Studies towards Simalikalactone D and Quassimarin: Construction of an Advanced Pentacyclic Intermediate**

Tony K. M. Shing,* Xue Y. Zhu, and Yeung Y. Yeung[a]

Abstract: An advanced pentacyclic intermediate, amenable to further elaboration into the target molecules simalikalactone D and quassimarin, has been synthesized from (*S*)-(+)-carvone in 21 steps and with an overall yield of 12%. The synthesis is efficient, stereocontrolled, enantiospecific, and chirality productive, creating eight new chiral centres in pentacycle, and should provide opportunities for rapid access to simalikalactone D analogues and other bioactive quassinoids. The reaction sequence involves a regioselective bishydroxylmethylation, a stereocontrolled epoxidation, an epoxymethano-bridge formation, a 1,3-sigmatropic rearrangement and an intramolecular Diels–Alder reaction as the key steps.

Keywords: antitumor agents · lactones · terpenoids · total synthesis

Introduction

The quassinoids[1] constitute a diverse and constantly expanding group of terpenoid bitter compounds isolated from *Simaroubaceae*,[2] a large botanical family of pantropical distribution.[3] The discovery of a wide spectrum of biological properties[1, 4] of quassinoids has attracted the attention of synthetic chemists in recent years.[5] Continued studies on the bioactivity profile of quassinoids have reported that these substances display, amongst other things, antifeedant and insecticidal,[6] antiprotozoal,[7] antimalarial,[8] and antitumor activities.[9] The highly oxygenated tetracyclic/pentacyclic carbon frameworks of the C_{20} picrasane family, comprising a number of contiguous stereocenters, pose a formidable synthetic challenge and therefore have stimulated massive synthetic efforts from many research teams. The pioneer and the major contributor in this area of research has been Grieco and co-workers, producing astute and exquisite total syntheses of a number of tetracyclic and pentacyclic members, namely (±)-quassin,[10] (±)-catelanolide,[11] (±)-klaineanone,[12, 5t] (±)-chaparrinone,[5p] (±)-glaucarubolone and (±)-holacanthone,[5j] (+)-simalikalactone D (**1**),[5i] (−)-chaparrinone, (−)-glaucarubolone and (+)-glaucarubinone,[5e] (±)-bruceantin,[5f] and (+)-quassimarin (**2**).[5g] Recently, the first total synthesis of *dl*-samaderin B, belonging to the C_{19} picrasane family, has been acheived by the same group.[5a] Other synthetic accomplishments are contributed from groups led by Takahashi [(±)-amarolide],[13] Murae [relay synthesis of (−)-bruceantin],[5m] Valenta [(±)-quassin],[5k] and Fuchs [15-deoxy-16β-ethoxybruceantin].[5b] Additional interests on enantioselective routes to quassinoids began with early investigations by Dias,[14] Graf,[15] Ziegler,[16] Fukumoto[17] and Schlessinger[18] and resulted the first total syntheses of (+)-picrasin B, (+)-Δ^2-picrasin B and (+)-quassin by Watt's group[5n,r,s] using the (−)-enantiomer of the Wieland–Miescher ketone as the starting material.

Plant natural products continue to supply clinically useful antitumor agents, novel structural prototypes for the development of analogues, and biochemical tools for the elucidation of unprecedented mechanism of tumor growth control.[19] Among the quassinoids, simalikalactone D (**1**)[20] and quassimarin (**2**)[21] (Scheme 1) are of considerable interest because they display potent activity in vivo against the P-388 lymphocytic leukemia in mice (PS) and possess differential solid tumour selectivity.[5i,g, 22] Recent findings have indicated that **1** and **2** were significantly active against the growth of a panel of human tumour cell lines (KB, A-549, HCT-8, CAKI-1, MCF-7, and SK-MEL-2).[23] The antiviral activity of simalikalactone D (**1**) has also been demonstrated.[24] Both compounds share a pentacyclic carbon skeleton **3** (rings A–E) with common stereochemical features, but with different butyrate esters at C-15. The essential structural requirements for potent antineoplastic activity could well be the presence of an epoxymethano bridge (ring E) between C-8 and C-13, an α,β-enone unit with a free hydroxyl group in ring A, and an ester group at C-15.[25] The ester group is believed to be important for the transport of the drug across the cell

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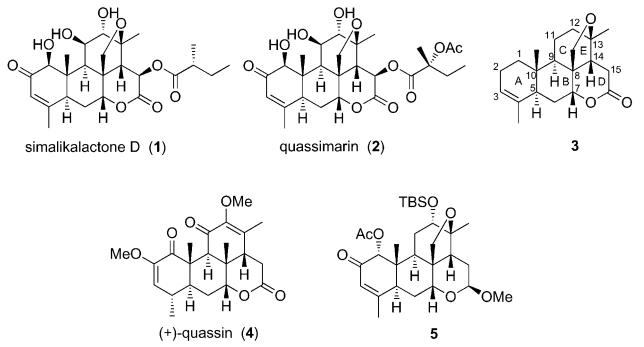
[**] Part of this work was published as a preliminary communication: T. K. M. Shing, X. Y. Zhu, T. C. W. Mak, *Chem. Commun.* **1996**, 2369–2370.

 DOI: 10.1002/chem.200305158

membranes and to increase the lipophilicity of the molecule.[26] The enone unit may be involved in reactions with biological nucleophiles and therefore be central to the activity of these compounds.[27]

In our own quest for an enantiospecific entry to optically active quassinoids, we recently reported the total synthesis of quassin (**4**) which has the general ABCD ring system with seven chiral centers common to numerous quassinoids via a series of regioselective and stereocontrolled reactions from (*S*)-(+)-carvone (**10**) with one stereogenic center (Scheme 2).[28a] Our synthetic strategy for its construction is based on the C → ABC → ABCD ring annulation sequence and the major hurdle in the synthesis of quassinoids is the stereocontrolled construction of the angular methyl groups.[28b,c] We described two solutions to this problem by employing an aldol reaction [**6** (R = CH_3) + **7** → **8**] and an intramolecular Diels–Alder (IMDA) reaction (**8** → **9**), leading to a *trans*,*anti*,*trans*-perhydrophenanthrene nucleus **9** (R = CH_3) with excellent stereocontrol.[28d,e]

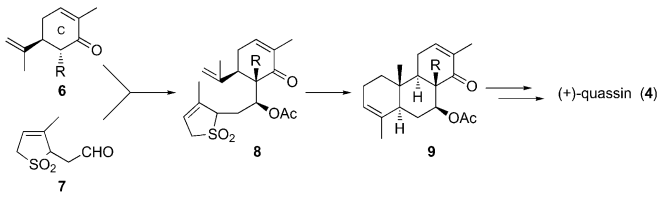
Now, we would like to exploit this approach to synthesise optically active pentacyclic simalikalactone D (**1**) and quassimarin (**2**). This paper we describe in detail our effort in the construction of the advanced pentacyclic intermediate **5** (Scheme 1), which is amenable for further elaboration into the target molecules.



Scheme 1. Pentacyclic quassinoids.

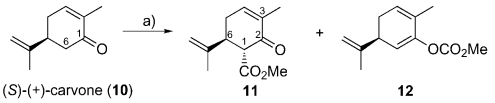
Results and Discussion

On the basis of the synthetic strategy shown in Scheme 2, we reasoned that substitution of the methyl group in **6** with a hydroxymethyl group or a suitable synthetic equivalent and taking it (**6**, R = CH_2OH) through the same sequence of reactions as in the preparation of tricycle **9** would allow formation of the ring E at a later stage.



Scheme 2. Synthesis of quassin.

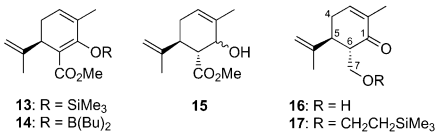
This task appeared trivial in principle, but proved troublesome in practice. Our first problem was the introduction of a suitable functional group at C-6 of (*S*)-(+)-carvone (**10**) and the attachment of different hydroxymethyl equivalents to that position. Thus, deprotonation of (*S*)-(+)-carvone (**10**) with LDA followed by addition of methyl chloroformate gave a 1:1 mixture of products, the carbon-alkylated β-ketoester **11** and the oxygen-alkylated carbonate **12** (Scheme 3). When methyl cyanoformate, Mander's reagent,[29] was used instead,



Scheme 3. Acylation of carvone **10**. a) i) LDA, THF; ii) $ClCO_2Me$ or $CNCO_2Me$.

the β-ketoester **11** was isolated in 95% yield as a single diastereomer. The ^{1}H NMR spectrum of **11** showed that H_1 appeared at δ 3.51 as a doublet. A large coupling constant of 12 Hz between H_1 and H_6 provided evidence of their pseudo-*trans*-diaxial relationship and suggested that the acylation took place at the less hindered α face. At this stage, we had high hopes that β-ketoester **11** would react with aldehyde **7** to furnish the desired aldol product (**8**, R = CO_2Me) [c.f. the conversion of **6** (R = Me) + **7** → **8** (R = Me) in Scheme 2]. Unfortunately, under a variety of basic reaction conditions, the aldolisation failed to furnish any aldol adducts. Attempts to stabilize the aldol product by metal chelation,[30] by conducting Lewis acid ($TiCl_4$ or $ZnCl_2$) catalyzed aldolisation of silyl enol ether **13** or by reaction with boron enolate,[31] **14** were unsuccessful.

Selective reduction of the ketone moiety in **11** with sodium borohydride in methanol in the presence of $CeCl_3$ afforded a 1:1 mixture of diastereomeric alcohols **15** in 88% yield (Scheme 4). However, aldolisation of the bisanion derived from β-hydroxyester **15** with aldehydes (benzaldehyde, hexanal or aldehyde **7**) also met with failures although the alkylation of β-hydroxyester has literature precedence.[32]

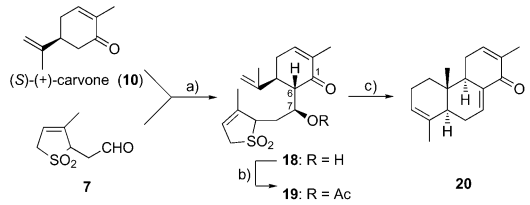


Scheme 4. Enolisation of carvone derivatives.

Another pathyway aimed at preparing the bisanion was also attempted. Enolisation of (*S*)-(+)-carvone **10** with LDA in THF/*N*,*N*′-dimethylpropyleneurea (DMPU) 3:1 at −78 °C followed by addition of gaseous formaldehyde afforded α-hydroxymethylcarvone **16** in 90% yield as a single diastereomer. The ^{1}H NMR spectrum of the alcohol **16** showed that H_6 appeared at δ 2.46 as a ddd ($J_{6,7\text{ or }7'} = 3.5$, $J_{6,7\text{ or }7'} = 7$, and $J_{6,5} = 13$ Hz) and H_5 appears at δ 2.68 also as a ddd ($J_{5,4\alpha} = 4.5$, $J_{5,4\beta} = 11$, and $J_{5,6} = 13$ Hz). The pseudo-*trans*-diaxial relationship between H_6 and H_5 was evident from their large coupling constant of 13 Hz and this suggested that the aldol reaction occurred at the less hindered α face. However, treatment of

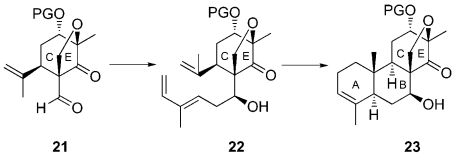
alcohol **16** with 2–4 equivalents of LDA in the presence of DMPU at −78 °C followed by addition of aldehydes failed to give any aldol adduct. Masked hydroxymethyl derivative such as 6-SEM-carvone **17**[33] also failed to enolise under the conditions as confirmed by deuterium exchange experiments (Scheme 4).

With the problems of effecting the aldol reaction, we decided to introduce the hydroxymethyl group at C-6 of (*S*)-(+)-carvone **10** in a later stage of our synthesis and envisaged that bicycle **8** (R = H) could be synthesized from (*S*)-(+)-carvone **10** and aldehyde **7**. We reasoned that kinetic deprotonation of tricycle **9** (R = H) with LDA followed by reaction with methanal should give us the desired tricyclic alcohol **9** (R = CH_2OH). Thus aldolisation of the enolized (*S*)-(+)-carvone **10** with aldehyde **7** proceeded smoothly to give alcohol **18** which was acetylated with acetic anhydride to furnish ester **19** in an overall yield of 62%. However, the IMDA reaction of sulfolene **19** gave enone **20** instead (Scheme 5). Obviously, the acetate group at C-7 was eliminated during the Diels–Alder reaction to give the thermodynamically more stable enone product **20**.



Scheme 5. a) LDA, THF/DMPU 3:1, −78 °C, 1 h, 62%; b) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 10 h, 100%; c) PhCN, methylene blue, sealed tube, 190 °C, 110 h, 40%.

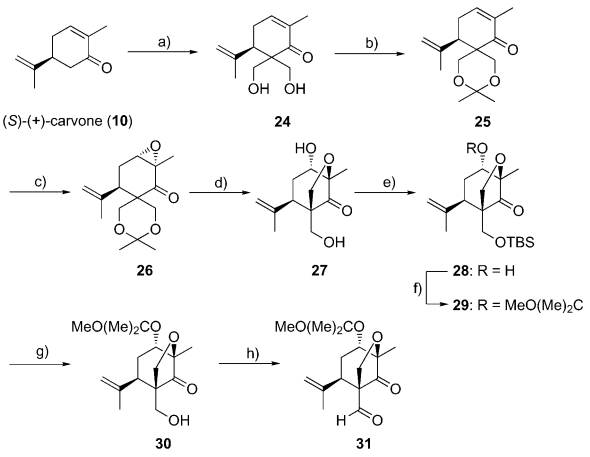
In view of the failures, we had to revise our synthetic approach and attempted to construct first an E ring **21** with reversed polarity so that a nucleophilic diene equivalent could be introduced in order to set up the IMDA precursor **22** (Scheme 6). Thermolysis of the diene **22** should provide the



Scheme 6. Synthetic approach towards ABCE ring system.

trans,*anti*,*trans* fused ABC ring system **23**. This change of strategy proved successful and now we describe a simple solution to the synthesis of epoxymethano-bridge in pentacyclic quassinoids. Thus reaction of (*S*)-(+)-carvone **10** with LDA followed by an excess of formaldehyde from −78 °C to room temperature gave 6,6-bishydroxymethylated carvone **24** in 75% yield (Scheme 7). Enolisation of the intermediate compound **16** must have occurred at the α position, but it appeared that this enolate would only react with formaldehyde.

We envisaged that formation of an oxirane across the electrophilic alkene moiety in **24** would allow one of the

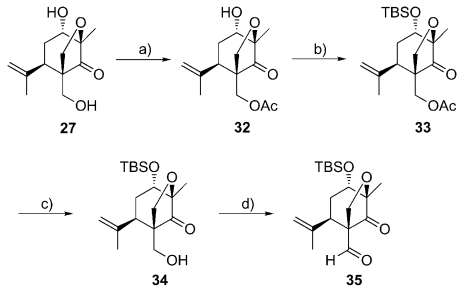


Scheme 7. Synthesis of keto-aldehyde **31**. a) LDA, DMPU, THF, HCHO, −78 → −40 °C then rt, 24 h, 75%; b) DMP, *p*TsOH, CH_2Cl_2, rt, 2 h, 96%; c) *t*BuOOH, 2 N NaOH, MeOH, 45 °C, 24 h, 94%; d) TFA, EtOH, 50 °C, 48 h, 85%; e) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 48 h, 92%; f) 2-methoxypropene, PPTS, CH_2Cl_2, 0 °C, 4 h, 96%; g) TBAF, THF, rt, 96%; h) PCC, CH_2Cl_2, rt, 70%.

primary alcohols to ring open the epoxide, leading to an epoxymethano bridge. By analogy with the reactivity of α-haloketones, the epoxide ring opening is expected to proceed at the α position regioselectively. However, exposure of enone **24** to alkaline *tert*-butylhydroperoxide caused a retro-aldol reaction, hence the primary alcohol units in **24** had to be protected first. Although the hydroxy groups in **24** could be protected as THP derivatives under standard conditions, these alcohols were best and conveniently protected as an acetonide. Thus the diol **24** was isopropylidenated under standard conditions to give the spiral compound **25**. Epoxidation of the electrophilic alkene in **25** with alkaline *tert*-butylhydroperoxide occurred smoothly at the less hindered α face to give the α-epoxide **26** in 94% yield. The alternative α-epoxide was not detectable by NMR or TLC. Acid hydrolysis of the acetonide protecting group in **26** proceeded with concomitant ring-opening reaction by the liberated alcohol to form the THF ring **27**. Again there was no other isomer isolable or detected. The structure **27** was confirmed by X-ray diffraction which demonstrated the nucleophilic opening of the oxirane **26** did proceed as anticipated.

Now the secondary alcohol moiety in **27** had to be protected for further synthetic manipulation. This could be achieved by a selective protection and deprotection sequence. Thus silylation of the primary alcohol in **27** could be effected smoothly and selectively to give the silyl ether **28** in 92% yield. The remaining secondary alcohol was treated with 2-methoxypropene in CH_2Cl_2, catalyzed by PPTS, affording the mixed acetal **29** in 96% yield. Removal of the silyl protecting group with nBu_4NF (TBAF) in THF (96% yield) followed by PCC oxidation of the resulting alcohol **30** gave aldehyde **31** in 70% yield (Scheme 7). However, aldehyde **31** was unstable even at 0 °C under N_2 due to the acid liability of the mixed acetal functionality. We circumvented this problem by choosing an alternative silane protecting group. Thus selective acylation of the primary alcohol in diol **27** with acetyl chloride in the presence of diisopropylethylamine according to the Yamamoto protocol[34] gave the monoacetate **32** in

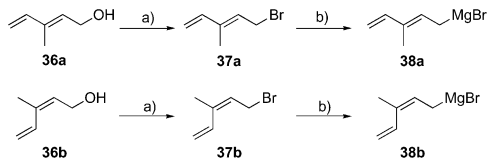
excellent yield (Scheme 8). The silylation of the free secondary alcohol in **32** was best effected with TBS-triflate, affording the silyl ether **33** in quantitative yield. The ester



Scheme 8. Synthesis of keto-aldehyde **35**. a) AcCl, iPr$_2$EtN, CH_2Cl_2, 0 °C to rt, 4 h, 97 %; b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 100 %; c) NaOH, MeOH, THF, rt, 4 h, 96 %; d) TPAP, NMO, CH_2Cl_2, rt, 2 h, 84 %.

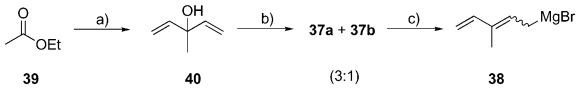
group in **33** was hydrolysed under basic conditions without incident to give alcohol **34** that was subjected to a number of oxidation protocols [PDC, PCC, Swern, tetrapropylammonium perruthenate (TPAP)[35]]. The most efficient transformation was achieved using TPAP, leading to the aldehyde **35** in 84 % yield.

With both an efficient and facile approach to the optically active aldehyde **35** available, the stage was set for the IMDA reaction and the installation of the diene unit onto **35** was our next mission. In our synthetic plan, the required diene unit might be provided by 3-methyl-pentadienyl carbanion. We reasoned that the Grignard equivalent of pentadienyllithium carbanion could be prepared easily on a large scale from 5-bromo-3-methylpenta-1,3-diene. Thus, treatment of a solution of (*E*)-pentadienyl alcohol **36a** with PBr_3 provided a mixture of (*E*)- and (*Z*)-3-methyl-5-bromopenta-1,3-diene[36] **37a** and **37b** in a ratio of 5:1 (combined yield 83 %). (*Z*)-Pentadienyl alcohol **36b** gave a mixture of (*Z*)- and (*E*)-bromopentadiene **37b** and **37a** in a ratio of 6:1 (combined yield 80 %). Initially, pentadienyl alcohols **36a** and **36b** could be made by partial hydrogenation of *trans*-3-methyl-2-penten-4-yn-1-ol and *cis*-3-methyl-2-penten-4-yn-1-ol with P_2Ni as catalyst, respectively (Scheme 9).[37] Unfortunately, both



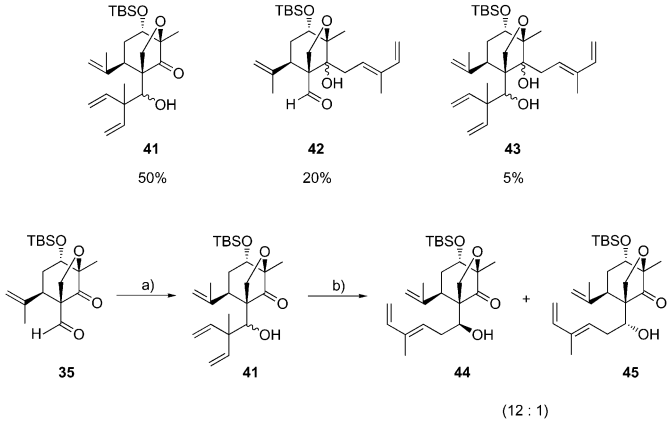
Scheme 9. Synthesis of Grignard reagent **38**. a) PBr_3, pyridine, Et_2O, −30 °C, 30 min, 83 % for **37a**, 80 % for **37b**; b) Mg, Et_2O, −10 → −5 °C, 12 h.

trans-3-methyl-2-penten-4-yn-1-ol and *cis*-3-methyl-2-penten-4-yn-1-ol are no longer commercially available and an alternative route had to be devised for the bromopentadiene (**37a** and **37b**). After considerable experimentation, a simple entry was developed. Treatment of ethyl acetate **39** with vinylmagnesium bromide afforded the divinyl carbinol **40**[38] which with PBr_3 furnished a mixture of (*E*)- and (*Z*)-3-methyl-5-bromopenta-1,3-diene, **37a** and **37b** in a ratio of 3:1. The attack of the bromide should be at the less hindered primary carbon. Reaction of bromide **37** with magnesium then gave the desired Grignard reagent 3-methylpentadienylmagnesium bromide **38** (Scheme 10).



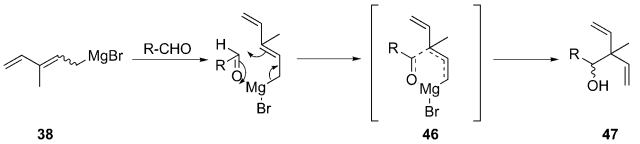
Scheme 10. Synthesis of Grignard reagent **38**. a) Vinyl magnesium bromide, THF, 0 °C to rt, 4 h, 70 %; b) PBr_3, pyridine, Et_2O, −10 °C, 30 min, 80 %; c) Mg, Et_2O, −10 → −5 °C, 12 h.

First examination of the addition of 3-methylpentadienylmagnesium bromide **38** to aldehyde **35** at room temperature was encouraging, giving a mixture of 1,4-diene **41** (50 %), 1,3-diene **42** (20 %), and polyene **43** (5 %). After several trials, the conditions for the chemoselective addition of Grignard reagent **38** to aldehyde **35** in the presence of a ketone functionality were optimized. When a dilute solution of Grignard reagent **38** was used, the addition occurred exclusively at the aldehyde function and afforded 1,4-diene **41** in a yield of 80 % (Scheme 11). Presumably, the addition of the



Scheme 11. Synthesis of IMDA precursor **44** and **45**. a) Grignard reagent **38**, Et_2O, rt, 5 min, 80 %; b) KH, dibenzo-[18]crown-6, THF, rt, 4 h, 85 %.

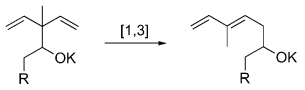
pentadienyl carbanion proceeded through an allylic rearrangement via a cyclic six-membered transition state **46**, leading to the exclusive formation of the 1,4-diene product **47** (Scheme 12). Previous report had indicated that the addition of 3-methylpentadienyllithium to aldehyde gave 1,4-diene as



Scheme 12. Proposed mechanism for the addition of 3-methylpentadienyl magnesium bromide to aldehyde.

the minor product.[39] Our results of the addition of 3-methylpentadienylmagnesium bromide to aldehyde to give 1,4-diene as the major product was possibly the first example. A

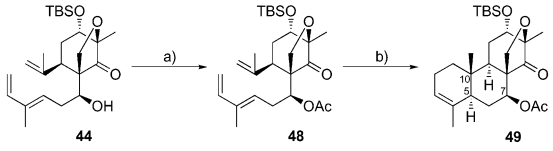
skipped 1,4-diene unit has now been introduced, but in order to perform the IMDA reaction, transformation into the corresponding 1,3-diene had to be performed. The conversion was realized via an anion accelerated [1,3]-sigmatropic shift (Scheme 13).[40] The effect of cations on the acceleration of the shift was investigated and potassium salt had a dramatic



Scheme 13. [1,3]-Sigmatropic shift.

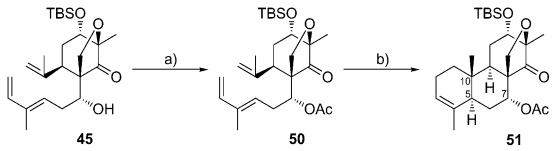
acceleration effect. We found that the use of crown ether was essential for our shift to proceed in a reasonable rate. An important feature of the [1,3]-sigmatropic shift was that the geometry of the double bond in the product was exclusively (*E*). Thus, triene **41** was treated with KH in the presence of dibenzo-[18]crown-6 in THF at room temperature. The rearrangement was completed in 4 h, giving *trans*-trienes **44** and **45** in a ratio of 12:1 and a combined yield of 85% (Scheme 11). The stereochemistry of the hydroxy group in the major product **44** was undesirable whereas that in the minor **45** was correct. This was determined after the IMDA reaction.

Our previous work on quassin synthesis[28b] had shown that the β-hydroxyketone moiety underwent a retrol-aldol reaction on heating. Thus the major triene **44** was acetylated to the corresponding acetate **48** which was dissolved in toluene in sealed tube in the presence of methylene blue. The IMDA reaction proceeded smoothly, offering tetracyclic acetate **49** in quantitative yield (Scheme 14). The reaction provided two new stereocenters at C-5 and C-10, which are founded in most



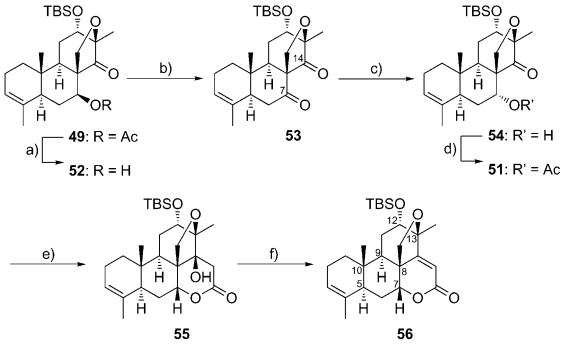
Scheme 14. Intramolecular Diels–Alder reaction of triene **44**. a) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h, 100%; b) toluene, methylene blue, sealed tube, 170 °C, 120 h, 100%.

tetracyclic and pentacyclic quassinoids. The stereochemistry of the acetate was determined by the *J* coupling constant in the ^{1}H NMR spectrum of **49**. The proton resonance at 5.77 ppm, assigned to H-7, was a doublet of doublets with $J_{7ax,6ax} = 12$, $J_{7ax,6eq} = 4.8$ Hz, which indicates that the C-7 acetate was α oriented. The high reaction temperature (170 °C) and long reaction time (120 h) revealed that the IMDA reaction was simply thermodynamically controlled. The major drawback of the approach is that inversion of the configuration at C-7 is required before formation of the lactone D ring. The minor product **45** of the [1,3]-sigmatropic shift was also converted into the corresponding acetate **50**. The IMDA reaction of **50** then afforded tetracycle **51** in a yield of 85%. In the ^{1}H NMR spectrum of **51**, the H-7 resonance was a broad single peak ($\delta = 5.40$ ppm), thereby showing that the C-7 acetate was α oriented (Scheme 15).



Scheme 15. Intramolecular Diels–Alder reaction of triene **45**. a) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h, 96%; b) toluene, methylene blue, sealed tube, 170 °C, 120 h, 85%.

With an appreciable amount of the tetracyclic ketone **49** at hand, we initiated the construction of ring D. The transformation of tetracycle **49** into the pentacyclic lactone required the inversion of the configuration at C-7 into the desired α-oriented acetate **51**. This could be realised via an oxidation–reduction sequence. Thus, acetate **49** was saponified to alcohol **52** in a yield of 96%. (Scheme 16). Alcohol **52** was oxidized into diketone **53** using several oxidants, such as



Scheme 16. Synthesis of α,β-unsaturated lactone **56** a) NaOH, MeOH, rt, 12 h, 96%; b) Dess–Martin periodiane, CH_2Cl_2, rt, 6 h, 96%; c) K-selectride, THF, rt, 20 min, 97%; d) Ac_2O, DMAP, CH_2Cl_2, rt, 24 h, 100%; e) LDA, toluene/THF 2:1, –30 °C, 30 min, 87%; f) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C to rt, 12 h, 90%.

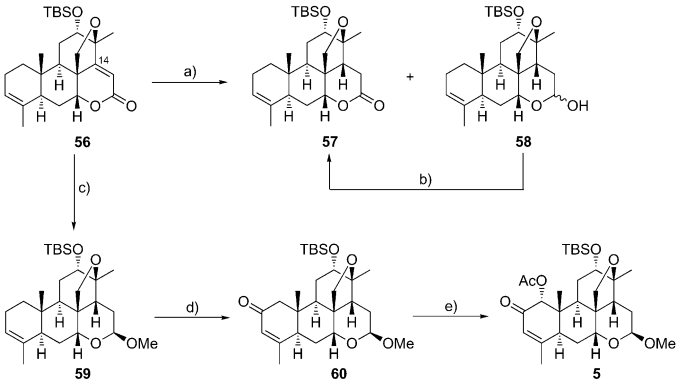
PCC, TPAP, and Dess–Martin periodinane.[41] The best conversion was achieved using Dess–Martin periodinane[41] at room temperature, affording ketone **53** in a yield of 96%. The regio- and stereoselective reduction of the C-7 ketone group in **53** to the desired α-oriented hydroxy group was accomplished employing K-selectride as the reducing agent. The hydride reduction at C-7 proceeded smoothly at room temperature, resulting in the exclusive formation of the α-oriented alcohol **54** in 97% yield. The successful reduction of ketone at C-7 was attributed to the bulky K-selectride and the shielded environment where the ketone at C-14 was situated.

Initially, acetylation of alcohol **54** was carried out in refluxing CH_2Cl_2 with acetic anhydride in the presence of pyridine and a catalytic amount of DMAP. After seven days, the acetate **51** was obtained in a 94% yield. It was found that the amount of DMAP had a dramatic effect on the speed of the formation of acetate. If ten equivalents of DMAP were used, the acetylation was complete in 20 min, providing acetate **51** in a quantitative yield. The constitution of the acetate was confirmed by an X-ray analysis (see preliminary communication).

With an efficient and expeditious route to the tetracyclic acetate **51** available, we anticipated that the cyclization to form the pentacyclic carbon framework could be accomplished via an LDA mediated intramolecular aldol addition.

However, the initial attempt to afford pentacyclic lactone failed because the solubility of acetate **51** in THF was poor. To overcome this problem, we used toluene as a co-solvent. Treatment of the acetate **51** in toluene/THF 2:1 with LDA (1.5 equiv) caused the cyclization to complete in 30 min, giving the pentacyclic lactone **55** in 87% yield. Elimination of the hydroxy group was realized using $SOCl_2$/pyridine to give the α,β-unsaturated lactone **56** in 90% yield. The driving force for this reaction was attributed to the formation of the thermodynamically more stable conjugated lactone **56** (Scheme 16). The pentacyclic carbon framework **56**, which possesses seven stereocenters at C-5, 7, 8, 9, 10, 12 and 13, in common in both simalikalactone D **1** and quassimarin **2**, has been constructed successfully.

At this stage, functionalisation of ring D to give an epoxide across the alkene moiety of the enoate was attempted. However, several experimental conditions (alkaline peroxides) examined failed to effect the desired epoxidation. With the above failure, the remaining work that could be done was to introduce 14β-oriented hydrogen (Scheme 17).



Scheme 17. Synthesis of pentacycle **5**. a) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, 0 °C to rt, 3 h, 100%; b) Dess–Martin periodinane, CH_2Cl_2, rt; c) i) $NaBH_4$, $NiCl_2 \cdot H_2O$, MeOH, rt, 3 h, ii) conc. HCl, 95%; d) $CrO_3 \cdot$DMP, CH_2Cl_2, 0 °C to rt, 24 h, 81%; e) $Mn(OAc)_3 \cdot 2H_2O$, benzene, reflux, 48 h, 80%.

This was realized by a regio- and stereoselective 1,4-reduction of the conjugated double bond in the unsaturated lactone **56** with $NaBH_4/NiCl_2 \cdot 6H_2O$. This protocol had been used in our previous synthesis of (+)-quassin **4**.[28b] The reduction occurred at the less hindered convex face, affording a mixture of saturated lactone **57** and lactol **58** in a ratio of 2:1, and with the correct stereochemistry at C-14 which was determined by an X-ray analysis (Figure 1). Lactol **58** could be oxidized into the saturated lactone **57** by Dess–Martin[41] oxidation.

Functionalisation of ring A was our next objective. The allylic oxidation of the C-2 methylene in ring A of alkene **57** to give enone **61** did pose problems and failed to give the desired enone under a number of different reaction conditions. Our studies on the synthesis of the tetracyclic quassin had indicated that the failure was probably due to the instability of the lactone D ring that could not survive the vigorous oxidation conditions (Scheme 18).[28a] Hence, the unsaturated lactone **56** was reduced to the corresponding lactol with

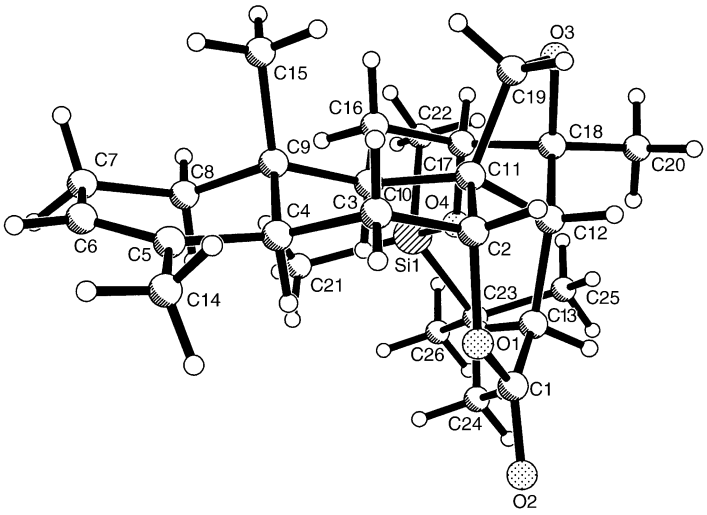
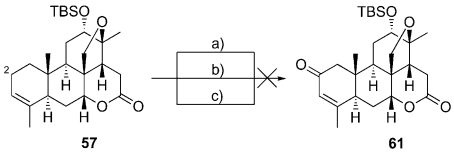


Figure 1. X-ray crystal structure of pentacycle **57**.



Scheme 18. Allylic oxidation of **57**. a) $CrO_3 \cdot$pyridine, CH_2Cl_2, reflux; b) $CrO_3 \cdot$pyridine, CH_3CN, reflux; c) $Cr(CO)_6$, *t*BuOOH, CH_3CN, reflux.

$NaBH_4/NiCl_2 \cdot 6H_2O$ in methanol which was then immediately treated with conc. HCl to effect the acetalisation; the reaction afforded the mixed acetal **59** in an excellent overall yield. Indeed, the allylic oxidation of ring A in acetal **59** was feasible without the lactone functionality and the best reagent was $CrO_3 \cdot$DMP, affording the enone **60** in 81% yield. Manganese(III) acetate had been proved to be an efficient reagent for α-acetoxylation of enones.[42] Thus, enone **60** was treated with $Mn(OAc)_3 \cdot 2H_2O$ in dry benzene under reflux using a Dean and Stark apparatus for separation of the water of crystallization in manganese acetate, furnishing the α-acetoxyenone **5** in 80% yield (Scheme 17). The structure and stereochemistry of the acetate **5** has been confirmed by an X-ray crystallographic study (Figure 2).

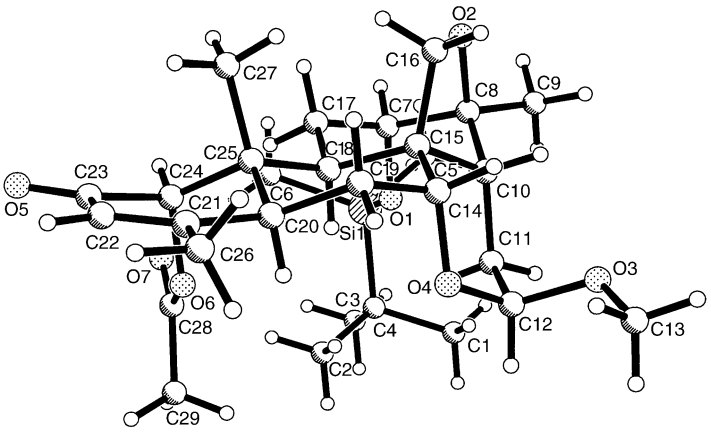


Figure 2. X-ray crystal structure of pentacycle **5**.

Conclusion

In summary, the advanced pentacyclic intermediate **5**, amenable to further elaboration into the target molecules simalikalactone D (**1**) and quassimarin (**2**), has been synthesized from (*S*)-(+)-carvone (**10**) in 21 steps and with an overall yield of 12%. The synthesis is efficient, stereocontrolled, enantiospecific, and chirality productive, creating eight new chiral centres in pentacycle **5**, and should provide opportunities for rapid access to simalikalactone D analogues and other bioactive quassinoids. Research in this direction is underway.

Experimental Section

General: Melting points were determined with a Reichert apparatus and are uncorrected. NMR spectra were recorded on a Bruker WM250 spectrometer at 250.13 MHz (^{1}H) or at 62.89 MHz (^{13}C), on a Bruker DPX300 spectrometer at 300.13 MHz (^{1}H) or at 75.47 MHz (^{13}C) and Bruker DPX500 spectrometer at 500.13 MHz (^{1}H) using $CDCl_3$ as solvent unless otherwise stated. Chemical shift positions were in ppm downfield from internal tetramethylsilane and coupling constants (*J* values) are given in Hz. Peak multiplicities were denoted by s (singlet), brs (broad singlet), d (doublet), brd (board doublet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), t (triplet), q (quartet) and m (multiplet). IR spectra were recorded on a Nicolet 20SXC Fourier transform spectrometer. Mass spectra were recorded on a VG Micromass 7070F mass spectrometer or on a ThermoFinnigan MAT 95 XL mass spectrometer. HRMS were recorded at Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China or on a Thermofinnigan MAT 95 XL masss spectrometer. Optical rotations were measured on a JASCO DIP-300 polarimeter using dichloromethane or chloroform as solvent. Elemental analyses were carried out at Shanghai Institute of Organic Chemistry, Academic Sinica, China or at MEDAC Ltd., Department of Chemistry, Brunel University, Uxbridge, U.K. All reactions were monitored by TLC on aluminium percoated with silica gel $60F_{254}$ (E. Merck) and compounds were visualized with a spray of 5% *w*/*v* dodecamolybdophosphoric acid in EtOH and subsequent heating. Flash chromatography was perfomed on Merck silica gel (230–400 mesh). Benzene, toluene, THF and Et_2O were freshly distilled from Na/benzophenone under N_2. Pyridine, Et_3N, *N*,*N*′-dimethylpropyleneurea (DMPU) and diisopropylamine were freshly distilled from calcium hydride.

(*S*)-(+)-6α-Methoxycarbonylcarvone 11: *n*BuLi in hexane (1.6 M in hexane; 3.12 mL, 4.67 mmol) was added under N_2 at −78 °C to a solution of diisopropylamine (0.70 mL, 5.00 mmol) in dry THF (10 mL). After the reaction mixture was stirred for 20 min at −78 °C, (*S*)-(+)-carvone **10** (0.5 g, 3.34 mmol) in THF (5 mL) containing DMPU (1 mL) was added dropwise. After the reaction mixture was stirred for 1 h at −78 °C, methyl cyanoformate (0.38 mL, 5.00 mmol) was added in one portion. The reaction mixture was stirred for 5 min at −78 °C and quenched with saturated aq. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (4×). The combined extracts were washed with brine (2×), dried ($MgSO_4$), and filtered. Concentration of the filtrate in vacuo followed by purification through silica gel flash column chromatography (petroleum ether/Et_2O 5:1) yielded the β-ketoester **11** (0.66 g, 95%) as a colorless oil. $R_f = 0.46$ (petroleum ether/Et_2O 5:1); $[\alpha] = +43.0$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (250 MHz): $\delta = 1.76$ (s, 3H), 1.81 (s, 3H), 2.33–2.43 (m, 2H), 3.13 (ddd, $J =$ 5, 11, 13 Hz, 1H), 3.51 (d, $J = 13$ Hz, 1H), 4.85–4.87 (m, 2H), 6.76–6.77 (m, 1H); IR (neat): $\tilde{\nu} = 1746$, 1674 cm^{-1}; MS (EI): *m*/*z*: 209 $[M+H]^+$; HRMS calcd for $C_{12}H_{20}NO_3$: 226.1443; found: 226.1433 $[M+NH_4]^+$.

Ester 15: $NaBH_4$ (36 mg, 0.96 mmol) was added at 0 °C in small batches over 20 min to a stirred solution of **11** (0.2 g, 0.96 mmol) and $CeCl_3$ (0.24 g, 0.96 mmol) in methanol (5 mL). The reaction mixture was stirred for 30 min at 0 °C and quenched with ice-cold saturated aq. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (4×) and the combined extracts were washed with brine (2×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by purification through silica gel flash column chromatography (petroleum ether/Et_2O 2:1) yielded the diasteriomeric mixture of **15** in a ratio of 1:1 (0.18 g, 88%) as a colourless oil. $R_f =$ 0.31 (petroleum ether/Et_2O 2:1); ^{1}H NMR (250 MHz): δ (selected) = 5.50 (brs, 0.5H), 5.56 (brs, 0.5H); IR (neat): $\tilde{\nu} = 3481$, 1730 cm^{-1}; MS (CI): *m*/*z*: 211 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{18}O_3$: C 68.55, H 8.63; found: C 68.43, H 8.57.

(*S*)-(+)-6α-Hydroxymethylcarvone 16: *n*BuLi (1.6 M in hexane; 2.29 mL, 3.67 mmol) at −78 °C was added under N_2 to a solution of diisopropylamine (0.51 mL, 3.67 mmol) in dry THF (10 mL). After the reaction mixture was stirred for 20 min at −78 °C, (*S*)-(+)-carvone **10** (0.5 g, 3.34 mmol) in THF (5 mL) containing DMPU (1 mL) was added dropwise. After the reaction mixture was stirred for 1 h at −78 °C, a N_2 stream containing gaseous formaldehyde, obtained by thermal decomposition of paraformaldehyde (2.0 g, dried over P_2O_5 in vacuo) on heating at 150 °C, was introduced into the reaction mixture. The reaction mixture was stirred for 5 min at −78 °C and quenched with saturated aq. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (4×). The combined extracts were washed with brine (2×), dried ($MgSO_4$), and filtered. Concentration of the filtrate in vacuo followed by purification through silica gel flash column chromatography (petroleum ether/Et_2O 5:1) yielded the **16** (0.54 g, 90%) as a colorless oil. $R_f = 0.20$ (petroleum ether/Et_2O 4:1); $[\alpha] = +13.0$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (250 MHz): $\delta = 1.62$ (s, 3H), 1.68 (s, 3H), 2.28 (dt, $J =$ 5, 18.5 Hz, 1H), 2.46 (ddd, $J = 3.5$, 7, 13.7 Hz, 1H), 2.47–2.49 (m, 1H), 2.68 (ddd, $J = 4.5$, 11, 13 Hz, 1H), 3.20 (brs, 1H), 3.52–3.70 (m, 2H), 4.85 (s, 2H), 6.76 (brs, 1H); IR (neat): $\tilde{\nu} = 3492$, 1661 cm^{-1}; MS (CI): *m*/*z*: 181 $[M+H]^+$; elemental analysis calcd (%) for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 72.94, H 9.25.

Silyl ether 17: Prepared using the method described in the previous experiment from (*S*)-(+)-carvone **10** (0.5 g, 3.34 mmol), diisopropylamine (0.51 mL, 3.67 mmol), *n*BuLi (1.6 M in hexane; 2.29 mL, 3.67 mmol), 2-(trimethylsilyl)ethoxymethyl chloride (0.65 mL, 3.67 mmol) in dry THF (15 mL) containing DMPU (1 mL). Fractionation through silica gel flash column chromatography (petroleum ether/Et_2O 2:1) yielded the **17** (0.77 g, 82%) as a colorless oil. $R_f = 0.48$ (petroleum ether/Et_2O 3:2); $[\alpha] = +10.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (250 MHz): $\delta = 0.01$ (s, 9H), 0.88–0.91 (m, 2H), 1.71 (s, 3H), 1.77 (s, 3H), 2.36–2.42 (m, 3H), 2.94 (ddd, $J = 5.5$, 10, 11.5 Hz, 1H), 3.40–3.43 (m, 3H), 3.88 (dd, $J = 3.2$, 9 Hz, 1H), 4.82 (brs, 2H), 6.68 (brs, 1H); IR (neat): $\tilde{\nu} = 1674$ cm^{-1}; MS (CI): *m*/*z*: 281 $[M+H]^+$; HRMS calcd for $C_{16}H_{28}O_2Si$: 280.1858; found: 280.1870 $[M]^+$.

Keto alcohol 18: *n*BuLi (1.6 M in hexane; 4.63 mL, 7.40 mmol) was added at −78 °C under N_2 to a solution of diisopropylamine (1.04 mL, 7.40 mmol) in dry THF (10 mL). After the reaction mixture was stirred for 10 min at −78 °C, (*S*)-(+)-carvone **10** (0.9 mL, 5.69 mmol) in THF (3 mL) containing DMPU (2 mL) was added dropwise. The reaction mixture was stirred for 1 h and a solution of the aldehyde **7**[25b] (0.90 g, 5.17 mmol) in THF (2 mL) was added in one portion. The reaction mixture was kept under stirring for 5 min at −78 °C under N_2, and quenched with saturated aq. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (4×) and the combined extracts were washed with brine (2×), dried ($MgSO_4$), and filtered. Concentration of the filtrate in vacuo followed by silica gel flash column chromatography (hexane/Et_2O 1:1) yielded **18** (1.04 g, 62%) as a colorless oil. $R_f = 0.20$ (hexane/Et_2O 1:3); ^{1}H NMR (250 MHz): δ (selected) = 6.70 (brs, olefin proton at position 11, 0.5H), 6.80 (brs, olefin proton at position 11, 0.5H); IR (neat): $\tilde{\nu} = 3501$, 1659 cm^{-1}; MS (EI): *m*/*z*: 325 $[M+H]^+$; HRMS calcd for $C_{17}H_{24}SO_4$: 324.1395; found: 324.1373 $[M]^+$.

Keto ester 19: Dry pyridine (0.13 mL, 1.6 mmol) and Ac_2O (0.20 mL, 1.6 mmol) at room temperature under N_2 was added to a solution of **18** (85 mg, 0.40 mmol) in Cl_2Cl_2 (2.5 mL). The reaction mixture was stirred for 10 h, then H_2O was added. Neutralization with saturated aq. $NaHCO_3$ and extracted with Cl_2Cl_2 (2×). The combined extracts was washed with brine (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo and followed by flash chromatography (hexane/EtOAc 5:1) gave **19** as a colorless oil (97 mg 90%). $R_f = 0.50$ (hexane/EtOAc 5:2); $[\alpha] = +104.8$ ($c = 0.8$ in Cl_2Cl_2); ^{1}H NMR (250 MHz): $\delta = 1.22$ (s, 3H), 1.70 (dd, $J = 3.3$, 14.2 Hz, 1H), 1.79 (s, 3H), 2.02 (s, 3H), 2.46 (ddd, $J = 4.1$, 13.7, 14.9 Hz, 1H), 2.71 (dd, $J = 4.3$, 13.5 Hz, 1H), 4.02 (d, $J = 9.0$ Hz, 1H), 4.16 (d, $J =$ 11.9 Hz, 1H), 4.29 (d, $J = 11.9$ Hz, 1H), 4.48 (d, $J = 9$ Hz, 1H), 4.89 (s, 2H), 5.12 (d, $J = 2.9$ Hz, 1H); IR (neat): $\tilde{\nu} = 1730$, 1630 cm^{-1}; MS (EI): *m*/*z*: 310 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{22}O_6$: C 61.92, H 7.15; found: C 61.91, H 7.48.

Tricycle 20: A solution of the **19** (0.3 g) and methylene blue (1 mg) in dry benzonitrile (80 mL) was heated under reflux in a sealed tube for 110 h. After the reaction mixture was cooled to room temperature, the solvent was removed in vacuo. Purification by silica gel flash column chromatography (hexane/Et_2O 7:1) afforded **20** (0.12 g, 40%) as a colorless oil. R_f = 0.30 (hexane/Et_2O 1:1); ^{1}H NMR (250 MHz): δ = 0.74 (s, 3H), 1.20–1.22 (m, 1H), 1.61 (s, 3H), 1.75 (dd, J = 4.5, 13 Hz, 1H), 1.80 (s, 3H), 1.82–2.60 (m, 8H), 5.39 (s, 1H), 6.17–6.18 (m, 1H), 7.03–7.07 (m, 1H); IR (neat): $\tilde{\nu}$ = 1666 cm^{-1}; MS (CI, NH_3): m/z: 243 $[M+H]^+$; HRMS calcd for $C_{17}H_{22}O$ 242.1671; found: 242.1670 $[M]^+$.

(*S*)-(+)-6,6-Dihydroxymethenylcarvone 24: *n*BuLi (1.6 M in hexane; 30 mL, 45 mmol) was added dropwise under N_2 at 0 °C to a solution of diisopropylamine (6.3 mL, 45.28 mmol) in dry THF (70 mL). After stirring for 30 min, the solution was cooled to −78 °C, followed by dropwise addition of a solution of (*S*)-(+)-carvone **10** (3.84 g, 25.2 mmol) and DMPU (3 mL, 25.2 mmol) in THF (15 mL). This mixture was kept under stirring for 1 h at −78 °C, and then formaldehyde was introduced into the mixture by decomposition of paraformaldehyde (3.0 g) at 150 °C, with smooth stream of N_2, over 2 h. The reaction mixture was allowed to warm up to −40 °C, followed by introduction of more formaldehyde (2.0 g). After finishing the introduction, the reaction mixture was allowed to warm up to room temperature and stand overnight, quenched with saturated aq. NH_4Cl and extracted with CH_2Cl_2 (3×). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give an oily residue. Flash chromatography on silica gel (hexane/EtOAc 8:3) afforded **24** as a white solid (3.1 g, 75%). R_f = 0.21 (hexane/EtOAc 5:2); m.p. 84–85 °C; $[\alpha]$ = +39.1, (c = 1.6 in CH_2Cl_2); ^{1}H NMR (250 MHz): δ = 1.61 (s, 3H), 1.78 (s, 3H), 2.32 (d, J = 20.4 Hz, 1H), 2.77 (d, J = 20.4 Hz, 1H), 2.98 (dd, J = 3.6, 6.3 Hz, 1H), 3.56 (d, J = 9.9 Hz, 2H), 3.76–3.98 (m, 4H), 4.77 (s, 2H), 6.67 (s, 1H); ^{13}C NMR (62.89 MHz): δ = 15.4, 21.6, 18.74, 44.4, 52.6, 64.0, 64.5, 114.4, 134.6, 143.1, 144.7, 204.1; IR (neat): $\tilde{\nu}$ = 3300, 1630 cm^{-1}; MS (EI): m/z: 192 $[M-H_2O]^+$; elemental analysis calcd (%) for $C_{12}H_{18}O_3$: C 68.54, H 8.62; found: C 68.29, H 8.86.

(*S*)-(+)-6,6-(*O*,*O*-Isopropylidenebishydroxymethyl)-carvone (25): 2,2-Dimethoxypropane (3.0 mL, 24.5 mmol) and *p*-TsOH (25 mg) were added to a solution of **24** (0.5 g, 23.8 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature for 2 h. Subsequent purification by flash chromatography on silica gel (hexane/EtOAc 9:1) gave **25** as a colourless oil (0.7 g, 96%). R_f = 0.8 (hexane/EtOAc 5:1); $[\alpha]$ = +149.7, (c = 1.9 in CH_2Cl_2); ^{1}H NMR (250 MHz): δ = 1.41 (s, 3H), 1.44 (s, 3H), 1.60 (s, 3H), 1.75 (s, 3H), 2.30 (dd, J = 3.6, 14.2 Hz), 1H), 2.90 (dd, J = 3.6, 13.5 Hz, 1H), 3.48 (d, J = 12.2 Hz, 1H), 3.64–3.85 (m, 3H), 4.43 (d, J = 3.3 Hz, 1H), 4.79 (d, J = 8.6 Hz, 2H), 6.61 (s, 1H); ^{13}C NMR (62.89 MHz): δ = 15.1, 19.5, 21.1, 25.3, 27.1, 45.2, 48.6, 59.5, 61.9, 63.2, 97.9, 113.8, 144.9, 200.4; IR (neat): $\tilde{\nu}$ = 1662 cm^{-1}; MS (EI): m/z: 250 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_{22}O_3$: C 71.69, H 8.86; found: C 72.02, H 8.74.

Epoxide 26: *tert*-Butyloxyperoxide (13.9 mL, 101.5 mmol, 70% aq. solution) and 2 N NaOH solution (20 mL) were added to a solution of **25** (5 g, 20.0 mmol) in MeOH (70 mL). The reaction mixture was stirred for 24 h at 45 °C and then poured into H_2O, extracted with Et_2O (2×), dried ($MgSO_4$) and filtered. Concentration under vacuo and flash chromatogaphy on silica gel (hexane/EtOAc 10:1) gave **26** as a white solid (5 g, 94%). R_f = 0.48 (hexane/EtOAc 5:1); m.p. 68–68.5 °C; $[\alpha]$ = +81.8, (c = 0.88 in CH_2Cl_2); ^{1}H NMR (250 MHz): δ = 1.36 (s, 3H), 1.39 (s, 6H), 1.65 (s, 3H), 1.98 (ddd, J = 1.8, 4.9, 16.3 Hz, 1H), 2.66 (dd, J = 7.3, 16.3 Hz, 1H), 3.29 (d, J = 7.2 Hz, 1H), 3.46 (d, J = 4.7 Hz, 1H), 3.55(dd, J = 2.1, 12.2 Hz, 1H), 3.81 (d, J = 12.0 Hz, 1H), 4.24 (d, J = 12.2 Hz, 1H), 4.25 (dd, J = 2.1, 12 Hz, 1H), 4.75 (s, 1H), 4.83 (t, J = 1.4 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = 15.1, 19.5, 21.1, 25.3, 27.1, 45.2, 48.6, 59.5, 61.9, 63.2, 63.7, 97.9, 113.8, 144.9, 200.4; IR (neat): $\tilde{\nu}$ = 1693.4 cm^{-1}; MS (EI): m/z: 267 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{22}O_4$: C 67.64; H 8.3; found: C 67.26, H 8.3.

Alcohol 27: CF_3CO_2H (1 mL) was added under stirring at room temperature to a solution of **26** (0.7 g, 2.63 mmol) in EtOH (10 mL). Then the mixture was stirred for 24 h at 50 °C. The EtOH was removed in vacuo and then saturated aq. Na_2CO_3 was added. The mixture was extracted with EtOAc (3×). The combined extracts were washed with brine (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 4:1) afforded **27** as colourless crystals (0.5 g, 85%). R_f = 0.2 (hexane/EtOAc 1:1); m.p. 150–153 °C; $[\alpha]$ = +64.0 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz): δ = 1.3 (s, 3H), 1.66 (dd, J = 4.4, 15 Hz, 1H), 1.73 (d, J = 4.3 Hz, 1H), 1.8 (s, 3H), 2.27 (t, J = 7.2 Hz, 1H), 2.43 (dt, J = 3.8, 14.2 Hz, 1H), 2.88 (dd, J = 4.6, 13.6 Hz, 1H), 3.55 (dd, J = 7.7, 12.5 Hz, 1H), 3.82 (dd, J = 6.6, 12.3 Hz, 1H), 4.06 (br s, 1H), 4.07 (d, J = 9.0 Hz, 1H), 4.40 (d, J = 8.8 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = 15.3, 22.0, 33.0, 47.9, 55.6, 60.0, 65.1, 78.8, 80.2, 114.8, 143.0, 210.3; IR (film): $\tilde{\nu}$ = 3430, 3300, 2900, 1770, 1500, 1085 cm^{-1}; MS (L-SIMS); m/z: 227 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{18}O_4$: C 63.70, H 8.02; found: C 63.41, H 7.84.

Silyl ether 28: Et_3N (1 mL), DMAP (100 mg) and *tert*-butyldimethylsilyl chloride (1.17 g, 7.7 mmol) were added at room temperature to a solution of **27** (0.7 g, 3.1 mmol) in dry Cl_2Cl_2 (12 mL). The reaction mixture was stirred for 48 h, then poured into H_2O, extracted with Cl_2Cl_2 (2×), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc 5:1) gave **28** as a white solid (0.94 g, 92%). R_f = 0.6 (hexane/EtOAc 2:1); m.p. 70–72 °C; $[\alpha]$ = +67.4 (c = 0.9 in Cl_2Cl_2); ^{1}H NMR (250 MHz): δ = 0.02 (s, 3H), 0.4 (s, 3H), 0.81 (s, 9H), 1.24 (s, 3H), 1.58 (dd, J = 4.3, 14.5 Hz, 1H), 1.74 (s, 3H), 2.38 (dt, J = 3.6, 13.5, 14.5 Hz, 2H), 2.68 (dd, J = 4.4, 13.5 Hz, 1H), 3.44 (d, J = 10.5 Hz, 1H), 3.82 (d, J = 10.5 Hz, 1H), 3.98 (d, J = 3.6 Hz, 1H), 4.19 (d, J = 8.7 Hz, 1H), 4.38 (d, J = 8.7 Hz, 1H), 4.77 (s, 1H), 4.81 (s, 1H); ^{13}C NMR (62.89 MHz): δ = −5.8, −5.7, 15.3, 18.1, 21.5, 25.7, 32.9, 49.3, 55.9, 59.7, 65.5, 78.6, 80.7, 114.3, 143.3, 211.4; IR (neat): $\tilde{\nu}$ = 3300, 1768 cm^{-1}; MS (EI): m/z: 340 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{32}SiO_4$: C 63.48, H 9.47; found: C 63.51, H 9.85.

Acetal 29: PPTS (10 mg) was added to a solution of **28** (145 mg, 0.42 mmol) in dry Cl_2Cl_2 (2 mL). The solution was cooled to 0 °C, followed by addition of 2-methoxypropene (0.081 mL, 0.85 mmol). The reaction was stirred for 4 h at 0 °C and then Et_3N (0.07 mL) and H_2O were added. The aqueous layer was extracted with Et_2O (2×), dried ($MgSO_4$) and filtered. Concentration under vacuo and flash chromatography on silica gel (hexane/Et_2O 10:1) gave **29** as a colorless oil (171 mg, 96%). R_f = 0.46 (hexane/Et_2O 5:1); $[\alpha]$ = +46.0 (c = 1.3 in Cl_2Cl_2); ^{1}H NMR (250 MHz): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9H), 1.18 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.68 (dd, J = 4.3, 14.7 Hz, 1H), 1.74 (s, 3H), 2.28 (dt, J = 3.7, 14.2 Hz, 1H), 2.65 (dd, J = 4.3, 13.4 Hz, 1H), 3.12 (s, 3H), 3.45 (d, J = 10.5 Hz, 1H), 3.85 (d, J = 10.5 Hz, 1H), 4.00 (d, J = 2.1Hz, 1H), 4.16 (d, J = 8.1 Hz, 1H), 4.36 (d, J = 8.1 Hz, 1H), 4.74 (s, 1H), 4.79 (s, 1H); ^{13}C NMR (62.89 MHz): δ = −5.7, 15.8, 18.1, 21.3, 24.9, 25.2, 25.7, 31.2, 49.3, 55.1, 59.7, 65.5, 78.2, 79.8, 101.1, 113.9, 143.8, 210.0; IR (neat): $\tilde{\nu}$ = 1771 cm^{-1}; MS (EI): m/z: 381 $[M-MeO]^+$; elemental analysis calcd (%) for $C_{22}H_{40}O_5Si$: C 64.02, H 9.77; found: C 64.22, H 9.54.

Alcohol 30: 1.0 M Tetrabutylammonium fluoride in THF (5.0 mL) was added to a solution of **29** (1.0 g, 2.5 mmol) in dry THF (20 mL) at room temperature. The reaction mixture was stirred for 0.5 h and poured into H_2O, extracted with Et_2O (2×), dried ($MgSO_4$) and filtered. Concentration under vacuo and flash chromatograhpy on silica gel (hexane/EtOAc 5:1) gave **30** as a white solid (0.72 g, 96%). R_f = 0.20 (hexane/Et_2O 5:2); m.p. 90–92 °C; $[\alpha]$ = +64.8 (c = 0.7 in Cl_2Cl_2); ^{1}H NMR (250 MHz): δ = 1.23 (s, 3H), 1.33 (s, 6H), 1.74 (dd, J = 4.4, 14.2 Hz, 1H), 1.80 (s, 3H), 2.30 (dt, J = 3.6, 14.2 Hz, 1H), 2.83 (dd, J = 3.6, 13.5 Hz, 1H), 3.18 (s, 3H), 3.55 (d, J = 12.2 Hz, 1H), 3.85 (d, J = 12.2 Hz, 1H), 4.04 (d, J = 3.3 Hz, 1H), 4.04 (d, J = 8.6 Hz, 1H), 4.38 (d, J = 8.6 Hz, 1H), 4.83–4.90 (m, 2H); IR (neat): $\tilde{\nu}$ = 1769.6 cm^{-1}; MS (EI): m/z: 209 $[M-OC(Me)_2OMe]^+$; elemental analysis calcd (%) for $C_{16}H_{26}O_5$: C 64.40, H 8.78; found: C 64.34, H 9.14.

Keto ester 32: *i*Pr_2EtN (129 mg, 1 mmol) and then AcCl (50 mg, 0.6 mmol) was added dropwise under stirring at 0 °C under N_2 to a solution of **27** (115 mg, 0.5 mmol) in Cl_2Cl_2 (2 mL). After stirring for a further 4 h at room temperature, the reaction mixture was purified directly by flash chromatography (hexane/EtOAc 4:1) to afford **32** as colourless crystals (134 mg, 97%). R_f = 0.50 (hexane/EtOAc 1:1); m.p. 130–131 °C, $[\alpha]$ = +105.0 (c = 1.1 in Cl_2Cl_2); ^{1}H NMR (250 MHz): δ = 1.32 (s, 3H), 1.66 (dd, J = 4.4, 14.8 Hz, 1H), 1.73 (d, J = 4.5 Hz, 1H), 1.79 (s, 3H), 2.00 (s, 3H), 2.45 (dt, J = 3.9, 14 Hz, 1H), 2.82 (dd, J = 4.5, 13.5 Hz, 1H), 4.03 (d, J = 9.0 Hz, 1H), 4.05 (t, J = 3.8 Hz, 1H), 4.09 (d, J = 11.9 Hz, 1H), 4.22 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 9.0 Hz, 1H), 4.87 (s, 1H), 4.89 (s, 1H); ^{13}C NMR (62.89 MHz): δ = 15.3, 20.5, 21.2, 32.8, 48.9, 53.2, 60.7, 65.1, 78.3, 80.4, 115.1, 142.5, 170.6, 209.4; IR (film): $\tilde{\nu}$ = 3500, 2950, 1760, 1740, 1250 cm^{-1}; MS (L-SIMS): m/z: 269 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{20}O_5$: C 62.67, H 7.51; found: C 62.70, H 7.54.

Silyl ether 33: 2,6-Lutidine (0.45 mL, 3.7 mmol) and TBSOTf (0.64 mL, 2.8 mmol) were sequentially added dropwise under stirring at room

temperature under N_2 to a solution of **32** (0.5 g, 1.86 mmol) in Cl_2Cl_2 (10 mL). After stirring for a further 2 h, the mixture was purified directly by flash chromatography (hexane/EtOAc 9:1) to give **33** as a white solid (0.72 g, 100 %). $R_f = 0.80$ (hexane/EtOAc 4:1); m.p. 87.5–88 °C; $[\alpha] = +88.0$ ($c = 1.2$ in Cl_2Cl_2); ^{1}H NMR (500 MHz): $\delta = 0.01$ (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.24 (s, 3H), 1.52 (dd, $J = 3.6$, 14.8 Hz, 1H), 1.78 (s, 3H), 2.0 (s, 3H), 2.42 (dt, $J = 3.5$, 13.7 Hz, 1H), 2.75 (dd, $J = 4.4$, 13.5 Hz, 1H), 3.96 (brs, 1H), 3.99 (d, $J = 8.9$ Hz, 1H), 4.05 (d, $J = 11.9$ Hz, 1H), 4.24 (d, $J = 11.9$ Hz, 1H), 4.43 (d, $J = 9.0$ Hz, 1H), 4.84 (s, 1H), 4.85 (s, 1H); ^{13}C NMR (62.89 MHz): $\delta = -5.1$, −4.6, 15.8, 17.8, 20.5, 21.3, 25.5, 33.6, 48.5, 52.9, 60.8, 65.3, 78.8, 80.4, 114.9, 143.0, 170.4, 207.5; IR (film): $\tilde{\nu} = 3500$, 2950, 1760, 1740, 1250 cm^{-1}; MS (EI): m/z: 382 $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{34}O_5Si$: C 62.79, H 8.96; found: C 63.01, H 9.00.

Keto alcohol 34: Solid NaOH (40 mg, 1 mmol) was added under stirring to a solution of **33** (200 mg, 0.52 mmol) in MeOH (5 mL). After stirring for 4 h at room temperature, the mixture was concentrated in vacuo and the residue was purified by chromatography (hexane/EtOAc 4:1) to give **34** as a white solid (170 mg, 96 %). $R_f = 0.60$ (hexane/EtOAc 4:1); m.p. 74–75 °C; $[\alpha] = +80.0$ ($c = 1.1$ in Cl_2Cl_2); ^{1}H NMR (500 MHz): $\delta = 0.01$ (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.24 (s, 3H), 1.53 (ddd, $J = 1.6$, 4.3, 14.3 Hz, 1H), 1.80 (s, 3H), 2.30 (brs, 1H), 2.38 (dt, $J = 1.6$, 13.7 Hz, 1H), 2.82 (dd, $J = 4.3$, 13.4 Hz, 1H), 3.55 (dd, $J = 7.7$, 12.3 Hz, 1H), 3.80 (dd, $J = 6.3$, 12.3 Hz, 1H), 3.96 (q, $J = 11.8$ Hz, 1H), 4.03 (dd, $J = 0.8$, 8.8 Hz, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.88 (brs, 2H); ^{1}H NMR (500 MHz, $CDCl_3$+D_2O): $\delta = 0.02$ (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H, 1.2 (s, 3H), 1.53 (ddd, $J = 1.6$, 4.3, 14.3 Hz, 1H), 1.80 (s, 3H), 2.38 (dt, $J = 1.6$, 13.7 Hz, 1H), 2.82 (dd, $J = 4.3$, 13.4 Hz, 1H), 3.54 (d, $J = 12.3$ Hz, 1H), 3.79 (d, $J = 12.3$ Hz, 1H), 3.96 (brs, 1H), 4.03 (d, $J = 8.8$ Hz, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.88 (brs, 2H); ^{13}C NMR (62.89 MHz): $\delta = -5.1$, −4.6, 15.5, 17.8, 22.0, 25.5, 33.6, 47.3, 55.0, 60.0, 65.0, 78.9, 80.2, 114.3, 143.4, 211.6; IR (film): $\tilde{\nu} = 3400$, 2950, 2880, 1780, 1260, 1130 cm^{-1}; MS (EI): m/z: 339 $[M-H]^+$; elemental analysis calcd (%) for $C_{18}H_{32}O_4Si$: C 63.33, H 9.45; found: C 63.40, H 9.67.

Keto aldehyde 35: TPAP (15 mg) was added at room temperature to a mixture of **34** (285 mg, 0.85 mmol), NMO (172 mg, 1.47 mmol) and 4 Å MS (50 mg) in Cl_2Cl_2 (4 mL). The mixture was stirred for 2 h and then filtered through a short silica gel column. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 9:1) afforded **35** as a white solid (242 mg, 84 %). $R_f = 0.70$ (hexane/EtOAc 3:1); m.p. 66–67 °C; $[\alpha] = +121.0$ ($c = 3.0$ in Cl_2Cl_2); ^{1}H NMR (500 MHz): $\delta = 0.001$ (s, 6H), 0.83 (s, 9H), 1.16 (s, 3H), 1.66 (s, 1H), 1.71 (ddd, $J = 2.9$, 4.5, 13.2 Hz, 1H), 2.25 (dt, $J = 3.4$, 13.4 Hz, 1H), 3.39 (dd, $J = 4.4$, 13.1 Hz, 1H), 3.90 (brs, 1H), 4.31 (d, $J = 9.4$ Hz, 1H), 4.43 (d, $J = 9.3$ Hz, 1H), 4.63 (s, 1H), 4.80 (brs, 1H), 9.64 (brs, 1H); ^{13}C NMR (62.89 MHz): $\delta = -5.1$, −4.6, 15.4, 17.8, 21.7, 25.5, 33.4, 47.5, 63.7, 64.2, 78.4, 81.8, 114.1, 142.5, 198.2, 201.7; IR (film): $\tilde{\nu} = 2950$, 1698, 1518 cm^{-1}; MS (FAB): m/z: 339 $[M+H]^+$; HRMS calcd for $C_{19}H_{30}O_4Si$: 339.1986; found: 339.1987 $[M+H]^+$.

(*Z*)-3-Methyl-5-bromopenta-1,3-diene (37b) (from *cis*-3-methyl-2-penten-4-yn-1-ol): $NaBH_4$ (0.8 g, 21 mmol) was added under stirring under H_2 atmosphere to a solution of $Ni(OAc)_2 \cdot 4H_2O$ (5 g, 20 mmol) in EtOH (150 mL). The resulting black suspension was stirred for 30 min and *cis*-3-methyl-2-penten-4-yn-1-ol (11 mL, 0.1 mol) and ethandiamine (2.6 mL) were added under stirring at room temperature under H_2. The mixture was stirred overnight under H_2 at atmospheric pressure and filtered through a short pad of Celite. The filtrate was concentrated and anhydrous Et_2O was added to the residue. The mixture was filtered through a short silica gel column. The eluant was concentrated in vacuo, giving a crude product which was purified by distillation in vacuo to yield (*Z*)-3-methylpenta-1,3-dien-5-ol (**36b**) as a colorless liquid (7.3 g, 86 %): b.p. 42 °C at 1 mmHg.

PBr_3 (2 mL, 21 mmol) was added dropwise under stirring at −30 °C under N_2 within 10 min to a solution of (*Z*)-3-methylpenta-1,3-dien-5-ol (**36b**; 5 g, 51 mmol) in pyridine (200 mg) and Et_2O (50 mL). The mixture was continued for 30 min at −30 °C, then quenched with ice-water. The organic layer was separated and the aqueous was extracted with Et_2O (2 ×). The combined organic extracts were washed with brine (3 ×), dried ($MgSO_4$) and filtered. Concentration of filtrate and followed by distillation in vacuo afforded (*Z*)-3-methyl-5-bromopenta-1,3-diene (**37b**), together with a small amount of the (*E*)-isomer **37a** as a pale yellow liquid (*Z*:*E* 6:1, determined by ^{1}H NMR) (6.8 g, 83 %). B.p. 90 °C at 20 mmHg (lit.:[36c] 52 °C, 14 mmHg).

5-Bromo-3-methylpenta-1,3-diene (37) (from ethyl acetate 39)[38]: Vinyl bromide (29 mL, 0.42 mol) was added dropwise by condensation with a cold finger containing dry ice in acetone to a vigorously stirred suspension of magnesium powder (10 g, 0.42 mol) in dry THF (400 mL) under N_2 at −78 °C. The suspension was stirred at 0 °C and 1,2-dibromoethane (0.04 mL, 0.04 mol) was added as an initiator. When the solution started to reflux, it was allowed to stirred at 0 °C for 1 h and then at room temperature for 2 h. A solution of ethyl acetate **39** (18 mL, 0.19 mol) in THF (30 mL) was added dropwise to the suspension at 0 °C over 1 h. The suspension was allowed to stir at room temperature for 4 h and then quenched with saturated aq. NH_4Cl. The mixture was extracted with Et_2O (3 ×) and the combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo, giving a crude product which was purified by distillation in vacuo to yield 3-methyl-1,4-pentadien-3-ol (**40**) as a colorless liquid (13 g, 70 %). B.p. 55 °C at 40 mmHg; ^{1}H NMR (300 MHz, C_6D_6): $\delta = 1.22$ (s, 3H), 1.86 (brs, 1H), 4.91 (dd, $J = 1.2$, 10.5 Hz, 2H), 5.19 (dd, $J = 1.2$, 17.4 Hz, 2H), 5.83 (dd, $J = 10.5$, 17.4 Hz, 2H); ^{13}C NMR (75.47 MHz): $\delta = 27.9$, 73.5, 111.9, 144.3.

PBr_3 (4 mL, 0.42 mol) was added dropwise under stirring at −10 °C under N_2 in 10 min to a solution of 3-methyl-1,4-penta-dien-3-ol (**40**; 10 g, 0.1 mol) in pyridine (400 mg) and Et_2O (100 mL). The mixture was stirred for 30 min and was then quenched with ice water. The mixture was extracted with Et_2O (3 ×). The combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo, giving a crude product which was purified by distillation in vacuo to yield 5-bromo-3-methylpenta-1,3-diene (**37**) (*E*:*Z* 3:1, based on NMR analysis) as a pale yellow liquid (13.1 g, 80 %). B.p. 50 °C at 10 mmHg (lit.:[26c] 53–56 °C, 10 mmHg).

E Isomer **37a**: ^{1}H NMR (300 MHz): $\delta = 1.85$ (s, 3H), 4.15 (d, $J = 8.7$ Hz, 2H), 5.12 (d, $J = 10.5$ Hz, 1H), 5.30 (d, $J = 17.4$ Hz, 1H), 5.78 (t, $J = 8.7$ Hz, 1H), 6.38 (dd, $J = 10.5$, 17.4 Hz, 1H); ^{13}C NMR (75.47 MHz): $\delta = 11.8$, 29.3, 115.2, 127.1, 140.2, 140.5; (*Z*)-isomer **37b**: ^{1}H NMR (300 MHz): $\delta = 1.89$ (s, 3H), 4.15 (d, $J = 8.7$ Hz, 2H), 5.30 (d, $J = 10.5$ Hz, 1H), 5.39 (d, $J = 17.4$ Hz, 1H), 5.69 (t, $J = 8.7$ Hz, 1H), 6.80 (dd, $J = 10.5$, 17.4 Hz, 1H); ^{13}C NMR (75.47 MHz): $\delta = 20.3$, 28.2, 117.5, 125.3, 132.3, 138.6.

3-Methyl-2,4-pentadienyl magnesium bromide (38): A catalytic amount of I_2 was added to a suspension of magnesium powder (900 mg, 37.4 mmol) in Et_2O (40 mL). A solution of **37** (2 g, 12.4 mmol) in Et_2O (10 mL) was added dropwise to the suspension with vigorous stirring at −10 °C under N_2 in 4 h. After stirring at −10 °C for 2 h and at room temperature for 2 h, the Grignard reagent **38** was ready for use.

Triene 41: *tert*-Butyloxyperoxide (13.9 mL, 101.5 mmol, 70 % aq. solution) and 2 N NaOH solution (20 mL) was added to a solution of aldehyde **35** (64 mg, 0.19 mmol) in Et_2O (2 mL). After stirring for 5 min, the reaction was quenched with saturated aq. NH_4Cl and extracted with Et_2O (3 ×). The combined organic extracts was washed with brine (3 ×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 9:1) afforded **41** as a colourless oil (68 mg, 80 %). $R_f = 0.80$ (hexane/EtOAc 5:1); $[\alpha] = -6.5$ ($c = 2.6$ in Cl_2Cl_2); ^{1}H NMR (500 MHz): $\delta = 0.01$ (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.13 (s, 3H), 1.16 (s, 3H), 1.52 (dd, $J = 4.7$, 14.0 Hz, 1H), 1.8 (s, 3H), 2.30 (dt, $J = 3.5$, 14.0 Hz, 1H), 3.30 (dd, $J = 4.2$, 13.6 Hz, 1H), 3.67 ($J = 11.3$ Hz, 1H), 3.90 (brs, 1H), 4.07 (d, $J = 9.5$ Hz, 1H), 4.36 (d, $J = 9.8$ Hz, 1H), 4.83 (d, $J = 11.6$ Hz, 1H), 4.93–5.16 (m, 6H), 5.72 (dd, $J = 10.7$, 17.5 Hz, 1H), 5.91 (dd, $J = 10.9$, 17.5 Hz, 1H); ^{13}C NMR (62.89 MHz): $\delta = -5.2$, −4.6, 15.9, 17.7, 22.3, 23.0, 25.5, 33.7, 48.6, 50.1, 56.2, 65.9, 78.0, 79.5, 81.1, 112.6, 114.6, 115.1, 141.8, 144.2, 192.5; IR (film) $\tilde{\nu} = 3458$, 2932, 1748, 1112 cm^{-1}; MS (EI): m/z: 421 $[M+H]^+$; HRMS calcd for $C_{24}H_{40}O_4Si$: 420.2695; found: 420.2691 $[M]^+$.

Triene 44 and 45: KH (33 mg, 0.83 mmol) was added under stirring at room temperature under N_2 to a solution of triene **41** (30 mg, 0.07 mmol) and dibenzo-[18]crown-6 (25 mg, 0.07 mmol) in THF (4 mL). The mixture was stirred for 4 h at room temperature and then quenched with H_2O, extracted with Et_2O (2 ×). The combined extracts were washed with brine (3 ×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 19:1) gave **44** and **45** (**44** 24 mg and **45** 2 mg, 85 %).

Triene 44: white solid; $R_f = 0.60$ (hexane/EtOAc 5:1); m.p. 90–91 °C; $[\alpha] = +38.0$ ($c = 2.0$ in Cl_2Cl_2); ^{1}H NMR (500 MHz): $\delta = 0.02$ (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.2 (s, 3H), 1.50 (dd, $J = 1.6$, 4.5 Hz, 1H), 1.72 (s, 3H), 1.85 (s, 3H), 2.26–2.33 (m, 1H), 2.39 (dt, $J = 3.5$, 13.9 Hz, 1H), 2.50 (dd,

J = 5.8, 15.4 Hz, 1H), 2.8 (d, J = 7.1 Hz, 1H), 3.03 (dd, J = 4.3, 13.5 Hz, 1H), 3.78–3.82 (m, 1H), 3.94 (brs, 1H), 4.04 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 9.1 Hz, 1H), 4.92 (brs, 1H), 4.95 (d, J = 10.7 Hz, 1H), 4.98 (brs, 1H), 5.10 (d, J = 17.4 Hz, 1H), 5.57 (t, J = 7.1Hz, 1H), 6.38 (dd, J = 10.7, 17.4 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = −5.2, −4.7, 11.8, 15.6, 17.7, 22.2, 25.4, 31.5, 34.2, 47.8, 57.8, 65.8, 70.7, 78.8, 80.6, 110.8, 114.7, 129.1, 135.6, 141.2, 144.9, 195.5; IR (film): $\tilde{\nu}$ = 3500, 2930, 1758, 1150 cm^{-1}; MS (EI): m/z: 419 $[M-H]^+$; HRMS calcd for $C_{24}H_{40}O_4Si$: 420.2696; found: 420.2691 $[M]^+$.

Triene 45: colourless oil; R_f = 0.50 (hexane/EtOAc 5:1); $[\alpha]$ = +68.0 (c = 0.7, in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.02 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.2 (s, 3H), 1.54 (ddd, J = 1.6, 4.5, 14.4 Hz, 1H), 1.74 (s, 3H), 1.87 (s, 3H), 2.28–2.44 (m, 3H), 2.62–2.72 (m, 1H), 2.94 (dd, J = 4.3, 13.3 Hz, 1H), 3.76–3.80 (m, 1H), 3.94 (brs, 1H), 4.17 (d, J = 9.0 Hz, 1H), 4.44 (d, J = 9.0 Hz, 1H), 4.89–4.96 (m, 3H), 5.11 (d, J = 17.4 Hz, 1H), 5.56 (t, J = 7.1 Hz, 1H), 6.39 (dd, J = 10.7, 17.4 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = −5.0, −4.5, 11.9, 15.8, 17.8, 22.1, 25.6, 30.7, 34.6, 48.1, 57.7, 66.0, 71, 78.7, 80.8, 111.1, 114.7, 129.3, 136.2, 141.3, 145.4, 196.6; IR (film): $\tilde{\nu}$ = 3500, 2930, 1758, 1150 cm^{-1}; MS (EI): m/z: 419 $[M-H]^+$; HRMS calcd for $C_{24}H_{40}O_4Si$: 420.2696; found: 420.2690 $[M]^+$.

Acetate 48: DMAP (10 mg) and Ac_2O (0.5 mL, 4.9 mmol) at room temperature under N_2 were added under stirring to a solution of **44** (400 mg, 0.95 mmol) in Cl_2Cl_2 (10 mL) and Et_3N (1 mL, 7.2 mmol). Stirring was continued overnight. Direct flash chromatography (hexane/EtOAc 19:1) gave acetate **48** as a white solid (440 mg, 100%). R_f = 0.60 (hexane/EtOAc 5:1); m.p. 80–82 °C; $[\alpha]$ = +54.0 (c = 2.0 in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.2 (s, 3H), 1.49 (ddd, J = 2.6, 8.9, 14.4 Hz, 1H), 1.70 (s, 3H), 1.86 (s, 3H), 1.92 (s, 3H), 2.43 (dt, J = 2.8, 13.4 Hz, 1H), 2.61–2.70 (m, 2H), 3.04 (dd, J = 4.7, 13.2 Hz, 1H), 3.92 (brs, 1H), 3.99 (d, J = 8.8 Hz, 1H), 4.43 (d, J = 9.0 Hz, 1H), 4.89–4.94 (m, 3H), 5.06 (d, J = 17.7 Hz, 1H), 5.28 (dd, J = 3.5, 9.6 Hz, 1H), 5.39 (t, J = 8.7 Hz, 1H), 6.33 (dd, J = 10.7, 17.4 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.7, 11.6, 15.8, 17.8, 20.6, 20.7, 25.5, 29.3, 34.5, 47.6, 56.1, 67.1, 72.2, 78.4, 80.7, 111.0, 115.3, 127.7, 136.3, 141.1, 145.0, 169.6, 200.0; IR (film): $\tilde{\nu}$ = 2957, 2659, 1767, 1745, 1252, 1231, 1116 cm^{-1}; MS (EI): m/z: 462 $[M]^+$; HRMS calcd for $C_{26}H_{42}O_5SiNa$: 485.2699, found: 485.2735 $[M+Na]^+$.

Tetracycle 49: A solution of **48** (440 mg, 0.95 mmol) and methylene blue (10 mg) in toluene (5 mL) was refluxed under stirring in a sealed tube for 110 h at 170 °C. Direct flash chromatography (hexane/EtOAc 19:1) gave **49** as a colourless oil (440 mg, 100%). R_f = 0.58 (hexane/EtOAc 6:1); $[\alpha]$ = +130.0 (c = 0.4 in Cl_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.002 (s, 3H), 0.02 (s, 3H), 0.73 (s, 3H), 0.88–1.04 (m, 11H), 1.42–1.67 (m, 12H), 1.73–1.85 (m, 3H), 2.03 (dt, J = 3.3, 13.6 Hz, 1H), 2.29 (ddd, J = 2.6, 4.8, 12.2 Hz, 1H), 3.95 (brs, 1H), 4.49 (dd, J = 9.6 Hz, 2H), 5.2 (brs, 1H), 5.62 (dd, J = 4.9, 12 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.5, 12.3, 15.7, 17.8, 21.0, 21.3, 22.4, 25.5, 26.7, 28.0, 34.8, 36.2, 45.3, 49.8, 54.6, 64.9, 69.7, 78.7, 79.4, 121.1, 132.9, 169.4, 199.9; IR (film): $\tilde{\nu}$ = 2955, 2856, 1769, 1742, 1375, 1237, 1092 cm^{-1}; MS (EI): m/z: 462 $[M]^+$; HRMS calcd for $C_{26}H_{42}O_5Si$: 462.2801; found: 462.2801 $[M]^+$.

Acetate 50: DMAP (5 mg) and Ac_2O (0.2 mL, 2 mmol) were added under stirring at room temperature under N_2 to a solution of **45** (114 mg, 0.27 mmol) in Cl_2Cl_2 (4 mL) and Et_3N (0.5 mL, 3.6 mmol). Stirring was continued overnight. Direct flash chromatography (hexane/EtOAc 19:1) afforded **50** as a colourless oil (120 mg, 96%). R_f = 0.55 (hexane/EtOAc 5:1); $[\alpha]$ = +56.0 (c = 3.2 in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.2 (s, 3H), 1.53 (ddd, J = 1.5, 4.3, 14.4 Hz, 1H), 1.74 (s, 3H), 1.83 (s, 3H), 1.93 (s, 3H), 2.39–2.42 (m, 2H), 2.92 (dd, J = 4.2, 13.1 Hz, 1H), 3.10 (dt, J = 9.6, 14.8 Hz, 1H), 3.93 (brs, 1H), 3.95 (d, J = 9.1Hz, 1H), 4.44 (d, J = 9.2 Hz, 1H), 4.83 (s, 1H), 4.85 (s, 1H), 4.93 (d, J = 10.7 Hz, 1H), 5.08 (d, J = 17.3 Hz, 1H), 5.15 (dd, J = 2.7, 10.1 Hz, 1H), 5.32 (t, J = 7.7 Hz, 1H), 6.30 (dd, J = 10.7, 17.3 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.6, 11.8, 15.9, 17.8, 20.6, 21.1, 25.5, 28.5, 34.5, 49.4, 55.9, 65.8, 71.3, 78.7, 80.9, 111.1, 115.3, 127.9, 136.5, 141.2, 143.6, 170.2, 199.8; IR (film): $\tilde{\nu}$ = 2954, 2858, 1767, 1743, 1443, 1372, 1233 cm^{-1}; MS (EI): m/z: 462 $[M]^+$; HRMS calcd for $C_{26}H_{43}O_5Si$: 463.2874; found: 463.2862 $[M+H]^+$.

Tetracycle 51 (from Diels–Alder reaction): A solution of **50** (120 mg, 0.26 mmol) and methylene blue (10 mg) in toluene (5 mL) was refluxed under stirring sealed in a tube for 110 h at 170 °C. Direct flash chromatography (hexane/EtOAc 19:1) gave **51** as a white solid (68 mg, 85%) and recoveed **50** (40 mg). R_f = 0.55 (hexane/EtOAc 6:1); m.p. 145–147 °C; $[\alpha]$ = +14.2 (c = 1.4 in Cl_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ = −0.07 (s, 3H), −0.04 (s, 3H), 0.71 (s, 3H), 0.84–0.93 (m, 1H), 0.95 (s, 9H), 1.16–1.22 (m, 1H), 1.29 (s, 3H), 1.50–1.58 (m, 5H), 1.75 (brd, J = 14.4 Hz, 1H), 1.83–1.92 (m, 2H), 1.97–2.06 (m, 4H), 2.25 (dd, J = 4.2, 13.4 Hz, 1H), 2.62 (brd, J = 13.4 Hz, 1H), 3.46 (d, J = 8.8 Hz, 1H), 3.86 (brs, 1H), 4.29 (d, J = 8.8 Hz, 1H), 5.27 (brs, 1H), 5.58 (brs, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.4, 12.7, 15.9, 17.8, 21.2, 21.3, 22.5, 25.5, 27.7, 35.3, 36.4, 40.2, 44.8, 51.5, 68.3, 69.2, 78.3, 79.8, 121.0, 133.7, 170.4, 201.3; IR (film): $\tilde{\nu}$ = 2954, 2857, 1767, 1745, 1248, 1107 cm^{-1}; MS (EI): m/z: 462 $[M]^+$; HRMS calcd for $C_{26}H_{42}O_5SiNa$: 485.2699; found: 485.2718 $[M+Na]^+$.

Tetracycle 51 (from tetracycle 54): DMAP (100 mg) and Ac_2O (0.1 mL, 1 mmol) was added to a stirred solution of **54** (40 mg, 0.097 mmol) in Cl_2Cl_2 (4 mL). The mixture was stirred overnight under N_2 and direct flash chromatography (hexane/EtOAc 19:1) afforded **51** as a white solid (44 mg, 100%). R_f = 0.60 (hexane/EtOAc 6:1); m.p. 145–147 °C; $[\alpha]$ = +14.2 (c = 1.4 in Cl_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ = −0.07 (s, 3H), −0.04 (s, 3H), 0.71 (s, 3H), 0.84–0.93 (m, 1H), 0.95 (s, 9H), 1.16–1.22 (m, 1H), 1.29 (s, 3H), 1.50–1.58 (m, 5H), 1.76 (d, J = 14.4 Hz, 1H), 1.88–1.97 (m, 2H), 1.97–2.06 (m, 4H), 2.26 (dd, J = 4.2, 13.4 Hz, 1H), 2.62 (d, J = 13.4 Hz, 1H), 3.46 (d, J = 8.8 Hz, 1H), 3.86 (brs, 1H), 4.29 (d, J = 8.8 Hz, 1H), 5.27 (brs, 1H), 5.58 (brs, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.4, 12.7, 15.9, 17.8, 21.2, 21.3, 22.5, 25.5, 27.7, 35.3, 36.4, 40.2, 44.8, 51.5, 68.3, 69.2, 78.3, 79.8, 121.0, 133.7, 170.4, 201.3; IR (film): $\tilde{\nu}$ = 2954, 2857, 1767, 1745, 1248, 1107 cm^{-1}; MS (EI): m/z: 462 $[M]^+$; HRMS calcd for $C_{26}H_{42}O_5SiNa$: 485.2699; found: 485.2718 $[M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{42}O_5Si$: C 67.49, H 9.15; found: C 67.86, H 8.94.

Tetracycle 52: Solid NaOH (20 mg, 0.5 mmol) was added under stirring at room temperature to a solution of **49** (120 mg, 0.26 mmol) in MeOH (5 mL). The mixture was further stirred at 12 h. Concentration of the reaction mixture in vacuo followed by flash chromatography (hexane/EtOAc 19:1) gave **52** as a colourless oil (115 mg, 96%). R_f = 0.35 (hexane/EtOAc 6:1); $[\alpha]$ = +78.0 (c = 2.6 in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 0.88 (s, 3H), 1.07–1.10 (m, 1H), 1.14–1.28 (m, 5H), 1.62–1.68 (m, 5H), 2.0–2.27 (m, 6H), 3.97 (brs, 1H), 4.19–4.23 (m, 1H), 4.34 (d, J = 8.6 Hz, 1H), 4.44 (d, J = 8.6 Hz, 1H), 5.32 (brs, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.5, 12.2, 15.6, 17.7, 21.3, 22.4, 25.5, 28.0, 29.6, 34.9, 36.3, 45.8, 49.5, 56.7, 64.1, 67.8, 78.9, 79.2, 120.8, 133.3, 196.9; IR (film): $\tilde{\nu}$ = 3458, 2953, 1766, 1255, 1114 cm^{-1}; MS (EI): m/z: 420 $[M]^+$; HRMS calcd for $C_{24}H_{40}O_4Si$: 420.2696; found: 420.2712 $[M]^+$.

Tetracycle 53: Dess–Martin periodiane[41] (120 mg, 0.28 mmol) was added under stirring at room temperature under N_2 to a solution of **52** (100 mg, 0.24 mmol) in Cl_2Cl_2 (10 mL). After stirring for 6 h, the reaction mixture was filtered through a short silica gel column. Concentrated of the eluant in vacuo followed by flash chromatography (hexane/EtOAc 97:3) gave **53** as a white solid (96 mg, 96%). R_f = 0.55 (hexane/EtOAc 6:1); m.p. 133–135 °C; $[\alpha]$ = +94.0 (c = 2.1 in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 0.91 (s, 3H), 1.10–1.23 (m, 4H), 1.55 (s, 3H), 1.74–1.76 (m, 2H), 2.00–2.12 (m, 4H), 2.31 (dd, J = 9.8, 13.3 Hz, 1H), 2.42 (d, J = 14.7 Hz, 1H), 2.78 (dd, J = 4.6, 18.1 Hz, 1H), 3.97 (brs, 1H), 4.04 (d, J = 8.2 Hz, 1H), 4.49 (d, J = 8.2 Hz, 1H), 5.39 (brs, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.5, 12.0, 15.7, 17.7, 20.6, 22.1, 25.5, 27.6, 33.6, 35.1, 40.1, 44.8, 50.4, 64.0, 70.9, 78.4, 81.9, 122.0, 131.9, 201.0, 203.5; IR (film): $\tilde{\nu}$ = 2959, 2931, 1781, 1728, 1272, 1121 cm^{-1}; MS (EI): m/z: 418 $[M]^+$; HRMS calcd for $C_{24}H_{38}O_4Si$: 418.2539; found: 418.2528 $[M]^+$.

Tetracycle 54: K-selectride (0.1 mL, 1M in THF) was added under stirring by syringe under N_2 at room temperature to a solution of **53** (33 mg, 0.078 mmol) in THF (4 mL). After stirring for 20 min, wet Et_2O (10 mL) was added to quench the reaction which was filtered through a short silica gel. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 19:1) afforded **54** as a white solid (32 mg, 97%). R_f = 0.65 (hexane/EtOAc 6:1); m.p. 105–107 °C; $[\alpha]$ = +7.5 (c = 2.7 in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.01 (s, 6H), 0.83 (s, 9H), 0.89 (s, 3H), 1.18 (s, 3H), 1.16–1.23 (m, 3H), 1.60–1.72 (m, 4H), 2.69–2.74 (d, J = 13.3 Hz, 1H), 3.67–3.71 (d, J = 8.8 Hz, 1H), 3.96–3.98 (t, J = 2.1 Hz, 1H), 4.24 (brs, 1H), 4.50 (d, J = 8.8 Hz, 1H), 5.29 (brs, 1H), 5.32 (d, J = 2.4 Hz, 1H); ^{1}H NMR (500 MHz, $CDCl_3$+D_2O): δ0.01(s, 3H), 0.04 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 1.09–1.36 (m, 8H), 1.60–1.72 (m, 4H), 1.92–2.04 (m, 3H), 2.08–2.26 (m, 2H), 2.71 (d, J = 14.2 Hz, 1H), 3.68 (d, J = 8.8 Hz, 1H), 3.97 (brs, 1H), 4.24 (brs, 1H), 4.54 (brs, 1H); ^{13}C NMR (62.89 MHz): δ = −5.1, −4.4, 12.5, 15.6, 17.8, 21.4, 22.5, 25.6, 27.6, 28.5, 35.3, 36.4, 38.8, 45.1, 52.8, 69.1, 79.0, 80.3, 120.5, 134.4, 192.0; IR (film): $\tilde{\nu}$ = 3496, 2954, 2858,

1747, 1253, 1108 cm^{-1}; MS (EI): *m/z*: 420 $[M]^+$; HRMS calcd for $C_{24}H_{40}O_4Si$: 420.2696; found: 420.2675 $[M]^+$.

Pentacycle 55: LDA (0.5 mL, 0.32 M, 0.16 mmol) dropwise at −30 °C was added to a stirred solution of **51** (60 mg, 0.13 mmol) in toluene/THF (4 mL, 2:1). The mixture was stirred at −30 °C for 0.5 h, quenched by 1% aq. HCl, extracted with Cl_2Cl_2 (3×). The combined extracts were washed with brine (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 3:1) gave **55** as a colourless oil (52 mg, 87%). R_f = 0.30 (hexane/EtOAc 3:1); $[\alpha]$ = +45.0 (c = 1.4 in Cl_2Cl_2); ^{1}H NMR (500 MHz): δ = 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 3H), 0.89 (s, 9H), 1.17–1.25 (m, 1H), 1.28 (s, 3H), 1.58–2.04 (m, 11H), 2.21–2.25 (m, 3H), 2.46–2.52 (m, 2H), 2.76 (d, J = 14 Hz, 1H), 3.03 (t, J = 7.5 Hz, 1H), 3.67 (d, J = 9.3 Hz, 1H), 3.82 (s, 1H), 4.36 (d, J = 9.3 Hz, 1H), 4.43 (d, J = 5.3 Hz, 1H), 5.39 (br s, 1H), 5.92–5.93 (d, J = 2.7 Hz, 1H); ^{13}C NMR (62.89 MHz): δ = −5.0, −4.7, 12.1, 17.3, 17.7, 21.1, 22.1, 25.6, 27.7, 28.7, 33.6, 33.7, 37.8, 38.8, 41.4, 46.3, 75.2, 78.1, 78.4, 82.7, 121.6, 133.1, 172.8; IR (film): $\tilde{\nu}$ = 3389, 2952, 1753, 1260, 1196 cm^{-1}; MS (CI): *m/z*: 463 $[M+H]^+$; HRMS calcd for $C_{26}H_{43}O_5Si$: 463.2874; found: 463.2867 $[M+H]^+$.

Pentacycle 56: A solution of **55** (20 mg, 0.043 mmol) in Cl_2Cl_2 (5 mL) at 0 °C was added dropwise by syringe under stirring to a solution of pyridine (0.2 mL) and $SOCl_2$ (0.1 mL) in Cl_2Cl_2 (10 mL). The mixture was stirred for 12 h at room temperature under N_2, quenched with saturated aq. $NaHCO_3$ and extracted with Cl_2Cl_2 (3×). The combined extracts was washed with brine (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo and followed by flash chromatography (Cl_2Cl_2) provided **56** as a white solid (14.4 mg, 90%). R_f = 0.48 (hexane/EtOAc 3:1); m.p. 186–188 °C; $[\alpha]$ = −38.0 (c = 0.5 in Cl_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.01 (s, 3H), 0.02 (s, 3H), 0.72 (s, 3H), 0.92–1.01 (m, 10H), 1.35 (s, 3H), 1.44–1.47 (m, 3H), 1.53 (dd, J = 3.0, 13.7 Hz, 1H), 1.61 (s, 3H), 1.78–2.00 (m, 4H), 2.45 (d, J = 13.2 Hz, 1H), 3.23 (d, J = 8.4 Hz, 1H), 3.80 (br s, 1H), 4.06 (br s, 1H), 4.22 (d, J = 8.37 Hz, 1H), 5.33 (s, 1H), 5.81 (s, 1H); ^{13}C NMR (62.89 MHz): δ = −5.0, −4.4, 11.8, 17.4, 17.8, 21.2, 22.3, 25.6, 27.4, 34.4, 34.7, 40.7, 46.9, 47.1, 72.1, 77.3, 79.0, 82.9, 107.4, 121.3, 133.1, 164.3, 167.1; IR (film): $\tilde{\nu}$ = 2953, 2856, 1723, 1102 cm^{-1}; MS (EI): *m/z*: 445 $[M+H]^+$; HRMS calcd for $C_{26}H_{40}O_4Si$: 444.2696; found: 444.2683 $[M]^+$; elemental analysis calcd (%) $C_{26}H_{40}O_4Si$: C 70.23, H 9.07; found: C 70.11, H 9.17.

Pentacycle 57: $NaBH_4$ (32 mg, 0.8 mmol) at 0 °C was added under stirring to a solution of **56** (80 mg, 0.18 mmol) and $NiCl_2 \cdot 6H_2O$ (10 mg, 0.045 mmol) in MeOH (20 mL). The mixture was stirred for 1 h at 0 °C and then room temperature for 2 h, quenched with saturated aq. NH_4Cl and extracted with EtOAc (3×). The combined extracts were washed with brine (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 17:3) afforded **57** as a white solid (55 mg, 70%) and **58** (25 mg, 30%, which was subsequently oxidized to **57** by Dess–Martin periodinane[41]). R_f = 0.46 (hexane/EtOAc 3:1); m.p. 156–158 °C; $[\alpha]$ = +28.5 (c = 0.8 in Cl_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.7 (s, 3H), 0.84–1.10 (m, 11H), 1.29 (s, 3H), 1.47–1.60 (m, 6H), 1.70 (dd, J = 4.0, 17.5 Hz, 1H), 1.81 (dt, J = 4.0, 9.5 Hz, 1H), 1.90 (br s, 1H), 2.00 (dt, J = 3.0, 14.5 Hz, 1H), 2.33 (d, J = 13.5 Hz, 1H), 2.56 (dd, J = 6.0, 18.5 Hz, 1H), 3.10 (d, J = 8.5 Hz, 1H), 3.57 (dd, J = 14.0, 18.5 Hz, 1H), 3.71 (d, J = 4.0 Hz, 1H), 4.00 (t, J = 3.0 Hz, 1H), 4.16 (d, J = 8.0 Hz, 1H), 5.33 (s, 1H); ^{13}C NMR (300 MHz): δ = −4.6, −4.0, 12.4, 18.3, 21.7, 22.3, 22.8, 26.3, 28.4, 28.7, 29.0, 33.1, 34.6, 35.1, 36.4, 40.8, 43.2, 50.2, 50.3, 73.0, 75.6, 75.7, 81.3, 84.6, 121.7, 133.6, 171.2; IR (film): $\tilde{\nu}$ = 2980, 1730, 1200, 1085 cm^{-1}; MS (EI): *m/z*: 446 $[M]^+$; HRMS calcd for $C_{26}H_{42}O_4Si$: 446.2852; found: 446.2844 $[M]^+$.

Pentacycle 59: $NaBH_4$ (20 mg, 0.5 mmol) was added under stirring at room temperature to a solution of **56** (50 mg, 0.113 mmol) and $NiCl_2 \cdot 6H_2O$ (14 mg, 0.06 mmol) in MeOH (10 mL). After stirring for 3 h, concentrated HCl (36%) was added. The reaction was quenched by saturated aq. $NaHCO_3$, extracted with EtOAc (3×). The combined extracts were washed with brine (2×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (hexane/EtOAc 19:1) gave **59** a colourless oil (49.5 mg, 95%). R_f = 0.73 (hexane/EtOAc 3:1); $[\alpha]$ = +76.7 (c = 1.2 in Cl_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.06 (s, 3H), 0.10 (s, 3H), 0.89 (s, 3H), 1.00–1.04 (m, 11H), 1.24–1.29 (m, 2H), 1.47–1.48 (m, 4H), 1.62–1.66 (m, 5H), 1.90–2.21 (m, 6H), 2.62 (dt, J = 4.0, 13.6 Hz, 1H), 2.92 (d, J = 13.5 Hz, 1H), 3.28–3.31 (m, 3H), 3.40 (d, J = 8.0 Hz, 1H), 3.80 (br s, 1H), 3.85 (br s, 1H), 4.36 (d, J = 8.0 Hz, 1H), 4.84 (br s, 1H), 5.40 (br s, 1H); ^{13}C NMR (62.89 MHz): δ = −5.0, −4.3, 12.1, 18.1, 21.6, 22.5, 23.0, 26.0, 28.0, 28.8, 34.8, 35.5, 35.6, 40.9, 44.1, 46.2, 54.3, 71.8, 72.9, 76.0, 81.4, 98.2, 120.7, 134.9; IR (film): $\tilde{\nu}$ = 2880, 1125, 1080 cm^{-1}; MS (EI): *m/z*: 462 $[M]^+$; HRMS calcd for $C_{27}H_{46}O_4Si$: 462.3165; found: 462.3119 $[M]^+$.

Pentacycle 60: A solution of **59** (18 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0 °C to a solution of CrO_3 (60 mg, 0.6 mmol) and 3,5-dimethylpyrazole (60 mg, 0.6 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 24 h and filtered through a pad of Celite. Concentration of the filtrate in vacuo followed by flash column chromatography (hexane/Et_2O 4:1) afforded **60** (10 mg, 81%) as a colorless oil and recovered the starting material **59** (6 mg). R_f = 0.31 (hexane/EtOAc 2:1); $[\alpha]$ = +81.5 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz): δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 0.93 (s, 3H), 1.24 (s, 3H), 1.92 (s, 3H), 1.47–2.56 (m, 9H), 3.09 (d, J = 13.2 Hz, 1H), 3.35 (d, J = 10.2 Hz, 1H), 3.36 (s, 3H), 3.63 (s, 1H), 3.84 (s, 1H), 4.14 (d, J = 8.1 Hz, 1H), 4.83 (d, J = 3 Hz, 1H), 5.89 (s, 1H); ^{13}C NMR (75.47 MHz): δ = −4.6, −4.0, 13.9, 18.3, 22.4, 22.8, 26.2, 27.6, 28.4, 28.8, 30.2, 35.7, 40.8, 42.8, 43.8, 45.8, 52.5, 55.2, 71.0, 72.4, 75.2, 82.0, 98.4, 127.0, 164.1, 199.3; IR (film): $\tilde{\nu}$ = 1697, 1650, 1517, 1459 cm^{-1}; MS (CI): *m/z* (%): 477 $[M+H]^+$; HRMS calcd for $C_{27}H_{44}O_5Si$: 477.3020; found: 477.3031 $[M+H]^+$.

Pentacycle 5: $Mn(OAc)_3 \cdot 2H_2O$ (50 mg, 0.2 mmol) was added to a solution of **60** (20 mg, 0.04 mmol) in dry benzene (10 mL). The reaction mixture was heated under refluxed with a Dean and Stark trap for 48 h under N_2. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue purified by flash column chromatography (hexane/Et_2O 4:1) to give **5** (18 mg, 80%) as a white solid. R_f = 0.24 (hexane/EtOAc 9:1); m.p. 163–164 °C; $[\alpha]$ = +125.2 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 0.96 (s, 3H), 1.23 (s, 3H), 1.94 (s, 3H), 2.03 (s, 3H), 1.48–2.45 (m, 8H), 3.36 (d, J = 9.9 Hz, 1H), 3.38 (s, 3H), 3.44 (d, J = 12.3 Hz, 1H), 3.60 (d, J = 4.2 Hz, 1H), 3.82 (s, 1H), 4.18 (d, J = 8.1 Hz, 1H), 4.88 (d, J = 3.3 Hz, 1H), 5.07 (s, 1H), 5.86 (t, J = 1.2 Hz, 1H); ^{13}C NMR (75.47 MHz): δ = −4.9, −4.1, 12.5, 18.1, 21.5, 22.6, 23.1, 26.3, 27.7, 27.9, 28.0, 28.3, 30.2, 37.6, 43.0, 46.0, 55.2, 70.8, 72.6, 74.4, 75.2, 82.1, 98.4, 124.8, 164.6, 169.3, 193.5; IR (film): $\tilde{\nu}$ = 1740, 1682, 1540, 1516 cm^{-1}; MS (CI): *m/z*: 535 $[M+H]^+$; HRMS calcd for $C_{29}H_{46}O_7Si$: 535.3093; found: 535.3086 $[M+H]^+$.

X-ray analysis: CCDC-194634 (**57**) and -201545 (**5**) contain the supplementary crystallographic 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 CB2 1EZ, UK; fax: (+44) 1223–336–033; or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgement

This work was supported by the RGC earmarked grant (ref. no.: CUHK 4185/97P).

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Received: May 19, 2003 [F5158]