Synthetic Approaches to Rapamycin: Synthesis of a C10–C26 Fragment via a One-Pot Julia Olefination Reaction

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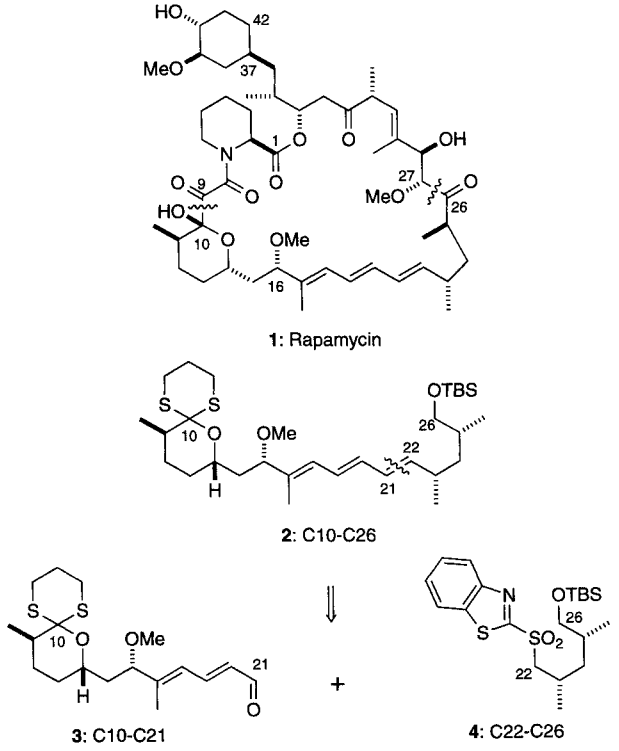
Received 4 October 1995

Keys steps in a synthesis of the C10–C26 fragment of the immunosuppressant Rapamycin include (a) the use of a metallated benzothiazolyl sulfone in a one-pot Julia olefination to create the C21–C22 alkene stereoselectively and (b) a diastereoselective acid-catalysed cyclisation of a hydroxyl function onto a ketenedithioacetal (1,4-asymmetric induction) in order to create the oxane ring and fix the stereochemistry at C11.

Rapamycin (**1**) is a metabolite of *Streptomyces hygroscopicus* with potent cytotoxic and immunosuppressive activity.[1,2] Four total syntheses of Rapamycin have appeared[3-6] as well as syntheses of various fragments.[7-24] The conjugated triene unit was the subject of special address by all four groups who have completed total syntheses of Rapamycin (**1**). The Nicolaou group[4] accomplished the triple feat of generating the C18–C19 and C20–C21 bonds whilst creating the macrocycle simultaneously using Pd(0)-catalysed cross coupling chemistry. Stille coupling was also a feature of the Smith total synthesis[6] whereby the C20–C21 was generated as part of a macrocyclisation reaction. One of the approaches of Danishefsky and co-workers[3] used a Julia olefination to create the central C19–C20 alkene of the triene unit whereas Schreiber's group created the C21–C22 bond using a Horner–Wittig reaction.[5] We now record a synthesis of the C10–C26 fragment **2** (Scheme 1) which harbours the conjugated triene unit of Rapamycin. The fulcrum of our synthetic plan was the use of a new one-pot variant of the Julia olefin synthesis involving union of benzothiazolyl sulfone **4** and aldehyde **3** in order to create the C21–C22 alkene stereoselectively.

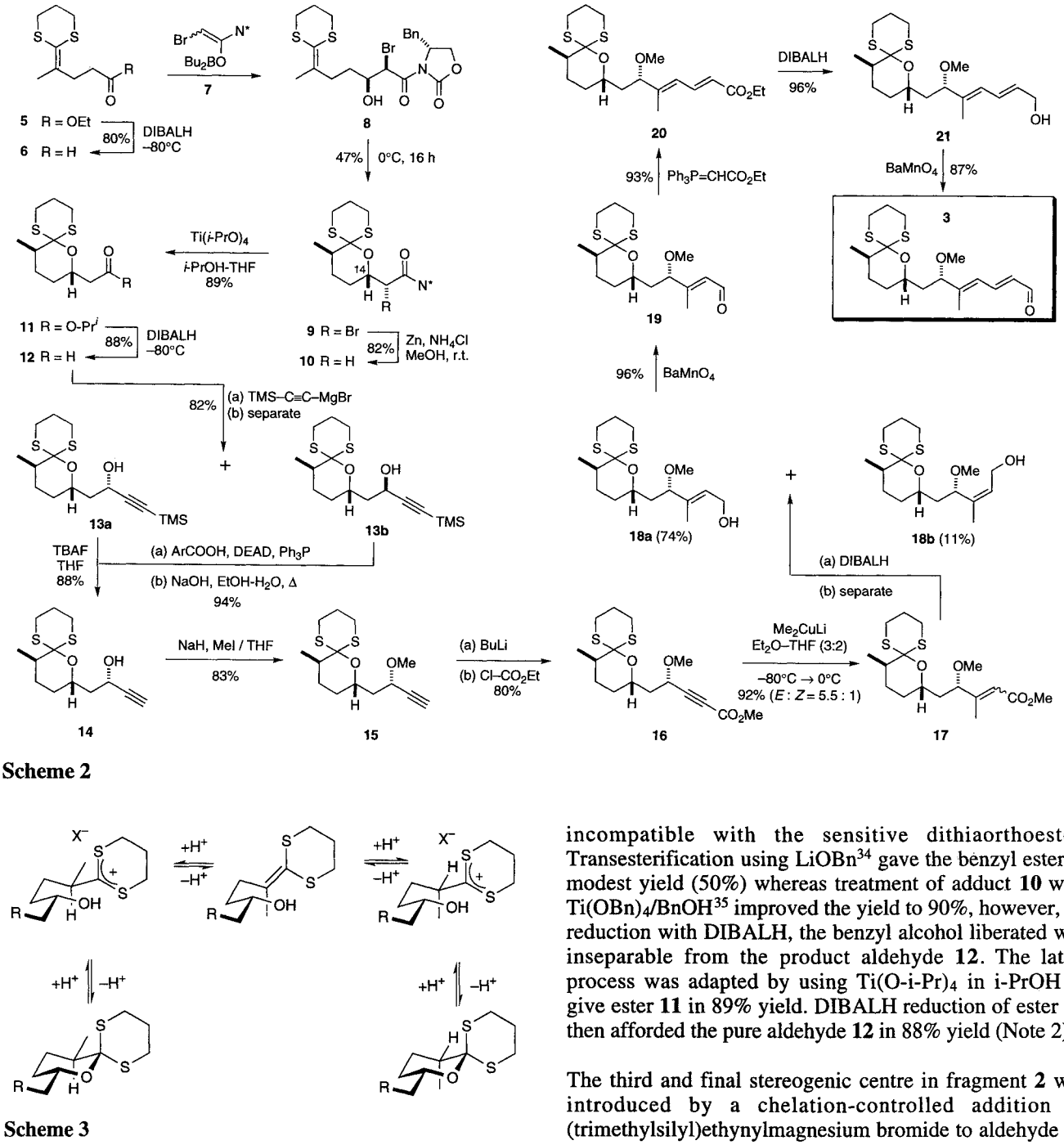


Scheme 1

Synthesis of C10–C21 Fragment 3

Formation of the ketenedithioacetal **5** (Scheme 2) from ethyl levulinate was achieved cleanly by employing the procedure of Comins.[25] Reduction of the ester functionality to aldehyde **6** with DIBALH was capricious owing to over-reduction with yields of aldehyde **6** ranging from 50% on large scale to 80% on small scale. Consistently good yields (80% on 0.1 mol scale) were obtained using the workup procedure of Baeckstrom:[26] hence, the cold reaction mixture was transferred via cannula to a rapidly stirred slurry of ice, water and sodium potassium tartrate. These conditions ensure rapid hydrolysis of intermediate diisobutylaluminum alkoxides which themselves are reducing agents causing over-reduction during aqueous workup.

The primary stereogenic centre at C14 (Rapamycin numbering) of lactone derivative **9** was introduced using a diasteroselective aldol reaction between aldehyde **6** and the dibutylboron enolate derivative **7** of (*R*) -4-benzyl-3-(bromoacetyl)oxazolidinone.[27,28] Although the boron enolates were generated with poor stereocontrol (*Z*:*E* = 3:1), the faster reaction of the (*Z*)-enolate resulted in a d.r. >10:1 in favour of adduct **8**. After aqueous workup and chromatography, the aldol adduct **8** cyclised on storage at 0°C overnight to give the spirocyclic dithiaorthoester **9** in 47% overall yield from aldehyde **6**. The acid-catalysed cyclisation of hydroxyl-substituted ketenedithioacetals was first reported by Corey[29] as a method for lactone protection, but it was Suzuki and co-workers[30] who later observed and exploited the high 1,4-asymmetric induction of the cyclisation leading to a powerful and highly diastereoselective method for preparing 3,6-disubstituted lactones. In the present case, the diastereoselection was excellent (d.r. 19:1) with the acid-catalyst presumably coming from decomposition of the rather labile α-bromoamide **8** on storage (Note 1). Suzuki postulates[30] that the ratio of products obtained reflects their stability in accord with a thermodynamically controlled process summarised in Scheme 3. The mechanism gains credence from Okuyama's[31,32] observation that acid-catalysed hydrolysis of 2-methylene-1,3-dithiolane involves initial rapid and reversible protonation of the alkene to form a sulfur-stabilised carbocation which can then be trapped by suitable nucleophiles.



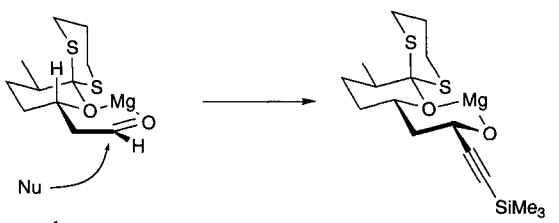
Scheme 2

Scheme 3

The bromine and oxazolidinone groups, having discharged their stereocontrol function, were next removed. Reductive cleavage of the bromine atom in **9** was attempted by a number of methods, ($NaBH_3CN$, Mg/MeOH, and Bu_3SnH) but powdered zinc and ammonium chloride in methanol at r.t. with continuous sonication proved best. The adduct **10** was then recrystallised from acetone–diethyl ether to remove the minor diastereoisomers present.

Removal of the oxazolidinone auxiliary, whilst retaining the benefits of dithiaorthoester protection of the lactone, proved more troublesome. The conditions used to make the Weinreb amide [MeNH(OMe)/$AlMe_3$][33] or the carboxylic acid ($LiOOH/H_2O$) derivative were incompatible with the sensitive dithiaorthoester. Transesterification using LiOBn[34] gave the benzyl ester in modest yield (50%) whereas treatment of adduct **10** with $Ti(OBn)_4$/BnOH[35] improved the yield to 90%, however, on reduction with DIBALH, the benzyl alcohol liberated was inseparable from the product aldehyde **12**. The latter process was adapted by using $Ti(O\text{-}i\text{-}Pr)_4$ in i-PrOH to give ester **11** in 89% yield. DIBALH reduction of ester **11** then afforded the pure aldehyde **12** in 88% yield (Note 2).

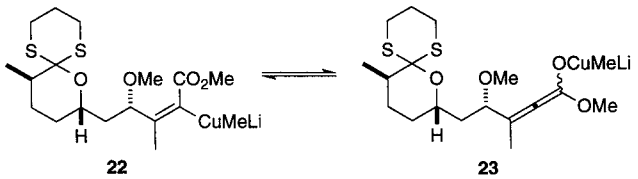
The third and final stereogenic centre in fragment **2** was introduced by a chelation-controlled addition of (trimethylsilyl)ethynylmagnesium bromide to aldehyde **12** in the sense depicted in Scheme 4. The poor diastereocontrol [2.5:1 in favour of the desired (*S*)-propargylic alcohol **13a**] was compensated in part by the easy chromatographic separation of the adducts (ΔR_f = 0.2). Furthermore, the minor (*R*)-propargylic alcohol **13b** underwent efficient Mitsunobu[36] inversion followed by



Scheme 4

treatment with aqueous NaOH which simultaneously hydrolysed the ester and the TMS group yielding propargylic alcohol **14** (94% for two steps). Alcohol **14** was also generated from (*S*)-propargylic alcohol **13a** using TBAF. *O*-Methylation with sodium hydride and methyl iodide gave crystalline propargylic ether **15** whose relative stereochemistry was confirmed by X-ray analysis.

With all three stereogenic centres of fragment **3** now in place, it only remained to fashion a trisubstituted alkene from the alkyne as a prelude to chain extension. Carbomethoxylation of alkyne **15** followed by conjugate addition of Me_2CuLi gave the α,β-unsaturated ester **17** as an inseparable mixture of double bond isomers (*E*:*Z* = 5.5:1). The formation of the desired (*E*)-isomer results from isomerisation of the kinetic *cis*-adduct **22** via the corresponding allenolate **23** to the *trans*-adduct **24** which benefits from coordination to the neighbouring methoxy group as shown in Scheme 5 (Notes 3 and 4).

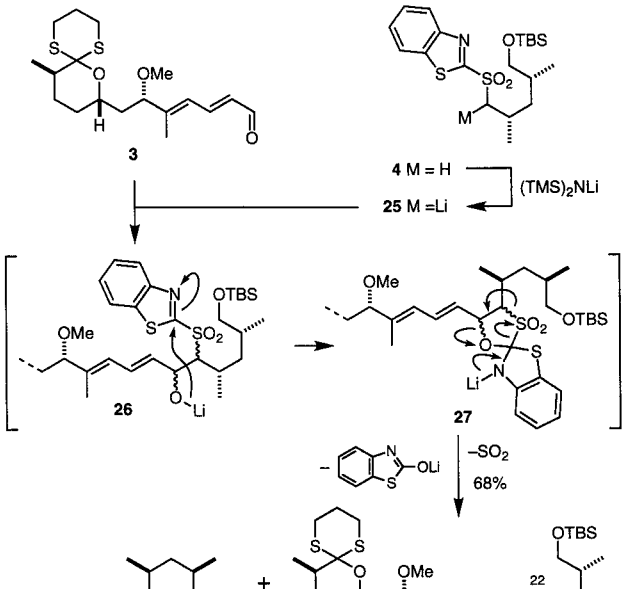


Scheme 5

After reduction of the ester function, the allylic alcohols were easily separable by column chromatography and the major (*E*)-isomer **18a** was oxidised to the aldehyde **19** using barium manganate[37,38] without detriment to the sulfur atoms.[39] The remaining two carbon atoms were introduced by reaction of the aldehyde **19** with (ethoxycarbonylmethylene)triphenylphosphorane to give the dienoate **20** as a mixture of isomers (*E*:*Z* = 95:5). After chromatographic separation, the ester function in the (*E*,*E*)-isomer was first reduced to an allylic alcohol with DIBALH and finally oxidation, again with barium manganate, returned the desired dienal **3** in 84% yield for the two steps.

Forging the C21–C22 Bond — a New Fragment Linkage Reaction

Sylvestre Julia and his co-workers[40,41] recently reported a remarkable one-pot olefination reaction which we have used for the synthesis of the triene in fragment **2**. The sequence entailed the addition of lithium hexamethyldisilazide to a mixture of a benzothiazolyl sulfone **4** and aldehyde **3**. Under the reaction conditions, the sulfone was selectively metallated and the resultant anion **25** underwent reversible addition to the aldehyde. The adduct **26** then cyclised by addition of the metal alkoxide to the C=N bond of the benzothiazole unit leading to a spirocycle **27** whose fragmentation was accompanied by loss of SO_2 and the lithium derivative of benzothiazolone to give the alkenes **2** and **28** (*E*:*Z* = 19:1) in 68% yield (Notes 5 and 6).



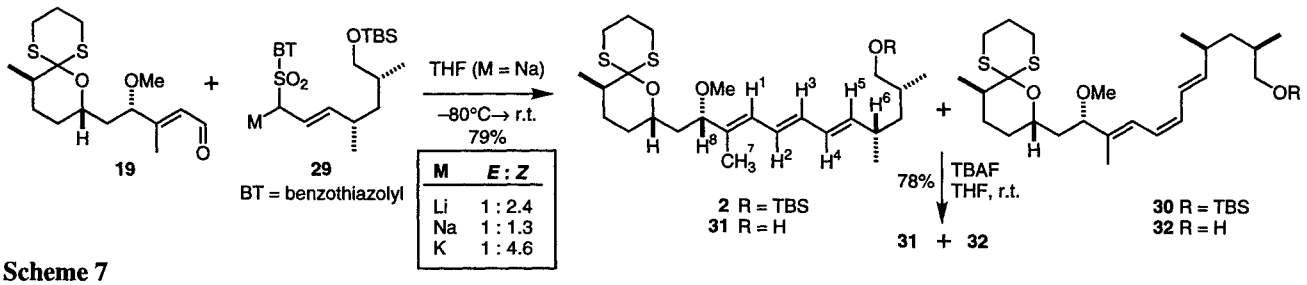
Scheme 6

Further studies revealed that the favourable *trans*-selectivity was substrate dependent. Thus, attempts to generate triene **2** by the union of aldehyde **19** (Scheme 7) and sulfone **29** under the same conditions used to conjoin **3** and **4** gave an inseparable mixture of **2** and the (*Z*)-isomer **30** in 75% yield in which now the (*Z*)-isomer predominated (**2**:**30** = 1:2.4). Use of sodium or potassium hexamethyldisilazide as base also gave the undesired (*Z*)-isomer preferentially. Deprotection of the tert-butyldimethylsilyl ethers gave a separable mixture of trienes **31** and **32** for which a complete NMR assignment was obtained (Table, Note 7).

In conclusion, we have shown that a single stereogenic centre at C14 created by an asymmetric aldol reaction enabled diastereoselective construction of the stereogenic centres at C11 (via ketenedithioacetal cyclisation) and C16 (via chelation-controlled addition). We have also shown that the stereochemistry of Julia's one-pot olefin synthesis (Note 8) can be tuned by judicious choice of base and substrate.

Notes

(1) In the absence of adventitious acid, the cyclisation can be induced by dissolving the ketenedithioacetal in cold (0°C) 0.03 M HCl(g) in CH_2Cl_2. We noted that the stereoselectivity increases with decreasing acid concentration but the yield also decreases. Under the conditions described above, the cyclisation is complete in 5 min.

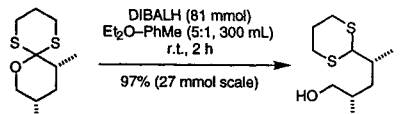


Scheme 7

Table. Chemical Shifts (δ) and Coupling Constants (Hz) for the Triene Segment of Compounds **2, 31,** and **32**

	H^1	H^2	H^3	H^4	H^5	H^6	H^7	H^8	$J_{1,7}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
2	6.14	6.41	6.23	6.16	5.55	2.37–2.18	1.69	3.75	1.1	11.1	14.1	11.2	14.7	8.6
31	6.17	6.42	6.25	6.13	5.49	2.36–2.17	1.71	3.77	1.2	11.1	14.9	10.7	15.1	8.5
32	6.77	6.21	6.10	6.72	5.52	2.37–2.18	1.70	3.82	1.4	11.1	10.9	10.8	15.0	8.5

(2) At higher temperatures, DIBALH can cause reductive cleavage of the dithiaorthoester as shown in the following example:



(3) The stereochemistry of the isomeric esters **17** is evident from the ^1H NMR spectrum of the mixture. The resonance of the methyl group in the (*E*)-isomer appeared at $\delta = 2.10$ whereas the corresponding signal in the (*Z*)-isomer appeared at $\delta = 1.88$.[42]

(4) Acetylenic esters are known to react with lithium dialkylcuprates at –78°C by a carbocupration mechanism leading to the *cis*-adduct **22** as the kinetic product. The isomerisation via the allenolate **23** requires higher temperatures (0°C).

(5) The mechanism we have outlined here is but one of a complex manifold of possibilities. For a detailed discussion of the stereochemistry and mechanism, see the papers of Julia and co-workers.[40,41]

(6) The yield and stereochemistry of the olefination was strongly dependent on the base used. With sodium hexamethyldisilazide, a 21% yield of trienes **2** and **28** was obtained (*E*:*Z* = 3.3:1).

(7) ^1H–^1H COSY spectroscopy was used to assign the NMR signals in **2, 31** and **32** and the assignments were confirmed by computer simulation using the gNMR program®.

(8) The present one-pot olefination reaction developed by Sylvestre Julia is not to be confused with its now classical predecessor devised by Marc Julia.[43]

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry nitrogen. Tetrahydrofuran was freshly distilled from sodium and benzophenone. Et_2O, benzene and toluene were stored over sodium wire prior to use. MeOH and i-PrOH were distilled from magnesium methoxide and magnesium isopropoxide respectively. CH_2Cl_2 and diethyl chlorophosphate were distilled from calcium hydride. Copper(I) iodide was purified by continuous extraction with refluxing THF. Molecular sieves were activated by heating in a flask with a bunsen burner until water ceased to be evolved. MeI was distilled from calcium hydride and stored over copper wire and 4Å molecular sieves. Dibutylboron triflate was prepared and distilled by the method of Mukaiyama.[44] Grignard reagent concentrations were determined by iodometric titration; alkyllithium concentrations were determined by titration against 1,3-diphenylacetone-*p*-toluenesulfonylhydrazone. All other reagents and solvents were used as supplied. Quantitative chromatographic separation was performed by column chromatography on Sorbsil C60 silica. The symbol Ø refers to the diameter of the column throughout the experimental.

IR spectra were recorded using a Perkin-Elmer 1600 series FT-IR spectrophotometer using a thin film supported on NaCl plates or KBr discs where stated. Details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: s = strong, m = medium, w = weak or br = broad. ^1H and ^{13}C NMR spectra were recorded in Fourier Transform mode at the field strength specified. All spectra were obtained in $CDCl_3$ solution in 5 mm diameter tubes unless otherwise specified, and the chemical shift in ppm is quoted relative to the residual signals of $CHCl_3$ ($\delta_H = 7.27$ or $\delta_C = 77.2$) as the internal standard. Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. Numbers in parenthesis following the chemical shift in the ^{13}C NMR spectra refer to the number of protons attached to that carbon as revealed by the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Low (LRMS) and high (HRMS) resolution mass spectra were run on a VG 70-250-SE spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%). Mass spectra were recorded on samples judged to be ≥95% pure by ^1H and ^{13}C NMR spectroscopy unless otherwise stated.

Ethyl 4-(1,3-Dithian-2-ylidene)pentanoate (5):

Diisopropylamine (30.4 g, 0.30 mol) in THF (360 mL) was cooled, with mechanical stirring, to –80°C. BuLi (115 mL of 2.54 M, 0.30 mol) was added over 10 min and the solution stirred for 30 min at –80°C. Freshly sublimed 1,3-dithiane (18.1 g, 0.150 mol) in THF (50 mL) was then added over 5 min, and the solution stirred at –80°C for 30 min before the addition of diethyl chlorophosphate (26.1 g, 0.150 mol) in THF (50 mL) over 1 min. The internal temperature rose to –40°C and the reaction mixture stirred at this temperature for 1 h. Freshly distilled ethyl levulinate (21.7 g, 0.150 mol) in THF (50 mL) was then added as a single portion. The cooling bath was then removed and the solution allowed to warm to r.t. over 1.5 h. The solution was then poured into sat. aq NH_4Cl (750 mL) and the aqueous phase extracted with Et_2O (3 x 400 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and distilled through a short path distillation apparatus (bp 145–155°C, 0.5 mbar) to give ester **5** (30.69 g, 0.125 mol, 83%) as a yellow oil.

IR (film): ν = 2979 (s), 2909 (s), 1732 (s), 1590 (w) cm^{-1}.

^1H NMR (270 MHz): δ = 4.13 (2H, q, J = 7.1Hz), 2.86 (4H, m), 2.69–2.63 (2H, m), 2.40–2.34 (2H, m), 2.15–2.06 (2H, m), 1.90 (3H, s), 1.25 (3H, t, J = 7.1 Hz).

^{13}C NMR (67.5 MHz): δ = 173.0 (0), 137.5 (0), 121.3 (0), 60.5 (2), 32.5 (2), 31.2 (2), 30.2 (2), 30.0 (2), 24.8(2), 20.0 (3), 14.3 (3).

LRMS (EI mode, 70eV): m/z = 246 ($M^{+\bullet}$, 46%), 201 (5), 159 (100), 85 (16).

4-(1,3-Dithian-2-ylidene)pentanal (6):
Ester **5** (30.69 g, 0.125 mol) in CH_2Cl_2 (500 mL) was cooled with mechanical stirring to –80°C and treated with DIBALH (102 mL of 1.5 M in toluene, 0.153 mol) over 20 min. The reaction mixture was stirred at this temperature for 30 min before being transferred *via* cannula to a rapidly stirring slurry of ice-water (500 mL) and sodium potassium tartrate (120 g). Rapid stirring was continued for 10 h before the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 400 mL). The combined organic phases were dried (Na_2SO_4), filtered, evaporated and distilled through a short path distillation apparatus (bp 130–134°C, 0.2 mbar) to give aldehyde **6** (20.20g, 0.10 mol, 80%) as a colourless oil.

IR (film): ν = 2909 (s), 2826 (m), 2721 (m), 1721 (s), 1682 (w), 1590 (w) cm^{-1}.

^1H NMR (270 MHz): δ = 9.74 (1H, t, J = 1.7 Hz), 2.82 (4H, m), 2.66–2.54 (2H, m), 2.51–2.44 (2H, m), 2.11–2.02 (2H, m), 1.86 (3H, s).

^{13}C NMR (67.5 MHz): δ = 201.9 (1), 137.2 (0), 121.4 (0), 42.0 (2), 30.1 (2), 30.0 (2), 28.5 (2), 24.7 (2), 20.2 (3).

LRMS (EI mode, 70 eV): m/z = 202 ($M^{+\bullet}$, 35%), 174 (10), 159 (100), 146 (54), 127 (12), 85 (23).

(8*S*,11*R*)-11-Methyl-8-{(1*R*)-1-bromo-2-oxo-2-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]ethyl}-7-oxa-1,5-dithiaspiro-[5.5]undecane (9):
(*R*)-4-Benzyl-3-(bromoacetyl)oxazolidinone (18.73 g, 0.063 mol) in Et_2O (400 mL) was cooled to –80°C with mechanical stirring and treated with Et_3N (8.90 g, 0.088 mol) over 1 min followed by dibutylboron triflate (18.97 g, 0.069 mol) over 1 min. The cooling bath was removed and the reaction mixture allowed to warm to r.t. and stirred for 1.5 h. The solution was then cooled to –80°C before aldehyde **6** (12.70 g, 0.063 mol) in Et_2O (30 mL) was added over 5 min. The solution was then allowed to warm to 0°C over 1.5 h and stirred at 0°C for 30 min before being poured into saturated aq $NaHCO_3$ (200 mL) and extracted with Et_2O (3 x 400 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude oil chromatographed (15 cm Ø x 20 cm, 25–30% EtOAc in hexanes) to give **8** as a foam which cyclised on storage at –10°C. The product was then triturated with Et_2O to give **9** (14.70 g, 0.029 mol, 47%) as an off-white powder: mp 124–127°C; $[\alpha]_D$ = +111.3° (c = 0.48, $CHCl_3$).

IR ($CHCl_3$): ν = 3020 (m), 2981 (m), 2932 (m), 1785 (s), 1700 (s), 1605 (w), 1455 (m), 1384 (s), 1306 (m), 1226 (s), 1105 (m), 1066 (m), 1005 (m), 983 (m), 956 (m), 670 (w), 626 (w) cm^{-1}.

^1H NMR (270 MHz): δ = 7.40–7.23 (5H, m), 5.85 (1H, d, J = 9.1 Hz), 4.76–4.67 (1H, m), 4.50 (1H, ddd, J = 11.4, 9.1, 2.3 Hz), 4.27 (1H, dd, J = 9.6, 0.6 Hz), 4.23 (1H, dd, J = 9.6, 4.1 Hz), 3.66 (1H, td, J = 13.7, 2.5 Hz), 3.42–3.28 (2H, m, overlapping signals), 2.82 (1H, dd, J = 13.5, 9.6 Hz), 2.70–2.55 (2H, m), 2.22–1.30 (7H, m), 1.17 (3H, d, J = 6.6 Hz).

^{13}C NMR (67.5 MHz): δ = 167.4 (0), 152.4 (0), 134.8 (0), 129.5 (1), 129.1 (1), 127.5 (1), 94.0 (0), 71.8 (1), 66.3 (2), 55.4 (1), 46.2 (1), 41.7 (1), 37.0 (2), 28.4 (2), 27.2 (2), 26.5 (2), 25.7 (2), 24.8 (2), 18.2 (3).

LRMS (CI mode, NH_3): m/z = 501 (M^+, 1%), 419 (20), 314 (32), 286 (23), 230 (21), 178 (93), 137 (60), 106 (100), 91 (96), 81 (86), 41 (98).

Anal. (Calcd. for $C_{21}H_{26}BrNO_4S_2$, M = 501): C, 50.40; H, 5.24; N, 2.80; S, 12.81. Found: C, 50.46; H, 5.12; N, 2.71; S, 12.68.

(8*S*,11*R*)-11-Methyl-8-{2-oxo-2-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]ethyl}-7-oxa-1,5-dithiaspiro[5.5]undecane (10):
The α-bromo carbonyl compound **9** (14.60 g, 0.029 mol), zinc dust (18.69 g, 0.29 mol), NH_4Cl (6.98 g, 0.13 mol) and MeOH (700 mL) were sonicated in an ultrasonic cleaning bath for 1 h. The solution was then concentrated in vacuo and the residue dissolved in CH_2Cl_2 (100 mL). The resulting suspension was filtered through a pad of Celite and the residue washed with CH_2Cl_2 (3 x 100 mL). The resulting organic solution was evaporated and triturated with Et_2O to give **10** (11.14 g, 0.026 mol, 91%) as a white powder which was recrystallised from acetone/Et_2O to give pure **10** (10.10 g, 0.024 mol, 82%) as a white crystalline solid: mp 148-150°C; $[\alpha]_D$ = +56.5° (c = 0.69, $CHCl_3$).

IR ($CHCl_3$): ν = 3020 (m), 2981 (m), 2933 (m), 1783 (s), 1703 (s), 1604 (w), 1454 (m), 1388 (s), 1352 (m), 1300 (m), 1224 (s), 1100 (w), 1060 (m), 1002 (m), 986 (m), 908 (w) cm^{-1}.

^1H NMR (360 MHz): δ = 7.40–7.22 (5H, m), 4.71 (1H, m), 4.63–4.52 (1H, m), 4.23 (1H, dd, J = 9.3, 0.5 Hz), 4.17 (1H, dd, J = 16.8, 9.3 Hz), 3.47 (1H, dd, J = 17.0, 8.2 Hz), 3.31 (1H, dd, J = 13.2, 3.3 Hz), 3.53–3.35 (2H, m), 3.02 (1H, dd, J = 17.0, 4.3 Hz), 2.79 (1H, dd, J = 13.3, 9.6 Hz), 2.66–2.56 (2H, m), 2.11–1.51 (7H, m), 1.14 (3H, d, J = 6.6 Hz).

^{13}C NMR (90 MHz): δ = 170.6 (0), 153.4 (0), 135.2 (0), 129.5 (1), 129.1 (1), 127.5 (1), 93.6 (0), 68.2 (1), 66.2 (2), 55.1(1), 41.8 (1), 41.7 (2), 38.0 (2), 31.2 (2), 27.7 (2), 26.7 (2), 25.8 (2), 24.7 (2), 18.4 (3).

LRMS (EI mode, 70 eV): m/z = 421 ($M^{+\bullet}$, 76%), 287 (93), 230 (86), 178 (48), 111 (100), 41 (65).

Anal. (Calcd. for $C_{21}H_{27}NO_4S_2$, M = 501): C, 59.53; H, 6.46; N, 3.32; S, 15.21. Found: C, 59.68; H, 6.47; N, 3.28; S, 15.09.

(8*S*,11*R*)-8-(Isopropoxycarbonylmethyl)-11-methyl-7-oxa-1,5-dithiaspiro[5.5]undecane (11):
Oxazolidinone **10** (10.0 g, 0.024 mol) in THF (80 mL) at r.t. was treated sequentially with i-PrOH (72 g, 1.2 mol) and titanium(IV) isopropoxide (20.4 g, 0.072 mol) and the solution refluxed for 24 h. After cooling the reaction mixture was concentrated in vacuo. The crude oil was diluted with CH_2Cl_2 (200 mL) and poured into aq sodium potassium tartrate (60 g in 400 mL) and the two-phase mixture stirred rapidly for 30 min. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were dried (Na_2SO_4), filtered, evaporated and the crude product chromatographed (7 cm Ø x 15 cm, 20% ether in hexanes) to give the isopropyl ester **11** (6.5 g, 0.021 mol, 89%) as a colourless oil: $[\alpha]_D$ = +124.3° (c = 0.37, $CHCl_3$).

IR (film): ν = 2976 (m), 2929 (s), 1731 (s), 1454 (w), 1383 (w), 1287 (m), 1108 (m), 1002 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 5.03 (1H, septet, J = 6.3 Hz), 4.43 (1H, dddd, J = 11.4, 9.3, 3.6, 2.3 Hz), 3.42 (1H, ddd, J = 13.9, 12.8, 2.9 Hz), 3.24 (1H, ddd, J = 14.1, 12.7, 2.9 Hz), 2.62 (1H, dd, J = 15.5, 9.3 Hz), 2.66–2.52 (2H, m), 2.43 (1H, dd, J = 15.5, 3.6 Hz), 2.12–1.30 (7H, m), 1.26 (3H, d, J = 6.3 Hz), 1.25 (3H, d, J = 6.3 Hz), 1.12 (3H, d, J = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 171.0 (0), 93.2 (0), 69.1 (1), 67.9 (1), 41.7 (1), 41.3 (2), 31.2 (2), 27.6 (2), 26.6 (2), 25.7 (2), 24.6 (2), 22.0 (3), 21.9 (3), 18.4 (3).

LRMS (CI mode, NH_3): *m/z* = 304 [$(M+NH_4)^+$, 3%], [$(M+H)^+$, 100], 199 (6), 106 (5), 35 (35).

HRMS (CI mode, NH_3): Found $(M+1)^+$, 305.1245. $C_{14}H_{24}O_3S_2$+H requires 305.1242.

(8*S*,11*R*)-11-Methyl-8-(2-oxoethyl)-7-oxa-1,5-dithiaspiro[5.5]-undecane (12):

Ester **11** (6.35 g, 0.021 mol) in CH_2Cl_2 (200 mL) was cooled to –80°C and treated with DIBALH (15.3 mL of 1.5 M solution in toluene, 0.023 mol) over 10 min. The solution was stirred at –80°C for 30 min before being transferred via cannula to a rapidly mechanically stirred slurry of sodium potassium tartrate (14.5 g, 0.069 mol) in ice-water (400 mL). Rapid stirring was continued for 4 h. The organic phase was then separated and the aqueous phase extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was chromatographed (7 cm Ø x 10 cm, 25% Et_2O in hexanes) to give aldehyde **12** (4.57 g, 0.019 mol, 88%) as a clear colourless oil: $[\alpha]_D$= +112.1° (*c* = 1.16, $CHCl_3$).

IR (film): ν = 2929 (s), 2828 (w), 1726 (s), 1453 (m), 1433 (m), 1380 (m), 1278 (m), 1067 (m), 1002 (m), 968 (m), 907 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 9.88 (1H, dd, *J* = 2.3, 1.5 Hz), 4.60–4.45 (1H, m), 3.37 (1H, ddd, *J* = 13.5, 12.7, 2.5, Hz), 3.07 (1H, ddd, *J* = 13.7, 13.0, 2.3 Hz), 2.83 (1H, ddd, *J* = 16.6, 9.1, 2.3 Hz), 2.63 (1H, dt, *J* = 13.7, 3.8 Hz), 2.52 (1H, ddd, *J* = 16.6, 3.7, 1.6 Hz), 1.98–1.44 (7H, m), 1.13 (3H, d, *J* = 6.4 Hz).

^{13}C NMR (67.5 MHz): δ = 200.8 (1), 93.6 (0), 67.6 (1), 49.5 (2), 41.8 (1), 31.5 (2), 27.7 (2), 26.7 (2), 25.7 (2), 25.1 (2), 18.5 (3).

LRMS (CI mode, NH_3): *m/z* = 246 [$(M+H)^+$, 100%], 218 (4), 35 (38).

HRMS (CI mode, NH_3): Found $(M+1)^+$, 247.0824. $C_{11}H_{18}O_2S_2$+H requires 247.0827.

Addition of Trimethysilylethynylmagnesium Bromide to Aldehyde 12:

Trimethylsilylacetylene (2.51 g, 0.026 mol) in THF (40 mL) was cooled to –80°C and subsequently treated with MeMgBr (8.0 mL of 3.0 M solution in Et_2O, 0.024 mol) over 2 min. The cooling bath was then removed and the solution allowed to warm to r.t. and then heated to reflux for 2 h before cooling to r.t. In a separate flask aldehyde **12** (4.20 g, 0.0171 mol) in THF (80 mL) was cooled to –80°C under N_2 with magnetic stirring and treated with $Me_3SiC{\equiv}CMgBr$ (40 mL of the solution prepared above). The solution was stirred at –80°C for 30 min and then the cooling bath removed and the solution allowed to warm to –10°C before being quenched by the addition of sat. aq NH_4Cl (100 mL). The aqueous phase was separated and extracted with Et_2O (3 x 150 mL), and the combined organic phases dried ($MgSO_4$), filtered, evaporated and chromatographed (7 cm Ø x 10 cm, 10–25% Et_2O in hexanes) to give in order of elution:

(8S,11R)-11-Methyl-8-[(2R)-2-hydroxy-4-trimethylsilylbut-3-ynyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (**13b**) (1.38 g, 4.0 mmol, 24%) as a colourless oil: $[\alpha]_D$= +149.4° (*c* = 0.50, $CHCl_3$).

IR (film): ν = 3455 (br m), 2957 (s), 2170 (w), 1454 (w), 1423 (w), 1379 (w), 1249 (m), 1061 (m), 842 (s) cm^{-1}.

^{1}H NMR (300 MHz): δ = 4.68 (1H, td, *J* = 7.2, 3.1 Hz), 4.42 (1H, tt, *J* = 10.6, 2.7 Hz), 3.35 (1H, ddd, *J* = 13.7, 12.5, 2.7 Hz), 3.25 (1H, ddd, *J* = 13.8, 12.5, 2.7 Hz), 3.00 (1H, d, *J* = 7.2 Hz), 2.72–2.50 (2H, m), 2.16–1.40 (9H, m), 1.13 (3H, d, 6.8 Hz), 0.14 (9H, s).

^{13}C NMR (75 MHz): δ = 106.7 (0), 93.6 (0), 89.6 (0), 69.8 (1), 60.5 (1), 42.8 (2), 42.1 (1), 31.7 (2), 27.7 (2), 27.0 (2), 25.6 (2), 25.0 (2), 18.7 (3), 0.0 (3).

LRMS (EI mode, 70 eV): *m/z* = 344 ($M^{+\bullet}$, 25%), 237 (100), 221 (21), 159 (47), 106 (70), 73 (59), 55 (33), 41 (45).

(8S,11R)-11-Methyl-8-[(2S)-2-hydroxy-4-trimethylsilylbut-3-ynyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (**13a**) (3.37 g, 9.8 mmol, 58%) as a colourless oil: $[\alpha]_D$= +296.7° (*c* = 0.87, $CHCl_3$).

IR (film): ν = 3604 (w), 3481 (br w), 2962 (s), 2933 (s), 2173 (w), 1455 (w), 1426 (w), 1381 (w), 1252 (s), 1050 (m), 999 (m), 908 (m), 846 (m).

^{1}H NMR (270 MHz): δ = 4.79 (1H, dd, *J* = 7.9, 6.6 Hz), 4.21 (1H, ddt, *J* = 11.2, 10.3, 2.7 Hz), 3.38 (1H, ddd, *J* = 13.7, 12.6, 2.7 Hz), 3.12 (1H, ddd, *J* = 13.9, 12.7, 2.7 Hz), 2.71–2.51 (2H, m), 2.45 (1H, br s), 2.20–1.40 (9H, m), 1.13 (3H, d, *J* = 6.8 Hz), 0.17 (9H, s).

^{13}C NMR (67.5 MHz): δ = 106.2 (0), 93.4 (0), 90.2 (0), 70.7 (1), 61.2 (1), 43.8 (2), 42.0 (1), 31.8 (2), 27.7 (2), 26.8 (2), 25.6 (2), 25.2 (2), 18.6 (3), 0.0 (3).

LRMS (EI mode, 70 eV): *m/z* = 344 ($M^{+\bullet}$, 30%), 237 (100), 221 (26), 159 (39), 106 (59), 73 (52), 41 (35).

(8*S*,11*R*)-11-Methyl-8-[(2*S*)-2-hydroxybut-3-ynyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (14):

Silyl acetylene **13a** (3.162 g, 9.19 mmol) in THF (30 mL) was cooled to 0°C and treated with TBAF (8.8 mL of 1.1 M solution in THF) over 5 min and the solution stirred for 10 min. Silica (20 mL) was then added and the reaction mixture concentrated in vacuo and chromatographed (3cm Ø x 15 cm, 60% Et_2O in hexanes) to give (*S*)-alcohol (3.5.9) (2.19 g, 8.06 mmol, 88%) as a clear colourless oil: $[\alpha]_D$= +168.8° (*c* = 0.75, $CHCl_3$).

IR (film): ν = 3287 (s), 2918 (s), 2112 (w), 1454 (m), 1379 (m), 1277 (m), 1100 (m), 999 (m), 907 (m), 800 (m) cm^{-1}.

^{1}H NMR (300 MHz): δ = 4.69 (1H, ddd, *J* = 8.4, 6.5, 2.1 Hz), 4.17 (1H, tt, *J* = 10.5, 2.7 Hz), 3.35 (1H, td, *J* = 13.4, 2.5 Hz), 3.05 (1H, ddd, *J* = 13.8, 12.7, 2.8 Hz), 2.90 (1H, br s), 2.68–2.51 (2H, m), 2.49 (1H, d, *J* = 2.1 Hz), 2.17–1.35 (9H, m), 1.09 (3H, d, *J* = 6.7 Hz).

^{13}C NMR (75 MHz): δ = 93.5 (0), 84.5 (0), 73.6 (1), 70.6 (1), 60.6 (1), 43.7 (2), 42.0 (1), 31.7 (2), 27.6 (2), 26.8 (2), 25.5 (2), 25.0 (2), 18.6 (3).

LRMS (EI mode, 70 eV): *m/z* = 272 ($M^{+\bullet}$, 22%), 199 (25), 165 (36), 106 (100), 55 (55), 41 (73).

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 272.0905. $C_{13}H_{20}O_2S_2$ requires 272.0890.

Alternatively, a solution of Ph_3P (1.011 g, 3.86 mmol), *p*-nitrobenzoic acid (645 mg, 3.86 mmol) and (*R*)-alcohol **13b** (1.107 g, 3.22 mmol) in THF (30 mL) was treated with DEAD (672 mg, 3.86 mmol) in THF (10 mL). The reaction mixture was allowed to stir at r.t. for 15 h before the addition of silica (20 mL). The reaction mixture was then concentrated in vacuo and chromatographed (7 cm Ø x 15 cm, 20% Et_2O in hexanes) to give the inverted *p*-nitrobenzoate ester (1.407 g, 2.85 mmol, 89%) as a yellow oil: $[\alpha]_D$= +111.3° (*c* = 0.48, $CHCl_3$).

IR (film): ν = 2961 (m), 2934 (m), 1729 (s), 1608 (w), 1531 (s), 1351 (m), 1276 (s), 1101 (m), 848 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 8.33–8.20 (4H, m), 5.95 (1H, dd, *J* = 10.6, 4.8 Hz), 4.29 (1H, tt, *J* = 10.0, 2.7 Hz), 3.50 (1H, td, *J* = 12.9, 2.5 Hz), 3.20 (1H, td, *J* = 12.9, 2.5 Hz), 2.72–2.52 (2H, m), 2.30–1.40 (9H, m), 1.13 (3H, d, *J* = 6.6 Hz), 0.17 (9H, s).

^{13}C NMR (67.5 MHz): δ = 163.5 (0), 150.8 (0), 135.5 (0), 131.1 (1), 123.7 (1), 101.6 (0), 93.3 (0), 92.7 (0), 69.0 (1), 63.8 (1), 42.1 (1), 41.2 (2), 31.8 (2), 27.7 (2), 26.9 (2), 25.7 (2), 25.5 (2), 18.6 (3), –0.1 (3).

LRMS (EI mode, 70 eV): *m/z* = 493 ($M^{+\bullet}$, 70%), 359 (38), 269 (23), 224 (33), 209 (32), 150 (100), 120 (25), 106 (92), 73 (75), 41 (31).

The *p*-nitrobenzoate ester (1.307 g, 2.65 mmol) in EtOH (20 mL) was then treated with NaOH (233 mg, 5.83 mmol) in H_2O (10 mL) over 5 min and the reaction mixture stirred for 1 h at r.t. The reaction mixture was then evaporated and partitioned between CH_2Cl_2 (50 mL) and H_2O (100 mL). The aqueous phase was then extracted with CH_2Cl_2 (4 x 40 mL) and the combined organic phases dried ($MgSO_4$), filtered, evaporated and the crude product chromatographed (3 cm Ø x 5 cm, 50% Et_2O in hexanes) to give (*S*)-alcohol **14** (692 mg, 2.54 mmol, 96%) identical to the sample prepared from **13a**.

(8*S*,11*R*)-11-Methyl-8-[(2*S*)-2-methoxybut-3-ynyl)-7-oxa-1,5-dithiaspiro[5.5]undecane (15):

(*S*)-Alcohol **14** (2.80 g, 10.3 mmol) in THF (40 mL) was treated with NaH (617 mg of 60% dispersion in mineral oil = 370 mg of NaH, 15.4 mmol) as a single portion. The reaction mixture was then gently warmed until effervescence occurred; the solution was then cooled to 0°C and treated with MeI (1.61 g, 11.3 mmol) and the solution allowed to warm to r.t. and stirred for 1.5 h. The reaction mixture was quenched by the dropwise addition of MeOH (5 mL) followed by silica (ca 20 mL). The solution was then concentrated in vacuo and chromatographed (5 cm Ø x 12 cm, 0-10% Et_2O in hexanes) to give a white solid that was crystallised from EtOAc in hexanes to give methyl ether **15** (2.44 g, 8.51 mmol, 83%) as white crystals: mp 91–92°C; $[\alpha]_D$= +172.5° (*c* = 0.48, $CHCl_3$).

IR ($CHCl_3$): ν = 3305 (w), 2932 (m), 2253 (s), 1793 (w), 1709 (w), 1643 (w), 1455 (m), 1381 (m), 1096 (m), 1000 (m), 800 (w) cm^{-1}.

^{1}H NMR (270 MHz): δ = 4.25 (1H, ddd, *J* = 9.9, 5.2, 2.1 Hz), 4.25–4.14 (1H, m), 3.42 (3H, s), 3.50–3.37 (1H, m), 3.12 (1H, ddd, *J* = 13.8, 12.8, 2.8 Hz), 2.70–2.52 (2H, m), 2.49 (1H, d, 2.1 Hz), 2.20–1.40 (9H, m), 1.12 (3H, d, *J* = 6.6 Hz).

^{13}C NMR (67.5 MHz): δ = 93.4 (0), 82.5 (0), 74.9 (1), 69.3 (1), 68.8 (1), 56.7 (3), 42.2 (1), 41.8 (2), 31.8 (2), 27.8 (2), 26.9 (2), 25.8 (2), 25.2 (2), 18.6 (3).

LRMS (CI mode, NH_3): *m/z* = 286 [$(M+H)^+$, 100%], 35 (47).

HRMS (CI mode, NH_3): Found $(M+1)^+$, 287.1139. $C_{14}H_{22}O_2S_2$+H requires 287.1133.

(8*S*,11*R*)-11-Methyl-8-[(2*S*)-2-methoxy-4-methoxycarbonyl-but-3-ynyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (16):

BuLi (5.6 mL, 1.4 M, 7.8 mmol) was added to a solution of **15** (1.706 g, 6.0 mmol) in dry THF (40 mL) at –80°C. After 10 min the cooling bath was removed and replaced by an ice bath. After 1 h at 0°C the reaction mixture was recooled to –80°C and methyl chloroformate (0.85 g, 9.0 mmol) was added dropwise. The temperature was allowed to rise to 0°C over 3 h before quenching by addition of sat. aq NH_4Cl (40 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (2 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by chromatography (hexanes/Et_2O, 5:1 → 1:1) to give **16** (1.646 g, 4.78 mmol, 80%) as a colourless oil: $[\alpha]_D$= +153° (*c* =1.27, $CHCl_3$).

IR (film): ν = 2930 (s), 2234 (s), 1716 (s), 1434 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 4.39 (1H, dd, *J* = 9.5, 5.2 Hz), 4.19 (1H, ill-defined tt, *J* = 10.0, 2.9 Hz), 3.77 (3H, s), 3.44 (3H, s), 3.48–3.36 (1H, m), 3.08 (1H, ddd, *J* = 14.3, 12.8, 2.7 Hz), 2.64 (2H, tm, *J* = 12.4Hz), 2.23–2.06 (2H, m), 2.00–1.24 (7H, m), 1.12 (3H, d, *J* = 6.6 Hz),

^{13}C NMR (67.5 MHz): δ = 153.7 (0), 93.4 (0), 86.0 (0), 78.3 (0), 68.9 (1), 68.6 (1), 57.3 (3), 53.0 (3), 42.1 (1), 41.0 (2), 31.8 (2), 27.7 (2), 27.0 (2), 25.8 (2), 25.1 (2), 18.6 (3).

LRMS (CI mode, NH_3): *m/z* = 345 [$(M+1)^+$, 100%], 271 (6), 239 (7), 185 (6), 159 (5), 127 (8), 106 (12).

(8*S*,11*R*)-11-Methyl-8-[(2*S*)(3*E*,*Z*)-2-methoxy-4-methoxycarbonyl-3-methylbut-3-enyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (17):

To a suspension of freshly purified copper(I) iodide (0.833 g, 3.3 mmol) in THF (22 mL) at 0°C under argon, was added MeLi (3.1 mL, 1.14 M in Et_2O, 3.5 mmol). After stirring for 10 min a clear pale yellow solution was obtained. The solution was then cooled to –80°C and a solution of ester **16** (0.833 g, 2.42 mmol) in Et_2O (33 mL) was added. The reaction mixture was warmed to 0°C during 3 h and then stirred at that temperature for a further 3 h. Sat. aq NH_4Cl (60 mL) was added, the organic layer was separated and the aqueous layer extracted with Et_2O (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by chromatography (hexanes/Et_2O, 10:1 → 1:1) to give **17** as an inseparable mixture (*E*:*Z* = 5.5:1) (0.798 g, 2.22 mmol, 92%). In the following data recorded on the mixture, only the NMR signals for the (*E*)-isomer are given:

IR (film): ν = 2929 (s), 2825 (m), 1715 (s), 1655 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 5.90 (1H, s with fine splitting), 4.05–3.94 (1H, m), 3.73–3.64 (1H, m), 3.71 (3H, s), 3.46 (1H, app dt, *J* = 13.1, 2.9 Hz), 3.21 (3H, s), 2.98 (1H, app dt, *J* = 13.3, 2.7 Hz), 2.69–2.54 (2H, m), 2.10 (3H, d, *J* = 1.3 Hz), 2.18–1.45 (9H, m), 1.12 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 167.0 (0), 158.1 (0), 117.1 (1), 93.6 (0), 83.7 (1), 69.7 (1), 56.9 (3), 51.3 (3), 42.1 (1), 40.4 (2), 31.5 (2), 27.9 (2), 26.8 (2), 25.9 (2), 25.1 (2), 18.5 (3), 14.2 (3).

LRMS (CI mode, NH_3): *m/z* = 360 (M^+, 100%), 329 (8), 254 (6), 159 (13), 143 (95), 125 (15), 106 (42).

HRMS (EI mode, 70 eV): Found: $M^{+\bullet}$, 360.1429. $C_{17}H_{28}O_4S_2$ requires 360.1432.

Reduction of Esters 17:

To a solution of esters **17** (0.788 g, 2.19 mmol) in CH_2Cl_2 (50 mL), at –80°C, was added DIBALH (2.92 mL of 1.5 M in toluene, 4.38 mmol). The solution was stirred at –80°C for 15 min and then treated with sat. potassium sodium tartrate (50 mL). The mixture was stirred at r.t. for 4 h, then the organic layer was separated and the water layer extracted with CH_2Cl_2. The combined organic layers were concentrated and the residue purified by chromatography (Et_2O/hexanes, 33:77 → 100:0) to give in order of elution:

(8S,11R)-11-Methyl-8-[(2S)(3Z)-5-hydroxy-2-methoxy-3-methyl-pent-3-enyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (**18b**) (0.078 g, 0.23 mmol, 11%) as a colourless oil:

IR (film): ν = 3430 (m), 2928 (s), 1451 (s), 1380 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 5.61 (1H, dm, *J* = 6.9 Hz), 4.21 (2H, dm, *J* = 7.0 Hz), 4.15 (1H, dd, *J* = 4.6, 8.5 Hz), 4.08–3.97 (1H, m), 3.47 (1H, ddd, *J* = 2.9, 12.6, 13.7 Hz), 3.19 (3H, s), 2.97 (1H, ddd, *J* = 2.7, 12.3, 14.1 Hz), 2.70-2.53 (2H, m), 2.13–1.35 (10H, m), 1.70 (3H, d, *J* = 1.2 Hz), 1.11 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 138.8 (0), 128.2 (1), 94.0 (0), 75.9 (1), 70.3 (1), 58.3 (2), 56.1 (3), 42.1 (1), 40.2 (2), 31.0 (2), 28.0 (2), 26.7 (2), 25.8 (2), 25.1 (2), 18.4 (3), 18.1 (3).

LRMS (EI mode, 70): *m/z* = 332 ($M^{+\bullet}$, 7%), 203 (6), 159 (11), 115 (18), 114 (100), 113 (5), 106 (41), 98 (7), 97 (7), 95 (8), 83 (39), 81 (9), 73 (14).

HRMS (CI mode, NH_3): Found $(M+1)^+$, 333.1553. $C_{16}H_{28}O_3S_2$+H requires 333.1558.

(8S,11R)-11-Methyl-8-[(2S)(3E)-5-hydroxy-2-methoxy-3-methyl-3-pentenyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (**18a**) (0.540 g, 1.63 mmol, 74%) as a colourless oil: $[\alpha]_D$= +87° (*c* = 1.62, $CHCl_3$).

IR (CCl_4): ν = 3623 (w), 3471 (m), 2931 (s) 1453 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 5.64 (1H, dm, *J* = 5.6 Hz), 4.24 (2H, d, *J* = 6.6 Hz), 4.00–3.89 (1H, m), 3.67 (1H, t, *J* = 6.8 Hz), 3.49 (1H, ddd, *J* = 2.9, 12.7, 13.5 Hz), 3.18 (3H, s), 3.03 (1H, ddd, *J* = 2.7, 12.6, 13.7 Hz), 2.70–2.53 (2H, m), 2.18-1.32 (10H, m), 1.61 (3H, bs), 1.11 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 137.6 (0), 128.1 (1), 93.8 (0), 83.9 (1), 69.9 (1), 59.2 (2), 56.1 (3), 42.2 (1), 40.0 (2), 31.5 (2), 28.0 (2), 26.8 (2), 25.9 (2), 25.2 (2), 18.6 (3), 11.1 (3).

LRMS (CI mode, NH_3): *m/z* = 333 [$(M+1)^+$, 100%], 315 (14), 301 (18), 283 (21), 203 (13), 193 (8), 175 (5), 159 (7), 114 (60), 106 (24).

HRMS (CI mode, NH_3): Found $(M+1)^+$, 333.1566. $C_{16}H_{28}O_3S_2$+H requires 333.1558.

(8S,11R)-11-Methyl-8-[(2S)(3E)-2-methoxy-3-methyl-5-oxopent-3-enyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (19):
To a solution of allylic alcohol **18a** (0.425 g, 1.28 mmol) in CH_2Cl_2 (23 mL) $BaMnO_4$ (2.33 g, 9.1 mmol) was added and the mixture was stirred at r.t. for 12 h. Then the mixture was filtered through Celite and concentrated to give a crude aldehyde (0.407 g, 1.23 mmol, 96%) which was used in the next step without further purification.

IR (film): ν = 2929 (s), 1674 (s), 1453 (m), 1380 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 10.08 (1H, d, *J* = 7.9 Hz), 6.05 (1H, dm, *J* = 7.9 Hz), 4.07-3.96 (1H, m), 3.76 (1H, dd, *J* = 4.4, 7.5 Hz), 3.44 (1H, ddd, *J* = 2.9, 12.6, 13.7 Hz), 3.24 (3H, s), 2.96 (1H, ddd, *J* = 2.7, 12.8, 13.7 Hz), 2.69–2.53 (2H, m), 2.15–1.33 (9H, m), 2.13 (3H, d, *J* =1.4 Hz), 1.12 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 191.3 (1), 161.3 (0), 127.9 (1), 93.9 (0), 83.3 (1), 69.6 (1), 57.1 (3), 42.1 (1), 40.2 (2), 31.4 (2), 27.8 (2), 26.8 (2), 25.8 (2), 25.2 (2), 18.5 (3), 13.0 (3).

LRMS (CI mode, NH_3): *m/z* = 331 [$(M+1)^+$, 100%], 299 (6), 223 (12), 203 (5), 191 (7), 159 (5), 145 (9), 112 (37), 105 (12), 95 (7), 85 (11).

(8S,11R)-11-Methyl-8-[(2S)(3E,5E)-6-ethoxycarbonyl-2-methoxy-3-methylhexa-3,5-dienyl]-7-oxa-1,5-dithiaspiro[5.5]un-decane (20):
To a solution of aldehyde **19** (0.401 g, 1.22 mmol) in CH_2Cl_2 (46 mL) Ph_3P=CHCOOEt (0.898 g, 2.58 mmol) was added and the solution was stirred at r.t. for 48 h. Additional Ph_3P=CHCOOEt (0.400 g, 1.15 mmol) was added and the mixture stirred for a further 24 h. The solvent was removed in vacuo and the residue purified by chromatography (hexanes/Et_2O, 5:1 → 1:1) to give **20** (0.450 g, 1.13 mmol, 93%) as a colourless oil: $[\alpha]_D$= +105° (*c* = 1.64, $CHCl_3$).

IR (film): ν = 2929 (s), 1714 (s), 1640 (s), 1613(s), 1452 (s), 1367 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.59 (1H, dd, *J* = 11.6, 15.1 Hz), 6.19 (1H, d, *J* = 11.6 Hz), 5.87 (1H, d, *J* = 15.3 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 4.01–3.90 (1H, m), 3.74 (1H, dd, *J* = 5.8, 7.5 Hz), 3.48 (1H, ddd, *J* = 2.9, 12.5, 13.5 Hz), 3.19 (3H, s), 3.00 (1H, ddd, *J* = 2.7, 12.6, 13.7 Hz), 2.64–2.55 (2H, m), 2.15–1.37 (7H, m), 1.85 (3H, d, *J* = 1.2 Hz), 1.31 (3H, t, *J* = 7.1 Hz), 1.12 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 167.4 (0), 147.6 (0), 139.8 (1), 125.6 (1), 121.6 (1), 93.8 (0), 83.9 (1), 69.8 (1), 60.5 (2), 56.5 (3), 42.2 (1), 40.4 (2), 31.7 (2), 27.9 (2), 26.8 (2), 25.9 (2), 25.1 (2), 18.6 (3), 14.5 (3), 12.6 (3).

LRMS (CI mode, NH_3): *m/z* = 401 [$(M+1)^+$, 100%], 369 (32), 347 (12), 309 (8), 261 (7), 203 (11) (5), 103 (24), 159 (6), 139 (11), 109 (14), 106 (18), 90 (7).

HRMS (CI mode, NH_3): Found $(M+1)^+$, 401.1812. $C_{20}H_{32}NO_4S_2$+H requires 401.1820.

UV (EtOH): λ_{max} (ε) = 272 nm (25000).

(8S,11R)-11-Methyl-8-[(2S)(3E,5E)-7-hydroxy-2-methoxy-3-methylhepta-3,5-dienyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (21):
To a solution of ester **20** (0.423 g, 1.06 mmol) in CH_2Cl_2 (30 mL), at –80°C, DIBALH (1.55 mL, 1.5 M in toluene, 2.32 mmol) was added and the solution stirred at –80°C for 15 min. Then sat. sodium potassium tartrate (50 mL) was added, the mixture warmed to r.t. and stirred for 2 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were concentrated and the residue purified by chromatography (hexanes/Et_2O, 5:1 → Et_2O) to give the allylic alcohol **21** (0.363 g, 1.01 mmol, 96%) as a colourless oil: $[\alpha]_D$= +103° (*c* = 1.33, $CHCl_3$).

IR (film): ν = 3432 (m), 2928 (s), 1453 (m), 1380 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 6.52 (1H, ddt, *J* = 11.0, 15.3, 1.5 Hz), 6.05 (1H, d, *J* = 11.0 Hz), 5.82 (1H, dt, *J* = 15.3, 5.8 Hz), 4.23 (2H, dd, *J* = 5.8, 1.2 Hz), 3.98–3.87 (1H, m), 3.69 (1H, t, *J* = 7.0 Hz), 3.50 (1H, ddd, *J* = 2.9, 12.6, 13.5 Hz), 3.17 (3H, s), 3.04 (1H, ddd, *J* = 2.7, 12.6, 13.7 Hz), 2.70–2.50 (2H, m), 2.15–1.24 (8H, m), 1.70 (3H, d, *J* = 1.0 Hz), 1.11 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 137.0 (0), 132.4 (1), 127.6 (1), 126.5 (1), 93.4 (0), 84.0 (1), 69.6 (1), 63.1 (2), 55.8 (3), 41.9 (1), 40.1 (2), 31.5 (2), 27.7 (2), 26.6 (2), 25.6 (2), 24.7 (2), 18.3 (3), 11.2(3).

LRMS (CI mode, NH_3): *m/z* = 359 [$(M+1)^+$, 37%], 327 (100), 203 (14), 140 (37), 106 (15), 81 (23).

(8S,11R)-11-Methyl-8-[(2S)(3E,5E)-2-methoxy-3-methyl-7-oxohepta-3,5-dienyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (3):
To a solution of allylic alcohol **21** (0.317 g, 0.89 mmol) in CH_2Cl_2 (17 mL) $BaMnO_4$ (1.60 g, 6.25 mmol) was added and the mixture was strirred at r.t. for 12 h. Then the mixture was filtered through Celite and concentrated to give a crude aldehyde (0.300 g) which was purified by chromatography (hexanes/Et_2O, 5:1 → 1:2) to give aldehyde **3** (0.273 g, 0.77 mmol, 87%) as a colourless oil: $[\alpha]_D$= +105° (*c* = 1.07, $CHCl_3$).

IR (film): ν = 2930 (s), 2715 (w), 1687 (s), 1637 (s), 1597 (s), 1452 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 9.63 (1H, d, *J* = 7.9 Hz), 7.43 (1H, dd, *J* = 15.1, 11.4 Hz), 6.34 (1H, d, *J* = 11.6 Hz), 6.15 (1H, dd, *J* = 15.1, 7.9 Hz), 4.06-3.92 (1H, m), 3.77 (1H, dd, *J* = 6.9, 5.6 Hz), 3.46 (1H, ddd, *J* = 2.9, 12.4, 13.5 Hz), 3.22 (3H, s), 2.99 (1H, ddd, *J* = 2.7, 12.4, 13.7 Hz), 2.70–2.50 (2H, m), 2.15-1.24 (7H, m), 1.90 (3H, d, *J* = 1.2 Hz), 1.12 (3H, d, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz): δ = 193.8 (1), 150.6 (0), 147.0 (1), 131.9 (1), 125.3 (1), 93.8 (0), 83.6 (1), 69.6 (1), 56.7 (3), 42.1 (1), 40.4 (2), 31.5 (2), 27.8 (2), 26.7 (2), 25.8 (2), 25.0 (2), 18.5 (3), 12.8 (3).

LRMS (CI mode, NH_3): *m/z* = 357 [$(M+1)^+$, 100%], 327 (35), 203 (10), 138 (25), 106 (17), 81 (9).

UV (EtOH): λ_{max} (ε) = 286 nm (16900).

(8*S*,11*R*)-11-Methyl-8-[(2*S*,9*S*,11*R*)(3*E*,5*E*,7*E*)-12-(*tert*-butyldimethylsiloxy)-2-methoxy-3,9,11-trimethyldodeca-3,5,7-trienyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (2):

To a solution of aldehyde **3** (0.052 g, 0.147 mmol) and sulfone **4** (0.063 g, 0.147 mmol) in THF (6 mL), at –80°C was added $LiN(TMS)_2$ (0.294 mL, 1 M in THF, 0.294 mmol). After 3 h at –80°C the solution was allowed to stir at ambient temperature for another 1 h. The reaction mixture was then treated with sat. aq NH_4Cl (10 mL), the organic layer separated, the water layer extracted with Et_2O, and the combined organic layers dried and concentrated in vacuo. The residue was purified by chromatography (hexanes/Et_2O, 10:1 → 2:1) to give triene **2** (0.057 g, 0.10 mmol, 68%) contaminated with ≤ 5% of the (*Z*)-isomer **28**: $[\alpha]_D$ = +72° (*c* = 1.02, $CHCl_3$).

IR (CCl_4): ν = 3026 (w), 2957 (s), 2929 (s), 2857 (s), 1482 (m), 1381 (m), 1256 (m) cm^{-1}.

^{1}H NMR (270 MHz, C_6D_6): δ = 6.41 (1H, dd, *J* = 14.1, 11.1 Hz), 6.23 (1H, dd, *J* = 14.1, 11.2 Hz), 6.16 (1H, dd, *J* = 14.7, 11.2 Hz), 6.14 (1H, app dq, *J* = 11.1, 1.1 Hz), 5.55 (1H, dd, *J* = 14.7, 8.6 Hz), 4.21–4.08 (1H, m), 3.75 (1H, app dd, *J* = 7.1, 6.5 Hz), 3.46 (1H, ddd, *J* = 13.5, 12.8, 2.7 Hz), 3.39 (1H, dd, *J* = 9.6, 5.9 Hz), 3.35 (1H, dd, *J* = 9.6, 6.6 Hz), 3.08 (3H, s), 2.99 (1H, ddd, *J* = 13.9, 13.1, 2.8 Hz), 2.37–2.18 (4H, m), 1.98–1.18 (12H, m), 1.69 (3H, d, 1.1 Hz), 1.24 (3H, d, *J* = 6.6 Hz), 1.02 (3H, d, *J* = 6.6), 0.99 (9H, s), 0.92 (3H, d, *J* = 6.6 Hz), 0.06 (6H, s).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 141.5 (1), 136.3 (0), 133.6 (1), 129.1 (1), 128.9 (1), 126.3 (1), 93.7 (0), 84.4 (1), 69.9 (1), 68.9 (2), 56.0 (3), 42.2 (1), 41.0 (2), 40.5 (2), 34.8 (1), 33.7 (1), 31.9 (2), 27.9 (2), 26.9 (2), 26.2 (3), 26.0 (2), 25.0 (2), 21.9 (3), 18.6 (3), 18.6 (0), 16.8 (3), 11.5 (3), –5.1(3). The two coincident signals at 18.6 ppm in $CDCl_3$ can be distinguished in benzene: 18.9 (3) and 18.7 (0) ppm.

LRMS (EI mode, 70 eV): *m/z* = 568 ($M^{+\bullet}$, 21%), 538 (22), 537 (40), 536 (100), 511 (19), 510 (10), 480 (10), 479 (27), 438 (15), 405 (13), 351 (20), 350 (52), 297 (14), 293 (15), 279 (32), 277 (15), 219 (31), 239 (58), 203 (55), 187 (29), 185 (30), 175 (22), 159 (94), 147 (21), 145 (33), 111 (52).

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 568.3475. $C_{31}H_{56}O_3S_2Si$ requires 568.3440.

UV (EtOH): λ_{max} (ε) = 267 nm (41000), 276 (52000), 287 (42000).

Julia Olefination Reaction Between Aldehyde 19 and Sulfone 29:

To a solution of aldehyde **19** (0.020 g, 0.063 mmol) and sulfone **29** (0.063 g, 0.063 mmol) in THF (4 mL) at –80°C $NaN(TMS)_2$ (0.076 mL, 1M in THF, 0.076 mmol) was added and the solution stirred at –80°C for 3 h and then warmed to r.t. and stirred for another 1 h. The reaction mixture was treated with sat. aq NH_4Cl (10 mL), the organic layer separated, and the water layer extracted with Et_2O. The combined organic layers were then dried and concentrated in vacuo and the residue purified by chromatography (silica gel, hexanes/Et_2O, 10:1 → 2:1) to give an inseparable mixture of trienes **2** and **30** (0.027 g, 0.048 mmol, 79%) as a colourless oil (*E*:*Z* = 1:1.3 by NMR analysis). The mixture of trienes was dissolved in THF (2 mL), TBAF (0.1 mL, 1M in THF, 0.1 mmol) was added and the solution stirred overnight. The reaction mixture was poured into H_2O (5 mL) and extracted with Et_2O (2 x 10 mL). The combined extracts were dried ($MgSO_4$), concentrated and the residue purified by chromatography (hexanes/Et_2O, 5:1 → neat Et_2O) to give in order of elution (*E,E,E*)-isomer **31** (3 mg, 0.0066 mmol, 14%), mixed fractions (5 mg, 0.011 mmol, 23%), and finally (*E,Z,E*)-isomer **32** (9 mg, 0.0198 mmol, 41%).

(8S,11R)-11-Methyl-8-[(2S,9S,11R)(3E,5E,7E)-12-hydroxy-2-methoxy-3,9,11-trimethyldodeca-3,5,7-trienyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (**31**):

IR (CCl_4): ν = 3640 (w), 3026 (w), 2928 (s), 1550 (m), 1454(m), 1380 (w), 1248 (w) cm^{-1}.

^{1}H NMR (270 MHz, C_6D_6): δ = 6.42 (1H, dd, *J* = 14.9, 11.1 Hz), 6.25 (1H, dd, *J* = 14.9, 10.7 Hz), 6.17 (1H, app dq, *J* = 11.1, 1.2 Hz), 6.13 (1H, dd with fine splitting, *J* = 15.1, 10.7 Hz), 5.49 (1H, dd, *J* = 15.1, 8.5 Hz), 4.23–4.08 (1H, m), 3.77 (1H, dd, *J* = 7.2, 6.1 Hz), 3.46 (1H, ddd, *J* = 13.3, 12.6, 2.67 Hz), 3.18 (1H, dd, *J* = 10.4, 6.0 Hz), 3.16 (1H, dd, *J* = 10.3, 6.3 Hz), 3.09 (3H, s), 2.98 (1H, app ddd, *J* = 13.7, 13.1, 2.8 Hz), 2.36–2.17 (4H, m), 1.98–1.20 (11H, m), 1.71 (3H, d, *J* = 1.2 Hz), 1.24 (3H, d, *J* = 6.9 Hz), 0.98 (3H, d, *J* = 6.7 Hz), 0.83 (3H, d, *J* = 6.6 Hz), 0.61 (1H, br s).

^{13}C NMR (67.5 MHz): δ = 141.0 (1), 136.6 (0), 133.3 (1), 129.4 (1), 128.7 (1), 126.6 (1), 93.8 (0), 84.4 (1), 69.9 (1), 68.9 (2), 56.0 (3), 42.2 (1), 40.9 (2), 40.5 (2), 34.9 (1), 33.8 (1), 31.8 (2), 28.0 (2), 26.9 (2), 26.0 (2), 25.1 (2), 21.9 (3), 18.6 (3), 16.5 (3), 11.6 (3).

LRMS (EI mode, 70 eV): *m/z* = 454 ($M^{+\bullet}$, 19%), 423 (30), 422 (100), 324 (17), 237 (42), 236 (56), 205 (15), 203 (52), 159 (66).

HRMS (EI mode, 70 eV): Found $M^{+\bullet}$, 454.2567. $C_{25}H_{42}O_3S_2$ requires 454.2575.

UV (EtOH): λ_{max} (ε) = 267 nm (34000), 277 (41000), 288 (35000).

(8S,11R)-11-Methyl-8-[(2S,9S,11R)(3E,5Z,7E)-12-hydroxy-2-methoxy-3,9,11-trimethyldodeca-3,5,7-trienyl]-7-oxa-1,5-dithiaspiro[5.5]undecane (**32**):

IR (CCl_4): ν = 3644 (w), 3475 (br), 2928 (s), 1455 (m), 1380 (m) cm^{-1}.

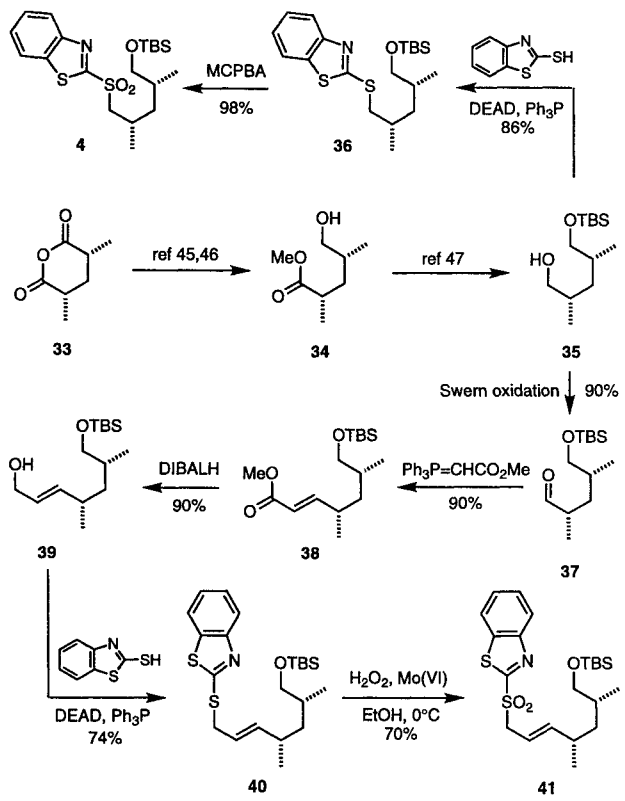
^{1}H NMR (270 MHz, C_6D_6): δ = 6.77 (1H, app dq, *J* = 11.1, .1.4 Hz), 6.72 (1H, dd, *J* = 15.0, 10.8 Hz), 6.21 (1H, dd, *J* = 11.1, 10.9 Hz), 6.10 (1H, dd, *J* = 10.9, 10.8 Hz), 5.52 (1H, dd, *J* = 15.0, 8.5 Hz), 4.22–4.10 (1H, m), 3.82 (1H, dd, *J* = 7.3, 6.0 Hz), 3.49 (2H, ddd, *J* = 13.8, 12.6, 2.9 Hz), 3.16 (1H, dd, *J* = 10.3, 6.0 Hz), 3.11 (1H, dd, *J* = 10.1, 6.0 Hz), 3.05 (3H, s), 3.04 (1H, ddd, *J* = 13.9, 12.6, 2.9 Hz), 2.37–2.18 (4H, m), 1.98–1.16 (12H, m), 1.70 (3H, d, *J* = 1.4 Hz), 1.25 (3H, d, *J* = 6.9 Hz), 0.94 (3H, d, *J* = 6.7 Hz), 0.78 (3H, d, *J* = 6.6 Hz).

^{13}C NMR (67.5 MHz): δ = 142.3 (1), 137.5 (0), 129.9 (1), 124.4 (1), 123.5 (1), 122.9 (1), 93.8 (0), 84.5 (1), 69.9 (1), 68.8 (2), 56.2 (3), 42.2 (1), 40.9 (2), 40.6 (2), 35.2 (1), 33.8 (1), 31.9 (2), 27.9 (2), 26.8 (2), 25.9 (2), 25.2 (2), 21.9 (3), 18.6 (3), 16.7 (3), 11.4 (3).

UV (EtOH): λ_{max} (ε) = 267 nm (23000), 276 (28000), 287 (21000).

Preparation of Thiazolyl Sulfones 4 and 41 (Scheme 8):

The starting material for the synthesis of sulfones **4** and **41** was the crystalline 2,4-dimethylglutaric anhydride **33** which is readily accessible in mole quantities in 4 steps from cheap reagents.[45] Methanolysis followed by an easy resolution[46] converted anhydride **33** to the enantiomerically pure intermediate **34** from which the alcohol **35** was prepared according to published procedures.[47]



Scheme 8

2-[(3*S*,5*R*)-6-(*tert*-Butyldimethylsiloxy)-3,5-dimethylhexylthio]benzothiazole (36):
To a solution of alcohol **35** (1.0 g, 4.07 mmol), Ph_3P (1.18 g, 4.5 mmol) and 2-mercaptobenzothiazole (0.75 g, 4.5 mmol) in THF (53 mL), a solution of DEAD (0.78 g, 4.5 mmol) in THF (4 mL) was added dropwise at r.t. The solution was stirred at r.t. overnight and then concentrated in vacuo. The residue was treated with a mixture of hexanes/EtOAc (5:1, v/v), the precipitate removed by filtration, and the solid washed twice with the same mixture of solvents. The filtrate was concentrated and the residue purified by chromatography (hexanes → hexanes/Et_2O, 1 : 1) to give **36** (1.375 g, 3.48 mmol, 86%) as a colouress oil: $[\alpha]_D$= +20° (c = 1.47, $CHCl_3$).

IR (film): ν = 3064 (w), 2955 (s), 2855 (s), 1462 (s), 1428 (s), 1251 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.86 (1H, dm, J = 8.11 Hz), 7.74 (1H, dm, J = 7.9 Hz), 7.41 (1H, tm, J = 7.3 Hz), 7.28 (1H, tm, J = 7.7 Hz), 3.51 (1H, dd, J = 12.7, 4.8 Hz), 3.47 (1H, dd, J = 10.0, 5.6 Hz), 3.40 (1H, dd, J = 9.9, 6.2 Hz), 3.10 (1H, dd, J = 12.6, 7.9 Hz), 2.19–2.00 (1H, m), 1.82 (1H, oct, J = 6.6 Hz), 1.58 (1H, dt, J = 13.7, 7.0 Hz), 1.16–1.04 (1H, m), 1.11 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.6 Hz), 0.91 (9H, s), 0.05 (6H, s).

^{13}C NMR (62.5 MHz): δ = 167.5 (0), 153.3 (0), 135.2 (0), 125.9 (1), 124.0 (1), 121.4 (1), 120.8 (1), 68.1 (2), 40.6 (2), 40.4 (2), 33.2 (1),30.8 (1), 25.9 (3),20.2 (3), 18.3 (0), 17.4 (3), –5.4 (3).

LRMS (CI mode, NH_3): m/z = 396 [(M+1)$^+$, 100%], 377 (5), 338 (51), 231 (18), 190 (10), 168 (62), 136 (9).

2-[(3*S*,5*R*)-6-(*tert*-Butyldimethylsiloxy)-3,5-dimethylhexylsulfonyl]benzothiazole (4):
To a solution of thioether **36** (0.965 g, 2.44 mmol) in CH_2Cl_2 (20 mL) was added $NaHCO_3$ (1.008 g, 12 mmol) followed by a solution of MCPBA (1.035 g, 6.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at r.t. overnight and then poured into a mixture of sat. $NaHCO_3$ (25 mL) and sodium thiosulfate (25 mL). The organic layer was separated and the water layer extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and the residue purified by chromatography (50% Et_2O in hexanes) to give **4** (1.025 g, 2.40 mmol, 98%) as a colourless oil: $[\alpha]_D$= +11° (c = 1.13, $CHCl_3$).

IR (film): ν = 2956 (s), 2856 (s), 1472 (s), 1327 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 8.24–8.19 (1H, m), 8.05–7.99 (1H, m), 7.68–7.56 (2H, m), 3.60 (1H, dd, J = 14.5, 3.7 Hz), 3.38 (1H, dd, J = 9.8, 6.0 Hz), 3.34 (1H, dd, J = 9.5, 6.0 Hz), 3.28 (1H, dd, J = 14.5, 9.0 Hz), 2.46–2.28 (1H, m), 1.75–1.59 (1H, m), 1.53 (1H, ddd, J = 13.5, 7.9, 5.8 Hz), 1.19 (3H, d, J = 6.8 Hz), 1.16–1.04 (1H, m), 0.85 (9H, s), 0.81 (3H, d, J = 6.6 Hz), 0.002 (6H, s).

^{13}C NMR (62.5 MHz): δ = 166.8 (0), 152.7 (0), 136.7 (0), 128.0 (1), 127.7 (1), 125.3 (1), 122.4 (1), 67.9 (2), 60.7 (2), 41.1 (2), 33.1 (1), 26.4 (1), 25.9 (3), 20.9 (3), 18.3 (0), 17.1 (3), –5.4 (3).

LRMS (CI mode, NH_3): m/z = 428 [(M+1)$^+$, 100%], 370 (47), 296 (5), 256 (28), 231 (33), 190 (23), 136 (95), 97 (25).

HRMS (CI mode, NH_3): Found (M+1)$^+$, 428.1740. $C_{20}H_{34}NO_3S_2Si$+H requires 428.1749.

Enantiomeric purity of **4** was determined by (a) deprotection using HF in MeCN and (b) esterification with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) in the presence of DCC and DMAP. Comparison of the ^1H- and ^{13}C-NMR spectra of the Mosher ester with an authentic sample prepared from the corresponding racemate revealed a single diastereoisomer.

(2*S*,4*R*)-5-(*tert*-Butyldimethylsiloxy)-2,4-dimethylpentan-1-al (37):
Aldehyde **37** was prepared in 90% yield on a 45 mmol scale by Swern oxidation of alcohol **35** according to the procedure of Seebach and co-workers.[47]

Methyl (4*S*,6*R*)-(7-*tert*-Butyldimethylsiloxy)-4,6-dimethylhept-2-enoate (38):
A mixture of the crude aldehyde **37** (5.0 g, 20.3 mmol) and Ph_3P=$CHCO_2Me$ (13.6 g, 40.6 mmol) in dry CH_2Cl_2 (70 mL) was stirred for 48 h at r.t. Solvent was then removed in vacuo and cooled hexanes (20 mL) was added to the residue. The triphenylphosphine oxide was filtered and washed with cooled hexanes (3 x 20 mL) and the filtrate concentrated in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 10:1) to give **38** (5.5 g, 18.3 mmol, 90%) as a colourless oil: $[\alpha]_D$ = +18.75° (c = 2, $CHCl_3$).

IR (film): ν = 2956, 2857, 1728, 1657, 1462, 1435, 1360, 1274, 1256, 1178, 1093, 837 cm^{-1}.

^1H NMR (270 MHz): δ = 6.82 (1H, dd, J= 15.7, 8.3 Hz), 5.79 (1H, dd, J= 15.7, 1.0 Hz), 3.70 (3H, s), 3.40 (1H, dd, J= 11.8, 6.0 Hz), 3.35 (1H, dd, J= 11.8, 6.0 Hz), 2.49–2.37 (1H, m), 1.64–1.43 (2H, m), 1.16–1.05 (1H, m), 1.05 (3H, d, J= 6.8 Hz), 0.89 (9H, s), 0.86 (3H, d, J= 6.6 Hz), 0.05 (6H, s).

^{13}C NMR (67.5 MHz): δ = 167.4 (0), 154.9 (1), 119.5 (1), 68.5 (2), 51.5 (3), 40.0 (2), 34.4 (1), 33.55 (1), 26.1 (3C, 3), 20.7 (3), 18.5 (0), 16.7 (3), –5.0 (2C, 3).

LRMS (CI mode, NH_3): m/z = 318 [(M+NH_4)$^+$, 100%], 301 [(M+1)$^+$, 64], 285 (4), 269 (7), 243 (40), 211 (6), 186 (1), 169 (15), 35 (11).

HRMS (CI mode, NH_3): Found (M+1)$^+$, 301.2198. $C_{16}H_{32}O_3Si$+H requires 301.2174.

(4*S*,6*R*)-7-(*tert*-Butyldimethylsiloxy)-4,6-dimethylhept-2-en-1-ol (39):
A solution of DIBALH in toluene (12.2 mL, 1.5 M) was added to ester **38** (5.5 g, 18.3 mmol) in dry toluene (100 mL) at –78°C.

After stirring for 30 min at this temperature the reaction mixture was transferred via cannula to an ice-cooled sat. aq sodium potassium tartrate (80 mL). The two phase solution was stirred for 4 h, before being decanted. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give alcohol **39** (4.5 g, 16.5 mmol, 90%) as a colourless oil which was used without further purification.

IR (film): ν = 3340, 2857, 1669, 1462, 1388, 1361, 1255, 1093, 1006, 979, 837 cm^{-1}.

^1H NMR (270 MHz): δ = 5.62 (1H, dt, J = 15.5, 5.6 Hz), 5.50 (1H, dd, J = 15.5, 7.2 Hz), 4.95 (2H, d, J = 5.6 Hz), 3.41 (1H, dd, J = 9.9, 5.8 Hz), 3.34 (1H, dd, J = 9.9, 6.4 Hz), 2.35–2.10 (1H, m), 1.70–1.55 (1H, m), 1.45 (1H, br s), 1.40 (1H, ddd, J = 13.7, 9.4, 5.1 Hz), 1.00 (3H, d, J = 6.8 Hz), 1.03–0.89 (1H, m), 0.89 (9H, s), 0.88 (3H, d, J = 6.8 Hz), 0.05 (6H, s).

^{13}C NMR (67.5 MHz): δ = 139.0 (1), 127.6 (1), 68.8 (2), 63.9 (2), 40.7 (2), 34.0 (1), 33.5 (1), 26.1 (3C, 3), 21.7 (3), 18.5 (0), 16.8 (3), –5.19 (2C, 3).

2-[(4*S*,6*R*)-7-(*tert*-Butyldimethylsiloxy)-4,6-dimethylhept-2-enylthio]benzothiazole (40):

DEAD (0.436 g, 2.5 mmol) in dry THF (2 mL) was slowly added to a mixture of alcohol **39** (0.62 g, 2.3 mmol), Ph_3P (0.657 g, 2.5 mmol) and 2-mercaptobenzothiazole (0.42 g, 2.5 mmol) in dry THF (30 mL) at r.t. After 5 h stirring, solvent was removed in vacuo and a 5:1 mixture of hexanes/EtOAc (20 mL) was added to the residue. The precipitate was removed by filtration, washed with hexanes/EtOAc (3 x 10 mL) and the filtrate concentrated in vacuo. The yellow-orange residue was purified by chromatography (hexanes/CH_2Cl_2, 4 : 1) to give thioether **40** (0.7 g, 1.7 mmol, 74%) as a colourless oil: $[\alpha]_D$= +11.9° (c = 2.6, $CHCl_3$).

IR (film): ν = 2954-2849, 1661, 1560, 1461, 1425, 1390, 1361, 1302, 1249, 1090, 996, 967, 832 cm^{-1}.

^1H NMR (270 MHz): δ = 7.88 (1H, d, J = 7.92 Hz), 7.76 (1H, d, J = 7.92 Hz), 7.42 (1H, t, J = 7.92 Hz), 7.3 (1H, t, J = 7.92 Hz), 5.67–5.54 (2H, m), 4.02–3.89 (2H, m), 3.34 (1H, dd, J = 9.9, 6.3 Hz), 3.28 (1H, dd, J = 9.9, 6.3 Hz), 2.30–2.18 (1H, m), 1.60–1.46 (1H, m), 1.32 (1H, ddd, J = 11.7, 8.1, 4.0 Hz), 0.96 (3H, d, J = 6.6 Hz), 1.07–0.94 (1H, m), 0.89 (9H, s), 0.8 (3H, d, J = 6.6 Hz), 0.30 (6H, s).

^{13}C NMR (67.5 MHz): δ = 167.25 (0), 153.7 (0), 142.1 (1), 135.6 (0), 126.2 (1), 124.35 (1), 122.2 (1), 121.7 (1), 121.1 (1), 68.8 (2), 40.7 (2), 36.3 (2), 34.35 (1), 33.5 (1), 26.1 (3C, 3), 21.6 (3), 18.5 (0), 16.7 (3), –5.2 (2C, 3).

LRMS (EI mode, 70 eV): m/z = 421 ($M^{+\bullet}$, 8%), 388 (6), 364 (37), 224 (100), 197 (15), 167 (11), 123 (100), 75 (19).

HRMS (EI mode, 70eV): Found $M^{+\bullet}$, 421.1898. $C_{22}H_{35}NOS_2Si$ requires 421.1929.

2-[(4*S*,6*R*)-7-(*tert*-Butyldimethylsiloxy)-4,6-dimethylhept-2-enylsulfonyl]benzothiazole (41):

Ammonium molybdate (0.518 g, 0.42 mmol) was added to 30% H_2O_2 (0.68 mL, 6.6 mmol) at 0°C. The bright yellow solution was then added to thioether **40** (0.7 g, 1.7 mmol) in EtOH (10 mL) at 0°C. When the oxidation reaction was complete according to TLC (silica gel, CH_2Cl_2/hexanes, 4:1), H_2O (10 mL) was added and the two phase mixture concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography (hexanes/CH_2Cl_2, 7:3) to give sulfone **41** (0.54 g, 1.2 mmol, 70%) as a viscous, colourless oil: $[\alpha]_D$= +14.5° (c = 0.93, $CHCl_3$).

IR (film): ν = 2954-2853, 1467, 1325, 1249, 1149, 1085, 1020, 976, 837 cm^{-1}.

^1H NMR (270 MHz): δ = 8.22 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 7.64 (1H, t, J = 8.8 Hz), 7.58 (1H, t, J = 8.8 Hz), 5.67–5.46 (2H, m), 4.20 (2H, d, J = 6.4 Hz), 3.20 (1H, dd, J = 9.68, 5.8 Hz), 3.15 (1H, dd, J = 9.68, 5.8 Hz), 2.20 (1H, m), 1.35–1.10 (2H, m), 0.87 (9H, s), 0.95–0.80 (1H, m), 0.78 (3H, d, J = 6.6 Hz), 0.65 (3H, d, J = 6.6 Hz), 0.01 (6H, s).

^{13}C NMR (67.5 MHz): δ = 165.4 (0), 152.9 (0), 149.2 (1), 137.0 (0), 128.1 (1), 127.7 (1), 125.6 (1), 122.4 (1), 113.1 (1), 68.45 (2), 58.8 (2), 40.2 (2), 34.6 (1), 33.25 (1), 26.1 (3C, 3), 21.0 (3), 18.5 (0), 16.5 (3), –5.2 (2C, 3).

LRMS (CI mode, NH_3): m/z = 471 [M + NH_4)$^+$, 48%,] 454 [(M+H)$^+$, 93], 357 (20), 340 (43), 256 (26), 199 (6), 136 (100), 123 (14).

HRMS (CI mode, NH_3): Found (M+1)$^+$, 454.1959. $C_{22}H_{35}NO_3S_2Si$+H requires 454.1879.

We thank Glaxo Group Research and SmithKline Beecham Pharmaceuticals for financial support. We also thank Dr. Georges Hareau-Vittini for helpful advice.

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