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New Domino Silyl Enol Ether Reactions in the Synthesis of a Tetrodecamycin Fragment

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On heating in toluene at 180 °C for four days the TMS enol ether **7** underwent a domino acid catalysed rearrangement, Diels–Alder cycloaddition and further rearrangement to give the bicyclic TMS enol ether **17**, which was converted into a tetrodecamycin precursor **3** in three synthetic steps. Further, monocyclic silyl enol ethers were consecutively treated with *m*CPBA and bromine to give *syn* α-hydroxy α′-bromo ketones in a one-pot reaction sequence.

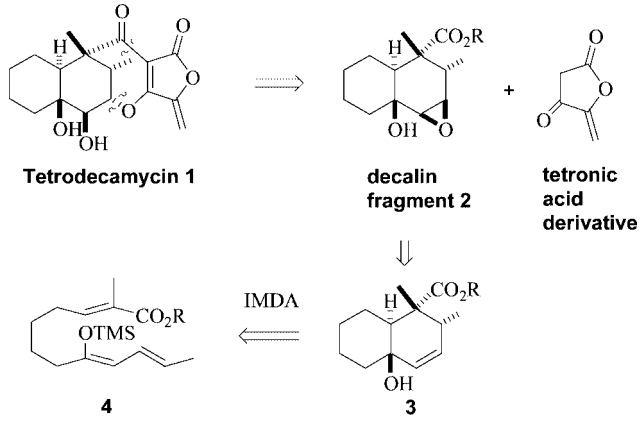
Introduction

Reactions of silylated enol ethers possessing bulky alkyl substituents on silicon with electrophiles were noticed to proceed through an ene-type mechanism as shown in Scheme 1.[1,2] For example, the oxonium species **B** generated on electrophilic addition to the silyl enol ether **A** is stabilized not by the loss of the bulky trialkylsilyl group, but by a proton loss from the adjacent α′-position resulting in an ene-type product – silyl enol ether **C**.

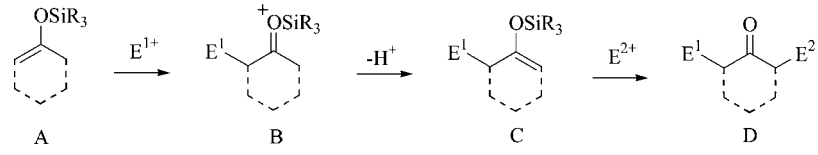
An extended process, which would involve a direct transformation of the silyl enol ether **C** to product **D** would be of even more interest, as it will lead to an increase in structural complexity of the substrate; however, examples of such domino silyl enol ether reactions[3] are few. Herein, we present some of our recent findings in this area arising from an approach to the decalin fragment of tetrodecamycin (**1**).

Tetrodecamycin (**1**) is a novel α-(γ-hydroxyacyl)tetronic acid based polyketide antibiotic isolated from the culture broth of *Streptomyces nashvillensis* in 1994 by Takeuchi and co-workers.[4] It shows distinct activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus anthracis*. The unique structure of tetrodecamycin combined with its interesting biological properties have attracted synthetic effort, and syntheses of partial structures have been reported.[5,6]

Our initial synthetic plan is presented in Scheme 2. Disconnection of the tetracycle into two components leads to an epoxide-containing decalin fragment **2**,[7] which would



Scheme 2. Initial approach to tetrodecamycin (**1**).



Scheme 1. Ene-type reactions of silyl enol ethers.

be derived by a stereoselective epoxidation of the allylic alcohol **3**, which itself would be obtained through an intramolecular Diels–Alder cycloaddition of the silyl enol ether **4**; no cycloadditions of silyl enol ethers of type **4** have been previously reported in the literature.

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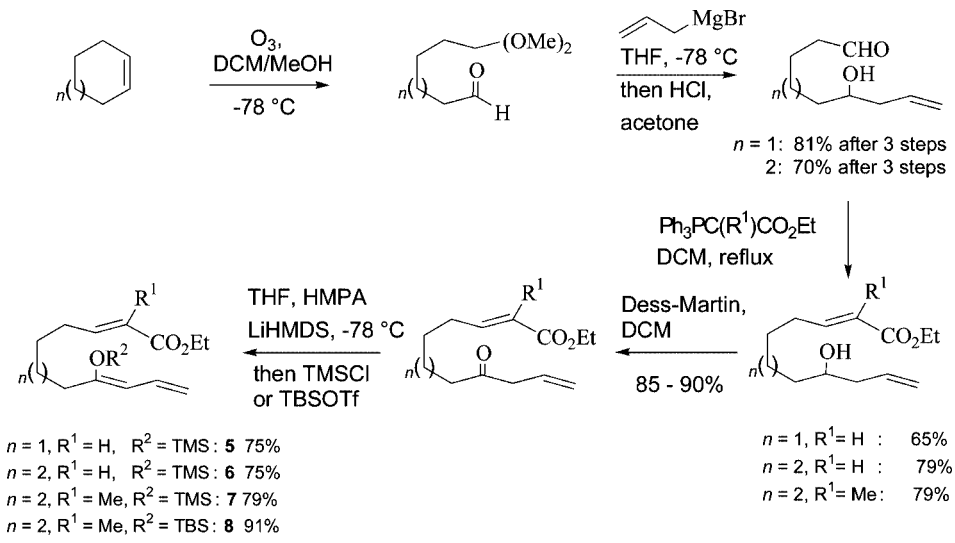


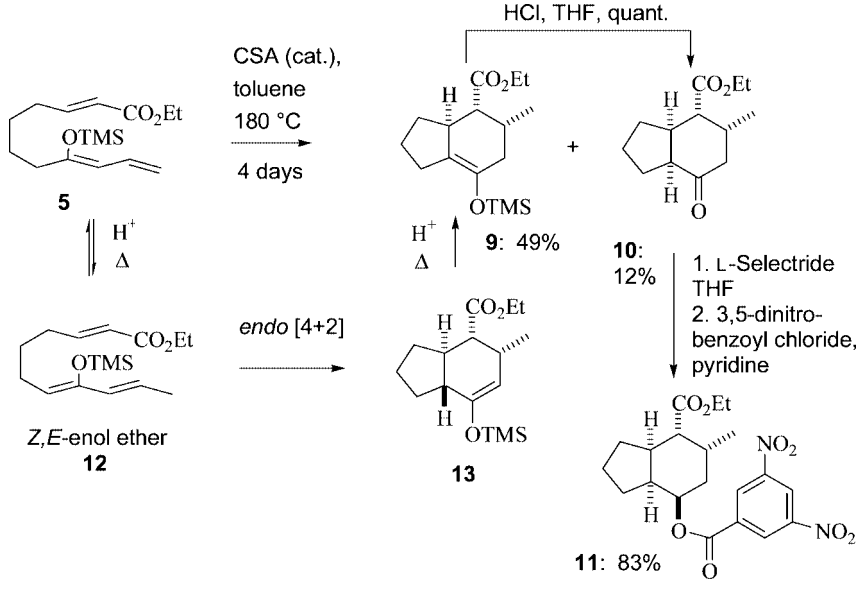
Scheme 3. Synthesis of silyl enol ethers **5**, **6**, **7** and **8**.

Preparation of Diels–Alder Precursors

To test our idea we prepared a model silyl enol ether **5** together with analogous silyl enol ethers **6**, **7** and **8** by standard sequences of cycloalkene ozonolysis,[8] Grignard addition, Wittig reaction, Dess–Martin oxidation[9] and an enolisation/silylation as shown in Scheme 3. After initial attempts to prepare silyl enol ethers in the absence of HMPA led to the isolation of 1:1 mixtures of *E* and *Z* silyl enol ethers, our attention was drawn by reports of Xie et al.[10] on the use of HMPA, which destabilizes Ireland's chair transition state[11] and leads to selective formation of the kinetic *Z*-silyl enol ether. The use of LiHMDS and HMPA in our case led to selective formation of the desired *Z*-silyl enol ethers **5**, **6**, **7** and **8**, stereochemistries of which were confirmed by NOE analysis.

Model Cycloaddition of the TMS Enol Ether 5

Having synthesised the model silyl enol ether **5**, we set out to perform the cycloaddition. To our surprise, compound **5** was stable under a variety of reaction conditions. Reflux in toluene in the presence of mild Lewis acids ($BF_3{\cdot}Et_2O$ or Et_2AlCl) led only to the recovery of the starting material. However, when heated at 180 °C in toluene in a sealed tube in the presence of CSA (cat.), **5** was converted into two new products. The reaction took four days to reach completion and led to the isolation of two unexpected products (Scheme 4); instead of the anticipated decalin, e.g. desmethyl-**3**, the bicyclic [3.4.0]nonane products **9** and **10** were obtained. The silyl enol ether **9** was readily converted into the keto form on treatment with dilute HCl in tetrahydrofuran, from which the relative stereochemistry of the



Scheme 4. Model cycloaddition of enol ether **5**.

bicyclic ketone **10** was established by NOE analysis and confirmed by a single-crystal X-ray crystallography (Figure 1)[12] of the product derived from stereoselective reduction of the ketone[13] followed by conversion into the 3,5-dinitrobenzoate[14] **11**.

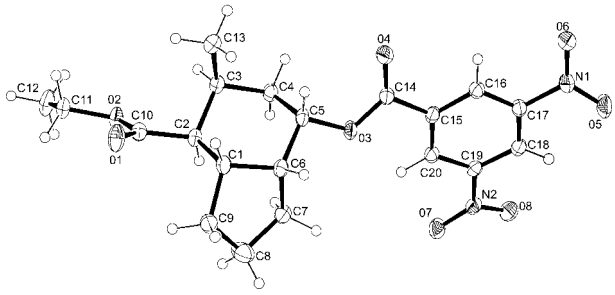


Figure 1. Crystal structure of **11**.

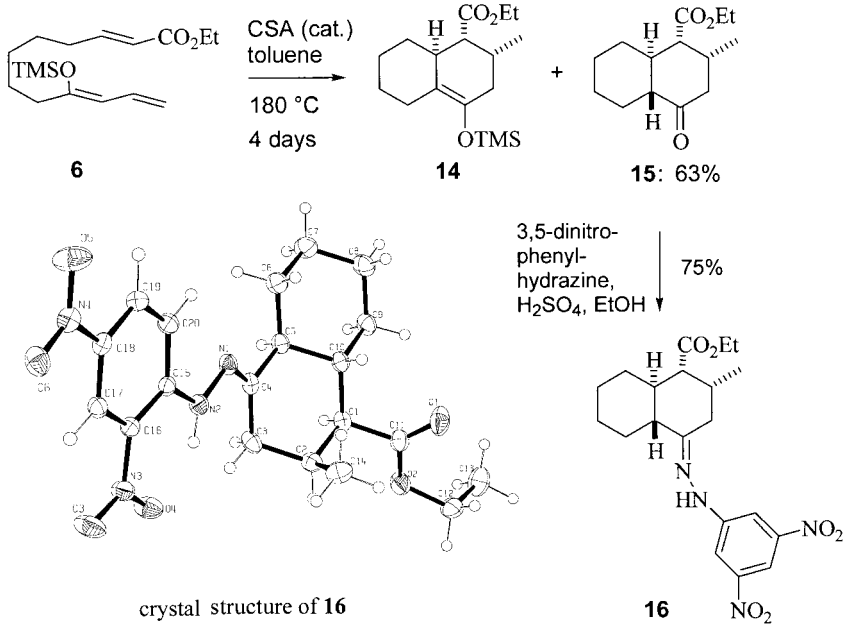
Our mechanistic explanation of the observed process is presented in Scheme 4. Upon being heated, the silyl enol ether **5** undergoes acid-catalysed tautomerisation into the *Z,E*-silyl enol ether **12**, which is set for *endo*-cycloaddition producing the bicyclo[3.4.0]nonane framework of **13**.[15] The cycloadduct **13** undergoes yet another acid-catalysed rearrangement to give the more thermodynamically stable tetrasubstituted double bond in the silyl enol ether **9**, which upon acidification gives a kinetic *cis*-bicyclononane **10**.

The inability of **5** to undergo an intramolecular cycloaddition directly may be attributed to the fact that HOMO/LUMO coefficients disfavour orbital overlap from the silyl enol ether **5** as opposed to that from the isomerised form **12**. The first isomerisation is presumably the rate-limiting step, the subsequent cycloaddition and final silyl enol ether rearrangement happening much faster. This provides an interesting example of domino silyl enol ether chemistry where the first isomerisation facilitates a number of further processes.

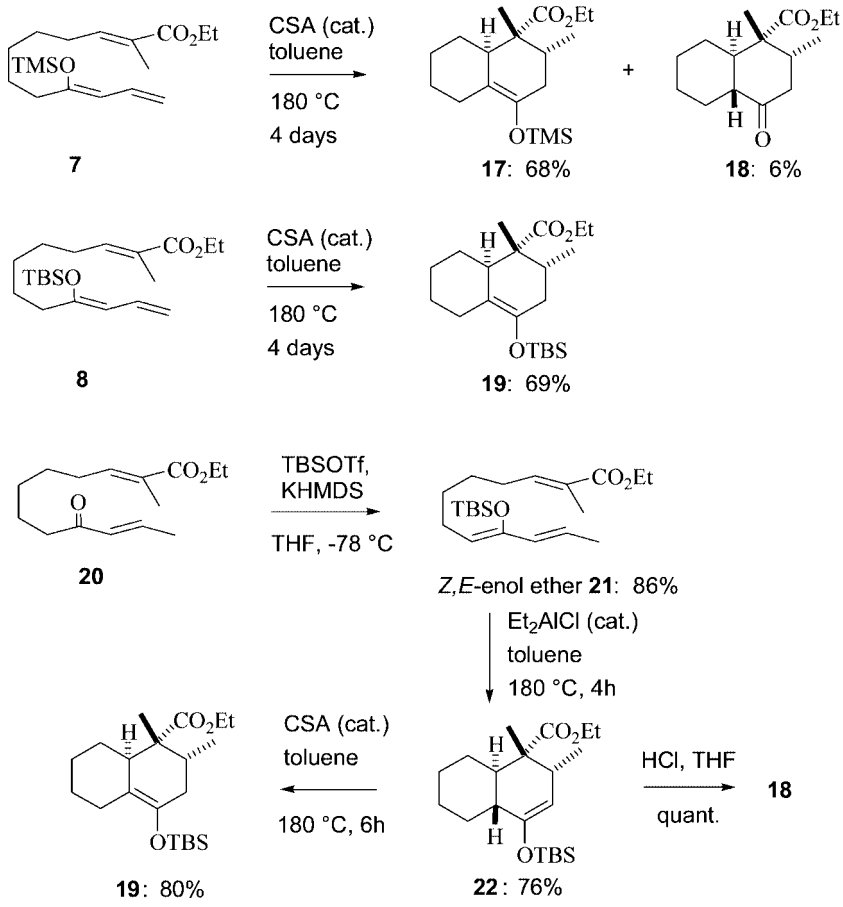
Cycloadditions Leading to Decalin Derivatives

Next, our attention centred on the possibility of performing a cycloaddition of a homologue of **5**, which would provide entry into the substituted decalins. Thus the TMS enol ether **6** possessing an extra methylene group in the tether was treated under similar conditions [CSA (cat.), toluene, 180 °C, four days], resulting to our delight in the formation of decalins **14** and **15**. In situ hydrolysis of the silyl enol ether form **14** led to a more thermodynamically stable *trans*-decalin **15**, the structure of which was established by a combination of NMR and X-ray spectroscopy of its crystalline derivative, hydrazone **16**.[16] Pleasingly, the three contiguous stereogenic centres of the cycloadduct **14** possess the same relative stereochemistry as in tetrodecamycin (**1**). This encouraged us to investigate cycloadditions of silyl enol ethers **7** and **8** possessing the extra methyl substituent, which would provide the complete carbon framework of the tetrodecamycin fragment (Scheme 5).

Thus, when silyl enol ether **7** was heated at 180 °C in a sealed tube for four days in the presence of CSA (cat.), the desired decalin adducts **17** and **18** were formed in good overall yield, with formation of the ketone **18** attributed to low stability of the TMS enol ether **17** towards acidic conditions. As we were interested in further oxidation of the TMS enol ether **17** to set the tertiary hydroxy group at the ring junction, we investigated the cycloaddition of a TBS enol ether **8**, which resulted in the formation of the desired TBS enol ether **19** as a major product (Scheme 6).



Scheme 5. Cyclisation of TMS enol ether **6**.



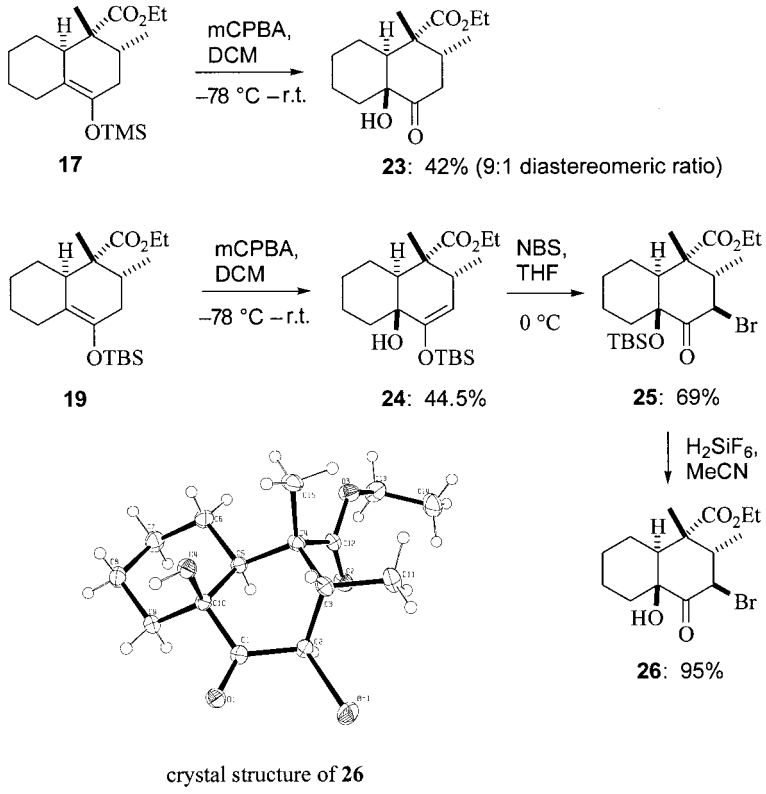
Scheme 6. Cyclisations of enol ethers **7** and **8**.

Interestingly, despite numerous attempts to optimize the reaction conditions for selective conversion of the TMS enol ether **7** into **17**, a substantial amount of the (*E*)-enone **20** was always formed. This could be converted into the TBS enol ether **21** following Corey's procedure,[15] whose structure was confirmed by NOE NMR analysis. This (*Z,E*)-TBS-enol ether **21** (whose analogue **12** we postulate to be an intermediate in the previously described cycloadditions) as expected underwent a fast Diels–Alder reaction when heated at 180 °C in the presence of Et_2AlCl (cat.). The product **22** obtained after 4 h could be hydrolysed in quantitative yield to the ketone **18** or isomerised into **19** on heating in toluene in the presence of CSA (cat.) (Scheme 6). This provided experimental evidence for our proposal (Scheme 4) of an intermediate (*Z,E*)-silyl enol ether structure and the *endo* mode of the cycloaddition.

Completion of the Decalin Fragment 3

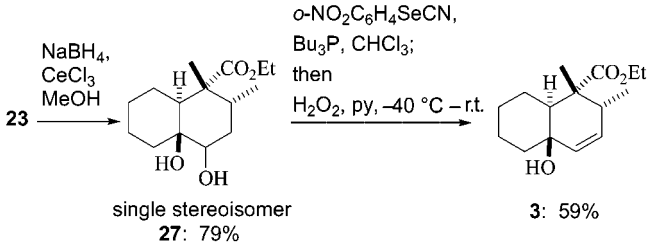
Next, we attempted the oxidation of the silyl enol ethers **17** and **19**. When treated with *m*CPBA at –78 °C in dichloromethane the TMS enol ether **17** produced, after protic work-up, the expected hydroxy ketone **23** as a 9 to 1 mixture of epimers, favouring the desired *trans*-decalin product **23**, which was separated and characterized by observation of NOE enhancements upon irradiation of the hydroxy proton in deuteriated benzene. The stereoselectivity of the oxidation was unexpected, but welcome in the context of tetrodecamycin synthesis. (Our explanation of the observed selectivity is presented in Scheme 9). The TBS enol ether **19**, on the contrary, gave the TBS enol ether **24** as the major oxidation product. In this case the TBS enol ether was retained by isomerisation rather than conversion to the ketone, as was observed for the TMS derivative **17** (Scheme 7).

Furthermore, the treatment of the TBS enol ether **24** with *N*-bromosuccinimide led to clean formation of the bromide **25** as a single diastereoisomer accompanied by TBS migration. Unfortunately, numerous attempts to access the allylic alcohol **3** by Kishner eliminative reduction[17] of the α-bromo ketone **25** or its deprotected version **26** met with failure. The white crystalline solid alcohol **26** allowed for X-ray analysis, which shows that the more substituted six-membered ring adopts an unusual boat-like conformation in a *trans*-fused decalin system. This allows the bulky halogen to adopt a pseudo-equatorial position contributing no doubt to the difficulty observed in attempted alkene-forming reactions.



Scheme 7. Oxidation of enol ethers **17** and **19**.

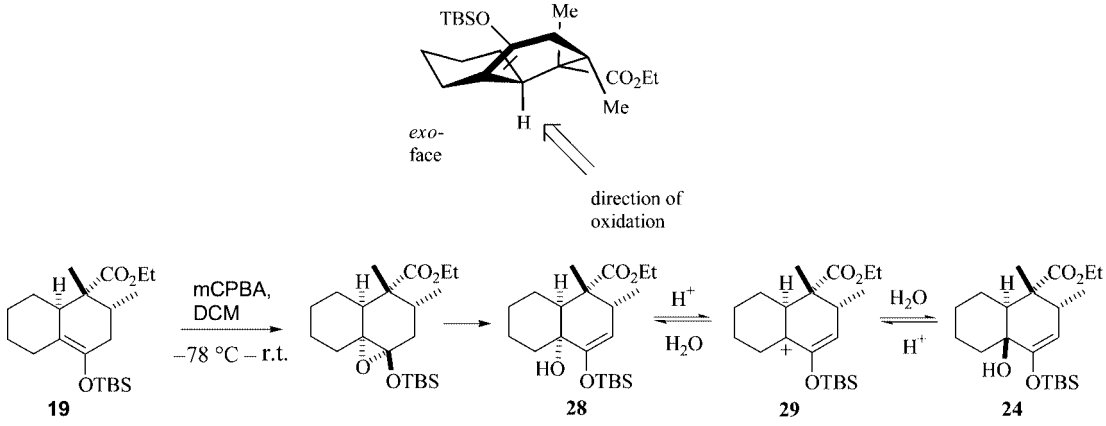
Finally, Luche reduction[18] of the hydroxy ketone **23** produced the diol **27** as a single diastereomer. The stereochemistry of the secondary hydroxy group was not established, as in the next step it was converted into a selenide followed by an in situ oxidative elimination,[19] resulting in the desired key intermediate, the allylic alcohol **3** (Scheme 8).



Scheme 8. Completion of synthesis of **3**.

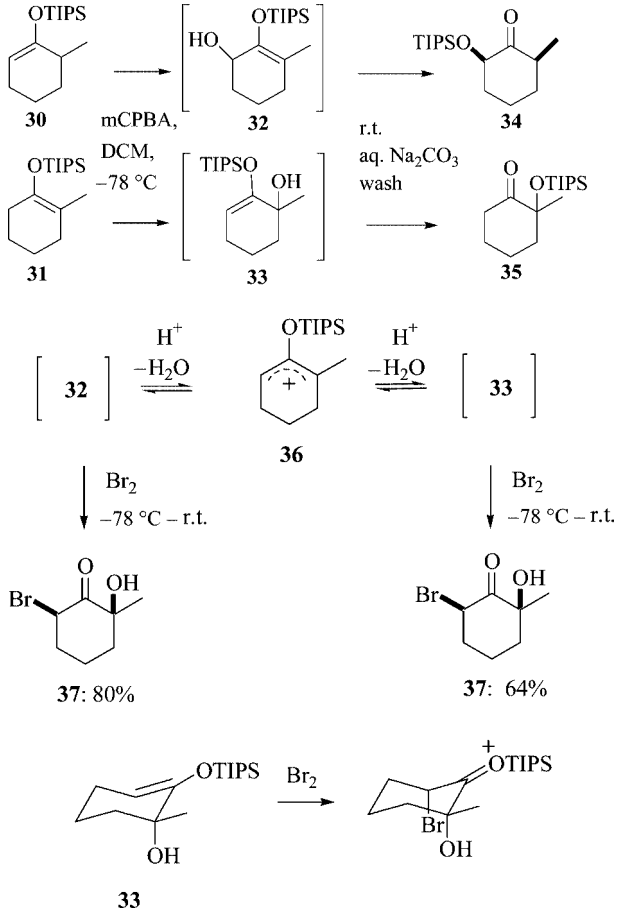
Stereoselectivity in the Oxidation of Silyl Enol Ethers 17 and 19

Simple molecular modelling of the silyl enol ether **19** predicts that epoxidation would occur on the "*exo*" face (the same side as the hydrogen at the ring junction) of the molecule to produce a *cis*-decalin product. In order to account for the oxidation of **19** into the *trans*-decalin product **24** we



Scheme 9. Postulated formation of **24**.

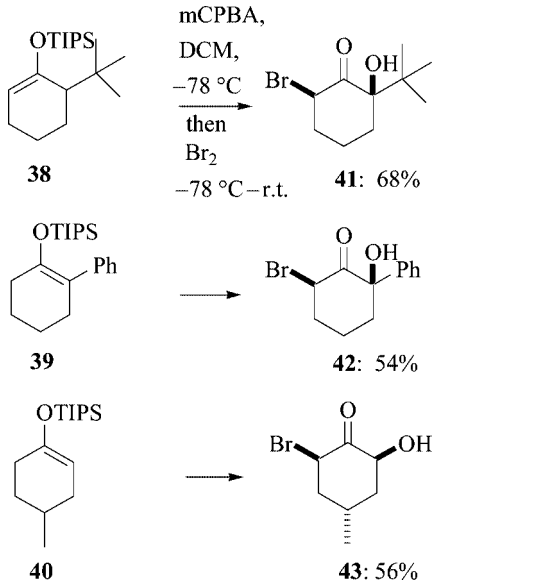
postulate initial formation of a *cis*-decalin structure **28**, which is equilibrated into a more stable *trans*-decalin product **24** under nonbuffered acidic conditions via an intermediate tertiary allylic cation **29** (Scheme 9). Further evidence in favour of the intermediate carbocation **29** and its possible equilibration was obtained in our attempted α,α′-functionalisation of silyl enol ether derivatives of simple cyclic ketones (see Scheme 10 and Scheme 11).



Scheme 10. Consecutive oxidation and bromination of silyl enol ethers **30** and **31**.

Double Functionalisation of Simple Cyclic Enolates

Our success in the sequential oxidation and bromination of the bicyclic silyl enol ether **19** (Scheme 7) prompted us to investigate the application of the same reaction sequence to simple monocyclic silyl enol ethers. We were also interested in development of a one-pot procedure leading to α,α′-disubstituted ketones. Preparations of silyl enol ethers **30**, **38** and **40** under kinetic conditions and those of **31** and **39** under thermodynamic conditions were previously reported by Magnus et al.[1] When the 2-methylcyclohexanone derivatives **30** and **31** were treated with *m*CPBA in DCM at –78 °C, two new silyl enol ethers **32** and **33** were formed. Unfortunately, we were unable to isolate these unstable hydroxy silyl enol ethers, although we found that formation of the intermediates **32** and **33** could be monitored



Scheme 11. Double functionalisation of simple enol ethers.

by means of GCMS. Work-up of the reaction mixture resulted in isolation of the silyloxy ketones **34** and **35**. Treatment of both reaction mixtures from **30** and **31** on completion of the oxidation with bromine at –78 °C followed by slow warming to room temperature led to the isolation of a single bromide **37** in both cases. Formation of the same product starting from two isomeric silyl enol ethers can be explained by equilibration of the two enol ethers via a carbocation species **36** and a higher reactivity of the trisubstituted silyl enol ether **33** towards bromination. The products of α,α′-derivatisation were obtained as single stereoisomers, and the relative stereochemistry was established by NOE analysis. Our model accounting for the observed stereochemical outcome of the reactions is presented in Scheme 10. The hydroxy group in the intermediate species **33** adopts an axial position due to the stabilizing anomeric interaction between the σ* (C–OH) and the π system.[1] Subsequently approach of bromine from an axial trajectory results in a relative *syn* orientation of newly introduced bromine and hydroxy substituents.

In a similar manner the silyl enol ethers **38**, **39** and **40** were converted into an α-hydroxy-α′-bromo derivatives **41**, **42** and **43** (Scheme 11). These observations provide supporting evidence for our proposed formation of a stabilized allylic carbocation **29** during oxidation of the bicyclic silyl enol ether **19** (Scheme 9).

Conclusions

We have observed an unusual silyl enol ether isomerisation followed by an intramolecular Diels–Alder cycloaddition and further silyl enol ether isomerisation cascade to give for example the bicyclic silyl enol ether **17** from the acyclic silyl enol ether **7**. Compound **17** was further transformed into a key intermediate **3** in our proposed total synthesis of tetrodecamycin (**1**). The mechanism of this inter-

esting reaction sequence has been probed. In addition, a new procedure for a one-pot α-hydroxylation, α′-bromination of silyl enol ethers of cyclic ketones was investigated. Further work will focus on widening the scope of the cyclic ketone α,α′-bis-derivatisation and completion of the total synthesis of tetrodecamycin.

Experimental Section

General Experimental: All solvents were distilled before use. All reagents were used as obtained from commercial sources unless otherwise stated and were purified by standard techniques.[20] All reactions were carried out under dry, oxygen-free nitrogen or argon and in glassware that had been dried at

100 °C overnight unless otherwise stated. Flash column chromatography was performed on silica gel (0.125–0.25 mm, 60–120 mesh) as the stationary phase. Thin-layer chromatography was carried out on aluminium plates pre-coated with silica (Merck silica gel 60 F_{254}), which were visualized by quenching of UV fluorescence (λ_{max} = 254 nm), and/or by staining with 1% w/v potassium permanganate in aqueous alkaline solution followed by heating, as appropriate. Infrared spectra were recorded as thin films between NaCl plates or as KBr disks with a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer or Bruker Tensor 27 with internal referencing. Absorption maxima are reported in wavenumbers [$\tilde{\nu}_{max}$, cm^{-1}], and only selected peaks are reported. Magnetic resonance spectra were recorded at ambient temperature. Proton magnetic resonance spectra (^1H NMR) were recorded at 400 and 500 MHz with Bruker DQX 400, Bruker DPX 400 and Bruker AMX 500 instruments. Coupling constants (J) are reported to ± 0.1 Hz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100.6 and 125.7 MHz with Bruker DQX 400 and Bruker AMX 500. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. High resolution mass spectra were recorded by chemical ionization (CI) operating at a resolution of 10000 (10% valley). The quoted masses are accurate to ±5 ppm.

General Method for Ozonolysis of Cycloalkenes: A 500-mL, three-necked, round-bottomed flask was fitted with a glass tube to admit ozone, a tube to output oxygen, a glass stopper and a magnetic stirring bar and was charged with cycloalkene (75.0 mmol), dichloromethane (250 mL) and methanol (50 mL). The flask was cooled to –78 °C (acetone/dry ice), and ozone was bubbled through the solution. When the solution turned blue, ozone addition was stopped. Oxygen was passed through the solution until the blue colour was discharged and then the cold bath was removed. The ozone inlet and outlet tubes were replaced with a stopper and vaccine cap, and *p*-toluenesulfonic acid (1.22 g) was added. The solution was warmed to room temperature as it was stirred under nitrogen for 90 min. Anhydrous sodium hydrogen carbonate (2.15 g, 4 equiv.) was added to the flask, and the mixture was stirred for 15 min, and then dimethyl sulfide (12 mL, 150 mmol) was added. After stirring for 12 h, the heterogeneous mixture was concentrated to approximately 50 mL by evaporation. Dichloromethane (100 mL) was added, and the mixture was washed with water (75 mL). The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed with water (100 mL). After extracting the aqueous layer with dichloromethane (100 mL), the organic layers were dried with anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product (colourless oil) was used without further purifications in the next step.

General Method for Vinyl Grignard Addition and Acetal Hydrolysis: To a solution of aldehydes (65 mmol) in THF (500 mL) was added dropwise allylmagnesium chloride (2 M in THF, 39.8 mL, 79.6 mmol) at –78 °C. After stirring at low temperature for 3 h the solution was warmed to room temperature, ammonium chloride (satd. solution, 200 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated in vacuo. To the pale yellow oily residue was added acetone (500 mL), water (100 mL) and aqueous HCl (1 N, 15 mL), and the resulting solution was stirred at room temperature for 12 h. Addition of saturated aqueous sodium hydrogen carbonate (300 mL) was followed by ethyl acetate extraction (3 × 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography gave aldehydes (70–81% over three steps) as colourless oils.

General Method for Wittig Olefinations: To a solution of aldehydes (42.5 mmol) in dichloromethane (500 mL) was added (ethoxycarbonylethylidene)triphenylphosphorane (18.55 g, 51.2 mmol), and the reaction mixture was refluxed for 24 h. The solvent was removed in vacuo, and the residue was extracted with diethyl ether/hexane (1:1, 300 mL, 3×). The combined extracts were concentrated and chromatographed over silica gel, eluted with ethyl acetate/petroleum ether (1:9) to give the enolates (65–79%) as colourless oils.

General Method for DMP Oxidations of Homoallylic Alcohols: Dess–Martin reagent (31.40 g, 67.0 mmol) was added in one portion to a solution of allylic alcohols (38.0 mmol) in dry DCM (400 mL). After 2 h of stirring at room temperature the mixture was diluted with DCM (200 mL) and subsequently washed with saturated aqueous $Na_2S_2O_3$ solution (200 mL), and 5% $NaHCO_3$ solution (200 mL). The combined aqueous layers were extracted once with DCM (100 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel (EtOAc/petroleum ether, 1:6) to yield the ketones as colourless oils (85–90%).

General Method for *cis*-Enolisation of Homoallylic Ketones: To a stirred solution of homoallylic ketones (10.0 mmol) in dry THF (100 mL) was added HMPA (1.97 g, 11.0 mmol), and the mixture was cooled to –78 °C when LiHMDS (1 M soln. in THF, 12.0 mL, 12.0 mmol) was added. After 15 min of stirring the enolate was quenched with freshly distilled TMSCl (1.30 g, 12.0 mol) or TBSOTf (3.17 g, 12.0 mmol). After being stirred for 1 h, the reaction mixture was warmed to room temperature and poured into pentane (100 mL) in a separation funnel. The mixture was washed twice with saturated $NaHCO_3$ (100 mL), once with brine and the organic layer was dried with anhydrous $MgSO_4$. The solution was concentrated and chromatographed over silica gel (Et_2O/petroleum ether, 1:100) to yield the (*Z*)-enol ethers as colorless oils (75–91%).

TMS Enol Ether 5: The TMS enol ether **5** (490 mg, 75%) was obtained from the corresponding homoallylic ketone (500 mg, 2.23 mmol) as a colourless oil by following the general enolisation method: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 9 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.44–1.56 (m, 4 H), 2.07 (t, J = 7.4 Hz, 2 H), 2.22 (dt, J = 7.2, 7.1 Hz, 2 H), 4.19 (q, J = 7.0 Hz, 2 H), 4.83 (dd, J = 10.5, 2.0 Hz, 1 H), 5.05 (dd, J = 17.2, 2.0 Hz, 1 H), 5.29 (d, J = 10.5 Hz, 1 H), 5.83 (d, J = 15.5 Hz, 1 H), 6.54 (ddd, J = 17.2, 10.5, 10.5 Hz, 1 H), 6.95 (dt, J = 15.5, 7.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.6, 14.3, 26.3, 27.4, 32.0, 36.3, 60.1, 110.6, 111.9, 121.5, 131.5, 148.9, 152.8, 166.7 ppm. MS (CI^+): m/z found MH^+ 297.1901 $C_{16}H_{29}O_3Si$ requires 297.1886. IR (thin film): $\tilde{\nu}_{max}$ = 2939 (s), 1722 (s), 1650 (s) cm^{-1}.

TMS Enol Ether 6: The TMS enol ether **6** (1.19 g, 75%) was obtained from the corresponding homoallylic ketone (1.22 g, 5.14 mmol) as a colourless oil by following the general enolisation method: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 9 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.25–1.38 (m, 2 H), 1.44–1.54 (m, 4 H), 2.06 (t, J = 7.2 Hz, 2 H), 2.18–2.24 (m, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.82 (dd, J = 10.5, 1.8 Hz, 1 H), 5.00 (dd, J = 17.2, 1.8 Hz, 1 H), 5.29 (d, J = 10.5 Hz, 1 H), 5.82 (dt, J = 15.7, 1.5 Hz, 1 H), 6.55 (ddd, J = 17.2, 10.5, 10.5 Hz, 1 H), 6.96 (dt, J = 15.7, 7.2 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.6, 14.3, 26.6, 27.8, 28.6, 32.1, 36.5, 60.1, 110.4, 111.7, 121.3, 131.6, 149.2, 153.2, 173.4 ppm. MS (CI^+): m/z = found MH^+ 311.2032 $C_{17}H_{31}O_3Si$ requires 311.2042. IR (thin film): $\tilde{\nu}_{max}$ = 2935 (s), 1721 (s), 1650 (m), 1254 (m), 1181 (m), 1044 (m), 847 (s) cm^{-1}.

TMS Enol Ether 7: The corresponding homoallylic ketone (2.52 g, 10.0 mmol) was converted into the titled compound (2.46 g, 79%) by following the general enolisation method: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 9 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.35 (m, 2 H), 1.42–1.55 (m, 4 H), 1.83 (d, J = 1.3 Hz, 3 H), 2.06 (t, J = 7.4 Hz, 2 H), 2.17 (dt, J = 7.2, 7.1 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.81 (dd, J = 10.4, 1.9 Hz, 1 H), 5.00 (dd, J = 17.2, 1.9 Hz, 1 H), 5.30 (d, J = 10.7 Hz, 1 H), 6.55 (ddd, J = 17.2, 10.7, 10.4 Hz, 1 H), 6.75 (tq, J = 7.2, 1.3 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.6, 12.3, 14.3, 26.7, 28.4, 28.9, 36.5, 60.4, 110.4, 111.7, 127.8, 131.6, 142.1, 153.3, 168.2. MS (CI^+): m/z found MH^+ 325.2200 $C_{18}H_{33}O_3Si$ requires 325.2199. IR (thin film): $\tilde{\nu}_{max}$ = 2934 (s), 1710 (s), 1264 (m) cm^{-1}.

TBS Enol Ether 8: The TBS enol ether **8** (167 mg, 91%) was obtained from the corresponding homoallylic ketone (126 mg, 0.5 mmol) as a colourless oil by following the general enolisation method: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 1.02 (s, 9 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.40 (m, 2 H), 1.49–1.58 (m, 4 H), 1.88 (s, 3 H), 2.11 (t, J = 7.5 Hz, 2 H), 2.23 (dt, J = 7.3, 7.1 Hz, 2 H), 4.24 (q, J = 7.1 Hz, 2 H), 4.85 (d, J = 10.4 Hz, 1 H), 5.03 (d, J = 17.0 Hz, 1 H), 5.31 (d, J = 10.7 Hz, 1 H), 6.66 (ddd, J = 17.0, 10.7, 10.4 Hz, 1 H), 6.80 (t, J = 7.3 Hz, 1 H), ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –3.8, 12.3, 14.4, 25.7, 25.8, 26.9, 28.5, 28.6, 29.0, 36.6, 60.5, 110.0, 111.6, 127.9, 131.8, 142.2, 153.4, 168.4 ppm. MS (CI^+): m/z MH^+ found 367.2688 $C_{21}H_{39}O_3Si$ requires 367.2668. IR (thin film): $\tilde{\nu}_{max}$ = 2933 (s), 1710 (s), 1257 (m) cm^{-1}.

General Method for Cycloaddition of Silyl Enol Ethers 5,6,7 and 8: A solution of enol ether (0.3 mmol) and freshly recrystallised camphorsulfonic acid (4 mol-%) in dry toluene (5 mL) was placed in an argon-filled sealed tube and was heated at 180 °C for 4 d while being stirred. Cooling and concentration was followed by flash chromatography (diethyl ether/petroleum ether, 1:10) to yield the cycloadducts.

TMS Enol Ether 9: Compound **9** (137.2 mg, 49%) was obtained from TMS enol ether **5** (280 mg, 0.94 mmol) following the general cycloaddition method as a colourless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 0.95 (d, J = 7.4 Hz, 3 H), 0.99 (m, 1 H), 1.27 (t, J = 7.0 Hz, 2 H), 1.54–1.63 (m, 1 H), 1.68–1.82 (m, 2 H), 2.06–2.24 (m, 3 H), 2.27–2.36 (m, 1 H), 2.40–2.48 (m, 2 H), 2.59 (m, 1 H), 4.18 (m, 2 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 0.6, 14.2, 15.4, 23.4, 26.1, 31.1, 33.2, 37.3, 37.6, 49.6, 59.9, 119.7, 139.1, 174.6 ppm. MS (CI^+): m/z found MH^+ 297.1881 $C_{16}H_{29}O_3Si$ requires 297.1886; IR (thin film): $\tilde{\nu}_{max}$ = 1734 (s), 1449 (s), 1252 (s), 1180 (s) cm^{-1}.

Bicyclic Ketone 10: Compound **10** (25.6 mg, 12%) was obtained from TMS enol ether **5** (280 mg, 0.94 mmol) following the general cycloaddition method as a colourless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.7 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.35 (m, 1 H), 1.56 (m, 1 H), 1.69–1.78 (m, 2 H), 1.83 (m, 1 H), 2.07 (m, 1 H), 2.41–2.48 (m, 3 H), 2.65–2.73 (m, 2 H), 2.81 (dd, J = 14.4, 7.6 Hz, 1 H), 4.19 (m, 2 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.7, 17.9, 23.4, 27.4, 31.5, 32.3, 42.3, 45.2, 48.0, 51.2, 60.8, 174.5, 213.2 ppm. MS (CI^+): m/z found MH^+ 225.1488 $C_{13}H_{21}O_3$ requires 225.1491; IR (thin film): $\tilde{\nu}_{max}$ = 1731 (s), 1728 (s), 1179 (s) cm^{-1}.

Reduction of Bicyclic Ketone 10: To a stirred solution of the ketone **10** (110 mg, 0.49 mmol) in dry THF (10 mL) at 0 °C was added a 1 M solution of L-selectride in THF (0.74 mL, 0.74 mmol, 1.5 equiv.) under nitrogen. After the reaction mixture had been stirred for 30 min, diethyl ether and water were added. The aqueous layer was thoroughly extracted with diethyl ether and the combined extracts were washed successively with 10% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine. The ethereal solution was then dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:7) to give a alcohol (39.6 mg, 36%) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.45 (m, 1 H), 1.54–1.76 (m, 6 H), 1.76–1.85 (m, 1 H), 2.26–2.41 (m, 3 H), 2.47 (m, 1 H), 4.08–4.26 (m, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 14.7, 21.1, 22.3, 31.1, 31.2, 35.3, 36.8, 45.0, 46.2, 60.1, 66.6, 174.7 ppm. MS (CI^+): m/z found MH^+ 227.1647 $C_{13}H_{23}O_3$ requires 227.1647. IR (thin film): $\tilde{\nu}_{max}$ = 3418 (s, br.), 1715 (s), 1462 (m), 1384 (s) cm^{-1}.

Dinitrobenzoate 11: The product of reduction of ketone **10** (39.6 mg, 0.18 mmol) was stirred in pyridine (5 mL) for 30 min and then treated with 3,5-dinitrobenzoyl chloride (60.4 mg, 0.26 mmol). The reaction mixture was left to stir overnight. Water was then added, and the mixture was extracted with diethyl ether. The combined organic fractions were washed with saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$ and water, then dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was purified on silica gel (DCM/petroleum ether, 2:1) to afford **11** as white prisms (61.3 mg, 83%); m.p. 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, J = 7.07 Hz, 3 H), 1.29 (t, J = 7.07 Hz, 3 H), 1.57 (m, 1 H), 1.65–1.80 (m, 4 H), 1.84–1.92 (m, 2 H), 2.00 (m, 1 H), 2.48 (m, 2 H), 2.59 (m, 2 H), 4.11–4.24 (m, 2 H), 5.64 (m, 1 H), 9.12 (d, J = 2.27 Hz, 2 H), 9.23 (t, J = 2.27 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 14.9, 21.3, 23.8, 30.2, 31.0, 32.0, 37.3, 41.4, 46.1, 60.3, 74.2, 122.2, 129.3, 134.4, 148.7, 162.0, 174.1 ppm. MS (CI^+): m/z found MH^+ 227.1659 $C_{20}H_{25}N_2O_8$ requires 227.1647. IR (thin film): $\tilde{\nu}_{max}$ = 1730 (s),1720 (s), 1550 (m), 1347 (m), 1286 (m) cm^{-1}.

Cycloadduct 15: Adduct **15** (65.3 mg, 63%) was obtained from TMS enol ether **6** (135.0 mg, 0.43 mmol) by following the general cycloaddition method as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, J = 6.8 Hz, 3 H), 0.98–1.08 (m, 2 H), 1.17–1.33 (m, 3 H), 1.28 (t, J = 6.8 Hz, 3 H), 1.70–1.74 (m, 1 H), 1.80–1.82 (m, 1 H), 1.90–2.01 (m, 3 H), 2.26 (dd, J = 10.2, 2.0 Hz, 1 H), 2.60–2.68 (m, 2 H), 2.73 (dd, J = 10.2, 3.4 Hz, 1 H), 4.15–4.20 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 16.3, 24.7, 25.9, 26.5, 30.1, 30.8, 37.1, 45.7, 50.2, 51.9, 60.3, 175.7, 212.2 ppm. MS (CI^+): m/z MH^+ 239.1647 $C_{14}H_{23}O_3$ requires 239.1647. IR (thin film): $\tilde{\nu}_{max}$ = 2934 (s), 2840 (m), 1740 (s), 1712 (m), 1175 (s), 1030 (m) cm^{-1}.

3,5-Dinitrophenyl Hydrazone 16: To aqueous 3,5-dinitrophenylhydrazine (30% in water, 311.1 mg, 1.10 mmol) was added EtOH (7.8 mL), water (2.3 mL) and concd. H_2SO_4 (1.5 mL). The resulting solution was mixed with a solution of ketone **15** (65.3 mg, 0.27 mmol) in EtOH (0.73 mL). Hydrazone **16** crystallised on shaking and was separated by filtration as orange prisms (89.6 mg,

75.4%); m.p. 119–120 °C. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.90 (d, J = 7.3 Hz, 3 H), 1.08 (t, J = 7.1 Hz, 3 H), 1.15–1.34 (m, 2 H), 1.47–1.64 (m, 3 H), 1.68–1.73 (m, 2 H), 1.85–1.95 (m, 2 H), 2.05–2.23 (m, 3 H), 2.35 (dd, J = 10.6, 4.6 Hz, 1 H), 2.47 (dd, J = 14.4, 4.3 Hz, 1 H), 4.02–4.08 (m, 2 H), 7.62 (d, J = 9.5 Hz, 2 H), 7.64 (d, J = 9.5 Hz, 1 H), 11.03 (br. s, 1 H) ppm. ^{13}C NMR (100.6 MHz, C_6D_6): δ = 14.5, 15.4, 26.1, 26.2, 27.5, 32.8, 33.0, 33.8, 41.3, 47.8, 52.4, 60.4, 115.9, 123.6, 145.5, 159.4, 172.9, 173.9 ppm. MS (CI$^+$): m/z MH$^+$ 419.1930 $C_{20}H_{27}N_4O_6$ requires 419.1931 IR (KBr): $\tilde{\nu}_{max}$ = 3440 (s), 2963 (s), 1730 (s), 1620 (s), 1338 (m), 1308 (m), 1161 (m) cm^{-1}.

TMS Enol Ether 17: Compound **17** (61.2 mg, 68%) was obtained from the triene **7** (90 mg, 0.28 mmol) as a colourless oil by following the general cycloaddition method: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 0.87 (d, J = 6.82 Hz, 3 H), 1.02–1.15 (m, 2 H), 1.13 (s, 3 H), 1.25 (t, J = 7.17 Hz, 3 H), 1.32–1.42 (m, 2 H), 1.68–1.84 (m, 4 H), 1.96 (m, 1 H), 2.44 (m, 1 H), 2.60 (m, 1 H), 2.84 (m, 1 H), 4.08–4.20 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.6, 14.3, 16.2, 20.1, 26.0, 26.3, 26.5, 28.4, 31.0, 34.1, 36.2, 47.1, 60.0, 115.9, 137.9, 176.9 ppm. MS (CI$^+$): found MH$^+$ 325.2193 $C_{18}H_{33}O_3Si$ requires 325.2199. IR (thin film): $\tilde{\nu}_{max}$ = 2929 (s), 1728 (s), 1253 (m), 1183 (m) cm^{-1}.

Bicyclic Ketone 18: Compound **18** (5.4 mg, 6%) was obtained from TMS enol ether **7** (90 mg, 0.28 mmol) as a colourless oil by following the general cycloaddition method: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.83 Hz, 3 H), 1.09–1.23 (m, 4 H), 1.27 (t, J = 6.83 Hz, 3 H), 1.45 (s, 3 H), 1.77 (m, 2 H), 2.06 (m, 2 H), 2.14 (dd, J = 13.65, 3.41 Hz, 1 H), 2.16–2.31 (m, 3 H), 2.75 (dd, J = 13.65, 5.12 Hz, 1 H), 4.11–4.23 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 16.8, 18.4, 25.6, 25.7, 26.0, 28.6, 41.2, 43.0, 44.1, 48.3, 49.2, 60.4, 175.5, 211.5 ppm. MS (CI$^+$): found MH$^+$ 253.1803 $C_{15}H_{25}O_3$ requires 253.1804. IR (thin film): $\tilde{\nu}_{max}$ = 1739 (s), 1713 (s), 1270 (m), 1213 (m), 1134 (m) cm^{-1}.

TBS Enol Ether 19: The enol ether **19** (345 mg, 69%) was obtained from the triene **8** (500 mg, 1.36 mmol) as a colourless oil by following the general cycloaddition method: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.16 (s, 6 H), 0.93 (d, J = 6.94 Hz, 3 H), 1.00 (s, 9 H), 1.08–1.15 (m, 1 H), 1.17 (s, 3 H), 1.30 (t, J = 6.75 Hz, 3 H), 1.30 (t, J = 7.25 Hz, 3 H), 1.08–1.14 (m, 1 H), 1.34–1.49 (m, 3 H), 1.56–1.67 (m, 1 H), 1.72–1.86 (m, 2 H), 1.97–2.05 (m, 1 H), 3.47 (m, 1 H), 2.64 (m, 1 H), 2.95 (m, 1 H), 4.13–4.23 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –3.9, –3.8, 14.3, 16.3, 18.3, 20.2, 26.0, 26.4, 26.5, 28.5, 34.4, 36.3, 38.5, 47.2, 60.1, 115.6, 138.2, 177.0 ppm. MS (CI$^+$): m/z MH$^+$ found 367.2668 $C_{21}H_{39}O_3Si$ requires 367.2668. IR (thin film): $\tilde{\nu}_{max}$ = 2931 (s), 1728 (s), 1257 (m), 1179 (s) cm^{-1}.

***trans*-Enone 20:** Obtained in small quantities as a byproduct of previously described cycloadditions as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.37 (m, 2 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.45 (m, 2 H), 1.62 (m, 2 H), 1.82 (s, 3 H), 1.90 (dd, J = 6.8 and 1.7 Hz, 3 H), 2.17 (m, 2 H), 2.52 (t, J = 7.3 Hz, 2 H), 4.18 (q, J = 7.2 Hz, 2 H), 6.12 (m, 1 H), 6.74 (m, 1 H), 6.86 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 200.5, 168.3, 142.4, 142.0, 131.9, 127.8, 60.4, 39.8, 29.0, 28.5, 28.4, 24.0, 18.2, 14.3, 12.3 ppm. MS (CI$^+$): found MH$^+$ 253.1805 $C_{15}H_{25}O_3$ requires. IR (thin film): $\tilde{\nu}_{max}$ = 1720 (s), 1709 (s), 1270 (m) cm^{-1}.

(*Z,E*)-TBS Enol Ether 21: To a solution of the enone **20** (0.250 g, 0.99 mmol) and *tert*-butyldimethylsilyl triflate (0.40 g, 1.50 mmol) in anhydrous THF (20 mL) was added potassium hexamethyldisilazide (3 mL, 0.5 M in toluene, 1.50 mmol) dropwise at –78 °C under nitrogen. The resulting solution was stirred at –78 °C for 30 min and at room temperature for 1 h. The solution was quenched with aqueous $NaHCO_3$ solution and extracted with Et_2O (3 × 20 mL). The combined organic phase was dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (ether/petroleum ether, 1:100) to give the product as a colourless oil (0.310 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.99 (s, 9 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.37 (m, 2 H), 1.46 (m, 2 H), 1.73 (d, J = 6.2 Hz, 3 H), 1.82 (s, 3 H), 2.09 (m, 2 H), 2.16 (m, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.63 (t, J = 7.2 Hz, 1 H), 5.71–5.86 (m, 2 H), 6.75 (t, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –3.7, 12.3, 14.2, 17.6, 18.4, 25.8, 26.0, 28.4, 28.5, 29.4, 60.3, 112.5, 123.9, 126.1, 127.8, 142.3, 148.2, 168.3. MS (CI$^+$): found MH$^+$ 367.2651 $C_{21}H_{39}O_3Si$ requires 367.2668. IR (thin film): $\tilde{\nu}_{max}$ = 2964 (s), 1730 (s), 1550 (s), 1347 (s) cm^{-1}.

TBS Enol Ether 22: A solution of (*Z,E*)-enol ether **21** (68 mg, 0.19 mmol) in dry toluene (5 mL) and diethylaluminium chloride (1 M solution in THF, 10 µL) was placed in a sealed tube under argon and heated at 180 °C for 4 h while stirring. Cooling to room temperature, concentration and flash column chromatography (petroleum ether/diethyl ether, 20:1) afforded the title compound **22** (51.6 mg, 76%) as a colourless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.13 (s, 3 H), 0.14 (s, 3 H), 0.93 (s, 9 H), 0.94 (d, J = 3.13 Hz, 3 H), 1.17 (s, 3 H), 1.27 (t, J = 7.04 Hz, 3 H), 1.68–1.90 (m, 6 H), 2.02–2.36 (m, 5 H), 4.06- 4.25 (m, 2 H), 4.41 (dd, J = 5.48, 1.96 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = –3.9, 14.2, 16.2, 18.2, 20.6, 25.9, 26.0, 26.3, 26.4, 28.5, 34.3, 36.2, 38.4, 47.1, 60.1, 115.5, 138.2, 176.9 ppm. MS (CI$^+$): MH$^+$ found 367.2668 $C_{18}H_{33}O_3Si$ requires 367.2668. IR (thin film): $\tilde{\nu}_{max}$ = 2931 (s), 1728 (s), 1257 (m), 1179 (s) cm^{-1}.

Hydroxy Ketone 23: To a stirred solution of TMS cycloadduct **17** (29 mg, 0.09 mmol) in DCM (5 mL) was added a solution of *m*CPBA (18 mg, 0.10 mmol) in DCM (5 mL) at –78 °C. The mixture was left to warm to room temperature gradually over 12 h and then washed with saturated aqueous $NaHCO_3$ (4 mL) and extracted with DCM (3 × 5 mL). The crude product was purified by flash chromatography (diethyl ether/petroleum ether, 1:25) to give the title compound as a colourless oil (11.5 mg, 43.0%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, J = 7.2 Hz, 3 H), 1.18–1.40 (m, 3 H), 1.25 (t, J = 7.04 Hz, 3 H), 1.44 (s, 3 H), 1.47–1.85 (m, 6 H), 2.20 (m, 2 H), 2.33 (dd, J = 13.20, 7.03 Hz, 1 H), 2.96 (dd, J = 13.20, 4.30 Hz, 1 H), 4.11 (q, J = 7.04 Hz, 2 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.3, 16.7, 19.4, 21.0, 23.6, 26.2, 33.9, 39.3, 41.3, 44.6, 48.8, 60.6, 75.1, 176.3, 212.3 ppm. MS (CI$^+$): m/z found MH$^+$ 269.1753, $C_{15}H_{25}O_4$ requires 269.1755. IR (thin film): $\tilde{\nu}_{max}$ = 3485 (s, br.), 1739 (s), 1715 (s), 1236 (m), 1148 (m) cm^{-1}.

Hydroxy Enol Ether 24: To a stirred solution of TBS cycloadduct **19** (402 mg, 1.10 mmol) in DCM (10 mL) was added a solution of *m*CPBA (210.5 mg, 1.22 mmol) in DCM (10 mL) at –78 °C. The mixture was left to warm to room temperature gradually over 12 h, and then washed with saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The crude product was purified by flash chromatography (diethyl ether/petroleum ether, 1:25) to give the title compound as a colourless oil (187 mg, 44.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.92 (m, 1 H), 0.95 (s, 9 H), 1.22–1.30 (m, 2 H), 1.27 (t, J = 7.59 Hz, 3 H), 1.35 (s, 3 H), 1.38–1.43 (m, 1 H), 1.51 (m, 1 H), 1.60–1.82 (m, 4 H), 2.10 (m, 1 H), 2.20 (m, 1 H), 4.08–4.18 (m, 2 H), 4.71 (d, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = –4.61, –4.23, 14.2, 18.3, 18.9, 19.1, 21.5, 22.5, 25.8, 26.5, 36.4, 39.5, 42.7, 47.8, 60.0, 70.9, 107.5, 151.1, 176.3 ppm. MS (CI$^+$): m/z MH$^+$ found 383.2622, $C_{21}H_{39}O_4Si$ MH$^+$ requires 383.2618. IR (thin film): $\tilde{\nu}_{max}$ = 2933 (s), 1726 (s), 1203 (s) cm^{-1}.

Bromo Ketone 25: To a stirred solution of TBS enol ether **24** (83.5 mg, 0.22 mmol) in anhydrous THF (10 mL) was added solu-

tion of *N*-bromosuccinimide (46.7 mg, 0.26 mmol) in THF (10 mL) at –78 °C, and the resulting mixture was stirred at –78 °C for 4 h, warmed to room temperature and poured into a separation funnel containing ether (15 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (ether/petroleum ether, 1:100) to give the bromide **25** as a pale yellow oil (69.2 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 3 H), 0.31 (s, 3 H), 0.91 (s, 9 H), 0.98 (d, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.4 Hz, 3 H), 1.40 (s, 3 H), 1.46–1.63 (m, 4 H), 1.80–1.89 (m, 4 H), 2.31 (dd, J = 11.4, 2.9 Hz, 1 H), 2.45 (qd, J = 7.4, 2.4 Hz, 1 H), 4.12 (q, , 1 H, J = 7.2 Hz, 2 H), 4.27 (d, J = 2.4 Hz) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –2.98, –2.47, 14.1, 18.1, 20.4, 24.0, 25.8, 26.2, 26.3, 30.2, 37.7, 43.1, 47.6, 57.4, 60.6, 74.3, 85.3, 175.8, 203.8 ppm. MS (CI$^+$): found MH$^+$ 461.1714, $C_{21}H_{38}BrO_4Si$ [MH$^+$] requires 461.1723. IR (thin film): $\tilde{\nu}_{max}$ = 2933 (s), 1750 (s), 1728 (s), 1171 (m) cm^{-1}.

Tertiary Alcohol 26: To a stirred solution of the bromide **25** (63.5 mg, 0.14 mmol) in acetonitrile (1.5 mL) was added fluorosilicic acid solution (25% in water, 0.15 mL). After 1 h the reaction mixture was washed with water, extracted with diethyl ether, dried ($MgSO_4$), and the solvents were evaporated. Flash chromatography of the residue gave alcohol **26** as white needles (45.3 mg, 95%); m.p. 147–149 °C. ^{1}H NMR (500 MHz, C_6D_6): δ = 0.97 (t, J = 7.2 Hz, 3 H), 0.95–1.04 (m, 2 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.29–1.35 (m, 2 H), 1.43 (s, 3 H), 1.40–1.49 (m, 2 H), 1.56 (m, 1 H), 1.71 (dd, J = 12.8, 3.7 Hz, 1 H), 1.78 (d, J = 14.1 Hz, 1 H), 2.32 (m, 1 H), 2.43 (dd, J = 14.5, 2.1 Hz, 1 H), 3.97 (m, 2 H), 5.44 (d, J = 13.5 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 17.0, 20.0, 20.6, 23.8, 26.1, 35.4, 43.0, 44.4, 51.4, 60.0, 60.7, 75.2, 175.7, 203.7 ppm. MS (CI$^+$): *m*/*z* found MH$^+$ 347.0856 $C_{15}H_{24}BrO_4$ requires 347.0856. IR (KBr): $\tilde{\nu}_{max}$ = 3449 (s, br.), 2938 (s), 1728 (s), 1702 (s), 1259 (m), 1171 (m) cm^{-1}.

Diol 27: To a stirred solution of the hydroxy ketone **23** (76 mg, 0.28 mmol) and cerium trichloride heptahydrate (103 mg, 0.3 mmol) in methanol (3 mL) was added sodium borohydride (13 mg, 0.3 mmol), and the resulting mixture was stirred for 30 min at room temperature, quenched with satd. aqueous NH_4Cl (3 mL) and extracted with diethyl ether (3×5 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give a crude product. Purification by flash column chromatography (petroleum ether/diethyl ether, 1.5:1) gave the diol **27** (60 mg, 79%) as a colourless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, J = 7.25 Hz, 3 H), 1.30, (t, J = 7.04 Hz, 2 H), 1.32–1.40 (m, 2 H), 1.44 (s, 3 H), 1.47–1.67 (m, 6 H), 1.68–1.85 (m, 2 H), 1.90–2.02 (m, 2 H), 2.37 (ddd, J = 14.50, 6.02, 4.10 Hz, 1 H), 2.46 (ddd, J = 14.50, 5.04, 3.47 Hz, 1 H), 3.54 (dd, J = 3.47, 3.15 Hz, 1 H), 4.16 (q, J = 7.04 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 19.4, 19.6, 21.6, 24.2, 26.4, 31.5, 36.6, 36.8, 37.0, 49.1, 60.0, 73.5, 75.3, 176.9 ppm. MS (CI$^+$): *m*/*z* found MH$^+$ 271.1913, $C_{15}H_{27}O_4$ requires 271.1909. IR (thin film): $\tilde{\nu}_{max}$ = 3509 (br.), 2935 (s), 1721 (s), 1389 (s), 1258 (s) cm^{-1}.

Allylic Alcohol 3: To a stirred solution of the diol **27** (21 mg, 0.08 mmol) and *o*-nitrophenylselenocyanate (20 mg, 0.085 mmol) in dry chloroform (5 mL) was added tri-*n*-butylphosphane (20 μL, 0.085 mmol), and the resulting solution was stirred overnight at room temperature after which TLC showed complete consumption of the starting material **27**. The solution was cooled to –40 °C, pyridine (20 μL) was added followed by an aqueous solution of hydrogen peroxide (30%, 0.1 mL). The resulting solution was warmed to room temperature over a period of 6 h, and a saturated solution of sodium bisulfite (1 mL) was added. The reaction mixture was extracted with ethyl acetate (2×10 mL), the organic extracts were washed with water (2×5 mL), dried ($MgSO_4$) and concentrated to give a crude product. Purification by flash chromatography (petroleum ether/diethyl ether, 4:1) gave the title compound **3** (11.9 mg, 59%) as a colourless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, J = 7.25 Hz, 3 H), 1.23 (s, 3 H), 1.31 (t, J = 6.94 Hz, 3 H), 1.34–1.40 (m, 2 H), 1.44–1.54 (m, 2 H), 1.60–1.76 (m, 2 H), 1.78 (dd, J = 12.30, 4.73 Hz, 1 H), 1.85 (ddd, J = 12.30, 5.67, 2.84 Hz, 1 H), 1.94–2.00 (m, 1 H), 2.01–2.11 (m, 2 H), 4.19 (dq, J = 14.50, 6.94 Hz, 2 H), 5.91–5.97 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 16.5, 19.9, 21.8, 24.9, 25.1, 32.5, 37.8, 38.7, 50.0, 60.1, 67.4, 120.0, 139.2, 176.3 ppm. MS (CI$^+$): *m*/*z* found MH$^+$ 253.1808 $C_{15}H_{25}O_3$ requires 253.1804. IR (thin film): $\tilde{\nu}_{max}$ = 3500 (br.), 1726 (s) cm^{-1}.

General Procedure for Sequential Oxidation and Bromination of TIPS Enol Ethers: To a solution of the TIPS enolate (0.5 mmol) in DCM (5 mL) cooled to –78 °C was added dropwise a solution of *m*CPBA (94.6 mg, 0.55 mmol) in DCM (3 mL). After 2 h of stirring at –78 °C, a solution of bromine (88 mg, 0.55 mmol) in DCM (0.55 mL) was added dropwise. The mixture was stirred at –78 °C for another 2 h, and then warmed to room temp. Removal of the solvent under reduced pressure and flash silica gel chromatography of the residue (Et_2O/petroleum ether, 1:50) led to the isolation of pure α-hydroxy α′-bromo ketones.

6-Bromo-2-hydroxy-2-methylcyclohexanone (37): Bromide **37** (82.7 mg, 80%) was produced from the TIPS enol ether **30** (134.0 mg, 0.50 mmol) as a colourless oil by following the general oxidation and bromination method: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81–1.89 (m, 2 H), 1.92 (s, 3 H), 2.03–2.12 (m, 2 H), 2.18–2.29 (m, 1 H), 2.36–2.45 (m, 1 H), 2.62–2.69 (m, 1 H), 5.59 (dd, J = 13.4, 6.3 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.6, 28.8, 39.4, 43.3, 52.2, 64.9, 196.2 ppm. MS (CI$^+$): *m*/*z* found MH$^+$ 207.0021 $C_7H_{12}BrO_2$ requires 207.0021. IR (thin film): $\tilde{\nu}_{max}$ = 2867 (s), 1731 (s), 1447 (m), 1303 (w), 1176 (m), 1073 (m), 731 (m), 666 (m) cm^{-1}.

6-Bromo-2-*tert*-butyl-2-hydroxycyclohexanone (41): Bromide **41** (2.23 g, 68%) was produced from TIPS enol ether **38** (4.11 g, 13.2 mmol) as a colourless oil by following the general oxidation and bromination method. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 1.85–1.92 (m, 1 H), 1.98–2.12 (m, 3 H), 2.20–2.32 (m, 1 H), 2.42–2.48 (m, 1 H), 2.58–2.65 (m, 1 H), 5.72 (dd, J = 13.5, 6.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.7, 30.3, 36.6, 38.9, 39.7, 54.6, 81.7, 194.6 ppm. MS (CI$^+$): *m*/*z* found MH$^+$ 249.0494 $C_{10}H_{18}BrO_2$ requires 249.0490. IR (thin film): $\tilde{\nu}_{max}$ = 2963 (s), 1728 (s), 1448 (m), 1367 (m), 1089 (m) cm^{-1}.

6-Bromo-2-hydroxy-2-phenylcyclohexanone (42): Following the general oxidation and bromination method the bromide **42** (2.88 g, 54%) was produced from TIPS enol ether **39** (6.59 g, 19.94 mmol) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03–2.10 (m, 2 H), 2.18–2.25 (m, 1 H), 2.37–2.48 (m, 1 H), 2.53–2.61 (m, 1 H), 2.71–2.78 (m, 2 H), 5.80 (dd, J = 12.8 and 6.0 Hz, 1 H), 7.34–7.40 (m, 3 H), 7.49–7.52 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.2, 38.9, 41.1, 52.5, 56.8, 128.0, 128.7, 138.9, 194.6 ppm. MS (CI$^+$): *m*/*z* found MH$^+$ 269.0175 $C_{12}H_{14}BrO_2$ requires 269.0177. IR (thin film): $\tilde{\nu}_{max}$ = 3445 (w), 2943 (s), 1725 (s), 1464 (m), 1170 (m), 1055 (m) cm^{-1}.

2-Bromo-6-hydroxy-4-methylcyclohexanone (43): Bromide **43** (65.7 mg, 56%) was produced from TIPS enol ether **40** (153.0 mg, 0.57 mmol) as a colourless oil by following the general oxidation and bromination method. ^{1}H NMR (400 MHz, $CDCl_3$): δ = δ_H 1.08 (d, J = 6.3 Hz, 3 H), 1.52 (br. s, 1 H), 1.82–1.98 (m, 2 H), 2.31 (m, 1 H), 2.54–2.64 (m, 2 H), 4.55 (t, , 1 H, J = 3.0 Hz, 1 H), 5.49 (dd, J = 13.5, 5.8 Hz) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ =

195.8, 50.1, 49.2, 47.0, 42.6, 28.4, 20.1 ppm. MS (CI^+): *m/z* found MH^+ 207.0013 $C_7H_{12}BrO_2$ requires 207.0021. IR (thin film): $\tilde{\nu}_{max}$ = 2986 (s), 1729 (s), 1429 (m), 1369 (w), 1070 (m) cm^{-1}.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectroscopic data for all novel compounds.

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