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Total synthesis of the *Fusarium* toxin equisetin

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A short stereoselective synthesis of the *Fusarium* toxin equisetin, a potent inhibitor of HIV-1 integrase enzyme is described, using as the key step a stereoselective intramolecular Diels–Alder reaction of a fully conjugated *E*,*E*,*E*-triene with a trisubstituted γ,δ-unsaturated β-ketothioester.

Introduction

Numerous biologically active natural products contain the tetramic acid (pyrrolidine-2,4-dione) ring system as a central element of their structure. The range of biological activities possessed by individual members of this series includes potent antibiotic, antiviral, and antiulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumors as well as fungicidal action. Moreover, certain members of this class are responsible for pigmentation of some sponges and molds.[1]

The structural complexity, together with the extraordinary biological activity, of many tetramic acids makes the total synthesis of these compounds an attractive goal for organic chemists, particularly in those cases where the natural supply is scarce. In this context, our group has been engaged in the development of new methods for the construction of the acyl tetramic acid subunit.[2] This effort has culminated in the total syntheses of several natural products containing this heterocyclic unit.[3]

The *Fusarium* toxin equisetin **1** (Fig. 1) is a fungal metabolite first isolated in 1974 from the white mold *Fusarium equiseti*.[4] It belongs to the acyl tetramic acid family of natural products by virtue of its *N*-methylserine-derived heterocycle. In addition, the compound comprises a substituted octalin skeleton bearing five stereogenic centers including one which is quaternary. It also has an impressive biological activity profile including antibiotic and HIV inhibitory activity, cytotoxicity and mammalian DNA binding.[5]

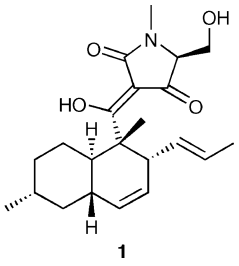
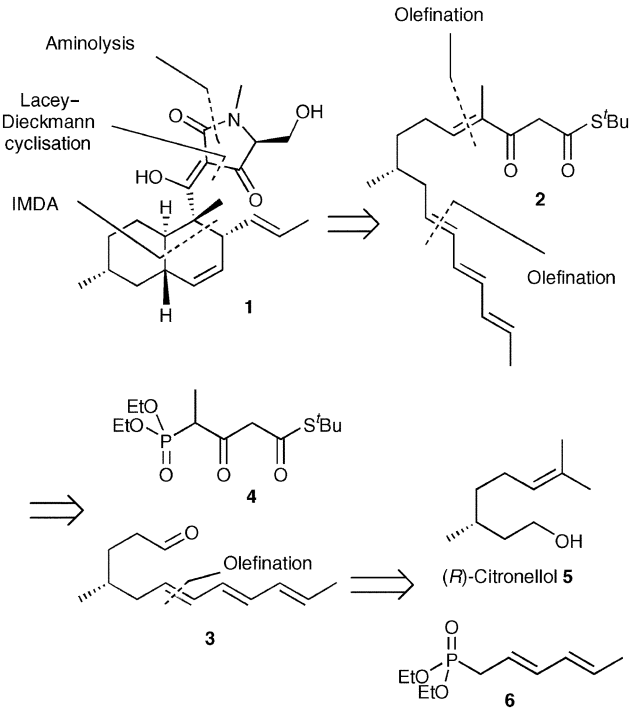


Fig. 1 Equisetin **1**.

Our experience in the synthesis of tetramic acids coupled with the complex structure of equisetin and its remarkable biological properties encouraged us to embark upon a total synthesis of this compound.[6] Here, we wish to report in full the details of these investigations and some improvements we have made leading to a more efficient total synthesis of this intriguing molecule.[7]

Results and discussion

The approach to equisetin **1** was guided by the perception that the formation of the octalin skeleton of the molecule with all five stereogenic centers could be readily achieved by the intramolecular Diels–Alder (IMDA) reaction of **2** (Scheme 1). More specifically, previous work and modelling studies of this pivotal IMDA reaction suggested that employment of a Lewis acid would encourage an *endo*-mode of cyclisation, where the methyl substituent is disposed in a pseudoequatorial position of the reacting chair conformation.[8] It was also clear that the tetramic acid subunit could be easily obtained by manipulation of a serine derivative in a Lacey–Dieckmann cyclisation.[2] We envisaged that preparation of **2** would require a Horner–Wadsworth–Emmons (HWE) reaction of a novel phosphonate thioester **4** and aldehyde **3**. The triene aldehyde **3** was envisioned as originating from the phosphonate ester **6** and commercially available (*R*)-citronellol **5** (Scheme 1).[9]



Scheme 1 Retrosynthetic analysis.

The synthesis began with the protection of the hydroxyl group of (*R*)-citronellol **5** using acetic anhydride and pyridine in dichloromethane at rt (Scheme 2). Compound **7** thus obtained, was subjected to a standard reductive ozonolysis to give alcohol **8**, which was protected using *tert*-butyldimethylsilylchloride and imidazole in dimethylformamide at rt to get the differentially protected diol **9** in high yield over the three steps. A simple

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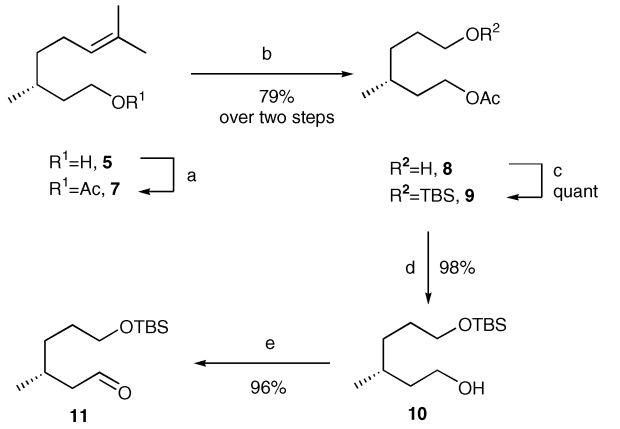
deprotection of the acetyl group under the Zemplin conditions (catalytic potassium carbonate in methanol) led to alcohol **10** which was oxidized to the corresponding aldehyde **11** following the Swern protocol (Scheme 2). It should be remarked that all these standard reactions were very high yielding allowing the multigram synthesis of **11** from the commercially available (*R*)-citronellol **5**.

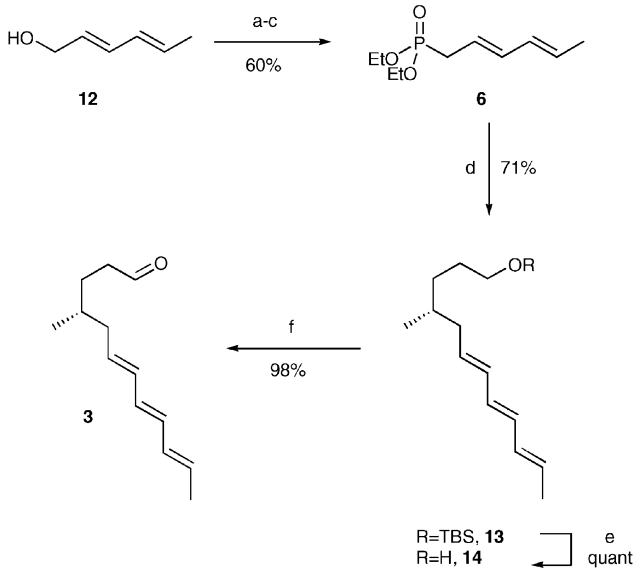


Scheme 2 Reagents and conditions: (a) Ac_2O, pyridine, CH_2Cl_2; (b) O_3, CH_2Cl_2, −78 °C then MeOH, $NaBH_4$, 0 °C; (c) TBSCl, imidazole, THF, rt, (d) MeOH, K_2CO_3 cat., rt; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt.

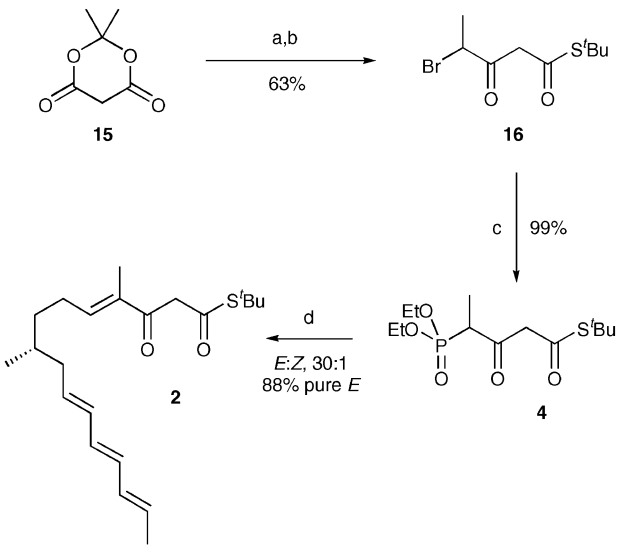
With aldehyde **11** in hand, its conversion into the fully conjugated *E*,*E*,*E*-triene derivative **3** was then investigated. The apparently trivial step—formation of the fully conjugated (*E*,*E*,*E*)-triene **13** from prepared aldehyde **11**— proved to be one of the most challenging of the entire synthesis (Scheme 3). Despite the multitude of literature procedures available, recounting the conditions necessary for transforming an aldehyde into an alkene, our difficulty was in obtaining a high *E* : *Z* selectivity. We believed the best chance of success was to use phosphonate chemistry. However, preparation of the necessary phosphonate **6** was not trivial. After several attempts using different reaction conditions, we found that treatment of commercially available and isomerically pure alcohol **12** in THF with BuLi, followed by treatment of the resulting alkoxide with TsCl gave the corresponding tosylated derivative which was treated *in situ* with sodium diethyl phosphite, at −10 °C, to give isomerically pure phosphonate **6** in 60% yield (Scheme 3).

With the phosphonate **6** available in quantity we were able to complete the synthesis of the triene **13**. Hence, treatment of the phosphonate **6** with a base at low temperature (−78 °C) yielded the corresponding phosphonate anion, to which was added the aldehyde **11** at −10 °C to give, after standard aqueous work-up, the triene **13**. The yield and selectivity (*E* : *Z*) of this reaction were highly dependent on the base used for the deprotonation of **6**. Thus, when KHMDS was used, a 1 : 1 mixture of *E* : *Z* isomers of triene **13** was obtained. However, success was achieved when lithium bases were employed. With butyllithium, the (*E*,*E*,*E*)-triene **13** was afforded in 60% yield with a very satisfactory *E* : *Z* ratio of 17 : 1 (attained from ^{1}H NMR 600 MHz analysis). The yield could be improved to 71%, maintaining the 17 : 1 *E* : *Z* selectivity, by the use of *sec*-butyllithium as base. With **13** in hand, TBS removal with TBAF in THF at 0 °C overnight gave the respective alcohol **14** in quantitative yield. Alcohol **14** crystallised on cooling in the freezer and was recrystallised from *n*-pentane at −20 °C to remove the small amount of minor geometrical isomer formed in the previous step. Finally, oxidation of alcohol **14** to the respective aldehyde **3** using the Swern protocol proceeded in high yield without incident.

For the synthesis of the key intermediate **2**, we required the preparation of the *tert*-butyl β-keto-γ-diethylphosphonothiolate **4** (Scheme 4). This was successfully accomplished starting from Meldrum's acid (**15**). Thus, treatment of this compound with 2-bromopropionyl bromide and pyridine in CH_2Cl_2 at 0 °C gave, after quenching with aqueous hydrobromic acid followed by a standard aqueous work-up, a brown oil which was subsequently transformed into intermediate **16** by treatment with *tert*-butylthiol in refluxing benzene (63%). This compound **16** was reacted with sodium hydride in THF at temperatures ranging between −30 °C and −20 °C, and then treated with a THF solution of sodium diethyl phosphite to obtain, after warming to rt, the desired phosphonate **4** (99%) as a red oil. The Horner–Wadsworth–Emmons reaction of the dianion of *tert*-butyl β-keto-γ-diethylphosphonothiolate **4** and aldehyde **3** led to the key intermediate **2**. It should be noted that the selectivity (*E* : *Z*) of this reaction was strongly dependent on the nature of the base used for the deprotonation of **4**. Thus, when BuLi was used, compound **2** was obtained as a 5 : 1 mixture of the *E* : *Z* diastereoisomers (56% isolated yield of the desired *E* diastereoisomer). On the other hand, when KHMDS was used



Scheme 3 Reagents and conditions: (a) BuLi, THF, −10 °C; (b) TsCl, −10 °C; (c) $(EtO)_2PONa$, −78 °C to rt; (d) ^{s}BuLi, THF, −78 °C, then **11**, −78 °C to rt; (e) TBAF, THF, 0 °C to rt; (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt.



Scheme 4 Reagents and conditions: (a) $CH_3CHBrCOBr$, pyridine, CH_2Cl_2 0 °C; (b) ^{t}BuSH, PhH, reflux; (c) NaH, THF, −30 °C to −20 °C, then $(EtO)_2PONa$, THF, −20 °C to rt; (d) KHMDS, THF, −78 °C, then **3**.

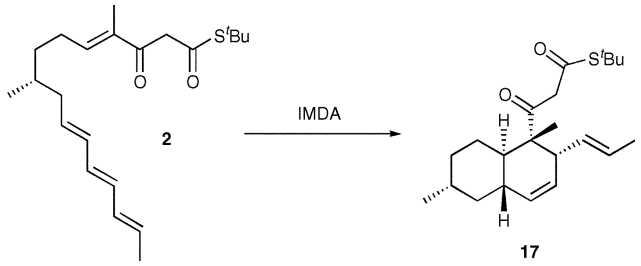
Table 1 Lewis acid-catalyzed intramolecular Diels–Alder reaction (IMDA) of **2**

Entry	Lewis acid	Conditions	Yield/%[a]	de/%[b]
1	$ZnCl_2$	CH_2Cl_2, rt	No reaction	—
2	$EtAlCl_2$	CH_2Cl_2, −78 °C	Decomposition	—
3	$MeAlCl_2$	CH_2Cl_2, −78 °C	Decomposition	—
4	Me_2AlCl	CH_2Cl_2, −78 °C	35	>95
5	Me_3Al	CH_2Cl_2, −78 °C	41	>95
6	$LiClO_4$	Et_2O, rt	70	85
7	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −78 °C to 0 °C	71	>95

[a] Isolated yield based on precursor **2**. [b] Determined by 600 MHz ^{1}H NMR analysis of the crude reaction mixture.

as base, the *E* : *Z* ratio was improved to 30 : 1. Chromatographic separation of the isomers allowed isolation of the desired *E* diastereoisomer **2** in a pleasing 88% yield (Scheme 4).

At this stage, with substantial quantities of isomerically pure polyene **2** in hand, we turned our attention to the study of the key reaction of our synthesis, the intramolecular Diels–Alder reaction (IMDA). Several reaction conditions using different Lewis acids were attempted (Scheme 5 and Table 1). The use of $ZnCl_2$, $EtAlCl_2$ or $MeAlCl_2$ resulted in the recovery of starting material **2** or in extensive decomposition to give mixtures of unidentified products (entries 1–3). When the Lewis acid was Me_2AlCl or Me_3Al the corresponding Diels–Alder adduct **17** could be isolated as a single diastereoisomer but in low yields (entries 4 and 5). More satisfactory results arose from the use of $LiClO_4$ (5 M in ether) as compound **17** could be isolated in 70% yield with 12 : 1 selectivity in favor of the desired isomer (entry 6). Finally, the best results were obtained from the treatment of **2** with two equivalents of $BF_3{\cdot}Et_2O$ in dichloromethane at −78 °C and further warming to 0 °C. These conditions led to the formation of **17** in >95% de (obtained from ^{1}H NMR 600 MHz analysis of the crude of the reaction) and in a pleasing 71% yield (entry 7). Although the structure of the minor diastereoisomer in the Diels–Alder reaction was not determined, the relative stereochemistry of **17** was proven by its subsequent conversion to equisetin (*vide infra*).



Scheme 5 Lewis acid-catalyzed intramolecular Diels–Alder reaction of **2**.

The notable levels of diastereocontrol in the intramolecular Diels–Alder reaction presumably arise from the methyl group, attached to the stereogenic centre, adopting a pseudo equatorial disposition in a chair-like transition state. Additionally, the Lewis acid activated dieneophile must adopt an *endo* approach to the "diene" of the conjugated (*E*,*E*,*E*)-triene (Fig. 2).

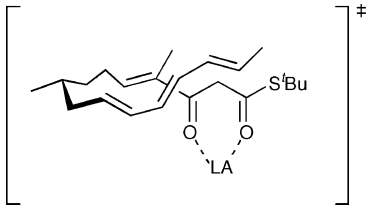
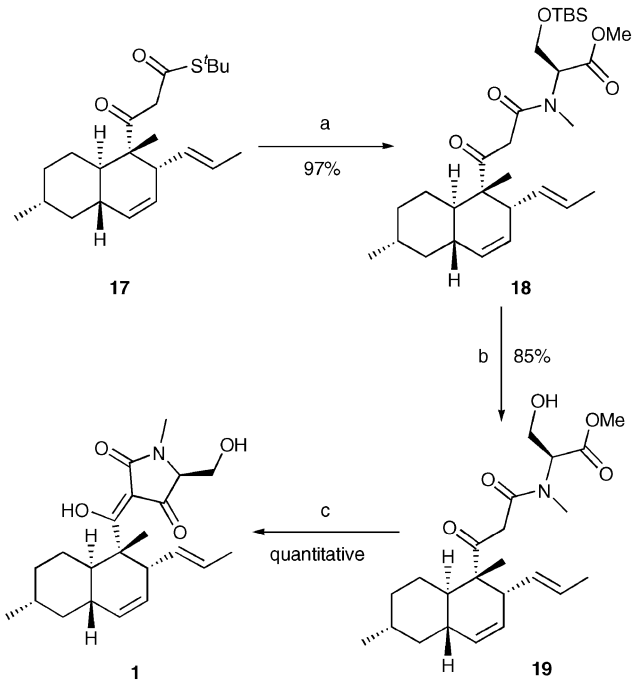


Fig. 2 Proposed transition state for the IMDA.

Completion of the equisetin synthesis from intermediate **17**, entailed the installation of the *N*-methyl serine tetramic acid component (Scheme 6). Firstly, direct aminolysis of the *tert*-butyl thioester group of **17** with *O*-*tert*-butyldimethylsilyl *N*-methyl serine methyl ester mediated by silver trifluoroacetate following the protocol introduced by our group,[2] afforded β-keto amide **18** in excellent yield. Then, removal of *tert*-butyldimethyl silyl protecting group with hydrofluoric acid in acetonitrile at rt for 15 min, gave the intermediate hydroxy compound **19** in 85% yield. Finally, treatment of **19** with sodium methoxide in methanol at rt for 10 min quantitatively afforded, after a simple aqueous work-up, pure equisetin **1**. The spectroscopic data as well as the specific rotation {$[a]_D^{28}$ −262 (*c* 0.038, $CHCl_3$) [Lit. (7b) $[a]_D^{23}$ −253, (*c* 0.038, $CHCl_3$)]} of our synthetic material was in complete agreement with the literature values.



Scheme 6 Reagents and conditions: (a) (*S*)-*N*-methyl-*O*-*tert*-butyldimethylsilyl serine methyl ester, CF_3CO_2Ag, THF, Et_3N, 0 °C; (b) HF, CH_3CN, rt; (c) MeONa, MeOH, rt.

Conclusions

The stereocontrolled synthesis of equisetin has been achieved in 13 steps from commercially available (*R*)-citronellol in an overall yield of 26.6%. This sequence has the potential to provide multigram quantities of equisetin which could allow detailed biological evaluation. The key step of this synthesis is a Lewis acid-mediated intramolecular Diels–Alder reaction of a fully conjugated *E*,*E*,*E*-triene with a trisubstituted γ,δ-unsaturated β-ketothioester. Other highlights of the synthesis include the development of a general route to allylic phosphonates and

a stereocontrolled Horner–Wadsworth–Emmons reaction to afford a trisubstituted alkene.

Experimental

General experimental details

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of dry argon. All glass apparatus was oven dried and allowed to cool under vacuum. In all cases, assessment of reaction diastereoselectivity was carried out by peak integration in the ^{1}H NMR spectrum of the crude reaction products. Petroleum ether refers to the fraction of petroleum ether boiling between 40 and 60 °C and was redistilled before use. Ether refers to diethyl ether. All other solvents were purified by standard procedures or used from commercial sources as appropriate. All reagents were used as supplied. Flash column chromatography was carried out using Merck 9385 Kieselgel 60 silica gel 0.040–0.063 mm (230–400 mesh). Thin layer chromatography (TLC) was performed on precoated glass-backed plates (Merck Kieselgel 60 F254). Visualisation was either by UV fluorescence ($\nu = 254$ nm) or by heating plates after being dipped in potassium permanganate solution. NMR spectra were recorded using either a Bruker AM400 (^{1}H; 400 MHz and ^{13}C; 100 MHz) or Bruker DRX600 (^{1}H; 600 MHz and ^{13}C; 150 MHz). All spectra were recorded using deuteriochloroform ($CDCl_3$) as solvent and internally referenced to residual protiochloroform (δ_H 7.27 ppm and δ_C 77.0 ppm). All chemical shifts (δ_H and δ_C) are quoted in ppm relative to tetramethylsilane (δ_H 0.00) and coupling constants (J) are given in Hertz. First order approximations are employed throughout. Both high and low resolution mass spectra were obtained on a Kratos MS890 spectrometer using EI (electron impact), chemical ionisation or positive FAB (fast atom bombardment) techniques on a Bruker BIOAPEX 4.7 T FTICR at the Department of Chemistry, University of Cambridge. All infra-red spectra were obtained using a Perkin-Elmer 1600 series FTIR spectrometer as thin film liquid samples between sodium chloride plates. Only selected absorbances (ν_{max}) are reported. Optical rotations ($[\alpha]_D$) were recorded using an Optical Activity AA-100 polarimeter which has a thermally jacketed 10 cm cell (path length of 1 dm) and are given in units of 10^{-1} deg cm^2 g^{-1} at 589 nm (sodium D-line).

(*R*)-(+)-6-Acetoxy-4-methylhexanol (8)

To a stirred solution of (*R*)-(+)-Citronellol **5** (5.00 g, 0.032 mol) and pyridine (3.36 ml, 0.042 mol) in dichloromethane (30 ml) at −10 °C was added acetic anhydride (3.62 ml, 0.038 mol). The reaction mixture was subsequently warmed to rt and left to stir overnight. The resulting solution was diluted with dichloromethane (50 ml) and washed with saturated copper sulfate (3 × 20 ml), sodium hydrogencarbonate, brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield the crude acetate product as a colourless oil. This material was used directly in the next step. A stirred solution of the crude acetate (6.34 g, 0.032 mol) in dichloromethane (30 ml) at −78 °C was subjected to a steady flow of ozone until a blue coloration was observed (30 min), and was then purged with oxygen (1 min). The resultant colourless solution was diluted with methanol (120 ml) and warmed to 0 °C (10 min), before sodium borohydride (13.0 g, 0.15 mol) was added portionwise with caution, over 1 h. After stirring for a further 90 min, the reaction material was partitioned between dichloromethane (30 ml) and water (30 ml), and further extracted with dichloromethane (2 × 20 ml). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification of this material by flash chromatography on silica gel [eluting with petroleum ether–diethyl ether (2 : 1, then 1 : 1); R_f (product) 0.44 (neat diethyl ether)] resulted in the title compound **8** (4.419 g, 79%). $[\alpha]_D^{30}$ +16.9° (*c* 0.445, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 3390s (OH), 2933, 2872, 1739s (OC=O), 1461, 1367, 1243s, 1056s; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.13$–4.02 (m, 2H; CH_2OCOCH$_3$), 3.59 (t, $J = 6.6$ Hz, 2H; CH_2OH), 2.01 (s, 3H; COCH_3), 1.85 (br s, 1H; OH), 1.70–1.32 and 1.22–1.13 (m, 7H; 3 × CH_2 and CHCH$_3$), 0.89 (3H, d, $J = 6.6$ Hz, CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$, 63.0, 62.9, 35.4, 32.8, 30.0, 29.6, 21.0, 19.4. *m/z* (EI$^+$): 175 (100%, MH$^+$), 115 (42%, MH$^+$–HOCOCH$_3$). HRMS (EI$^+$): Found, 175.1326. $C_9H_{18}O_3$(MH$^+$) requires, 175.1334.

(*R*)-(+)-1-*tert*-Butyldimethylsilyloxy-6-acetoxy-4-methylhexane (9)

To a stirred solution of **8** (4.32 g, 24.79 mmol) and imidazole (2.565 g, 37.68 mmol) in DMF (40 ml) at rt was added *tert*-butyldimethylsilylchloride in one portion and the reaction mixture was left to stir overnight. The resulting solution was diluted with diethyl ether (40 ml) and successively washed with water (2 × 30 ml), brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification of this material by flash chromatography on silica gel [eluting with petroleum ether–diethyl ether (gradient 50 : 1 to 5 : 1); R_f (product) 0.24 (10 : 1 petroleum ether–diethyl ether)] afforded the title compound **9** as a colourless oil (7.118 g, 100%). $[\alpha]_D^{30}$ +7.74° (*c* 1.03, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 2955s, 2859s, 2872m, 1743s (OC=O), 1472, 1388, 1366, 1248s, 1098s, 1034, 938, 836s, 775m. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.04$–4.03 (m, 2H; CH_2OCOCH$_3$), 3.53 (t, $J = 6.0$ Hz, 2H; CH_2OSi), 1.98 (s, 3H; COCH$_3$), 1.62–1.12 (m, 7H; 3 × CH$_2$ and CHCH$_3$), 0.86 (d, $J = 10.6$ Hz, 3H; CHCH_3), 0.84 (s, 9H; SiC(CH$_3$)$_3$), −0.01 (s, 6H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.0$, 63.3, 62.9, 35.5, 32.9, 30.1, 29.6, 25.9, 20.9, 19.4, 18.3, −5.4. *m/z* (EI$^+$): 289 (68%, MH$^+$), 231 (100%, MH$^+$–CH(CH$_3$)$_3$), 171 (51%, MH$^+$–C$_6$H$_{12}$(OH)$_2$), 117 (94%, C$_6$H$_{12}$O$_2$H). HRMS (EI$^+$): Found, 289.2200. $C_{15}H_{32}SiO_3$ (MH$^+$) requires, 289.2199.

(*R*)-(+)-1-*tert*-Butyldimethylsilyloxy-4-methylhexan-6-ol (10)

To a stirred solution of **9** (6.607 g, 22.94 mmol) in methanol (150 ml) at rt was added anhydrous potassium carbonate (250 mg) in one portion and the reaction mixture was left to stir overnight. The methanol was removed *in vacuo* resulting in a pale yellow viscous oil. This material was passed through a small plug of silica gel [eluting with neat diethyl ether; R_f (product) 0.43 (1 : 1 petroleum ether–diethyl ether)] affording the title compound **10** as a colourless oil (5.526 g, 98%). $[\alpha]_D^{30}$ +3.52° (*c* 1.42, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 3342m (OH), 2954, 2929, 2857, 1475, 1462, 1387, 1361, 1255s, 1097s, 1006, 938, 835s, 774s, 662. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.66$ (m, 2H, CH_2OH), 3.59 (t, $J = 6.6$ Hz, 2H; CH$_2$OSi), 1.64–1.11 (m, 8H, 3 × CH$_2$, CHCH$_3$ and OH), 0.91 (d, $J = 7.9$ Hz, 3H; CHCH_3), 0.89 (s, 9H; SiC(CH_3)$_3$), 0.04 (s, 6H; Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 63.5$, 61.1, 39.9, 33.0, 30.2, 29.3, 25.9, 19.6, 18.3, −5.3; *m/z* (EI$^+$): 247 (100%, MH$^+$), 189 (38%, MH$^+$–CH(CH$_3$)$_3$). HRMS (EI$^+$): Found, 247.2084. $C_{13}H_{30}SiO_2$ (MH$^+$) requires, 247.2093.

(*R*)-(+)-1-*tert*-Butyldimethylsilyloxy-3-methyl-hexanal (11)

To a stirred solution of oxalyl chloride (21.93 ml, 22.18 mmol) in dichloromethane (50 ml) at −78 °C was added DMSO (3.15 ml, 44.36 mmol) dropwise *via* syringe. The resultant colourless solution was left to stir for 20 min. A solution of **10** (2.717 g, 11.09 mmol) in dichloromethane (20 ml) was then added dropwise *via* cannula at −78 °C (10 min), and left to stir for 45 min before addition of triethylamine (9.33 ml, 66.54 mmol). Stirring was maintained at this temperature for a further 15 min before the reaction mixture was allowed to slowly warm to rt. The resulting solution was then poured into water (100 ml) and extracted with dichloromethane (2 × 60 ml). The combined organics were washed further with brine, dried (sodium sulfate),

filtered and concentrated *in vacuo* to afford a colourless oil. Purification of this material by flash chromatography on silica gel [eluting with petroleum ether–diethyl ether (1 : 1); R_f (product) 0.63 (1 : 1 petroleum ether–diethyl ether)] afforded the title compound **11** as a colourless oil (2.60 g, 96%). $[\alpha]_D^{30}$ +12.6° (*c* 1.04, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 2955s, 2930s, 2883s, 2857s, 1728s (C=O), 1475, 1462, 1387, 1361, 1255s, 1097s, 1006, 938, 836s, 813, 775s. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1H; CHO), 3.58 (t, J = 6.4 Hz, 2H; CH_2OSi), 2.42–2.01 (m, 2H, CH_2CO), 1.58–1.20 (m, 5H, 2 × CH_2 and $CHCH_3$), 0.95 (d, J = 6.7 Hz, 3H; $CHCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 63.1, 51.0, 33.0, 30.2, 28.0, 25.9, 19.9, 18.3, −5.3. *m/z* (EI$^+$): 243 (28%, [M–H]$^+$), 203 (87%, $C_7H_{13}(OH)OSi(CH_3)_3$), 185 (100%, M$^+$–$CH(CH_3)_3$). HRMS (EI$^+$): Found, 244.1871. $C_{13}H_{28}SiO_2$ (M$^+$) requires, 244.1859.

(2*E*,4*E*)-Hexadiene-1-diethylphosphonate (6)[9]

To a stirred solution of 2,4-hexadiene-1-ol **12** (2.23 ml, 20.0 mmol) in THF (40 ml) at −78 °C was added butyllithium (8.0 ml, 20.0 mmol) dropwise *via* syringe. The resultant yellow solution was stirred at −78 °C for 10 min. A solution of *p*-toluenesulfonylchloride (4.20 g, 22.0 mmol) in THF (20 ml) was then added dropwise *via* cannula to the reaction mixture. The resulting yellow solution was stirred for a further hour at −78 °C. Meanwhile, KHMDS (60.0 ml, 0.5 M in toluene, 30.0 mmol) was added slowly *via* syringe to a stirred solution of diethyl phosphite (4.35 ml, 33.0 mmol) in 40 ml THF at 0 °C. After 30 min, this solution was added to the −78 °C solution of the preformed tosylate *via* cannula. The reaction mixture was stirred at −78 °C for 10 min then slowly warmed to rt overnight. The residual solution was partitioned between pH 7 buffer (30 ml) and diethyl ether (50 ml) and the organic portion was washed with $NaHCO_3$ (2 × 20 ml) and water (2 × 20 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification of this material by flash chromatography on alumina [eluting with ether then neat ethyl acetate; R_f (product) 0.46 (neat ethyl acetate)] afforded the title compound **6** as a colourless oil (2.63 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13–6.08 (m, 1H; $CHCHCH_2P$), 6.01 (dd, J = 14.8 and 10.7 Hz, 1H; CH_3CHCH), 5.66–5.60 (m, 1H; $CHCH_2P$), 5.50–5.44 (dq, J = 14.9 and 7.1 Hz, 1H; CH_3CHCH), 4.12–4.03 (m, 6H; 2 × OCH_2CH_3), 2.58 (dd, J_{PH} = 22.3 Hz and J_{HH} = 7.6 Hz, 2H; $CHCH_2P$), 1.72 (d, J = 7.0 Hz, 3H; CH_3CHCH), 1.29 (t, J = 7.1 Hz, 6H; 2 × OCH_2CH_3).

(6*E*,8*E*,10*E*)-(*R*)-4-Methyl-1-*tert*-butyldimethylsilyloxydodeca–6,8,10-triene (13)

To a stirred solution of phosphonate **6** (1.683 g, 7.72 mmol) in THF (46 ml) at −78 °C was added *sec*-butyllithium (5.94 ml, 1.3 M, 7.72 mmol) dropwise *via* syringe. The resultant yellow solution was stirred at −78 °C for a further 20 min, before a solution of **11** (1.450 g, 5.94 mmol) in THF (17 ml) was then added dropwise *via* syringe. The resulting yellow solution was stirred for 15 min at −78 °C, warmed to rt and stirred for a further 18 h. The residual red–orange solution was quenched with phosphate buffer, then partitioned between water (50 ml) and diethyl ether (2 × 50 ml). The combined organics were washed further with brine (2 × 30 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification of this material by flash chromatography on alumina [eluting with petroleum ether–diethyl ether; (50 : 1 stepwise up to 30 : 1)] afforded the title compound **13** as a 17 : 1 mixture of geometrical isomers and as a colourless oil (1.30 g, 71%). $[\alpha]_D^{30}$ −0.502° (*c* 0.996, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 3013m (C=C), 2953s, 2928s, 2856s, 1684 (triene), 1652 (triene), 1471, 1462, 1377, 1360, 1254s, 1097s, 994s (−CH=CH-*trans*), 938s, 835s, 813, 775s. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09–5.99 (m, 4H; $CHCHCHCHCHCH_3$), 5.71–5.59 (m, 2H; $CH(CH)_4CHCH_3$), 3.60–3.56 (t, J = 6.7 Hz, 2H; CH_2OSi), 2.09–1.93 (m, 2H; $CHCH_2CH$), 1.76 (d, J = 6.6 Hz, 3H; $CHCHCH_3$), 1.59–1.43 and 1.39–1.25 and 1.17–1.05 (m, 5H; CH_2CH_2OSi, $CH_2CH_2CH_2OSi$ and $CH(CH_3)CH_2$), 0.89 (s, 9H; $SiC(CH_3)_3$), 0.87 (d, J = 6.7 Hz, 3H; $CHCH_3CH_2$), 0.05 (s, 6H; $Si(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.9, 131.7, 130.8, 130.6, 128.6, 125.9, 63.5, 40.3, 33.2, 32.7, 30.5, 26.0, 19.6, 18.3, 18.2, −5.3. *m/z* (EI$^+$) = 308 (20%, M$^+$), 251 (100%, M$^+$−$C(CH_3)_3$). HRMS (EI$^+$): Found, 308.2560. $C_{19}H_{36}SiO$ (M$^+$) requires, 308.2535.

(6*E*,8*E*,10*E*)-(*R*)-4-Methyl-1-hydroxydodeca-6,8,10-triene (14)

To a stirred solution of **13** (4.32 g, 14.0 mmol) in THF (100 ml) at 0 °C was added tetrabutylammonium fluoride (28.0 ml, 1 M in THF, 28.0 mmol) *via* syringe. The reaction mixture was concentrated *in vacuo* to afford a colourless oil. Purification by flash chromatography on silica gel [eluting with petroleum ether–diethyl ether; (gradient elution, 1 : 1 to 0 : 1); R_f (product) 0.29 (1 : 1 petroleum ether–diethyl ether)] afforded the title compound **14** as a colourless oil which crystallized on cooling (2.70 g, 100%). Isomerically pure material could be obtained by recrystallisation from pentane at −20 °C. $[\alpha]_D^{30}$ −1.05° (*c* 0.573, $CHCl_3$); ν_{max}(Nujol mull)/cm^{-1} = 3362m (OH), 2924s, 2854s, 1680 (triene), 1652 (triene), 1459s, 1377m, 1275, 1089, 1050, 994 (CH=CH *trans*), 880. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10–6.02 (m, 4H; $CHCHCHCHCHCH_3$), 5.71–5.59 (m, 2H; $CH(CH)_4CHCH_3$), 3.62 (dd, J = 12.0 and 6.4 Hz, 2H; CH_2OH), 2.10 and 1.95 (m, 2H; $CHCH_2CH$), 1.76 (d, J = 6.7 Hz, 3H; $CHCHCH_3$), 1.65–1.12 (m, 6H; CH_2CH_2OH, $CH_2CH_2CH_2OH$, $CH(CH_3)CH_2$ and OH), 0.89 (d, J = 6.7 Hz, 3H; CH_2CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.6, 131.7, 131.6, 130.9, 130.5, 128.9, 63.3, 40.3, 33.2, 32.5, 30.4, 19.5, 18.2. *m/z* (EI$^+$) = 194 (78%, M$^+$), 107 (85%, C_8H_{11}), 94 (54%, $(CH)_6CH_3$), 79 (100%, $CH_2(CH)_5$). HRMS (EI$^+$): Found, 194.1667. $C_{13}H_{22}O$ (M$^+$) requires, 194.1671.

(6*E*,8*E*,10*E*)-(*R*)-4-Methyl-1-dodecatriene-1-al (3)

To a stirred solution of oxalyl chloride (0.52 ml, 6.0 mmol) in dichloromethane (30 ml) at −78 °C was added DMSO (0.84 ml, 12.0 mmol) dropwise *via* syringe. The resultant colourless solution was left to stir for 30 min. A solution of **14** (0.58 g, 3.0 mmol) in dichloromethane (15 ml) was then added dropwise *via* cannula at −78 °C, and left to stir for 1 h before addition of triethylamine (2.43 ml, 18.0 mmol). Stirring was maintained at this temperature for a further 15 min before the reaction mixture was allowed to slowly warm to rt over 30 min. The resulting solution was then poured into water (100 ml) and extracted with dichloromethane (2 × 60 ml). The combined organics were washed further with brine, dried (sodium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil (0.566 g, 98%) which was used directly in the next step without further purification. ν_{max}(thin film)/cm^{-1} = 3012m, 2957s, 2928s, 2856, 2718, 1725s (C=O), 1684 (triene), 1652 (triene), 1558, 1540, 1521, 1506, 1456, 1410, 1378, 1138, 996s (−CH=CH-*trans*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1H; COH), 6.08–6.03 (m, 4H; $CHCHCHCHCHCH_3$), 5.70–5.57 (m, 2H; $CH(CH)_4CHCH_3$), 2.45–2.40 (m, 2H; CH_2CO), 2.10–1.97 (m, 2H, $CHCH_2CH$), 1.76 (d, J = 6.7 Hz, 3H; $CHCHCH_3$), 1.72–1.41 (m, 3H; CH_2CH_2CO and $CH(CH_3)CH_2$) 0.89 (d, J = 6.6 Hz, 3H; CH_2CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.6, 132.6, 131.7, 131.7, 131.2, 130.3, 128.9, 41.7, 40.0, 32.9, 28.4, 19.3, 18.2. *m/z* (EI$^+$) = 192 (100%, M$^+$), 107 (97%, C_8H_{11}). HRMS (EI$^+$): Found, 192.1505. $C_{13}H_{20}O$ (M$^+$) requires, 192.1514.

tert-Butyl-4-bromo-3-oxopentanethioate (16)

To a stirred solution of Meldrum's acid (**15**) (2.88 g, 20 mmol) and pyridine (3.3 ml, 40 mmol) in dichloromethane (30 ml) at

0 °C was added 2-bromopropionyl bromide (2.30 ml, 22.0 mmol) dropwise *via* syringe. The reaction mixture was stirred for a further 60 min before warming to rt and partitioning between DCM (2 × 100 ml) and aqueous hydrobromic acid (200 ml, 2 M). The organic layer was washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a brown oil. To a solution of this material in benzene (30 ml) was added *tert*-butylthiol (6.76 ml, 60 mmol) *via* syringe and the mixture heated for 1 h at reflux before cooling and evaporation *in vacuo* to give a red–brown oil. Purification of this material by flash chromatography on silica gel [eluting with 20 : 1 petroleum ether–diethyl ether→1 : 1 petroleum ether–diethyl ether] afforded the title compound **16** as an orange oil (3.35 g, 63%). In $CDCl_3$ at rt the title compound exists as a (5 : 2) *keto* : *enol* mixture. ν_{max}(thin film)/cm^{-1} = 2965, 2925, 1726, 1672, 1618, 1476, 1455, 1444, 1402, 1365, 1310, 1194, 1160, 1086, 1063, 1048, 973, 816, 781, 706. ^{1}H NMR (400 MHz, $CDCl_3$): δ(*major keto-form*) = 4.55 (q, J = 6.7 Hz, 3H; BrC*H*(CH$_3$)), 3.96 (d, J = 15.2 Hz, 1H; COC*H*H′CO), 3.70 (d, J = 15.2 Hz, 1H; COCH*H*′CO), 1.70 (d, J = 6.7 Hz, 3H; BrCH(C*H*$_3$)), 1.42 (s, 9H; C(CH$_3$)$_3$). δ (*minor enol-form*) = 5.50 (s, 1H; C(OH)C*H*CO), 4.32 (q, J = 6.7 Hz, 3H; BrC*H*(CH$_3$)), 1.77 (d, J = 6.7 Hz, 3H; BrCH(C*H*$_3$)), 1.46 (s, 9H; C(C*H*$_3$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*keto-form*) = 195.8, 192.5, 54.0, 49.2, 47.4, 29.6, 19.5. δ (*enol-form*) = 196.9, 171.1, 98.6, 48.8, 44.0, 30.0, 22.2. m/z (+ESI) = 290.99 (100%, M + Na$^+$), 288.99 (95%, M + Na$^+$). HRMS (+ESI$^+$): Found, 288.9872. $C_9H_{15}O_2SBrNa$ (M + Na$^+$) requires, 288.9874.

tert-Butyl-4-diethylphosphono-3-oxopentanethioate (4)

Sodium metal (0.336 g, 14.61 mmol) was washed (petroleum ether) and placed in a dry round bottom flask. THF (20 ml) and diethyl phosphite (1.74 ml, 13.49 mmol) were then added sequentially *via* syringe. The resulting mixture was refluxed for 2 h in order to prepare the phosphite anion. Meanwhile, sodium hydride (0.495 g, 12.36 mmol) in a dry round bottom flask was washed (petroleum ether), slurried with THF (30 ml), and cooled with stirring to −30 °C. A solution of **16** (3.00 g, 11.24 mmol) in THF (20 ml) was then added quickly *via* cannula to this chilled mixture; effervescence was observed. The resulting solution was stirred for a further 10 min, whilst warming to −20 °C, before addition of the THF solution of sodium diethyl phosphate *via* cannula. The reaction mixture was slowly warmed to rt with continuous stirring overnight. The residual solution was quenched with saturated ammonium chloride (30 ml), and partitioned between diethyl ether and water. The aqueous layer was back-extracted with diethyl ether (2 × 30 ml). The combined organics were then washed further with water (2 × 50 ml), brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* affording the title compound **4** (crude) as a red oil (3.605 g, 99%). This material was used without further purification. In $CDCl_3$ at rt the title compound exists as a (9 : 1) *keto* : *enol* mixture. ν_{max}(thin film)/cm^{-1} = 2966m, 1723s, 1673s, 1615s, 1478, 1456, 1393, 1365, 1314, 1250s, 1163, 1016s, 960, 836, 790, 732, 689. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (s, 1H; COC*H*COH *enol*) 4.18–4.08 (dq, J = 15.3 and 7.1 Hz, 4H; 2 × (OCH$_2$)), 4.05 (d, J = 15.1 Hz, 1H; COC*H*H′CO), 3.73 (d, J = 15.1 Hz, 1H; COCH*H*′CO), 3.47 (dq, J_{PH} = 26.1 Hz and J_{HH} = 7.0 Hz, 1H; POC*H*(CH$_3$) *keto*), 2.60 (dq, J_{PH} = 26.1 Hz and J_{HH} = 7.0 Hz, 1H; POC*H*(CH$_3$) *enol*), 1.46 (s, 9H; SC(CH$_3$)), 1.37 (d, J = 7.0 Hz, 3H; POCH(C*H*$_3$)), 1.35–1.30 (m, 6H; 2 × (OCH$_2$C*H*$_3$)). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 192.5, 171.5 (d, J = 6.0 Hz, CO*C*HCOH *enol*), 62.6 (dd, J = 19.0 and 7.4 Hz, 2 × (O*C*H2)), 58.0, 48.8, 48.2, 46.9 (d, J = 126.6 Hz, PO*C*H(CH$_3$)CO *keto*), 38.6 (d, J = 157.5 Hz, PO*C*H(CH$_3$)CO *enol*), 29.9, 16.2 (d, J = 6.0 Hz, POCH(*C*H$_3$)), 10.5 (d, J = 6.0 Hz, 2 × (OCH$_2$*C*H$_3$)). m/z (APCI) = 325.0 (100%, MH$^+$), 236.0 (65%), 209.1 (70%). HRMS (+ESI$^+$): Found, 347.1056. $C_{13}H_{25}O_5PSNa$ (M + Na$^+$) requires, 347.1058.

(4*E*,10*E*,12*E*,14*E*)-(*R*)-4,8-Dimethyl-hexadeca-4,10,12,14-butene-*β*-ketothioate (2)

To a stirred solution of phosphonate **4** (0.357 g, 1.1 mmol) in THF (10 ml) at −78 °C was added KHMDS (4.20 ml, 0.5 M in tol, 2.1 mmol) *via* syringe, slowly over 10 min. The resultant yellow solution was stirred at −78 °C for a further 15 min before a solution of aldehyde **3** (0.152 g, 0.79 mmol) in THF (3 ml) was added *via* cannula. The reaction mixture was stirred at −78 °C for 30 min, warmed to rt, and stirred for another hour. The residual solution was quenched with ammonium chloride, then partitioned between water and diethyl ether. The combined organics were washed further with water (3 × 20 ml), brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. ^{1}H NMR analysis of the crude material indicated a 30 : 1 (*E* : *Z*) ratio of isomers had been formed. Purification by flash chromatography on silica gel [eluting with petroleum ether–diethyl ether; (50 : 1)] afforded the title compound **2** as a red oil (0.252 g, 88% of pure *E* isomer). In $CDCl_3$ at rt the title compound exists as a (10 : 3) *keto* : *enol* mixture. ν_{max}(thin film)/cm^{-1} = 3013m, 2962s, 2926s, 1693s, 1661s, 1643s, 1584s, 1455m, 1375m, 1364m, 1295, 1161, 1100s, 1063s, 996s. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (t, J = 6.7 Hz, 1H; C*H*C(CH$_3$)CO *keto-form*), 6.55 (t, J = 7.1 Hz, 1H; C*H*C(CH$_3$)COH *enol-form*), 6.07–6.02 (m, 4H, C*H*C*H*C*H*C*H*CHCH$_3$), 5.69–5.57 (m, 2H; C*H*(CH$_2$)$_4$C*H*CH$_3$), 5.49 (s, 1H; C(OH)C*H*CO *enol*), 3.82 (s, 2H; COCH$_2$CO *keto*), 2.32–1.91 (m, 5H; C*H*$_2$CHC(CH$_3$)CO, CH$_3$CHC*H*$_2$CHCH and OH), 1.77 (d, J = 7.3 Hz, 3H; CHCHC*H*$_3$), 1.75 (s, 3H; CHC(C*H*$_3$)CO *keto*), 1.72 (s, 3H; CHC(C*H*$_3$)COH *enol*), 1.52 (s, 9H; C(CH$_3$)$_3$ *keto*), 1.46 (s, 9H; C(C*H*$_3$)$_3$ *enol*), 1.30–1.18 (m, 3H, C*H*$_2$CH$_2$CHC(CH$_3$)CO and C*H*(CH$_3$)CH$_2$), 0.89 (d, J = 6.7 Hz, 3H, CHC*H*$_3$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (*keto-form*) = 193.4, 193.2, 145.9, 137.0, 132.2, 131.9, 131.7, 131.1, 130.3, 129.0, 53.8, 48.8, 40.1, 35.0, 33.0, 29.6, 27.0, 19.4, 18.2, 11.3; δ (*enol-form*) = 196.4, 169.9, 137.0, 97.3, 48.2, 40.1, 35.1, 33.0, 30.2, 26.3, 19.4, 12.0. m/z (EI$^+$) = 362 (30%, M$^+$), 305.2 (26%, M$^+$–C(CH$_3$)$_3$), 203 (100% M$^+$–COCH$_2$COSC(CH$_3$)$_3$), 174 (94%, $C_{13}H_{18}$), 107 (70%, C_8H_{11}). HRMS (EI$^+$): Found, 362.2264. $C_{13}H_{28}SiO_2$ (M$^+$) requires, 362.2279.

3,4,5,6,7,8,9,10-Octahydro-4-diketothioate-4,7-dimethyl-(3*E*)-(prop-1,2-ene)naphthalene (17)

To a stirred solution of triene **3** (0.25 g; 0.69 mmol) in CH_2Cl_2 (30 ml) at −78 °C was added $BF_3{\cdot}Et_2O$ (0.16 ml; 1.38 mmol) dropwise *via* syringe. The reaction mixture was stirred at −78 °C for 1 h and then allowed to slowly warm to 0 °C over 8 h. Water (10 ml) was then added to the colourless solution, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (4 × 20 ml). The organics were dried over $MgSO_4$ and the solvents removed *in vacuo* to give a crude oil. ^{1}H NMR analysis of the crude material indicated only one diastereoisomer had been formed in the reaction. Purification by chromatography on silica gel [eluting with petroleum ether–diethyl ether; (50 : 1)] afforded the title compound (0.177 g; 71% yield) as a colourless oil. In $CDCl_3$ at rt the title compound exists as a (10 : 3) *keto* : *enol* mixture. $[\alpha]_D^{30}$ −139° (*c* 0.258, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 3015m, 2949s, 2913s, 2867, [1716s, 1682s, 1652, 1599s (*β*-ketothioester, overlaps triene region)], 1558, 1540, 1456s, 1394m, 1375m, 1384m, 1287, 1215, 1162, 1075s, 1044m, 975, 962, 923, 860, 832, 776, 753. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*major keto-form and some significant signals of enol-form*) = 5.43–5.29 (m, 3H; C*H*=C*H* of octalin and CH=C*H*CH$_3$), 5.15–5.11 (ddq, J = 15.1, 9.4 and 1.4 Hz, 1H; C*H*=CHCH$_3$), 3.62 (d, J = 15.5 Hz, 1H; COC*H*HCO), 3.46 (d, J = 15.6 Hz, 1H; COCH*H*CO), 2.54–2.52 (m, 1H; C*H*CH=CHCH$_3$), 2.40–2.38 (m, 1H; C*H*CH=CHCH$_3$ *enol*), 1.80–1.77 (m, 1H; CH$_3$CHC*H*$_{eq}$H$_{ax}$CH), 1.75–1.65, (m, 3H; CH$_3$CHCH$_2$C*H*$_{ringjunc.}$, CH$_3$CHCH$_2$CH$_{eq}$*H*$_{ax}$CH and CH$_3$CHC*H*$_{eq}$H$_{ax}$CH), 1.67–1.60 (m, 2H, CH$_3$C*H*CH$_2$CH and CH$_3$CHCH$_2$CH$_2$C*H*$_{ringjunc.}$), 1.62

(dd, J = 6.5 and 1.4 Hz, 3H; CH=CHCH_3), 1.51 (s, 9H; SC(CH_3)$_3$ *enol*), 1.46 (s, 9H; SC(CH_3)$_3$ *keto*), 1.22–0.99 (m, 1H; $CH_3CHCH_2CH_{eq}H_{ax}CH$), 1.17 (s,3H; C$H_3$CO *keto*), 1.05 (s, 3H; CH_3CO *enol*), 0.96–0.89 (m, 1H; $CH_3CHCH_{eq}H_{ax}CH_2$), 0.90 (d, J = 6.6 Hz, 3H; CH_3CHCH$_2$CH), 0.86 (d, J = 12.1 Hz, 1H; $CH_3CHCH_{eq}H_{ax}CH$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*keto* & *enol*) = 205.0, 193.1, 181.0, 131.7, 130.6, 130.5, 130.0, 127.5, 126.9, 126.4, 125.2, 99.6, 54.7, 53.5, 49.5, 48.6, 41.9, 39.7, 38.3, 35.5, 33.3, 29.7, 27.2, 22.4, 17.8, 16.8. m/z (EI$^+$) = 362 (71%, M$^+$). HRMS (EI$^+$): Found, 305.1589. $C_{22}H_{34}SO_2$ (M$^+$−57) requires, 305.1572.

3,4,5,6,7,8,9,10-Octahydro-4-diketo-*N*-methylserinemethyl-ester-4-diketothioate-4,7-dimethyl-(3*E*)-(prop-1,2-ene)-naphthalene (18)[7b]

A solution of (*S*)-*O*-*tert*-butyldimethylsilyl *N*-methylserine methyl ester (0.445g, 1.79 mmol) in THF (10 ml) was added *via* cannula to a stirred solution of **17** (0.260 g, 0.717 mmol) in THF at rt. Triethylamine (0.55 ml, 2.87 mmol) was then added dropwise *via* syringe. The reaction mixture was cooled to 0 °C before silver trifluoroacetate (0.33 g, 1.43 mmol) was added in one portion. The resulting solution was stirred for a further 2 h then concentrated *in vacuo*. Purification by chromatography on silica gel [eluting with petroleum ether–ethyl acetate (4 : 1); R_f (product) 0.35 (1 : 2 EtOAc–hexane)] afforded the title compound **18** as a colourless oil (0.36 g, 97%). In $CDCl_3$ at rt the title compound exists as a (5 : 2) *keto* : *enol* mixture. ^{1}H NMR is complicated by a mixture of amide rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41–5.36 and 5.29–5.08 (m, 4H; CHCHCH$_3$ and CHCHCHCHC(CH$_3$) and *enolic* COCHCOH), 4–42–4.37 (m, 1H; N(CH$_3$)CH), 4.15–4.11 and 4.01–3.97 (2 × m, 2H; CH_2OSi), 3.75 (d, J = 15.8 Hz, 1H; COCHHCO), 3.71 (s, 3H; OCH_3) 3.38 (d, J = 15.8 Hz, 1H; COCHHCO), 3.08–3.06 (m, 3H; NCH$_3$), 2.60–2.52 (m, 1H; CHCH=CHCH$_3$ *keto*), 2.42–2.40 (m, 1H; CHCH=CHCH$_3$ *enol*), 1.81–1.58, 1.47–1.43, 1.26–1.22 and 1.12–0.86 (4 × m, 10H; saturated protons of octalin ring), 1.60 (d, J = 6.2 Hz, 3H; CHCHCH_3), 1.22 (s, 3H; CHC(CH_3)CO), 0.90 (m, 3H; CH$_2$CH$_2$CH(CH_3)), 0.87 (s, 9H; SiC(CH_3)$_3$), 0.06 (s, 6H; Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*major keto-form*) = 195.8, 192.5, 54.0, 49.2, 47.4, 29.6, 19.5. δ (*minor enol-form*) = 196.9, 171.1, 98.6, 48.8, 44.0, 30.0, 22.2. HRMS (ES$^+$): Found, 542.3289. $C_{29}H_{49}SiO_5$ (M$^+$ + Na) requires, 542.3278.

Preparation of 19[7b]

To a stirred solution of silyl ether **18** (0.36 g; 0.69 mmol) in CH_3CN (25 ml) at rt was added 48% HF (0.3 ml). The reaction mixture was stirred for 15 min and then quenched by the careful addition of solid $NaHCO_3$ (1.5 g) and water (15 ml). The CH_3CN was removed *in vacuo* and the residue extracted with ethyl acetate (5 × 20 ml). The combined extracts were dried over $MgSO_4$ and evaporated. Purification by chromatography on silica gel [eluting with petroleum ether–ethyl acetate (4 : 1)] afforded **19** (0.24 g; 85% yield) as a colourless oil. ^{1}H NMR data were in complete accordance with literature values (see ref 7b). $[a]_D^{30}$ −192.0° (*c* 0.014, $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 169.8, 168.6, 130.8, 130.4, 126.8, 126.3, 60.9, 60.0, 53.4, 52.2, 49.7, 46.2, 41.8, 39.8, 38.3, 35.5, 35.4, 33.3, 27.1, 22.4, 17.8, 17.3. HRMS(EI): Found, 405.2528. $C_{23}H_{35}O_5N$ (M$^+$) requires, 405.2517.

Equisetin (1)

To a solution of ketoamide **19** (30 mg; 0.073 mmol) in methanol (12 ml) at rt was added 0.73 ml of a solution of sodium methoxide in methanol (5 eq) *via* syringe. After 10 min the reaction was quenched by the addition of 1 N HCl (3 ml). The mixture was then partitioned between water (10 ml) and CH_2Cl_2 (25 ml), and the aqueous phase was extracted with CH_2Cl_2 (5 × 20 ml). The combined organic portions were dried over $MgSO_4$ and concentrated *in vacuo* to give pure equisetin **1** (27 mg, 100%). Analytical data were in complete accordance with literature values (see ref 7b). $[a]_D^{28}$ = −262° (*c* 0.038, $CHCl_3$); ν_{max}(thin film)/cm^{-1} = 2923, 2854, 1602, 1453. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.40 (br s, 2H), 5.30–5.10 (m, 2H), 4.03 (dd, J = 11.5, 3.7 Hz, 1H), 3.95–3.82 (m, 1H), 3.64 (t, J = 4.4 Hz, 1H), 3.32 (br s, 1H), 3.06 (s, 3H), 2.10–1.65 (m, 4H), 1.56 (d, J = 4.8 Hz, 3H), 1.60–1.40 (m, 7H), 1.30–0.90 (m, 3H), 0.92 (d, J = 6.5 Hz, 3H); m/z (ES$^+$) 374 (100%), 356 (15%); HRMS(ES): Found, 396.2148. $C_{22}H_{31}O_4NNa$ (M$^+$ + Na) requires, 396.2151.

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