). Spectroscopic data were identical with those reported above.

General Procedure for the KMnO$_4$ Oxidation of 1,5,9-Trienoates. Ethyl (2*R)-2-Hydroxy-2-[(2*R**,2′*S**,5*S**)-5′-hydroxy-5′-(1-hydroxy-1-methylethyl)dimethyloctahydro-[2,2′]bifuranyl-5-yl]ethanoate (16a).** To a vigorously stirred mixture of trieneoate **12a** (400 mg, 1.51 mmol) and phosphate buffer (2 mL, pH 6.2) in acetone (25 mL) at −20 °C was added a solution of KMnO$_4$ (11.35 mL of 0.4 M (aq), 4.54 mmol) containing AcOH (365 μL). The purple mixture was stirred rapidly for 30−60 min during which time it became dark brown. The reaction was then quenched with sufficient ice-cooled saturated Na$_2$S$_2$O$_5$ (aq) to dissolve all of the manganese salts and the aqueous layer was saturated with NaCl then extracted repeatedly using CH$_2$Cl$_2$. The organic extracts were combined, dried (MgSO$_4$), filtered, and concentrated in vacuo to give a colorless oily solid. Purification on SiO$_2$ (2 × 15 cm) eluting with MeOH:CH$_2$Cl$_2$ (4:96) gave the title compound **16a** as a white solid (260 mg, 0.75 mmol, 50%): mp 89−90.5 °C; IR ν_{max} (neat) 3437, 1716 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.20 (2H, q, J = 7.2 Hz), 4.0 (1H, dd, J = 9.0, 6.5 Hz), 3.95 (1H, s), 2.38−2.30 (1H, m), 2.20−2.04 (2H, m), 1.84−1.63 (2H, m), 1.54−1.48 (1H, m), 1.25 (3H, t, J = 7.5 Hz), 1.20 (3H, s), 1.28 (3H, s), 1.1 (6H, s); ^{13}C NMR (100 MHz) 172.9, 109.6, 86.9, 85.2, 84.2, 76.7, 74.0, 62.1, 36.0, 33.1, 30.1, 28.3, 25.2, 25.0, 24.5, 23.8, 14.6; MS (ES$^+$) m/z (rel intensity) 369.5 (48, [M + Na]$^+$), 347.4 (5, [M + H]$^+$), 329.4 (20, [M − OH]$^+$), 127.1 (100). Anal. Calcd for $C_{17}H_{30}O_7$: C, 58.94; H, 8.73. Found: C, 58.47; H, 8.96.

General Procedure for Glycol Cleavage Using Pb(OAc)$_4$: Ethyl (2*R)-2-Hydroxy-2-[(2*R**,2′*S**,5*S**)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl]ethanoate (17a).** To a stirred solution of lactol **16a** (30 mg, 0.086 mmol) in dry

(20) Gibbs, R. A.; Krishnan, U.; Dolence, J. M.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 7821−7829.

CH_2Cl_2 (5 mL) was added Na_2CO_3 (9.5 mg, 0.09 mmol) followed by $Pb(OAc)_4$ (39 mg, 0.088 mmol). After 20 min Celite was added and the mixture stirred for a further 15 min. The solids were then removed by filtration through a short plug of SiO_2, washing with EtOAc. The resulting solution was washed with saturated $NaHCO_3$. The aqueous layer was saturated with NaCl and re-extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil. Purification on SiO_2 (1 × 7 cm) eluting with Et_2O afforded the title compound **17a** as a colorless oil (18 mg, 0.063 mmol, 73%). IR ν_{max} (neat) 3411, 1767, 1731 cm^{-1}; ^1H NMR (400 MHz) δ 4.31 (1H, dq, J = 7.4, 4.4 Hz), 4.24 (1H, dq, J = 7.4, 4.0 Hz), 4.02 (1H, dd, J = 9.0, 6.1 Hz), 4.01 (1H, d, J = 6.4 Hz), 3.10 (1H, d, J = 6.4 Hz), 2.73 (1H, ddd, J = 8.1, 10.6, 18.2 Hz), 2.52 (1H, ddd, J = 18.1, 10.5, 5.0 Hz), 2.28−2.45 (2H, m), 1.80−2.00 (2H, m), 1.63−1.80 (2H, m), 1.39 (3H, s), 1.34 (3H, s), 1.34 (3H, t, J = 4.0 Hz); ^{13}C NMR (100 MHz) 177.5, 173.1, 87.7, 85.6, 83.7, 76.6, 62.5, 35.8, 29.9, 28.9, 28.5, 24.3, 24.2, 14.6; MS (ES) *m/z* (rel intensity) 309 (38, $[M + Na]^+$), 304 (100, $[M + NH_4]^+$); HRMS (CI) calcd for $C_{14}H_{26}NO_6$ 304.1760 and $C_{14}H_{23}O_6$ 287.1495, found 304.1753 (62, $[M + NH_4]^+$), 287.1499 (16, $[M + H]^+$).

Ethyl (2*S)-2-Hydroxy-2-[(2*R**,2′*S**,5*S**)-5′-hydroxy-5′-(1-hydroxy-1-methylethyl)-5,2′-dimethyloctahydro[2,2′]-bifuranyl-5-yl]ethanoate (16b).** Following the general procedure for the $KMnO_4$ oxidation of trienoates, **12b** (360 mg, 1.36 mmol) afforded the crude title lactol **16b** (510 mg crude) as a colorless oil that was used in the next reaction without purification. Selected characterization data for the major epimer are given in the Supporting Information.

Ethyl (2*S)-2-Hydroxy-2-[(2*R**,2′*S**,5*S**)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl]ethanoate (17b).** To a vigorously stirred suspension of $NaIO_4$−SiO_2 reagent (6 g) in dry CH_2Cl_2 (20 mL) was added a solution of crude lactol **16b** (510 mg) in dry CH_2Cl_2 (10 mL). The resulting mixture was stirred for 40 min, then the solids were removed by filtration washing with $CHCl_3$. The resulting solution was concentrated under reduced pressure to give a yellow oil (400 mg). Purification on SiO_2 (35 g) eluting with CH_2Cl_2/EtOAc (85:15) gave the title lactone **17b** as a colorless oil (0.63 mmol, 180 mg, 46% from **12b**). Characterization data can be found in the Supporting Information.

Ethyl (2*R)-2-Hydroxy-2-[(2*R**,2′*R**,5*S**)-5′-hydroxy-5′-(1-hydroxy-1-methylethyl)-5,2′-dimethyloctahydro[2,2′]-bifuranyl-5-yl]ethanoate (16c).** Following the general procedure for the $KMnO_4$ oxidation of trienoates, **12c** (97 mg, 0.38 mmol) afforded the crude title lactol **16c** (140 mg crude) as a colorless oil that was used in the next reaction without purification. Selected characterization data are provided in the Supporting Information.

Ethyl (2*R)-2-Hydroxy-2-[(2*R**,2′*R**,5*S**)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl]ethanoate (17c).** Following the general procedure for the $Pb(OAc)_4$ cleavage of lactol **16a**, crude **16c** (110 mg, 0.31 mmol) afforded the title lactone **17c** as a pale yellow oil (37 mg, 0.14 mmol, 46% from **12c**). Characterization data can be found in the Supporting Information.

Ethyl (2*S)-2-Hydroxy-2-[(2*R**,2′*R**,5*S**)-5′-hydroxy-5′-(1-hydroxy-1-methylethyl)-5,2′-dimethyloctahydro[2,2′]-bifuranyl-5-yl]ethanoate (16d).** Following the general procedure for the $KMnO_4$ oxidation of trienoates, **12d** (200 mg, 0.76 mmol) afforded the crude title lactol **16d** (240 mg crude) as a colorless oil that was used in the next reaction without purification. Selected characterization data are provided in the Supporting Information.

Ethyl (2*S)-2-Hydroxy-2-(2*R**,2′*R**,5*S**)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl)ethanoate (17d).** Following the general procedure for the $Pb(OAc)_4$ cleavage of lactol **16a**, crude **16d** (60 mg, from 0.19 mmol of **12d**) afforded the title lactone **17d** (24 mg, 0.09 mmol, 44% from **12d**) as a colorless oil that solidified on standing. Recrystallization from EtOAc/hexane gave colorless needles suitable for X-ray structural determination.[16] Characterization data can be found in the Supporting Information.

Ethyl (2*S)-2-Hydroxy-2-(2*R**,2′*R**,5*S**)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl)ethanoate (17d).** Following the procedure used for the $NaIO_4$−SiO_2 cleavage of **16b**, crude **16d** (55 mg, from 0.174 mmol **12d**) afforded the title lactone **17d** (17 mg, 0.059 mmol, 34% from **12d**) as a colorless oil. Spectroscopic data were identical with those provided in the Supporting Information.

Pentafluorophenyl (2*E*,6*E*)-3,7,11-Trimethyl-2,6,10-dodecatrienoate (19). To a solution of the acid **18**[21] (203 mg, 0.86 mmol) and pentafluorophenol (168 mg, 0.90 mmol) in EtOAc (8 mL) was added dropwise a solution of DCC (188 mg, 0.91 mmol) in EtOAc (8 mL). After 24 h the mixture was diluted in hexane and the solids removed by filtration. The organic layer was washed with $NaHCO_3$ (saturated aq), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil (550 mg). Purification on SiO_2 (60 g) eluting with CH_2Cl_2/hexane (30:100) gave the title ester **19** as a yellow oil (342 mg, 0.85 mmol, 99%). IR ν_{max} (neat) 2910, 1763, 1635, 1518 cm^{-1}; ^1H NMR (400 MHz) δ 5.97 (1H, d, J = 1.2 Hz), 5.13 (1H, dt, J = 1.2, 6.8 Hz), 5.10 (1H, dt, J = 1.4, 6.8 Hz), 2.25 (3H, d, J = 1.3 Hz), 2.31−2.24 (4H, m), 2.08−2.02 (4H, m), 1.69 (3H, s), 1.64 (3H, s), 1.62 (3H, s); ^{13}C NMR (100 MHz) 167.8, 161.7, 136.7, 131.5, 124.1, 122.3, 112.1, 41.3, 39.6, 29.7, 26.6, 25.8 (×2), 17.6, 16.0; MS (ES) *m/z* (rel intensity) 443.5 (5 $[M + CH_3CN]^+$), 153 (100); HRMS (EI) calcd for $C_{21}H_{23}O_2F_5$ 402.1618, found 402.1617.

***N*-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienoyl)camphor-10,2-sultam (20).** To a solution of (2*R*)-10,2-camphorsultam (45 mg, 0.20 mmol) in dry THF (3 mL) was added *n*-BuLi (0.13 mL of 1.6 M in hexanes, 0.208 mmol) at −78 °C. The solution was allowed to warm to −20 °C over 1 h whereupon a solution of the activated ester **19** (80 mg, 0.199 mmol) in dry THF (3 mL) was added dropwise. The solution was then allowed to warm to room temperature. After 40 min the reaction was diluted in Et_2O and quenched with NH_4Cl (saturated aq). The layers were separated and the organic phase washed with $NaHCO_3$ (saturated aq), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil (200 mg). Purification was carried out on SiO_2 (20 g) eluting with hexane/CH_2Cl_2 (8:2 then 2:8) to give the title triene **20** as a colorless oil (55 mg, 0.127 mmol, 64%). $[\alpha]^{20}_D$ −11.3 (*c* 0.3, $CDCl_3$); IR ν_{max} (neat) 1681, 1632, 1329, 1133 cm^{-1}; ^1H NMR (400 MHz) δ 6.33 (1H, d, J = 1.2 Hz), 5.09 (1H, tt, J = 1.3, 6.6 Hz), 5.08 (1H, tq, J = 8.2, 1.4 Hz), 3.93 (1H, dd, J = 5.4, 7.3 Hz), 3.46 (1H, d, J = 13.7 Hz), 3.43 (1H, d, J = 13.7 Hz), 2.17 (3H, d, J = 1.3 Hz), 2.22−1.87 (13H, m), 1.68 (3H, d, J = 1.2 Hz), 1.60 (6H, s), 1.43−1.36 (2H, m), 1.18 (3H, s), 0.97 (3H, s); ^{13}C NMR (100 MHz) 164.6, 162.5, 136.1, 131.3, 124.3, 122.8, 115.5, 65.0, 53.1, 48.2, 47.7, 44.7, 38.7, 32.8, 26.6, 26.5, 26.0, 25.7, 20.8, 20.0, 19.9, 17.7, 16.0; MS (ES) *m/z* (rel intensity) 456.2 (34, $[M + Na]^+$), 434.3 (40, $[M + H]^+$), 153.0 (100); HRMS (ES) calcd for $C_{25}H_{39}NO_3SNa$ 456.2543, found 456.2550.

***N*-[(2*R*)-2-Hydroxy-2-((2*R*,2′*R*,5*S*)-2′,5-dimethyl-5′-oxooctahydro[2,2′]bifuranyl-5-yl)ethanoyl]camphor-10,2-sultam (22).** Following the general procedure for the oxidation of trienoate **12a**, oxidation of **20** (30 mg, 0.069 mmol) afforded the crude lactol **21** as a pale yellow oil (40 mg crude). Selected data: ^{13}C NMR (100 MHz) δ 174.2, 109.5, 84.8, 83.9, 83.4, 75.7, 73.0, 65.2, 53.1, 48.4, 47.7, 44.6, 38.0, 32.8, 32.2, 31.5, 27.4, 26.4, 24.4, 24.0, 23.9, 23.6, 20.9, 19.8. The crude lactol **21** was then treated with the $NaIO_4$−SiO_2 reagent according to the procedure described for the preparation of **17b**. Following purification on SiO_2 eluting with CH_2Cl_2/EtOAc (9:1) the title lactone was obtained as a colorless glass (18 mg, 0.040 mmol, 58%). Crystallization gave colorless needles suitable for X-ray structural determination.[18] Mp 151−154 °C (EtOAc/hexane);

(21) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568−1576.

$[\alpha]^{20}_D$ −49.5 (*c* 0.3, $CDCl_3$); IR ν_{max} (neat) 3499, 1763, 1701, 1375, 1134 cm^{-1}; ^1H NMR (400 MHz) δ 4.50 (1H, br s), 4.00 (1H, dd, J = 5.1, 7.8 Hz), 3.93 (1H, dd, J = 6.2, 9.4 Hz), 3.52 (1H, d, J = 13.7 Hz), 3.43 (1H, d, J = 13.7 Hz), 3.15 (1H, br s), 2.85−2.94 (1H, m), 2.51 (1H, dt, J = 2.8, 4.4 Hz), 2.33 (1H, ddd, J = 3.4, 9.1, 12.6 Hz), 1.86−2.30 (8H, m), 1.74 (1H, ddd, J = 8.4, 9.3, 12.6 Hz), 1.51−1.45 (3H, m), 1.35 (6H, s), 1.17 (3H, s), 0.96 (3H, s); ^{13}C NMR (100 MHz) δ 178.2, 169.8, 85.4, 84.4, 84.3, 75.0, 65.2, 52.9, 48.6, 47.7, 44.7, 38.1, 34.8, 32.7, 32.1, 29.5, 26.6, 26.3, 24.4, 23.6, 21.0, 19.9; MS (ES) *m*/*z* (rel intensity) 478.2 (5, $[M + Na]^+$), 456.2 (16, $[M + H]^+$), 153 (100); HRMS calcd for $C_{22}H_{33}NO_7SNa$ 478.1870, found: 478.1869 (65, $[M + Na]^+$).

Acknowledgment. The authors thank AstraZeneca for a CASE award (C.J.B.) and The Royal Society for a University Research Fellowship (R.C.D.B.). Pfizer, Merck Sharp and Dohme and Syngenta are also gratefully acknowledged for unrestricted support

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **7**, **8**, **11a**, **11b**, **11d**, **12a**−**d**, **17a**−**d**, **19**, **20**, and **22** and characterization data for compounds **11c**, **11d**, **12b**, **12d**, **16b**, **17b**, **16c**, **17c**, **16d**, and **17d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026295B