A Concise Synthesis of an Advanced Clerodin Intermediate through a Vaultier Tandem Reaction

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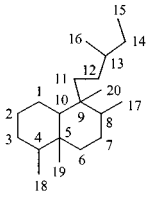
Keywords: Boron / Cycloadditions / Oxygenations / Terpenoids

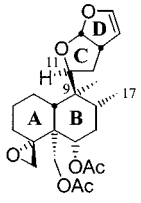
A highly functionalised precursor of the antifeedant natural product Clerodin has been synthesised with good diastereocontrol. Key steps include a three-component version of the Vaultier tandem sequence, and an oxidative decarboxylation with a simple experimental procedure.

Introduction

The Clerodanes[1] are an important class of diterpenes; many naturally occurring members of this family exhibit antifeedant activity against insects or other interesting properties. Clerodin (**1**),[2–6] first isolated in 1936 from *Clerodendron infortunatum*, is among the most active, and thus has potential for use in the protection of crops. This activity, together with its poor availability from natural sources and particularly interesting and challenging structure, has prompted several research groups to attempt the total synthesis of this molecule. The recently published total synthesis of dihydroclerodin by de Groot et al.[7] is the only example to date of a synthesis of a clerodane featuring a chiral C11 carbon atom.



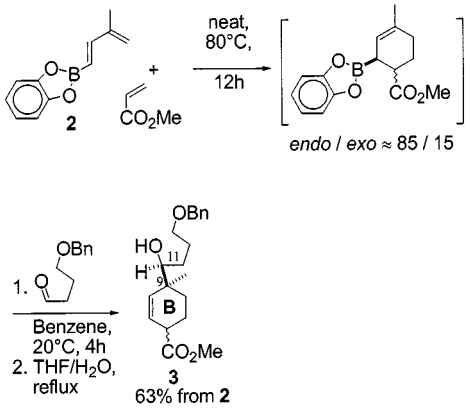
The skeleton of Clerodanes



Clerodin **1**

Previous Work

The establishment of the correct relative configurations at carbon centres C9 and C11 is clearly a major problem, decisive in the choice of any synthetic strategy. We have already published promising results involving approaches based on a Claisen rearrangement,[8,9] a stereoselective carbonyl reduction[10] and a [2+3] cycloaddition.[11] We have also reported a new route based on the tandem reaction developed by Vaultier et al.[12] This sequence enabled us to prepare the highly functionalised alcohol **3** in two steps from the bora-1,3-diene **2**, with *complete* control over the relative configurations at C9 and C11[13] (Scheme 1).



Scheme 1

We wanted to base our synthetic strategy on novel extensions of this result, involving more highly functionalised starting materials **4** (Scheme 2). The alcohol **5** formed in the key step would contain the C17 methyl group of clerodin, which would be difficult to introduce at a later stage. Moreover, an additional R group would facilitate the construction of ring A.

Retrosynthetic Analysis

In the light of previous research, we anticipated that decalin **7** could serve as a suitable precursor for the target molecule (Scheme 3); we have already reported the construction of the furo[2,3-*b*]furan bicyclic system [C,D] of clerodin from a 1,4-diol.[9] Furthermore, the synthesis of

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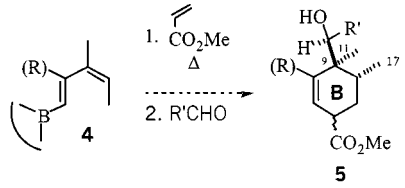
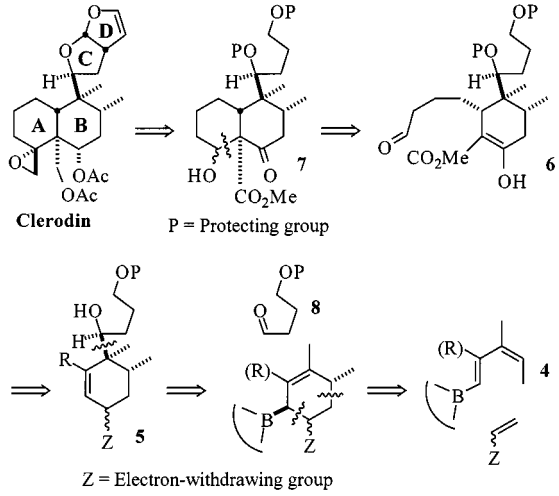


Scheme 2

the epoxy diacetate system of clerodin has previously been completed from model compounds similar to **7**.[14−17] We planned to close ring A by means of an intramolecular aldol reaction from **6**. A precursor of this aldehyde could be **5**, the product of the Vaultier tandem sequence involving diene **4**, a dienophile, and aldehyde **8**.

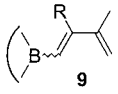


Scheme 3

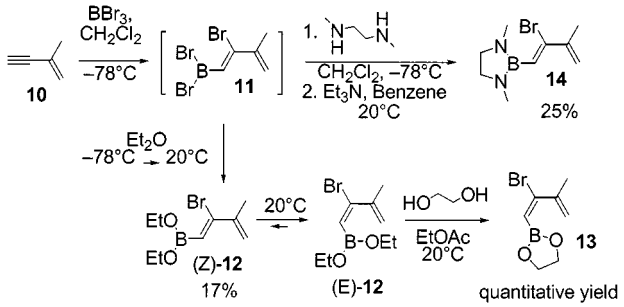
Results and Discussion

Synthesis of 2-Substituted 3-Methyl-1-bora-1,3-dienes

We first devoted our efforts towards the preparation and use of dienes of type **9**.

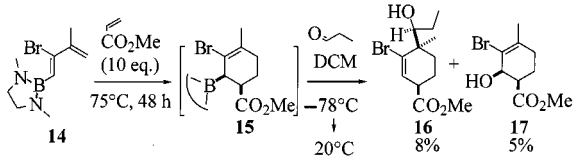


These can be synthesised via dibromoborane **11**, obtained by bromoboration of enyne **10** with tribromoborane (Scheme 4). Direct treatment of this intermediate with diethyl ether resulted in the formation of the diethyl boronate (*Z*)-**12**, which could be stored in a freezer for several days but which slowly isomerised to the more stable (*E*)-diene at room temperature. In contrast, the cyclic boronic amide **14** appeared to be much more tolerant towards heat. We also synthesised diene **13** by transesterification of (*E*)-**12** with ethylene glycol.



Scheme 4

We initially intended to substitute the bromine atoms of compounds **12**−**14** by carbon chains through a Negishi-type coupling under the conditions described by Suzuki et al.[18] However, none of our attempts [with either *n*BuZnCl or pent-4-enylzinc bromide as the coupling partner and either $Pd(Ph_3)_4$ or $Pd(PPh_3)_2Cl_2$ as the catalyst[19]] were successful. This failure was possibly due to the conjugation of the starting vinyl bromides. We then studied the direct Vaultier tandem sequence with **12**−**14**. This proved to be only somewhat successful with diene **14** as the starting material (Scheme 5).

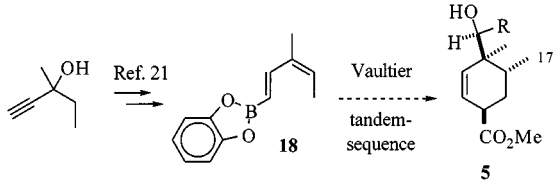


Scheme 5

The Diels−Alder adduct **15** was observed by NMR, and its formation was further confirmed by subsequent addition of propanal, which resulted in the isolation of the expected alcohol **16** accompanied by the by-product **17**.[20] The disappointing yields of **14** and **16** made us abandon this study and give priority to the more pressing problem of the obtention of the C17 methyl group of clerodin.

Introduction of the Clerodin C17 Methyl Group

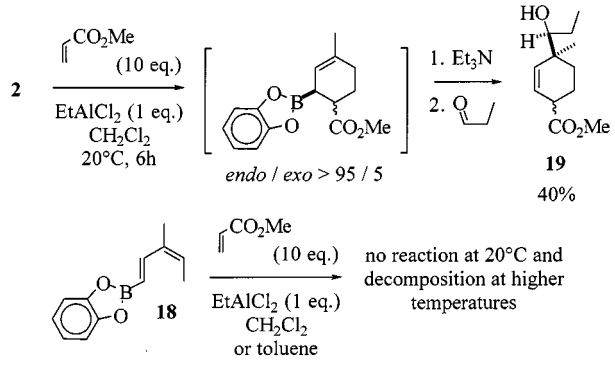
It was anticipated that the Vaultier tandem sequence from diene **18**[21] would provide a cyclohexene **5** featuring the C17 methyl group with the correct relative configuration (Scheme 6).



Scheme 6

Unfortunately, **18** was found to be particularly unreactive towards methyl acrylate under thermal conditions. We therefore studied the feasibility of Lewis acid activation of

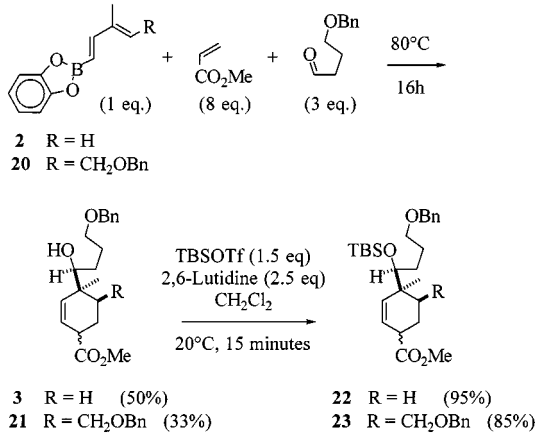
the cycloaddition. Preliminary work conducted from simple diene **2** showed that the use of a stoichiometric amount of dichloroethylaluminium induced significant activation.[22] However, this new procedure gave disappointing results when applied to diene **18** (Scheme 7).



Scheme 7

We therefore turned our attention towards other starting materials such as **20**, since the $-CH_2OBn$ group of the corresponding Vaultier sequence product **21** should be convertible into an *exo*-methylene[23] or a vinylic methyl group[15,24,25] at a later stage of the synthesis. Upon reduction, these functions are known to give the α-C17 methyl group of clerodin.

The intermediate allylboronic ester cycloadduct appeared to be unstable under the Diels–Alder reaction conditions, but this problem was solved by carrying out the tandem sequence as a three-component reaction[26] (Scheme 8).

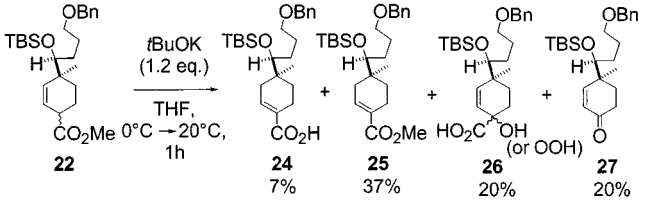


Scheme 8

Alcohol **21** was obtained in a nonoptimised 33% yield, which is satisfactory if one takes into account that this highly functionalised molecule was made in a single step from simple starting materials, with complete control over the relative configurations of three chiral centres. In order to pursue the synthesis, **21** was protected as the silyl ether **23**.

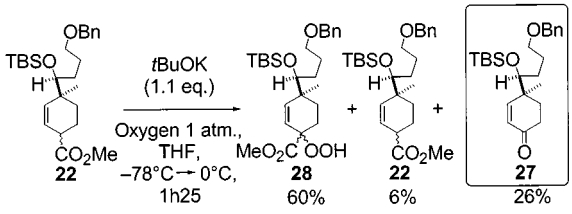
One-Step Conversion of a β,γ-Unsaturated Ester into a Conjugated Enone

It was found by accident that, under certain conditions (Scheme 9), a significant amount of enone **27** could be obtained from β,γ-unsaturated ester **22**.[27] This prompted us to investigate this transformation.



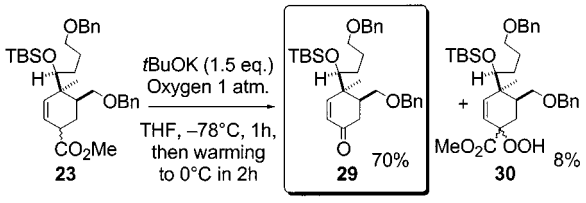
Scheme 9

Under basic conditions, **22** proved to react efficiently with molecular oxygen at −78 °C to give hydroperoxide **28** exclusively, in 82% yield. Under the same conditions, but when the temperature was subsequently allowed to increase to 0 °C, the formation of enone **27** was observed (Scheme 10).



Scheme 10

After further optimisation, we were able to achieve the conversion of ester **23** into conjugated enone **29** in 70% yield (Scheme 11). Hydroperoxide **30** was also isolated.

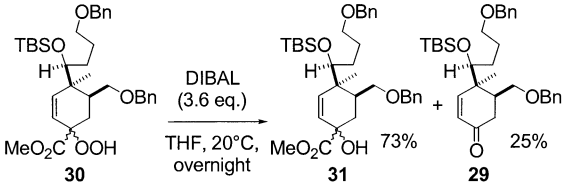


Scheme 11

The mechanism of the transformation giving rise to enones **27** and **29** has not been investigated, but probable intermediates are hydroperoxides **28** and **30**.[28–31] The evidence for their structures is as follows.

DIBAL reduction of **30** produced some enone **29** and a new compound **31**. The ^{13}C NMR, ^{1}H NMR, and IR spectra of **30** and **31** were almost identical, and the data for **31** were consistent with the structure shown (Scheme 12). Triphenylphosphane is known to react with hydroperoxides to give alcohols. A ^{1}H NMR spectrum of a sample of **30** was thus taken. After addition of excess triphenylphosphane, the only peaks observed were those of triphenylphosphane, triphenylphosphane oxide and compound **31**, which confirmed the existence of the hydroperoxide function in **30** and the alcohol function in **31**. The IR spectrum of alcohol **31** featured a sharp peak at 3533 cm^{-1}, whereas **30** featured a weaker peak at 3530 cm^{-1}, flanked by a broader signal.

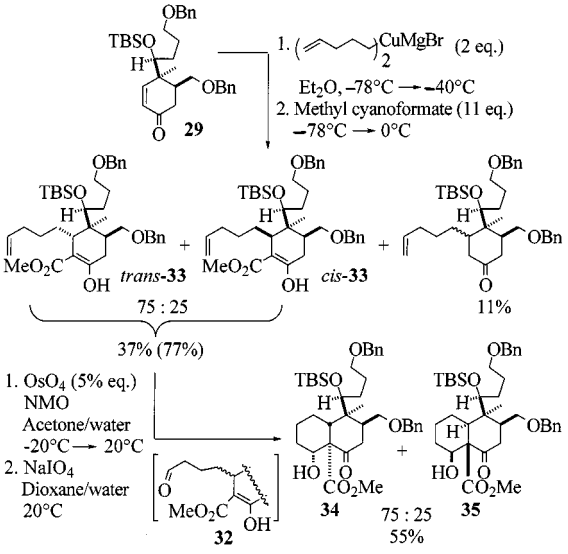
Compound **28** displayed a similar pattern, and so was also assigned a hydroperoxide structure.



Scheme 12

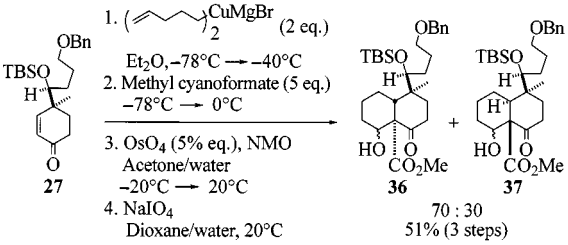
Construction of the A-Ring through an Intramolecular Aldol Reaction

With the unsaturated ketone **29** to hand, we could apply the methodology we had developed on model compounds to the closure of ring A.[14] Aldehyde **32** was thus obtained by 1,4-cuprate addition, followed by a two-step oxidative cleavage of the alkene function of enol intermediate **33** (Scheme 13). Although **32** could be characterised by NMR analysis of the crude reaction mixture, flash column chromatography on silica gel directly delivered the cyclised compound as a mixture of two diastereomers **34** and **35**.



Scheme 13

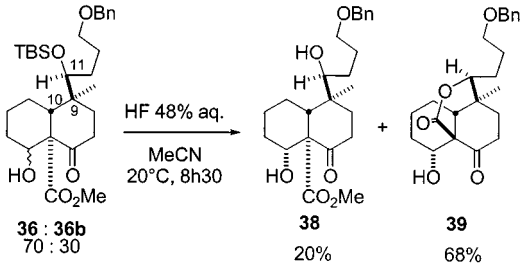
Model compounds **36** and **37** were also obtained from enone **27** by the same sequence (Scheme 14).



Scheme 14

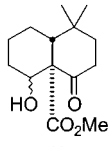
Stereochemical Study

Flash column chromatography (silica gel) of the mixture of **36** and **37** resulted in the isolation of **37** and a mixture containing mainly **36** along with another isomer **36b**. This indicated that the A-ring closure was reversible and that equilibration could operate. Treatment of this **36/36b** mixture with hydrofluoric acid in acetonitrile furnished deprotected compound **38** and a tricyclic alcohol **39** (Scheme 15), the structure of which was determined by X-ray diffraction.



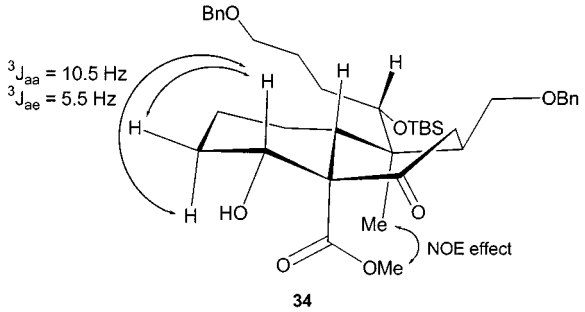
Scheme 15

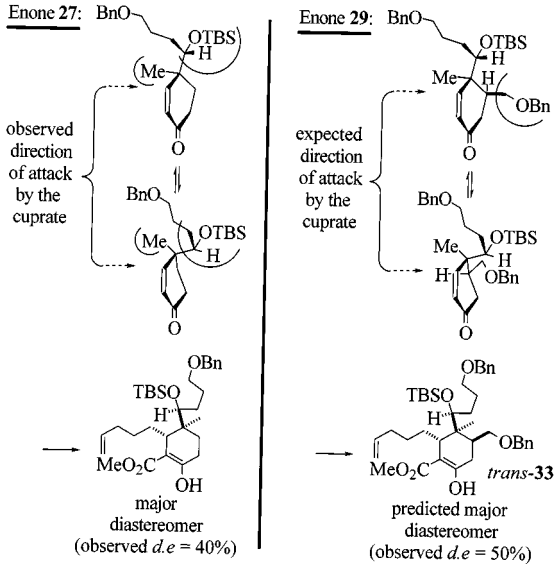
This unambiguously confirmed the relative configurations at carbon atoms C9, C10, and C11, thus demonstrating the correct selectivity of the Vaultier tandem sequence and of the cuprate addition onto enone **27**. The *trans*-decalin structures of **36** and **37** were assigned by ^{13}C NMR data comparison with the known model compound **40**.[14]



In the case of the more substituted compounds, it is reasonable to assume that the major direction of attack by the cuprate onto enone **29** should also be on the α-face, thus producing the compound *trans*-**33**. Indeed, the benzyloxymethyl group of **29** should favour the conformation in which it is pseudoequatorial and the silylated side-chain hinders the β-face. In the other possible conformation, the benzyloxymethyl group is pseudoaxial and also encumbers that face (Scheme 16).

As in the case of **36** and **37**, NMR data comparisons were in agreement with the depicted *trans*-decalin structures of **34** and **35**. Moreover, an NOE between the C20 methyl and the ester groups of **34** was observed, and the coupling constants of the 4β proton were found to be consistent with an equatorial orientation of the hydroxy group.





Scheme 16

Conclusion

The preparation of intermediate **34** from commercially available compounds has been achieved with a good level of stereocontrol in only eight linear steps. Even though this synthesis has no claim to rival de Groot's,[7] since it is still unfinished, we believe our approach represents an interesting contribution in the field and highlights the power of the three-component Vaultier tandem sequence for the diastereoselective construction of such systems.

Experimental Section

General Remarks: NMR spectra were recorded with WP 200 (^{1}H at 200 MHz, ^{13}C at 50.1 MHz) and AM 400 Bruker spectrometers (^{1}H at 400 MHz, ^{11}B at 128.3 MHz, and ^{13}C at 100.3 MHz). Chemical shifts are given in ppm, referenced to the solvent peak of $CDCl_3$, defined at δ = 7.26 (^{1}H NMR) or δ = 77.0 (^{13}C NMR). Infrared spectra were recorded with a Perkin−Elmer 1600 spectrometer. Flash column chromatography was performed on Merck 60 silica gel (230−400 mesh). All reactions were carried out under nitrogen unless indicated otherwise. Anhydrous THF, diethyl ether, pentane and benzene were distilled from sodium/benzophenone, dichloromethane was distilled from CaH_2, DMF was distilled under reduced pressure (ca. 40 Torr) from CaH_2. Enyne **10** was prepared according to a literature procedure[32] and stored at −15 °C with $MgSO_4/Na_2CO_3$. The preparation of dienylboronate **18** has already been reported.[21] 4-Benzyloxybutanal was synthesised as described below.

4-Benzyloxybutanal

Benzylation of 1,4-Butanediol: Sodium hydride (80% in oil, 1.0 equiv., 0.23 mol, 6.8 g) was added slowly at 0 °C to a solution of 1,4-butanediol (1.0 equiv., 0.23 mol, 20 mL) in dry THF (150 mL). Tetrabutylammonium iodide (1% equiv., 2.3 mmol, 0.83 g) and a solution of benzyl bromide (1.0 equiv., 0.23 mol, 27 mL) in THF (50 mL) were then added at room temperature. The mixture was stirred for 2 h and became white. It was then neutralised with saturated aqueous ammonium chloride solution and washed with water. The organic layer was separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 42 g of a red oil. Purification by flash column chromatography (ethyl acetate/petroleum ether, boiling range 40−60 °C, 30:70) resulted in the isolation of 4-benzyloxybutanol (39 g, 0.22 mol, 95%).

Alcohol Oxidation: Dichloromethane (150 mL) and 4-benzyloxybutanol (1.0 equiv., 0.10 mol, 18 g) were added to PDC (1.2 equiv., 0.12 mol, 44 g) and Celite® (35 g). The mixture was stirred for 22 h, and then diluted with diethyl ether (500 mL) and filtered through magnesium sulfate and silica gel. The resulting solution was concentrated to afford 19 g of the crude product. Purification by distillation yielded 4-benzyloxybutanal (10 g, 58 mmol, 56%). Colourless liquid; b.p. ca. 84 °C/4 mbar. MS (CI, NH_3): *m/z* = 108, 179 [MH^+], 195 [$MH^+ \cdot NH_3$], 212 [$MH^+ \cdot (NH_3)_2$]. IR: $\tilde{\nu}$ = 3066, 3031, 2933, 2858, 2817, 2716, 1729, 1496, 1454, 1360, 1099, 1028, 697 cm^{-1}. ^{1}H NMR: δ = 9.20 (s, 1 H), 7.37−7.28 (m, 5 H), 4.49 (s, 2 H), 3.51 (t, *J* = 6.0 Hz, 2 H), 2.55 (2 H, td, *J* = 7 and 1.5 Hz), 1.95 (2 H, quint, *J* = 6.5 Hz). ^{13}C NMR: δ = 202.0, 138.4, 128.4, 127.6, 73.0, 69.2, 40.9, 22.6. ***Note:*** The distillation residue contained ester resulting from the Tishchenko reaction of 4-benzyloxybutanal (4.3 g, 12 mmol, 24%). Column chromatography may be preferred to avoid this problem and increase the yield.

Diene 2: Catecholborane (1.0 equiv., 20 mmol, 2.1 mL) was added dropwise to a cooled (0 °C) solution of enyne **10** (1.5 equiv., 30 mmol, 2.8 mL) in dry pentane (20 mL). The mixture was heated at reflux for 24 h. After cooling, the slurry was filtered and concentrated to afford **2** (3.2 g, 17 mmol, 87%). ***Note:*** Diene **2** was generally used without any further purification. Distillation is, however, possible if high purity is needed. White crystalline solid; b.p. ca. 80 °C/4 mbar. MS (CI, NH_3): *m/z* = 185, 186 [MH^+, ^{10}B], 187 [MH^+, ^{11}B], 203 [$MH^+ \cdot NH_3$, ^{10}B], 204 [$MH^+ \cdot NH_3$, ^{11}B]. IR: $\tilde{\nu}$ = 1625, 1600, 1472, 1386, 1364, 1323, 1300, 1265, 1236, 1190, 994 cm^{-1}. ^{1}H NMR: δ = 7.47 (d, *J* = 17.0 Hz, 1 H), 7.25−7.23 (m, 2 H), 7.10−7.08 (m, 2 H), 5.88 (d, *J* = 17.0 Hz, 1 H), 5.31 (s, 2 H), 1.93 (s, 3 H). ^{13}C NMR: δ = 154.7, 148.4, 143.0, 122.7, 121.8, 112.4, 17.7.

Homoallylic Alcohol 3

Method A (Three-Component Reaction at 80 °C): Freshly distilled methyl acrylate (8.0 equiv., 46 mmol, 4.2 mL) and 4-benzyloxybutanal (3.0 equiv., 17 mmol, 3.1 g) were added at 0 °C to diene **2** (1.0 equiv., 5.8 mmol, 1.1 g). The mixture was heated at 80 °C for 16 h, and then diluted with petroleum ether (boiling range 40−60 °C, 50 mL) and stirred at room temperature for 30 min with saturated aqueous sodium hydrogen carbonate solution (50 mL). The organic layer was separated and the aqueous layer was extracted several times with petroleum ether (boiling range 40−60 °C, 50-ml portions). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 2.0 g of the crude product. Purification by flash column chromatography [10% ethyl acetate/petroleum ether (boiling range 40−60 °C)] resulted in the isolation of 4-benzyloxybutanal (0.63 g, 3.5 mmol) and of alcohol **3** (0.96 g, 2.9 mmol, 50%) as a mixture of two diastereomers (*cis*/*trans* ≈ 80:20).

Method B (Three-Component Reaction under High Pressure):[26] Freshly distilled methyl acrylate (5.0 equiv., 4.0 mmol, 0.36 mL)

and 4-benzyloxybutanal (1.5 equiv., 1.2 mmol, 0.22 g) were added at 0 °C to diene **2** (1.0 equiv., 0.8 mmol, 0.15 g). The mixture was allowed to warm to room temperature and placed in a small (ca. 2 mL) high-pressure cell, which was then filled with dry dichloromethane. The cell was submitted to a pressure of 10 kbar for 24 h at room temperature. The crude material, a red, partially polymerised jelly, was dissolved in dichloromethane (20 mL) and stirred for 30 min with saturated aqueous sodium hydrogen carbonate solution (10 mL). The organic layer was separated and the aqueous layer was extracted with petroleum ether (boiling range 40−60 °C, 3 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 0.14 g of the crude product. Purification by flash column chromatography [20% ethyl acetate/petroleum ether (boiling range 40−60 °C)] afforded *cis*-**3** (58 mg, 0.17 mmol, 22%) as a single diastereomer.

***cis* Isomer:** Viscous, pale yellow liquid. MS (GC, CI, NH_3): *m*/*z* = 71, 91, 237, 283, 315, 316, *333* [MH^+], 334, 350 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3029, 2951, 2859, 1738, 1454, 1434, 1363, 1196, 1172, 1101, 1028, 697 cm^{-1}. ^1H NMR: δ = 7.36−7.26 (m, 5 H), 5.82 (dd, 1 H, *J* = 10 and 4 Hz), 5.59 (dd, 1 H, *J* = 10 and 2 Hz), 4.51 (s, 2 H), 3.67 (s, 3 H, OMe), 3.50 (t, *J* = 6.0 Hz, 2 H), 3.36 (d, *J* = 10.5 Hz, 1 H), 3.05 (m, 1 H) 2.04−1.75 (m, 4 H), 1.75−1.63 (m, 1 H), 1.69 (2 H, quint, *J* = 5.5 Hz), 1.34 (dd, *J* = 10.5, 5.5 Hz, 1 H), 1.26 (m, 1 H), 0.95 (s, 3 H). ^{13}C NMR: δ = 174.4, 138.4, 136.6, 128.3, 127.6, 125.1 (CH−*C*H=CH), 77.2, 72.9, 70.5, 51.6, 40.7 (*C*HCO_2Me), 39.4, 28.4, 28.1, 27.2, 22.9, 21.9 (Cq-CH_2−CH_2).

***trans* Isomer (Characteristic Differences):** ^1H NMR: δ = 3.69 (s, 3 H, OMe). ^{13}C NMR: δ = 125.5 (CH−*C*H=CH), 41.5 (*C*HCO_2Me), 22.2 (Cq-CH_2−*C*H_2).

Bromo Diene 12: Tribromoborane (1 M solution in dichloromethane, 1.0 equiv., 10 mmol, 10 mL) was added dropwise at −78 °C to a solution of enyne **10** (1.0 equiv., 10 mmol, 0.95 mL) in dichloromethane (10 mL). The mixture was stirred for 1 h at −78 °C, and dry diethyl ether (25 equiv., 250 mmol, 26 mL) was then added. The solution was allowed to warm to room temperature, stirred overnight with exclusion of light and then concentrated. Distillation (100 °C, 3 mbar) of the crude material resulted in the isolation of pure **12** (0.41 g, 1.7 mmol, 17%) as a mixture of two isomers [(*Z*)/(*E*) ≈ 3:1]. IR (mixture of the two isomers): $\tilde{\nu}$ = 3629, 3584, 1589, 1437, 1389, 1358, 1325, 993, 911, 724 cm^{-1}. (*Z*) isomer: Colourless oil; b.p. ca. 35 °C/0.2 Torr. ^1H NMR: δ = 6.31 (s, 1 H), 5.57 (s, 1 H), 5.21 (s, 1 H), 3.97 (q, *J* = 7.0 Hz, 4 H), 2.01 (s, 3 H), 1.23 (t, *J* = 7.0 Hz, 6 H). ^{13}C NMR: δ = 141.8, 136.0, 119.3, 60.2, 20.4, 17.0. (*E*) isomer: Colourless oil; b.p. 100 °C/3 mbar. ^1H NMR: δ = 6.16 (s, 1 H), 5.63 (s, 1 H), 5.30 (s, 1 H), 4.02 (q, *J* = 7.0 Hz, 4 H), 2.04 (s, 3 H), 1.27 (t, *J* = 7.0 Hz, 6 H). ^{13}C NMR: δ = 140.1, 121.2, 58.8, 19.9, 17.2. ***Notes:*** a) Distillation at lower temperature at 0.2 Torr gave **12** in a higher (*Z*)/(*E*) ratio (5:1), but in lower yield (8%). b) Isomer (*Z*)-**12** is unstable and undergoes spontaneous conversion into the (*E*) isomer, two ^1H NMR spectra were run on the same sample at an interval of a few hours. The later one clearly displayed a higher proportion of the (*E*) isomer.

Bromo Diene 13: Ethylene glycol (1.1 equiv., 0.96 mmol, 50 μL) was added to a solution of diene (*E*)-**12** (1.0 equiv., 0.87 mmol, 0.21 g) in the minimum amount possible of dry, distilled ethyl acetate. The mixture was stirred for 4 h and then concentrated under reduced pressure. The residue (0.24 g) contained diene (*E*)-**13** (quantitative yield), along with a small amount of ethylene glycol. ^1H NMR: δ = 6.20 (s, 1 H), 5.67 (s, 1 H), 5.28 (s, 1 H), 4.30 (s, 4 H), 2.01 (s, 3 H). ^{13}C NMR: δ = 142.3, 121.5, 65.7, 20.7. ***Note:*** Compound (*E*)-**13** decomposed significantly when filtration through silica gel was attempted.

Bromo Diene 14: A solution of enyne **10** (1.0 equiv., 15 mmol, 1.4 mL) in dry dichloromethane (DCM; 15 mL) was added dropwise, at −78 °C over 30 min, to a solution of tribromoborane (1.0 equiv., 15 mmol) in dry DCM (30 mL). The mixture became very dark and was stirred for an additional 30 min at −78 °C. A solution of *N*,*N*′-dimethylethylenediamine (0.9 equiv., 14 mmol, 1.4 mL) in dry DCM (15 mL) was then slowly added over 1 h. The formation of white crystals was observed, and the yellow mixture was stirred for a further hour at −78 °C. The cold bath was then removed, and the solvent and the volatile fractions were removed under reduced pressure. The crystalline residue was redissolved in benzene (9 mL) and triethylamine (2.1 equiv., 31 mmol, 4.4 mL) was added over 30 min. A white precipitate was observed. The mixture was filtered (under nitrogen) and concentrated to afford 2.6 g of the crude product. Purification by distillation resulted in the isolation of pure diene **14** (0.82 g, 3.4 mmol, 25%). Colourless oil; b.p. ca. 70 °C/4 mbar. MS (CI, NH_3): *m*/*z* = 89, 129, 213, 215, 233, 235, 243 [MH^+, ^{11}B and ^{79}Br], 245 [MH^+,^{11}B and ^{81}Br], 261 [$MH^+ \cdot NH_3$,^{11}B and ^{79}Br]. IR: $\tilde{\nu}$ = 2969, 2847, 2789, 1596, 1499, 1475, 1440, 1406, 1371, 1319, 1290, 1256, 1210, 1123, 1066, 1010, 906 cm^{-1}. ^1H NMR: δ = 6.27 (s, 1 H), 5.57 (s, 1 H), 5.18 (s, 1 H), 3.22 (s, 4 H), 2.60 (s, 6 H), 2.04 (s, 3 H). ^{11}B NMR: δ = 30.4. ^{13}C NMR: δ = 141.9, 136.1, 118.7, 51.7, 34.2, 20.7. ***Note:*** Compound **14** is very sensitive to water and moderately sensitive to air. No significant decomposition occurs upon heating a solution at 80 °C under nitrogen for several hours.

Esters 15, 16, and 17: Diene **14** (1.0 equiv., 1.0 mmol, 0.24 g) was added dropwise at 0 °C to freshly distilled methyl acrylate (10 equiv., 10 mmol, 0.90 mL). The mixture was heated at 75 °C for 48 h and, after cooling, diluted with dry dichloromethane (5 mL). Distilled propanal (5.0 equiv., 5.0 mmol, 0.36 mL) was added at −78 °C, and the mixture was allowed to warm to room temperature. After 48 h of stirring, saturated aqueous ammonium chloride solution (5 mL) was added and stirring was maintained for two more hours. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 0.30 g of the crude product. Flash column chromatography [20% ethyl acetate/petroleum ether (boiling range 40−60 °C)] gave 34 mg of a mixture of alcohols **16** (22 mg, 8%) and **17** (12 mg, 5%). Both were single diastereomers and could be separated by further flash column chromatography.

Compound 15: ^1H NMR: δ = 3.67 (s, 3 H, OMe), 3.10 (m, 1 H, C*H*CO_2Me), 1.80 (s, 3 H, vinylic Me).

Compound 16: Viscous, colourless oil. MS (GC, CI, NH_3): *m*/*z* = 153, 193, 233, 275, 291 [MH^+, ^{79}Br], 293 [MH^+, ^{81}Br], 308 [$MH^+ \cdot NH_3$, ^{79}Br], 310 [$MH^+ \cdot NH_3$, ^{81}Br]. IR: $\tilde{\nu}$ = 3604, 2952, 2876, 1741, 1456, 1435, 1378, 1301, 1248, 1195, 1172, 978 cm^{-1}. ^1H NMR: δ = 6.34 (dd, *J* = 2.5, 0.5 Hz, 1 H), 3.71 (s, 3 H), 3.67 (d, *J* = 10.5 Hz, 1 H), 3.12 (ddd, 1 H, *J* = 10.5, 5.5 and 2.5 Hz), 2.08 (m, 1 H), 1.96 (1 H, td, *J* = 13 and 3 Hz), 1.80 (1 H, td, *J* = 10.5, 2.5 Hz), 1.59 (m, 1 H), 1.51 (m, 1 H), 1.30 (m, 1 H), 1.09 (s, 3 H), 1.05 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR: δ = 172.9, 134.9, 130.0, 77.9, 52.1, 45.9, 44.3, 28.7, 22.9, 22.6, 21.9, 11.7.

Compound 17: White crystals. MS (GC, CI, NH_3): *m*/*z* = 231, 232, 233, 234, 248, 249 [MH^+, ^{79}Br], 250, 251 [MH^+, ^{81}Br], 266 [$MH^+ \cdot NH_3$, ^{79}Br], 268 [$MH^+ \cdot NH_3$, ^{81}Br]. IR: $\tilde{\nu}$ = 3598, 2951, 2916, 1739, 1436, 1379, 1342, 1290, 1253, 1231, 1195, 1171, 1025 cm^{-1}. ^1H NMR: δ = 4.57 (d, *J* = 7.5 Hz, 1 H), 3.73 (s, 3 H), 2.74 (ddd, 1 H, *J* = 9, 7.5 and 3.5 Hz), 2.62 (s, 1 He, O*H*), 2.30−1.95 (m, 4 H), 1.84 (s, 3 H). ^{13}C NMR: δ = 173.7, 136.2,

121.4, 71.4, 52.1, 48.1, 31.6, 23.3, 23.0. ***Note:*** Dimethyl *N*,*N*′-Dimethylethylenediamine-*N*,*N*′-bis(propanoate), the Michael addition product of *N*,*N*′-dimethylethylenediamine with methyl acrylate, was always detected in various amounts when the cycloaddition step was performed.

Homoallylic Alcohol 19: Freshly distilled methyl acrylate (5.0 equiv., 15 mmol, 1.4 mL) was added at −78 °C to a solution of ethylaluminium dichloride (1.8 M in toluene, 1.0 equiv., 3.0 mmol, 1.6 mL), diluted with dry dichloromethane (5 mL). After 20 min of stirring at −78 °C, a solution of diene **2** (1.0 equiv., 3.0 mmol, 0.56 g) in dry dichloromethane (4 mL) was added dropwise. The cold bath was removed and the mixture was stirred for 6 h, during which NMR analysis showed the disappearance of diene **2** and the formation of the cycloaddition product. Triethylamine (1.0 equiv., 3.0 mmol, 0.45 mL) was then added at −78 °C. The reddish-brown solution turned yellow and was allowed to warm to room temperature. Distilled propanal (1.1 equiv., 3.3 mmol, 0.25 mL) was added at −78 °C. After 14 h of stirring at room temperature, petroleum ether (boiling range 40−60 °C) (100 mL) and saturated aqueous sodium hydrogen carbonate solution (70 mL) were added to the mixture, which was stirred for an additional hour. The organic phase was separated and the aqueous phase was extracted with petroleum ether (boiling range 40−60 °C, 2 × 100 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 0.32 g of the crude product. Flash column chromatography (30% ethyl acetate/petroleum ether, boiling range 40−60 °C) produced pure alcohol **19** (0.25 g, 1.2 mmol, 40%), mainly as the *cis* isomer (estimated *de* > 90%). ***Notes:*** a) The cycloaddition step could also be run at 0 °C in toluene. It was slower, however. The reaction was estimated to have reached ca. 85% completion after 40 h (^{1}H NMR analysis). b) Diisopropylethylamine was also used in place of triethylamine to give a comparable result.

Diels−Alder Adduct Intermediate: ^{1}H NMR: δ = 7.18−7.12 (m, 2 H), 7.03−6.97 (m, 2 H), 5.56 (s, 1 He, C=C*H*), 3.63 (s, 3 H), 3.02 (m, 1 H), 2.48 (m, 1 H), 2.25 (m, 2 H), 2.04 (s, 2 H), 1.69 (s, 3 H, Me). ^{13}C NMR: δ = 133.8, 122.0, 118.7, 112.1, 51.5, 41.4, 28.6, 24.3, 23.7. Major (*cis*) isomer of compound **19**: Viscous, colourless oil. MS (GC, CI, NH_3): *m*/*z* = 135, 195, 213 [MH^+], 230 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3639, 3024, 2952, 2875, 1738, 1456, 1435, 1296, 1251, 1196, 1171 cm^{-1}. ^{1}H NMR: δ = 5.83 (dd, 1 H, *J* = 10 and 4 Hz), 5.57 (dd, 1 H, *J* = 10 and 2 Hz), 3.68 (s, 3 H, OMe), 3.25 (dd, 1 H, *J* = 10.5 and 2 Hz), 3.04 (m, 1 H), 2.00−1.75 (m, 3 H), 1.67 (s, 1 He, O*H*), 1.57 (1 H, dqd, *J* = 14, 7.5 and 2 Hz), 1.32−1.23 (m, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H), 0.95 (s, 3 H). ^{13}C NMR: δ = 174.6, 136.8, 125.4, 79.2, 52.0, 40.6, 39.9, 28.0, 23.7, 23.0, 22.0, 11.6. Minor (*trans*) isomer of compound **19** (characteristic difference): ^{1}H NMR: δ = 3.69 (s, 3 H, OMe).

Diene 20

Alcohol Protection: Sodium hydride (80% suspension in oil, 1.1 equiv., 27 mmol, 0.82 g) was slowly added at 0 °C to a solution of (*E*)-3-methylpent-2-en-4-ynol (1.0 equiv., 25 mmol, 2.7 mL) in dry THF (15 mL). Tetrabutylammonium iodide (1% equiv., 0.25 mmol, 92 mg) and a solution of benzyl bromide (1.1 equiv., 27 mmol, 3.3 mL) in THF (5 mL) were then added. The mixture, stirred for 2 h 30 min, became cloudy. It was quenched with saturated aqueous ammonium chloride solution (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (10 mL), dried with magnesium sulfate, filtered, and concentrated to afford 6.9 g of the crude product. Flash column chromatography (ethyl acetate/petroleum ether, boiling range 40−60 °C, gradient from 2% to 10%) provided (*E*)-5-benzyloxy-3-methylpent-3-en-1-yne (4.0 g, 22 mmol, 87%).

Hydroboration: Catecholborane (1.0 equiv., 4.3 mmol, 0.46 mL) was added dropwise at 0 °C to (*E*)-5-benzyloxy-3-methylpent-3-en-1-yne (1.0 equiv., 4.3 mmol, 0.80 g). The mixture was stirred for 1 h at room temperature, and for 2 h at 70 °C. The reaction was then shown to be complete by ^{1}H NMR analysis. Dry petroleum ether, boiling range 40−60 °C (15 mL) was then added. The solution became clear after 1 h of stirring and was filtered (under nitrogen) and then concentrated under reduced pressure to leave 1.3 g of a brown oil. This contained a mixture of starting benzylated enyne and diene **20** (ratio ca. 1:4), which was used as such. Estimated yield 77%.

(*E*)-5-Benzyloxy-3-methylpent-3-en-1-yne: Colourless liquid; b.p. 73 °C/0.11 mbar. MS (GC, CI, NH_3): *m*/*z* = 79, 91, 157, 169, 187 [MH^+], 204 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3313, 3031, 2925, 2856, 1496, 1454, 1379, 1361, 1203, 1112, 1070, 1028, 697, 642, 614 cm^{-1}. ^{1}H NMR: δ = 7.38−7.28 (m, 5 H), 6.11 (1 H, td, *J* = 6.5 and 1 Hz), 4.52 (s, 2 H), 4.11 (d, *J* = 6.5 Hz, 2 H), 2.84 (s, 1 H), 1.82 (d, *J* = 1.0 Hz, 3 H). ^{13}C NMR: δ = 138.0, 135.1, 128.4, 127.8, 127.7, 120.4, 85.8, 75.2, 72.3, 66.0, 17.5.

Compound 20: Pale yellow liquid. MS (CI, NH_3): *m*/*z* = 198, 199, 215, 216, 323 [$MH^+ \cdot NH_3$, ^{10}B], 324 [$MH^+ \cdot NH_3$, ^{11}B]. MS (CI, EI): *m*/*z* = 65, 77, 91, 159, 215, 306 [$M^{+\cdot}$]. IR: $\tilde{\nu}$ = 1604, 1473, 1363, 1324, 1269, 1236 cm^{-1}. ^{1}H NMR: δ = 7.43 (d, *J* = 18.0 Hz, 1 H), 7.38−7.28 (m, 5 H), 7.25−7.24 (m, 2 H), 7.11−7.08 (m, 2 H), 6.02 (t, *J* = 6.5 Hz, 1 H), 5.89 (d, *J* = 18.0 Hz, 1 H), 4.57 (s, 2 H), 4.25 (d, *J* = 6.5 Hz, 2 H), 1.85 (s, 3 H). ^{13}C NMR: δ = 155.8, 148.3, 138.0, 137.4, 134.1, 128.5, 127.9, 127.8, 122.6, 112.3, 72.5, 66.7, 12.2.

Homoallylic Alcohol 21: Diene **20** was prepared according to the method described above, with 3.9 mmol of (3*E*)-5-benzyloxy-3-methylpent-3-en-1-yne and 4.3 mmol of catecholborane. The amount of diene **20** thus obtained was estimated by ^{1}H NMR analysis to be 3.1 mmol. Freshly distilled methyl acrylate (8.0 equiv., 25 mmol, 2.2 mL) and 4-(benzyloxy)butanal (3.0 equiv., 9.4 mmol, 1.7 g) were then added at 0 °C. The mixture was heated at 80 °C and stirred for 15 h 30. Dichloromethane/petroleum ether (boiling range 40−60 °C) (50%, 80 mL) and aqueous sodium hydroxide solution (0.1 M, 40 mL) were added. The organic phase was separated and the aqueous phase was extracted with 50% dichloromethane/petroleum ether (boiling range 40−60 °C) (2 × 40 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated to afford 4.2 g of the crude product. Flash column chromatography [10% ethyl acetate/petroleum ether (boiling range 40−60 °C)] resulted in the isolation of 4-benzyloxybutanal (0.20 g, 1.1 mmol) and alcohol **21** (0.46 g, 1.0 mmol, 33%) as a mixture of two diastereomers (*cis*/*trans* ≈ 4:1). ***Note:*** The ester resulting from the Tishchenko reaction of 4-benzyloxybutanal was also isolated and accounted for some of the in situ decomposition of that reagent.

Mixture (*cis*/*trans* ≈ 4:1) of the Two Isomers: Viscous, pale yellow liquid. MS (CI, NH_3): *m*/*z* = 196, 237, 345, 438, 453 [MH^+], 470 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3470, 3030, 2951, 2859, 1738, 1454, 1362, 1195, 1170, 1101, 1028, 697 cm^{-1}. Major (*cis*) isomer: ^{1}H NMR: δ = 7.38−7.27 (m, 10 H), 5.96 (d, *J* = 10.5 Hz, 1 H), 5.56 (dd, *J* = 10.5, 2.5 Hz, 1 H), 4.53 (s, 2 H), 4.50 (s, 2 H), 3.69 (s, 3 H), 3.65 (m, 1 H), 3.54−3.45 (m, 3 H), 3.39 (d, *J* = 10.5 Hz, 1 H), 3.14 (m, 1 H), 2.23 (q, *J* = 12.5 Hz, 1 H), 2.05 (m, 1 H), 1.88 (m, 1 H), 1.73−1.60 (m, 4 H), 1.39 (m, 1 H), 1.02 (s, 3 H). ^{13}C NMR: δ =

174.6, 138.5, 137.7, 133.6 (CHCH=*C*H), 128.4, 128.2, 127.7, 127.6, 127.4, 126.3, 76.4, 73.5, 72.7, 70.8, 70.2, 51.8, 44.9 (*C*HCH$_2$OBn), 42.0, 41.2, 29.2, 27.3, 27.2, 26.4. Minor (*trans*) isomer (characteristic differences): ^{13}C NMR: δ = 134.9 (CHCH=*C*H), 44.4 (*C*HCH$_2$OBn).

Silyl Ether 22: 2,6-Lutidine (2.5 equiv., 7.1 mmol, 0.83 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.5 equiv., 4.3 mmol, 0.98 mL) were added dropwise at 0 °C to a solution of alcohol **3** (1.0 equiv., 2.8 mmol, 0.95 g) in dry dichloromethane (3 mL). The mixture was stirred for 15 min at room temperature and then diluted with diethyl ether (30 mL). Saturated aqueous ammonium chloride solution (30 mL) was then slowly added at 0 °C. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated to afford 1.3 g of the crude product. Flash column chromatography [10% ethyl acetate/petroleum ether (boiling range 40−60 °C)] yielded silyl ether **22** (1.2 g, 2.7 mmol, 95%).

Mixture (*cis*/*trans* ≈ 4:1) of the Two Isomers: Colourless liquid. $C_{26}H_{42}O_4Si$: calcd. C 69.91, H 9.48; found C 70.03, H 9.35. MS (CI, NH_3): *m*/*z* = 223, 283, *315*, 316, 332, 447 [MH$^+$], 464 [MH$^+$ · NH_3], 465. IR: ṽ = 3029, 2953, 2929, 2856, 1739, 1472, 1462, 1454, 1434, 1361, 1255, 1195, 1166, 1093, 697 cm^{-1}. Major (*cis*) isomer: ^{1}H NMR: δ = 7.35−7.26 (m, 5 H), 5.72 (dd, 1 H, *J* = 10 and 4 Hz, CH=C*H*CHCO$_2$Me), 5.60 (dd, 1 H, *J* = 10 and 2 Hz, C*H*=CHCHCO$_2$Me), 4.49 (s, 2 H), 3.67 (s, 3 H, OMe), 3.42 (m, 3 H), 3.02 (1 H, tdt, *J* = 6, 4 and 2 Hz), 1.98−1.87 (m, 2 H), 1.84−1.72 (m, 2 H), 1.67−1.52 (m, 2 H), 1.42 (m, 1 H), 1.20 (m, 1 H), 0.93 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR: δ = 174.4, 138.7, 137.3, 128.3, 127.5, 127.4, 123.5, 77.8 (CH−OSi), 72.7, 70.7, 51.7, 40.8 (*C*HCO$_2$Me), 40.0, 29.8, 29.5, 27.5, 26.1, 23.2 (Cq-Me), 21.3 (*C*H$_2$CHCO$_2$Me), 18.3, −3.6, −3.9. Minor (*trans*) isomer (characteristic differences): ^{1}H NMR: δ = 5.68 (dd, 1 H, *J* = 7.5 and 2 Hz, CH=C*H*CHCO$_2$Me), 5.57 (dd, 1 H, *J* = 7.5 and 3 Hz, C*H*=CHCHCO$_2$Me), 3.70 (s, 3 H, OMe). ^{13}C NMR: δ = 78.9 (CH−OSi), 41.6 (*C*HCO$_2$Me), 23.7 (Cq-Me), 22.3 (*C*H$_2$CHCO$_2$Me).

Silyl Ether 23: 2,6-Lutidine (2.5 equiv., 3.2 mmol, 0.37 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.5 equiv., 1.9 mmol, 0.44 mL) were added dropwise at 0 °C to a solution of alcohol **21** (1.0 equiv., 1.3 mmol, 0.58 g) in dry dichloromethane (1.5 mL). The mixture was stirred for 15 min at room temperature and then diluted with diethyl ether (15 mL). Saturated aqueous ammonium chloride solution (15 mL) was then slowly added at 0 °C. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 0.75 g of the crude product. Flash column chromatography [10% ethyl acetate/petroleum ether (boiling range 40−60 °C)] resulted in the isolation of silyl ether **23** (0.62 g, 1.1 mmol, 85%). Mixture (*cis*/*trans* ≈ 4:1) of the two isomers: Colourless liquid. MS (GC, CI, NH_3): *m*/*z* = *237*, 238, 343, 435, 436, 584 [MH$^+$ · NH_3]. IR: ṽ = 3030, 2953, 2929, 2856, 1738, 1548, 1471, 1454, 1434, 1362, 1256, 1195, 1172, 1076, 697 cm^{-1}. Major (*cis*) isomer: ^{1}H NMR: δ = 7.36−7.25 (m, 10 H), 5.77 (dd, 1 H, *J* = 10 and 1.5 Hz), 5.50 (dd, 1 H, *J* = 10 and 2.5 Hz), 4.49 (d, *J* = 2.0 Hz, 2 H), 4.47 (s, 2 H), 3.87 (dd, 1 H, *J* = 10 and 3.5 Hz), 3.65 (s, 3 H, OMe), 3.44 (t, *J* = 10.0 Hz, 1 H), 3.40 (m, 1 H), 3.38 (t, *J* = 6.5 Hz, 2 H), 3.11 (m, 1 H), 2.31 (ddd, 1 H, *J* = 13, 6.5 and 3 Hz), 1.93−1.74 (m, 4 H), 1.52−1.36 (m, 2 H), 1.05 (s, 3 H, Cq-Me), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR: δ = 174.8, 138.7, 137.1, 128.3, 127.5, 127.4, 123.8, 79.2, 73.0, 72.8, 71.0, 70.4, 51.7, 43.9, 41.8, 41.5 (*C*HCO$_2$Me), 31.9, 28.4, 27.1, 26.2, 25.7, 18.4, −3.4, −3.8. Minor (*trans*) isomer, characteristic differences: ^{1}H NMR: δ = 3.70 (s, 3 H, OMe), 1.07 (s, 3 H, Cq-Me). ^{13}C NMR: δ = 41.8 (*C*HCO$_2$Me).

Vinylic Acid 24, Vinylic Ester 25 and α-Oxygenated Acid 26: Potassium *tert*-butoxide (1.2 equiv., 1.0 mmol, 0.11 g) was added at 0 °C to a solution of ester **22** (1.0 equiv., 0.85 mmol, 0.38 g) in dry THF (10 mL). After 30 min of stirring, the mixture became yellow. It was further stirred for 1 h at room temperature, and saturated aqueous ammonium chloride solution (15 mL) was then added at 0 °C. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (5 × 15 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated to afford 0.36 g of the crude product. Flash column chromatography [acetic acid/ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 0:0:100 to 2:98:0] resulted in the isolation of acid **24** (25 mg, 60 μmol, 7%), ester **25** (140 mg, 0.31 mmol, 37%), acid **26** (78 mg, 0.17 mmol, 20%) and enone **27** (70 mg, 0.17 mmol, 20%). Acid **26** was obtained as a 65:35 mixture of two diastereomers.

Compound 24: White solid. MS (CI, NH_3): *m*/*z* = 106, 132, 283, 301, 302, 318, 433 [MH$^+$], 450 [MH$^+$ · NH_3], 451. IR: ṽ = 2956, 2929, 2856, 1689, 1275, 1256, 1092, 832 cm^{-1}. ^{1}H NMR: δ = 7.35−7.28 (m, 5 H), 7.06 (s, 1 H), 4.51 (s, 2 H), 3.44 (2 H, td, *J* = 6.5, 1.5 Hz), 3.30 (dd, 1 H, *J* = 6.5 and 3 Hz), 2.39 (m, 1 H), 2.18 (m, 2 H), 1.89−1.75 (m, 2 H), 1.70−1.54 (m, 3 H), 1.48−1.32 (m, 2 H), 0.90 (s, 9 H), 0.82 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR: δ = 172.1, 141.5, 138.6, 128.5, 128.3, 127.6, 127.5, 79.7, 72.8, 70.6, 36.8, 35.3, 29.3, 29.3, 27.8, 26.1, 21.0, 19.1, 18.4, −3.3, −4.1.

Compound 25: Colourless liquid. MS (GC, CI, NH_3): *m*/*z* = 108, 223, 255, 283, 315, 316, 332, 447 [MH$^+$], 464 [MH$^+$ · NH_3], 465. IR: ṽ = 2951, 2929, 2856, 1716, 1472, 1462, 1454, 1436, 1360, 1255, 1087, 697 cm^{-1}. ^{1}H NMR: δ = 7.37−7.28 (m, 5 H, 6.91 (s, 1 H), 4.50 (s, 2 H), 3.73 (s, 3 H), 3.44 (2 H, td, *J* = 6.5, 1.5 Hz), 3.29 (dd, 1 H, *J* = 6.5 and 3 Hz), 2.38 (m, 1 H), 2.15 (m, 2 H), 1.85−1.77 (m, 2 H), 1.70−1.55 (m, 3 H), 1.46−1.32 (m, 2 H), 0.89 (s, 9 H), 0.81 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR: δ = 167.8, 138.8, 138.6, 129.1, 128.3, 127.6, 127.4, 79.8, 72.8, 70.6, 51.5, 36.8, 35.2, 29.4, 29.2, 27.8, 26.1, 21.4, 19.0, 18.3, −3.3, −4.1.

Compound 26 (65:35 Mixture of Two Isomers): White solid. MS (CI, NH_3): *m*/*z* = 108, 132, 178, 187, 289, 293, 294, 403, 420, 449 [MH$^+$]. Major isomer: ^{1}H NMR: δ = 7.37−7.27 (m, 5 H), 5.86 (d, *J* = 10.0 Hz, 1 H, CH=C*H*CqCO$_2$ H), 5.61 (d, *J* = 10.0 Hz, 1 H, C*H*=CHCqCO$_2$ H), 4.51 (s, 2 H), 3.46−3.43 (m, 3 H), 2.20−1.20 (m, 8 H), 1.00 (s, 3 H, Me), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR: δ = 179.4, 140.2, 138.3, 128.3, 127.7, 127.5, 125.0 (CH=*C*HCqCO$_2$ H), 89.1, 78.6, 72.7, 70.5, 40.6, 30.2, 29.8, 27.0, 26.0, 22.9, 22.4, 18.3, −3.6, −3.9. Minor isomer (characteristic differences): ^{1}H NMR: δ = 5.81 (d, *J* = 10.0 Hz, 1 H, CH=C*H*CqCO$_2$ H), 5.55 (d, *J* = 10.0 Hz, 1 H, C*H*=CHCqCO$_2$ H), 1.01 (s, 3 H, Me). ^{13}C NMR: δ = 126.1 (CH=*C*HCqCO$_2$ H).

Enone 27 and Hydroperoxide 28: A solution of ester **22** (1.0 equiv., 1.3 mmol, 0.59 g) in dry THF (15 mL) was flushed with oxygen and then cooled to −78 °C. Potassium *tert*-butoxide (purified by sublimation, 1.1 equiv., 1.4 mmol, 0.16 g) was then added. The solution was allowed to warm to 0 °C over 1 h 15 under a stream of oxygen. After 10 min at 0 °C, saturated aqueous ammonium chloride solution (30 mL) was added carefully. The pH was then adjusted to 7−8 with 1 N hydrochloric acid. The mixture was extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concen-

trated to afford 0.59 g of the crude product. Flash column chromatography [ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 0% to 10%] resulted in the isolation of starting ester **22** (34 mg, 6%) and enone **27** (0.14 g, 0.34 mmol, 26%), together with hydroperoxide **28** (0.37 g, 0.78 mmol, 59%) as a 65:35 mixture of two diastereomers.

Compound 27: Colourless liquid. $C_{24}H_{38}O_3Si$ (402.6): calcd. C 71.59, H 9.51; found C 71.81, H 9.51. MS (GC, CI, NH_3): *m*/*z* = 132, 178, 187, 293, 294, 403 [MH^+], 420 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3030, 2956, 2930, 2857, 1685, 1474, 1462, 1454, 1434, 1361, 1256, 1097, 1005, 697 cm^{-1}. ^1H NMR: δ = 7.36−7.28 (m, 5 H), 6.77 (dd, 1 H, *J* = 10 and 1 Hz), 5.91 (d, *J* = 10.0 Hz, 1 H), 4.49 (s, 2 H), 3.56 (dd, 1 H, *J* = 6 and 3 Hz), 3.44 (2 H, td), 2.47 (dd, 2 H, *J* = 8 and 5.5 Hz), 2.17 (dt, 1 H, *J* = 13.5 and 6 Hz), 1.82−1.44 (m, 5 H), 1.12 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR: δ = 199.6, 158.0, 138.4, 128.3, 128.1, 127.5, 77.9, 72.8, 70.3, 41.7, 33.9, 30.0, 29.7, 27.1, 26.0, 21.9, 18.2, −3.6, −4.0.

Compound 28 (65:35 Mixture of Two Isomers): Colourless oil. MS (CI, NH_3): *m*/*z* = 108, 132, 178, 187, 223, 293, 294, 313, 403, 420, 445 [$(M - OOH)^+$], 462 [$(M - OOH)^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3530, 2955, 2930, 2856, 1735, 1471, 1462, 1454, 1435, 1361, 1256, 1093, 1028, 697 cm^{-1}. Major isomer: ^1H NMR: δ = 8.94 (s, 1 H, OO*H*), 7.36−7.27 (m, 5 H), 6.01 (d, *J* = 10.0 Hz, 1 H, CH=C*H*CqOOH), 5.61 (d, *J* = 10.0 Hz, 1 H), 4.49 (s, 2 H), 3.80 (s, 3 H, OMe), 3.49−3.41 (m, 3 H), 2.24−1.87 (m, 3 H), 1.85−1.38 (m, 4 H), 1.33 (1 H, dm, *J* = 13.5 Hz), 1.02 (s, 3 H, CqMe), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR: δ = 174.0, 143.6 (CH=*C*HCq), 138.6, 128.3, 127.6, 127.5, 121.1 (*C*H=CHCq), 83.0, 78.6, 72.8 (*C*H_2Ph), 70.5, 52.6, 41.3 (CH=CH*Cq*), 29.9 (*C*H_2CHOTBS), 27.0 (*C*H_2CH_2OBn), 26.3 (*C*H_2CH_2CqOOH), 26.1, 24.6 (*C*H_2CqOOH), 22.5 (CqMe), 18.3, −3.6, −3.9. Minor isomer (characteristic differences): ^1H NMR: δ = 8.83 (s, 1 H, OO*H*), 5.93 (d, *J* = 10.0 Hz, 1 H, CH=C*H*CqOOH), 3.75 (s, 3 H, OMe), 1.01 (s, 3 H, CqMe). ^{13}C NMR: δ = 143.4 (CH=*C*HCq), 121.5 (*C*H=CHCq), 72.9 (*C*H_2Ph), 40.8 (CH=CH*Cq*), 30.1 (*C*H_2CHOTBS), 27.4 (*C*H_2CH_2OBn), 27.3 (*C*H_2CH_2CqOOH), 25.5 (*C*H_2CqOOH), 22.9 (CqMe). ***Notes:*** a) When the reaction was run at −78 °C for 3 h 20 min and quenched at that temperature, hydroperoxide **28** was isolated in 82% yield, along with 17% of starting material. b) Hydroperoxide **28** could be converted into enone **27** in two steps, albeit in modest yield. Reduction ($LiAlH_4$, THF, 0 °C) gave the corresponding 1,2-diol (47%). This was oxidatively cleaved ($NaIO_4$, $NaHCO_3$, water/dichloromethane) to afford **27** in 57% yield (88% based on the recovery of starting material).

Enone 29 and Hydroperoxide 30: A solution of ester **23** (1.0 equiv., 0.57 mmol, 0.32 g) in dry THF (7 mL) was flushed with oxygen for 20 min with vigorous stirring and then cooled to −78 °C. Potassium *tert*-butoxide (purified by sublimation, 1.5 equiv., 0.86 mmol, 97 mg) was quickly added. The solution was stirred for 1 h under a stream of oxygen and then allowed to warm to 0 °C over 2 h. After 10 min at 0 °C, saturated aqueous ammonium chloride solution (15 mL) was added carefully. The mixture was extracted with diethyl ether (4 × 15 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 0.32 g of a colourless liquid. Flash column chromatography [ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 0% to 20%] resulted in the isolation of α-hydroperoxyester **30** (27 mg, 47 μmol, 8%) and enone **29** (0.21 g, 0.40 mmol, 70%).

Compound 29: Colourless liquid. $C_{32}H_{46}O_4Si$ (522.8): C 73.52; H 8.87; found C 73.34, H 8.81. MS (CI, NH_3): *m*/*z* = 106, 108, 132, 178, 187, 248, 293, 294, 391, 523 [MH^+], 540 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 2956, 2930, 1683, 1472, 1462, 1454, 1362, 1252, 1240, 1097, 1049, 837, 697 cm^{-1}. ^1H NMR: δ = 7.36−7.24 (m, 10 H), 6.83 (d, *J* = 10.0 Hz, 1 H), 5.92 (d, *J* = 10.0 Hz, 1 H), 4.47 (s, 2 H), 4.47 (s, 2 H), 3.62 (m, 1 H), 3.60 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.42−3.36 (m, 3 H), 2.71 (dd, *J* = 17.5, 5.5 Hz, 1 H), 2.64 (dd, 1 H, *J* = 17.5 and 6 Hz), 2.29 (dddd, 1 H, *J* = 8.5, 6, 5.5 and 4.5 Hz), 1.80 (m, 1 H), 1.69 (m, 1 H), 1.47 (m, 2 H), 1.22 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR: δ = 199.0, 155.6, 138.5, 138.1, 128.3, 127.6, 127.6, 127.5, 75.8, 73.2, 72.8, 70.2, 69.8, 43.4, 43.1, 38.1, 29.8, 27.8, 26.1, 22.0, 18.4, −3.3, −3.9.

Compound 30: Colourless liquid. MS (CI, NH_3): *m*/*z* = 132, 178, 187, 253, 293, 359, 451, 478, 600 [MH^+]. IR: $\tilde{\nu}$ = 3528, 2954, 2929, 2856, 1737, 1550, 1472, 1454, 1435, 1362, 1256, 1100, 1075, 1043, 1028, 1004, 697 cm^{-1}. ^1H NMR: δ = 9.34 (1 H, br. s, OO*H*), 7.36−7.25 (m, 10 H), 5.85 (d, *J* = 10.0 Hz, 1 H), 5.71 (dd, 1 H, *J* = 10 and 1 Hz), 4.50 (s, 2 H), 4.47 (s, 2 H), 3.87 (dd, 1 H, *J* = 10 and 3.5 Hz), 3.74 (s, 3 H), 3.54−3.35 (m, 4 H), 2.48 (1 H, dbs, *J* = 11.0 Hz), 2.17−2.00 (m, 2 H), 1.77 (m, 2 H), 1.50−1.40 (m, 2 H), 1.09 (s, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H). ^{13}C NMR: δ = 173.6, 144.3, 138.6, 138.6, 128.3, 128.3, 127.5, 127.5, 127.5, 127.5, 121.4, 83.4, 78.7, 72.9, 72.8, 70.5, 70.4, 52.4, 42.8, 39.5, 32.0, 28.3, 28.3, 26.2, 26.2, 18.4, −3.5, −3.9.

Alcohol 31: Diisobutylaluminium hydride (DIBAL) (1 M in cyclohexane, 2.6 equiv., 0.54 mmol, 0.54 mL) was added at −78 °C to a solution of hydroperoxy ester **30** (1.0 equiv., 0.21 mmol, 0.13 g) in dry THF (4 mL). The temperature was increased to 0 °C over 1 h 30 and an extra equivalent of DIBAL was then added at −35 °C. The solution was stirred overnight at room temperature. Saturated aqueous Rochelle salt solution (2 mL) was added. After 30 min of stirring, the mixture was extracted with diethyl ether (4 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 0.13 g of a viscous, colourless liquid. Flash column chromatography [ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 5% to 20%] resulted in the isolation of enone **29** (27 mg, 52 μmol, 25%) and α-hydroxy ester **31** (89 mg, 0.15 mmol, 73%). Colourless liquid. MS (CI, NH_3): *m*/*z* = 108, 178, 187, 253, 293, 294, 391, 451, 601 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3533, 2954, 2929, 2856, 1734, 1471, 1454, 1362, 1256, 1219, 1075, 1028, 1004 cm^{-1}. ^1H NMR: δ = 7.36−7.25 (m, 10 H), 5.68 (2 H, AB system, J_{AB} = 16, *J* = 10.0 Hz), 4.52 (s, 2 H), 4.49 (s, 2 H), 3.89 (dd, 1 H, *J* = 9.5 and 3 Hz), 3.69 (s, 3 H), 3.51−3.46 (m, 2 H), 3.40 (t, *J* = 6.0 Hz, 2 H), 3.24 (1 H, br. s, O*H*), 2.18−2.06 (m, 3 H), 1.81 (m, 2 H), 1.55−1.41 (m, 2 H), 1.12 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR: δ = 176.9, 140.2, 138.5, 138.5, 128.3, 128.3, 127.4, 127.4, 127.4, 127.4, 125.1, 79.1, 72.7, 72.7, 71.6, 70.4, 70.4, 52.8, 42.2, 39.8, 34.9, 31.9, 28.3, 26.9, 26.1, 18.3, −3.5, −4.1.

Olefin 33

Preparation of (Pent-4-enyl)magnesium Bromide: Freshly distilled 5-bromopent-1-ene (4.4 equiv., 0.76 mmol, 91 μL) was added dropwise to magnesium (5.5 equiv., 0.96 mmol, 23 mg) in dry diethyl ether (2 mL). The mixture was refluxed for 30 min.

[1,4]-Addition: The solution of Grignard reagent was added dropwise at −10 °C to CuBr·Me_2S (2.2 equiv., 0.38 mmol, 79 mg) in dry diethyl ether (1 mL). The mixture was stirred for 20 min at −10 °C and became brownish red. A solution of enone **29** (1.0 equiv., 0.17 mmol, 91 mg) in dry diethyl ether (1 mL) was then added dropwise at −78 °C. The mixture was allowed to warm to −40 °C for 30 min and was then stirred at that temperature for an extra 30 min.

Enolate Trapping: Freshly distilled methyl cyanoformate (11 equiv., 1.91 mmol, 152 μL) was added at −78 °C to the above mixture. The mixture was allowed to warm to 0 °C over 2 h and then treated with saturated aqueous ammonium chloride solution (5 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated to afford 0.10 g of a colourless, viscous liquid. Flash column chromatography [ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 0% to 10%] resulted in the isolation of starting enone **29** (47 mg, 72 μmol, 52%), the simple [1,4]-addition product without enolate trapping (11 mg, 19 μmol, 11%) and the desired olefin **33** (42 mg, 65 μmol, 37%) as a 75:25 mixture of *trans* and *cis* diastereomers. ***Note:*** Better selectivity (80:20) was achieved in another experiment on a larger scale (0.15 g of starting enone **29**). However, the product **33** was isolated in somewhat lower yield: 35% (44%). *trans*/*cis* ≈ 75:25 mixture of the two isomers: Viscous, colourless liquid. MS (CI, NH_3): *m*/*z* = 106, 108, 132, 187, 293, 461, 636, 637, 651 [MH^+], 668 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 2951, 2929, 2856, 1655, 1615, 1440, 1360, 1258, 1219, 1096, 856, 697 cm^{-1}. Major (*trans*) isomer: ^1H NMR: δ = 12.32 (s, 1 H, enol), 7.36−7.27 (m, 10 H), 5.78 (m, 1 H), 5.01−4.92 (m, 2 H), 4.51−4.42 (m, 4 H), 3.78 (d, *J* = 8.5 Hz, 1 H), 3.73 (s, 3 H, OMe), 3.64 (t, *J* = 4.0 Hz, 1 H), 3.41 (m, 1 H), 3.37 (t, *J* = 4.5 Hz, 2 H), 2.72−2.53 (m, 2 H), 2.27−1.13 (m, 12 H), 0.99 (s, 3 H), 0.89 (s, 9 H, TBS), −0.01 (s, 3 H, TBS), −0.09 (s, 3 H, TBS). ^{13}C NMR: δ = 173.4 (C=*C*OH), 171.2 (C=O), 138.9, 138.5, 138.2, 128.3, 127.6, 114.3 (CH=*C*H_2), 102.3 (*C*=COH), 51.0, 44.4, 43.5, 26.2, 18.4, 17.1 (CHCq*Me*), −3.2, −5.2. Minor (*cis*) isomer (characteristic differences): ^1H NMR: δ = 12.21 (s, 1 H, enol), 3.96 (m, 1 H), 3.71 (s, 3 H, OMe), 0.92 (s, 9 H, TBS), 0.13 (s, 3 H, TBS), 0.10 (s, 3 H, TBS). ^{13}C NMR: δ = 173.6 (C=*C*OH), 170.4 (C=O), 114.4 (CH=*C*H_2), 101.4 (*C*=COH), 19.9 (CHCq*Me*).

Aldehyde 32, Decalins 34 and 35

Dihydroxylation: *N*-Methylmorpholine oxide (1.5 equiv., 87 μmol, 10 mg), acetone (0.35 mL), and water (70 μL) were added to a mixture (75:25) of isomers *trans*- and *cis*-**33** (1.0 equiv., 58 μmol, 38 mg). Osmium tetraoxide solution ($4 \cdot 10^{-2}$ M in *tert*-butyl alcohol, 5% equiv., 3 μmol, 72 μL) was then added at −20 °C. The mixture was allowed to warm to 0 °C over 1 h, and was then stirred at room temperature for 1 h 30 min. Water (0.12 mL), Florisil® (300 mg) and sodium hydrosulfite (30 mg) were added. The mixture was stirred for 10 min and then extracted with ethyl acetate (5 × 2 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated to afford 43 mg of the crude product.

Oxidative Cleavage of the 1,2-Diol: The above crude product was dissolved in dioxane (0.47 mL) and water (55 μL). Sodium periodate (1.7 equiv., 0.10 mmol, 22 mg) was added, and the mixture was stirred at room temperature for 1 h 45. Water (1 mL) was added. The solution was extracted with diethyl ether (4 × 2 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated to afford 42 mg of the crude product. ^1H and ^{13}C NMR analysis revealed the presence of aldehydes *trans*- and *cis*-**32**. Flash column chromatography [ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 0% to 30%] yielded a mixture (75:25) of diastereomeric alcohols **34** and **35** (21 mg, 32 μmol, 55%).

Compound *trans*-32: ^1H NMR: δ = 9.7 (s, 1 H, CHO) (no signal at δ = 5−7). ^{13}C NMR: δ = 202.5 (CHO).

Compounds 34/35 (75:25 Mixture): Viscous, colourless liquid. MS (CI, NH_3): *m*/*z* = 247, 293, 445, 446, 462, 521, 522, 577, 653 [MH^+], 670 [$MH^+ \cdot NH_3$]. IR: $\tilde{\nu}$ = 3547, 2952, 2930, 2857, 1742, 1705, 1471, 1462, 1454, 1362, 1255, 1235, 1216, 1202, 1086, 1028, 1004, 834, 697 cm^{-1}.

Major Diastereomer 34: ^1H NMR: δ = 7.36−7.24 (m, 10 H), 4.48−3.89 (m, 4 H), 3.81 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.72 (s, 3 H, OMe), 3.73−3.69 (m, 1 H), 3.59 (t, *J* = 8.5 Hz, 1 H), 3.45 (d, *J* = 6.5 Hz, 1 H), 3.38−3.35 (m, 2 H), 3.04 (dd, 1 H, *J* = 19 and 6 Hz), 2.63 (d, *J* = 16.0 Hz, 1 H), 2.44 (dd, 1 H, *J* = 19 and 11 Hz), 2.29 (dd, 1 H, *J* = 12.5 and 3 Hz), 2.10 (m, 1 H), 1.87−1.74 (m, 6 H), 1.45−1.14 (m, 4 H), 1.04 (s, 3 H, CHCq*Me*), 0.85 (s, 9 H, *t*Bu), 0.05 (s, 3 H, SiMe), 0.03 (s, 3 H, SiMe). ^{13}C NMR: δ = 211.9, 170.1, 138.3, 128.3, 127.6, 127.5, 80.3, 73.8, 73.0, 72.9, 71.6, 69.9, 61.9, 52.0 (OMe), 44.5 (ring junction CH), 42.9, 42.7, 41.3, 31.3, 30.9, 29.5, 27.9, 26.2 (*t*Bu), 23.5, 22.6, 18.5, −3.6, −3.7.

Diastereomer 35 (Characteristic Differences with Isomer 34): ^1H NMR: δ = 3.77 (s, 3 H, OMe), 1.12 (s, 3 H, CHCq*Me*), 0.90 (s, 9 H, *t*Bu), 0.11 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe). ^{13}C NMR: δ = 52.5 (OMe), 48.0 (ring junction CH), 26.0 (*t*Bu).

Decalins 36 and 37: The same experimental procedures were applied as for the preparation of alcohols **34** and **35** from enone **29**. The addition of pent-4-enylmagnesium bromide onto enone **27**, followed by trapping of the enolate intermediate with methyl cyanoformate, proceeded in 65% yield, starting from 0.35 g (0.88 mmol) of enone. Subsequent dihydroxylation (cat. OsO_4/NMO), oxidative cleavage ($NaIO_4$) and flash column chromatography provided diastereomeric alcohols **36** and **37** (70:30 mixture, 78% yield). ***Note:*** Compound **37** could be separated by repeated flash column chromatography. However, a new isomer **36b** appeared. We were not able to separate it from **36**.

Compounds 36/37 (70:30 Mixture): Viscous, colourless liquid. MS (CI, NH_3): *m*/*z* = 106, 325, 326, 342, 401, 402, 457, 533 [MH^+], 550 [$MH^+ \cdot NH_3$], 551. IR: $\tilde{\nu}$ = 3539, 2952, 2884, 2857, 1739, 1706, 1472, 1462, 1453, 1361, 1252, 1232, 1094, 1030, 1005, 836, 697 cm^{-1}.

Major Diastereomer 36: ^1H NMR: δ = 7.35−7.26 (m, 5 H), 4.54 (2 H, AB, *J* = 20 and 12 Hz, CH_2Ph), 3.76 (s, 3 H, OMe), 3.64−3.53 (m, 2 H), 3.51 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 2.61 (m, 2 H, CH_2C=O), 2.30−1.20 (m, 14 H), 0.88 (s, 9 H, TBS), 0.86 (s, 3 H, Me), 0.09 (s, 3 H, TBS), 0.02 (s, 3 H, TBS). ^{13}C NMR: δ = 213.3 (ketone), 173.0 (**C**O_2Me), 138.7 (aromatic Cq), 128.3, 127.5, 72.6, 70.2, 63.4 (*Cq*CO_2Me), 52.7 (OMe), 44.8 (ring junction CH), 43.8 (*Cq*CHOTBS), 36.8, 26.1, 18.4, 17.6.

Diastereomer 37 (Characteristic Differences Compared with Isomers 36 and 36b): ^1H NMR: δ = 3.76 (s, 3 H, OMe), 2.89 (1 H, td, *J* = 14 and 7.5 Hz, CH_2C=O), 2.33 (m, 1 H, CH_2C=O), 1.04 (s, 3 H, Me), 0.88 (s, 9 H, TBS), 0.05 (s, 3 H, TBS), −0.01 (s, 3 H, TBS). ^{13}C NMR: δ = 213.2 (ketone), 173.5 (*C*O_2Me), 77.5, 63.3 (*Cq*CO_2Me), 52.5 (OMe), 49.3 (ring junction CH), 15.8 (Me).

Isomer 36b (Characteristic Differences with Isomers 36 and 37): ^1H NMR: δ = 4.48 (s, 2 H, CH_2Ph, 3.71 (s, 3 H, OMe), 3.43 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 0.87 (s, 9 H, TBS), 0.83 (s, 3 H, Me), 0.07 (s, 3 H, TBS), 0.02 (s, 3 H, TBS). ^{13}C NMR: δ = 213.1 (ketone), 170.2 (*C*O_2Me), 138.4 (aromatic Cq), 61.9 (*Cq*CO_2Me), 51.9 (OMe), 43.7 (ring junction CH), 42.2 (*Cq*CHOTBS), 19.6 (Me).

Diol 38 and Lactone 39: Hydrogen fluoride (48% aqueous solution, 6 drops) was added to a solution of a 70:30 mixture of diastereomers **36** and **36b** (1.0 equiv., 0.20 mmol, 0.11 g) in acetonitrile (2 mL). The solution was stirred at room temperature for 8 h 30 min. Saturated aqueous sodium chloride solution (5 mL) was added (5

mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (5 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated to afford 79 mg of the crude product. Flash column chromatography [ethyl acetate/petroleum ether (boiling range 40−60 °C), gradient from 10% to 30%] resulted in the isolation of diol **38** (17 mg, 41 μmol, 20%) and lactone **39** (54 mg, 0.14 mmol, 68%).

Compound 38: MS (CI, NH_3): *m/z* = 387, 404, 405, 419 [MH^+], 420, 436 [$MH^+ \cdot NH_3$], 437. IR: $\tilde{\nu}$ = 3552, 3430, 2948, 2863, 1741, 1705, 1454, 1432, 1331, 1248, 1228, 1207, 1132, 1100, 1048, 697 cm^{-1}. ^1H NMR: δ = 7.35−7.29 (m, 5 H), 4.52 (s, 2 H), 3.97 (dd, 1 H, *J* = 10 and 5 Hz), 3.72 (s, 3 H), 3.56−3.44 (m, 3 H), 2.73 (m, 1 H), 2.59−1.25 (m, 16 H), 0.86 (s, 3 H) ^{13}C NMR: δ = 212.6, 170.7, 137.7, 128.5, 127.8, 75.6, 73.7, 73.2, 70.4, 62.5, 51.9, 46.0, 39.2, 36.9, 30.0, 28.8, 28.0, 27.4, 23.4, 20.8, 18.1.

Compound 39: Colourless crystals. MS (CI, NH_3): *m/z* = 387 [MH^+], 388, 404 [$MH^+ \cdot NH_3$]. ^1H NMR: δ = 7.35−7.26 (m, 5 H), 4.50 (s, 2 H), 4.28 (d, *J* = 9.5 Hz, 1 H), 3.75−3.49 (m, 3 H), 2.56 (1 H, td, *J* = 15 and 7.5 Hz), 2.32 (dd, 1 H, *J* = 15 and 5 Hz), 2.13−1.05 (m, 14 H), 0.94 (s, 3 H). ^{13}C NMR: δ = 202.2, 170.8, 138.2, 128.3, 127.6, 127.5, 90.7, 73.0, 73.0, 69.2, 61.6, 50.4, 38.6, 35.6, 28.9, 28.2, 26.5, 26.4, 23.5, 22.5, 22.3.

Crystal Structure Determination of 39: Crystals of **39**, $C_{23}H_{30}O_5$, were obtained from a petroleum ether (boiling range 40−60 °C) methanol solution of the compound. Data were collected at 123 ± 0.5 K with an Enraf−Nonius CAD-4 diffractometer using Mo-K_α (λ = 0.71073 Å) radiation and a graphite monochromator. The crystal structure was solved and refined using the Enraf−Nonius MolEN package. The compound crystallises in the space group $P2_12_12_1$, *a* = 7.98(1), *b* = 11.163(1), *c* = 44.678(7) Å; *V* = 3980(1) $Å^3$; *Z* = 8; $d_{calcd.}$ = 1.29 g/cm^3; μ = 0.084 cm^{-1}; *F*(000) = 1664. A total of 4829 unique reflections were recorded in the range 2.5° ≤ θ ≤ 28.04° of which 2933 were considered as unobserved [$F^2 < 3.0\sigma(F^2)$], leaving 1896 for solution and refinement. The hydrogen atoms were refined with isotropic temperature factors in the final stages of least squares while using anisotropic temperature factors for all other atoms. The final agreement factors were *R* = 0.041, R_w = 0.047, *G.O.F.* = 1.025. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165158. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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