HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 894-919. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 30th August, 2016, Accepted, 17th October, 2016, Published online, 13th December, 2016
DOI: 10.3987/COM-16-S(S)58

A REMARKABLY USEFUL SULFUR BRIDGE AS SYNTHETIC LEVER IN AN APPROACH TO JAVANICIN B

Amélie Dion and Claude Spino*

Département de chimie, Université de Sherbrooke, 2500 Boul. Université, Sherbrooke, QC, J1K 2R1

Abstract – A concise and efficient synthesis of a non-racemic advanced intermediate to the quassinoid javanicin B is disclosed. The strategy is centred on a triple diene-transmissive Diels-Alder cycloaddition to form the four rings of javanicin B. A sulfur bridge plays several crucial roles allowing an intramolecular cycloaddition to occur with complete stereoselectivity, controlling the stereochemical outcome of another cycloaddition, and transforming into a pivotal electrophile for the introduction of a particularly hindered methyl group.

INTRODUCTION

Javanicins are quassinoids isolated from the tree *Picrasma javanica* that grows in Indonesia and South-East Asia.[1] They possess the picrasane or the less frequently encountered 4-norpicrasane skeletons.[2,3] The structures of three members of this family of highly degraded triterpenes are displayed in Figure 1. Many quassinoids possess strong nematicidal[4] activities and anticancer properties,[5] which taken together with the recognized synthetic challenge their highly oxygenated carbon framework represents, makes them worthwhile synthetic targets.

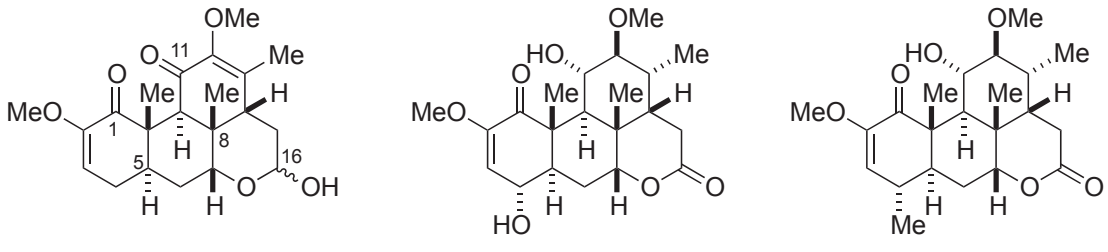
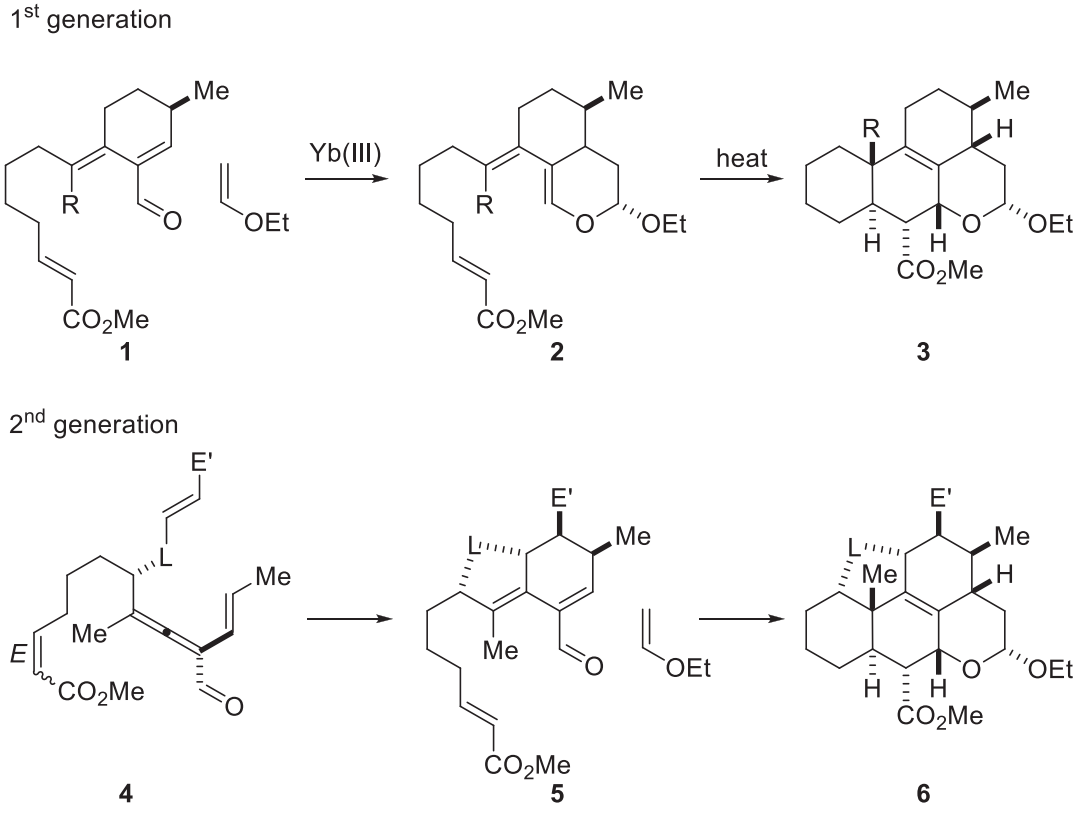


Figure 1. Three javanicins of the quassinoid family of triterpenes

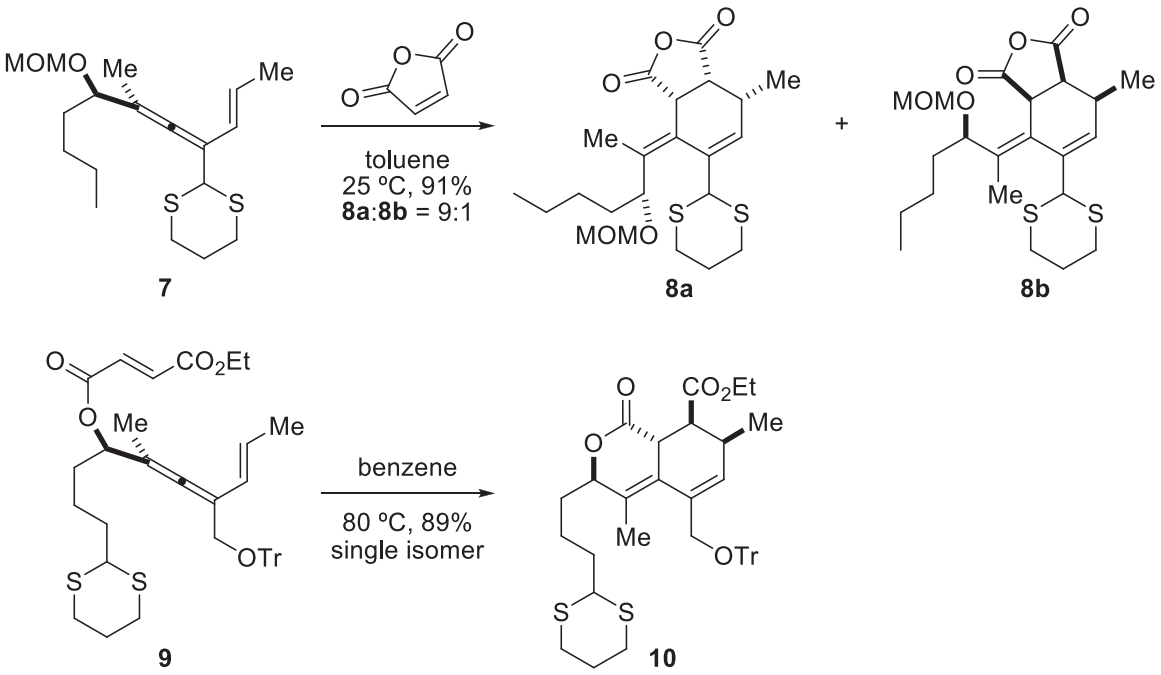
We have established a Diene-Transmissive Diels-Alder Cycloadditions (DTDAC) strategy to the picrasane framework, as summarized in Scheme 1.[6] However, our first-generation approach had a fatal flaw in that the tetrasubstituted exocyclic double bond in compound **1** (R = Me) could not be prepared from a cyclohexane-derived starting material. Only the trisubstituted exocyclic double bond (**1**, R = H) could be prepared and was shown to undergo a double DTDAC sequence to compound **3** (R = H).[7] Later, we developed a second approach involving a vinylallene **4** that not only solved the problem of the synthesis of the tetrasubstituted exocyclic double bond (as in **5**), but extended the DTDAC sequence to three Diels-Alder reactions, thus increasing its synthetic efficiency.[8] Finding a suitable linker (L) turned out to be a difficult task as was using the tetrasubstituted endocyclic double bond contained in the product **6** to further the synthesis. We herein describe the solution to these problems and the full account of the synthetic approach to the complete javanicin skeleton.



Scheme 1. The Diene-Transmissive Diels-Alder strategy to quassinoids

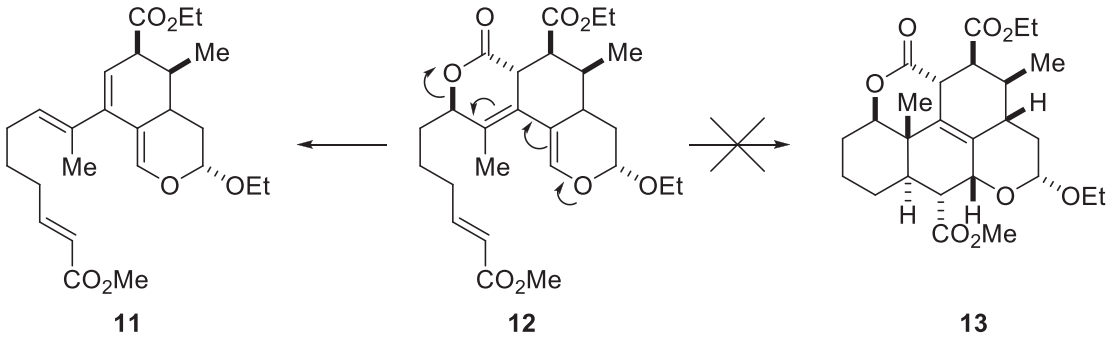
The intermolecular Diels-Alder cycloaddition on a vinylallene such as **7** proceeds to give the wrong geometry of the exocyclic double bond (**8a**) because of the preferential attack on the least-hindered face of **7** by the dienophile (Scheme 2).[9] Therefore, linking the dienophile for internal delivery to the correct face of the diene is not optional. Linking the dienophile per se was not difficult and vinylallene **9** was

easily prepared, its intramolecular Diels-Alder cycloaddition proceeding in 89% to give a single diastereomer of cycloadduct **10** (Scheme 2).[10] At this stage, we believed that the entire strategy was going to work as planned. Little did we know that a major hurdle would take years to overcome.



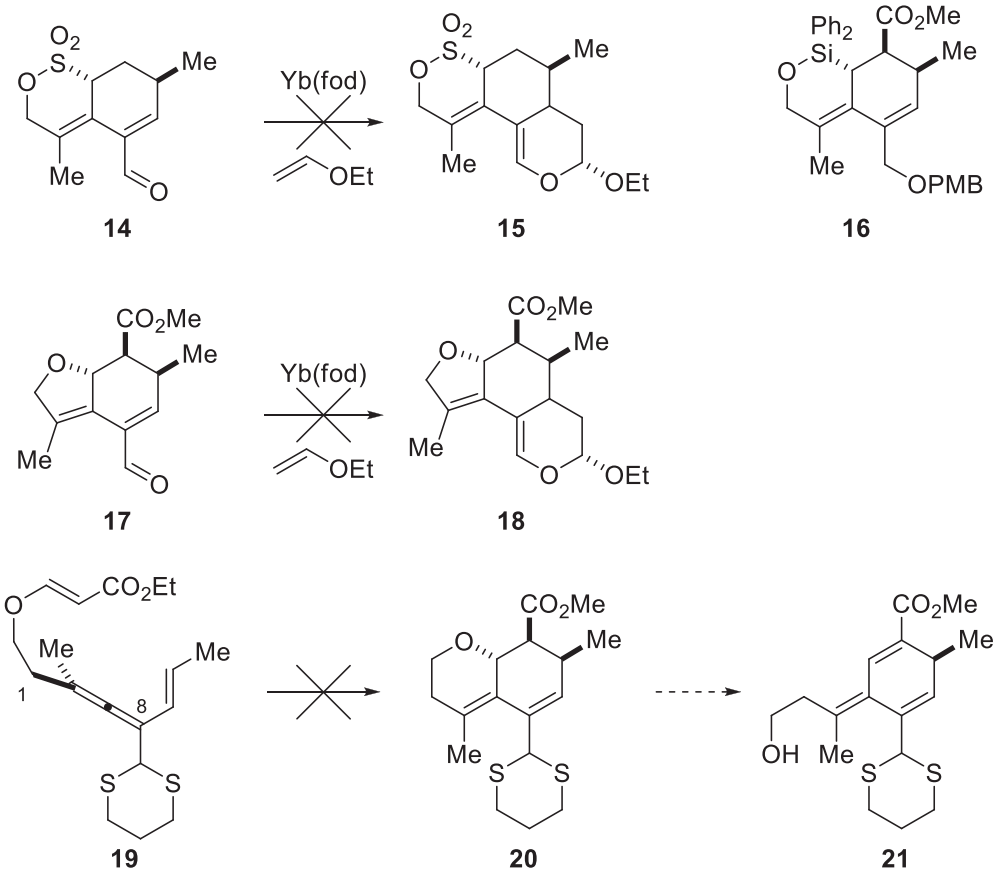
Scheme 2. Inter and intramolecular Diels-Alder cycloadditions of vinylallenes **7** and **9**

A major obstacle was awaiting us in the form of a secondary reaction pathway competing with the third Diels-Alder cycloaddition of compound **12** (Scheme 3).[7] No matter the reaction conditions and/or what Lewis acid was added, the unwanted reaction to give product **11** always prevailed. Much decomposition often accompanied the unwanted reaction. On other dienes similar to **12**, with some optimization, we were in fact able to get a good yield of the unwanted adduct corresponding to **11**.[8]



Scheme 3. Attempted intramolecular Diels-Alder cycloaddition of **11**

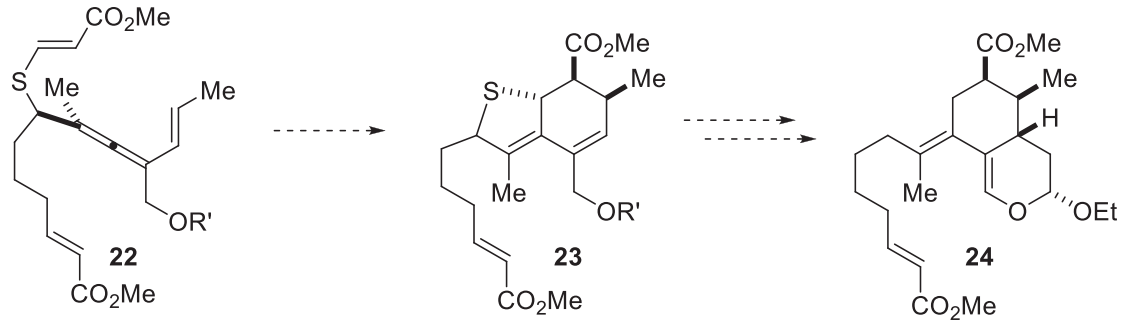
Scheme 4 shows examples of different linkers we have investigated to replace the faulty lactone in diene **12**, but none of them led to the desired cycloaddition. Cycloadducts **15** or **18** could not withstand the reaction conditions to make them from sulfonate **14** or ether **17**, respectively. They decomposed in the reaction conditions, presumably following the mechanistic pathway shown in Scheme 3. A silyloxy linker **16** also failed to resolve the issue. We even designed a linker lacking a heteroatom at C-1 (**19**) thereby blocking this decomposition pathway. The linker in the product **20** would then be released by an elimination reaction. Strangely, we were unable to find reaction conditions to allow the intramolecular Diels-Alder reaction of **19**, decomposition occurring under forcing conditions. Most of these dienes took months to prepare and we considered abandoning the strategy altogether.[10]



Scheme 4. Different linkers for the first intramolecular Diels-Alder reaction

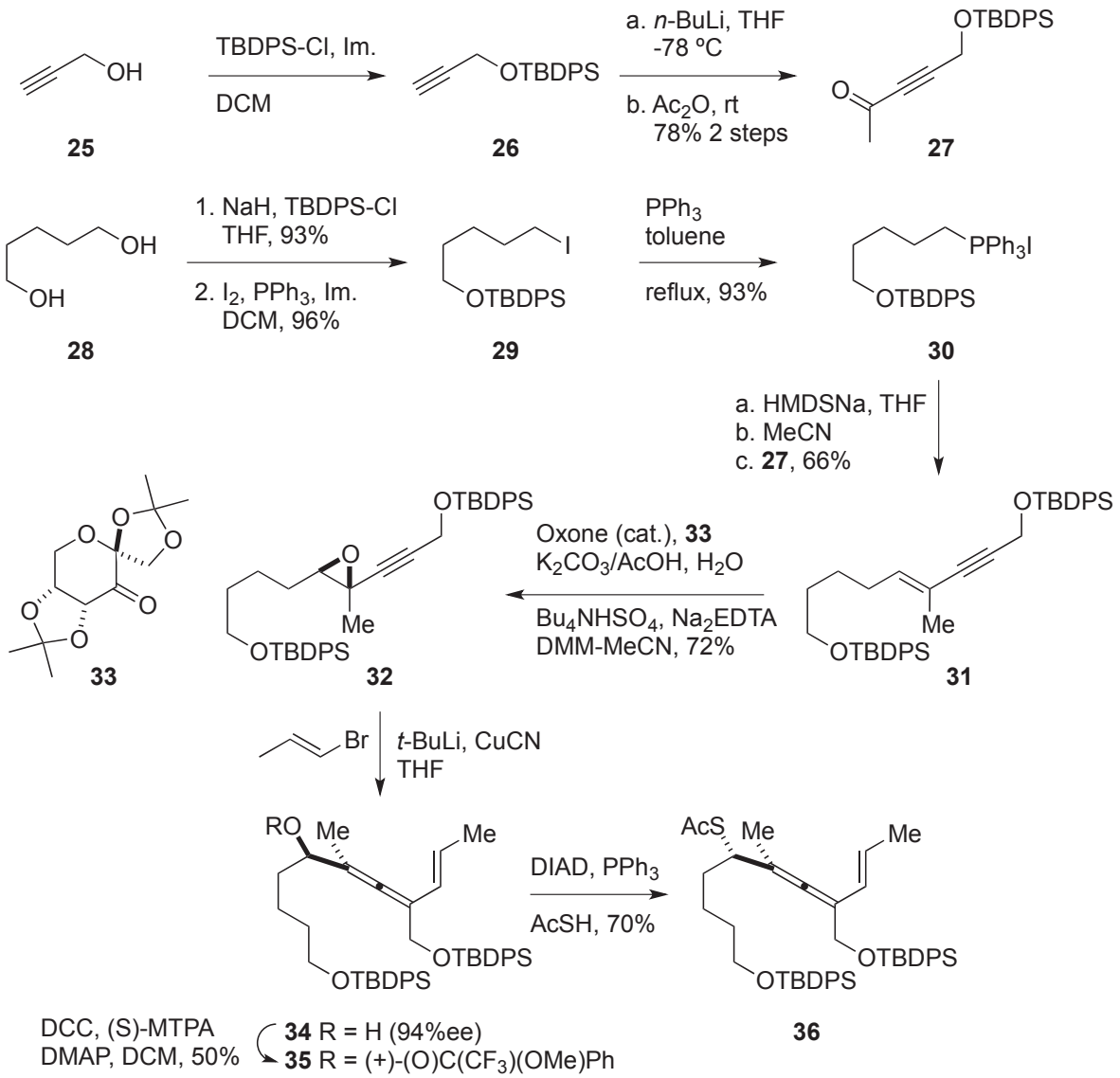
RESULTS AND DISCUSSION

An unexpected turn of events occurred when we planned to use a sulfur linker with the intention of removing the sulfur bridge before the problematic Diels-Alder reaction to prevent the unwanted pathway shown in Scheme 3 (Scheme 5). Indeed, Raney nickel should readily reduce the C-S bonds in **23** before continuing on with the DTDAC sequence.[11]



Scheme 5. Planned use of a removable sulfur bridge in the DTDAC sequence

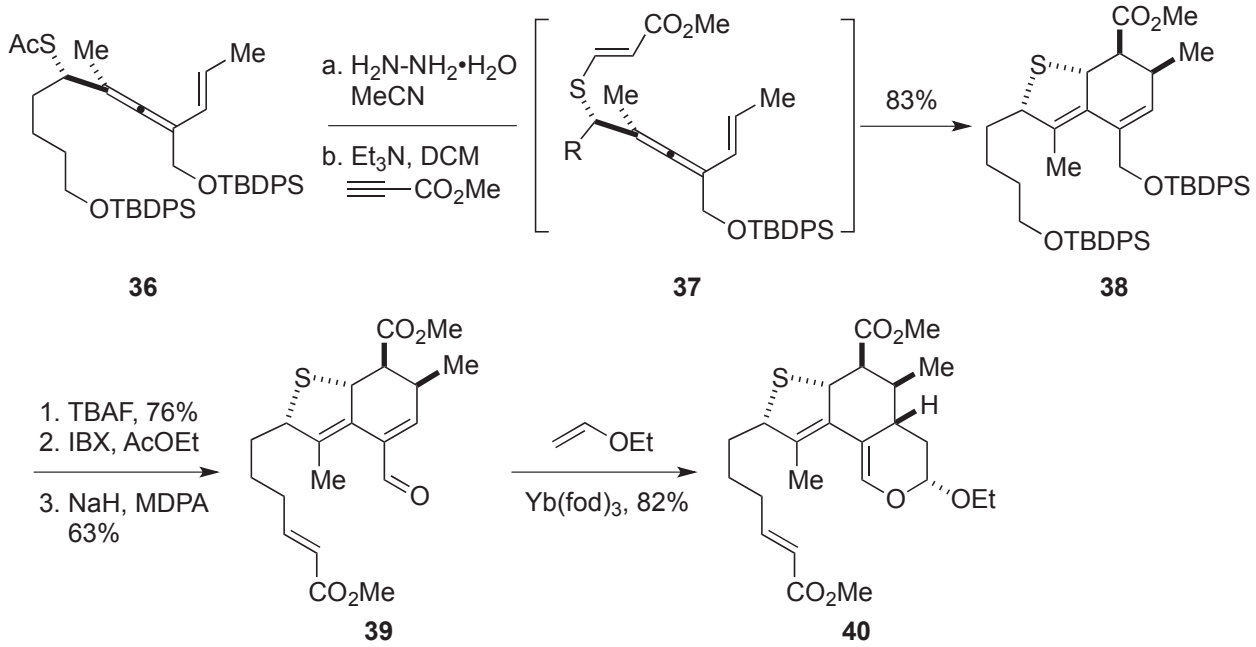
After exploring several different synthetic routes, a satisfactory synthesis of chiral non-racemic vinylallene **36** was found and is presented in Scheme 6. Propargyl alcohol **25** was transformed into ynone **27** and diol **28** was converted to the phosphonium iodide **30**, following standard chemistry. Their



Scheme 6. Synthesis of non-racemic vinylallene **36**

coupling under Wittig reaction conditions[12] gave enyne **31** as a 6:1 mixture of *E* and *Z* geometrical isomers. A carefully controlled Shi epoxidation[13] of this enyne gave chiral non-racemic epoxide **32**. Its enantiomeric purity was measured at >90% by first opening it with a vinylcuprate reagent and converting some of the resulting alcohol **34** to the corresponding Mosher ester **35**. Only very small amounts of diasteromers carried over from the *E*:*Z* mixture of enyne **31** were detected. The S_N2 reaction product **36** was the sole detectable product upon treatment of alcohol **34** with thioacetic acid under the Mitsunobu reaction conditions.

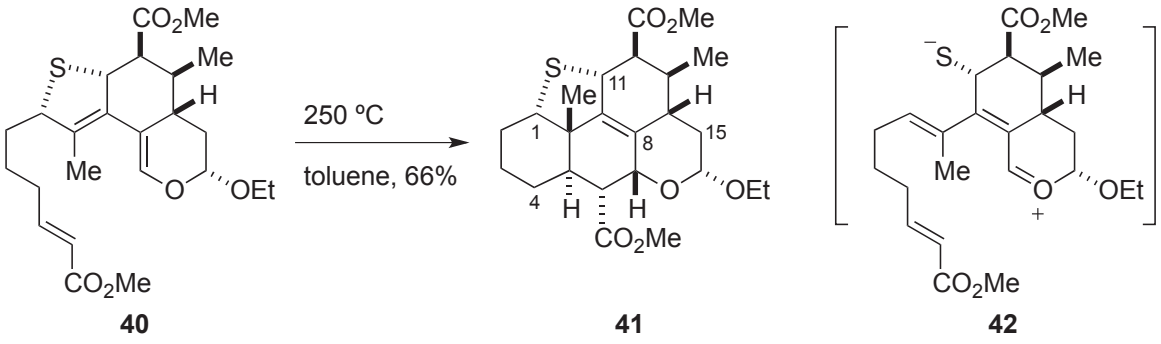
Liberation of the thiol group in **36** proved unexpectedly difficult because the free thiol is unstable. Eventually, we found that treatment of thioacetate **36** with hydrazine in acetonitrile to uncover the free thiol, a quick change of solvent to then react this free thiol directly with methyl propiolate, gave a purported intermediate **37** that could not be observed as it collapsed instantly to the desired cycloadduct **38**. The latter was isolated as a single diastereomer, in 83% yield for the three steps in one pot. Removal of the two silyl protecting groups and periodane oxidation gave a sensitive dialdehyde that reacted chemoselectively with the anion of methyl 2-(dimethoxyphosphono)acetate to give enoate **39**, isolated as a single geometrical isomer. The hetero-Diels-Alder reaction between diene **39** and ethyl vinyl ether proceeded uneventfully to give cycloadduct **40** in an endo approach of the dienophile on the least hindered side of the enal. No other stereoisomers could be detected.



Scheme 7. Synthesis of diene **40**

Although we fully expected diene **40** to decompose upon heating or upon treatment with Lewis acids, we nevertheless tried the intramolecular Diels-Alder reaction. To our astonishment, we obtained a 56% yield

(later optimized to 66%) of the long sought-after pentacyclic compound **41**. By comparison, derivatives of **18** (c.f. Scheme 4) decomposed above 50 ºC.[10] Actually, we believe that the cleavage of the dihydrothiophene moiety does occur to give intermediate **42**. However, instead of decomposing, intermediate **42** may revert back to diene **40** for lack of competing side reactions. In the case of other linkers, this intermediate could decarboxylate or loose SO_3 or abstract protons, for example. Sulfur is nucleophilic and may prefer to attack the oxonium system to give back diene **40**. Eventually, the intramolecular Diels-Alder cycloaddition occurs to give the stable pentacyclic compound **41**. Whatever the case may be, at last, the DTDAC strategy proved satisfactory for the synthesis of a quassinoid and moreover, the overall synthesis looked good, promising to be very efficient and allowing for an exquisite control of all stereocentres. The relative stereochemistry of all chiral centres in **41** was assigned beyond doubt from the single crystal X-ray analysis of its sulfone derivative (see **44** in Scheme 9).

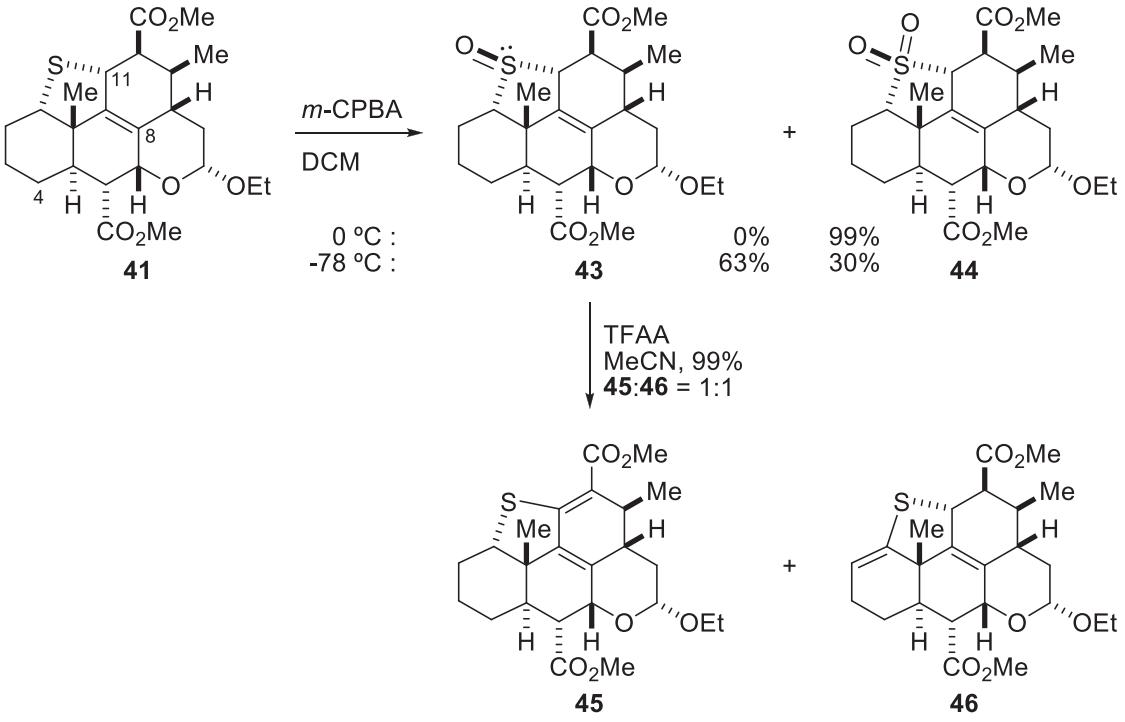


Scheme 8. Intramolecular Diels-Alder cycloaddtion of diene **40**

Now remained the last major challenge imposed by this strategy, i.e. the use of the endocyclic, tetrasubstituted, and rather severely hindered double bond in adduct **41** to introduce a methyl group at position 8 (cf numbering in Scheme 8). A model reveals the highly hindered nature of this double bond and we wondered if any carbon could actually be introduced at that position. Furthermore, we had not planned on the sulfur being there at this stage, but its presence opened new synthetic opportunities.

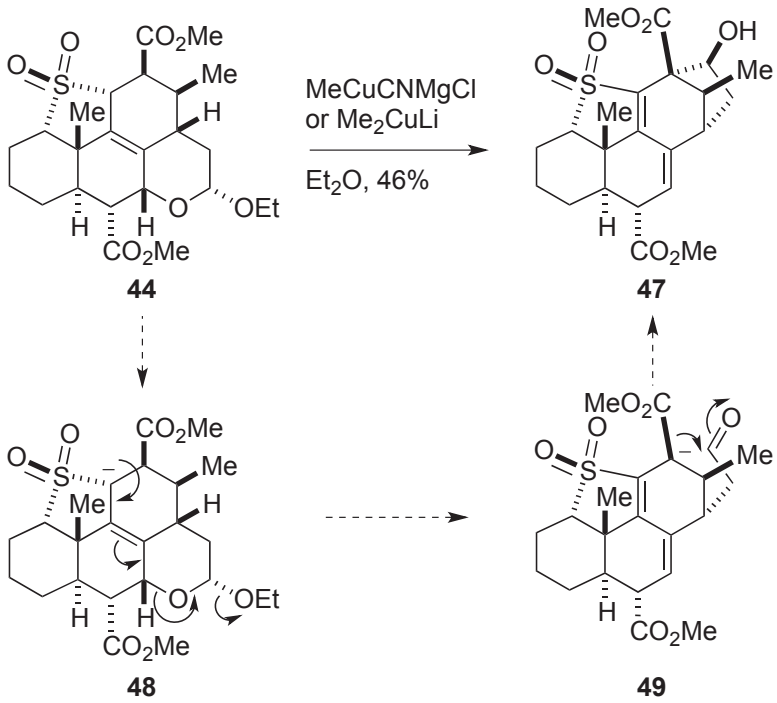
Three main strategies were considered: using the sulfur to introduce a carbonyl at position 11; converting the sulfur to a sulfone; converting the sulfur to a sulfonium salt. In all three cases, position 8 becomes electrophilic thus calling for a nucleophilic methyl to be used.

Oxidizing the sulfur to the sulfone **44** was easily achieved using *m*-CPBA (Scheme 9). It was more difficult, but possible, to stop the oxidation at the sulfoxide stage (**43**) by lowering the temperature. In any case, there was no need to optimize this oxidation as all our attempts to convert **43** to a C-11 ketone derivative failed, including the Pummerer reaction shown in Scheme 9. That reaction gave a 1:1 mixture of two unusable alkenes **45** and **46** instead of the expected thioacetal.



Scheme 9. Using the sulfur atom to convert **41** to an electrophilic species

All attempts to form a palladium π-complex from sulfone **44** and react it with a nucleophilic species failed. Cuprate reagents reacted with sulfone **44** to give a 46% yield of product **47**. Its structure was proven by an X-ray analysis and a probable mechanism is shown in Scheme 10. Deprotonation α to the

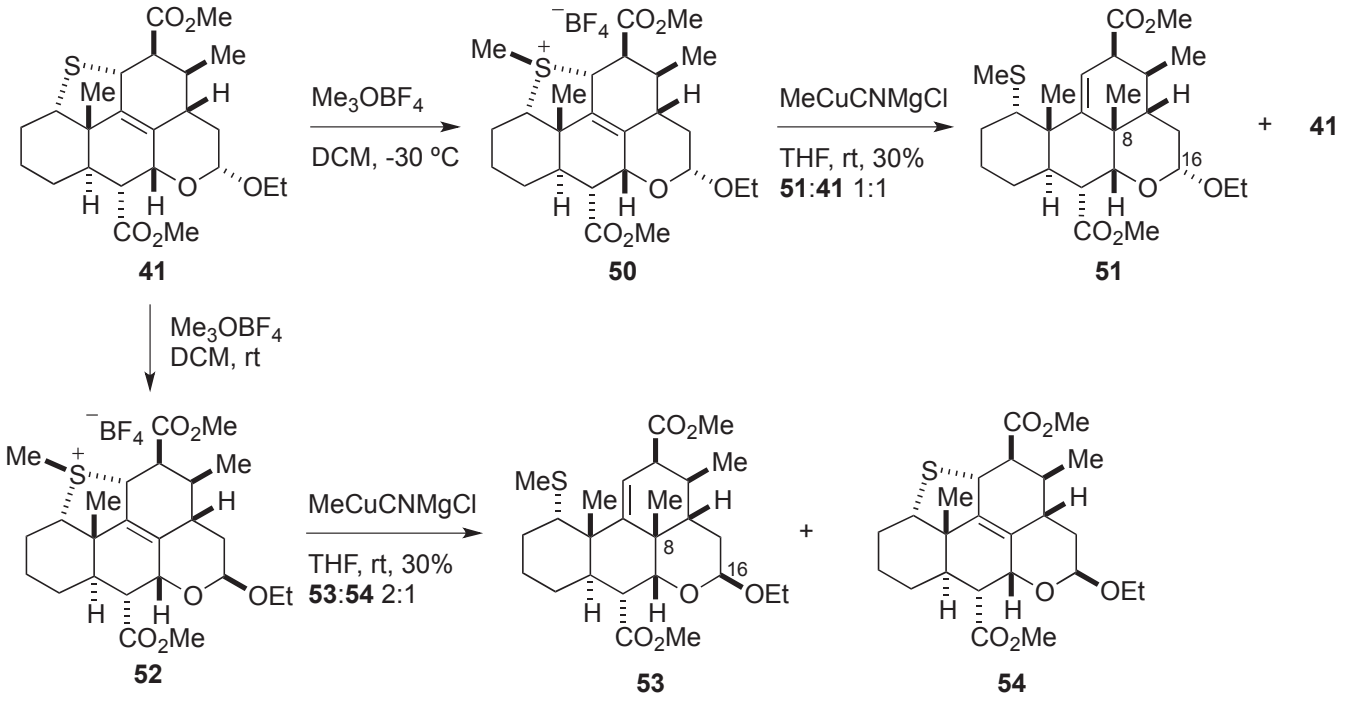


Scheme 10. Attempted cuprate reactions of sulfone **44**

sulfone group (**48**) results in the elimination of ethanol with concomitant opening of the tetrahydropyrane ring leading to the formation of aldehyde **49**. Then, a stereoselective aldol reaction takes place to give **47**. These experiments gave an early indication of the low accessibility of the internal alkene in such a sterically hindered and rigid pentacyclic structure.

Thinking that a sulfonium salt would be more electron-withdrawing than a sulfone for the S_N2' displacement reactions,[14] we tried to prepare compound **50** by reacting it with Meerwein's salt in DCM at room temperature (Scheme 11). At this stage, we had no reason to believe that the compound that we had isolated and characterized was in fact **52**, not **50**, possessing an epimerized β-OEt group at C-16. We submitted **52** to the action of methylcyanocuprate and to our delight, managed to get 30% yield of what we then thought was the desired addition product **51**, but was in fact adduct **53**, along with a demethylation product that, to our puzzlement, was not exactly the same as the expected starting compound **41**. Despite this problem, and an as of yet unusable yield of the cuprate adduct, we were encouraged because no other regioisomer or diastereomer was detected in this addition reaction.

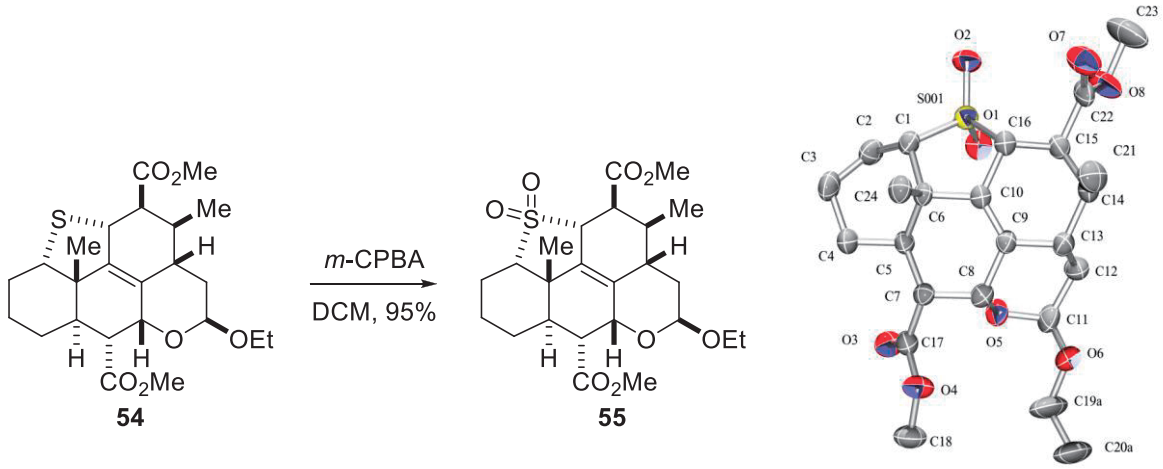
Wanting to improve on the preparation of the methylsulfonium salt, we carried out the reaction at -30 ºC and isolated a different isomeric salt **50**, which structure was secured from a single crystal X-ray diffraction analysis. The latter was the expected methylsulfonium salt, so obviously the previous one was not. We postulated that perhaps the two diastereomers differed by their stereochemistry at sulfur. How



Scheme 11. Cuprate reaction of sulfonium salts **50** and **52**

temperature could reverse this stereochemistry, we did not know and quite frankly, there was little room on the other face of the molecule to accommodate a methyl group.

Nonetheless, submitting the isomeric salts separately to the action of methylcyanocuprate, gave in each case two products (Scheme 11). Methylsulfonium salt **50**, obtained at -30 ºC, led to the formation of adduct **51** and the starting sulfur **41** in a 1:1 ratio. Methylsulfonium **52**, obtained at rt, led to the formation of **53** and **54** in a 2:1 ratio. The fact that the demethylation products **41** and **54** were different in structure invalidated the hypothesis that **50** and **52** were epimeric at sulfur. Were they epimeric at one of the carbons bearing an ester group? We oxidized the demethylation product **54** to the corresponding sulfone **55** and were able to obtain an X-ray structure of the latter compound (Scheme 12). To our surprise, the isomeric carbon was the acetal carbon, presumably caused by a ring-opening ring-closing event catalyzed by traces of acid present. We can obtain either of methylsulfonium salts **50** or **52** as the major product by carefully controlling the reaction time and temperature.

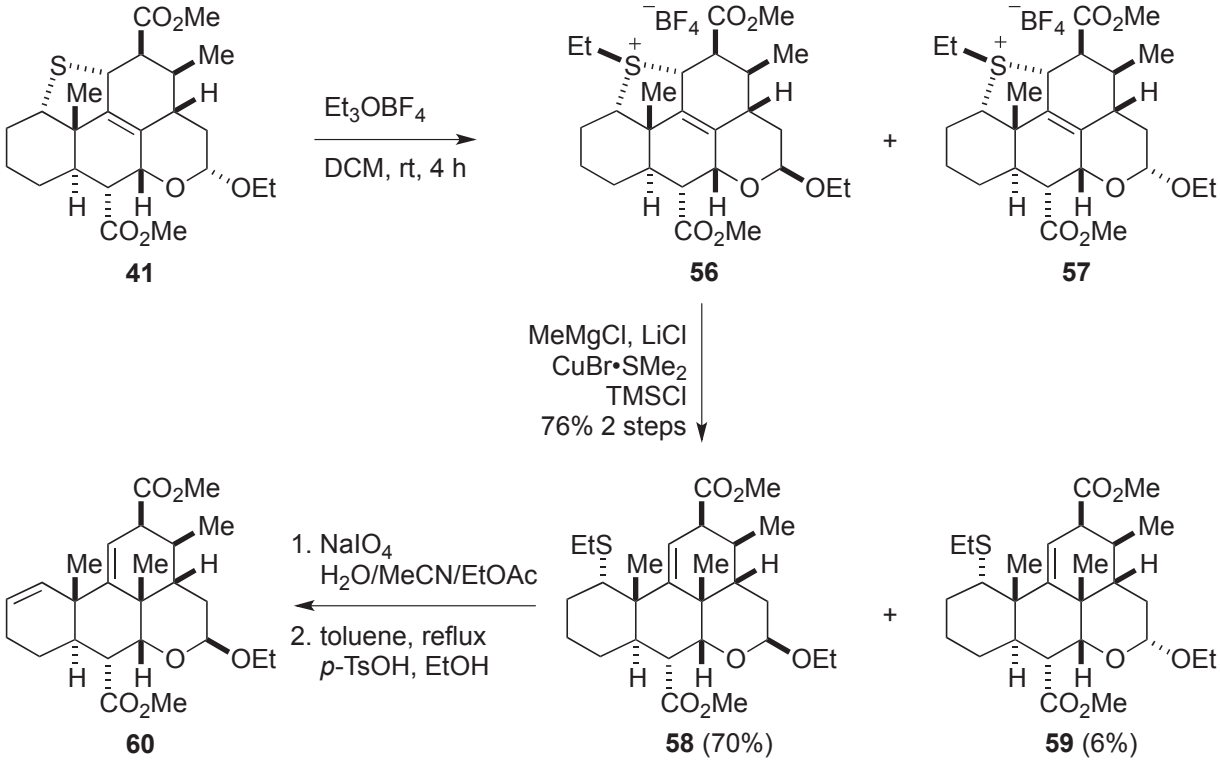


Scheme 12. Proof of the structure of the isomeric methylsulfonium **52**

This serendipitous event would have remained a simple curiosity, easily avoided by keeping the temperature low during the formation of sulfonium salt **50**, had it not turned out to be crucial in the overall scheme. We replaced the methyl group on sulfur by an ethyl group in order to reduce the S_N2 reaction of the cuprate reagent at the alkyl group on sulfur. It was also possible to control the formation of the corresponding epimeric ethylsulfonium salts **56** and **57** by regulating the temperature and reaction time, but it was easier and more efficient to let the reaction run at rt for long enough to form epimer **56**. Moreover, upon reaction with methylcyanocuprate, the non-epimerised ethylsulfonium salt **57** still suffered much de-ethylation to produce **41** along with the cuprate adduct **59**, all in low overall yield (30%). On the contrary, ethylsulfonium salt **56** gave a much cleaner product **58** and in higher yield. Ultimately, the crude mixture of ethylsulfonium salts **56** prepared at rt, containing traces of **57**, was made

to react with the cuprate reagent issued from a mixture of methylmagnesium chloride, lithium chloride, chlorotrimethylsilane, and copper bromide to give a 70% yield of the desired adduct **58** over two steps, along with traces of the epimer **59** (Scheme 13). The structure of adduct **58** was secured by a single crystal X-ray diffraction analysis.

Possibly, a subtle conformational effect may increase the desired reaction rate in the case of ethylsulfonium **56**. Alternatively, coordination of the cuprate reagent with the ethoxy oxygen could deliver it to the reactive site, an option not available in the case of ethylsulfonium **57**. It is important to note that the presence of TMSCl is necessary in the cuprate addition,[15] both to increase the yield of the desired reaction and to reduce attack of the cuprate reagent at the *S*-ethyl group. Other Lewis acids (BF_3•Et_2O, TMSBr) and other copper(I) sources (CuI, CuCN) were less effective.



Scheme 13. Optimized reaction conditions for the S_N2' addition of methylcuprate to **55**

The sulfur bridge had played its roles exceedingly well, providing stereoselectivity in the first intramolecular Diels-Alder reaction, allowing the third Diels-Alder reaction to proceed with complete stereoselectivity, being amenable to transformation into a leaving group (sulfonium salt) thus permitting a highly diastereo- and regioselective S_N2' addition of dimethylcuprate to introduce the last carbon of the picrasane skeleton. Last, but not least, the removal of the sulfur atom by oxidation to the sulfoxide and elimination occurred without difficulty, providing a useful C1-C2 alkene in **60** (Scheme 13). The plan

now calls for the use of these double bonds to introduce the requisite oxygen atoms and complete the synthesis of javanicin B.

In conclusion, we have shown that the Diene-Transmissive Diels-Alder Cycloaddition strategy is a viable one to construct the complete javanicin framework common to many quassinoids. All stereocentres were introduced with a high degree of stereoselectivity to provide the non-racemic advanced intermediate **60** in only 16 linear steps (18 total) from pentanediol and propargyl alcohol. The sulfur bridge was crucial in solving the main challenges of this synthetic approach. The completion of the synthesis of Javanicin B and other members of this family is currently underway.

EXPERIMENTAL

Unless otherwise noted all reactions were performed under an argon atmosphere. Solvents were distilled from potassium/benzophenone ketyl (THF, Et_2O, toluene), from calcium hydride (CH_2Cl_2, DMF). Proton nuclear magnetic resonance (**^{1}H NMR**) spectra were recorded on a 300 MHz or 400 MHz spectrometer. Carbon nuclear magnetic resonance (**^{13}C NMR**) spectra were recorded on a 75.5 MHz or 100.7 MHz spectrometer. NMR samples were dissolved in chloroform-*d* (unless specified otherwise) and chemical shifts are reported in ppm (δ units) relative to the residual undeuterated solvent. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet. LRMS analyses were performed on a GC system spectrometer (30 m length, 25μ OD, DB-5 ms column) coupled with a mass spectrometer. High-resolution mass spectrometry was performed by electrospray time-of-flight. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate visualized under UV (254 nm) and TLC stains such as vanillin, $KMnO_4$, PMA, Dragen Dorff, or by ^{1}H NMR and GCMS analysis. Silica gel (230-400 mesh) was used for flash chromatography.

5-((*tert*-Butyldiphenylsilyl)oxy)pent-3-yn-2-one (27). The known *tert*-butyldiphenyl-(prop-2-yn-1-yloxy)silane (**26**)[16] (57.4 g, 0.19 mol) was dissolved in THF (380 mL) and a *n*-butyllithium solution (1.96 M in pentane, 112 mL, 0.22 mol) was added slowly at -78 °C. The reaction mixture was stirred 30 min at -78 °C, followed by 10 min at -20 °C. In a 1 L three-neck rb flask with mechanical stirring, acetic anhydride (31.4 mL, 0.33 mol) was diluted in THF (190 mL) and the solution a was cooled to -78 °C. The organolithium solution was added to the acetic anhydride solution and the reaction mixture was stirred for 12 h while slowly warming up to rt. The reaction mixture was quenched with water and the two layers were separated. The aqueous layer was extracted twice with Et_2O, the organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give colorless oil. The crude product was purified by column chromatography using a 1:9 mixture of Et_2O and

hexanes as eluting solvent, to give ketone **27** (49.8 g, 78%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ (ppm) 7.70 (dd, 4H, *J* = 6.6, 2.2 Hz), 7.49-7.38 (m, 6H), 4.46 (s, 2H), 2.26 (s, 3H), 1.07 (s, 9H). **NMR ^{13}C** (75 MHz, $CDCl_3$) δ (ppm) 184.1 (s), 135.6 (d), 132.4 (s), 130.1 (d), 127.9 (d), 89.8 (s), 84.5 (s), 52.3 (t), 32.4 (q), 26.6 (q), 19.2 (s). **IR** ($CHCl_3$) ν (cm^{-1}) 3072, 2953, 1680, 1427. **LRMS** (*m/z*, (relative intensity)) 279 ($(M-C_4H_9)^+$, 100), 249 (72), 241 (35). **HRMS** calcd for $C_{17}H_{15}O_2Si$: 279.0841, found: 279.0846.

(5-((*tert*-Butyldiphenylsilyl)oxy)pentyl)iodotriphenylphosphane (30). *tert*-Butyl((5-iodopentyl)oxy)-diphenylsilane (**29**)[17] (115g, 0.25 mol) was dissolved in toluene (513 mL) and triphenylphosphine was added. The reaction mixture was stirred at reflux for 12 h and after this time, cooled slowly to 0 °C. Et_2O (200 mL) was added to precipitate the phosphonium salt. The slurry was stirred for 2 h at 0 °C and filtered. The cake was washed twice with Et_2O and dried under reduced pressure to give the desired phosphonium **30** as a white solid (167 g, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.81-7.64 (m, 15H), 7.58 (d, 4H, *J* = 7.7 Hz), 7.40-7.30 (m, 6H), 3.70-3.57 (m, 2H), 3.59 (t, 2H, *J* = 6.3 Hz), 1.74-1.51 (m, 6H), 0.97 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 135.4 (d), 135.2 (d), 133.6 (d), 133.5 (d), 130.6 (d), 130.5 (d), 129.5 (d), 127.6 (d), 118.5 (s), 117.3 (s), 63.2 (t), 31.7 (t), 26.8 (q), 23.4 (t), 22.8 (t), 22.3 (t), 19.1 (s). **IR** ($CHCl_3$) ν (cm^{-1}) 3064, 2932, 1587.

(*E*)-1,9-Bis((*tert*-butyldiphenylsilyl)oxy)-4-methylnon-4-en-2-yne (31). In a 3 L, three neck, rb flask with a mechanical stirrer was charged phosphane **30** (175.4 g, 0.245 mol) and THF (1 L). The solution was cooled to 0 °C and NaHMDS (259 mL, 1.0 M in THF, 0.259 mol) was added. The reaction mixture was stirred 45 min at 0 °C and 10 min at rt. The solution was cooled to -78 °C and MeCN (37.6 mL, 0.72 mol) was added. The reaction mixture was stirred for 10 min at -78 °C. A solution of ketone **27** (48.5 g, 0.144 mol) in THF (260 mL) was added via canula to the reaction mixture at -78 °C and the mixture was stirred for 1 h. The reaction mixture was quenched by adding a saturated solution of ammonium chloride and the aqueous layer was extracted 3 times with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography using a 20:80 mixture of AcOEt and hexanes as eluting solvent, to give alkyne **31** as colorless oil (61.2 g, 66%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.75 (dd, 4H, *J* = 7.4, 1.9 Hz), 7.69 (dd, 4H, *J* = 7.4, 1.9 Hz), 7.46-7.36 (m, 12H), 5.76 (t, 1H, *J* = 7.2 Hz), 4.46 (s, 2H), 3.68 (t, 2H, *J* = 6.1 Hz), 2.06 (q, 2H, *J* = 7.2 Hz), 1.71 (s, 3H), 1.71-1.44 (m, 4H), 1.08 (s, 9H), 1.07 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 138.1 (d), 135.6 (d), 134.0 (s), 133.3 (s), 129.7 (d), 129.5 (d), 127.6 (d), 117.4 (s), 88.3 (s), 83.9 (s), 63.6 (t), 53.2 (t), 32.1 (t), 28.1 (t), 26.9 (q), 26.7 (q), 25.3 (t), 19.2 (s), 17.0 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 3068, 2936, 2247, 2225, 1470. **LRMS** (*m/z*, (relative intensity)) 644 (M^+, 2), 587 ($(M-C_4H_9)^+$, 45), 237 (68), 207 (100). **HRMS** calcd for $C_{42}H_{52}O_2Si_2$: 644.3506, found: 644.3514.

(+)-Epoxide 32. In a 3 L-three neck rb flask with a mechanical stirrer, was charged a solution of alkyne **31** (61.2 g, 95.0 mmol) in a 1:2 mixture of MeCN and dimethoxymethane (765 mL). An aqueous buffer (prepared by mixing 100 mL 0.1 M aqueous K_2CO_3 with 0.5 mL acetic acid, pH 9.3, 484 mL), Bu_4NHSO_4 (3.20 g, 9.50 mmol), and fructose-derived ketone **33** (7.36 g, 28.5 mmol) were added. The mixture was cooled to -10 °C using a NaCl-ice bath. A solution of Oxone (87.6, 142.5 mmol) in aqueous Na_2EDTA (4 × 10-4 M, 376 mL) and a solution of K_2CO_3 (0.24 g, 1.73 mmol) in water (1.2 mL) were added dropwise simultaneously through two separate syringes via syringe pump over a period of 3 h. After stirring 1 h at -10 °C, the reaction mixture was quenched with pentane and water, the two layers were separated, and the organic layer was extracted twice with pentane. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography using a 5:95 mixture of Et_2O and hexanes as eluting solvent, to give epoxide **32** (45.4 g, 72%) as colorless oil. $[\alpha]_D$ +2.9 (c 1.08, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.72-7.67 (m, 8H), 7.44-7.36 (m, 12H), 4.33 (s, 2H), 3.69 (t, 2H, *J* = 6.1 Hz), 2.98 (t, 1H, *J* = 6.1 Hz), 1.60-1.48 (m, 6H), 1.39 (s, 3H), 1.07 (s, 18H). **IR** ($CHCl_3$) ν (cm^{-1}) 3069, 2933, 1471. **LRMS** (*m/z*, (relative intensity)) 678 ($(MNH_4)^+$, 100), 661 ($(MH)_+$, 30), 583 (35), 405 (77), 196 (52). **HRMS** calcd for $C_{42}H_{52}Si_2O_3$ $[MH]^+$: 661.3533, found: 661.3518.

(+)-Vinylallene 34. *tert*-Butyllithium (1.7 M in pentane, 445.0 mL, 756 mmol) was added slowly to a solution of (*E*)-1-bromo-1-propene (32.4 mL, 378 mmol) in THF (540 mL) at -78 °C. The mixture was stirred 30 min at -78 °C and was then transferred via canula to a suspension of copper(I) cyanide (16.9 g, 189 mmol) in THF (300 mL) at -78 °C. The reaction mixture was stirred 30 min at -78 °C, then cooled at -100 °C and a solution of epoxide **32** (25.0 g, 37.8 mmol) in THF (125 mL) was slowly added. The reaction mixture was stirred 45 min at -100 °C then quenched with a saturated aqueous solution of ammonium chloride containing 10% ammonium hydroxide. The biphasic mixture was stirred for 12 h, after which time the two layers were separated and the organic layer was extracted three times with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give vinylallene **34** (26.5 g, 100%), which was used in the next step without purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.69-7.65 (m, 8H), 7.44-7.34 (m, 12H), 5.84 (dd, 1H, *J* = 15.9, 1.7 Hz), 5.61 (dq, 1H, *J* = 15.9, 6.6 Hz), 4.33 (s, 2H), 3.99 (q, 1H, *J* = 6.1 Hz), 3.64 (t, 2H, *J* = 6.1 Hz), 1.70 (t, 3H, *J* = 6.6 Hz), 1.69 (s, 3H), 1.61-1.40 (m, 6H), 1.04 (s, 9H), 1.03 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 204.0 (s), 135.6 (d), 134.9 (d), 134.1 (s), 133.8 (s), 129.7 (d), 129.6 (d), 127.7 (d), 126.7 (d), 124.9 (d), 106.7 (s), 105.2 (s), 73.2 (s), 63.9 (t), 62.6 (t), 34.9 (t), 32.6 (t), 27.0 (q), 26.9 (q), 22.0 (t), 19.3 (s), 18.7 (q), 14.4 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 3633-3196, 3079, 2933, 1471. **LRMS** (*m/z*, (relative intensity)) 700 ($(M-H_2)^+$, 4), 645 ($(M-C_4H_9)^+$, 8), 199 (100), 135 (100). **HRMS**

calcd for $C_{45}H_{56}O_3Si_2$: 700.3768, found: 700.3757. $[\alpha]_D$ +9.8 (c 1.22, $CHCl_3$).

(+)-Mosher ester 35. Vinylallene **34** (50.0 mg, 0.071 mmol) was dissolved in DCM (1.0 mL) and the solution was cooled to 0 °C. (*S*)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (49 mg, 0.213 mmol), dimethylaminopyridine (8 mg, 0.06 mmol), and dicyclohexylcarbodiimide (51 mg, 0.247 mmol) were added to the solution at 0 °C. The reaction mixture was stirred 12 h at rt and quenched with water. The two layers were separated and the organic layer was extracted three times with DCM. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using a 20:80 mixture of AcOEt and hexanes as eluting solvent to give the Mosher ester **35** (43 mg, 50%). The enantiomeric excess (*ee* = 94%) was determined by integration of the appropriate proton NMR signals in the spectra of the crude product (methoxy signals at 3.47 and 3.5 and carbinol signals at 5.39 and 5.35 ppm). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.68-7.64 (m, 10H), 7.51 (d, 1H, *J* = 7.7 Hz), 7.43-7.29 (m, 14H), 5.75 (d, 1H, *J* = 15.9 Hz), 5.64 (dq, 1H, *J* = 15.9, 6.2 Hz), 5.39 (t, 1H, *J* = 6.6 Hz), 4.31 (ABq, 2H), 3.61 (t, 2H, *J* = 6.4 Hz), 3.47 (s, 3H), 1.76-1.71 (m, 2H), 1.68 (d, 3H, J = 6.2 Hz), 1.59 (s, 3H), 1.58-1.51 (m, 2H), 1.45-1.37 (m, 2H), 1.04 (s, 9H), 1.02 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 203.0 (s), 165.9 (s), 135.5 (d), 133.9 (s), 133.5 (s), 132.2 (s), 129.5 (d), 128.2 (d), 127.6 (d), 127.4 (d), 125.8 (d), 125.2 (s), 121.4 (s), 106.4 (s), 100.0 (s), 78.1 (d), 63.6 (t), 62.6 (t), 55.4 (q), 32.5 (t), 32.2 (t), 26.8 (q), 26.7 (q), 21.8 (t), 19.2 (s), 18.6 (q), 15.1 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 3079, 2934, 1960, 1745, 1429. **LRMS** (*m/z*, (relative intensity)) 918 (M^+, 5), 861 ($(M-C_4H_9)^+$, 22), 189 (100), 135 (74). **HRMS** calcd for $C_{55}H_{65}F_3O_5Si_2$: 918.4322, found: 918.4308. $[\alpha]_D$ +16.5 (c 0.99, $CHCl_3$).

(-)-Thioacetate 36. Triphenylphosphine (39.6 g, 151.2 mmol) was dissolved in THF (581 mL) and the solution was cooled at 0 ºC. Diisopropyl azodicarboxylate (29.8 mL, 151.2 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C. A solution of thioacetic acid (10.81 mL, 151.2 mmol) and vinylallene **34** (53 g, 75.6 mmol) in THF (290 mL) was added over 60 min at -20 °C. The reaction mixture was stirred at rt for 12 h and quenched with water. The two layers were separated and the organic layer was extracted three times with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography using a 5:95 mixture of AcOEt and hexanes as eluting solvent to give thioacetate **36** (40.2 g, 70%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.70-7.64 (m, 8H), 7.39-7.37 (m, 12H), 5.84 (m, 1H), 5.79-5.55 (m, 1H), 4.29 (d, 2H, *J* = 3.3 Hz), 3.97 (t, 1H, *J* = 7.2 Hz), 3.6 (t, 2H, *J* = 6.1 Hz), 2.30 (s, 3H), 1.76-1.24 (m, 6H), 1.73 (s, 3H), 1.70 (d, 3H, *J* = 6.6 Hz), 1.04 (s, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 202.9 (s), 195.7 (s), 135.6 (d), 134.1 (s), 133.7 (s), 129.5 (d), 127.5 (d), 126.2 (s), 125.1 (d), 106.5 (s), 102.1 (s), 63.8 (t), 62.6 (t), 47.6 (d), 34.0 (t), 30.5 (q), 26.8 (q), 23.4 (t), 19.2 (s), 18.6 (q), 17.6 (q). **IR**

($CHCl_3$) ν (cm^{-1}) 3075, 2931, 2858, 1691. **LRMS** (*m/z*, (relative intensity)) 678 (($M^{+\cdot}$), 2), 703 ($(M-C_4H_9)^+$, 15), 199 (90), 136 (100). **HRMS** calcd for $C_{47}H_{60}Si_2O_3S$ $[M]^+$: 760.3801, found: 760.3795. $[\alpha]_D$ -37.2 (c 1.10, $CHCl_3$).

(+)-Cycloadduct 38. A hydrazine hydrate solution (1.0 M in MeCN, 130 mL, 130.2 mmol) was added to a solution of thiocacetate **36** (33.0 g, 43.4 mmol) in MeCN (435 mL), and the reaction mixture was stirred for 12 h. The reaction mixture was concentrated under reduce pressure to remove the MeCN and hydrazine and the concentrate were dissolved in DCM (645 mL). Triethylamine (9.7 mL, 64.4 mmol) and a solution of methyl propiolate (5.73 mL, 64.4 mmol) in DCM (645 mL) were successively added at 0 °C. The reaction mixture was slowly warmed to rt over a period of 4 h. The reaction mixture was then concentrated under reduced pressure and the concentrate purified by column chromatography using a 5:95 mixture of AcOEt and hexanes as eluting solvent to give cycloadduct **38** (28.8 g, 83%) as thick colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.69-7.65 (m, 8H), 7.45-7.35 (m, 12H), 5.56 (d, 1H, *J* = 4.4 Hz), 4.58 (d, 1H, *J* = 13.2 Hz), 4.35 (d, 1H, *J* = 13.2 Hz), 4.26 (d, 1H, *J* = 12.1 Hz), 4.07 (br s, 1H), 3.72 (s, 3H), 3.66 (t, 2H, *J* = 6.1 Hz), 2.86 (dd, 1H, *J* = 6.0 Hz, 12.1 Hz), 2.67 (q, 1H, 6.6 Hz), 1.87 (s, 3H), 1.83-1.34 (m, 6H), 1.05 (s, 18H), 0.84 (d, 3H, *J* = 7.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.6 (s), 135.6 (d), 135.0 (s), 134.1 (s), 133.6 (s), 133.2 (s), 132.2 (d), 130.0 (s), 129.7 (d), 129.5 (d), 127.6 (d), 65.6 (t), 63.7 (t), 58.4 (q), 54.1 (d), 51.5 (q), 49.0 (d), 35.6 (t), 33.1 (d), 32.4 (d), 26.8 (q), 22.7 (t), 19.2 (q), 16.4 (t), 14.6 (s). **IR** ($CHCl_3$) ν (cm^{-1}) 2939, 2857, 1735. **LRMS** (*m/z*, (relative intensity)) 802 (M^+, 5), 745 ($(M-C_4H_9)^+$, 50), 489 (65), 290 (65), 199 (90), 86 (100). **HRMS** calcd for$C_{49}H_{62}Si_2O_4S$: 802.3907, found: 802.3890. $[\alpha]_D$ +83.3 (c 1.55, $CHCl_3$).

(+)-Ester 39. A solution of tetrabutylammonium fluoride (1.0 M in THF, 95.7 mL, 95.7 mmol) was added to a solution of **38** (25.6 g, 31.9 mmol) in THF (320 mL) at rt. The reaction mixture was stirred 12 h and neutralized with a saturated aqueous solution of ammonium chloride. The two layers were separated and the aqueous layer was extracted three times with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using a 70:30 mixture of AcOEt and hexanes as eluting solvent to give diol **61** (7.9 g, 76%), which was unstable and slowly decomposed at ambient temperature. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.75 (d, 1H, *J* = 4.4 Hz), 4.48 (br d, 1H, *J* = 12.7 Hz), 4.25 (br d, 2H, *J* = 10.4 Hz), 4.06 (br d, 1H, *J* = 7.2 Hz), 3.71 (s, 3H), 3.60 (t, 2H, *J* = 6.1 Hz), 2.85 (dd, 1H, *J* = 6.6 Hz, 12.1 Hz), 2.73 (sextuplet, 1H, 6.6 Hz), 2.06 (m, 1H), 1.91 (s, 3H), 1.87 (m, 1H), 1.70-1.23 (m, 6H), 0.90 (d, 3H, *J* = 7.2 Hz). **IR** ($CHCl_3$) ν (cm^{-1}) 3701-3099, 2939, 2874, 1735. **LRMS** (*m/z*, (relative intensity)) 326 (M^+, 10), 308 ($(M-H_2O)^+$, 25), 249 (60), 175 (50), 84 (100). **HRMS** calcd for $C_{17}H_{26}O_4S$: 326.1552, found: 326.1556. $[\alpha]_D$ +193.6 (c 0.6, $CHCl_3$).

IBX (31.9 g, 114 mmol) was added to a solution of diol **61** (9.3 g, 28.5 mmol) in AcOEt (245 mL) and the reaction mixture was heated to reflux for 3 h. The reaction then cooled down to rt and filtered. The filtrate was concentrated under reduced pressure to give dialdehyde **62** (9.10 g, 100%), which was used without any purification in next step. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.74 (s, 1H), 9.50 (s, 1H), 6.62 (d, 1H, *J* = 4.4 Hz), 4.23-4.15 (m, 1H), 4.21 (d, 1H, *J* = 11.8 Hz), 3.74 (s, 3H), 3.05 (dq, 1H, *J* = 7.3, 3.9 Hz), 2.95 (dd, 1H, *J* = 11.8, 6.3 Hz), 2.47-2.38 (m, 2H), 1.82-1.76 (m, 2H), 1.73 (s, 3H), 1.71-1.49 (m, 2H), 0.99 (d, 3H, *J* = 7.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 202.1 (d), 190.5 (d), 172.6 (s), 153.5 (d), 138.9 (s), 136.8 (s), 126.4 (s), 57.7 (d), 55.1 (d), 51.8 (q), 48.6 (d), 43.5 (t), 34.8 (t), 34.4 (d), 18.8 (t), 16.4 (q), 15.1 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 1730, 1447. **LRMS** (*m/z*, (relative intensity)) 322 (42), 263 (40), 163 (100), 84 (90). **LRMS** calcd for $C_{17}H_{22}O_4S$ $[M]^+$: 322.1239, found: 322.1231.

Sodium hydride (1.43 g, 60% in mineral oil, 35.6 mmol) was added to THF (265 mL) at 0 °C. Methyl 2-(diethoxyphosphoryl)acetate (5.7 mL, 34.2 mmol) was added to the resulting suspension and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was cooled to -78 °C and a solution of dialdehyde **62** (9.10 g, 28.5 mmol) in THF (20 mL) was added. The reaction mixture was stirred for a further 12 h and then neutralized with a saturated aqueous solution of ammonium chloride. The two layers were separated and the aqueous layer was extracted three times with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using a 20:80 mixture of AcOEt and hexanes as eluting solvent to give ester **39** (6.80 g, 63%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 9.52 (s, 1H), 6.93 (dt, *J* = 15.4, 7.3 Hz, 1H), 6.63 (d, *J* = 3.9 Hz, 1H), 5.81 (d, *J* = 15.4 Hz, 1H), 4.22-4.16 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.13-3.02 (m, 1H), 2.95 (dd, *J* = 11.8, 6.3 Hz, 1H), 2.25-2.17 (m, 2H), 1.88-1.78 (m, 1H), 1.72 (s, 3H), 1.64-1.36 (m, 3H), 1.01 (d, *J* = 7.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 190.4 (d), 172.4 (s), 166.7 (s), 153.6 (d), 148.8 (d), 138.8 (s), 136.7 (s), 126.2 (s), 121.1 (d), 57.7 (d), 55.1 (d), 51.6 (q), 51.2 (q), 48.5 (d), 34.9 (t), 34.3 (d), 31.8 (t), 24.7 (t), 16.2 (q), 15.0 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2948, 2934, 2856, 1724, 1697, 1436. **LRMS** (*m/z*, (relative intensity)) 378 (M^+, 20), 346 (50), 163 (75), 84 (100). **HRMS** $C_{20}H_{26}O_5S$: calcd for 378.1501, found: 378.1491. $[\alpha]_D$ +136.9 (c 0.7, $CHCl_3$).

(-)-Cycloadduct 40. Ester **39** (6.80 g, 18.0 mmol) was dissolved in ethyl vinyl ether (180 mL) and the solution was degassed for 20 min by bubbling argon through. Then, $Yb(fod)_3$ (1.36 g, 20% p/p) was added and the reaction mixture was purged again 3 times with argon. The reaction mixture was stirred 16 h at rt and then concentrated under reduced pressure. The crude product was purified by column chromatography using a 20:80 mixture of AcOEt and hexanes as eluting solvent to give cycloadduct **40** (6.66 g, 82%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.96 (dt, 1H, *J* = 15.4, 7.2 Hz), 6.91 (s, 1H), 5.83 (d,

1H, *J* = 16.0 Hz), 4.97 (bd, 1H, *J* = 8.8 Hz), 3.94 (quint., 1H, *J* = 7.2 Hz), 3.83 (d, 1H, *J* = 8.9 Hz) 3.73 (s, 3H), 3.70 (s, 3H), 3.67 (quint., 1H, *J* = 7.2 Hz), 2.98 (m, 1H), 2.70 (q, 1H, *J* = 8.7 Hz), 2.27 (br q, 1H, *J* = 9.2 Hz), 2.24-2.20 (m, 2H), 2.17 (s, 3H), 1.95-1.83 (m, 1H), 1.80-1.63 (m, 3H), 1.60-1.43 (m, 3H), 1.25 (t, 3H, *J* = 7.2 Hz), 1.10 (d, 3H, *J* = 6.6 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 174.3 (s), 167.0 (s), 149.0 (d), 139.8 (d), 130.0 (s), 129.3 (s), 121.2 (d), 112.5 (s), 99.3 (d), 64.5 (t), 58.9 (d), 56.7 (d), 51.7 (d), 51.4 (q), 35.7 (d), 35.3 (t), 34.0 (d), 32.7 (t), 32.0 (t), 24.9 (q), 15.1 (q), 14.6 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2922, 1727. **LRMS** (*m/z*, (relative intensity)) 450 (M^+, 70), 346 (50), 277 (50), 185 (75), 163 (100). **HRMS** calcd for $C_{24}H_{34}O_6S$: 450.2076, found: 450.2079. $[\alpha]_D$ -51.6 (c 1.24, $CHCl_3$).

(+)-Cycloadduct 41. Cycloadduct **40** (300 mg, 0.67 mmol) was dissolved in toluene (9 mL) and charged in a sealable tube. The solution was degassed 5 times by freeze-thaw technique using liquid nitrogen. Then, the tube was sealed and the reaction mixture was heated 36 h at 250 °C. After cooling to rt, the tube was broken and the solution transferred in a rb flask and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with AcOEt/hexanes (30:70), to give pentacycle **41** (198 mg, 66%). **Mp** 164 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.55 (dd, *J* = 9.4, 1.7 Hz, 1H), 4.12 (d, *J* = 9.9 Hz, 1H), 4.05 (dd, *J* = 6.1, 1.7 Hz, 1H), 3.78 (dq, *J* = 9.9, 7.2 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.44 (dq, *J* = 9.6, 7.2 Hz, 1H), 3.16 (dd, *J* = 11.3, 5.8 Hz, 1H), 2.95 (dd, *J* = 12.4, 6.3 Hz, 1H), 2.50 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.27 (dt, *J* = 12.4, 5.9 Hz, 1H), 2.14-2.01 (m, 3H), 1.90-1.76 (m, 3H), 1.65-1.53 (m, 2H), 1.50-1.31 (m, 1H), 1.24-1.05 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 3H), 0.91 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.8 (s), 171.4 (s), 143.3 (s), 122.7 (s), 101.5 (d), 70.9 (d), 64.1 (t), 53.2 (d), 51.9 (q), 51.2 (q), 47.2 (d), 45.0 (s), 41.2 (d), 39.3 (t), 35.5 (d), 31.7 (d), 26.5 (t), 24.1 (q), 20.6 (t), 19.7 (t), 15.7 (q), 15.1 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2949, 2869, 1736, 1435. **LRMS** (*m/z*, (relative intensity)) 450 (M^+, 1), 435 ($(M\text{-}CH_3)^+$, 1), 404 ($(M\text{-}C_2H_5OH)^+$, 100). **HRMS** calcd for $C_{24}H_{34}O_6S$: 450.2076, found: 450.2079. $[\alpha]_D$ +91.7 (c 1.11, $CHCl_3$).

Sulfoxide 43. Pentacyclic sulfur **41** (200 mg, 0.44 mmol) was dissolved in DCM (4.0 mL) and the solution was cooled to -78 °C. *m*-CPBA (109 mg, 0.489 mmol) was added in small portions and after stirring the resulting mixture 4 h at -78 ºC, it was neutralized by adding a saturated aqueous solution of sodium thiosulfate. The biphasic system was vigorously stirred for 30 min at rt, the phases were separated and the aqueous layer extracted 3 times with DCM. The organic layers were combined, washed once with saturated aqueous $NaHCO_3$ and once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a 30:70 to 50:50 mixture of AcOEt and hexanes as eluting solvent to give tetracyclic sulfoxide **43** (130 mg, 63%) and sulfone **44** (64 mg, 30%). For the characterisation data of

sulfone **44**, see the next experimental procedure. Sulfoxide **43**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.55 (dd, 1H, *J* = 9.4, 1.7 Hz), 4.15 (dt, 1H, *J* = 8.8, 2.5 Hz), 4.07 (dd, 1H, *J* = 6.3, 2.5 Hz), 3.75 (dq, 1H, *J* = 9.6, 6.9 Hz), 3.75 (s, 3H), 3.68 (s, 3H), 3.43 (dq, 1H, *J* = 9.3, 7.2 Hz), 3.00-2.93 (m, 3H), 2.22-1.75 (m, 8H), 1.60-1.42 (m, 2H), 1.41-1.03 (m, 1H), 1.20 (s, 3H), 1.17 (t, 3H, *J* = 7.2 Hz), 0.94 (d, 3H, *J* = 7.2 Hz). **IR** ($CHCl_3$) ν (cm^{-1}) 2951, 1741, 1157. **LRMS** (*m/z*, (relative intensity)) 466 (M^+, 50), 449 (58), 371 (100), 335 (68), 303 (72), 225 (100). **HRMS** calcd for $C_{24}H_{34}O_7S$: 466.2025, found: 466.2030.

Sulfone 44. Pentacyclic sulfur **41** (200 mg, 0.44 mmol) was dissolved in DCM (4.0 mL) and the solution was cooled to 0 °C. *m*-CPBA (218 mg, 0.978 mmol) was added in small portions and after stirring the resulting mixture 2 h at 0 ºC, it was neutralized by adding a saturated aqueous solution of sodium thiosulfate. The biphasic system was vigorously stirred for 30 min at rt, the phases were separated and the aqueous layer extracted 3 times with DCM. The organic layers were combined, washed once with saturated aqueous $NaHCO_3$ and once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a 30:70 to 50:50 mixture of AcOEt and hexanes as eluting solvent to give tetracyclic sulfone **44** (210 mg, 99%). The X-ray diffraction analysis data is available in this SI. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.56 (dd, 1H, *J* = 9.3, 2.2 Hz), 4.18 (dd, 1H, *J* = 9.9, 2.2 Hz), 4.05 (dd, 1H, *J* = 6.0, 2.2 Hz), 3.77 (s, 3H), 3.80-3.72 (m, 1H), 3.69 (m, 3H), 3.42 (dq, 1H, *J* = 9.4, 7.2 Hz), 3.12-3.06 (m, 2H), 2.93 (dd, 1H, *J* = 12.6, 6.1 Hz), 2.34-2.17 (m, 2H), 2.10-2.01 (m, 1H), 1.97-1.89 (m, 3H), 1.70-1.59 (m, 3H), 1.51-1.41 (m, 1H), 1.39-1.06 (m, 1H), 1.17 (t, 3H, *J* = 7.2 Hz), 1.17 (s, 3H), 0.90 (d, 3H, *J* = 7.2 Hz). **IR** ($CHCl_3$) ν (cm^{-1}) 2952, 2874, 1742, 1444. **LRMS** (*m/z*, (relative intensity)) 481 ($(M-H)^+$, 1), 437 ($(M-EtOH)^+$, 10), 418 ($(M-SO_2)^+$, (20), 344 (60), 313 (55), 269 (60), 225 (100), 169 (55). **HRMS** calcd for $C_{24}H_{33}O_8S$: 481.1896, found: 481.1899.

Dienes 45 and 46. Sulfoxide **43** (35.0 mg, 0.075 mmol) was dissolved in MeCN (0.7 mL) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (32.0 µL, 0.225 mmol) and 2,6-lutidine (26.0 µL, 0.225 mmol) were added and the mixture was stirred 1.5 h at 0 ºC. Then, the solvent was evaporated and the residu was filtered on a silica gel pad to give a 1:1 mixture of two inseparable regioisomeric dienes **45** and **46** (33 mg, 99%). Regioisomer **45**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.60-4.56 (m, 1H), 4.30 (d, 1H, *J* = 5.5 Hz), 3.83-3.74 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.45 (dq, 1H, *J* = 9.3, 7.2 Hz), 3.20 (dd, 1H, *J* = 11.5, 6.6 Hz), 3.04 (dd, 1H, *J* = 12.1, 5.5 Hz), 2.67 (q, 1H, *J* = 7.0 Hz), 2.37 (td, 1H, *J* = 12.5, 3.9 Hz), 2.32-2.04 (m, 4H), 1.96-1.71 (m, 2H), 1.65-1.24 (m, 2H), 1.18-1.14 (m, 1H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.08 (s, 3H), 1.04 (d, 3H, *J* = 8.8 Hz). Regioisomer **46**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.23 (t, 1H, *J* = 3.9 Hz), 4.60-4.56 (m, 1H), 4.44 (d, 1H, *J* = 10.5 Hz), 4.09 (dd, 1H, *J* = 5.2, 1.9 Hz), 3.83-3.74 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.45 (dq, 1H, *J* = 9.3, 7.2 Hz), 2.82 (dd, 1H, *J* = 12.6, 5.5 Hz), 2.57 (dd,

1H, *J* = 11.0, 3.3 Hz), 2.32-2.04 (m, 5H), 1.96-1.71 (m, 1H), 1.65-1.24 (m, 2H), 1.18-1.14 (m, 1H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.05 (s, 3H), 0.96 (d, 3H, *J* = 7.1 Hz). Both regioisomers: **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.9 (s), 171.3 (s), 171.0 (s), 167.9 (s), 150.1 (s), 143.9 (s), 139.6 (s), 132.1 (s), 125.7 (s), 113.4 (d), 101.8 (d), 101.4 (d), 71.9 (d), 71.7 (d), 64.2 (t), 57.1 (d), 52.0 (q), 51.4 (q), 51.3 (q), 49.2 (d), 46.5 (d), 46.2 (s), 45.9 (d), 44.3 (s), 42.7 (d), 42.1 (d), 40.8 (d), 39.9 (t), 37.6 (d), 36.0 (d), 33.6 (d), 27.1 (t), 25.8 (t), 24.9 (q), 22.0 (q), 20.2 (q), 19.4 (t), 18.6 (t), 16.4 (q), 15.1 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2951, 2869, 1737, 1688, 755. **LRMS** (*m/z*, (relative intensity)) 448 (M^+, 100), 112 (80). **HRMS** calcd for $C_{24}H_{32}O_6S$: 448.1919, found: 448.1928.

Tetracyclic aldol adduct 47. A solution of methyllithium (1.4 M in Et_2O, 0.68 mL, 0.96 mmol) was slowly added to a solution of copper(I) iodide (91 mg, 0.48 mmol) in Et_2O (0.8 mL) at -78 °C. The reaction mixture was stirred 30 min at -40 °C after which time, a solution of sulfone **44** (40 mg, 0.08 mmol) in Et_2O (0.4 mL) was slowly added at -78 °C. The reaction mixture was stirred while allowing it to warm to 0 °C over a 2.5 h period. Then, it was neutralized by adding a solution of ammonium chloride containing 10% (v/v) ammonium hydroxide. The biphasic system was vigorously stirred for 3 h at rt, the phases were separated and the aqueous layer extracted 3 times with Et_2O. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a 50:50 mixture of AcOEt and hexanes as eluting solvent to give tetracyclic compound **47** (15 mg, 46%). The X-ray diffraction analysis data is available in this SI. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.76 (d, 1H, *J* = 2.2 Hz), 4.54 (dd, 1H, *J* = 7.1, 2.8 Hz), 3.88 (s, 3H), 3.74 (s, 3H), 3.13 (dd, 1H, *J* = 10.7, 1.9 Hz), 3.02 (dd, 1H, *J* = 13.2, 5.5 Hz), 2.75-2.72 (m, 2H), 2.10-1.93 (m, 4H), 1.88 (dd, 1H, *J* = 14.3, 7.7 Hz), 1.75-1.47 (m, 3H), 1.43-1.33 (m, 1H), 1.26 (s, 3H), 0.98 (d, 3H, *J* = 6.1 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 172.9 (s), 169.7 (s), 147.3 (s), 136.8 (s), 129.7 (s), 127.0 (d), 80.2 (d), 69.0 (d), 60.4 (s), 52.4 (t), 46.1 (d), 44.1 (d), 43.0 (q), 38.6 (d), 38.2 (d), 21.9 (q), 19.4 (t), 19.0 (t), 18.1 (t), 11.1 (q). **LRMS** (*m/z*, (relative intensity)) 436 (M^+, 7), 404 (100). **HRMS** calcd for $C_{22}H_{28}O_7S$: 436.1556, found: 436.1544.

Methylsulfonium tetrafluoroborate 50. Cycloadduct **41** (30 mg, 0.067 mmol) was dissolved in DCM (0.67 mL) and the reaction was cooled to -30 °C. Trimethyloxonium tetrafluoroborate (20 mg, 0.13 mmol) was added and the reaction mixture was stirred 3 h at -30 °C. Water was added and the two layers were separated. The aqueous layer was extracted 3 times with DCM and the organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give crude sulfonium **50** (36 mg, 99%) which was used without further purification for next step. The X-ray diffraction analysis data is available in this SI. **Mp** 129-134 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.96 (bd, 1H, *J* = 10.5 Hz), 4.60 (dd, 1H, *J* = 9.4, 2.2 Hz), 4.14 (dd, 1H, *J* = 6.0, 1.7 Hz), 3.92 (dd, 1H, *J* = 10.5, 6.6

Hz), 3.81 (s, 3H), 3.68 (s, 3H), 3.73-3.63 (m, 1H), 3.45 (dq, 1H, *J* = 9.9, 7.1 Hz), 3.37 (s, 3H), 3.05 (dd, 1H, *J* = 11.8, 6.6 Hz), 2.88 (dd, 1H, *J* = 10.5 Hz), 2.35 (m, 1H), 2.26-2.10 (m, 3H), 2.03-1.81 (m, 3H), 1.70-1.45 (m, 2H), 1.32 (s, 3H), 1.25-1.19 (m, 2H), 1.14 (t, 3H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 7.1 Hz). **IR** ($CHCl_3$) ν (cm^{-1}) 3037, 2952, 1737, 1052.

Methylsulfonium tetrafluoroborate 52. Pentacyclic compound **41** (200 mg, 0.44 mmol) was dissolved in DCM (4.4 mL) and the solution was cooled down to 0 °C. A solution of trimethyloxonium tetrafluoroborate (130 mg, 0.88 mmol) was added and the reaction mixture was stirred 4 h while letting it warm up to rt. After this time, the solvent was evaporated and the crude methylsulfonium salt **52** (245 mg, 0.44 mmol) was immediately used in the next step without purification.

Cuprate adduct 51. Methylmagnesium chloride (0.20 mL, 3.0 M in Et_2O, 0.60 mmol) was added slowly to a suspension of copper(I) cyanide (27 mg, 0.30 mmol) in THF (0.6 mL) at -78 °C. The reaction mixture was stirred 30 min at -78 °C, then a solution of sulfonium **50** (45 mg, 0.08 mmol) and trimethylsilyl chloride (76 μL, 0.60 mmol) in THF (0.4 mL) was slowly added. The reaction was slowly warmed to rt and stirred for 12 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride containing 10% (v/v) ammonium hydroxide and the biphasic mixture was vigorously stirred for 5 h, after which time the two layers were separated. The aqueous layer was extracted 3 times with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using a 10:90 mixture of AcOEt and hexanes as eluting solvent to give the sulfide **51** and cycloadduct **41** as a 1:1 mixture (20 mg, 52%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.56 (d, 1H, *J* = 2.4 Hz), 4.33 (d, 1H, *J* = 6.5 Hz), 3.77 (dq, 1H, *J* = 9.3, 7.2 Hz), 3.69 (s, 3H), 3.65 (s, 3H), 3.55 (dd, 1H, *J* = 7.4, 2.7 Hz), 3.40-3.31 (m, 2H), 3.03 (bd, 1H), 2.86 (dd, 1H, *J* = 12.3 and 2.4 Hz), 2.63 (dt, 1H, *J* = 11.4 and 2.4 Hz), 2.50 (dd, 1H, *J* = 9.2, 1.9 Hz), 1.96 (s, 3H), 2.18 (t, 1H, *J* = 7.6 Hz), 2.12-1.93 (m, 2H), 1.80-1.00 (m, 6H), 1.34 (s, 3H), 1.25 (s, 3H), 1.17 (t, 3H, *J* = 7.2 Hz), 1.05 (d, 3H, *J* = 7.2 Hz).

Cuprate adduct 53 and demethylation product 54. To a suspension of copper(I) cyanide (27 mg, 0.30 mmol) in THF (0.6 mL) at -78 °C was slowly added a solution of methylmagnesium chloride (3.0 M in Et_2O, 0.20 mL, 0.60 mmol). After 30 min of stirring, a solution of methylsulfonium salt **52** (45 mg, 0.08 mmol) and chlorotrimethylsilane (76 μL, 0.60 mmol) in THF (0.4 mL) was added, keeping the temperature at -78 °C. The reaction mixture was stirred while it was allowed to warm to rt over a period of 12 h. Then, it was neutralized by adding a saturated aqueous solution of ammonium chloride containing 10% (v/v) ammonium hydroxide. The biphasic mixture was vigorously stirred for 3 h at rt and the phases were separated. The aqueous phase was extracted three times with Et_2O the organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered, and

concentrated under reduced pressure. The crude product was purified by column chromatography using a 10:90 mixture of AcOEt and hexanes as eluting solvent to give tetracyclic compound **53** (8 mg, 20%) and pentacyclic sulfur **54** (4 mg, 11%). Cuprate adduct **53**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.58 (d, 1H, *J* = 2.8 Hz), 4.87 (d, 1H, *J* = 2.2 Hz), 3.76 (bs, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.56 (dd, 1H, *J* = 7.4, 2.8 Hz), 3.49 (dq, 1H, *J* = 9.5, 7.2 Hz), 3.37 (dq, 1H, *J* = 9.9, 7.2 Hz), 3.10 (bs, 1H), 2.89 (dd, 1H *J* = 12.4, 2.2 Hz), 2.57 (td, 1H, *J* = 12.4, 2.8 Hz), 2.17-1.90 (m, 4H), 1.98 (s, 3H), 1.84-1.74 (m, 3H), 1.48-1.39 (m, 2H), 1.39 (s, 3H), 1.29-1.16 (m, 1H), 1.27 (s, 3H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 7.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 175.0 (s), 173.4 (s), 143.0 (s), 119.1 (d), 96.2 (d), 72.1 (d), 61.9 (t), 53.3 (d), 51.4 (q), 51.3 (q), 43.9 (d), 43.6 (d), 43.5 (d), 43.5 (s), 36.9 (s), 33.9 (d), 33.5 (t), 33.1 (d), 31.1 (q), 24.7 (t), 24.3 (t), 24.1 (q), 20.4 (t), 19.6 (q), 2 signals at 15.1 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2950, 1738. **LRMS** (*m/z*, (relative intensity)) 480 (M^+, 45), 465 ($(M\text{-}Me)^+$, 100). **HRMS** calcd for $C_{26}H_{40}O_6S$: 480.2545, found: 480.2555. Demethylation product **54**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.90 (bs, 1H), 4.50 (bd, 1H, *J* = 6.1 Hz), 4.12 (d, 1H, *J* = 9.9 Hz), 3.72 (s, 3H), 3.68 (s, 3H), 3.65 (dq, 1H, *J* = 9.9, 7.2 Hz), 3.39 (dq, 1H, *J* = 9.9, 7.2 Hz), 3.15 (dd, 1H, *J* = 11.3, 6.0 Hz), 2.92 (dd, 1H, *J* = 12.0, 6.3 Hz), 2.50 (dd, 1H, *J* = 9.9, 3.6 Hz), 2.44 (d, 1H, *J* = 9.4 Hz), 2.22 (dd, 1H, *J* = 12.0, 6.1 Hz), 2.15-2.04 (m, 1H), 1.99 (dq, 1H, *J* = 11.0, 3.6 Hz), 1.84-1.76 (m, 4H), 1.62-1.35 (m, 2H), 1.23 (t, 3H, *J* = 7.1 Hz), 1.18-1.01 (m, 1H), 0.97 (s, 3H), 0.89 (d, 3H, *J* = 7.1 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 174.0 (s), 171.7 (s), 142.3 (s), 123.7 (s), 97.4 (d), 65.6 (d), 62.1 (t), 53.3 (d), 52.0 (q), 51.2 (q), 47.0 (d), 46.5 (d), 44.8 (s), 41.2 (d), 38.3 (t), 37.4 (d), 35.3 (d), 31.6 (d), 26.6 (t), 24.1 (q), 20.5 (t), 19.7 (t), 15.2 (q), 15.0 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2949, 2900, 1434, 754. **LRMS** (*m/z*, (relative intensity)) 450 (M^+, 75), 404 ($(M\text{-}EtOH)^+$, 100). **HRMS** calcd for $C_{24}H_{34}O_6S$: 450.2076 found: 450.2088. $[\alpha]_D$ +120.9 (c 0.45, $CHCl_3$).

Pentacyclic sulfone 55. Prepared as per sulfone **44** from pentacyclic sulfur **54** (40 mg, 0.089 mmol) to give, after purification by silica gel column chromatography using AcOEt and hexanes (50:50) as eluant, sulfone **55** (25 mg, 58%). The X-ray diffraction analysis data is available in this SI. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.87 (s, 1H), 4.48 (d, 1H, *J* = 5.5 Hz), 4.20 (d, 1H, *J* = 10.5 Hz), 3.77 (s, 3H), 3.75-3.58 (m, 1H), 3.68 (s, 3H), 3.44-3.54 (m, 1H), 3.13-3.07 (m, 2H), 2.89 (dd, 1H, *J* = 11.8, 5.5 Hz), 2.51 (t, 1H, *J* = 8.8 Hz), 2.28-2.06 (m, 3H), 1.96-1.84 (m, 2H), 1.95 (d, 1H, *J* = 7.7 Hz), 1.84-1.81 (m, 1H), 1.82 (d, 1H, *J* = 7.7 Hz), 1.57-1.39 (m, 1H), 1.22 (t, 3H, *J* = 7.1 Hz), 1.17 (s, 3H), 1.20-1.05 (m, 1H), 0.88 (d, 3H, *J* = 7.1 Hz). **IR** ($CHCl_3$) ν (cm^{-1}) 3577-3183, 3020, 2952, 1741.

Ethylsulfonium tetrafluoroborates 56. Pentacyclic compound **41** (600 mg, 1.33 mmol) was dissolved in DCM (13.3 mL) and the solution was cooled down to 0 °C. A solution of triethyloxonium tetrafluoroborate (1.0 M in DCM, 4.0 mL, 4.00 mmol) was added and the reaction mixture was stirred 4 h while letting it warm up to rt. After this time, water was added and the phases were separated. The

aqueous layer was extracted 3 time with DCM and the organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude products were immediately used in the next step without purification.

Cuprate adducts (+)-58. Freshly recrystallized CuBr•Me_2S (875 mg, 4.26 mmol) and lithium chloride (180 mg, 4.26 mmol) were charged in a 25 mL dried rb flask under argon. The solids were heated using a heat gun under a gentle stream of argon. This procedure was repeated twice, letting the solids cool in between. Then, THF (9 mL) was added and the suspension was cooled to -78 °C. A titrated solution of methylmagnesium chloride (3.2 M in Et_2O, 1.25 mL, 3.99 mmol) was slowly added. After 30 min of stirring at -78 °C, a solution of the crude ethylsulfoniums **56** and **57** (740 mg, 1.33 mmol) and freshly distilled chlorotrimethylsilane (0.54 mL, 4.26 mmol) in THF (4.3 mL) were successively added. The reaction mixture was stirred while slowly warming to rt over a 12 h period. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride containing 10% (v/v) ammonium hydroxide. The biphasic mixture was vigorously stirred for 3 h at rt and the phases were separated. The aqueous phase was extracted three times with Et_2O the organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using a 10:90 mixture of AcOEt and hexanes as eluting solvent to give tetracyclic compound **58** (460 mg, 70%) and its C16 epimer **59** (40 mg, 6%). The X-ray diffraction analysis data for compound **58** is available in this SI. Tetracyclic compound **58**: **Mp** 182-186 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.58 (d, 1H, *J* = 2.8 Hz), 4.87 (d, 1H, *J* = 2.2 Hz), 3.75 (d, 1H, *J* = 1.7 Hz), 3.69 (s, 3H), 3.65 (s, 3H), 3.54 (dd, 1H, *J* = 7.7, 2.8 Hz), 3.49 (dq, 1H, *J* = 9.9, 7.2 Hz), 3.36 (dq, 1H, *J* = 9.9, 7.2 Hz), 3.20 (bs, 1H), 2.88 (dd, 1H *J* = 12.4, 2.2 Hz), 2.56 (td, 1H, *J* = 12.4, 2.8 Hz), 2.43 (q, 2H *J* = 7.2 Hz), 2.13-1.94 (m, 4H), 1.78-1.71 (m, 3H), 1.52-1.41 (m, 2H), 1.38 (s, 3H), 1.26 (s, 3H), 1.22-1.14 (m, 1H), 1.18 (q, 6H, *J* = 7.2 Hz), 1.07 (d, 3H, *J* = 7.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 175.0 (s), 173.5 (s), 143.0 (s), 119.4 (d), 96.2 (d), 72.2 (d), 61.9 (t), 51.4 (q), 51.3 (q), 51.1 (d), 44.0 (d), 43.6 (d), 43.9 (d), 43.4 (s), 37.0 (s), 33.9 (d), 33.5 (t), 33.1 (d), 31.1 (q), 25.5 (t), 25.8 (t), 24.7 (t), 24.1 (q), 20.4 (t), 19.6 (q), 15.0 (q), 14.7 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2949, 1739, 1434. **LRMS** (*m/z*, (relative intensity)) 494 (M^+, 50), 479 (100). **HRMS** calcd for $C_{27}H_{42}O_6S$: 494.2702, found: 494.2697. $[\alpha]_D$ +86.7 (c 1.59, $CHCl_3$).

C16 epimer **59**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.57 (d, 1H, *J* = 2.8 Hz), 4.32 (d, 1H, *J* = 6.6 Hz), 3.79 (dq, 1H, *J* = 9.3, 7.2 Hz), 3.70 (s, 3H), 3.65 (s, 3H), 3.55 (dd, 1H, *J* = 7.4, 2.8 Hz), 3.42-3.32 (m, 2H), 3.37 (d, 1H, *J* = 2.2 Hz), 3.13 (d, 1H, *J* = 2.8 Hz), 2.86 (dd, 1H, *J* = 12.4 and 2.2 Hz), 2.59 (dt, 1H, *J* = 12.4 and 2.8 Hz), 2.42 (q, 1H, *J* = 7.2 Hz), 2.18 (t, 1H, *J* = 7.7 Hz), 2.11-1.94 (m, 2H), 1.78-1.48 (m, 6H), 1.33 (s, 3H), 1.25 (s, 3H), 1.19 (t, 3H, *J* = 7.2 Hz), 1.18 (t, 3H, *J* = 7.2 Hz), 1.21-1.15 (m, 1H), 1.07 (d,

3H, *J* = 7.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 175.0 (s), 173.5 (s), 142.5 (s), 119.2 (d), 101.1 (d), 79.5 (d), 63.2 (t), 51.4 (q x 2), 51.3 (d), 49.9 (d), 44.8 (d), 43.4 (d), 43.4 (s), 36.6 (s), 35.7 (t), 34.2 (d), 33.3 (d), 30.6 (q), 25.8 (t), 25.4 (t), 24.9 (t), 23.9 (q), 20.3 (t), 19.4 (q), 15.1 (q), 14.7 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2949, 1739, 1434. **LRMS** (*m/z*, (relative intensity)) 494 (M^+, 50), 479 (100). **HRMS** calcd for $C_{27}H_{42}O_6S$: 494.2702, found: 494.2697. $[\alpha]_D$ +86.7 (c 1.59, $CHCl_3$).

(+)-Diene 60. Sulfur **58** (265.0 mg, 0.536 mmol) was dissolved in a 4:4:1 mixture of AcOEt, MeCN, and water (5.4 mL) and sodium periodate (344.0 mg, 1.61 mmol) was then added all at once. The reaction mixture was stirred at rt for 12 h and was then neutralized with a saturated aqueous sodium thiosulfate solution. The biphasic system was vigorously stirred for 30 min and the phases were separated. The aqueous phase was extracted three times with AcOEt, the organic layers were combined, washed once with saturated aqueous $NaHCO_3$, once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using a 1:99 mixture of MeOH and DCM as eluting solvent to give sulfoxide **63** (237 mg, 87%) as a 1:1 mixture of 2 inseparable isomers. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.78 (d, 1H, *J* = 3.3 Hz), 5.09 (d, 1H, *J* = 2.8 Hz), 4.90 (br s, 1H), 3.82 (d, 1H, *J* = 1.7 Hz), 3.80 (d, 1H, *J* = 2.2 Hz), 3.68 (s, 3H), 3.66 (s, 3H), 3.65 (s, 6H), 3.60-3.41 (m, 4H), 3.40-3.31 (m, 3H), 3.17 (d, 1H, *J* = 2.8 Hz), 2.96-2.53 (m, 10H), 2.26-1.44 (m, 12H), 1.39-1.29 (m, 5H), 1.38 (s, 6H), 1.37 (t, 3H, *J* = 7.4 Hz), 1.33 (s, 3H), 1.31 (t, 3H, *J* = 7.4 Hz), 1.30 (s, 3H), 1.25-1.21 (m, 1H), 1.17 (t, 6H, *J* = 7.2 Hz), 1.08 (t, 3H, *J* = 7.7 Hz), 1.07 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 174.8 (s), 174.3 (s), 173.2 (s), 146.2 (s), 140.5 (s), 121.3 (d) , 118.1 (d), 96.5 (d), 95.9 (d), 72.0 (d), 67.7 (d), 66.8 (s), 64.3 (d), 61.9 (t), 51.6 (q), 51.4 (q), 45.6 (t), 44.3 (d), 43.8 (d), 43.4 (d), 43.3 (d), 43.0 (d), 37.5 (s), 37.1 (s), 34.0 (d), 33.7 (d), 33.5 (q), 33.1 (d), 31.2 (t), 30.6 (q), 25.4 (q), 24.7 (q), 24.3 (t), 24.1 (t), 21.7 (t), 21.5 (t), 21.1 (t), 20.1 (t), 19.9 (q), 19.6 (q), 15.0 (q), 8.5 (q), 7.9 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 2949, 1734, 1439, 1041. **LRMS** (*m/z*, (relative intensity)) 510 (M^+, 5), 465 ($(M\text{-}EtOH)^+$, 15), 432 ($(M\text{-}EtSOH)^+$, 5), 387 (60), 283 (100). **HRMS** calcd for $C_{27}H_{42}O_7S$: 510.2651, found: 510.2643. $[\alpha]_D$ + 96.8 (c 0.47, $CHCl_3$).

Sulfoxide **63** (195.0 mg, 0.38 mmol) was dissolved in toluene (3.8 mL) and the reaction mixture was heated to reflux temperature and stirred for 12 h. Then the reflux was stopped, *p*-toluenesulfonic acid (80 mg, 0.42 mmol) and EtOH (0.15 mL) were added and the reaction mixture was stirred and extra 12 h at rt. It was then neutralized using a saturated aqueous solution of Na_2CO_3. The aqueous phase was extracted 3 times with Et_2O, the organic layers were combined, washed once with water and once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using a 10:90 mixture of AcOEt and hexanes as eluting solvent to give diene **60** (123 mg, 65%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.11 (d, 1H, *J* = 10.5 Hz), 5.83 (d,

1H, *J* = 4.4 Hz), 5.52 (dd, 1H, *J* = 10.5, 3.3 Hz), 4.81 (t, 1H, *J* = 4.4 Hz), 3.91 (d, 1H, *J* = 3.3 Hz), 3.69 (s, 3H), 3.68 (s, 3H), 3.64-3.51 (m, 1H), 3.40-3.30 (m, 1H), 3.26 (t, 1H, *J* = 3.3 Hz), 3.02 (dd, 1H, *J* = 12.9, 3.3 Hz), 2.19-2.10 (m, 2H), 2.06-1.91 (m, 3H), 1.89-1.75 (m, 2H), 1.60-1.39 (m, 1H), 1.36 (s, 3H), 1.21-1.16 (m, 1H), 1.20 (s, 3H), 1.19 (t, 3H, *J* = 7.2 Hz), 1.00 (d, 3H, *J* = 6.1 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 174.3 (s), 173.0 (s), 145.5 (s), 135.6 (d), 123.4 (d), 117.2 (d), 96.4 (d), 73.1 (d), 62.1 (t), 51.4 (q), 51.2 (q), 44.7 (d), 44.7 (d), 43.5 (d), 40.5 (s), 38.6 (s), 37.6 (d), 33.4 (d), 29.6 (q), 25.6 (t), 24.7 (q), 21.6 (t), 18.3 (q), 15.0 (q). **IR** ($CHCL_3$) ν (cm^{-1}) 2971, 1738, 755. **LRMS** (*m/z*, (relative intensity)) 432 (M^+, 20), 386 (48), 360 (90), 327 (74), 283 (78), 267 (85), 223 (100). **HRMS** calcd for $C_{25}H_{36}O_6$: 432.2512, found: 432.2503. $[\alpha]_D$ + 4.5 (c 1.4, $CHCl_3$).

(+)-Triene 64. Simple reflux in toluene of the sulfoxide **63** (without subsequent treatment with acid and EtOH) gives primarily triene **64**, which could be isolated and was characterized. The X-ray diffraction analysis data is available in this SI. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 6.45 (dd, 1H, *J* = 6.0, 1.7 Hz), 6.22 (d, 1H, *J* = 10.5 Hz), 5.88 (s, 1H), 5.52-5.48 (m, 1H), 4.43 (dd, 1H, *J* = 6.0, 2.2 Hz), 3.88 (d, 1H, *J* = 1.7 Hz), 3.72 (s, 3H), 3.71 (s, 3H), 3.39 (dd, 1H, *J* = 4.4, 1.1 Hz), 3.08 (dd, 1H, *J* = 12.4, 1.7 Hz), 2.28-1.98 (m, 5H), 1.84-1.78 (m, 1H), 1.50-1.36 (m, 1H), 1.46 (s, 3H), 1.25 (s, 3H), 1.02 (d, 3H, *J* = 7.0 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm) 175.1 (s), 172.8 (s), 144.4 (d), 140.7 (s), 136.3 (d), 123.0 (d), 117.2 (d), 104.9 (d), 80.1 (d), 51.6 (q), 51.6 (q), 47.0 (d), 44.5 (s), 42.1 (d), 40.6 (s), 38.1 (d), 36.6 (d), 34.4 (d), 29.8 (q), 26.1 (q), 25.8 (t), 21,4 (t), 16.8 (q). **IR** ($CHCl_3$) ν (cm^{-1}) 3020, 2951, 2918, 1736. **LRMS** (*m/z*, (relative intensity)) 386 (M^+, 5), 354 (100), 326 (25), 267 (80), 223 (55). **HRMS** calcd for $C_{23}H_{30}O_5$: 386.2093, found: 386.2084. $[\alpha]_D$ + 24.6 (c 0.41, $CHCl_3$).

ACKNOWLEDGEMENTS

We thank the University of Sherbrooke and the Natural Sciences and Engineering Research Council of Canada for financial support.

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