A diene-transmissive approach to the quassinoid skeleton

Claude Spino, Bryan Hill, Pascal Dubé, and Stéphane Gingras

Abstract: Several tetracyclic molecules were prepared by diene-transmissive Diels–Alder cycloadditions. Control over the stereochemical outcome of the cycloaddition was achieved and the structural features of the precursors affecting the stereochemistry is discussed. Useful information was gathered concerning the factors governing this stereocontrol, which will be indispensable for the future of this strategy.

Key words: quassinoid, anticancer agent, diene-transmissive Diels–Alder cycloaddition, oxadiene, hetero Diels–Alder.

Résumé : On a préparé plusieurs molécules tétracycliques en faisant appel à des réactions de cycloaddition de Diels–Alder à dienes-transmissibles. On a pu contrôler le résultat stéréochimique des cycloadditions et on discute des caractéristiques des structures des précurseurs qui affectent la stéréochimie. Des informations utiles ont été accumulées concernant les facteurs qui gouvernent ce contrôle stéréochimique et celles-ci seront indispensables pour le futur de cette stratégie.

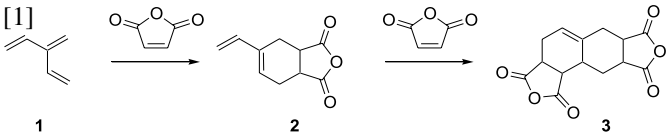
Mots clés : quassinoïde, agent antinéoplasique, cycloaddition de Diels–Alder à dienes-transmissibles, oxadiène, hétéro-Diels–Alder.

[Traduit par la Rédaction]

Introduction

Blomquist and Bailey and co-workers (1) reported the first diene-transmissive Diels–Alder cycloaddition in 1955. They coupled the unstable cross-conjugated triene 3-methylene-1,4-pentadiene **1** with excess maleic anhydride and obtained tetracyclic adduct **3** in moderate yield (eq. [1]) (1). Later, Tsuge and co-workers and others (2–4) investigated a series of intermolecular diene-transmissive [4 + 2]-cycloadditions on simple substituted cross-conjugated trienes. For several reasons that are explained in previous publications, this strategy stayed without a useful application until our report of a diene-transmissive Diels–Alder approach to the synthesis of anticancer quassinoids (eq. [2]) (5). In this synthetic route to quassinoids, a cross-conjugated oxadiene **4** was transformed into tetracycle **6** via an intermolecular hetero Diels–Alder reaction followed by an intramolecular normal [4 + 2]-cycloaddition. In 1999, Fallis and co-workers (6) reported the use of diene-transmissive Diels–Alder reactions for the construction of advanced intermediates toward the synthesis of other terpenoids.

[1]



1 **2** **3**

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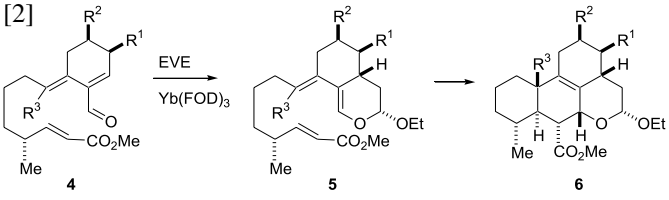
[2]



4 **5** **6**

Quassinoids are formidable synthetic targets. The extent of the oxygenation of their carbon skeleton contributes to the synthetic difficulties (7). Subtropical shrubs of the plant family *Simaroubaceae* constitute the most common source for these degraded triterpenoid natural products (8). They possess a large spectrum of biological activities, including antiviral, antimalarial, antineoplastic, and insect antifeedant properties (8). Recently reported biological activities have increased the interest in the synthesis of this family of triterpenes (9). The vast majority of quassinoids possess a C-20 picrasane skeleton, of which quassin **7**, glaucarubolone **8**, and bruceantin **9** are typical examples (Fig. 1) (8). We report herein a comprehensive investigation of the diene-transmissive double Diels–Alder approach to quassinoids. The quassinoid numbering and lettering shown in Fig. 1, will be used throughout this manuscript on all structures for ease of reference to the potential target molecules.

Several stereochemical issues arise from the key cycloaddition reactions. The substituents on the cyclohexene ring in **4** direct the incoming ethylvinyl ether to the α face of the diene but they may also affect the stereochemical outcome of the intramolecular Diels–Alder reaction (eq. [2]) (10). The appendages on the exocyclic chain serve to differentiate the energies of the two *endo* transition states (TS) accessible to the intermediate **5** (Fig. 2). They must be brought in with

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Scheme 1.

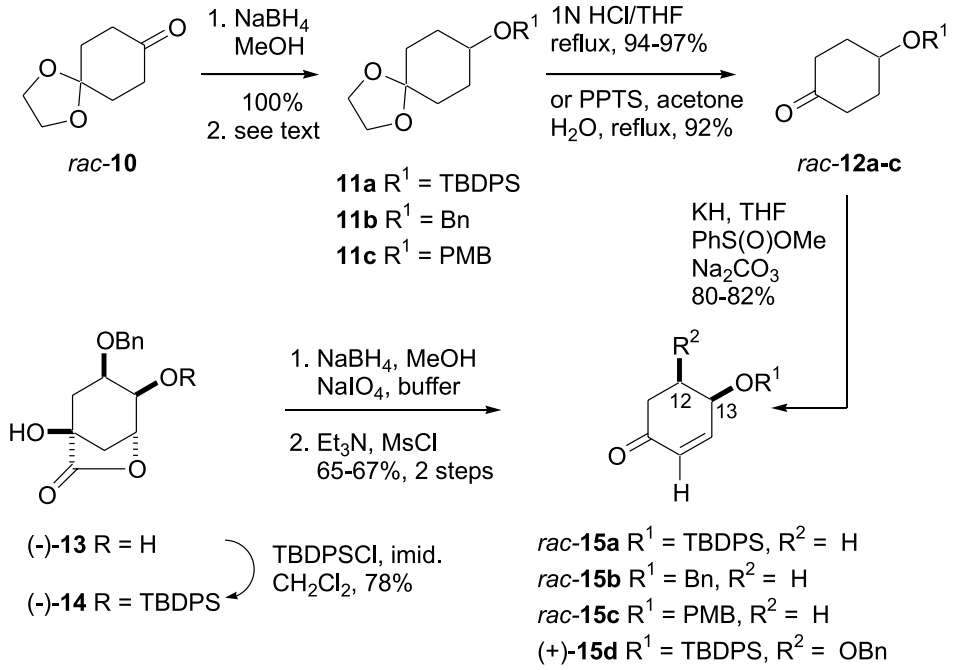


Fig. 1. Three examples of quassinoids.

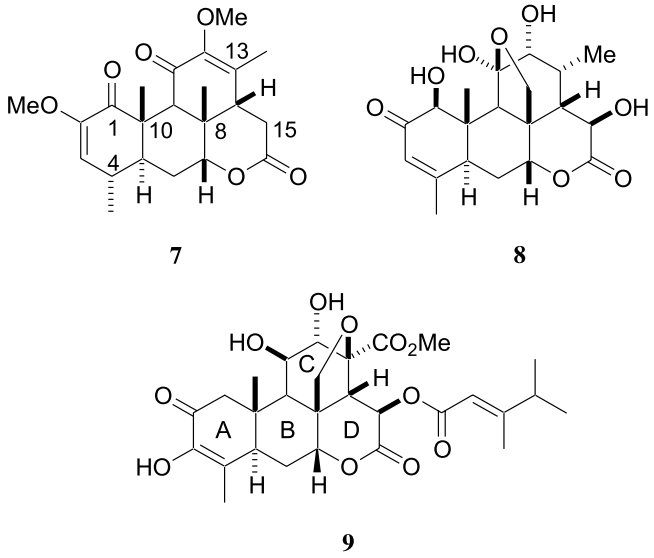
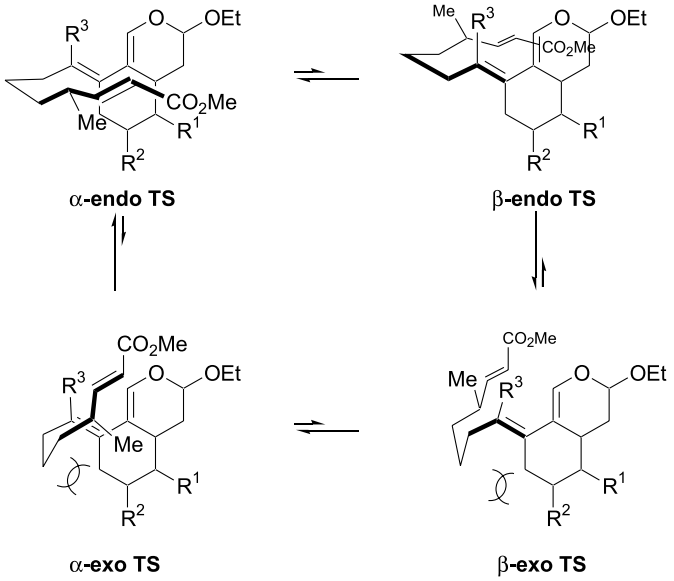


Fig. 2. The four chair-like transition states of **5**.

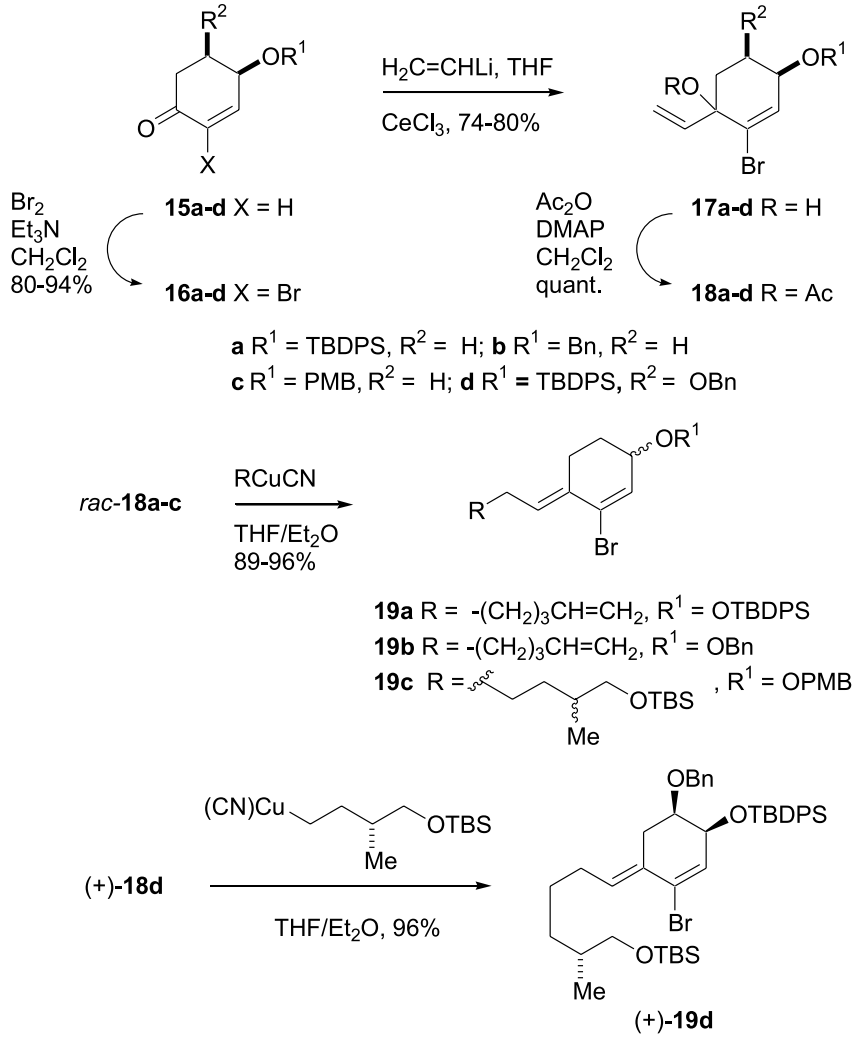


the exact stereochemistry shown for all-equatorial α-*endo* TS that will lead to the tetracyclic nucleus **6** having the correct stereochemistry for quassinoids.

Synthesis of the precursor oxadienes

Besides the introduction of the ring and chain substituents in **4** with the correct stereochemistry, the formation of the exocyclic double bond with the correct geometry represents a fierce challenge (eq. [2]) (11). Compounding the problem is the fact that the exocyclic double bond in **4** and **5** should preferably be a tetra-substituted double bond (R^3 = Me), otherwise the C-10 methyl group (cf. Fig. 1) would have to be introduced at a later stage of the synthesis, a more difficult (though possible) task than introducing the methyl group as part of the Diels–Alder strategy. Several ways to construct the exocyclic double bonds were envisioned. It was initially thought that starting with an appropriately substituted cyclohexenone would be most expeditious. In that respect, the known compound **13** (12), derived from (–)-quinic acid, presented itself as an attractive starting material (Scheme 1). Protection of the C-13 alcohol as a TBDPS ether was achieved, and reduction of the lactone in **14** followed by in situ oxidative cleavage of the resulting diol afforded a β-hydroxycyclohexanone, which was dehydrated to the desired substituted cyclohexenone **15d**. For simpler model compounds, 1,4-cyclohexadione monoketal **10** was an adequate starting material. It was reduced with $NaBH_4$ and then protected as its silyl ether **11a** (TBDPSCl, imid., DMF, quant.),

Scheme 2.

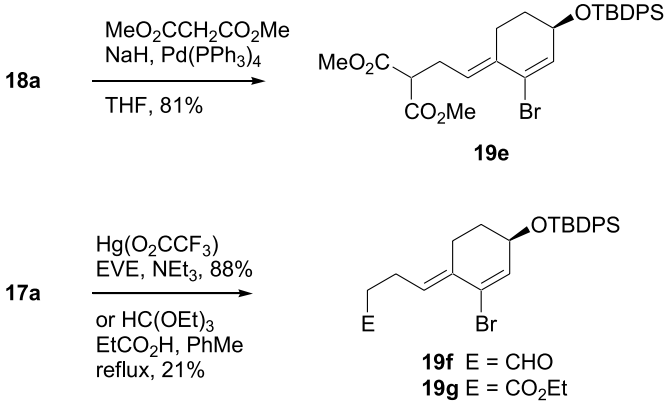


benzyl ether **11b** (KH, BnBr, THF, 83%), or PMB ether **11c** (KH, PMBCl, THF, 96%). Conversion of **11a–c** to **15a–c**, respectively, was straightforward as shown in Scheme 1.

Bromination and dehydrobromination of each cyclohexenone **15** gave the corresponding vinylbromide **16** in 80–94% yield (Scheme 2). Subsequent addition of vinyllithium to **16a–d** in the presence of anhydrous $CeCl_3$ afforded **17a–d**, which were converted to the corresponding acetates **18a–d** under standard conditions. Compounds **19a–g**, possessing a tri-substituted exocyclic double bond of *E* configuration, were prepared in one of three ways. Cuprate displacements of allylic acetates **18a–d** with alkylcyanocuprates gave the corresponding products **19a–d** in 89–96% yield (Scheme 2).[2] Alternatively, the palladium-catalyzed substitution of **18a** with malonate furnished **19e** in 81% yield as a single stereoisomer (Scheme 3). Aldehyde **19f** or ester **19g** could be accessed directly from a Claisen rearrangement of **17a**.

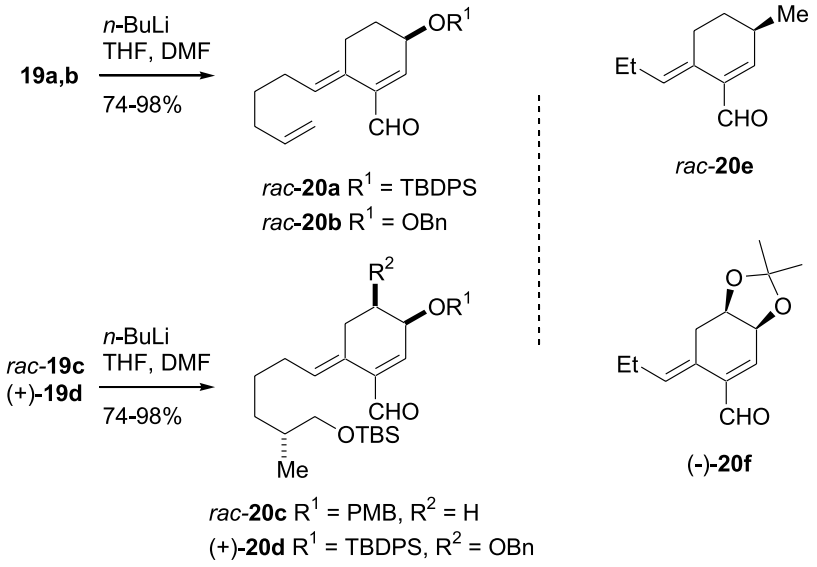
Vinyl bromides **19a–d** were separately treated with *n*-BuLi and the resulting vinyllithium intermediates trapped with DMF to give **20a–d** (Scheme 4). The syntheses of **20e** and **20f** were reported elsewhere (5*a*). Compounds **20c** and **20d** were further transformed in four steps to **24a** and **24b**,

Scheme 3.

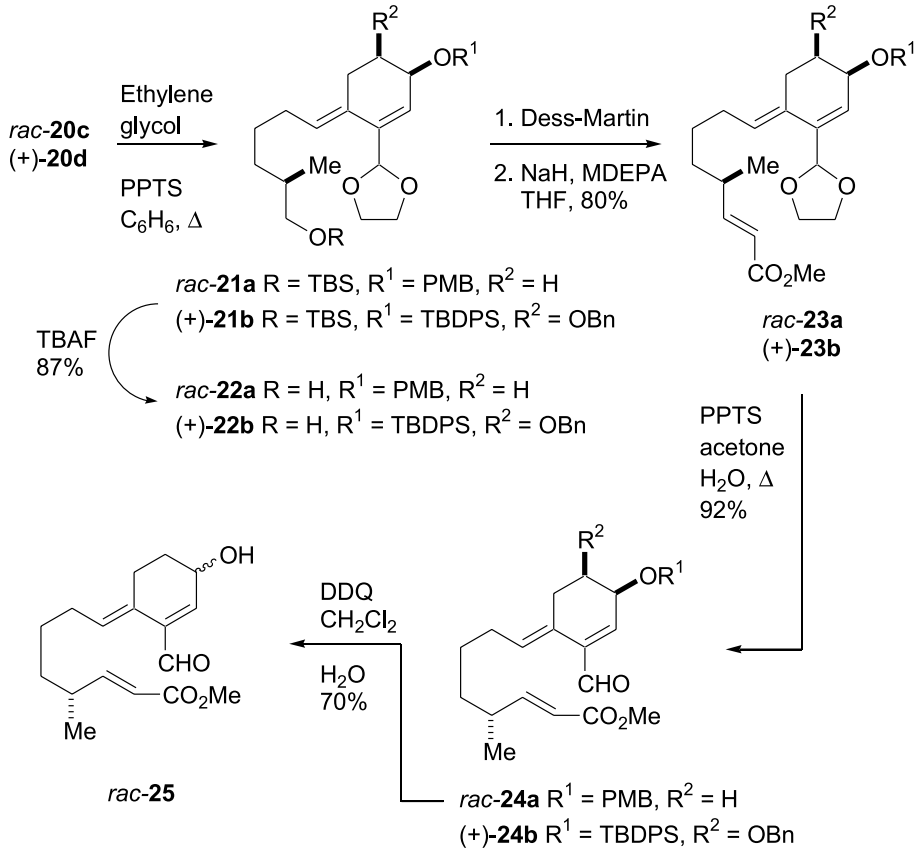


[2] Compound **19c** was prepared using a racemic cuprate reagent and was isolated as an inseparable mixture of stereoisomers (for clarity, only the diastereomer of interest is shown in Scheme 2). All isomers of **19c** were separated at a later stage (vide infra). Compound **19d** was prepared with the enantiomerically pure cuprate reagent and was isolated diastereo- and enantiomerically pure.

Scheme 4.



Scheme 5.



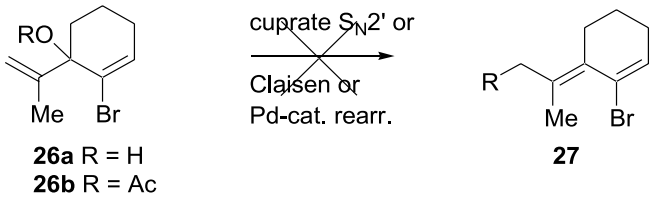
respectively, and **24a** was deprotected under oxidizing conditions to give **25** (Scheme 5).

All synthesized alkenes **19a**–**g** had exclusively the *E*-geometry. This selectivity is attributable to the flatness of the structural system **19** that brings the vinylic hydrogen and the bromine atom in a rigid *syn*-pentane-like relationship (Fig. 3). Any group larger than hydrogen is likely to raise the energy of the system considerably. Basic MM2 calculations placed the *Z*-isomer **B** 5.1 kcal mol^{-1} above the *E*-isomer **A** for R = Me.

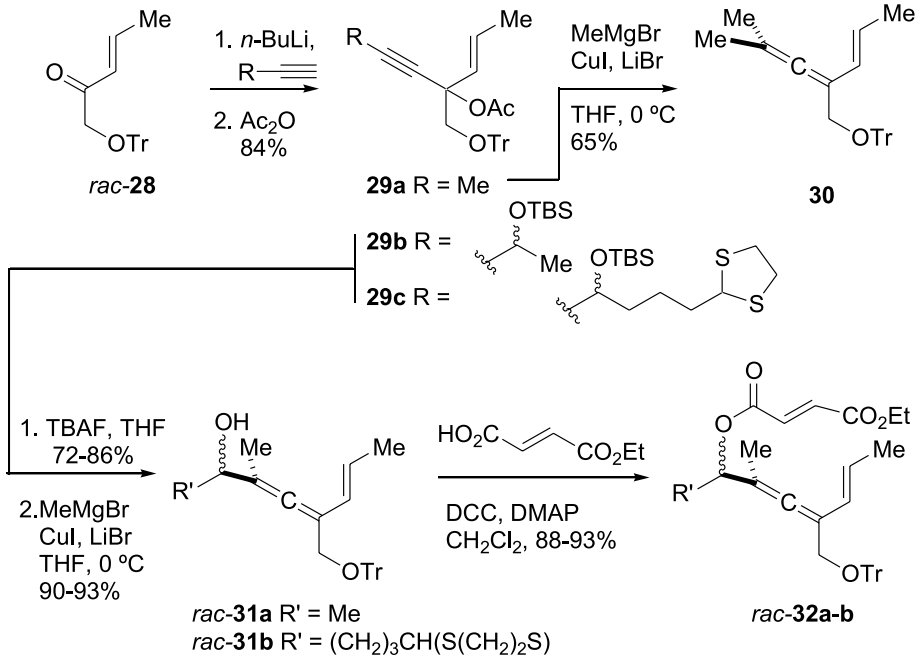
This finding was corroborated by the fact that not a trace of product **27** was formed starting from compound **26a** or **26b** using any of the reactions described in Schemes 2 and 3 under many different reaction conditions (Scheme 6). Most reactions with **26a** and **26b** gave the starting material back or decomposition products under forcing conditions.

Fig. 3. Relative energies of the *E* and *Z* geometries in a structural system like **19**.

Scheme 6.



Scheme 7.



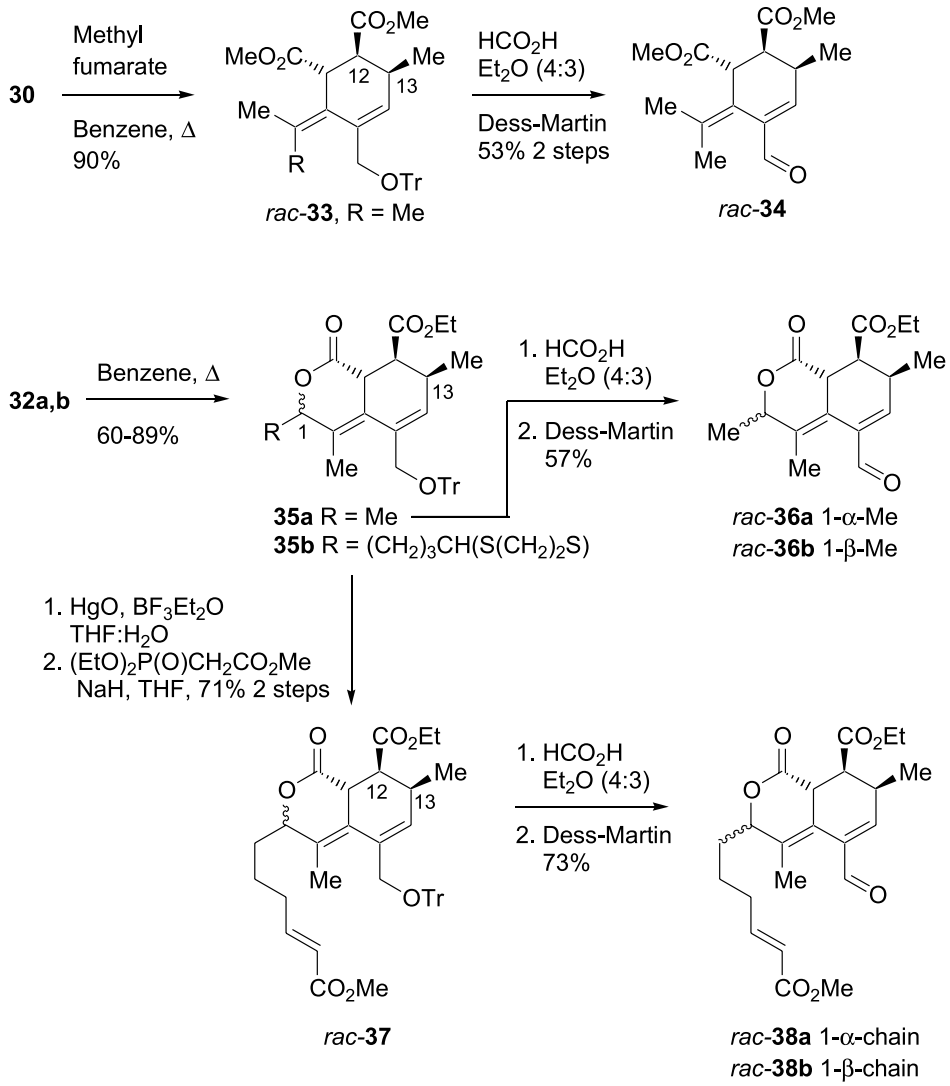
McMurry coupling between **16** and 2-butanone also failed to give any usable yields of an exocyclic alkene (13). The prospect of achieving the stereocontrolled synthesis of this tetra-substituted double bond appeared bleak. A reaction was needed that would simultaneously generate the required cyclohexene and the tetra-substituted, exocyclic double bond.

A solution to the problem of the exocyclic, tetra-substituted double bond was found in the [4 + 2]-cycloaddition of vinylallene **30** and **32a** and **32b**. The syntheses of **30** and **32a** and **32b** starting from α,β-unsaturated ketone **28** are shown in Scheme 7. The addition of methylcuprate to acetate **29a** yielded **30** accompanied with 27% of a product resulting from the addition on the alkene. This side product was difficult to separate at this stage, but it was innocuous because it is an enyne incapable of undergoing a Diels–Alder reaction. Compounds **29b** and **29c** were first treated with fluoride and the resulting alcohols underwent methylcuprate addition to give high yields of vinylallene **31a** and **31b**, respectively, as 1:1 mixtures of two diastereomers. This time, less than 10% of alkene-addition products were formed in each case.

Vinylallene **30** reacted with methyl fumarate at the refluxing temperature of benzene to give a single cycloadduct **33** (Scheme 8). The structure of **33** was secured by a single crystal X-ray diffraction analysis of a later derivative **41** (vide infra). The temperature at which this Diels–Alder reaction occurs is remarkable considering the steric interactions in the final product. In fact, we have reported the synthesis of a series of cycloadducts like **33**, with much larger substituents around the exocyclic double bond and in some cycloadducts, the exocyclic double bond was twisted by more than 20° (14). It can be argued that the Diels–Alder reaction has an early transition state, the structure of which resembles the starting vinylallene where the severe steric interactions of the cycloadduct **33** are not present.

The dienophile always comes from the least-hindered face of the vinylallene in an intermolecular Diels–Alder cycloaddition (12, 15). This would give a cycloadduct with the wrong geometry of the double bond for quassinoid synthesis (as if R were larger than Me in **33**). It was necessary to attach the dienophile to the tether to accomplish the desired synthesis as shown by the conversion of **32a** and **32b** to **35a** and **35b**, respectively. The yields of cycloadducts **35a** and **35b** were good to excellent and the stereochemistry was completely controlled. The stereochemistry of **35a** was deduced by 2D-NOESY spectroscopy and by analogy with the NMR spectra with that of **33**. Note that the enyne side product formed along with **30** and **31a** and **31b** (cf. Scheme 7) are easily removed at this stage. Deprotection of the trityl group in **33** and **35a** and oxidation of the resulting alcohols

Scheme 8.



afforded the required aldehydes **34** and **36** respectively (Scheme 8). The tether in cycloadduct **35b**, was elaborated to enoate-aldehyde **38**, in preparation for the intramolecular Diels–Alder reaction. The deprotection of **35a** and **37** yielded separable diastereomeric alcohols. The subsequent reactions were performed on each isomer separately.

Hetero Diels–Alder cycloaddition

With the problem of the exocyclic double bond solved, efforts were directed at the investigation of the hetero Diels–Alder reaction for the construction of bicyclic adducts. A series of cycloadditions was performed on model compounds **20** and **24**, bearing oxygen or carbon substituents at C-12 and (or) C-13 (Scheme 9). Most quassinoids possess a carbon at C-13 (either methyl or carboxy ester) and an oxygen atom at C-12. The C-13 position is also often linked to an oxygen atom (cf. Fig. 1). Contrary to oxadienes **20a**–**f**, oxadienes **24a** and **24b** and **25** (cf. Scheme 4) bear a tethered dienophile capable of undergoing an intramolecular Diels–Alder immediately after the hetero Diels–Alder. In these cases, the intermediates **40a**–**c** are in fact not isolated (except for 13β,14β-**40c**) and their stereochemistry were therefore deduced from the stereochemistry of the corresponding final tetracycle adducts **48**–**52** (vide infra). The tether in racemic oxadienes **24a** and **25** contains a chiral center that creates up to four possible diastereomers for each of **40a** and **40c**, respectively. Oxadiene **24b** is homochiral, however, and there are only two possible diastereomers for **40b** (Scheme 9). Table 1 displays the results of the intermolecular hetero Diels–Alder cycloadditions of ethylvinyl ether with **20a**, **20b**, **20e**, **20f**, and **24a** and **24b**, and **25** catalyzed by $Yb(FOD)_3$. Only the ratios of 14β- to 14α-diastereomers are important to the discussion at this stage.

From earlier studies, we knew that a single carbon substituent R^1 was enough to differentiate between the two faces of the oxadiene (Table 1, entry 3) (5*a*). However, an alcohol or a protected hydroxyl offers little bias for the incoming dienophile, giving nearly equal mixtures of 14β and 14α adducts (entries 2, 5–7). A bulky protecting group is β-face selective (entry 1), presumably because of a preferred conformation **20-A** where the protecting group is eclipsed with the carbinol hydrogen at C-13, placing the bulky phenyl rings underneath the oxadiene as drawn in Fig. 4. It seems

Scheme 9.

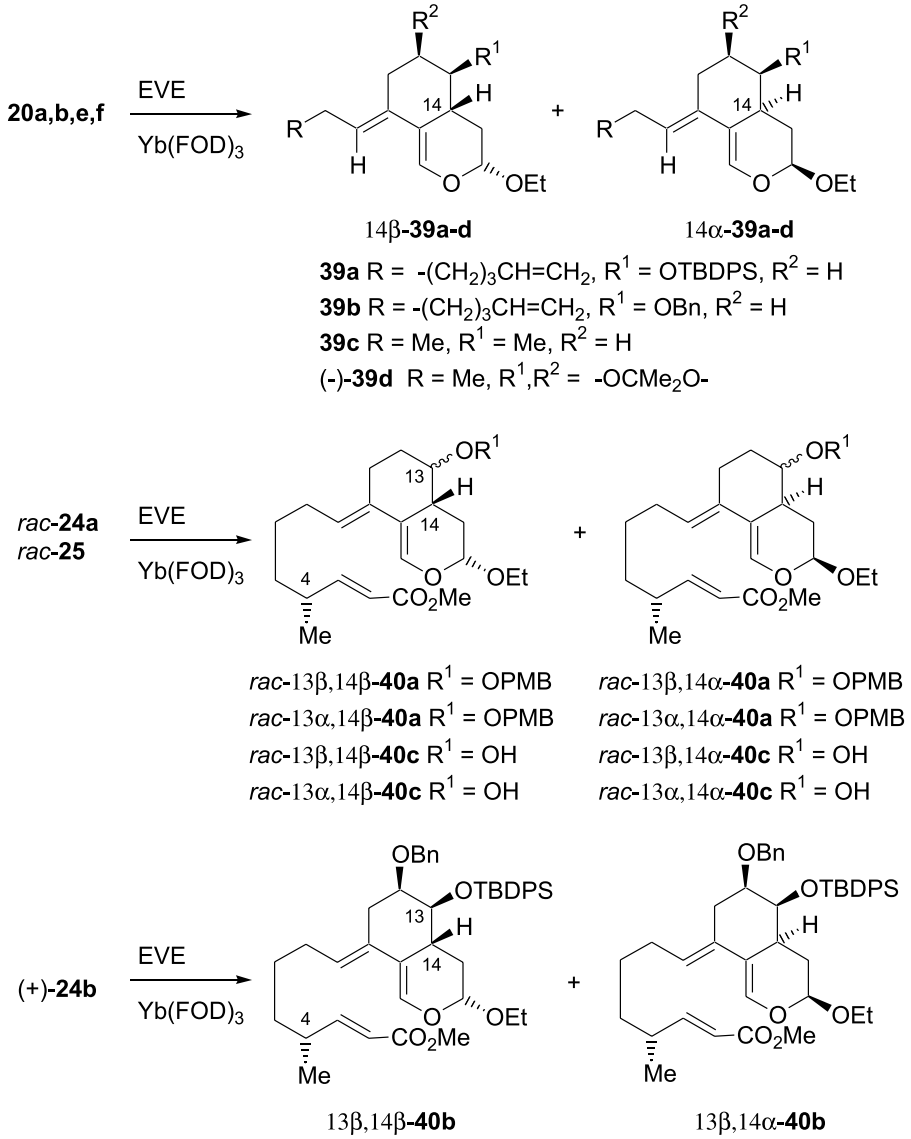


Table 1. 14α/14β-Ratio of adducts **39a**–**d** and **40a**–**c** from the hetero Diels–Alder reaction (cf. Scheme 9).

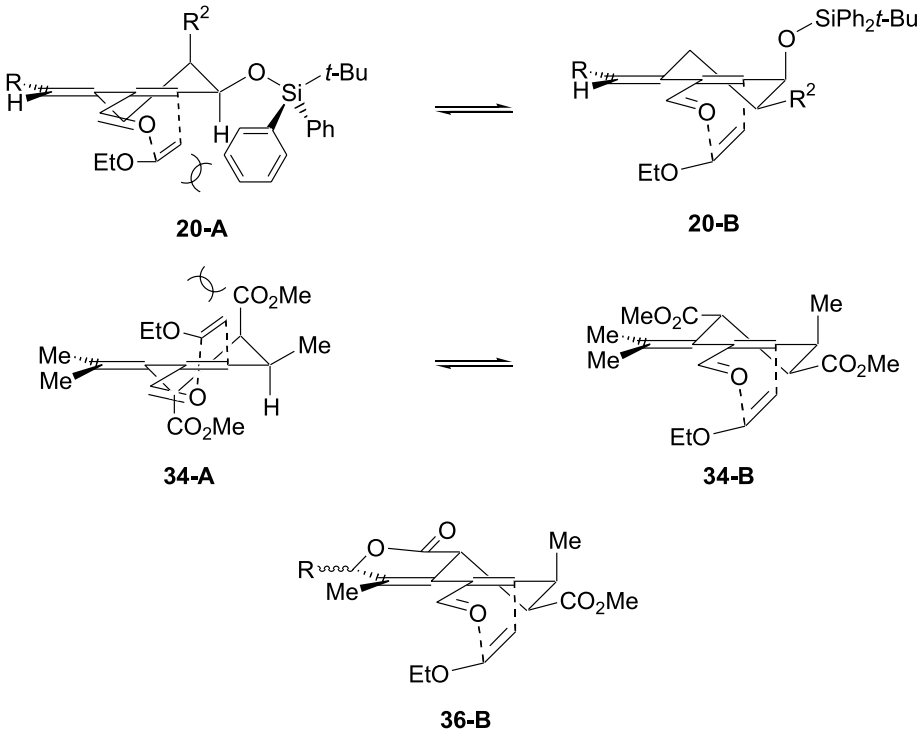
Entry	Enal	Product	14β:14α[a]	Yield (%)
1	**20a**	**39a**	1:4	96
2	**20b**	**39b**	1:1.6	82
3	**20e**	**39c**	4:1	96
4	**20f**	**39d**	11:1	95
5	**24a**	**40a**	1:1	92
6	**24b**	**40b**	1:3	82
7	**25**	**40c**	1:1	83

[a]Determined by ^{1}H NMR.

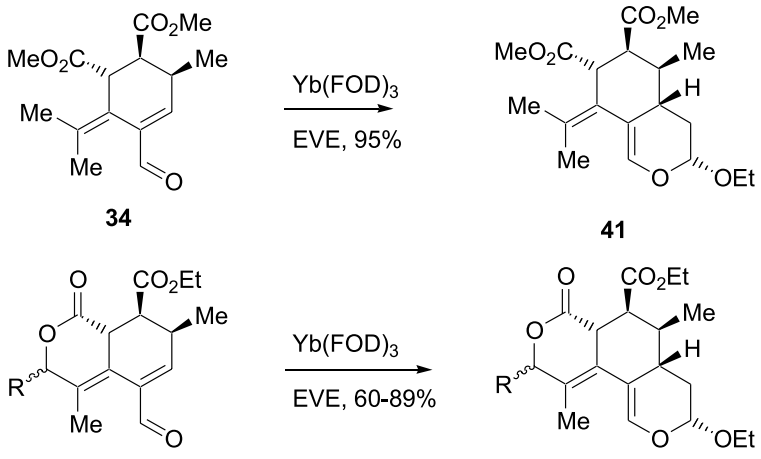
obvious that if conformation **20**-**B** were preferred, it would effectively shield the β-face of the oxadiene. To obtain better results, the oxadiene must be induced to adopt the conformation **20**-**B** or force the C-13 substituent to orient its atoms away from the α-face. The latter case is exemplified by the isopropylidene-protected C-12/C-13 diol **20f** that was able to hinder sufficiently the β-face of the oxadiene (entry 4) (5*a*). In contrast, protected diol **24b** gave a 3:1 ratio favoring the undesired 13β,14α-**40b** diastereomer (entry 6). Again, the *tert*-butyldiphenylsilyl group is likely responsible for this result, shielding the α-face through a preferred conformation **20**-**A** (R^2 = OBn, Fig. 4).

In contrast to the results obtained in the hetero Diels–Alder cycloadditions of oxadienes **20a**, **20b**, **20e**, **20f**, **24a** and **24b**, and **25**, results obtained with compounds **34**, **36a** and **36b**, and **38a** and **38b** are particularly helpful (Scheme 10). The cycloadditions of **34**, **36a**, **36b**, **38a**, and **38b** gave only one detectable isomer **41**, **42a**, **42b**, **43a**, and **43b**, respectively. The stereochemistry of **41** was secured from a single crystal X-ray diffraction analysis. Compounds **42a** and **42b** and **43a** and **43b** were characterized by 2D-NMR experiments and their NMR spectra compared well with that of **41**. Most likely, the oxadienes take on conformations **34**-**B** or **36**-**B**, forcing the methyl group into a pseudo-axial orientation (Fig. 4).

Fig. 4. Possible transition states for the intermolecular hetero Diels–Alder reaction of **20a**, **34**, **36**, and **38**.



Scheme 10.



36a R = α-Me
36b R = β-Me
38a R = α-$(CH_2)_3CH{=}CHCO_2Me$
38b R = β-$(CH_2)_3CH{=}CHCO_2Me$

42a R = α-Me
42b R = β-Me
43a R = α-$(CH_2)_3CH{=}CHCO_2Me$
43b R = β-$(CH_2)_3CH{=}CHCO_2Me$

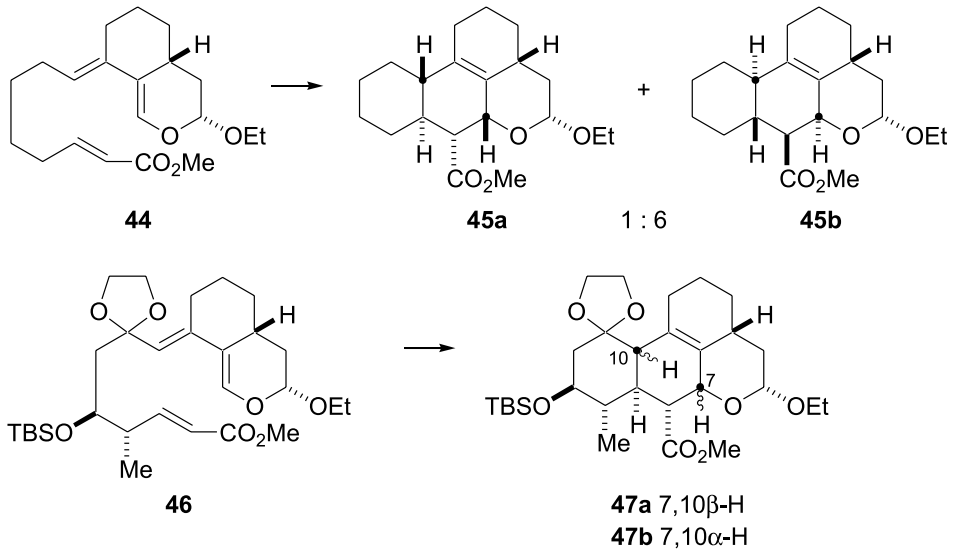
Intramolecular Diels–Alder cycloaddition

The substituents on ring C and D and the substituents on the tether are able to affect the stereochemical outcome of the intramolecular Diels–Alder cycloaddition. This concern had to be addressed first and two things were known from earlier studies (5*a*): (*a*) in absence of substituent on the tether and on the ring (**44**), the β-*endo* TS (cf. Fig. 1) is favored by a factor of six leading to the formation of **45b** as the major product (Scheme 11); (*b*) two tether substituents in **46** are able to completely reverse this selectivity in favor of the desired α-*endo* TS (**47a**, Scheme 11). However, it was also evident that an α-C-3 substituent (the α-oxygen of the dioxolane in **47a**) should be avoided as it increases the energy of both α- and β-*endo* TS to the advantage of the α-*exo* TS leading to the formation of **47b**.

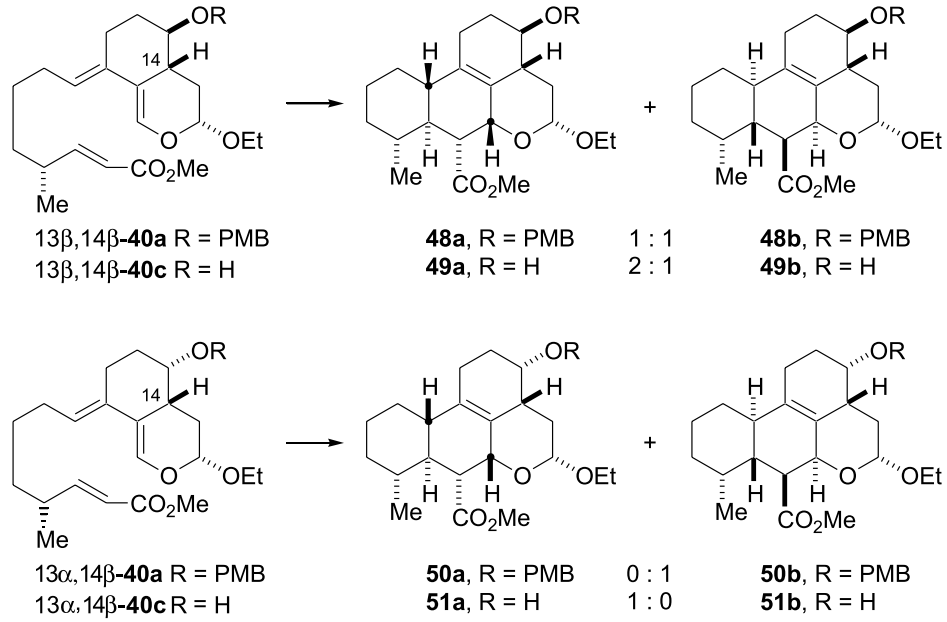
Intramolecular Diels–Alder cycloaddition: Results

Since intermediates 13β,14β–**40a**, **40b**, **40c** and 13α,14β–**40a**, **40c** were not isolated, their structures were deduced

Scheme 11.



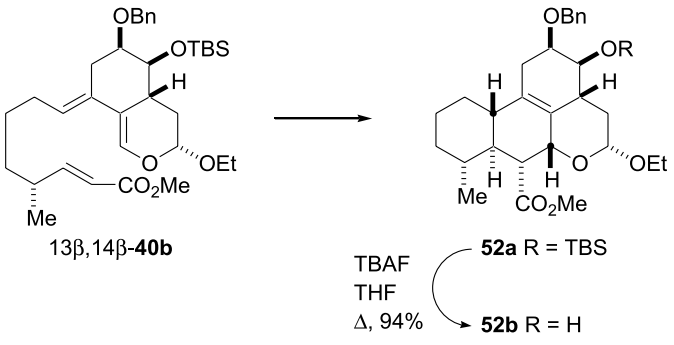
Scheme 12.



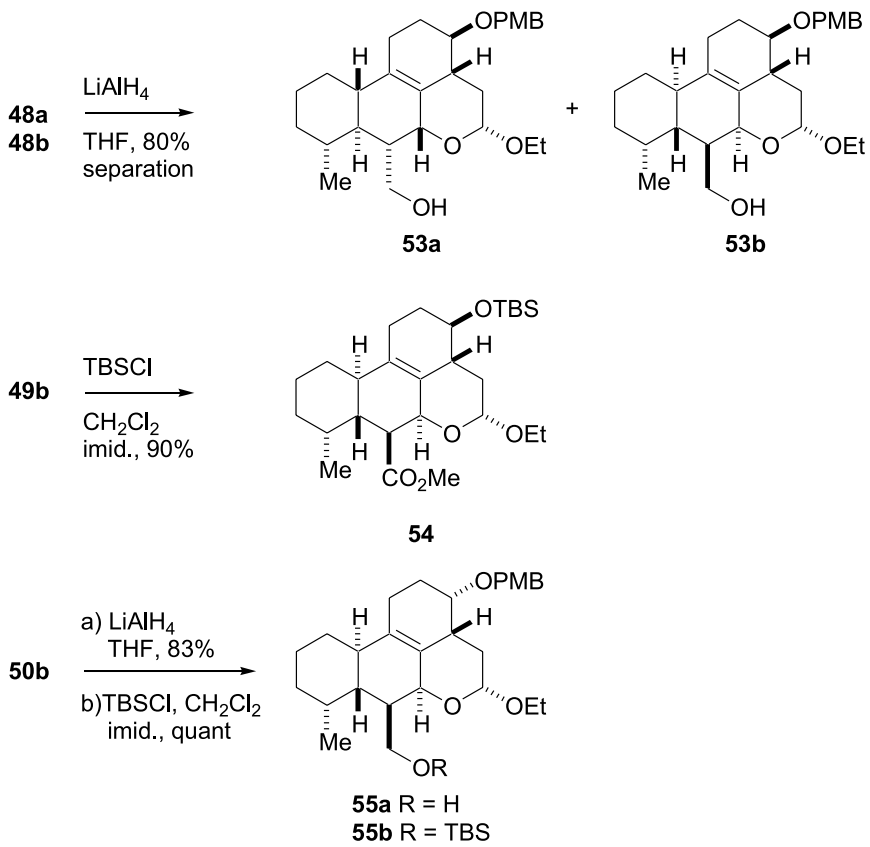
from those of the corresponding tetracycles **48**–**52** (Schemes 12 and 13). Note that intermediates 13β,14α–**40a**, **40b**, **40c** and 13α,14α–**40a**, **40c** (cf. Scheme 9) are of no interest for quassinoids because they possess the wrong 14-α stereochemistry. Although their corresponding tetracycles were isolated and fully characterized, they will not be discussed further.

Aldehyde **24a** (racemic mixture of diastereomers) gave a mixture of cycloadducts, of which **48a**, **48b**, and **50b** could be obtained partially pure (Scheme 12). Each cycloadduct was treated with $LiAlH_4$ and separation of the resulting alcohols yielded pure **53a**, **53b**, and **55a**, respectively, (Scheme 14). The structure of **53a** was deduced from a single crystal X-ray diffraction analysis, which secured the structure of **48a**. The structure of **48b** was correlated with

Scheme 13.



Scheme 14.



that of **49b** (vide infra) because the structure of **53b** could not be determined unambiguously. The primary alcohol in compound **55a** was silylated under standard conditions to give **55b**, for which an X-ray analysis was obtained, confirming the structure for **50b**. With the structures secured, we were able to determined the ratios of tetracycles in the crude mixture of **48** and **50**. Tetracycles **48a** and **48b** were found in a 1:1 ratio while compound **50b** was the sole tetracycle to emanate from intermediate 13α,14β-**40a**. All of **48a**, **48b**, and **50b** possess the desired 14β-stereochemistry. However, **48b** and **50b** have the wrong configuration at C-5, C-7, and C-10. As explained later, the OPMB group is responsible for the formation of these two diastereomers.

Aldehyde **24b** (diastereo- and enantiomerically pure) gave two tetracycles that were desilylated to separate them more easily. Compound **52a** was the sole product having the 14β-stereochemistry and thus to arise from intermediate 13β,14β–**40b** (Scheme 13). The other tetracycle had the 14-α stereochemistry and must have come from intermediate 13β,14α–**40b**. The stereochemistry of **52b** was determined from careful NMR and 2D-NMR analysis of both tetracycles.

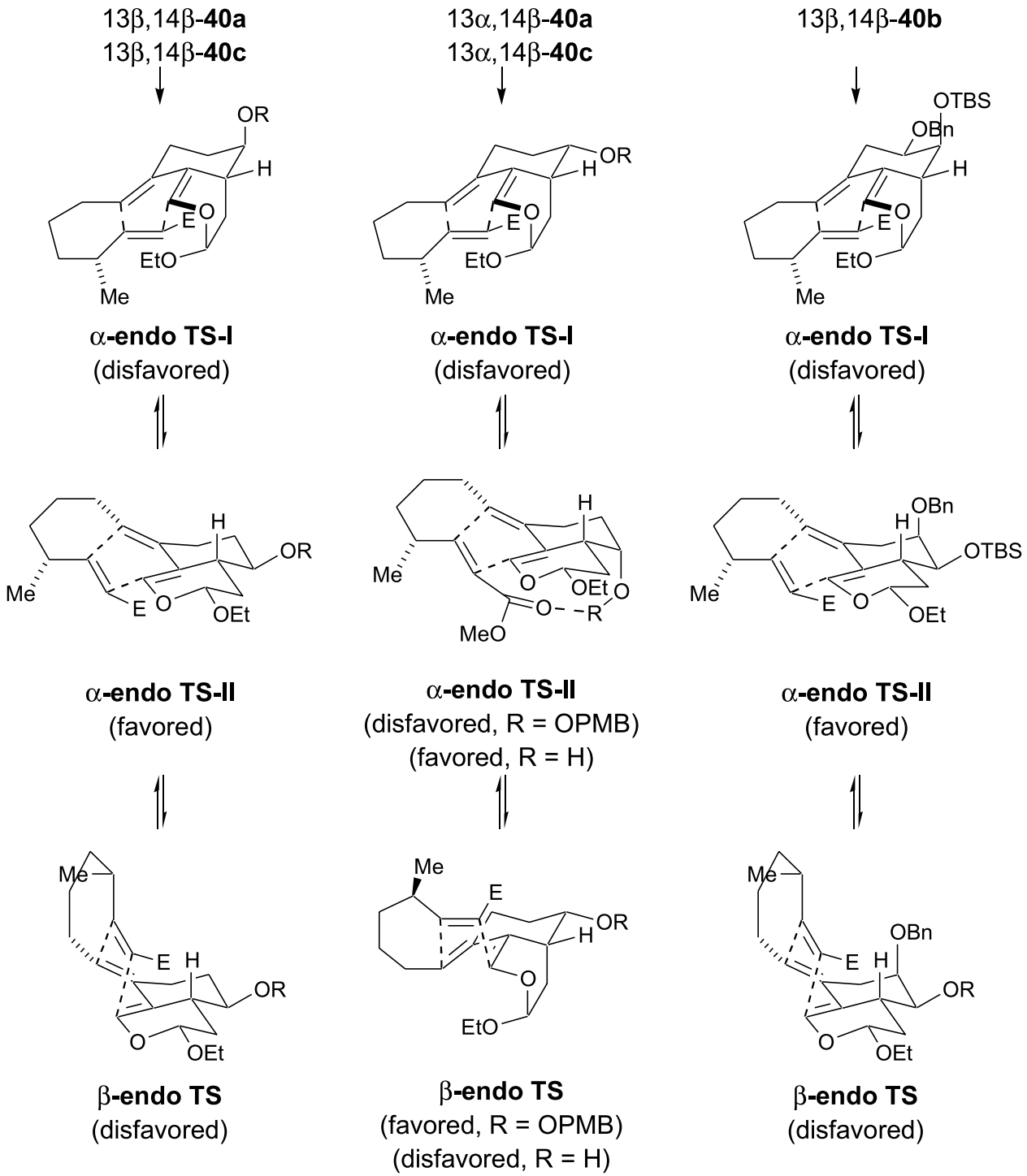
Lastly, aldehyde **25** led to a mixture of cycloadducts, of which **49a**, **49b**, and **51a** were separated and isolated in a pure state (Scheme 12). The stereochemistry of **51a** was deduced from a single crystal X-ray diffraction analysis. Cycloadduct **49b** was silylated to afford **54** that was crystalline and amenable to X-ray diffraction analysis (Scheme 14). Conversion of **49b** to **48b** confirmed the structure of the latter. The now known product **48a** was converted to **49a** using DDQ, which proved the structure of **49a**. With the structure of each cycloadduct secured, it was established that **49a** and **49b** were formed in a 2:1 ratio and arose from the intramolecular Diel–Alder reaction of intermediate 13β,14β-**40c** (Scheme 12). Cycloadduct **51a** was the sole tetracycle to emanate from intermediate 13α,14β-**40c**. All three diastereomers **49a**, **49b**, and **51a** have the desired 14β-stereochemistry and only **49b**, the minor isomer from 13β,14 β-**40c**, has the wrong stereochemistry at C-5, C-7, and C-10. Therefore, removing the PMB group on the C-13 alcohol proved beneficial.

Intramolecular Diels–Alder cycloaddition: Analysis

It was clear, from the cycloaddition of **44**, that a 14β-stereochemistry favors a β-face attack of the dienophile (5*a*). Fortunately, this trend was partly overcome by the presence of a single methyl group on the tether at C-4 as shown in the conversion of 13β,14β-**40c** into a 2:1 mixture of **49a** and **49b** (Scheme 12). With a protected alcohol (13β,14β-**40a**) the ratio **48a**:**48b** was 1:1. It was particularly informative to observe the cycloaddition results with alcohol 13α,14β-**40c** and PMB-protected alcohol 13α,14β-**40a**. The free alcohol 13α,14β-**40c** gave a single isomer **51a** arising from an α-endo transition state (Scheme 12). By contrast, the protected alcohol 13α,14β-**40a** underwent the IMDAC to give a single adduct **50b** that emerged from a preferred β-*endo* transition state having the methyl axial.

These results are explained as follows (Fig. 5): two α-*endo* TS can be considered, namely α-*endo* TS-I and α-*endo*

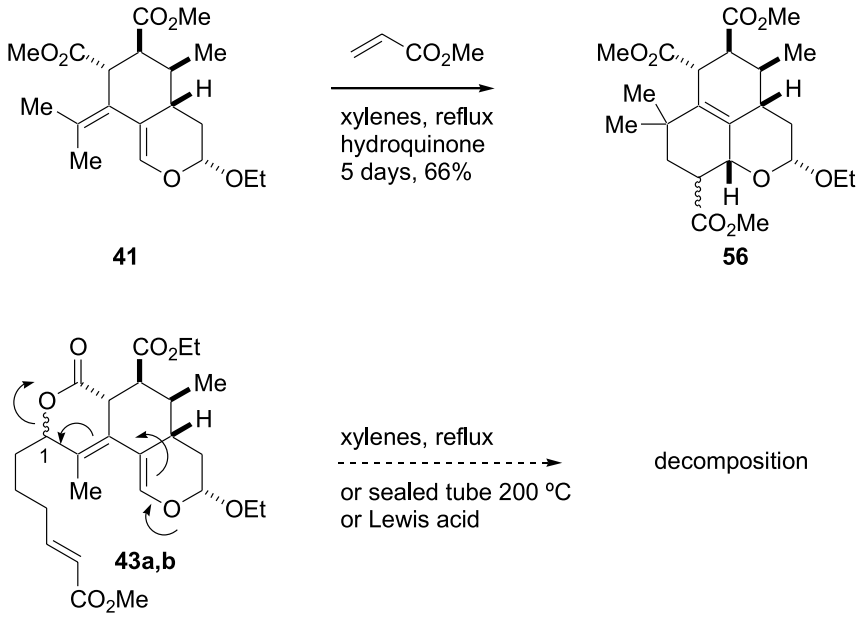
Fig. 5. Possible transition states for the intramolecular DAC of **40a–c**.



TS-II. All α-*endo* TS-Is have the ethoxy group and the dienophile in close proximity resulting in a steric interaction. It is doubtful that any α-attack would take place via α-*endo* TS-I. This is corroborated by MM2 calculations. Therefore, only the α-*endo* TS-IIs will be considered in our analysis and their energies will be compared with that of the β-*endo* TSs.

In the absence of substituents on the ring or on the chain, β-endo TS is favored over α-*endo* TS-II by approximately 2 kcal mol^{-1} (cf. **44** → **45b**, Scheme 11). An α-C-4 methyl group will be axial on a β-endo TS and should destabilize it by roughly 2 kcal mol^{-1}, approximately counterbalancing the advantage β-*endo* TS enjoys when there are no substituents. This is what was observed, 13β,14β-**40a** and 13β,14β-**40c** giving nearly equal mixtures of adducts regardless of the C-13 β-substituent. The slight difference between the ratios of 13β,14β-**40a** and 13β,14β-**40c** may be attributable to small conformational perturbations. However, an α-protected

Scheme 15.



alcohol at C-13 (13α,14β-**40a**) dramatically raises the energy of the corresponding α-endo TS-II (or alternatively, it could force a high-energy conformation like α-endo TS-I). This explains why compound 13α,14β-**40a** gave a single tetracycle **50b** via a β-endo TS. The fact that 13α,14β-**40c** gave only **51a** can only be explained by a hydrogen bond in α-endo TS-II. As a matter of fact, the cycloaddition of alcohol 13β,14β-**40c** was slower than that of alcohol 13α,14β-**40c**, the former requiring benzene at reflux to go to completion while the latter occurs rapidly at room temperature. This is consistent with a hydrogen bond activating the ester in β-endo TS for 13α,14β-**40c**.

If our analysis is correct, two β-substituents at C-12 and C-13 (as in 13β,14β-**40b**) should come together to lead to a single tetracycle resulting from α-*endo* TS-II. Indeed, regardless of the conformation of the C-ring, one of the substituents at C-12 or C-13 has to be pseudoaxial, thereby significantly raising the energy of the β-*endo* TS due to steric interaction with the incoming dienophile (Fig. 5, right). Comparatively, the energy of the α-*endo* TS-II should not be raised as much. We were pleased to find that diene 13 β,14β-**40b** gave a single tetracycle **52a**, thereby confirming our hypothesis (Scheme 13).

There is now a good indication that a single stereodefined substituent on the tether and two β-substituents at C-12 and C-13 will force the intramolecular Diels–Alder to take place through an α-*endo* TS. Adding a methyl group on the exocyclic double bond should not change anything. However, it became clear in preliminary studies that such a methyl substituent considerably slows down the rate of cycloaddition. For example, compound **41** underwent a clean Diels–Alder cycloaddition reaction at the refluxing temperature of xylenes for 5 days to give **56** as a mixture of two stereoisomers (Scheme 15, ratios and stereochemistry of **56** not determined). While this result indicated that the Diels–Alder is definitely possible, trials with **43a** or **43b** always gave decomposition products because it could not withstand such harsh conditions. The use of Lewis acids also led to decomposition products only. We have established that the main reason for the decomposition of **43a** and **43b** is the lability of the C-1 oxygen functionality as shown in Scheme 15. We are working to build different models in the hopes of overcoming this obstacle. Those results will be reported in due course.

Experimental section

All reactions were carried out under an argon atmosphere. Ethyl ether, toluene, and benzene were dried over metallic sodium using benzophenone as an indicator, while tetrahydrofuran was dried over both sodium and potassium using the same indicator. Dichloromethane, dimethyl formamide, carbon tetrachloride, 1,2-dichloroethane, triethylamine, pyridine, acetonitrile, and diisopropylamine were distilled over calcium hydride. Hexanes were purchased in anhydrous form from Aldrich. Ethyl vinyl ether was distilled prior to use. Cerium trichloride was purchased in hydrated form and dried at 200°C under high vacuum overnight. Thin layer chromatography was performed using 0.25 mm Silica Gel 60 F254 (EM Science-Merck) and flash chromatography using silica gel Kieselgel 60 (230–400 mesh ASTM).

All NMR spectra were taken in deuterated chloroform on a Brüker AC-300 (^{1}H (300 MHz), ^{13}C (75 MHz)). Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. The splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and AB quartet (ABq). The IR spectra were determined on a Perkin-Elmer 1600 FT spectrometer. The IR spectra were determined neat, unless otherwise stated. The melting points were performed on a Mettler Toledo model 62. High- and low-resolution mass spectra (HR-MS and LR-MS) were obtained with a micromass spectrometer ZAB-1F model VG.

tert-Butyldiphenylsilyl ether 11a

To a cooled 0°C solution of cyclohexanedione, monoethylene ketal (22.1 g, 141 mmol) and methanol was added, in portions, sodium borohydride (5.35 g, 141 mmol). The reaction was stirred for 3 h before being brought to pH 7 by the addition of 1 N HCl. The mixture was partitioned between dichloromethane and brine, and the aqueous phase extracted with CH_2Cl_2. The aqueous layer was concentrated until a precipitate began to form and this layer was extracted again with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude alcohol (22.69 g, 100%) was coevaporated with benzene and used without further purification. ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 4H), 3.67–3.66 (m, 1H), 2.67 (bs, 1H), 1.80–1.68 (m, 4H), 1.61–1.43 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 108.2 (s), 67.7 (d), 64.0 (t), 31.7 (t), 31.4 (t). LR-MS (*m/z* (relative intensity)): 158 ([M]$^+$, 10), 99 (100). HR-MS calcd. for $C_8H_{14}O_3$: 158.0943; found: 158.0937. To a solution of this alcohol (5.00 g, 31.6 mmol), imidazole (5.38 g, 79.0 mmol) in DMF (20 mL) was added TBDPSCl (9.86 mL, 37.9 mmol) at room temperature. The mixture was stirred at room temperature for 4 h before being poured into hexane (30 mL). The layers were separated and the DMF layer washed with hexanes (2 × 30 mL) and ethyl ether (30 mL). The combined hexanes – ethyl ether layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography eluted with hexanes:EtOAc (9:1) to give 12.5 g (100%) of ketal **11a** as a colourless oil. IR (cm^{-1}): 3446, 3070, 1589, 1472, 1427. ^{1}H NMR ($CDCl_3$) δ: 7.73–7.65 (m, 4H), 7.45–7.34 (m, 6H), 3.98–3.85 (m, 5H), 1.97–1.88 (m, 2H), 1.71–1.63 (m, 4H), 1.51–1.43 (m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 135.7 (d), 134.8 (d), 134.5 (s), 129.5 (d), 127.6 (d), 127.4 (d), 108.6 (s), 68.4 (d), 64.1 (t), 31.7 (t), 30.8 (t), 26.9 (q), 19.2 (s). LR-MS (*m/z* (relative intensity)): 339 ([M$^+$ – C_4H_9], 10), 199 (100), 200 (25). HR-MS calcd. for $C_{20}H_{23}O_3Si$: 339.1416; found: 339.1412. Anal. calcd. for $C_{24}H_{32}O_3Si$: C 72.68, H 8.13, O 12.10, Si 7.08; found: C 72.53, H 8.18, O 11.98.

Benzyl ether 11b

To an oil-free suspension of KH (10.19 g, 254 mmol) in THF (400 mL) was added a solution of the same alcohol used to make **11a** (16.4 g, 102 mmol) in THF (50 mL) via cannula at 0°C. After hydrogen evolution had ceased, the mixture was warmed to room temperature and the reaction stirred for 3 h. Benzyl bromide (18.1 mL, 152 mmol) was added neat and the reaction stirred overnight. The reaction was quenched with satd. aq NH_4Cl, and the product extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes:EtOAc (9:1 to 3:1)) yielded 20.8 g (83%) of ketal **11b** as a colourless oil. IR (cm^{-1}): 3030, 2949, 1370. ^{1}H NMR ($CDCl_3$) δ: 7.34–7.26 (m, 5H), 4.53 (s, 2H), 3.94–3.92 (m, 4H), 3.56–3.50 (m, 1H), 1.89–1.79 (m, 6H), 1.58–1.53 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 128.2 (d), 127.3 (d), 108.4 (s), 74.0 (d), 69.8 (t), 64.2 (t), 31.2 (t), 28.5 (t). LR-MS (*m/z* (relative intensity)): 248 ([M]$^+$, 5), 99 (100), 86 (98). HR-MS calcd. for $C_{15}H_{20}O_3$: 248.1412; found: 248.1408. Anal. calcd. for $C_{15}H_{20}O_3$: C 72.55, H 8.12, O 19.33; found: C 72.51, H 8.23.

PMB ether 11c

To an oil-free suspension of KH (3.04 g, 75.8 mmol) in THF (200 mL) was added a solution of the same alcohol used to make **11a** (10.0 g, 63.2 mmol) in THF (70 mL) via cannula at 0°C. After hydrogen evolution had ceased (1 h), a solution of PMBCl (10.4 g, 66.4 mmol) and THF (30 mL) was added via cannula. The ice bath was removed and the reaction stirred overnight. The reaction was quenched with satd. aq NH_4Cl, and the product extracted with ether (3 × 80 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes:EtOAc (3:1 to 1:1)) yielded 16.9 g (96%) of ketal **11c** as a clear oil. IR (cm^{-1}): 2943, 1611, 1513. ^{1}H NMR ($CDCl_3$) δ: 7.26 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 4.45 (s, 2H), 3.92 (s, 4H), 3.78 (s, 3H), 3.52–3.47 (m, 1H), 1.86–1.75 (m, 6H), 1.56–1.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ: 158.9 (s), 131.0 (s), 128.8 (d), 113.6 (d), 108.4 (s), 73.7 (d), 69.4 (t), 64.2 (t), 55.1 (q), 31.2 (t), 28.5 (t). LR-MS (*m/z* (relative intensity)): 278 ([M]$^+$, 10), 86 (100), 121 (90), 99 (90), 142 (65). HR-MS calcd. for $C_{16}H_{22}O_4$: 278.1518; found: 278.1515. Anal. calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97, O 22.99; found: C 69.05, H 7.95.

Ketone 12a

A mixture of ketal **11a** (12.5 g, 31.6 mmol), THF (226 mL), and 1 N HCl (75 mL) was heated to reflux for 3 h. The mixture was cooled, neutralized by the addition of satd. aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was crystallized by the addition of petroleum ether. Three crystallizations yielded 10.8 g (97%) of ketone **12a** as a white solid; mp: 106.0°C. IR (cm^{-1}): 3069, 1716, 1427. ^{1}H NMR ($CDCl_3$) δ: 7.69–7.67 (m, 4H), 7.45–7.36 (m, 6H), 4.16–4.13 (m, 1H, *J* = 2.6 Hz), 2.79–2.69 (m, 2H), 2.25–2.17 (dt, 2H, *J* = 14.4, 5.3 Hz), 1.99–1.93 (m, 2H), 1.83–1.78 (m, 2H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 211.5 (s), 135.6 (d), 133.8 (s), 129.7 (d), 127.6 (d), 66.9 (d), 36.9 (t), 33.7 (t), 26.9 (q), 19.2 (s). LR-MS (*m/z* (relative intensity)): 295 ([M$^+$ – C_4H_9], 92), 199 (100). HR-MS calcd. for $C_{18}H_{19}O_2Si$: 295.1154; found: 295.1151. Anal. calcd. for $C_{22}H_{28}O_2Si$: C 74.95, H 8.01, O 9.08, Si 7.97; found: C 74.86, H 8.02, O 8.99.

Ketone 12b

Followed the same procedure as per **12a**, starting with ketal **11b** yielding 7.70 g (94%) of ketone **12b** as a colourless oil. IR (cm^{-1}): 3031, 2941, 1716, 1103. ^{1}H NMR ($CDCl_3$) δ: 7.37–7.28 (m, 5H), 4.59 (s, 2H), 3.83–3.79 (m, 1H), 2.67–2.56 (m, 2H), 2.30–2.22 (m, 2H), 2.19–2.09 (m, 2H), 2.00–1.89 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 211.0 (s), 138.4 (s), 128.3 (d), 127.4 (d), 127.3 (d), 72.1 (d), 70.1 (t), 37.1 (t), 30.3 (t). LR-MS (*m/z* (relative intensity)): 204 ([M]$^+$, 7), 91 (100). HR-MS calcd. for $C_{13}H_{16}O_2$: 204.1150; found: 204.1152. Anal. calcd. for $C_{13}H_{16}O_2$: C 76.44, H 7.90, O 15.67; found: C 76.44, H 7.95.

Ketone 12c

A solution of ketal **11c** (15.28 g, 54.9 mmol) and PPTS (4.1 g, 16.5 mmol) in wet acetone (550 mL) was heated to reflux for 5.5 h. The mixture was cooled and the solvent removed in vacuo. The residue was taken up in ethyl ether and washed with satd. aq $NaHCO_3$, and brine, dried over $MgSO_4$. Flash chromatography using a mixture of hexanes:EtOAc (3:1 to 1:1) procured 11.89 g (92%) of ketone **12c** as a white solid; mp: 34.9°C. IR ($CHCl_3$, cm^{-1}): 3011, 1708, 1612, 1513. ^1H NMR ($CDCl_3$) δ: 7.29 (d, 2H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.6 Hz), 4.53 (s, 2H), 3.81 (s, 3H), 3.82–3.78 (m, 1H), 2.67–2.56 (m, 2H), 2.31–2.22 (m, 2H), 2.17–2.10 (m, 2H), 2.00–1.91 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 211.2 (s), 159.0 (s), 130.4 (s), 128.9 (d), 113.7 (d), 71.8 (d), 69.8 (t), 55.1 (q), 37.1 (t), 30.4 (t). LR-MS (*m/z* (relative intensity)): 234 ($[M]^+$, 35), 121 (100). HR-MS calcd. for $C_{14}H_{18}O_3$: 234.1256; found: 234.1259. Anal. calcd. for $C_{14}H_{18}O_3$: C 71.77, H 7.74, O 20.49; found: C 71.82, H 7.88.

Lactone 14

To a stirred solution of known diol **13** (8.05 g, 30.4 mmol), imidazole (10.3 g, 152.0 mmol), DMAP (750 mg, 6.08 mmol), and dichloromethane (300 mL) was added TBDPSCl (7.9 mL, 30.4 mmol) at room temperature. The reaction was stirred for 7 days before being partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography eluted with hexanes:EtOAc (9:1 to 6:1 to 1:1) yielded 12.0 g (78%) of silyl ether **14** and 1.82 g (22%) of starting diol **13**, resulting in a corrected overall yield of 100%. $[\alpha]_D$: –48.4° (*c* 1.59, $CHCl_3$). IR (cm^{-1}): 3439, 3069, 1794, 1427. ^1H NMR ($CDCl_3$) δ: 7.73–7.59 (m, 4H), 7.44–7.23 (m, 9H), 7.07–7.04 (m, 2H), 4.40 (t, 1H, J = 5.4 Hz), 4.27–4.21 (m, 3H), 3.48–3.41 (m, 1H), 2.84 (d, 1H, J = 11.3 Hz), 2.66 (s, 1H), 2.31–2.13 (m, 3H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 177.8 (s), 137.5 (s), 136.0 (d), 135.6 (d), 133.2 (s), 132.4 (s), 129.9 (d), 129.6 (d), 128.0 (d), 127.6 (d), 127.3 (d), 76.1 (d), 73.3 (d), 72.3 (s), 70.7 (t), 65.8 (d), 36.8 (t), 36.5 (t), 26.8 (q), 19.2 (s). LR-MS (*m/z* (relative intensity)): 445 ($[M^+ - C_4H_9]$, 20), 353 (65), 91 (90), 277 (100). HR-MS calcd. for $C_{26}H_{25}O_5Si$: 445.1471; found: 445.1465. Anal. calcd. for $C_{30}H_{34}O_5Si$: C 71.68, H 6.82, O 15.91, Si 5.59; found: C 71.64, H 6.84, O 16.01.

Enone 15a

To a solution of ketone **12a** (10.59 g, 30.0 mmol) and $PhSO_2Me$ (4.70 g, 30.0 mmol) in THF (70 mL) was added an oil-free suspension of KH (3.01 g, 75.2 mmol) in THF (60 mL) via cannula at room temperature. The mixture was stirred at room temperature for 30 min before being concentrated to dryness. The residue was partitioned between dichloromethane (100 mL) and 0.5 M aq H_3PO_4 (50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 70 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was taken up in toluene (300 mL) and Na_2CO_3 (15.9 g, 150 mmol) was added. The suspension was heated to reflux for 30 min, cooled, filtered through Celite, and concentrated. Purification by flash chromatography using hexanes:EtOAc (20:1 to 9:1) gave 9.80 g (93%) of enone **15a** as a clear liquid. IR (cm^{-1}): 3056, 1824, 1684, 1472. ^1H NMR ($CDCl_3$) δ: 7.72–7.67 (m, 4H), 7.48–7.38 (m, 6H), 6.78 (dd, 1H, J = 10.2, 2.5 Hz), 5.86 (d, 1H, J = 10.2 Hz), 4.52–4.47 (m, 1H), 2.52 (dt, 1H, J = 16.4, 4.5 Hz), 2.25–2.17 (m, 1H), 2.15–2.03 (m, 2H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 198.8 (s), 153.1 (d), 135.7 (d), 133.3 (s), 129.9 (d), 129.5 (d), 128.7 (d), 127.7 (d), 67.5 (d), 35.2 (t), 32.5 (t), 26.8 (q), 19.0 (s). LR-MS (*m/z* (relative intensity)): 293 ($[M^+ - C_4H_9]$, 65), 199 (100). HR-MS calcd. for $C_{18}H_{17}O_2Si$: 293.0998; found: 293.0996. Anal. calcd. for $C_{22}H_{26}O_2Si$: C 75.38, H 7.48, O 9.13, Si 8.01; found: C 75.44, H 7.40, O 9.11.

Enone 15b

Following the procedure outlined for enone **15a**, enone **15b** was prepared starting from ketone **12b**. The yield of enone **15b** was 3.18 g (70%) isolated as a colourless oil. IR (cm^{-1}): 3031, 2954, 2870, 1693, 1454, 1201, 1093. ^1H NMR ($CDCl_3$) δ: 7.38 (m, 5H), 7.00–6.96 (m, 1H, J = 10.4 Hz), 5.99 (dt, 1H, J = 10.6, 1.2 Hz), 4.29–4.23 (m, 1H), 2.65–2.56 (m, 1H), 2.39–2.27 (m, 2H), 2.11–1.98 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 198.6 (s), 150.4 (d), 137.7 (s), 129.6 (d), 128.4 (d), 127.8 (d), 127.6 (d), 127.3 (d), 72.4 (d), 70.9 (t), 35.2 (t), 29.1 (t). LR-MS (*m/z* (relative intensity)): 203 ([M + 1], 48), 220 ([M + NH_4], 38), 91 (100). HR-MS calcd. for $C_{13}H_{15}O_2$: 203.1072; found: 203.1077. Anal. calcd. for $C_{13}H_{14}O_2$: C 77.20, H 6.98, O 15.82; found: C 77.12, H 7.05.

Enone 15c

Followed the same procedure as per **15a** yielding 7.80 g (82%) of enone **15c** as a colourless oil. IR (cm^{-1}): 2999, 2955, 2836, 1681, 1613, 1514, 1249, 1087. ^1H NMR ($CDCl_3$) δ: 7.29 (d, 2H, J = 8.6 Hz), 6.96 (d, 1H, J = 10.3 Hz), 6.90 (d, 2H, J = 8.6 Hz), 5.98 (d, 1H, J = 10.3 Hz), 4.58 (AB quartet, 2H, J = 11.4, 5.9 Hz), 4.27–4.21 (m, 1H), 3.81 (s, 3H), 2.64–2.56 (m, 1H), 2.39–2.29 (m, 2H), 2.09–1.98 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 198.5 (s), 159.2 (s), 150.6 (d), 129.5 (s), 129.3 (d), 129.2 (d), 113.8 (d), 71.9 (d), 70.4 (t), 55.1 (q), 35.1 (t), 28.9 (t). LR-MS (*m/z* (relative intensity)): 232 ($[M]^+$, 40), 122 (60), 121 (100). HR-MS calcd. for $C_{14}H_{16}O_3$: 232.1099; found: 232.1094. Anal. calcd. for $C_{14}H_{16}O_3$: C 72.39, H 6.94, O 20.66; found: C 72.40, H 6.90.

Enone 15d

$NaBH_4$ (499 mg, 13.2 mmol) was added to a 0°C solution of lactone **14b** (6.66 g, 13.2 mmol) and ethyl alcohol (45 mL). The reaction mixture was stirred at 0°C for a total of 2 h before being quenched by the slow addition of aq NH_4Cl. The ice bath was removed and phosphate buffer and water were added, followed by sodium periodate (3.67 g, 17.1 mmol). The reaction mixture was stirred overnight and the resulting suspension filtered through Celite. The alcohol was extracted with dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes:EtOAc, 3:1) yielded 4.67 g (75%) of a keto alcohol as a colourless oil. $[\alpha]_D$: –22.6° (*c* 3.16, $CHCl_3$). IR (cm^{-1}): 3433, 3061, 2930, 2854, 1714, 1471, 1427, 1136, 1112. ^1H NMR ($CDCl_3$) δ: 7.76–7.67 (m,

4H), 7.45–7.18 (m, 11H), 4.42 (d, 1H, *J* = 11.7 Hz), 4.32 (d, 1H, *J* = 11.7 Hz), 4.17–4.15 (m, 1H), 4.08 (dd, 1H, *J* = 6.4, 2.3 Hz), 3.84–3.79 (m, 1H), 2.91–2.81 (m, 2H), 2.48 (dd, 1H, *J* = 14.2, 3.9 Hz), 2.31–2.24 (m, 1H), 1.77 (d, 1H, *J* = 3.1 Hz), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 207.5 (s), 138.0 (s), 136.1 (d), 135.8 (d), 133.6 (s), 132.9 (s), 130.0 (d), 129.8 (d), 128.2 (d), 127.8 (d), 127.5 (d), 127.3 (d), 75.5 (d), 73.5 (d), 70.9 (t), 69.5 (d), 44.8 (t), 43.4 (t), 27.0 (q), 19.3 (s). LR-MS (*m/z* (relative intensity)): 417 ([$M^+ - C_4H_9$], 8), 249 (95), 91 (100). HR-MS calcd. for $C_{25}H_{25}O_4Si$: 417.1522; found: 417.1533. Anal. calcd. for $C_{29}H_{34}O_4Si$: C 73.38, H 7.22, O 13.48, Si 5.92; found: C 73.41, H 7.35, O 13.32.

To a cooled 0°C solution of the keto alcohol (4.51 g, 9.49 mmol), methanesulfonyl chloride (880 µL, 11.4 mmol), and dichloromethane (32 mL) was added triethylamine (4 mL, 28.5 mmol). After 15 min at 0°C, the reaction was quenched with water. After extraction with dichloromethane, the organic layers were washed with satd. aq NaHCO3, and brine, dried over MgSO4. Filtration, concentration, and purification by flash chromatography (hexanes:ethyl acetate, 3:1) yielded 4.03 g (93%) of enone **15d** as an oil. $[\alpha]_D$: +78.1° (*c* 3.61, $CHCl_3$). IR (cm^{-1}): 3069, 1682, 1427. ^{1}H NMR ($CDCl_3$) δ: 7.73–7.65 (m, 4H), 7.47–7.24 (m, 11H), 6.60 (dd, 1H, *J* = 10.3, 3.2 Hz), 5.93 (d, 1H, *J* = 10.5 Hz), 4.62 (d, 1H, *J* = 12.2 Hz), 4.60–4.57 (m, 1H), 4.54 (d, 1H, *J* = 12.2 Hz), 3.84–3.80 (m, 1H), 2.89 (dd, 1H, *J* = 16.5, 7.1 Hz), 2.43 (dd, 1H, *J* = 16.5, 3.2 Hz), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 197.1 (s), 148.5 (d), 138.0 (s), 135.8 (d), 133.3 (s), 132.9 (s), 129.9 (d), 129.6 (d), 128.2 (d), 127.7 (d), 127.4 (d), 76.6 (d), 71.3 (t), 68.4 (d), 40.9 (t), 26.8 (q), 19.2 (s). LR-MS (*m/z* (relative intensity)): 399 ([$M^+ - C_4H_9$], 8), 231 (38), 91 (100). HR-MS calcd. for $C_{25}H_{23}O_3Si$: 399.1416; found: 399.1422. Anal. calcd. for $C_{29}H_{32}O_3Si$: C 76.28, H 7.06, O 10.51, Si 6.15; found: C 76.29, H 7.09, O 10.54.

Bromoenone 16a

To a solution of enone **15a** (19.0 g, 54.3 mmol) in CCl_4 (500 mL) was added over 1 h a solution of bromine (8.25 g, 51.6 mmol) in CCl_4 (100 mL) at 0°C. Once complete the mixture was stirred for 45 min at 0°C before a solution of triethylamine (9.89 g, 97.8 mmol) in carbon tetrachloride (100 mL) was added over a 20 min period. The reaction mixture was stirred for 20 min and filtered. The filtrate was washed with 1 N HCl and satd. aq $NaHCO_3$. The aqueous layers were extracted with ether and combined organic layers dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography using a mixture of hexanes:EtOAc (20:1 to 8:1) gave 21.0 g (90%) of bromoenone **16a** as a white solid and trace amounts of a dibromoketone; mp: 78.2°C. IR (cm^{-1}): 3060, 2955, 1699. ^{1}H NMR ($CDCl_3$) δ: 7.68–7.65 (m, 4H), 7.48–7.38 (m, 6H), 7.20 (d, 1H, *J* = 3.1 Hz), 4.48 (dt, 1H, *J* = 6.4, 3.1 Hz), 2.76 (dt, 1H, *J* = 16.7, 5.0 Hz), 2.33 (dt, 1H, *J* = 16.4, 8.2 Hz), 2.13–2.06 (m, 2H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 190.6 (s), 153.1 (d), 135.7 (d), 132.9 (s), 130.2 (d), 127.9 (d), 124.1 (s), 68.8 (d), 34.7 (t), 32.4 (t), 26.8 (q), 19.1 (s). LR-MS (*m/z* (relative intensity)): 373 ([$M^+ - C_4H_9$], 50), 371 ([$M^+ - C_4H_9$], 48), 199 (100). HR-MS calcd. for $C_{18}H_{16}BrO_2Si$: 371.0103; found: 371.0098.

Bromoenone 16b

Followed the same procedure as per **16a**. Purification by flash chromatography using a mixture of hexanes:EtOAc (6:1) gave 7.23 g (78%) of bromoketone **16b** as a thick oil. IR (cm^{-1}): 3066, 2959, 2871, 1703, 1454, 1317, 1096. ^{1}H NMR ($CDCl_3$) δ: 7.45 (dd, 1H, *J* = 13.0, 1.2 Hz), 7.39–7.32 (m, 5H), 4.64 (s, 2H), 4.29–4.24 (m, 1H), 2.84 (ddd, 1H, *J* = 16.8, 5.6, 4.5 Hz), 2.53–2.32 (m, 2H), 2.18–2.08 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 190.4 (s), 150.5 (d), 137.2 (s), 128.5 (d), 128.0 (d), 127.7 (d), 125.0 (s), 73.6 (d), 71.1 (t), 34.7 (t), 29.0 (t). LR-MS (*m/z* (relative intensity)): 280 ([M]$^+$, 5), 282 ([M]$^+$, 5), 201 ([M^+ – Br], 40), 175 (100). HR-MS calcd. for $C_{13}H_{13}BrO_2$: 280.0099; found: 280.0107.

Bromoenone 16c

Same procedure as per **16a**. Purification by flash chromatography eluting with a mixture of hexanes:EtOAc (3:1 to 1:1) gave 9.58 g (92%) of **16c** as a white solid; mp: 62.7°C. IR (cm^{-1}): 2955, 1697, 1611, 1513, 1463, 1318, 1249, 1174, 1032, 1000, 817. ^{1}H NMR ($CDCl_3$) δ: 7.42 (d, 1H, *J* = 3.5 Hz), 7.28 (d, 2H, *J* = 8.6 Hz), 6.90 (d, 2H, *J* = 8.6 Hz), 4.57 (s, 2H), 4.27–4.22 (m, 1H), 3.81 (s, 3H), 2.83 (dm, 1H, *J* = 16.8, 10.7 Hz), 2.47 (m, 1H, *J* = 16.8, 11.7 Hz), 2.37–2.28 (m, 1H), 2.16–2.04 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 190.4 (s), 159.3 (s), 150.7 (d), 132.0 (s), 129.3 (d), 124.8 (s), 113.9 (d), 73.2 (d), 70.7 (t), 55.2 (q), 34.6 (t), 29.0 (t). LR-MS (*m/z* (relative intensity)): 310 ([M]$^+$, 8), 136 (27), 121 (100). HR-MS calcd. for $C_{14}H_{15}O_3Br$: 310.0204; found: 310.0195.

Bromoenone 16d

Followed the same procedure as per **16a**. Flash chromatography eluting with a mixture of hexanes:EtOAc (6:1) gave 9.27 g (94%) of **16d** as a thick oil. $[\alpha]_D$: +81.9° (*c* 1.81, $CHCl_3$). IR (cm^{-1}): 3069, 2957, 1700, 1427, 1113, 1066, 741, 702. ^{1}H NMR ($CDCl_3$) δ: 7.73–7.63 (m, 4H), 7.48–7.22 (m, 11H), 6.99 (d, 1H, *J* = 4.2 Hz), 4.58 (d, 1H, *J* = 12.3 Hz), 4.56–4.52 (m, 1H), 4.50 (d, 1H, *J* = 12.2 Hz), 3.80 (dt, 1H, *J* = 7.1, 3.2 Hz), 3.10 (dd, 1H, *J* = 16.4, 7.7 Hz), 2.60 (dd, 1H, *J* = 16.4, 3.2 Hz), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 189.1 (s), 148.7 (d), 137.6 (s), 135.8 (d), 132.9 (s), 132.6 (s), 130.1 (d), 128.3 (d), 127.9 (d), 127.5 (d), 125.1 (s), 75.9 (d), 71.3 (t), 69.7 (d), 40.3 (t), 26.8 (q), 19.3 (s). LR-MS (*m/z* (relative intensity)): 477 ([$M^+ - C_4H_9$], 5), 479 ([$M^+ - C_4H_9$], 5), 311 (30), 309 (30), 91 (100). HR-MS calcd. for $C_{25}H_{22}O_3SiBr$: 477.0521; found: 477.0511.

Alcohol 17a

To a 0°C solution of tetravinyl tin (320 mg, 1.41 mmol) in THF (20 mL) was added 1.08 M *n*-butyl lithium (4.73 mL, 5.11 mmol). After 30 min at 0°C the ice bath was removed and the mixture stirred for 1 h. This solution was added via cannula to a cooled –78°C suspension of $CeCl_3$ (2.86 g, 7.67 mmol) and ketone **16a** (1.10 g, 2.55 mmol) in THF (40 mL). The reaction mixture was stirred for 4 h at –78°C before being quenched with satd. aq NH_4Cl. The layers were separated (a portion of 1 N HCl was added for clarification) and the aqueous layer extracted with ethyl ether. The organic layers were washed (brine), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography eluting with a mixture of hexanes:EtOAc (9:1) gave 447 mg and 646 mg of two

diastereomeric alcohols (93%) as thick oils. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ: 7.73–7.65 (m, 4H), 7.46–7.35 (m, 6H), 6.12 (d, 1H, *J* = 3.6 Hz), 5.72 (dd, 1H, *J* = 17.1, 10.6 Hz), 5.26 (d, 1H, *J* = 17.1 Hz), 5.17 (d, 1H, *J* = 10.6 Hz), 4.15 (q, 1H), 2.18–2.10 (m, 1H), 1.83–1.67 (m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 141.2 (d), 135.7 (d), 135.4 (d), 133.7 (s), 131.1 (s), 129.7 (d), 127.6 (d), 114.9 (t), 74.1 (s), 68.3 (d), 33.0 (t), 28.2 (t), 26.9 (q), 19.1 (s). More polar isomer: IR (cm^{-1}): 3548, 3435, 3066, 2953, 2861, 1630, 1589, 1471, 1425, 1364, 1323, 1076. ^{1}H NMR ($CDCl_3$) δ: 7.72–7.64 (m, 4H), 7.47–7.35 (m, 6H), 6.10 (d, 1H, *J* = 3.1 Hz), 5.88 (dd, 1H, *J* = 17.3, 10.6 Hz), 5.35 (d, 1H, *J* = 17.2 Hz), 5.27 (d, 1H, *J* = 10.6 Hz), 4.29–4.23 (m, 1H), 2.07–2.01 (m, 1H), 1.87–1.80 (m, 1H), 1.77–1.70 (m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 141.0 (d), 135.9 (d), 135.7 (d), 133.7 (s), 129.8 (d), 127.6 (d), 115.3 (t), 74.4 (s), 69.1 (d), 34.1 (t), 29.0 (t), 26.8 (q), 19.1 (s). LR-MS (*m*/*z* (relative intensity)): 399 ([$M^+ - C_4H_9$], 5), 199 (100), 200 (41). HR-MS calcd. for $C_{20}H_{20}BrO_2Si$: 399.0416; found: 399.0424. Anal. calcd. for $C_{24}H_{29}BrO_2Si$: C 63.01, H 6.39, Br 17.47, O 6.99, Si 6.14; found: C 62.97, H 6.40, O 6.95.

Acetate 18a

To a 0°C solution of tetravinyl tin (464 µL, 2.55 mmol) in THF (30 mL) was added 1.0 M *n*-butyl lithium (9.30 mL, 9.30 mmol). After 2.5 h at 0°C this solution was added via cannula to a cooled –78°C suspension of $CeCl_3$ (5.19 g, 13.9 mmol) and ketone **16a** (1.99 g, 4.64 mmol) in THF (70 mL). The reaction mixture was stirred for 5 h at –78°C before being quenched with acetic anhydride (10 mL) and warmed to room temperature. After 30 min, satd. aq NH_4Cl was added and the layers were separated. The aqueous layer extracted with ethyl ether, and the organic layers washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography eluting with a mixture of hexanes:EtOAc (15:1) gave 786 mg and 1.05 g (79%) of acetate **18a**. Less polar acetate: ^{1}H NMR ($CDCl_3$) δ: 7.72–7.65 (m, 4H), 7.46–7.35 (m, 6H), 6.10 (d, 1H, *J* = 4.5 Hz), 5.87 (dd, 1H, *J* = 10.8, 17.4 Hz), 5.23 (d, 1H, *J* = 10.8 Hz), 5.17 (d, 1H, *J* = 17.4 Hz), 4.10 (q, 1H, *J* = 4.3 Hz), 3.00 (dt, 1H, *J* = 11.7, 3.2 Hz), 2.12 (s, 3H), 1.97–1.89 (m, 1H), 1.82–1.62 (m, 2H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 168.9 (s), 136.4 (d), 135.8 (d), 135.7 (d), 135.2 (d), 133.7 (s), 129.7 (d), 127.6 (d), 116.3 (t), 82.3 (s), 66.7 (d), 28.2 (t), 28.0 (t), 26.8 (q), 22.0 (q), 19.1 (s). More polar acetate: IR (cm^{-1}): 3056, 1743, 1635, 1471. ^{1}H NMR ($CDCl_3$) δ: 7.69–7.63 (m, 4H), 7.45–7.34 (m, 6H), 6.25 (d, 1H, *J* = 2.5 Hz), 5.88 (dd, 1H, *J* = 17.3, 10.7 Hz), 5.37 (d, 1H, *J* = 16.8 Hz), 5.33 (d, 1H, *J* = 10.4 Hz), 4.42–4.38 (m, 1H), 2.43 (dt, 1H, *J* = 13.2, 3.8 Hz), 2.03 (s, 3H), 2.00–1.92 (m, 1H), 1.81–1.69 (m 2H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 169.1 (s), 137.9 (d), 136.7 (d), 135.7 (d), 133.4 (s), 129.8 (d), 127.7 (d), 127.6 (d), 124.4 (s), 116.6 (t), 82.4 (s), 69.5 (d), 30.6 (t), 29.8 (t), 26.8 (q), 21.9 (q), 19.1 (s). LR-MS (*m*/*z* (relative intensity)): 441 ([$M^+ - C_4H_9$], 18), 443 ([$M^+ - C_4H_9$], 16), 241 (100), 199 (70). HR-MS calcd. for $C_{22}H_{22}O_3BrSi$: 441.0521; found: 441.0529. Anal. calcd. for $C_{26}H_{31}BrO_3Si$: C 62.52, H 6.26, Br 16.00, O 9.61, Si 5.62; found: C 62.66, H 6.19, O 9.44.

Acetate 18b

Followed the same procedure as per **18a**, starting from **17b**. Flash chromatography using a hexanes:EtOAc (8:1 to 4:1) mixture yielded 2.29 g (83%) of a mixture of acetates **18b** as a colourless oil. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ: 7.36–7.28 (m, 5H), 6.45 (d, 1H, *J* = 4.5 Hz), 5.95 (dd, 1H, *J* = 10.8, 17.3 Hz), 5.30 (d, 1H, *J* = 10.8 Hz), 5.28 (d, 1H, *J* = 17.5 Hz), 4.59 (s, 2H), 3.88 (q, 1H, *J* = 4.3 Hz), 2.93–2.83 (m, 1H), 2.09 (s, 3H), 2.07–1.81 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 169.1 (s), 138.3 (s), 136.3 (d), 132.9 (d), 128.4 (d), 127.7 (d), 116.4 (t), 82.4 (s), 71.4 (d), 70.4 (t), 28.5 (t), 24.9 (t), 22.0 (q). More polar isomer: IR (cm^{-1}): 3030, 1745. ^{1}H NMR ($CDCl_3$) δ: 7.36–7.30 (m, 5H), 6.45 (dd, 1H, *J* = 3.5, 2.3 Hz), 5.90 (dd, 1H, *J* = 17.3, 10.7 Hz), 5.38 (d, 1H, *J* = 17.2 Hz), 5.33 (d, 1H, *J* = 10.7 Hz), 4.58 (ABq, 2H, *J* = 22.1 Hz), 4.17 (ddd, 1H, *J* = 2.3, 5.4, 9.8 Hz), 2.63 (m, 1H, *J* = 3.2, 12.9 Hz), 2.14–2.03 (m, 2H), 2.09 (s, 3H), 1.80–1.68 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 168.9 (s), 137.8 (s), 136.6 (d), 135.0 (d), 128.3 (d), 127.5 (d), 116.7 (t), 82.2 (s), 74.5 (d), 70.3 (t), 30.5 (t), 26.5 (t), 21.9 (q). LR-MS (*m*/*z* (relative intensity)): 368 ([M + NH_4], 25), 308 ([M + NH_4 – AcOH], 25), 291 ([M^+ – AcOH], 25), 211 (100). HR-MS calcd. for $C_{17}H_{23}NO_3Br$: 368.0861; found: 368.0857. Anal. calcd. for $C_{17}H_{19}BrO_3$: C 58.13, H 5.45, Br 22.75, O 13.67; found: C 58.22, H 5.35, O 13.74.

Acetate 18c

Followed the same procedure as per acetate **18a**, starting from **17c**. Purification by flash chromatography eluting with hexanes:EtOAc (6:1) yielded 10.01 g (82%) of **20d** as a mixture of two diastereomers. First isomer: ^{1}H NMR ($CDCl_3$) δ: 7.25 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 6.42 (d, 1H, *J* = 1.1 Hz), 5.89 (dd, 1H, *J* = 17.3, 10.7), 5.37 (d, 1H, *J* = 18.8 Hz), 5.32 (d, 1H, *J* = 10.9 Hz), 4.50 (ABq, 2H, *J* = 13.5 Hz), 4.17–4.10 (m, 1H), 3.80 (s, 3H), 2.68–2.58 (m, 1H), 2.22–2.20 (m, 2H), 2.08 (s, 3H), 1.77–1.65 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 169.1 (s), 159.1 (s), 136.5 (d), 135.1 (d), 129.8 (s), 129.2 (d), 125.2 (s), 116.7 (t), 113.7 (d), 82.5 (s), 74.2 (d), 70.1 (t), 55.1 (q), 30.4 (t), 26.5 (t), 21.8 (q). Second isomer: IR (cm^{-1}): 3035, 1744, 1612, 1513. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 6.43 (d, 1H, *J* = 4.5 Hz), 5.94 (dd, 1H, J = 17.3, 10.9 Hz), 5.29 (d, 1H, *J* = 10.3 Hz), 5.25 (d, 1H, *J* = 17.0 Hz), 4.51 (s, 2H), 3.86 (q, 1H, *J* = 4.4 Hz), 3.80 (s, 3H), 2.86 (dt, 1H, *J* = 11.8, 3.4), 2.09 (s, 3H), 2.06–1.99 (m, 1H), 1.92–1.89 (m, 1H), 1.85–1.79 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 168.9 (s), 159.0 (s), 136.2 (d), 132.9 (d), 130.2 (s), 129.1 (d), 128.9 (s), 116.2 (t), 113.6 (d), 82.2 (s), 70.9 (d), 69.9 (t), 55.1 (q), 28.3 (t), 24.7 (t), 21.8 (q). LR-MS (*m*/*z* (relative intensity)): 323 ([M^+ – OAc], 10), 321 ([M^+ – OAc], 10), 184 (40), 121 (100). HR-MS calcd. for $C_{16}H_{18}BrO_2$: 321.0490; found: 321.0485. Anal. calcd. for $C_{18}H_{21}BrO_4$: C 56.70, H 5.55, Br 20.96, O 16.79; found: C 56.85, H 5.71, O 16.90.

Acetate 18d

Followed the same procedure as per **18a**, starting from **17d**. Flash chromatography using hexanes:EtOAc (9:1) as the eluent gave 8.77 g (83%) of a single acetate **18d** as a clear oil. $[\alpha]_D$: +126.5° (*c* 4.443, $CHCl_3$). IR (cm^{-1}): 3068,

1749, 1472. ^{1}H NMR ($CDCl_3$) δ: 7.78–7.74 (m, 4H), 7.44–7.28 (m, 9H), 7.18–7.15 (m, 2H), 5.98 (d, 1H, *J* = 6.0 Hz), 5.84 (dd, 1H, *J* = 17.3, 10.7 Hz), 5.20 (d, 1H, *J* = 10.7 Hz), 5.16 (d, 1H, *J* = 17.3 Hz), 4.39 (d, 1H, *J* = 12.0 Hz), 4.30 (d, 1H, *J* = 12.0 Hz), 4.14–4.12 (m, 1H), 3.38 (dt, 1H, *J* = 12.2, 3.0 Hz), 3.24 (dd, 1H, *J* = 12.0, 11.7 Hz), 2.33–2.29 (m, 1H), 2.12 (s, 3H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 168.4 (s), 138.0 (s), 136.1 (d), 134.1 (s), 133.3 (s), 132.5 (d), 129.6 (d), 129.0 (s), 128.1 (d), 127.4 (d), 116.6 (t), 82.4 (s), 73.1 (d), 69.8 (t), 66.2 (d), 32.7 (t), 26.7 (q), 21.8 (q), 19.3 (s). LR-MS (*m*/*z* (relative intensity)): 547 ([$M^+ - C_4H_9$], 1), 399 (100). HR-MS calcd. for $C_{29}H_{28}BrO_4Si$: 547.0940; found: 547.0947. Anal. calcd. for $C_{33}H_{37}BrO_4Si$: C 65.44, H 6.16, Br 13.19, O 10.57, Si 4.64; found: C 65.41, H 6.22, O 10.50.

Diene 19a

To a suspension of Mg turnings (336 mg, 13.8 mmol) in ethyl ether (28 mL) was added 1-bromo-5-propene (2.07 g, 13.9 mmol) drop wise, resulting in a refluxing mixture. The reaction was kept at reflux for 3 h, until all the magnesium was consumed. The Grignard was cooled and added via cannula to a suspension of copper(I) iodide (968 mg, 5.08 mmol) in ethyl ether (24 mL) at 0°C. After 25 min at 0°C a solution of acetate **18a** (1.269 g, 2.54 mmol) in Et_2O (8 mL) was added via cannula. The resulting mixture was stirred for 1 h at 0°C then quenched by the addition of satd. aq NH_4Cl. The product was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (100% hexanes to 25:1 hexanes: EtOAc) to provide 1.24 g (96%) of **19a** as a slightly yellow-coloured liquid. IR (cm^{-1}): 3070, 2930, 2856, 1427, 1105. ^{1}H NMR ($CDCl_3$) δ: 7.69–7.65 (m, 4H), 7.46–7.35 (m, 6H), 6.09 (d, 1H, *J* = 3.7 Hz), 5.92 (t, 1H, *J* = 7.4 Hz), 5.79 (ddt, 1H, *J* = 17.0, 10.2, 6.7 Hz), 5.03–4.92 (m, 2H), 4.33–4.28 (m, 1H), 2.61 (dt, 1H, *J* = 14.9, 5.9 Hz), 2.23–2.01 (m, 4H), 1.76–1.69 (m, 2H), 1.45–1.37 (m, 4H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 138.8 (d), 135.8 (d), 134.0 (s), 133.9 (s), 133.7 (d), 132.6 (d), 131.7 (s), 129.7 (d), 127.7 (d), 126.1 (s), 114.4 (t), 69.0 (d), 33.6 (t), 31.5 (t), 28.7 (t), 28.6 (t), 27.9 (t), 26.9 (q), 23.0 (t), 19.2 (s). LR-MS (*m*/*z* (relative intensity)): 453 ([$M^+ - C_4H_9$], 6), 451 ([$M^+ - C_4H_9$], 6), 199 (100), 200 (23). HR-MS calcd. for $C_{29}H_{37}OBrSi$: 508.1797; found: 508.1793

Diene 19b

Followed the same procedure as per **19a**, starting from **18b**. The crude residue was purified by flash chromatography (hexanes:EtOAc, 9:1) to provide 737 mg (89%) of **19b** as a colourless liquid. ^{1}H NMR ($CDCl_3$) δ: 7.36–7.27 (m, 5H), 6.32 (d, 1H, *J* = 3.8 Hz), 5.98 (t, 1H, *J* = 7.5 Hz), 5.80 (ddt, 1H, *J* = 17.0, 10.2, 6.7 Hz), 5.04–4.92 (m, 2H), 4.59 (s, 2H), 4.10–4.06 (m, 1H), 2.65–2.60 (m, 1H), 2.37–2.28 (m, 1H), 2.19–1.91 (m, 5H), 1.87–1.77 (m, 1H), 1.47–1.38 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 138.7 (d), 138.3 (s), 133.2 (d), 131.5 (s), 130.6 (d), 128.3 (d), 127.6 (d), 114.4 (t), 73.9 (d), 70.2 (t), 33.5 (t), 28.6 (t), 28.0 (t), 27.8 (t), 23.0 (t).

Diene 19c

To a cooled –78°C solution of 4-(*tert*-butyldimethylsilyloxy)-3-methylbutyl iodide (4.51 g, 13.7 mmol) in Et_2O (126 mL) was added a 1.31 M solution of *tert*-butyl lithium (20.9 mL, 27.4 mmol). After 5 min this solution was warmed to 0°C and stirred for 30 min before being cooled to –78°C. This cooled solution was added via cannula to a stirred suspension of CuCN (1.22 g, 13.7 mmol) in THF (103 mL) at –68°C. This suspension was stirred for 1 h further before a solution of acetate **18c** (3.48 g, 9.13 mmol) in THF (70 mL) was added via cannula at –50°C. The reaction mixture was gradually warmed to 0°C over 1 h, and stirred 2 h at 0°C before being quenched with a solution of satd. aq NH_4Cl:conc. NH_4OH (9:1). The mixture was extracted with ethyl ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes:EtOAc (15:1) to give 4.43 g (92%) of **19c** as a colourless oil. IR (cm^{-1}): 2952, 2855, 1612, 1513, 1462, 1248, 1089, 1038, 835. ^{1}H NMR ($CDCl_3$) δ: 7.27 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 6.31 (d, 1H, *J* = 3.7 Hz), 5.97 (t, 1H, *J* = 7.4 Hz), 4.51 (s, 2H), 4.08–4.03 (m, 1H), 3.80 (s, 3H), 3.39 (ddd, 2H, *J* = 9.8, 6.5, 6.0 Hz), 2.66–2.59 (m, 1H), 2.36–2.31 (m, 1H), 2.16–2.09 (m, 2H), 1.98–1.89 (m, 1H), 1.84–1.77 (m, 1H), 1.61–1.52 (m, 1H), 1.46–1.37 (m, 3H), 1.09–1.02 (m, 1H), 0.89 (s, 9H), 0.86 (d, 3H, *J* = 6.7 Hz), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 159.1 (s), 133.2 (d), 131.4 (s), 130.7 (d), 130.3 (s), 129.2 (d), 127.3 (s), 113.7 (d), 73.6 (d), 69.9 (t), 68.2 (t), 51.2 (q), 35.6 (d), 32.8 (t), 28.3 (t), 28.0 (t), 26.6 (t), 25.8 (q), 23.0 (t), 18.2 (s), 16.6 (q), –5.4 (q). LR-MS (*m*/*z* (relative intensity)): 465 ([$M - C_4H_9$], 5), 467 ([$M^+ - C_4H_9$], 5), 122 (50), 74 (50), 121 (100). HR-MS calcd. for $C_{23}H_{34}BrO_3Si$: 465.1460; found: 465.1470. Anal. calcd. for $C_{27}H_{43}BrO_3Si$: C 61.93, H 8.28, Br 15.26, O 9.17, Si 5.36; found: C 61.99, H 8.35, O 9.34.

Diene 19d

Followed the same procedure as per **19c**, starting from **18d**. Purified by flash chromatography using hexanes:EtOAc (25:1) to give 3.79 g (96%) of **19d** as a colourless oil. $[\alpha]_D$: +94.6 (*c* 1.80, $CHCl_3$). IR (cm^{-1}): 2929, 2856, 1471, 1427, 1361, 1250, 1111, 836, 700. ^{1}H NMR ($CDCl_3$) δ: 7.76–7.64 (m, 5H), 7.44–7.22 (m, 10H), 6.02 (t, 1H, *J* = 7.3 Hz), 5.90 (d, 1H, *J* = 5.5 Hz), 4.51 (d, 1H, *J* = 12.1 Hz), 4.37 (d, 1H, *J* = 12.1 Hz), 4.33–4.30 (m, 1H), 3.49–3.34 (m, 3H), 2.84–2.81 (m, 1H), 2.62–2.56 (m, 1H), 2.18–2.11 (m, 2H), 1.60–1.37 (m, 5H), 1.08 (s, 9H), 0.89 (s, 9H), 0.87 (d, 3H, *J* = 6.6 Hz), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 138.4 (s), 136.0 (d), 134.9 (d), 134.1 (s), 133.6 (s), 130.5 (s), 130.1 (d), 129.7 (d), 128.2 (d), 127.8 (s), 127.6 (d), 75.4 (d), 70.4 (t), 68.2 (t), 67.8 (d), 35.7 (d), 33.0 (t), 28.5 (t), 27.9 (t), 26.9 (q), 26.6 (t), 25.9 (q), 19.4 (s), 18.3 (s), 16.7 (q), –5.3 (q). LR-MS (*m*/*z* (relative intensity)): 691 ([$M^+ - C_4H_9$], 18), 689 ([$M^+ - C_4H_9$], 16), 91 (100), 74 (65), 199 (58), 135 (52). HR-MS calcd. for $C_{38}H_{50}BrO_3Si_2$: 689.2482; found: 689.2489. Anal. calcd. for $C_{42}H_{59}BrO_3Si$: C 67.44, H 7.95, Br 10.68, O 6.42, Si 7.51; found: C 67.65, H 7.90, O 6.38.

Diene 19e

Oil-free NaH (45 mg, 1.129 mmol) was suspended in THF (8 mL) and dimethyl malonate (117 μL, 1.03 mmol) was slowly added at 25°C. The reaction was stirred until gas evolution ceased. Then, this solution was transfered via can-

nula to a solution of acetate **18a** (256 mg, 0.513 mmol) and $Pd(PPh)_4$ (29 mg, 0.026 mmol). The reaction was stirred at room temperature for 1 h before the THF was evaporated. The residue taken up in Et_2O and the organic phase washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using hexanes:EtOAc (15:1) to give 217 mg (74%) of diester **19e** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 7.68–7.63 (m, 4H), 7.46–7.33 (m, 6H), 6.13 (d, 1H, *J* = 3.5 Hz), 5.83 (t, 1H, *J* = 7.2 Hz), 4.28 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.45 (t, 1H, *J* = 7.6 Hz), 2.73 (t, 2H, *J* = 7.6 Hz), 2.7–2.6 (m, 1H), 2.25–2.17 (m, 1H), 1.8–1.65 (m, 2H), 1.06 (s, 9H).

Diene 19f

To a stirred solution of alcohol **17a** (1.74 g, 3.80 mmol), ethylvinyl ether (50 mL), and triethylamine (1 mL) was added mercury(II) trifluoroacetate (1.62 g, 3.80 mmol) at room temperature. The mixture was stirred a total of 3 days before the solvent was removed in vacuo. The residue was taken up in ethyl ether, washed with 10% aq KOH and satd. aq $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography using a mixture of hexanes:EtOAc (15:1 to 9:1) yielded 1.61 g (88%) of aldehyde **19f**. ^{1}H NMR ($CDCl_3$) δ: 9.79 (s, 1H), 7.72–7.68 (m, 4H), 7.48–7.38 (m, 6H), 6.16 (d, 1H, *J* = 3.7 Hz), 5.87 (t, 1H, *J* = 7.2 Hz), 4.37–4.31 (m, 1H), 2.70–2.63 (m, 1H), 2.60–2.56 (m, 2H), 2.49–2.42 (m, 2H), 2.26–2.21 (m, 1H), 1.80–1.74 (m, 2H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 201.2 (d), 135.7 (d), 134.6 (d), 133.8 (s), 132.9 (s), 129.7 (d), 129.6 (d), 127.6 (d), 125.4 (s), 68.8 (d), 43.2 (t), 31.5 (t), 26.8 (q), 22.9 (t), 20.6 (t), 19.1 (s). LR-MS (*m*/*z* (relative intensity)): 425 ([$M^+ - C_4H_9$], 25), 199 (100). HR-MS calcd. for $C_{22}H_{22}O_2BrSi$: 425.0572; found: 425.0575.

Diene 19g

Alcohol **17a** was dissolved in toluene (2 mL) along with propionic acid (2 drops) and ethyl orthoacetate (575 µL, 3.14 mmol). The mixture was refluxed overnight and the solvent was removed in vacuo. Purification by flash chromatography using a mixture of hexanes:EtOAc (25:1 to 9:1) yielded 38.9 mg (21%) of ester **19g** and 113 mg of starting alcohol (92% corrected yield). ^{1}H NMR ($CDCl_3$) δ: 7.70–7.65 (m, 4H), 7.46–7.36 (m, 6H), 6.12 (d, 1H, *J* = 3.7 Hz), 5.88 (t, 1H, *J* = 7.2 Hz), 4.31 (m, 1H), 4.13 (q, 2H, *J* = 6.9 Hz), 2.70–2.63 (m, 1H), 2.48–2.38 (m, 4H), 2.29–2.15 (m, 1H), 1.80–1.70 (m, 2H), 1.25 (t, 3H, *J* = 6.9 Hz), 1.06 (s, 9H).

Aldehyde 20a

To a cooled –78°C solution of vinyl bromide **19a** (1.10 g, 2.17 mmol) in THF (28 mL) was added 2.0 M *n*-butyl lithium (2.17 mL, 4.34 mmol). After 20 min DMF (1.26 mL, 16.3 mmol) was added at –78°C and the reaction stirred for 1 h further before being quenched with satd. aq NH_4Cl. The layers were separated and the product extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude aldehyde was purified by flash chromatography (100% hexanes to hexanes:EtOAc (15:1)) to provide 977 mg (98%) of aldehyde **20a** as a faintly yellow-coloured oil. IR (cm^{-1}): 3069, 2932, 2857, 1696, 1427, 1107. ^{1}H NMR ($CDCl_3$) δ: 9.42 (s, 1H), 7.71–7.67 (m, 4H), 7.47–7.37 (m, 6H), 6.64 (t, 1H, *J* = 7.3 Hz), 6.32 (d, 1H, *J* = 2.9 Hz), 5.78 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz), 5.01–4.91 (m, 2H), 4.54–4.48 (m, 1H), 2.55 (dt, 1H, *J* = 15.5, 4.9 Hz), 2.13–1.99 (m, 4H), 1.85–1.77 (m, 1H), 1.73–1.61 (m, 1H), 1.43–1.36 (m, 4H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 193.9 (d), 151.8 (d), 138.8 (d), 137.1 (s), 135.7 (d), 133.7 (s), 131.3 (d), 129.9 (d), 127.7 (d), 114.3 (t), 68.4 (d), 33.6 (t), 31.2 (t), 28.6 (t), 27.9 (t), 26.8 (q), 22.9 (t), 19.1 (s). LR-MS (*m*/*z* (relative intensity)): 458 ([$M]^+$, 8), 401 ([$M^+ - C_4H_9$], 25), 199 (100), 241 (95), 86 (49). HR-MS calcd. for $C_{30}H_{38}O_2Si$: 458.2641; found: 458.2650

Aldehyde 20b

Followed the same procedure as per aldehyde **20a**, starting with **19b**. The crude aldehyde was purified by flash chromatography (hexanes:EtOAc, 15:1) to provide 320 mg of aldehyde **20b** (74%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 9.56 (s, 1H), 7.38–7.30 (m, 5H), 6.69 (t, 1H, *J* = 7.5 Hz), 6.55 (d, 1H, *J* = 2.9 Hz), 5.80 (ddt, 1H, *J* = 17.0, 10.2, 6.7 Hz), 5.02–4.92 (m, 2H), 4.67 (ABq, 2H, *J* = 18.4 Hz), 4.28–4.26 (m, 1H), 2.62 (m, 1H), 2.19–2.04 (m, 6H), 1.75–1.68 (m, 1H), 1.45–1.39 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 193.7 (d), 148.6 (d), 138.7 (d), 137.9 (s), 131.7 (d), 128.4 (d), 127.7 (s), 127.6 (d), 114.2 (t), 73.3 (d), 70.6 (t), 33.5 (t), 28.5 (t), 27.9 (t), 27.7 (t), 22.8 (t).

Aldehyde 20c

Followed the same procedure as per aldehyde **20a**, starting with **19c**. The residue was purified by flash chromatography using hexane:EtOAc (9:1) as the eluent, providing 2.73 g (90%) of aldehyde **20c** as a clear colourless oil. IR (cm^{-1}): 2953, 2855, 1698, 1612, 1513, 1248, 1090, 836. ^{1}H NMR ($CDCl_3$) δ: 9.55 (s, 1H), 7.29 (d, 2H, *J* = 8.6 Hz), 6.89 (d, 2H, *J* = 8.6 Hz), 6.68 (t, 1H, *J* = 7.4 Hz), 6.52 (d, 1H, *J* = 2.8 Hz), 4.60 (ABq, 2H, *J* = 18.2 Hz), 4.28–4.23 (m, 1H), 3.80 (s, 3H), 3.43 (dd, 1H, *J* = 9.8, 5.9 Hz), 3.35 (dd, 1H, *J* = 9.8, 6.5 Hz), 2.63 (dt, 1H, *J* = 15.3, 4.8 Hz), 2.22–2.05 (m, 4H), 1.73–1.54 (m, 2H), 1.48–1.34 (m, 3H), 1.12–1.02 (m, 1H), 0.89 (s, 9H), 0.86 (d, 3H, *J* = 6.7 Hz), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 193.8 (d), 159.3 (s), 148.8 (d), 138.0 (s), 131.8 (d), 130.1 (s), 129.3 (d), 127.8 (s), 113.8 (d), 73.0 (d), 70.4 (t), 68.2 (t), 55.2 (q), 35.6 (d), 32.9 (t), 28.5 (t), 27.8 (t), 26.6 (t), 25.9 (q), 22.9 (t), 18.3 (s), 16.6 (q), –5.3 (q). LR-MS (*m*/*z* (relative intensity)): 415 ([$M^+ - C_4H_9$], 3), 122 (50), 74 (54), 121 (100). HR-MS calcd. for $C_{24}H_{35}O_4Si$: 415.2304; found: 415.2313.

Aldehyde 20d

Followed the same procedure as per **20c**, starting with **19d**. Purification by flash chromatography using hexane:EtOAc (25:1) as the eluent, provided 2.81 g (80%) of aldehyde **20d** as a clear colourless oil. $[\alpha]_D$: +47.3° (*c* 1.10, $CHCl_3$). IR (cm^{-1}): 3070, 2954, 2856, 1700, 1471, 1427, 1255, 1112, 836, 702. ^{1}H NMR ($CDCl_3$) δ: 9.38 (s, 1H), 7.74–7.65 (m, 4H), 7.46–7.28 (m, 11H), 6.78 (t, 1H, *J* = 7.4 Hz), 6.15 (d, 1H, *J* = 3.5 Hz), 4.61–4.58 (m, 1H), 4.56 (ABq, 2H, *J* = 19.4 Hz), 3.59–3.54 (m, 1H), 3.42 (dd, 1H,

J = 9.7, 5.8 Hz), 3.32 (dd, 1H, *J* = 9.7, 5.8 Hz), 2.79 (dd, 1H, *J* = 15.6, 7.2 Hz), 2.24–2.19 (m, 1H), 2.07 (q, 2H, *J* = 7.2 Hz), 1.57–1.26 (m, 5H), 1.11 (s, 9H), 0.87 (s, 9H), 0.85 (d, 3H, *J* = 6.6 Hz), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 193.4 (d), 148.6 (d), 138.5 (s), 137.5 (s), 135.9 (d), 133.7 (d), 133.3 (s), 129.9 (d), 128.2 (d), 127.7 (d), 127.4 (d), 125.8 (s), 75.2 (d), 71.1 (t), 69.3 (d), 68.2 (t), 35.6 (d), 33.0 (t), 28.6 (t), 28.1 (t), 26.9 (q), 26.6 (t), 25.9 (q), 19.3 (s), 18.3 (s), 16.6 (q), –5.4 (q). LR-MS (*m*/*z* (relative intensity)): 696 ([M]$^+$, 20), 639 ([M$^+$ – C_4H_9], 68), 91 (100), 74 (99), 199 (99), 135 (88), 531 (70), 197 (68). HR-MS calcd. for $C_{43}H_{60}O_4Si_2$: 696.4030; found: 696.4037.

Acetal 21a

A solution of aldehyde **20c** (5.15 g, 10.9 mmol), PPTS (547 mg, 2.18 mmol), and ethylene glycol (6.07 mL, 109 mmol) in benzene (140 mL) was heated to reflux for 6 h. The solvent was removed in vacuo and the residue taken up in Et_2O. The ether layer was washed with satd. aq $NaHCO_3$, and brine. The combined aqueous layers were extracted once with ethyl ether. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 5.71 g (100%) of acetal **21a** as an oil. The crude acetal was used in the next step without further purification. IR (cm^{-1}): 3030, 1612. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 6.21 (d, 1H, *J* = 2.9 Hz), 5.69 (t, 1H, *J* = 7.2 Hz), 5.55 (s, 1H), 4.54 (s, 2H), 4.12–4.07 (m, 1H), 4.04–3.99 (m, 2H), 3.97–3.92 (m, 2H), 3.80 (s, 3H), 3.43 (dd, 1H, *J* = 9.7, 5.8 Hz), 3.33 (dd, 1H, *J* = 9.7, 6.6 Hz), 2.56 (dt, 1H, *J* = 15.4, 5.5 Hz), 2.22–2.07 (m, 3H), 2.04–1.94 (m, 1H), 1.74–1.66 (m, 1H), 1.62–1.54 (m, 1H), 1.46–1.32 (m, 3H), 1.08–1.02 (m, 1H), 0.88 (s, 9H), 0.86 (d, 3H, *J* = 6.7 Hz), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 158.9 (s), 135.2 (s), 131.4 (s), 130.7 (s), 129.0 (d), 126.9 (d), 126.4 (d), 113.6 (d), 101.2 (d), 72.5 (d), 69.6 (t), 68.1 (t), 64.7 (t), 55.0 (q), 35.5 (d), 32.8 (t), 28.2 (t), 26.8 (t), 25.8 (t and q), 22.8 (t), 18.2 (s), 16.6 (q), –5.4 (q). LR-MS (*m*/*z* (relative intensity)): 516 ([M]$^+$, 2), 459 ([M – C_4H_9], 8), 186 (70), 74 (75), 121 (100). HR-MS calcd. for $C_{26}H_{39}O_5Si$: 459.2567; found: 459.2574.

Acetal 21b

Followed the same procedure as per **21a**, starting with **20d**. Purification by flash chromatography eluting with a hexanes:EtOAc (15:1 to 6:1) mixture provided 2.46 g (95%) of acetal **21b** as a colourless oil. $[\alpha]_D$: +105.3° (*c* 0.74, $CHCl_3$). IR (cm^{-1}): 3070, 2954, 1471. ^{1}H NMR ($CDCl_3$) δ: 7.77–7.66 (m, 4H), 7.43–7.22 (m, 11H), 5.82 (d, 1H, *J* = 5.1 Hz), 5.75 (t, 1H, *J* = 7.1 Hz), 5.54 (s, 1H), 4.52 (d, 1H, *J* = 12.2 Hz), 4.41–4.37 (m, 2H), 3.91–3.81 (m, 4H), 3.47–3.41 (m, 2H), 3.34 (dd, 1H, *J* = 9.7, 6.6 Hz), 2.80–2.72 (m, 1H), 2.54–2.47 (m, 1H), 2.17–2.12 (m, 2H), 1.59–1.33 (m, 5H), 1.07 (s, 9H), 0.89 (s, 9H), 0.86 (d, 3H, *J* = 6.7 Hz), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 138.8 (s), 136.1 (d), 135.7 (s), 134.5 (s), 134.0 (s), 130.7 (s), 129.5 (d), 128.6 (d), 128.1 (d), 127.4 (d), 127.2 (d), 125.3 (d), 101.2 (d), 76.0 (d), 70.2 (t), 68.3 (t), 66.2 (d), 64.7 (t), 35.7 (d), 33.0 (t), 28.5 (t), 27.2 (t), 27.0 (q), 26.9 (q), 25.9 (d), 19.3 (s), 18.3 (s), 16.7 (q), –5.3 (q). LR-MS (*m*/*z* (relative intensity)): 683 ([M$^+$ – C_4H_9], 30), 91 (100). HR-MS calcd. for $C_{41}H_{55}O_5Si_2$: 683.3588; found: 683.3593.

Alcohol 22a

TBAF (12.6 mL, 12.6 mmol) was added to a solution of acetal **21a** (5.45 g, 10.5 mmol) in THF (105 mL) at room temperature. After 6 h, a solution of EtOAc:ethyl ether (1:1) was added to the mixture. The resulting mixture was washed with satd. aq NH_4Cl, and the aqueous layer extracted once with EtOAc:ethyl ether (1:1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography using a mixture of hexanes:EtOAc (3:1 to 1:1) as the eluent to give 3.66 g (87% for two steps) of alcohol **22a** as a colourless oil. IR (cm^{-1}): 3441, 2931, 1613, 1513, 1463, 1247, 1172, 1048, 821. ^{1}H NMR ($CDCl_3$) δ: 7.28 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 6.21 (d, 1H, *J* = 2.9 Hz), 5.68 (t, 1H, *J* = 7.2 Hz), 5.55 (s, 1H), 4.54 (s, 2H), 4.12–4.07 (m, 1H), 4.04–3.99 (m, 2H), 3.97 (m, 2H), 3.80 (s, 3H), 3.49 (dd, 1H, *J* = 9.5, 5.8 Hz), 3.41 (dd, 1H, *J* = 9.5, 6.4 Hz), 2.58 (dt, 1H, *J* = 15.3, 5.3 Hz), 2.23–2.09 (m, 3H), 2.01–1.94 (m, 1H), 1.74–1.59 (m, 2H), 1.49–1.35 (m, 3H), 1.17–1.08 (m, 1H), 0.91 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 158.9 (s), 135.2 (s), 131.4 (s), 130.6 (s), 129.1 (d), 126.7 (d), 126.5 (d), 113.6 (d), 101.2 (d), 72.4 (d), 69.6 (t), 67.9 (t), 64.7 (t), 55.1 (q), 35.5 (d), 32.7 (t), 28.1 (t), 26.7 (t), 22.8 (t), 16.4 (q). LR-MS (*m*/*z* (relative intensity)): 402 ([M]$^+$, 1), 264 (45), 136 (50), 91 (55), 131 (60), 77 (60), 122 (90), 121 (100). HR-MS calcd. for $C_{24}H_{34}O_5$: 402.2406; found: 402.2397. Anal. calcd. for $C_{24}H_{24}O_5$: C 71.61, H 8.51, O 19.87; found: C 71.61, H 8.60.

Alcohol 22b

Followed the same procedure as per **22a**, starting with **21b**. Flash chromatography (6:1 to 3:1 to 1:1 hexanes:ethyl acetate, followed by 100% EtOAc) gave 2.10 g (58%) of alcohol **22b** as a clear colourless oil and 908 mg of diol as a by-product. $[\alpha]_D$: +70.6° (*c* 1.33, $CHCl_3$). IR (cm^{-1}): 3439, 3069, 1471. ^{1}H NMR ($CDCl_3$) δ: 7.81–7.70 (m, 4H), 7.46–7.27 (m, 11H), 5.88 (d, 1H, *J* = 6.0 Hz), 5.80 (t, 1H, *J* = 7.2 Hz), 5.59 (s, 1H), 4.57 (d, 1H, *J* = 12.3 Hz), 4.44 (d, 1H, *J* = 12.3 Hz), 4.46–4.42 (m, 1H), 3.93–3.83 (m, 4H), 3.52–3.47 (m, 2H), 3.41 (dd, 1H, *J* = 10.5, 6.4 Hz), 2.86–2.78 (m, 1H), 2.58–2.52 (m, 1H), 2.22–2.15 (m, 2H), 1.73 (s, 1H), 1.65–1.61 (m, 1H), 1.56–1.40 (m, 3H), 1.22–1.15 (m, 1H), 1.12 (s, 9H), 0.94 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 138.7 (s), 136.0 (d), 135.6 (s), 134.4 (s), 133.9 (s), 130.6 (s), 129.4 (d), 128.4 (d), 128.0 (d), 127.4 (d), 127.1 (d), 125.4 (d), 101.1 (d), 75.9 (d), 70.2 (t), 68.0 (t), 66.2 (d), 64.7 (t), 35.5 (d), 32.8 (t), 28.2 (t), 27.3 (t), 26.9 (q), 26.7 (d), 19.3 (s), 16.5 (q). LR-MS (*m*/*z* (relative intensity)): 626 ([M]$^+$, 1), 569 ([M$^+$ – C_4H_9], 20), 91 (100), 83 (80), 199 (65). HR-MS calcd. for $C_{39}H_{50}O_5Si$: 626.3427; found: 626.3417. Anal. calcd. for $C_{39}H_{50}O_5Si$: C 74.72, H 8.04, O 12.76, Si 4.48; found: C 74.61, H 8.01, O 12.79.

Enoate 23a

To a stirred solution of alcohol **22a** (3.02 g, 7.49 mmol) in dichloromethane (61 mL) at room temperature was added Dess–Martin periodinane (4.76 g, 11.2 mmol). After 1.5 h,

ethyl ether (100 mL) was added to the reaction mixture, followed by a solution (100 mL) of $Na_2S_2O_3$ (25 g) in satd. aq $NaHCO_3$. The mixture was stirred for 5 min until all the solids had entered solution. The layers were separated and the aqueous extracted with ethyl ether. The etheric layer was washed with sad. aq $NaHCO_3$, water, dried over $MgSO_4$, filtered, and concentrated, yielding 2.98 g (99%) of an aldehyde as a clear colourless oil that was used in the next step without further purification. IR (cm^{-1}): 2934, 2861, 1722, 1613, 1513, 1462, 1247, 1058, 945, 821. ^1H NMR ($CDCl_3$) δ: 9.61 (d, 1H, *J* = 1.9 Hz), 7.28 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 6.23 (d, 1H, *J* = 3.0 Hz), 5.66 (t, 1H, *J* = 7.2 Hz), 5.53 (s, 1H), 4.54 (s, 2H), 4.13–4.07 (m, 1H), 4.04–3.99 (m, 2H), 3.97–3.92 (m, 2H), 3.80 (s, 3H), 2.62–2.53 (m, 1H), 2.37–2.31 (m, 1H), 2.22–2.12 (m, 3H), 2.01–1.93 (m, 1H), 1.76–1.62 (m, 2H), 1.50–1.34 (m, 3H), 1.09 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 205.0 (d), 158.9 (s), 135.0 (s), 131.9 (s), 130.6 (s), 129.0 (d), 126.8 (d), 126.0 (d), 113.6 (d), 101.2 (d), 72.4 (d), 69.7 (t), 64.7 (t), 55.1 (q), 46.0 (d), 30.0 (t), 28.1 (t), 27.8 (t), 26.6 (t), 22.8 (t), 13.1 (q). LR-MS (*m*/*z* (relative intensity)): 400 ($[M]^+$, 1), 264 (35), 77 (58), 91 (61), 122 (63), 132 (70), 121 (100). HR-MS calcd. for $C_{24}H_{32}O_5$: 400.2250; found: 400.2253.

To a 0°C suspension of NaH (389 mg, 9.74 mmol) in THF (40.5 mL) was added MDEPA (1.78 mL, 9.74 mmol). After 1.25 h at 0°C this clear colourless solution was added via cannula to a solution of the crude aldehyde (2.98 g, 7.49 mmol) in THF (37.5 mL) at 0°C. After 30 min at 0°C the reaction was quenched with satd. aq NH_4Cl and the layers separated. The mixture was extracted with ethyl ether and the combined organic layers dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography eluting with a mixture of hexanes:EtOAc (3:1) yielding 2.72 g (80% for two steps) of **23a** as a single isomer. IR (cm^{-1}): 3035, 1712, 1655, 1612, 1513. ^1H NMR ($CDCl_3$) δ: 7.27 (d, 2H, *J* = 8.6 Hz), 6.89–6.81 (m, 3H), 6.21 (d, 1H, *J* = 3.0 Hz), 5.77 (d, 1H, *J* = 15.7 Hz), 5.65 (t, 1H, *J* = 7.1 Hz), 5.53 (s, 1H), 4.54 (s, 2H), 4.12–4.06 (m, 1H), 4.04–3.99 (m, 2H), 3.97–3.92 (m, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 2.59–2.52 (m, 1H), 2.32–2.27 (m, 1H), 2.22–2.10 (m, 3H), 2.00–1.94 (m, 1H), 1.74–1.66 (m, 1H), 1.39–1.36 (m, 4H), 1.03 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 167.1 (s), 158.9 (s), 154.5 (d), 135.1 (s), 131.6 (s), 130.6 (s), 129.0 (d), 126.6 (d), 126.3 (d), 119.2 (d), 113.6 (d), 101.2 (d), 72.4 (d), 69.6 (t), 64.7 (t), 55.0 (q), 51.2 (q), 36.3 (d), 35.6 (t), 28.1 (t), 27.8 (t), 26.9 (t), 22.8 (t), 19.2 (q). LR-MS (*m*/*z* (relative intensity)): 456 ($[M]^+$, 15), 320 (30), 77 (55), 91 (60), 122 (80), 121 (100). HR-MS calcd. for $C_{27}H_{36}O_6$: 456.2512; found: 456.2509. Anal. calcd. for $C_{27}H_{36}O_6$: C 71.03, H 7.95, O 21.03; found: C 71.00, H 7.92.

Enoate 23b

Followed the same procedure as per **23a**, starting with **22b**. The aldehyde (clear colourless oil) was used in the next step without further purification. IR (cm^{-1}): 3069, 2930, 2856, 1724, 1427, 1116. ^1H NMR ($CDCl_3$) δ: 9.60 (d, 1H, *J* = 1.9 Hz), 7.76–7.65 (m, 4H), 7.44–7.22 (m, 11H), 5.84 (d, 1H, *J* = 5.1 Hz), 5.73 (t, 1H, *J* = 7.2 Hz), 5.52 (s, 1H), 4.52 (d, 1H, *J* = 12.3 Hz), 4.41–4.37 (m, 2H), 3.91–3.81 (m, 4H), 3.49–3.42 (m, 1H), 2.80–2.72 (m, 1H), 2.51–2.45 (m, 1H), 2.20–2.10 (m, 2H), 1.74–1.69 (m, 1H), 1.51–1.37 (m, 3H), 1.23–1.18 (m, 1H), 1.08 (d, 3H, *J* = 6.9 Hz), 1.06 (s, 9H). LR-MS (*m*/*z* (relative intensity)): 624 ($[M]^+$, 1), 567 ($[M^+ - C_4H_9]$, 25), 199 (100), 91 (92), 135 (60). HR-MS calcd. for $C_{39}H_{48}O_5Si$: 624.3271; found: 624.3261.

The crude enoate from the following step was purified by flash chromatography eluting with a mixture of hexanes:EtOAc (6:1) yielding 1.34 g (66% for two steps) of **23b** as clear colourless oil. $[\alpha]_D$: +19.5° (*c* 1.32, $CHCl_3$). IR (cm^{-1}): 3046, 2929, 2856, 1722, 1427, 1272, 1111, 983. ^1H NMR ($CDCl_3$) δ: 7.78–7.67 (m, 4H), 7.44–7.23 (m, 11H), 6.87 (dd, 1H, *J* = 15.7, 8.0 Hz), 5.85 (d, 1H, *J* = 5.1 Hz), 5.79 (d, 1H, *J* = 15.9 Hz), 5.74 (t, 1H, *J* = 7.1 Hz), 5.54 (s, 1H), 4.53 (d, 1H, *J* = 12.3 Hz), 4.42–4.40 (m, 1H), 4.40 (d, 1H, *J* = 12.3 Hz), 3.92–3.82 (m, 4H), 3.72 (s, 3H), 3.45 (dt, 1H, *J* = 10.0, 3.5 Hz), 2.81–2.73 (m, 1H), 2.53–2.47 (m, 1H), 2.34–2.29 (m, 1H), 2.15–2.13 (m, 2H), 1.42–1.39 (m, 4H), 1.08 (s, 9H), 1.05 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 167.2 (s), 154.7 (d), 138.8 (s), 136.1 (d), 135.7 (s), 134.5 (s), 134.0 (s), 131.0 (s), 129.5 (d), 128.1 (d), 127.4 (d), 127.3 (d), 125.6 (d), 119.3 (d), 101.2 (d), 76.0 (d), 70.3 (t), 66.2 (d), 64.8 (t), 51.4 (q), 36.5 (d), 35.8 (t), 28.1 (t), 27.3 (t), 27.0 (q), 19.4 (q). LR-MS (*m*/*z* (relative intensity)): 680 ($[M]^+$, 2), 623 ($[M^+ - C_4H_9]$, 35), 91 (100). HR-MS calcd. for $C_{42}H_{52}O_6Si$: 680.3533; found: 680.3526. Anal. calcd. for $C_{42}H_{52}O_6Si$: C 74.08, H 7.70, O 14.10, Si 4.12; found: C 73.97, H 7.77, O 14.12.

Aldehyde 24a

A solution of enoate **23a** (2.67 g, 5.84 mmol), PPTS (440 mg, 1.75 mmol), and wet acetone (117 mL) was heated to reflux for 3 h. The solvent was removed in vacuo and the residue taken up in ethyl ether (200 mL) and washed with saturated aq $NaHCO_3$ (60 mL) and brine (60 mL). The combined aqueous layers were back-extracted once with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes:EtOAc, 3:1) yielded 2.23 g (92%) of aldehyde **24a** as a colourless oil. IR (cm^{-1}): 2932, 2857, 1722, 1694, 1656, 1612, 1513, 1435, 1248, 1072, 822. ^1H NMR ($CDCl_3$) δ: 9.53 (s, 1H), 7.29 (d, 2H, *J* = 8.6 Hz), 6.89 (d, 2H, *J* = 8.6 Hz), 6.84 (dd, 1H, *J* = 15.7, 8.0 Hz), 6.66 (t, 1H, *J* = 7.3 Hz), 6.53 (d, 1H, *J* = 2.8 Hz), 5.77 (d, 1H, *J* = 15.6 Hz), 4.59 (ABq, 2H, *J* = 18.4 Hz), 4.28–4.22 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.65–2.57 (m, 1H), 2.31–2.26 (m, 1H), 2.20–2.02 (m, 4H), 1.72–1.60 (m, 1H), 1.44–1.37 (m, 4H), 1.03 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 193.7 (d), 167.1 (s), 159.2 (s), 154.5 (d), 149.2 (d), 137.7 (s), 131.1 (d), 129.9 (s), 129.2 (d), 127.9 (s), 119.2 (d), 113.7 (d), 72.8 (d), 70.3 (t), 55.1 (q), 51.2 (q), 36.3 (d), 35.5 (t), 28.0 (t), 27.7 (t), 26.7 (t), 22.8 (t), 19.2 (q). LR-MS (*m*/*z* (relative intensity)): 412 ($[M]^+$, 3), 122 (100), 121 (75). HR-MS calcd. for $C_{25}H_{32}O_5$: 412.2250; found: 412.2247.

Aldehyde 24b

Followed the same procedure **24a**, starting from **23b**. After purification by flash chromatography (hexanes:ethyl acetate, 6:1) 467 mg (92%) of aldehyde **24b** were collected as a clear colourless oil. $[\alpha]_D$: +16.4 (c 0.63, $CHCl_3$). IR (cm^{-1}): 3069, 2930, 2857, 1722, 1698, 1428, 1272, 1112. ^1H NMR

($CDCl_3$) δ: 9.39 (s, 1H), 7.76–7.68 (m, 4H), 7.48–7.24 (m, 11H), 6.86 (dd, 1H, *J* = 15.7, 8.0 Hz), 6.80 (t, 1H, *J* = 7.4 Hz), 6.20 (d, 1H, *J* = 3.5 Hz), 5.78 (d, 1H, *J* = 15.6 Hz), 4.64–4.62 (m, 1H), 4.59 (ABq, 2H, *J* = 21.0 Hz), 3.71 (s, 3H), 3.62–3.58 (m, 1H), 2.81 (dd, 1H, *J* = 15.6, 7.0 Hz), 2.32–2.20 (m, 2H), 2.14–2.05 (m, 2H), 1.46–1.34 (m, 4H), 1.13 (s, 9H), 1.04 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 193.3 (d), 167.1 (s), 154.5 (d), 149.0 (d), 138.4 (s), 137.3 (s), 135.8 (d), 133.5 (s), 133.2 (s), 133.0 (d), 129.8 (d), 127.6 (d), 127.4 (d), 127.3 (d), 125.9 (s), 119.2 (d), 75.1 (d), 71.1 (t), 69.2 (d), 51.2 (q), 36.4 (d), 35.6 (t), 28.1 (t), 26.8 (q), 19.3 (q). LR-MS (*m/z* (relative intensity)): 636 ([M]$^+$, 10), 579 ([M$^+$ – C_4H_9], 25), 471 (100), 91 (48). HR-MS calcd. for $C_{40}H_{48}O_5Si$: 636.3271; found: 636.3277.

Alcohol 25

To a cooled 0°C biphasic mixture of aldehyde **24a** (744 mg, 1.80 mmol), dichloromethane (15 mL), and water (830 μL) was added DDQ (532 mg, 2.34 mmol) resulting in a deep green coloured mixture. The mixture was stirred for 2.5 h at which time the colour had become orange and TLC indicated reaction completion. The mixture was poured into a separatory funnel containing dichloromethane and satd aq $NaHCO_3$. The mixture was vigorously shaken and the layers separated. After extraction with dichloromethane, a brine wash, drying over $MgSO_4$, filtration, and concentration in vacuo, the crude product was purified by flash chromatography (hexanes:EtOAc, 3:1 to 1:1) yielded 367 mg (70%) of aldehyde **25** as a colourless oil. IR (cm^{-1}): 3426, 2930, 2858, 1719, 1694, 1436, 1274, 1199, 1035, 870. ^1H NMR ($CDCl_3$) δ: 9.53 (s, 1H), 6.83 (dd, 1H, *J* = 15.7, 8.0 Hz), 6.65 (t, 1H, *J* = 7.3 Hz), 6.48 (d, 1H, *J* = 2.9 Hz), 5.75 (d, 1H, *J* = 15.7 Hz), 4.57–4.51 (m, 1H), 3.70 (s, 3H), 2.56 (dt, 1H, *J* = 15.4, 4.9 Hz), 2.32–2.02 (m, 6H), 1.58 (dt, 1H, *J* = 12.3, 4.4 Hz), 1.43–1.33 (m, 4H), 1.02 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 193.9 (d), 167.3 (s), 154.7 (d), 150.8 (d), 137.5 (s), 131.4 (d), 127.7 (s), 119.2 (d), 66.9 (d), 51.4 (q), 36.5 (d), 35.6 (t), 31.2 (t), 28.1 (t), 26.7 (t), 22.9 (t), 19.3 (q). LR-MS (*m/z* (relative intensity)): 292 ([M]$^+$, 1), 261 ([M$^+$ – MeO], 10), 133 (100), 77 (60), 95 (60). HR-MS calcd. for $C_{17}H_{24}O_4$: 292.1674; found: 292.1664. Anal. calcd. for $C_{27}H_{36}O_6$: C 71.03, H 7.95, O 21.03; found: C 71.00, H 7.92.

Acetate 29a

Propyne (1.65 mL, 29.3 mmol) was condensed at –78° C in a 100 mL round-bottomed flask. THF (15 mL) was added followed by a solution of *n*-BuLi (4.66 mL, 1.88 M in pentane, 8.76 mmol). The resulting white suspension was stirred for 1 h at –78° C. Then, (*E*)-1-triphenylmethoxy-3-penten-2-one **28** (1.96 g, 5.72 mmol) in THF (7 mL) was added to the white suspension. The reaction mixture was warmed to –20° C and stirred for 2 h. Acetic anhydride (1.42 mL, 15.0 mmol) was added and the reaction mixture warmed to 0°C. The reaction was quenched with saturated ammonium chloride and the two phases were separated. The aqueous phase was extracted with Et_2O, the combined organic fractions were washed with satd. aq $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 2.64 g of **29a** as a yellow oil. Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) yielded a white solid (2.04 g, 84%). IR (neat, cm^{-1}): 3058, 1747. ^1H NMR (C_6D_6) δ: 7.67–7.62 (m, 6H), 7.15–6.99 (m, 9H), 6.27 (dq, 1H, *J* = 15.3, 6.6 Hz), 5.92 (dd, 1H, *J* = 15.3, 1.6 Hz), 3.88 (d, 1H, *J* = 9.0 Hz), 3.66 (d, 1H, *J* = 9.0 Hz), 1.71 (s, 3H), 1.54 (dd, 3H, *J* = 6.6, 1.6 Hz), 1.47 (s, 3H). LR-MS (*m/z* (relative intensity)): 424 ([M]$^+$, 2), 243 (100), 165 (55). HR-MS calcd. for $C_{29}H_{28}O_3$: 424.2038; found: 424.2047.

Acetate 29b

Followed the same procedure as per acetate **29a**. Flash chromatography on silica gel eluting with EtOAc and hexanes (10:90) gave **29b** as a colourless oil (4.63 g, 90%). IR (neat, cm^{-1}): 3060, 2930, 1749, 1229, 1100, 837, 704. ^1H NMR (C_6D_6) δ: 7.49–7.45 (m, 6H), 7.36–7.14 (m, 9H), 6.10–5.97 (m, 1H), 5.63 (dm, 1H, *J* = 15.4 Hz), 4.59 (qd, 1H, *J* = 6.5, 2.2 Hz), 3.41–3.28 (m, 2H), 2.02 (s, 3H), 1.72 (dd, 3H, *J* = 6.6, 1.0 Hz), 1.41 (dd, 3H, *J* = 6.5, 1.8 Hz), 0.86 (s, 9H), 0.07–0.05 (m, 6H). LR-MS (*m/z* (relative intensity)): 568 ([M]$^+$, 1), 243 (100), 165 (50). HR-MS calcd. for $C_{36}H_{44}O_4Si$: 568.3009; found: 568.3000.

Acetate 29c

Followed the same procedure as per acetate **29a**. Flash chromatography on silica gel eluting with EtOAc and hexanes (5:95) gave a colourless oil (5.36 g, 85%). IR (neat, cm^{-1}): 3059, 2928, 1748. ^1H NMR ($CDCl_3$) δ: 7.48–7.44 (m, 6H), 7.33–7.21 (m, 9H), 6.10–5.96 (m, 1H), 5.63 (dm, 1H, *J* = 14.7 Hz), 4.42–4.36 (m, 2H), 3.39 (d, 1H, *J* = 9.0 Hz), 3.29 (d, 1H, *J* = 9.0 Hz), 3.23- 3.11 (m, 4H), 2.03 (s, 3H), 1.85–1.49 (m, 6H), 1.72 (d, 3H, *J* = 6.5 Hz), 0.86 (s, 9H), 0.06–0.04 (m, 6H). LR-MS (*m/z* (relative intensity)): 700 ([M]$^+$, 5), 640 ([M$^+$ – AcOH], 20), 243 (100), 165 (100). HR-MS calcd. for $C_{41}H_{52}O_4S_2Si$: 700.3076; found: 700.3085.

Allene 30

Copper iodide (2.70 g, 14.2 mmol) and lithium bromide (1.23 g, 14.2 mmol) were suspended in THF (30 mL) and the suspension was cooled to 0° C. A suspension of magnesium bromide (4.73 mL, 3.0 M in Et_2O, 14.2 mmol) was added and the resulting yellow suspension was stirred for 0.5 h. Acetate **29a** (1.00 g, 2.36 mmol) in THF (10 mL) was added drop wise and the reaction mixture was stirred for an additional 0.5 h at 0° C. Then, Et_2O was added (40 mL) and the mixture was poured into a saturated aqueous NH_4Cl–NH_4OH (9:1) solution and vigourously stirred in an atmosphere of air for 1 h. The phases were separated, the aqueous phase was extracted with Et_2O, the combined organic fractions were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 1.1 g of a yellow oil. Flash chromatography on silica gel eluting with EtOAc and hexanes (5:95) yielded a colourless oil (837 mg, 93%). IR (neat, cm^{-1}): 3058, 1955, 1491. ^1H NMR (C_6D_6) δ: 7.66–7.61 (m, 6H), 7.15–6.99 (m, 9H), 6.08 (dd, 1H, *J* = 15.8, 1.6 Hz), 5.54 (dq, 1H, *J* = 15.8, 6.6 Hz), 3.96 (s, 2H), 1.74 (s, 6H), 1.54 (dd, 3H, *J* = 6.6, 1.6 Hz). LR-MS (*m/z* (relative intensity)): 380 ([M]$^+$, 1), 243 (100). HR-MS calcd. for $C_{28}H_{28}O$: 380.2140; found: 380.2147.

Allene 31a

Acetate **29b** (4.60 g, 8.09 mmol) was dissolved in THF (20 mL). Tetrabutylammonium fluoride (16.17 mL, 1.0 M in THF, 16.17 mmol) was added and the orange solution was stirred for 12 h. Then, the mixture was poured into sat. NH_4Cl, the phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic fractions were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 3.70 g of an orange oil. Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) gave a fluffy white powder (2.80 g, 76%). IR (neat, cm^{-1}): 3467, 3023, 1738, 1449. ^1H NMR (C_6D_6) δ: 7.49–7.44 (m, 6H), 7.33–7.22 (m, 9H), 6.10–5.96 (m, 1H), 5.61 (dd, 1H, *J* = 15.4, 1.6 Hz), 4.63–4.56 (m, 1H), 3.39–3.30 (m, 2H), 2.04 (s, 3H), 1.73 (dd, 3H, *J* = 6.6, 1.6 Hz), 1.46 (d, 3H, *J* = 6.6 Hz). LR-MS (*m/z* (relative intensity)): 454 ([M]$^+$, 1), 243 (100), 165 (75). HR-MS calcd. for $C_{30}H_{30}O_4$: 454.2144; found: 454.2151.

The cuprate addition on this compound was performed as per allene **30**. Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) gave **31a** as a white powder (2.54 g, 100%) as a mixture of two inseparable isomers. IR (neat, cm^{-1}): 3588–3146, 3058, 1950, 1448. ^1H NMR (C_6D_6) δ: 7.50–7.42 (m, 6H), 7.32–7.21 (m, 9H), 5.85 (dm, 1H, *J* = 15.7 Hz), 5.49–5.36 (m, 1H), 4.34–4.25 (m, 1H), 3.75–3.65 (m, 2H), 1.86 (d, 3H, *J* = 1.8 Hz), 1.69 (dd, 3H, *J* = 6.6, 1.6 Hz), 1.36 (dd, 3H, *J* = 6.4, 1.8 Hz). LR-MS (*m/z* (relative intensity)): 409 ([M – 1], 10), 259 (50), 243 (100). HR-MS calcd. for $C_{29}H_{29}O_2$: 409.2167; found: 409.2149.

Allene 31b

Followed the same procedure as per allene **31a**, starting from **29c**. Flash chromatography of the intermediate alcohol on silica gel eluting with EtOAc and hexanes (30:70) gave a white powder (5.09 g, 89%). IR (neat, cm^{-1}): 3407, 3022, 1738. ^1H NMR ($CDCl_3$) δ: 7.48–7.44 (m, 6H), 7.34–7.22 (m, 9H), 6.03 (dq, 1H, *J* = 15.4, 6.6 Hz), 5.62 (dd, 1H, *J* = 15.4, 1.7 Hz), 4.44 (q, 1H, *J* = 5.7 Hz), 4.38 (td, 1H, *J* = 7.0, 1.8 Hz), 3.39–3.30 (m, 2H), 3.26–3.12 (m, 4H), 2.05 (s, 3H), 1.85–1.70 (m, 4H), 1.74 (dd, 3H, *J* = 6.6, 1.7 Hz), 1.64–1.52 (m, 2H), 1.56 (s, 1H). LR-MS (*m/z* (relative intensity)): 568 ([M$^+$ – H_2O]), 3), 508 (5), 243 (100), 105 (100). HR-MS calcd. for $C_{35}H_{36}O_3S_2$: 568.2106; found: 568.2114.

The alcohol was submitted to the cuprate reaction as per the alcohol precursor of **31a**. Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) gave **31b** as a white powder (4.31 g, 93%) containing an inseparable mixture of two isomers. IR (cm^{-1}): 3559, 3431, 3021, 1952, 1597. ^1H NMR ($CDCl_3$) δ: 7.49–7.42 (m, 12H), 7.32–7.21 (m, 18H), 5.86 (dd, 2H, *J* = 16.0, 1.6 Hz), 5.44 (dm, 2H, *J* = 16.0 Hz), 4.41 (q, 2H, *J* = 7.1 Hz), 4.16–4.06 (m, 2H), 3.75–3.65 (m, 4H), 3.27–3.13 (m, 8H), 1.89–1.72 (m, 4H), 1.83 (s, 6H), 1.71–1.48 (m, 8H), 1.70 (dd, 6H, *J* = 6.6, 1.6 Hz), 1.55 (s, 2H). LR-MS (*m/z* (relative intensity)): 542 ([M]$^+$, 1), 513 ([M$^+$ – C_2H_5], 3), 299 (10), 243 (100). HR-MS calcd. for $C_{34}H_{38}O_2S_2$: 542.2313; found: 542.2309.

Diester 32a

Allene **31a** (1.84 g, 4.49 mmol), fumaric acid, monoethyl ester (775 mg, 5.38 mmol), and DMAP (110 mg, 0.90 mmol) were dissolved in CH_2Cl_2 (40 mL). The solution was cooled to 0°C and stirred for 0.5 h. DCC (1.11 g, 5.38 mmol) was added in small portions and the reaction mixture stirred for 2.5 h during which time a white precipitate formed. The solvent was evaporated and the product purified by flash chromatography on silica gel eluting with EtOAc and hexanes (15:85) giving **32a** as a colourless oil (2.24 g, 93%) containing a 1:1 mixture of inseparable diastereomers. IR (neat, cm^{-1}): 3039, 1957, 1722, 1449. ^1H NMR (C_6D_6) δ: 7.64–7.57 (m, 6H), 7.16–7.09 (m, 9H), 7.06–7.00 (m, 2H), 5.93 (dm, 1H, *J* = 15.8 Hz), 5.74–5.59 (m, 1H), 5.51–5.39 (m, 1H), 3.94–3.92 (m, 2H), 3.90–3.78 (m, 2H), 1.77 (d, 3H, *J* = 7.8 Hz), 1.45 (dd, 3H, *J* = 6.6, 1.6 Hz), 1.36 (t, 3H, *J* = 6.1 Hz), 0.84–0.80 (m, 3H). LR-MS (*m/z* (relative intensity)): 537 ([M + 1], 2), 243 (95), 167 (90), 105 (100). HR-MS calcd. for $C_{35}H_{37}O_5$: 537.2641; found: 537.2622.

Diester 32b

Followed the same procedure as per diester **32a**, starting from **31b**. Flash chromatography on silica gel eluting with EtOAc and hexanes (15:85) gave a colourless oil (1.83 g, 88%) containing a mixture of two isomers. IR (neat, cm^{-1}): 3026, 1958, 1723, 1646. ^1H NMR ($CDCl_3$, integrated for two isomers) δ: 7.48–7.42 (m, 12H), 7.32–7.20 (m, 18H), 6.85–6.80 (m, 4H), 5.88–5.73 (m, 2H), 5.47–5.37 (m, 4H), 4.42–4.19 (m, 6H), 3.67 (s, 4H), 3.27–3.10 (m, 8H), 1.95–1.74 (m, 14H), 1.71–1.64 (m, 6H), 1.55–1.41 (m, 4H), 1.30 (t, 3H, *J* = 7.1 Hz), 1.29 (t, 3H, *J* = 7.1 Hz). LR-MS (*m/z* (relative intensity)): 623 ([M$^+$ – OEt], 5), 381 (20), 243 (100). HR-MS calcd. for $C_{38}H_{39}O_4S_2$: 623.2290; found: 623.2303.

Cycloadduct 33

Allene **30** (837 mg, 2.2 mmol) and methyl fumarate (634 mg, 4.4 mmol) were dissolved in benzene (10 mL) and refluxed for 12 h. Benzene was evaporated to yield 1.6 g of a yellow oil. Flash chromatography on silica gel eluting with EtOAc and hexanes (5:95) afforded 1.04 g of a colourless oil (90%). IR (neat, cm^{-1}): 3059, 1732, 1448. ^1H NMR ($CHCl_3$) δ: 7.46–7.42 (m, 6H), 7.32–7.19 (m, 9H), 5.92 (d, 1H, *J* = 2.7 Hz), 4.04 (d, 1H, *J* = 5.1 Hz), 3.75–3.62 (m, 2H), 3.71 (s, 3H), 3.51 (s, 3H), 2.89 (dd, 1H, *J* = 7.9, 5.1 Hz), 2.43–2.33 (m, 1H), 1.76 (s, 3H), 1.43 (s, 3H), 1.20 (d, 3H, *J* = 7.2 Hz). LR-MS (*m/z* (relative intensity)): 524 ([M]$^+$, 0.5), 443 (1), 243 (100), 165 (5). HR-MS calcd. for $C_{34}H_{36}O_5$: 524.2563; found: 524.2569.

Aldehyde 34

Cycloadduct **33** (369 mg, 0.75 mmol) was dissolved in Et_2O (2 mL). An 88% aqueous solution of formic acid (23 mL) in Et_2O (17 mL) was added and the mixture was stirred for 20 min. It was poured into EtOAc (100 mL). The phases were separated, the organic phase was washed with water, satd. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 215 mg of a yellow oil. Flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) yielded a colourless oil (156 mg, 73%). IR (neat, cm^{-1}): 3454, 1732, 1435. ^1H NMR ($CHCl_3$) δ: 5.69 (d, 1H, *J* = 3.1 Hz), 4.48 (dd, 1H, *J* = 12.3, 5.5 Hz), 4.13 (dd, 1H, *J* = 12.3, 5.5 Hz), 4.08 (d, 1H, *J* = 4.9 Hz), 3.72 (s, 3H), 3.67 (s, 3H), 2.73 (dd, 1H, *J* = 7.0,

4.9 Hz), 2.51–2.39 (m, 1H), 2.28 (t, 1H, *J* = 5.5 Hz), 1.82 (s, 3H), 1.79 (s, 3H), 1.10 (d, 3H, *J* = 7.3 Hz). LR-MS (*m/z* (relative intensity)): 282 ([M]$^+$, 1), 264 ([M$^+$ – H_2O], 5), 232 (20), 204 (100), 173 (85), 145 (60), 91 (30). HR-MS calcd. for $C_{15}H_{22}O_5$: 282.1467; found: 282.1471.

This alcohol (146 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (5 mL). Dess–Martin periodinane (288 mg, 0.68 mmol) was added and the mixture was stirred for 0.5 h. Et_2O (10 mL) was added provoking the formation of a white precipitate. The suspension was neutralized with satd. $NaHCO_3$ (20 mL) containing 5 g of sodium thiosulfate. The resulting bilayered mixture was vigorously stirred for 0.5 h. The phases were separated, the aqueous phase was extracted with Et_2O, the combined organic fractions were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 146 mg of **34** as a colourless oil (146 mg, 100%). IR (neat, cm^{-1}): 2954, 2713, 1732, 1694. ^{1}H NMR (C_6D_6) δ: 9.30 (s, 1H), 6.10 (d, 1H, *J* = 3.0 Hz), 4.24 (d, 1H, *J* = 4.2 Hz), 3.26 (s, 3H), 3.20 (s, 3H), 3.05 (dd, 1H, *J* = 6.3, 4.2 Hz), 2.69 (quint, 1H, *J* = 7.1, 3.0 Hz), 1.71 (s, 3H), 1.61 (s, 3H), 1.02 (d, 3H, *J* = 7.3 Hz). LR-MS (*m/z* (relative intensity)): 280 ([M]$^+$, 50), 221 (65), 161 (100). HR-MS calcd. for $C_{15}H_{20}O_5$: 280.1311; found: 280.1306.

Cycloadducts 35a

Allene **32a** (2.32 g, 4.32 mmol) was dissolved in benzene (100 mL). The solution was refluxed for 15 h. The solvent was evaporated and the crude product (2.75 g) was purified by flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) giving a white powder (1.59 g, 69%) containing an inseparable mixture of two diastereomers. IR (neat, cm^{-1}): 3022, 2978, 1732, 1449. ^{1}H NMR (C_6D_6, integrated for two isomers) δ: 7.57–7.52 (m, 12H), 7.15–7.01 (m, 18H), 6.38 (d, 1H, *J* = 7.5 Hz), 6.36 (d, 1H, *J* = 7.5 Hz), 4.17–4.00 (m, 6H), 3.96–3.70 (m, 6H), 3.32 (dd, 1H, *J* = 11.2, 4.8 Hz), 3.23 (dd, 1H, *J* = 11.7, 5.0 Hz), 2.77–2.61 (m, 2H), 1.25–1.02 (m, 12H), 0.99 (d, 6H, *J* = 7.0 Hz), 0.93 (d, 6H, *J* = 7.0 Hz). LR-MS (*m/z* (relative intensity)): 536 ([M]$^+$, 1), 491 ([M$^+$ – C_2H_5O], 5), 243 (100). HR-MS calcd. for $C_{33}H_{31}O_4$: 491.2222; found: 491.2230.

Cycloadducts 35b

Followed the same procedure as per **35a**, starting from **32b**. Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) gave a colourless oil (1.41 g, 69%) containing an inseparable mixture of two isomers. IR (neat, cm^{-1}): 3023, 1732, 1597. ^{1}H NMR ($CDCl_3$, integrated for two isomers) δ: 7.48–7.38 (m, 12H), 7.33–7.22 (m, 18H), 6.43 (d, 1H, *J* = 7.3 Hz), 6.38 (d, 1H, *J* = 7.0 Hz), 4.82 (dm, 1H, *J* = 8.4 Hz), 4.49–4.40 (m, 3H), 4.24 (q, 2H, *J* = 7.1 Hz), 4.23 (q, 2H, *J* = 7.1 Hz), 3.87–3.73 (m, 4H), 3.68 (dm, 1H, *J* = 11.6 Hz), 3.59 (dt, 1H, *J* = 11.3, 2.4 Hz), 3.26–3.12 (m, 8H), 3.04 (dd, 1H, *J* = 11.3, 4.8 Hz), 2.97 (dd, 1H, *J* = 11.6, 5.0 Hz), 2.89–2.74 (m, 2H), 1.97–1.52 (m, 12 H), 1.60 (s, 3H), 1.57 (s, 3H), 1.32 (t, 3H, *J* = 7.1 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 0.95 (d, 3H, *J* = 7.0 Hz), 0.93 (d, 3H, *J* = 7.0 Hz). LR-MS (*m/z* (relative intensity)): 668 ([M]$^+$, 3), 381 (20), 243 (100). HR-MS calcd. for $C_{40}H_{44}O_5S_2$: 668.2630; found: 668.2643.

Aldehydes 36a and 36b

Followed the same procedure as for the deprotection of **33** and the Dess–Martin oxidation to **34**. Flash chromatography on silica gel eluting with EtOAc and hexanes (40:60) gave two diastereomeric alcohols as a colourless oils (each 256 mg for a total of 512 mg, 82%). Less polar isomer: ^{1}H NMR ($CDCl_3$) δ: 6.27 (d, 1H, *J* = 7.0 Hz), 5.08 (q, 1H, 6.8 Hz), 4.42–4.31 (m, 2H), 4.21 (q, 1H, *J* = 7.2 Hz), 4.21 (q, 1H, *J* = 7.2 Hz), 3.63 (dt, 1H, *J* = 10.9, 2.5 Hz), 3.04 (dd, 1H, *J* = 10.9, 4.8 Hz), 2.86–2.74 (m, 1H), 2.03–2.00 (m, 3H), 1.57 (d, 3H, *J* = 6.8 Hz), 1.48–1.42 (m, 1H), 1.29 (t, 3H, *J* = 7.2 Hz), 0.94 (d, 3H, *J* = 7.1 Hz). More polar isomer: IR (neat, cm^{-1}): 3453, 1732, 1454. ^{1}H NMR ($CDCl_3$) δ: 6.20 (d, 1H, *J* = 6.9 Hz), 4.74 (q, 1H, *J* = 6.9 Hz), 4.41 (dd, 1H, *J* = 12.6, 5.2 Hz), 4.32 (dd, 1H, *J* = 12.6, 6.2 Hz), 4.23 (q, 2H, *J* = 7.1 Hz), 3.71 (dt, 1H, *J* = 11.6, 1.8 Hz), 2.94 (dd, 1H, *J* = 11.6, 5.1 Hz), 2.80–2.69 (m, 1H), 2.04 (d, 3H, *J* = 2.4 Hz), 1.56 (d, 3H, *J* = 6.9 Hz), 1.41 (t, 1H, *J* = 5.8 Hz), 1.30 (t, 3H, *J* = 7.1 Hz), 0.95 (d, 3H, *J* = 7.1 Hz). LR-MS (*m/z* (relative intensity)): 294 ([M]$^+$, 45), 203 (75), 175 (55), 159 (100). HR-MS calcd. for $C_{16}H_{22}O_5$: 294.1467; found: 294.1473.

Each of the isomeric alcohols were oxidized separately and each crude product obtained was purified by flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) to give a colourless oil. Aldehyde **36a** having the α-methyl group (44 mg, 76%). IR (neat, cm^{-1}): 2981, 2730, 1732, 1699. ^{1}H NMR ($CDCl_3$) δ: 9.55 (s, 1H), 7.04 (d, 1H, *J* = 6.3 Hz), 5.11 (q, 1H, *J* = 6.7 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 3.62 (dt, 1H, *J* = 8.5, 2.6 Hz), 3.16 (dd, 1H, *J* = 8.5, 4.5 Hz), 2.98–2.86 (m, 1H), 1.81 (s, 3H), 1.59 (d, 3H, *J* = 6.7 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.17 (d, 3H, *J* = 7.2 Hz). LR-MS (*m/z* (relative intensity)): 292 ([M]$^+$, 20), 247 (25), 86 (90), 78 (100). HR-MS calcd. for $C_{16}H_{20}O_5$: 292.1311; found: 292.1315. Aldehyde **36b** having the β-methyl group (42 mg, 70% yield): ^{1}H NMR ($CDCl_3$) δ: 9.57 (s, 1H), 6.97 (d, 1H, *J* = 6.1 Hz), 4.84 (qd, 1H, *J* = 7.1, 0.9 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 3.69 (dt, 1H, *J* = 8.4, 2.1 Hz), 3.19 (dd, 1H, *J* = 8.4, 4.6 Hz), 2.88–2.77 (m, 1H), 1.80 (d, 3H, *J* = 2.5 Hz), 1.59 (d, 3H, *J* = 7.1 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 1.19 (d, 3H, *J* = 7.2 Hz).

Enoates 37

Mercuric oxide red (520 mg, 2.4 mmol) was dissolved in THF:water (85:15) (8.2 mL) and $BF_3{\cdot}OEt_2$ (0.30 mL, 2.4 mmol) was added drop wise. Cycloadduct **35b** (800 mg, 1.2 mmol) in THF (2 mL) was slowly added to the orange mixture, which was stirred for 0.5 h. Et_2O (30 mL) was added and the resulting precipitate was filtered through a cintered glass. The organic phase was washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a white powder (711 mg, 100%) containing an inseparable mixture of two diastereomers. IR (neat, cm^{-1}): 3060, 2724, 1730, 1709, 1598. ^{1}H NMR ($CDCl_3$) δ: 9.77 (s, 2H), 7.48–7.39 (m, 12H), 7.33–7.20 (m, 18H), 6.42 (d, 1H, *J* = 7.3 Hz), 6.38 (d, 1H, *J* = 7.0 Hz), 4.84 (dm, 1H, *J* = 7.4 Hz), 4.43 (dm, 1H, *J* = 10.1 Hz), 4.24 (q, 2H, *J* = 7.1 Hz), 4.23 (q, 2H, *J* = 7.1 Hz), 3.86–3.73 (m, 4H), 3.65 (dm, 1H, *J* = 11.7 Hz), 3.60 (dt, 1H, *J* = 11.5, 2.4 Hz), 3.03 (dd, 1H, *J* = 11.5, 4.8 Hz), 2.97 (dd, 1H, *J* = 11.7, 5.0 Hz), 2.90–2.75 (m, 2H), 2.52 (t, 4H, *J* =

5.9 Hz), 2.00–1.65 (m, 8 H), 1.60 (s, 3H), 1.57 (s, 3H), 1.32 (t, 3H, *J* = 7.1 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 6.6 Hz). LR-MS (*m/z* (relative intensity)): 610 ([M + NH_4], 5), 566 (5), 243 (100). HR-MS calcd. for $C_{38}H_{44}NO_6$: 610.3168; found: 610.3154.

Sodium hydride (58 mg, 60% in oil, 1.44 mmol) was suspended in THF (7 mL) at 0°C. Methyl diethoxyphosphonoacetate (0.27 mL, 1.44 mmol) was added slowly and the mixture was stirred for 0.5 h. The anion was added via cannula to a solution of the above aldehyde (711 mg, 1.2 mmol) in THF (7 mL) at 0°C. After 1 h, the reaction was poured into a saturated solution of NH_4Cl, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic fractions were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 800 mg of a yellow powder. Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) gave **37** as a white powder (544 mg, 70%) containing an inseparable mixture of two isomers. IR (neat, cm^{-1}): 3058, 1729, 1657. ^1H NMR (C_6D_6, integrated for two isomers) δ: 7.45–7.40 (m, 12H), 7.33–7.22 (m, 18H), 6.95 (dt, 1H, *J* = 15.7, 6.7 Hz), 6.93 (dt, 1H, *J* = 15.7, 6.8 Hz), 6.42 (d, 1H, *J* = 7.3 Hz), 6.38 (d, 1H, *J* = 7.0 Hz), 5.84 (dd, 2H, *J* = 15.7, 2.1 Hz), 4.82 (dm, 1H, *J* = 8.3 Hz), 4.42 (dm, 1H, *J* = 10.6 Hz), 4.24 (q, 2H, *J* = 7.1 Hz), 4.23 (q, 2H, *J* = 7.1 Hz), 3.86–3.72 (m, 4H), 3.74 (s, 3H), 3.73 (s, 3H), 3.66 (dm, 1H, *J* = 11.7 Hz), 3.59 (dt, 1H, *J* = 11.3, 2.4 Hz), 3.04 (dd, 1H, *J* = 11.3, 4.8 Hz), 2.97 (dd, 1H, *J* = 11.7, 5.0 Hz), 2.88–2.73 (m, 2H), 2.31–2.19 (m, 4H), 1.93–1.50 (m, 14 H), 1.31 (t, 3H, *J* = 7.1 Hz), 1.30 (t, 3H, *J* = 7.1 Hz), 0.95 (d, 3H, *J* = 7.3 Hz), 0.93 (d, 3H, *J* = 7.3 Hz). LR-MS (*m/z* (relative intensity)): 666 ([M + NH_4], 2), 407 (15), 243 (100), 165 (20). HR-MS calcd. for $C_{41}H_{48}NO_7$: 666.3431; found: 666.3420.

Aldehydes 38a and 38b

Followed the same procedure as per the deprotection of **33** and oxidation to give **34**. Flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) gave two separable alcohols as colourless oils (153 mg, 46% and 153 mg, 46%). Less polar isomer: ^1H NMR ($CDCl_3$) δ: 6.97 (dt, 1H, *J* = 15.7, 6.9 Hz), 6.28 (d, 1H, *J* = 7.0 Hz), 5.86 (d, 1H, *J* = 15.7 Hz), 4.89 (dm, 1H, *J* = 8.9 Hz), 4.40–4.30 (m, 2H), 4.21 (q, 2H, *J* = 7.1 Hz), 3.73 (s, 3H), 3.61 (dt, 1H, *J* = 10.8, 2.5 Hz), 3.03 (dd, 1H, *J* = 10.8, 4.8 Hz), 2.84–2.74 (m, 1H), 2.30 (q, 2H, *J* = 6.9 Hz), 2.00 (s, 3H), 1.99–1.78 (m, 3H), 1.72–1.60 (m, 1H), 1.57 (s, 1H), 1.29 (t, 3H, *J* = 7.1 Hz), 0.93 (d, 3H, *J* = 7.1 Hz). More polar isomer: IR (neat, cm^{-1}): 3480, 1732, 1658. ^1H NMR ($CDCl_3$) δ: 6.95 (dt, 1H, *J* = 15.7, 7.0 Hz), 6.19 (d, 1H, *J* = 6.8 Hz), 5.86 (d, 1H, *J* = 15.7 Hz), 4.54 (dm, 1H, *J* = 10.2 Hz), 4.42–4.29 (m, 2H), 4.22 (q, 2H, *J* = 7.1 Hz), 3.73 (s, 3H), 3.67 (dm, 1H, *J* = 11.4 Hz), 2.95 (dd, 1H, *J* = 11.4, 5.1 Hz), 2.79–2.69 (m, 1H), 2.34–2.23 (m, 2H), 2.04 (d, 3H, *J* = 2.5 Hz), 2.00–1.55 (m, 4H), 1.30 (t, 3H, *J* = 7.1 Hz), 0.94 (d, 3H, *J* = 7.1 Hz). LR-MS (*m/z* (relative intensity)): 406 ([M]$^+$, 15), 297 (50), 175 (100). HR-MS calcd. for $C_{22}H_{30}O_7$: 406.1991; found: 406.1999.

Each alcohol was then oxidized separately. Flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) gave a colourless oil. Aldehyde **38a** with the α-chain (180 mg, 87%): IR (neat, cm^{-1}): 2728, 1738, 1714, 1694. ^1H NMR ($CDCl_3$) δ: 9.53 (s, 1H), 7.04 (d, 1H, *J* = 6.3 Hz), 6.97 (dt, 1H, *J* = 15.7, 7.0 Hz), 5.87 (d, 1H, *J* = 15.7 Hz), 4.94 (dm, 1H, *J* = 8.7 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 3.74 (s, 3H), 3.61 (dt, 1H, *J* = 8.5, 2.6 Hz), 3.15 (dd, 1H, *J* = 8.5, 4.5 Hz), 2.97–2.86 (m, 1H), 2.31 (q, 2H, *J* = 7.0 Hz), 2.00–1.82 (m, 3H), 1.79 (s, 3H), 1.78–1.60 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.16 (d, 3H, *J* = 7.2 Hz). LR-MS (*m/z* (relative intensity)): 422 ([M + NH_4], 15), 405 ([M + H^+], 100). HR-MS calcd. for $C_{22}H_{29}O_7$: 405.1913; found: 405.1911. Aldehyde **38b** with the β-chain (52 mg, 100%): ^1H NMR ($CDCl_3$) δ: 9.55 (s, 1H), 6.96 (d, 1H, *J* = 5.6 Hz), 6.95 (dt, 1H, *J* = 15.6, 7.0 Hz), 5.86 (d, 1H, *J* = 15.6 Hz), 4.66 (dm, 1H, *J* = 9.7 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 3.73 (s, 3H), 3.63 (dt, 1H, *J* = 7.4, 2.2 Hz), 3.27 (dd, 1H, *J* = 7.4, 4.8 Hz), 2.82–2.72 (m, 1H), 2.34–2.25 (m, 2H), 1.96–1.75 (m, 3H), 1.79 (d, 3H, *J* = 2.2), 1.72–1.60 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.22 (d, 3H, *J* = 7.2 Hz).

Cycloadducts 14β-39a and 14α-39a

Followed the same procedure as per the preparation of cycloadduct **39b**. The crude mixture was purified by flash chromatography (mixture of hexanes:EtOAc, 15:1) to provide 145 mg (84%) of cycloadducts as an approximate 4:1 mixture of two separable diastereomers. 14α-**39a**: ^1H NMR ($CDCl_3$) δ: 7.7–7.3 (m, 10H), 6.51 (d, 1H, *J* = 0.5 Hz), 5.80 (ddt, 1H, *J* = 17.0, 10.3, 6.6 Hz), 5.28 (t, 1H, *J* = 6.8 Hz), 4.97 (dt, 1H, *J* = 17.0, 1.0 Hz), 4.90 (dt, 1H, *J* = 10.3, 1.0 Hz), 4.78 (dd, 1H, *J* = 7.8, 0.5 Hz), 4.09 (m, 1H), 3.88 (dq, 1H, *J* = 9.5, 7.0 Hz), 3.55 (dq, 1H, *J* = 9.5, 7.0 Hz), 2.40–2.33 (m, 1H), 2.21–2.17 (m, 3H), 2.06–1.87 (m, 3H), 1.85–1.77 (m, 2H), 1.48–1.37 (m, 1H), 1.36–1.28 (m, 3H), 1.23–1.07 (m, 2H), 1.21 (t, 3H, *J* = 7.0 Hz), 1.09 (s, 9H). 14 β-**39a**: ^1H NMR ($CDCl_3$) δ: 7.7–7.3 (m, 10H), 6.60 (d, 1H, *J* = 0.5 Hz), 5.81 (ddt, 1H, *J* = 17.0, 10.3, 6.6 Hz), 5.08–4.90 (m, 3H), 4.94 (dd, 1H, *J* = 7.8, 0.5 Hz), 4.03 (m, 1H), 3.96 (dq, 1H, *J* = 9.5, 7.0 Hz), 3.11 (dq, 1H, *J* = 9.5, 7.0 Hz), 2.55–2.41 (m, 1H), 2.25–2.00 (m, 4H), 1.85–1.79 (m, 1H), 1.77–1.20 (m, 9H), 1.27 (t, 3H, *J* = 7.0 Hz), 1.05 (s, 9H).

Cycloadducts 14β-39b and 14α-39b

To a stirred solution of aldehyde **20b** (307 mg, 0.990 mmol) and ethyl vinyl ether (4.6 mL) was added $Yb(FOD)_3$ (127 mg, 0.120 mmol) at room temperature. The reaction mixture was stirred for 1 day before a solution of brine was added. This mixture was stirred for about 1 h then separated and the product extracted with ethyl ether, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by flash chromatography (mixture of hexanes: EtOAc, 15:1) to provide 308 mg (81%) of cycloadducts as an approximate 1:1 mixture of inseparable diastereomers. IR (neat, cm^{-1}): 3076, 1640. ^1H NMR ($CDCl_3$) δ: 7.35–7.24 (m, 5H), 1 isomer 6.44 (d, 1H, *J* = 2.1 Hz), one isomer 6.39 (d, 1H, *J* = 1.9 Hz), 5.80 (ddt, 1H, *J* = 17.0, 10.3, 6.6 Hz), 5.34–5.26 (m, 1H), 5.03–4.91 (m, 2H), 4.85–4.81 (m, 1H), one isomer 4.67 (d, 1H, *J* = 11.4 Hz), one isomer 4.64 (d, 1H, *J* = 12.1 Hz), one isomer 4.47 (d, 1H, *J* = 11.4 Hz), one isomer 4.42 (d, 1H, *J* = 12.2 Hz), 4.01–3.91 (m, 1H), one isomer 3.64–3.61 (m, 1H), 3.61–3.53 (m, 1H), one isomer 3.20–3.12 (m, 1H), one isomer 2.64 (dt, 1H, *J* = 14.3,

3.5 Hz), 2.54–1.94 (m, 7H), 1.83–1.74 (m, 1H), 1.63–1.52 (m, 1H), 1.44–1.29 (m, 5H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 138.9 (d), 138.6 (s), 136.7 (d), 136.4 (d), 134.3 (s), 133.9 (s), 128.4 (d), 128.2 (d), 127.8 (d), 127.6 (d), 127.3 (d), 122.3 (d), 121.5 (d), 116.8 (s), 116.2 (s), 114.2 (t), 100.1 (d), 99.9 (d), 82.5 (d), 74.1 (d), 73.7 (d), 71.0 (t), 70.5 (t), 64.5 (t), 64.4 (t), 39.9 (d), 38.8 (d), 33.7 (t), 33.5 (t), 30.9 (t), 30.1 (t), 29.4 (t), 28.5 (t), 27.7 (t), 27.6 (t), 27.4 (t), 25.4 (t), 21.3 (t), 15.2 (q). LR-MS (*m*/*z* (relative intensity)): 382 ([M]$^+$, 40), 91 (100). HR-MS calcd. for $C_{25}H_{34}O_3$: 382.2520; found: 382.2553.

Cycloadducts 40a–c

These cycloadducts were not isolated because they spontaneously underwent the subsequent intramolecular cycloaddition. Their stereochemistries were therefore deduced from the isolation of tetracycles **48**–**51**.

Cycloadduct 41

Aldehyde **34** (140 mg, 0.50 mmol) was dissolved in ethyl vinyl ether (5 mL) and $Yb(FOD)_3$ (79 mg, 0.075 mmol) was added. After 12 h, the solvant was evaporated and a colourless oil was obtained (260 mg). Flash chromatography on silica gel eluting with EtOAc and hexanes (10:90) yielded **41** as a white crystalline compound (167 mg, 95%). IR (neat, cm^{-1}): 2975, 1733, 1640, 1164, 1132. ^{1}H NMR (C_6D_6) δ: 6.47 (d, 1H, *J* = 2.3 Hz), 4.83 (dd, 1H, *J* = 9.3, 2.9 Hz), 4.21 (d, 1H, *J* = 3.1 Hz), 3.90 (dq, 1H, *J* = 9.5, 7.1 Hz), 3.38–3.27 (m, 2H), 3.32 (s, 3H), 3.32 (s, 3H), 2.36–2.24 (tm, 1H, *J* = 11.6 Hz), 1.97 (ddd, 1H, *J* = 12.7, 4.5, 3.1 Hz), 1.80 (s, 3H), 1.76 (s, 3H), 1.75–1.65 (m, 1H), 1.57–1.46 (m, 1H), 1.10 (t, 3H, *J* = 7.1 Hz), 0.91 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (C_6D_6) δ: 175.2 (s), 174.8 (s), 141.6 (d), 129.1 (s), 124.6 (s), 114.2 (s), 100.6 (d), 64.5 (t), 52.1 (q), 51.5 (q), 51.1 (d), 47.1 (d), 36.6 (d), 35.5 (d), 33.4 (t), 23.8 (q), 21.7 (q), 17.7 (q), 15.7 (q). LR-MS (*m*/*z* (relative intensity)): 352 ([M]$^+$, 60), 221 (80), 189 (50), 161 (100), 129 (40), 91 (40). HR-MS calcd. for $C_{28}H_{28}O$: 352.1886; found: 352.1875.

Cycloadducts 42a and 42b

Each aldehyde **36a** and **36b** were separately submitted to the same protocol as per cycloadduct **41**. Each crude product was purified by flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) to give a white powder. Cycloadduct **42a**: IR (neat, cm^{-1}): 2977, 1735, 1626. ^{1}H NMR (C_6D_6) δ: 6.02 (d, 1H, *J* = 2.3 Hz), 4.74 (dd, 1H, *J* = 7.5, 3.0 Hz), 4.24 (qd, 1H, *J* = 7.7, 1.9 Hz), 4.20–4.01 (m, 2H), 3.80 (qd, 1H, *J* = 9.4, 7.1 Hz), 3.52 (dt, 1H, *J* = 11.9, 2.5 Hz), 3.31 (qd, 1H, *J* = 9.4, 7.1 Hz), 3.09 (dd, 1H, *J* = 11.9, 4.8 Hz), 2.16–2.07 (m, 1H), 1.90–1.82 (m, 1H), 1.74–1.58 (m, 2H), 1.41 (d, 3H, *J* = 1.9 Hz), 1.11 (t, 3H, *J* = 7.1 Hz), 1.07–1.02 (m, 6H), 0.90 (d, 3H, *J* = 7.2 Hz). LR-MS (*m*/*z* (relative intensity)): 364 ([M]$^+$, 10), 318 (90), 78 (100). HR-MS calcd. for $C_{20}H_{28}O_6$: 364.1886; found: 364.1888. Cycloadduct **42b**: ^{1}H NMR (C_6D_6) δ: 6.12 (d, 1H, *J* = 2.2 Hz), 4.73 (dd, 1H, *J* = 7.4, 2.6 Hz), 4.28 (qd, 1H, *J* = 6.8, 1.2 Hz), 4.25–4.02 (m, 2H), 3.79 (qd, 1H, *J* = 9.4, 7.1 Hz), 3.72 (dt, 1H, *J* = 11.6, 1.9 Hz), 3.31 (qd, 1H, *J* = 9.4, 7.1 Hz), 3.07 (dd, 1H, *J* = 11.6, 6.0 Hz), 2.12–2.01 (m, 1H), 1.93–1.85 (m, 1H), 1.73 (ddd, 1H, *J* = 13.1, 5.9, 2.6 Hz), 1.62–1.52 (m, 1H), 1.30 (d, 3H, *J* = 2.4 Hz), 1.10 (t, 3H, *J* = 7.0 Hz), 1.06 (t, 3H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 7.1 Hz).

Cycloadducts 43a and 43b

Followed the same procedure as per **42a** and **42b**. Isomers **38a** and **38b** were reacted separately. Flash chromatography on silica gel eluting with EtOAc and hexanes (30:70) gave a white powder. Cycloadduct **43a** having the α-chain (41 mg, 72%): ^{1}H NMR (C_6D_6) δ: 6.89 (dt, 1H, *J* = 15.7, 6.9 Hz), 6.18 (d, 1H, *J* = 1.6 Hz), 5.80 (d, 1H, *J* = 15.7 Hz), 4.74 (dd, 1H, *J* = 7.4, 2.6 Hz), 4.19 (dm, 1H, *J* = 10.8 Hz), 4.16 (q, 1H, *J* = 7.1 Hz), 4.07 (q, 1H, *J* = 7.1 Hz), 3.81 (dq, 1H, *J* = 9.4, 7.1 Hz), 3.74 (dt, 1H, *J* = 11.3, 2.3 Hz), 3.45 (s, 3H), 3.32 (dq, 1H, *J* = 9.4, 7.0 Hz), 3.05 (dd, 1H, *J* = 11.3, 5.7 Hz), 2.07–1.94 (m, 2H), 1.79–1.71 (m, 1H), 1.70–1.52 (m, 3H), 1.48–1.20 (m, 4H), 1.36 (d, 3H, *J* = 2.3 Hz), 1.11 (t, 3H, *J* = 7.0 Hz), 1.06 (t, 3H, *J* = 7.1 Hz), 0.89 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (C_6D_6) δ: 173.4 (s), 171.1 (s), 166.6 (s), 148.6 (d), 142.1 (d), 128.8 (s), 126.0 (s), 125.1 (s), 121.8 (d), 99.0 (d), 82.9 (d), 64.2 (t), 60.7 (t), 51.0 (q), 45.0 (d), 39.5 (d), 35.6 (d), 34.5 (d), 33.6 (t), 31.5 (t), 30.9 (t), 24.3 (t), 17.0 (q), 16.6 (q), 15.3 (q), 14.3 (q). Cycloadduct **43b** having the β-chain (40 mg, 71%): IR (neat, cm^{-1}): 2955, 1729, 1630. ^{1}H NMR (C_6D_6) δ: 6.97 (dt, 1H, *J* = 15.7, 6.9 Hz), 6.09 (d, 1H, *J* = 2.2 Hz), 5.85 (d, 1H, *J* = 15.7 Hz), 4.76 (dd, 1H, *J* = 7.8, 2.7 Hz), 4.21 (dm, 1H, *J* = 7.2 Hz), 4.15 (q, 1H, *J* = 7.1 Hz), 4.08 (q, 1H, *J* = 7.1 Hz), 3.82 (dq, 1H, *J* = 9.4, 7.1 Hz), 3.60 (dt, 1H, *J* = 11.7, 2.2 Hz), 3.45 (s, 3H), 3.33 (dq, 1H, *J* = 9.4, 7.1 Hz), 3.11 (dd, 1H, *J* = 11.7, 5.0 Hz), 2.17–2.07 (m, 1H), 1.98–1.90 (m, 1H), 1.77–1.59 (m, 4H), 1.54–1.40 (m, 1H), 1.42 (d, 3H, *J* = 2.2 Hz), 1.39–1.15 (m, 3H), 1.12 (t, 3H, *J* = 7.1 Hz), 1.05 (t, 3H, *J* = 7.1 Hz), 0.93 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (C_6D_6) δ: 173.4 (s), 171.9 (s), 166.7 (s), 148.9 (d), 142.5 (d), 129.2 (s), 129.2 (s), 127.8 (s), 121.7 (d), 99.3 (d), 79.3 (d), 64.1 (t), 60.7 (t), 51.0 (q), 43.2 (d), 41.6 (d), 36.6 (d), 34.7 (d), 34.1 (t), 31.8 (t), 31.1 (t), 24.1 (t), 17.0 (q), 15.3 (q), 14.7 (q), 14.2 (q). LR-MS (*m*/*z* (relative intensity)): 476 ([M]$^+$, 1), 432 (65), 305 (100). HR-MS calcd. for $C_{26}H_{37}O_8$: 477.2488; found: 477.2477.

Tetracycles 53a and 53b

Aldehyde **24a** underwent the same procedure as per the formation of cycloadduct **41**. The crude tetracycles **48** (186 mg, 0.384 mmol) were isolated in 92% combined yield but only two could be obtained pure and characterized. Therefore, the crude mixture was mixed with $LiAlH_4$ (32 mg, 0.844 mmol) in THF (4 mL). The yield of the combined reduced tetracycles was 80% and the yield of pure tetracycle **53** was 45 mg (21% for two steps) and the yield of **53b** was 30 mg (14% for two steps). Tetracycle **53a**: mp 131.4°C. IR ($CHCl_3$, cm^{-1}): 3506, 3008, 2927, 2857, 1612, 1513, 1380, 1249, 1066, 1035. ^{1}H NMR (C_6D_6) δ: 7.24 (d, 2H, *J* = 8.6 Hz), 6.78 (d, 2H, *J* = 8.6 Hz), 4.52 (d, 1H, *J* = 11.4 Hz), 4.44 (dd, 1H, *J* = 9.6, 2.1 Hz), 4.23 (d, 1H, *J* = 11.4 Hz), 4.07–4.02 (m, 1H), 3.90 (dd, 1H, *J* = 9.4, 3.0 Hz), 3.87 (dq, 1H, *J* = 9.3, 7.0 Hz), 3.67–3.66 (m, 1H), 3.32 (dq, 1H, *J* = 9.3, 7.0 Hz), 3.28 (s, 3H), 3.01 (ddd, 1H, *J* = 11.5, 8.3, 3.2 Hz), 2.95 (bs, 1H), 2.63 (ddd, 1H, *J* = 12.6, 4.8, 2.1 Hz), 2.36 (m, 1H), 2.00–1.93 (m, 1H), 1.83–1.78 (m, 3H), 1.66–1.61 (m, 2H), 1.59–1.26 (m, 5H), 1.25 (s, 3H),

1.24–1.00 (m, 3H), 1.06 (t, 3H, *J* = 7.0 Hz), 0.79–0.70 (m, 1H). ^{13}C NMR (acetone *d*-6) δ: 160.6 (s), 135.2 (s), 132.8 (s), 130.6 (d), 129.2 (s), 114.9 (d), 103.1 (d), 82.0 (d), 74.1 (d), 71.4 (t), 64.9 (t), 63.6 (t), 56.0 (q), 49.7 (d), 47.9 (d), 45.8 (d), 43.1 (d), 40.4 (t), 38.5 (t), 35.2 (d), 30.1 (t), 28.3 (t), 27.9 (t), 27.0 (t), 24.4 (q), 16.2 (q). LR-MS (*m*/*z* (relative intensity)): 456 ([M]$^+$, 5), 121 (100), 122 (89). HR-MS calcd. for $C_{28}H_{40}O_5$: 456.2876; found: 456.2868. X-ray data can be found in the supplementary material.[3] Tetracycle **53b**: ^{1}H NMR (C_6D_6) δ: 7.25 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 5.00 (t, 1H, *J* = 7.3 Hz), 4.60 (d, 1H, *J* = 11.2 Hz), 4.37–4.33 (m, 2H), 3.84–3.74 (m, 1H), 3.79 (s, 3H), 3.68–3.61 (m, 1H), 3.49 (dq, 1H, *J* = 9.8, 7.0 Hz), 3.24 (dd, 1H, *J* = 11.2, 2.6 Hz), 3.08 (ddd, 1H, *J* = 11.6, 8.5, 3.1 Hz), 2.59 (ddd, 1H, *J* = 13.5, 7.0, 4.0 Hz), 2.35–2.10 (m, 4H), 2.07–1.96 (m, 2H), 1.90–1.81 (m, 2H), 1.57–1.40 (m, 5H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.17–0.99 (m, 3H), 0.96 (d, 3H, *J* = 7.0 Hz), 0.73–0.66 (m, 1H).

Tetracycles 49a and 49b

Aldehyde **25** underwent the same treatment as per the formation of cycloadduct **41**. A mixture of tetracyles **49a** and **49b** was isolated and purified by flash chromatography on silica gel eluting with EtOAc and hexanes (1:3) in 84% combined yield. Of this mixture, **49a** and **49b** could be isolated in pure form in 12 and 7%, respectively (the reported ratio was determined by GC from the crude mixture after characterization of the pure compounds). In this particular case, some of the precursor 13β,14β-**40c** (starting material) could be isolated pure. When 13β,14β-**40c** was refluxed in benzene overnight, it gave 97% of pure tetracycle **49a** and **49b** (same 2:1 ratio). Tetracycle **49a**: mp 159.4°C. IR (cm^{-1}): 3499, 1738, 1434. ^{1}H NMR ($CDCl_3$) δ: 4.50 (dd, 1H, *J* = 9.7, 1.8 Hz), 3.84–3.77 (m, 2H), 3.65 (s, 3H), 3.47–3.39 (m, 2H), 2.67 (dd, 1H, *J* = 11.9, 7.2 Hz), 2.36–2.29 (m, 1H), 2.15–2.00 (m, 4H), 1.96–1.76 (m, 3H), 1.67–1.58 (m, 3H), 1.50–1.21 (m, 4H), 1.17 (t, 3H, *J* = 7.1Hz), 1.02–0.89 (m, 1H), 0.83 (d, 3H, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.4 (s), 132.8 (s), 124.6 (s), 101.5 (d), 73.3 (d), 69.4 (d), 63.7 (t), 50.9 (q), 49.0 (d), 44.3 (d), 43.0 (d), 41.9 (d), 39.9 (d), 37.6 (t), 36.5 (t), 31.2 (t), 29.2 (t), 26.7 (t), 20.6 (q), 15.0 (q). LR-MS (*m*/*z* (relative intensity)): 363 ([M$^+$ – H], 5), 318 (70), 301 (100). HR-MS calcd. for $C_{21}H_{31}O_5$: 363.2171; found: 363.2180. Anal. calcd. for $C_{21}H_{32}O_5$: C 69.20, H 8.85, O 21.95; found: C 69.25, H 8.80. Tetracycle **49b**: ^{1}H NMR ($CDCl_3$) δ: 4.95 (t, 1H, *J* = 7.2 Hz), 4.28–4.25 (m, 1H), 3.75 (dq, 1H, *J* = 9.8, 7.1 Hz), 3.66 (s, 3H), 3.46 (dq, 1H, *J* = 9.8, 7.1 Hz), 3.45–3.36 (m, 1H), 2.91 (t, 1H, *J* = 8.4 Hz), 2.49 (ddd, 1H, *J* = 13.6, 6.8, 4.2 Hz), 2.37–2.30 (m, 1H), 2.16–2.05 (m, 2H), 2.02–1.77 (m, 4H), 1.69–1.58 (m, 4H), 1.56–1.42 (m, 4H), 1.28–1.23 (m, 1H), 1.19 (t, 3H, *J* = 7.1 Hz), 0.92 (d, 3H, *J* = 7.1 Hz).

Tetracycle 51a

Followed the same procedure as per cycloadduct **41**, starting with aldehyde **25**. IR (cm^{-1}): 3499, 1738, 1434. ^{1}H NMR ($CDCl_3$) δ: 4.61 (dd, 1H, *J* = 8.2, 2.3 Hz), 4.03–4.01 (m, 1H), 3.88–3.86 (m, 1H), 3.84 (dq, 1H, *J* = 9.5, 7.1 Hz), 3.66 (s, 3H), 3.44 (dq, 1H, *J* = 9.5, 7.0 Hz), 2.73 (dd, 1H, *J* = 11.5, 7.1 Hz), 2.50–2.47 (m, 1H), 2.28–2.20 (m, 2H), 2.15–2.07 (m, 1H), 1.99–1.69 (m, 5H), 1.65–1.44 (m, 4H), 1.38–1.20 (m, 2H), 1.17 (t, 3H, *J* = 7.1 Hz), 1.12–1.02 (m, 1H), 0.85 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 174.3 (s), 133.0 (s), 123.3 (s), 100.2 (d), 69.8 (d), 66.6 (d), 63.1 (t), 51.1 (q), 49.6 (d), 43.5 (d), 39.6 (d), 38.8 (d), 36.3 (t), 32.3 (t), 29.0 (t), 26.4 (t), 21.5 (t), 20.6 (q), 15.0 (q). LR-MS (*m*/*z* (relative intensity)): 363 ([M$^+$ – H], 5), 318 (70), 301 (100). HR-MS calcd. for $C_{21}H_{31}O_5$: 363.2171; found: 363.2180. Anal. calcd. for $C_{21}H_{32}O_5$: C 69.20, H 8.85, O 21.95; found: C 69.16, H 8.81. X-ray data can be found in the supplementary material.[3]

Tetracycle 52b

Followed the same procedure as per cycloadduct **41**, starting with aldehyde **24b**. Flash chromatography yielded 414 mg (82%) of **52** as a mixture of two tetracycles of which only the one with the 14α-stereochemistry could be isolated pure. Therefore, the crude mixture (440 mg, 0.62 mmol) was treated with a 1.0 M solution of TBAF (2.5 mL, 2.5 mmol) in THF (1 mL). The mixture was refluxed for 4 h before being cooled and concentrated to dryness. The crude residue was purified by flash chromatography (hexanes:EtOAc, 3–1:1) to give 69 mg (24%) of the TBS-hydrolysis product **52b** and 205 mg (70%) of its stereoisomers as amorphous solids for a combined yield of 94%. Tetracycle **52b**: IR (film, cm^{-1}): 3482, 2925, 1736. ^{1}H NMR (C_6D_6) δ: 7.25–7.07 (m, 5H), 4.43 (dd, 1H, *J* = 9.4, 1.9 Hz), 4.38 (s, 2H), 3.91 (dq, 1H, *J* = 9.5, 7.1 Hz), 3.80–3.78 (m, 1H), 3.55–3.52 (m, 1H), 3.48 (s, 3H), 3.39 (dq, 1H, *J* = 9.5, 7.1 Hz), 3.26 (dd, 1H, *J* = 8.0, 2.3 Hz), 2.59 (dd, 1H, *J* = 12.0, 7.7 Hz), 2.44–2.37 (m, 3H), 2.05–1.99 (m, 1H), 1.91–1.51 (m, 5H), 1.49–1.19 (m, 5H), 1.14 (t, 3H, *J* = 7.1 Hz), 0.99 (s, 3H), 0.87–0.76 (m, 1H). ^{13}C NMR (C_6D_6) δ: 172.7 (s), 139.5 (s), 130.6 (s), 128.6 (d), 128.3 (d), 127.7 (d), 126.2 (s), 101.9 (d), 76.7 (d), 74.1 (d), 71.6 (t), 69.4 (d), 63.7 (t), 50.6 (q), 49.3 (d), 43.7 (d), 42.8 (d), 40.5 (d), 39.2 (d), 37.6 (t), 36.9 (t), 30.8 (t), 29.8 (t), 26.9 (t), 21.1 (q), 15.5 (q). LR-MS (*m*/*z* (relative intensity)): 424 ([M$^+$ – EtOH], 35), 91 (100), 315 (72). HR-MS calcd. for $C_{26}H_{32}O_5$: 424.2250; found: 424.2248.

Tetracycle 54

Tetracycle **49b** (42 mg, 0.116 mmol) was mixed with imidazole (20 mg, 0.29 mmol), TBSCl (23 mg, 0.151 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred overnight and quenched with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (hexanes:EtOAc, 6:1) of the crude product gave **54** (50 mg, 90%). ^{1}H NMR ($CDCl_3$) δ: 4.93 (t, 1H, *J* = 7.2 Hz), 4.28–4.25 (m, 1H), 3.76 (dq, 1H, *J* = 9.7, 7.1 Hz), 3.66 (s, 3H),

[3] Supplementary data (DUD no. 3454) may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically). CCDC 199040, 199041, 199042, and 199044 contain the supplementary data for this paper. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, U.K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

3.45 (dq, 1H, *J* = 9.7, 7.1 Hz), 3.44–3.34 (m, 1H), 2.89 (t, 1H, *J* = 8.6 Hz), 2.43–2.27 (m, 2H), 2.18–2.07 (m, 1H), 2.05–1.82 (m, 6H), 1.70–1.55 (m, 3H), 1.51–1.44 (m, 3H), 1.20 (t, 3H, *J* = 7.1 Hz), 1.14–1.08 (m, 1H), 0.91 (d, 3H, *J* = 7.1 Hz), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). X-ray data can be found in the supplementary material.[3]

Tetracycles 55a and 55b

Tetracycle **50b** was reduced following the procedure for the reduction of **48a**. The alcohol **55a** was isolated in 80% yield (51 mg). ^{1}H NMR ($CDCl_3$) δ: 7.24 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 5.02 (t, 1H, *J* = 7.3 Hz), 4.55 (d, 1H, *J* = 11.9 Hz), 4.43–4.42 (m, 1H), 4.35 (d, 1H, *J* = 11.9 Hz), 3.84–3.74 (m, 1H), 3.79 (s, 3H), 3.68–3.60 (m, 2H), 3.48 (dq, 1H, *J* = 9.8, 7.0 Hz), 3.29 (dd, 1H, *J* = 11.1, 2.6 Hz), 2.36–2.31 (m, 1H), 2.17–1.89 (m, 9H), 1.76 (d, 1H t, *J* = 13.8, 7.8 Hz), 1.57–1.39 (m 5H), 1.21 (t, 3H, *J* = 7.0 Hz), 1.09–0.98 (m, 1H), 0.95 (d, 3H, *J* = 7.1 Hz), 0.78–0.72 (m, 1H). Alcohol **55a** was protected, as per the protection of tetracycle **49b**, which gave **55b** (186 mg, 100%); mp 221.8°C. IR (cm^{-1}): 3007, 2929, 2856, 1612, 1513, 1249, 1059, 1036. ^{1}H NMR ($CDCl_3$) δ: 7.24 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 4.97 (t, 1H, *J* = 7.2 Hz), 4.54 (d, 1H, *J* = 11.9 Hz), 4.36 (d, 1H, *J* = 11.9 Hz), 4.21–4.19 (m, 1H), 3.87 (dd, 1H, *J* = 9.5, 4.4 Hz), 3.79 (s, 3H), 3.76 (dq, 1H, *J* = 9.9, 7.1 Hz), 3.58–3.56 (m, 1H), 3.48 (dq, 1H, *J* = 9.9, 7.1 Hz), 3.23 (t, 1H, *J* = 9.5 Hz), 2.25–2.20 (m, 1H), 2.12–1.88 (m, 9H), 1.66 (dt, 1H, *J* = 13.7, 7.3 Hz), 1.51 (bs, 3H), 1.47–1.33 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz), 1.15–1.07 (m, 1H), 0.92 (d, 3H, *J* = 7.1 Hz), 0.87 (s, 9H), 0.01 (d, 6H, *J* = 2.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 158.9 (s), 131.1 (s), 129.5 (s), 129.3 (d), 113.6 (d), 98.1 (d), 72.3 (d), 69.9 (t), 66.8 (d), 64.3 (t), 62.5 (t), 55.3 (q), 43.6 (d), 43.4 (d), 34.2 (d), 33.8 (d), 33.2 (t), 33.1 (d), 30.9 (t), 30.2 (t), 25.9 (q), 25.5 (t), 20.9 (t), 20.2 (t), 18.2 (s), 15.4 (q), 13.4 (q), –5.2 (q). LR-MS (*m*/*z* (relative intensity)): 524 ([M^+ – C_2H_6O], 15), 74 (100), 403 (93). HR-MS calcd. for $C_{32}H_{48}O_4Si$: 524.3322; found: 524.3318. X-ray data can be found in the supplementary material.[3]

Tetracycles 56

Cycloadduct **41** (97 mg, 0.28 mmol), hydroquinone (1.5 mg, 0.014 mmol), and methyl acrylate (0.25 mL, 2.8 mmol) were dissolved in *m*-xylene (10 mL). The solution was heated to reflux for 5 days. Methyl acrylate (0.25 mL, 2.8 mmol) was added and reflux was continued for 2 days. Methyl acrylate (0.25 mL, 2.8 mmol) was added one last time and reflux was continued 1 more day and the reaction was monitored by TLC. The solvent was evaporated to give a yellow oil (150 mg). Flash chromatography on silica gel eluting with EtOAc and hexanes (20:80) gave **56** as a colourless oil (82 mg, 66%) containing two separable diastereomers. First isomer: ^{1}H NMR (C_6D_6) δ: 4.82–4.71 (m, 2H), 4.00–3.87 (m 1H), 3.81–3.75 (m, 1H), 3.44 (s, 3H), 3.43–3.33 (m, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 3.01–2.90 (m, 2H), 2.02–1.87 (m, 2H), 1.75–1.34 (m, 3H), 1.24 (t, 3H, *J* = 7.0 Hz), 1.20–0.98 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H), 0.83 (d, 3H, *J* = 6.6 Hz). Second isomer: IR (neat, cm^{-1}): 2954, 1738, 1435. ^{1}H NMR (C_6D_6) δ: 4.71 (m, 1H, *J* = 8.7, 5.4 Hz), 4.49 (dm, 1H, *J* = 7.3 Hz), 3.92–3.85 (m, 1H), 3.84–3.72 (m, 1H), 3.50 (s, 3H), 3.33–3.23 (m, 1H), 3.27 (s, 6H), 3.03–2.96 (m, 2H), 2.09–1.90 (m, 3H), 1.87–1.75 (m, 1H), 1.57–1.45 (m, 2H), 1.15 (t, 3H, *J* = 7.1 Hz), 1.00 (s, 3H), 0.93 (d, 3H, *J* = 6.7 Hz), 0.80 (s, 3H). ^{13}C NMR (C_6D_6) δ: 174.4 (s), 173.3 (s), 172.1 (s), 135.7 (s), 134.2 (s), 98.4 (d), 63.2 (d), 62.4 (t), 51.7 (q), 51.5 (q), 51.2 (q), 50.9 (d), 44.5 (d), 41.0 (d), 33.0 (t), 36.8 (d), 36.1 (d), 34.4 (t), 32.3 (s), 27.2 (q), 26.8 (q), 19.4 (q), 15.4 (q). LR-MS (*m*/*z* (relative intensity)): 456 ([M + NH_4], 5), 437 ([M – 1], 30), 393 (100), 361 (70). HR-MS calcd. for $C_{23}H_{33}O_8$: 437.2175; found: 437.2159.

Conclusion

We have successfully completed an in-depth study of the stereochemical aspect of the cycloadditions involved in the diene-transmissive Diels–Alder strategy. The results clearly show that the stereochemistry of both cycloadditions can be controlled by proper positioning of susbtituents in the precursors. The study also procured useful information about what structural features should be avoided in the cycloaddition precursors that lead to lower selectivity. Importantly, we were able to construct vinyl allene precursors possessing the C-10 methyl group and showed that those precursors underwent two highly stereoselective Diels–Alder cycloadditions. We were not yet able, however, to effect the third and last Diels–Alder reaction in those systems. Current investigations are aimed at solving this difficulty.

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