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A Stereoselective Synthesis of the Cabon Backbone of Phoslactomycin B

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Abstract: A convergent synthesis of the entire carbon framework of phoslactomycin B is disclosed. The first route aimed at creating the C8 tetrasubstituted stereocenter by a regioselective intermolecular coupling between an internal alkyne and allyl silyl ether, adopting Trost's protocol followed by [2,3] sigmatropic rearrangement was not successful. In the second approach, a propargylic sulfide was rearranged to an unsaturated ketone which was further reacted with lithio acetonitrile to create the C8 stereocenter selectively. The C4 and C5 stereocenters were introduced by the non-Evans *syn*-aldol reaction using Crimmins' protocol. The C9 and C11 carbinol centers were created by asymmetric transfer hydrogenation. The (*Z*,Z)-diene moiety was introduced by a partial reduction of a diyne following Hansen's modification of Boland reduction reaction.

Inroduction

Phoslactomycins A-F, (Figure 1) isolated in 1989 from a strain of *Streptomyces nigrescens*, were found to exhibit potent activity against phytopathogenic fungi.[1] These compounds possess common structural characteristics including an α,β-unsaturated δ-lactone, an alkene with (*E*)-configuration (C6-C7), a tertiary alcohol at C8 substituted by a 2-amino ethyl chain, a phosphate at C9, a secondary hydroxyl at C11 and conjugated (*Z*,*Z*) diene (C12-C15) with a cyclohexyl group at C15 and a variety of substituents at C18 on the cyclohexane ring. Phoslactomycin-B was also isolated from the fermentation broth of *Streptomyces hygroscopicus* and was reported to be active against L1210, P388 and EL4

murine cancer cell lines.[2] The structurally related leustroducsins A-C were isolated from the culture broth of *Streptomyces platensis*[3] (SANK 60191) and were shown to possess bioactivities such as antibacterial, antifungal and antitumor activity.[4] The mode of action of phoslactomycins[5] and leuctroducsins was shown to be via inhibition of serine-threonine phosphatase 2A,[6] an enzyme involved in the regulation of several biological events.

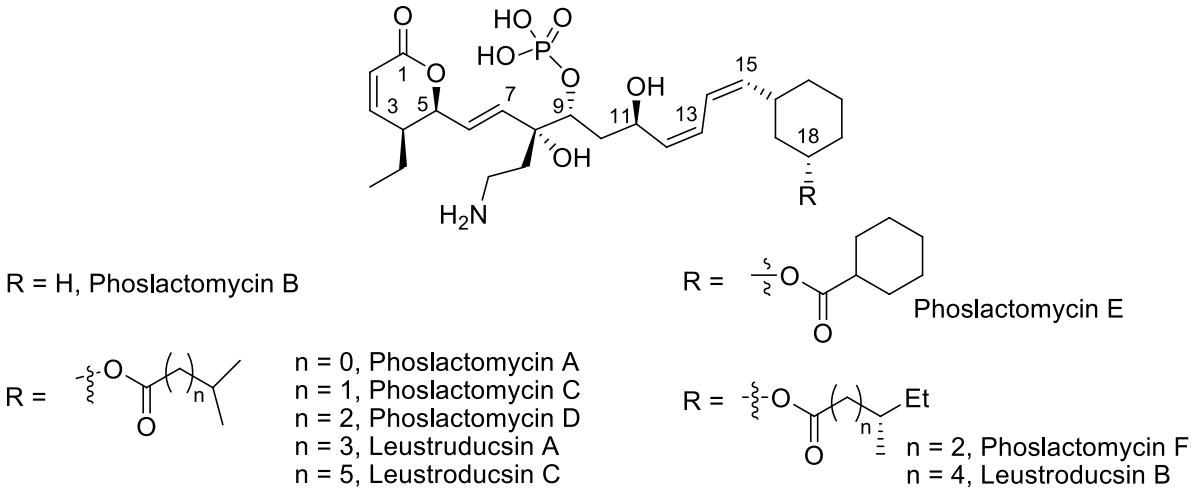
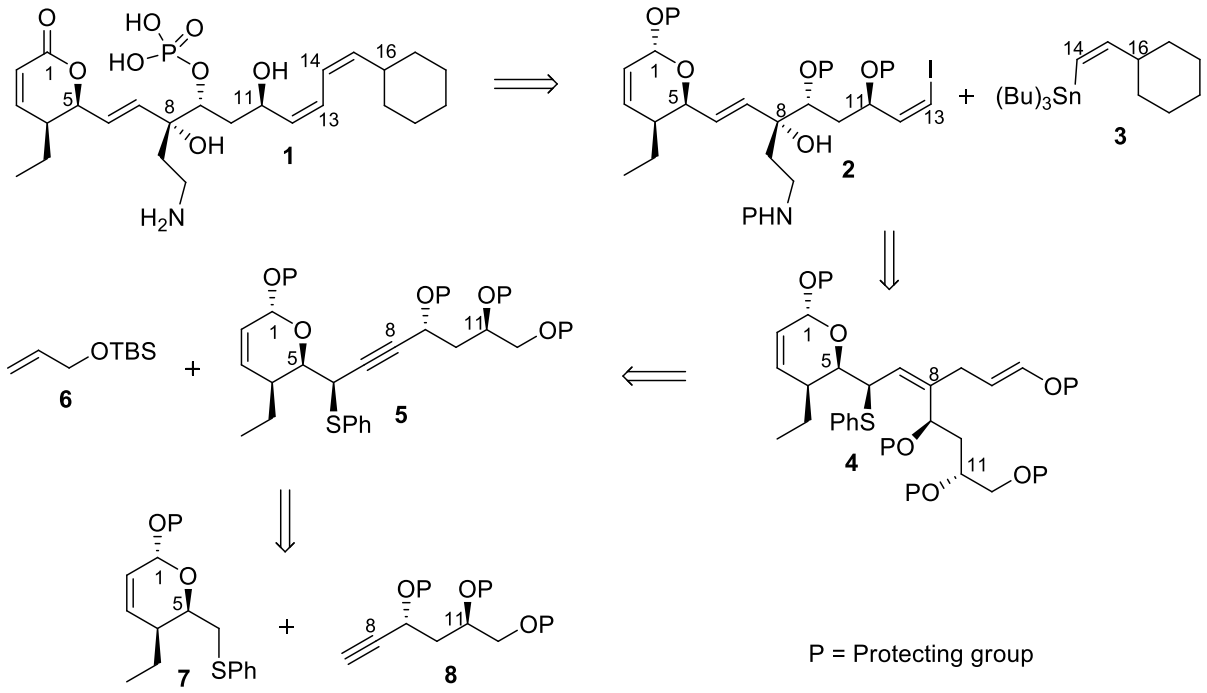


Figure-1. Phoslactomycins (PLMs) A-F and Leustroducsins A-C.

To date, five formal/total synthesis of PLMs[7,8,9,10] have been reported. Similarly, leuctroducsin B has been a target of interest for the synthetic community.[11] Evans aldol,[7,10] Brown-type pentenylation[8] and [2,3]-Wittig rearrangement[9] have been employed to control the configuration at C4 and C5 stereocenters. The 1,2-diol at C8-C9 has been installed by Sharpless' asymmetric dihydroxylation[8,10] or chelation controlled addition to a ketone,[7,9] and in all the syntheses, the C13-C14 bond is constructed by a Stille coupling.

Herein, we report a new convergent approach to the entire carbon chain of PLM B, using a unique protocol employing an α-chloro sulfide for C-C bond formation and Mislow-Evans rearrangement for C-O bond formation to create the C6-C7 bond and C8 stereocenter. The initial retrosynthetic analysis is depicted in Scheme 1.

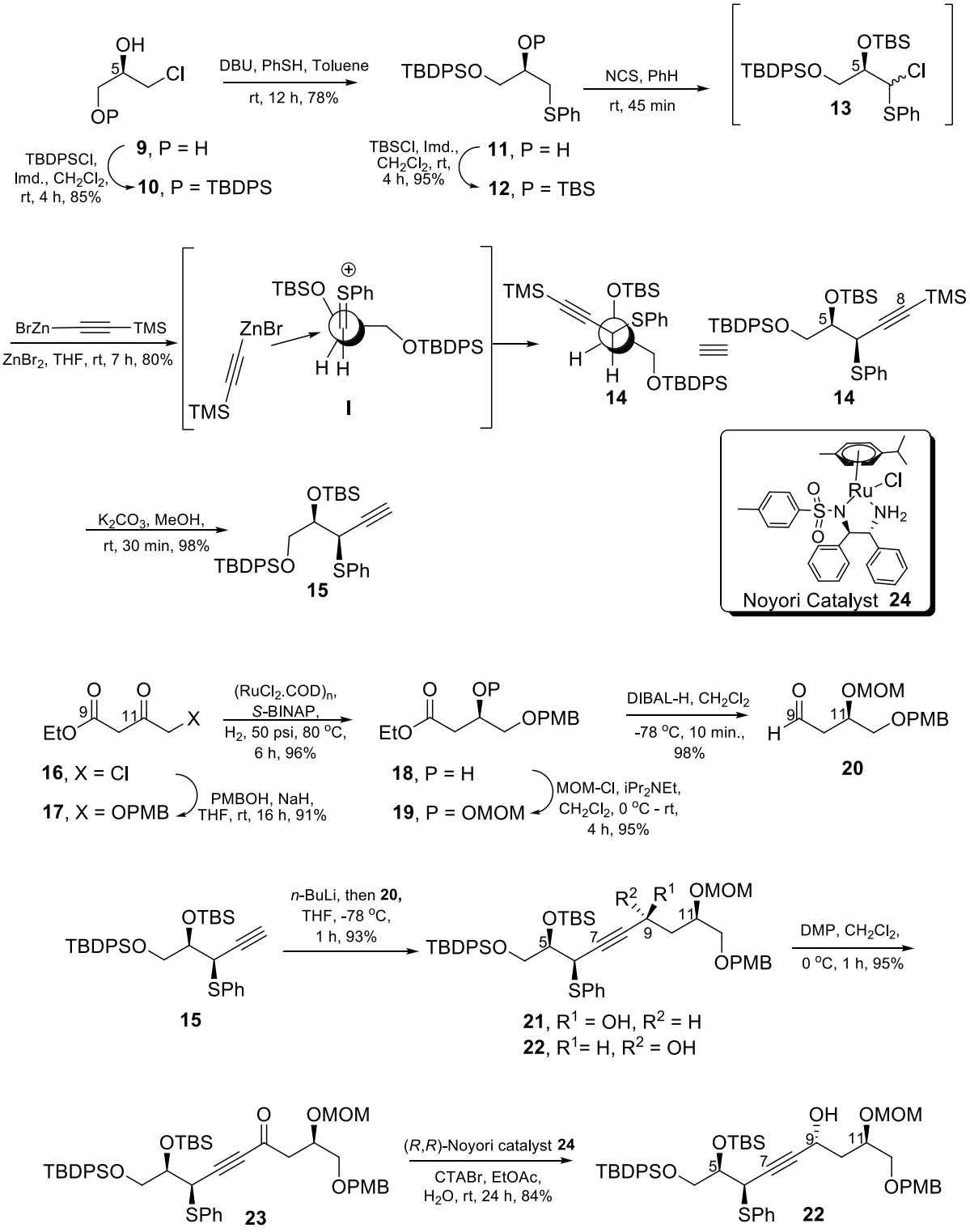


Scheme 1. Retrosynthetic Analysis of PLM B.

PLM B was envisaged to be obtained from the key intermediate **2** by elaboration of C13-C14 bond by reaction with alkenyl stannane **3**, phosphorylation of C9 OH, oxidation to lactone and global deprotection. The intermediate **2** was expected to be obtained by a [2,3] sigmatropic rearrangement of the sulfoxide, derived eventually from allylic sulfide **4,** which in turn was envisioned to be obtained by an ambitious regioselective intermolecular coupling between alkyne **5** and allyl ether **6** employing Trost's protocol[12] using Ru(II) catalyst. The propargylic sulfide **5** was imagined to be obtained from the reaction of the α-chloro sulfide derived from sulfide **7** with alkynylzinc bromide derived from alkyne **8**.

Result and discussion

In keeping with the above retrosynthetic analysis, since the eventual creation of the C8 stereocenter rested on the successful and regioselective intermolecular coupling of a densely functionalised internal alkyne **5** with an alkene such as **6**, it was deemed prudent to assess the practicality of the proposal on a simpler model substrate **22**, the synthesis of which is detailed in Scheme 2.

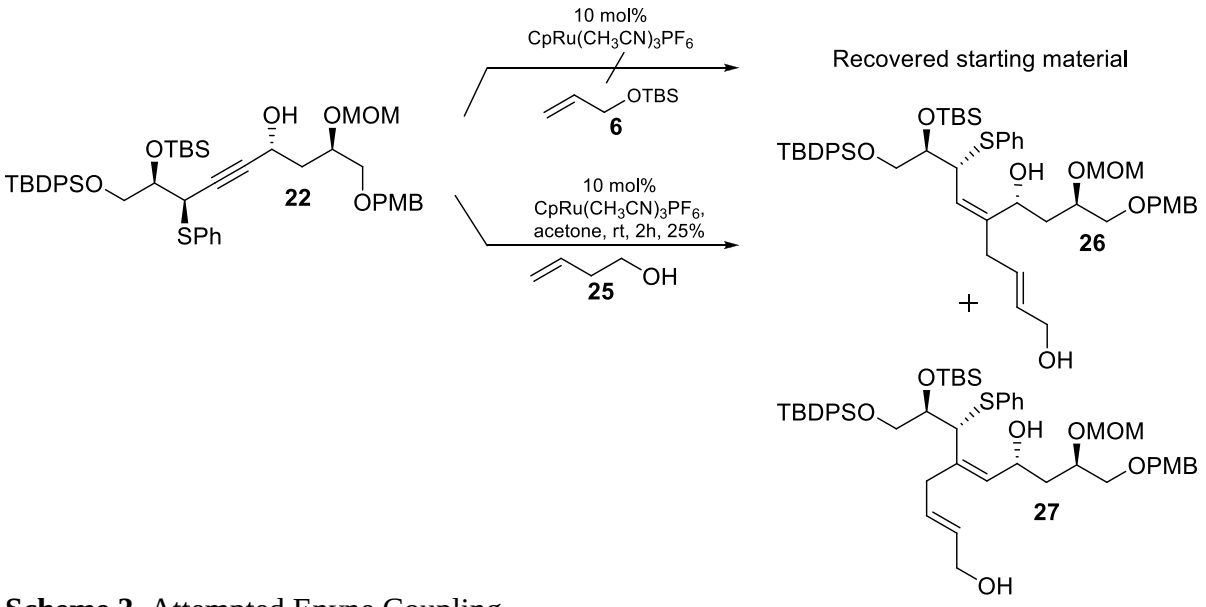


Scheme 2. Synthesis of Model Alkyne **22**.

The synthesis of alkyne **22** began with the diol **9**, obtained by hydrolytic kinetic resolution of *rac*-epichlorohydrin,[13] that on selective monoprotection furnished chlorohydrin **10**. Displacement of chlorine by thiophenol in the presence of DBU yielded sulfide **11** which

was protected as its TBS ether under standard conditions to afford compound **12**. The sulfide **12** on treatment with *N*-chlorosuccinimide afforded the α-chloro sulfide **13**, which on reaction with alkynylzinc bromide, prepared from TMS acetylene,[14] afforded propargylic sulfide **14** stereoselectively.[15] The observed diastereoselectivity can be rationalized by the reaction proceeding through a putative transition state **I** wherein the sulfenium ion is eclipsed by the OTBS group and the alkynylzinc reagent appoaches it from the face away from the bulky CH_2OTBDPS group. Deprotection of the TMS group with catalytic quantity of K_2CO_3 in methanol afforded alkyne **15**. The synthesis of aldehyde **20** began from commercially available α-chloroketo ester **16** which was converted to the *p*-methoxybenzyl ether **17** following literature precedent.[16] Asymmetric hydrogenation[17] employing Noyori's catalyst yielded alcohol **18** (99% ee) which was protected as its MOM ether **19.** Selective reduction of the ester to aldehyde **20** proceeded cleanly using DIBAL-H at low temperature. Reaction of aldehyde **20** with the lithium acetylide prepared from alkyne **15** yielded an inseparable mixture of epimeric alcohols **21** and **22** in a 1:1 ratio. Oxidation using DMP, furnished the ketone **23** in good yield. Stereoselective transfer hydrogenation of ketone **23** using Noyori's protocol[18] delivered alcohol **22**.

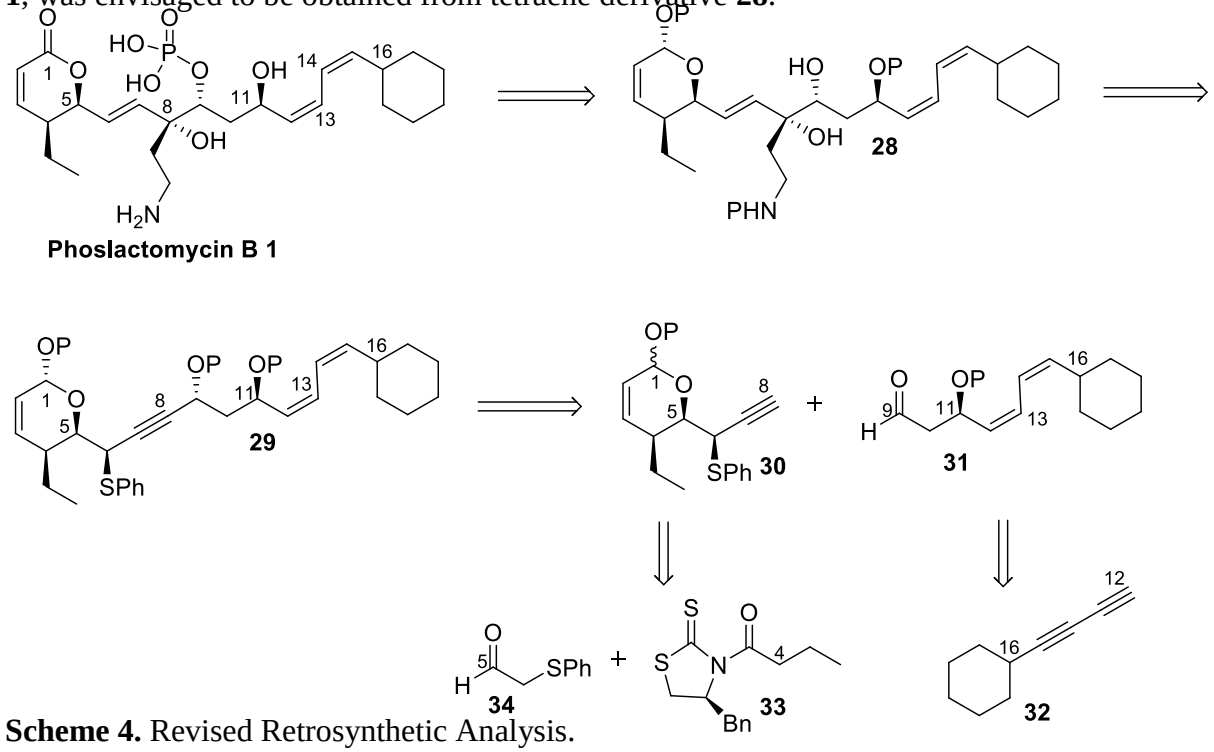
With the internal alkyne **22** becoming available, the enyne coupling was attempted with the silyl ether **6**. The product expected from the reaction was a silyl enol ether which was expected to be chemoselectively oxidized to an aldehyde[19] (eventually to be converted to the aminoethyl side chain) in the presence of the other double bond (C6-C7). In the event, reaction of **22** with silyl ether **6** resulted in only recovery of starting material under a variety of reaction conditions.



Scheme 3. Attempted Enyne Coupling.

The reaction of **22** with a less hindered alkene **25**, proceeded in a low yield 25% and poor regioselectivity (1:1) to furnish the trisubstituted alkenes **26** and **27**, Scheme 3. The above result illustrated that the intermolecular enyne coupling was not a viable disconnection to construct the trisubstituted alkene **4**.

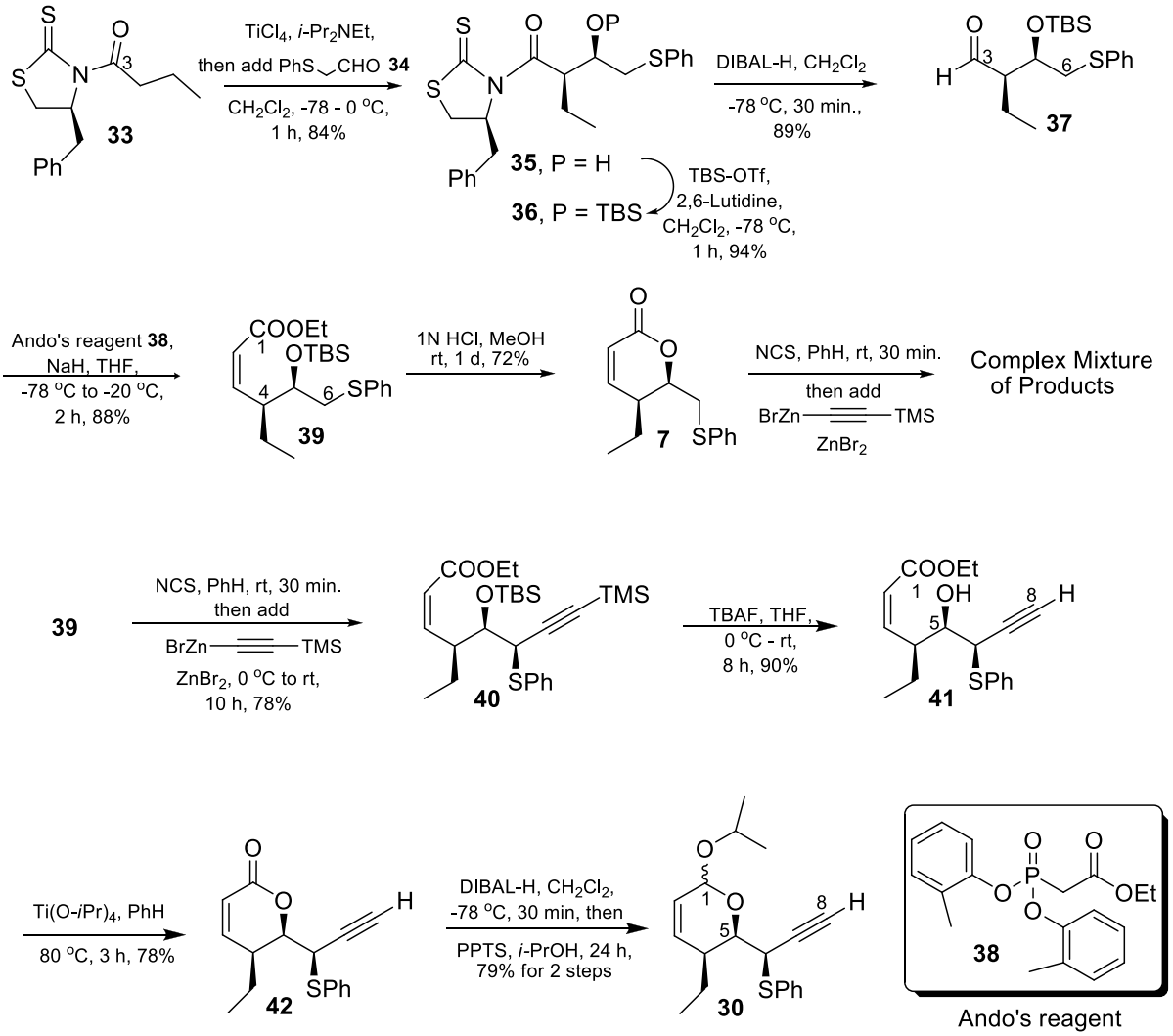
An alternate retrosynthetic disconnection of PLM B is depicted in Scheme 4. PLM B **1**, was envisaged to be obtained from tetraene derivative **28**.



Scheme 4. Revised Retrosynthetic Analysis.

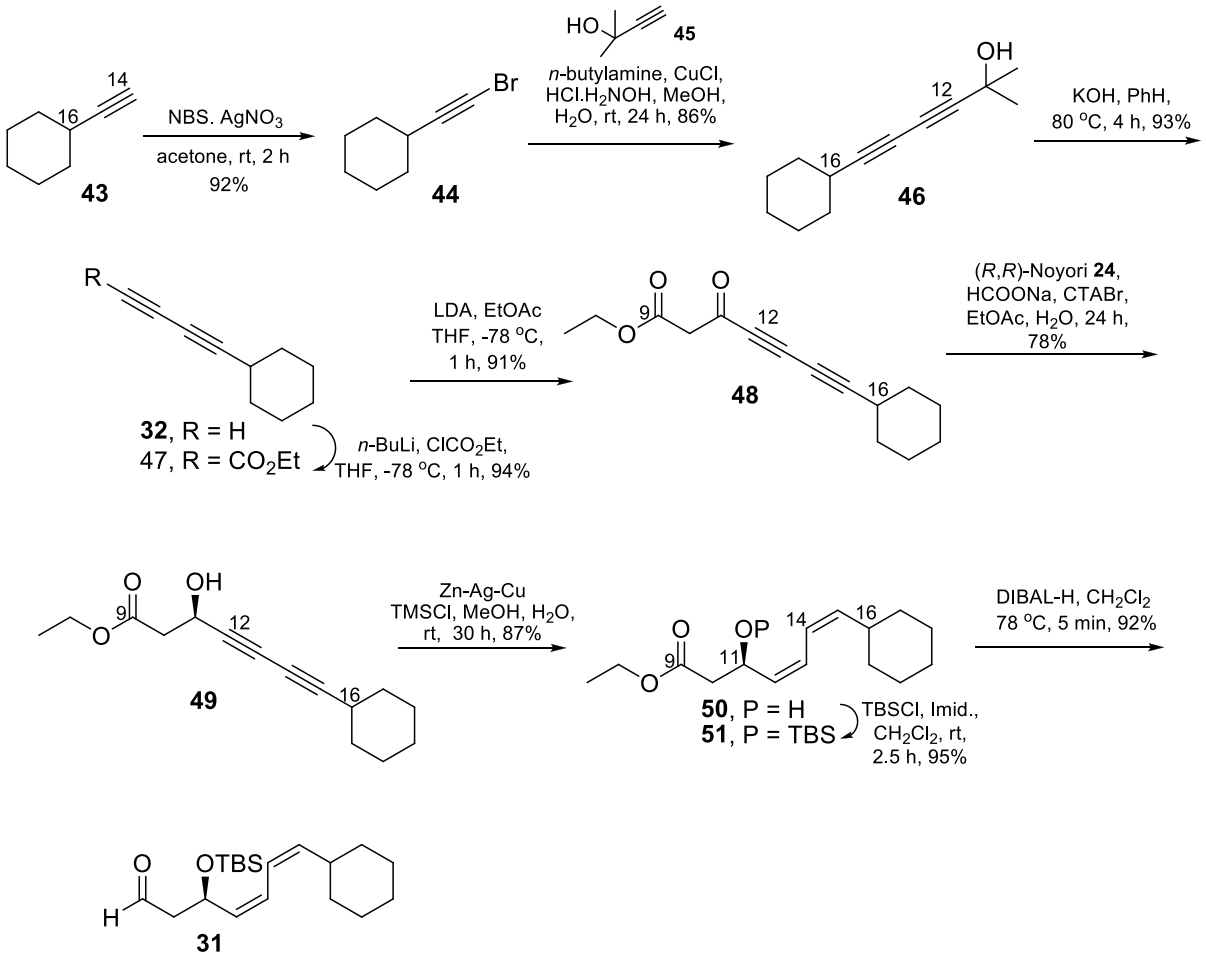
It was decided to incorporate the (*Z*,*Z*)-diene moiety even in the early stage of the synthesis, since intramolecular enyne coupling was no more an issue unlike the previous retrosynthetic disconnection wherein an intermolecular enyne coupling was envisaged. The C8 stereocenter in **28** was expected to be introduced by a stereoselective addition of a two-carbon nucleophile to the unsaturated ketone that would result from a [2,3] sigmatropic rearrangement of propargylic sulfide **29**. The sulfide **29** was envisioned to be obtained from sulfide **30** and aldehyde **31**. The aldehyde **31** itself can be obtained from diyne **32.** On the other hand, sulfide **30** can be traced back to thiazolidinethione **33** and aldehyde **34**.[20]

The synthesis of sulfide **30** began with non-Evans *syn*-aldol reaction[21] of thiazolidinethione **33** with phenylthio acetaldehyde **34**, obtained by oxidation of phenylthio ethanol with IBX, to yield compound **35**. Protection of the hydroxyl as its TBS ether yielded compound **36**. Removal of the auxiliary using DIBAL-H afforded aldehyde **37** that upon HWE olefination following Ando's protocol[22] furnished (*Z*)-alkene **39** (95:5). Acid treatment resulted in TBS deprotection followed by cyclisation to afford δ-lactone **7**, Scheme 5.



Scheme 5. Synthesis of Sulfide **30**.

The C-C bond formation reaction using the α-chloro sulfide, derived from **7**, was attempted using the alkynylzinc bromide derived from TMS-acetylene. A complex mixture of products resulted, probably as a consequence of elimination.[23] Pleasingly though, the reaction proceeded cleanly with α-chloro sulfide generated from sulfide **38** to yield the propargylic sulfide **40**.[15] The trimethylsilyl and *t*-butyldimethyl silyl groups of compound **40** were deprotected using TBAF to furnish alkynol **41**. Lactonisation to yield **42** proceeded cleanly in the presence of catalytic amount of titanium tetraisopropoxide in refluxing benzene.[7] Reduction of lactone to lactol using DIBAL-H followed by reaction with *iso*-propanol in presence of PPTS yielded acetal **30** as one of the key intermediates.

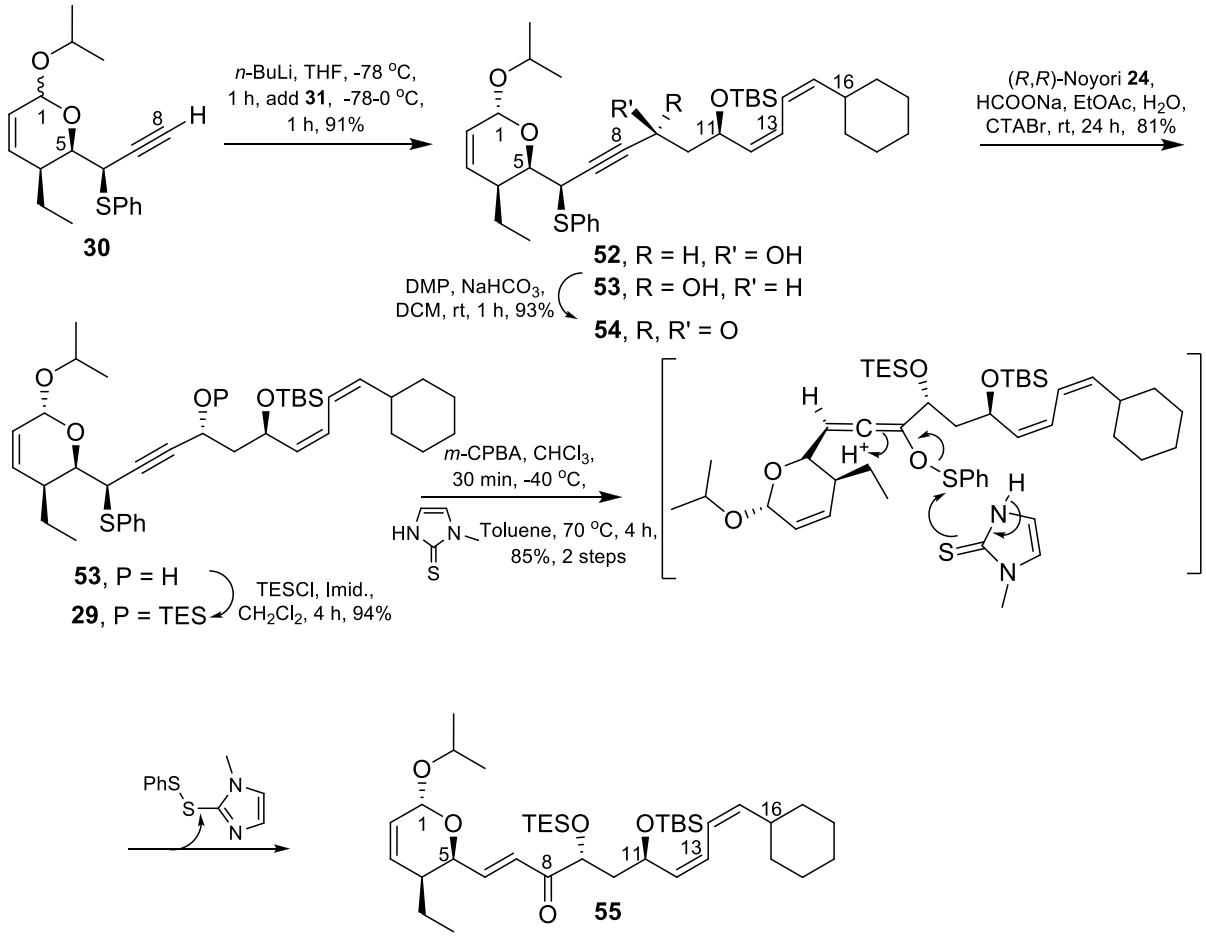


Scheme 6. Synthesis of Aldehyde **31**.

The synthesis of aldehyde **31** is depicted in Scheme 6. Commercially available ethynylcyclohexane **43** was converted to bromoalkyne **44** by treatment with *N*-bromosuccinimide in presence of silver nitrate. Cadiot-Chodkiewicz cross coupling[24] of compound **44** with 2-methyl-3-butyn-2-ol **45** furnished diyne **46**. Treatment with KOH yielded diyne **32**.[25] The lithio derivative of **32** was reacted with ethyl chloroformate to afford ester **47**. Further reaction of ester **47** with the anion of ethyl acetate furnished the keto ester **48**. Asymmetric transfer hydrogenation using Noyori's protocol[18] yielded alcohol **49**. The diyne was stereoselectively reduced to the *Z,Z*-diene **50** using Hansen's modification[26] to the Boland protocol.[27] Protection of the hydroxyl as its silyl ether **51** and reduction of the ester using DIBAL-H furnished aldehyde **31** constituting the C9-C21 subunit.

With both the partners being available the creation of the C8-C9 bond was explored.

The lithio anion of alkyne **30** was reacted with aldehyde **31** to furnish an inseparable mixture of alcohols **52** and **53**.

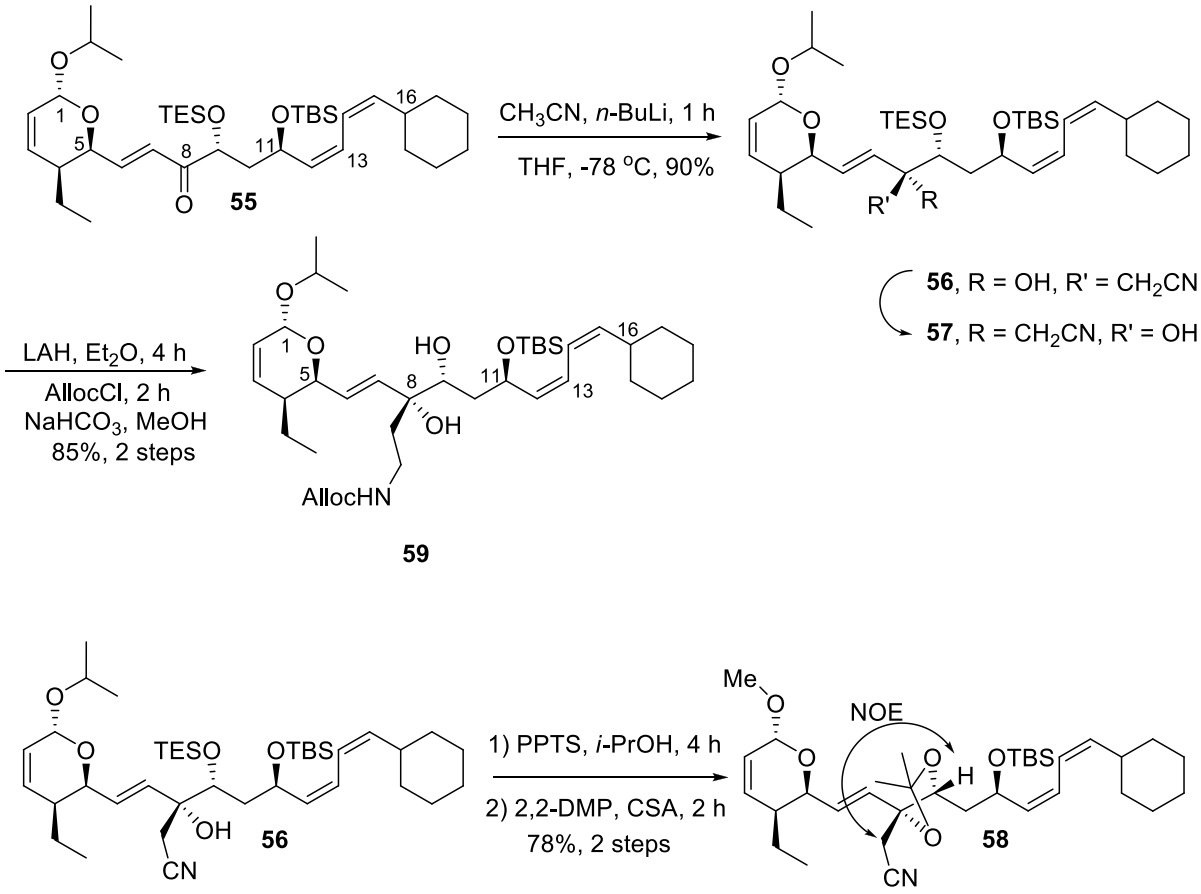


Scheme 7. Synthesis of Ketone **55**.

Oxidation of the epimeric alcohols using DMP[28] yielded the ketone **54** which was stereoselectively reduced by asymmetric transfer hydrogenation using Noyori's catalyst following Spur's protocol[29] to yield alcohol **53**. Protection employing standard conditions afforded TES ether **29**. Oxidation of the sulfide in **29** with *m*-CPBA afforded an equimolar mixture of sulfoxides which without isolation was subjected to [2,3] sigmatropic rearrangement[30] in the presence of 2-mercapto-1-methylimidazole[31] as a thiophilic agent, to yield unsaturated ketone **55**, Scheme 7.

The amino ethyl side chain was introduced by way of reaction of lithio acetonitrile with ketone **55** to afford a 4:1 mixture of tertiary alcohols **56** and **57**. The structure of the

major isomer **56** was unambiguously assigned by NOE studies on the acetonide **58**, obtained by selective deprotection of the TES ether and reaction of the ensuing diol with 2,2-dimethoxypropane. NOE between C9H and *CH*$_2$CN supported the structural assignment to compound **56**.



Scheme 8. Synthesis of Carbon Backbone of PLM-B.

The formation of **56** can be rationalized by a Felkin-Anh model wherein the acetonitrile anion attacks the carbonyl group from the face away from the OTES moiety. Reduction of the nitrile in **56** with LAH afforded the primary amine with concomitant deprotection of the TES ether. The primary amine was protected as its allyl carbamate **59** to provide the all carbon containing subunit of PLM-B, Scheme 8.

Conclusion

In conclusion, we have developed a new strategy to the entire carbon framework of PLM-B. The key steps include non-Evans *syn* aldol reaction to forge the C4 and C5

stereogenic centers, utilization of an α-chloro sulfide for the preparation of a propargylic sulfide, [2,3] sigmatropic rearrangement of a sulfoxide to prepare an unsaturated ketone and stereoselective introduction of the C8 stereocenter using lithio acetonitrile. Also unlike earlier reports the (*Z*,*Z*)-diene is introduced early in the synthesis. The C9 and C11 carbinols are stereoselectively introduced by transfer hydrogenation. The disclosed strategy would prove useful in the synthesis of related natural products.

Acknowledgements

J. S. Patel is thankful to Council of Scientific and Industrial Research (CSIR)-New Delhi for fellowship. S. R is grateful to the Department of Science and Technology, New Delhi for funding the project (SR/S1/OC-5/2011) and CSIR, New Delhi for funding under the XII five year plan programme entitled ORIGIN (CSC-108).

Experimental section

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-chloropropan-2-ol (10)

A 250 mL flask equipped with a stir bar and a thermometer was charged with (*R*,*R*)-Co(salen) complex (1.47 g, 2.15 mmol). The catalyst was dissolved in THF (13 mL) and cooled to 4 ^{o}C. The flask was charged with (±)-epichlorohydrin (8.45 mL, 108.0 mmol) followed by the addition of H_2O (901 μL, 50 mmol) over 1.5 h via syringe pump. The reaction mixture was stirred at 4 ^{o}C for 24 h. It was then cooled to –78 ^{o}C and diluted with CH_2Cl_2 (250 mL). The solution was transferred to a separating funnel and H_2O (75 mL) was added. The aqueous layer was separated, extracted with CH_2Cl_2 (15 mL x 2). The remaining catalyst was removed by filtration. The filtrate was concentrated in vacuo to give 5.96 g of (*R*)-3-chloro-1,2-propanediol (54 mmol, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.41-4.41 (bs, *OH*), 3.99-3.82 (m, 1H), 3.81-3.49 (m, 4H).

To a stirred solution of above diol (5.96 g, 54.0 mmol) in CH_2Cl_2 (200 mL) cooled to 0 ^{o}C was added imidazole (7.3 g, 108.0 mmol) followed by TBDPSCl (14.2 mL, 53.0 mmol)

dropwise over the period of 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched by the addition of H_2O (150 mL) and diluted with CH_2Cl_2 (100 mL). The layers were separated and the organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residual oil was purified by flash chromatography on silica gel using 5% EtOAc/hexane (v/v) as the eluent to give pure monoprotected silyl ether **10** (15.9 g, 85% yield) as a clear oil. TLC: R_f 0.2 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = –15.2 (*c* 1, $CHCl_3$); IR (neat): 3550, 2856, 1510, 1402, 1262, 1066, 1152, 805 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.70-7.63 (m, 4H), 7.46-7.38 (m, 6H), 3.95-3.88 (m, 1H), 3.78 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.73 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.68 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.63 (dd, *J* = 11.1, 5.5 Hz, 1H), 2.51 (d, *J* = 5.9 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 132.7, 129.8, 127.7, 71.4, 64.3, 45.7, 26.8, 19.2; MS (ESI): *m/z* 371 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{25}ClNaO_2Si$ 371.1205, Found 371.1223.

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(phenylthio)propan-2-ol (11)

To a stirred mixture of DBU (1.88 mL, 12.60 mmol) and thiophenol (1.28 mL, 12.60 mmol) in toluene (24 mL) cooled to 0 °C was added a solution of chloro alcohol **10** (4.38 g, 12.60 mmol) in toluene (8 mL) dropwise over 5 min. The resulting reaction mixture was stirred at room temperature for 12 h. The precipitated DBU·HCl salt was removed by filtration. The filtrate was washed with H_2O (8 mL) and dried over anhydrous Na_2SO_4. Toluene was evaporated in vacuo and the residue was purified by column chromatography using 1% ethyl acetate/hexane (v/v) as the eluent to furnish sulfide **11** (4.14 g, 78% yield) as a colorless liquid. TLC: R_f 0.2 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = –37.0 (*c* 1, $CHCl_3$); IR (neat): 3448, 2936, 2865, 1610, 1523, 1276, 1054, 1161, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66-7.62 (m, 4H), 7.47-7.33 (m, 8H), 7.29-7.24 (m, 2H), 7.21-7.17 (m, 1H), 3.85-3.80 (m, 1H), 3.75-3.72 (m, 2H), 3.15 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.03 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.65 (bs, 1H), 1.07

(s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5, 134.7, 132.9, 129.8, 129.4, 128.9, 127.7, 126.2, 70.2, 66.1, 37.1, 26.8, 19.2; MS (ESI): *m/z* 445 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{25}H_{30}NaO_2SSi$ 445.1628, Found 445.1629.

(*R*)-2,2,3,3,9,9-Hexamethyl-8,8-diphenyl-5-((phenylthio)methyl)-4,7-dioxa-3,8-disiladecane (12)

To a stirred solution of alcohol **11** (8.44 g, 20.0 mmol) in anhydrous CH_2Cl_2 (70 mL) cooled to 0 °C was added imidazole (2.72 g, 40.0 mmol) followed by TBS-Cl (3 g, 20 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched by the addition of H_2O (40 mL) and diluted with CH_2Cl_2 (80 mL). The layers were separated and the organic layer was washed with H_2O (80 mL), brine (40 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using pure hexane to afford silyl ether **12** (10.18 g, 95% yield) as a gummy oil. TLC: R_f 0.7 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = –12.0 (*c* 1, $CHCl_3$); IR (neat): 2936, 2856, 1502, 1322, 1445, 1275, 1024, 1161, 800 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.64 (m, 4H), 7.45-7.40 (m, 2H), 7.39-7.34 (m, 6H), 7.26-7.22 (m, 2H), 7.17-7.13 (m, 1H), 3.88-.84 (m, 1H), 3.68 (dd, *J* = 10.2 Hz, *J* = 4.6 Hz, 1H), 3.64 (dd, *J* = 10.2, 6.7 Hz, 1H), 3.41 (dd, *J* = 13.6, 4.6 Hz, 1H), 2.97 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.05 (s, 9H), 0.81 (s, 9H), –0.01 (s. 3H), –0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.3, 133.2, 129.6, 128.7, 128.6, 127.7, 125.5, 72.0, 66.7, 38.0, 26.8, 25.8, 19.2, 18.0, –4.6, –4.7; MS (ESI): *m/z* 559 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{31}H_{44}NaO_2SSi_2$ 559.2493, Found 559.2512.

(*R*)-2,2,3,3,9,9-Hexamethyl-8,8-diphenyl-5-((R)-1-(phenylthio)-3-(trimethylsilyl)prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (14)

To a solution of trimethylsilylacetylene (4.15 mL, 30.0 mmol) in anhydrous THF (30 mL) cooled to 0 °C was added *i*-PrMgCl·LiCl (1.5 M in THF, 20 mL, 30 mmol) and the mixture

stirred for 30 minutes at the same temperature. To the alkynyl Grignard reagent so generated was added a solution of $ZnBr_2$ (1.5 M in THF, 22 mL, 33 mmol) at 0 °C and the mixture stirred for 30 min. Separately, in another round-bottom flask, the α-chloro sulfide **13** was prepared by adding a solution of sulfide **12** (8 g, 15 mmol) in anhydrous benzene (75 mL) to NCS (1.99 g, 15.0 mmol) in anhydrous benzene (75 mL) and stirred for 45 min at 0 °C. To the organozinc reagent maintained at 0 °C the solution of α-chloro sulfide in benzene was added via canula and the reaction mixture was stirred for 10 h gradually, allowing it to attain room temperature. The reaction mixture was cooled to 0 °C and quenched by the addition of an aqueous saturated solution of NH_4Cl (30 mL). It was allowed to warm to room temperature and diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with H_2O (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using hexane as the eluent to afford the pure product compound **14** (7.34 g, 80% yield) as a light yellow liquid. TLC: R_f 0.8 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +75.0 (*c* 1, $CHCl_3$); IR (neat): 2933, 2856, 2239, 1510, 1448, 1276, 1161, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.70-7.61 (m, 4H), 7.59-7.54 (m, 2H), 7.45-7.34 (m, 6H), 7.30-7.20 (m, 3H), 4.29 (d, *J* = 2.8 Hz, 1H), 4.05-3.92 (m, 2H), 3.65 (dd, *J* = 9.6, 4.3 Hz, 1H), 1.05 (s, 9H), 0.85 (s. 9H), 0.11 (s, 9H), 0.05 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.5, 133.3, 133.1, 132.4, 129.7, 128.5, 127.6, 127.0, 105.0, 89.2, 74.9, 64.7, 44.1, 26.8, 25.7, 19.1, 18.0, –0.1, –4.5, –4.7; MS (ESI): *m/z* 633 $[M+H]^+$. HRMS (ESI): calcd. for $C_{36}H_{53}O_2SSi_3$ 633.3069, Found 633.3086.

(*R*)-2,2,3,3,9,9-Hexamethyl-8,8-diphenyl-5-((*R*)-1-(phenylthio)prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (15)

To a stirred solution of alkyne **14** (6.1 g, 10.0 mmol) in methanol (40 mL) was added potassium carbonate (27 mg, 2 mmol) and reaction mixture stirred ar room temperature for 30 minutes. Methanol was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and H_2O (10 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude product which was purified by flash chromatography on silica gel using 2% EtOAc/hexane (v/v) as the eluent to afford the alkyne **15** as colourless oil (5.5 g, 98% yield). TLC: R_f 0.7 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +112.0 (*c* 1, $CHCl_3$); IR (neat): 3320, 2935, 2855, 2235, 1540, 1442, 1274, 1027, 1168, 808 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66-7.63 (m, 4H), 7.55-7.53 (m, 2H), 7.44-7.40 (m, 2H), 7.38-7.34 (m, 4H), 7.32-7.27 (m, 2H), 7.26-7.23 (m, 1H), 4.27 (t, *J* = 2.9 Hz, 1H), 4.05-4.00 (m, 1H), 3.97 (dd, *J* = 10.0, 7.4 Hz, 1H), 3.65 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.35 (d, *J* = 2.6 Hz, 1H), 1.02 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5, 133.2, 131.4, 129.8, 129.7, 128.7, 127.6, 126.9, 83.4, 75.0, 72.6, 64.6, 43.2, 26.7, 25.7, 19.1, 18.0 –4.6, –4.7; MS (ESI): *m/z* 583 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{33}H_{44}NaO_2SSi_2$ 583.2493, Found 583.2504.

Ethyl 4-((4-methoxybenzyl)oxy)-3-oxobutanoate (17)

p-Methoxybenzyl alcohol (4.4 g, 31.9 mmol) was added dropwise to a stirred suspension of sodium hydride (60% in Nujol, 2.67 g, 66.80 mmol) in anhydrous THF (20 mL), occasional cooling was required with an ice bath to maintain ambient temperature. After hydrogen evolution ceased, the thick slurry was allowed to stir for 2 h. Ethyl 4-chloro-acetoacetate **16** (5 g, 30 mmol) was then added dropwise within 3 h, and the reaction mixture was stirred for 16 h. The reaction mixture was carefully added into 5% HCl solution (20 mL) cooled to 5 °C and extracted with EtOAc (10 mL x 3). The organic layer was washed with an aqueous saturated solution of $NaHCO_3$ (6 mL x 2), brine (6 mL), dried over anhydrous Na_2SO_4,

filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent to give **17** (7.26 g, 91% yield) as pale yellow oil. TLC: R_f 0.5 (20% EtOAc/hexane); IR (neat): 2933, 2856, 1735, 1710, 1448, 1276, 1161, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.52 (s, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.11 (s, 2H), 3.81 (s, 3H), 3.51 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 166.9, 159.4, 129.5, 128.8, 113.8, 74.4, 73.0, 61.3, 52.2, 45.9, 14.0; MS (ESI): *m/z* 289 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{18}NaO_5$ 289.1046, Found 289.1069.

(*R*)-Ethyl 3-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (18)

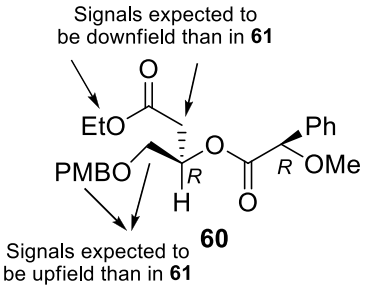
Catalyst Preparation: A 50 mL pressure tube was charged with a stir bar, $(RuC1_2.COD)_n$ (39.0 mg, 0.13 mmol), (*S*)-2,2'-bis(diphenylphosphino)-l,l'-binaphthyl (100.0 mg, 0.16 mmol), triethylamine (0.28 mL, 0.20 mmol), and toluene (4 mL). The tube was capped securely and then heated at 140 °C in an oil bath until the solution was clear homogeneous red in colour (4 h). The contents of the flask were transferred to a 100 ml, round-bottom flask with toluene (40 mL). The toluene was removed in vacuo, and the resulting red oil was taken up in anhydrous THF (10 mL). The brown THF suspension was divided into five x 2 mL portions, which were stored in stoppered vials under N_2.

Under N_2, a hydrogen reactor was charged with absolute EtOH (50 mL), β-keto ester **17** (26.6 g, 100.0 mmol), the catalyst as prepared above (4 mL, from 40 mg BINAP), and the autoclave was closed under N_2. Hydrogen was introduced three times and released each time through a valve into a ventilated hood. The pressure reactor was then filled with H_2 (50 bar) and heated to 80 °C (inner temperature), and the contents were stirred for 6 h. The reactor was cooled to room temperature. TLC analysis indicated consumption of the starting material. The reaction solution was concentrated in a rotary evaporator and the purification by flash chromatography on silica gel using 16% EtOAc/hexane (v/v) as the eluent yielded

the title compound **18** (25.7 g, 96% yield) as yellow coloured oil with enantiomeric purity of 99% as determined using chiral HPLC. TLC: R_f 0.3 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +52.0 (*c* 1, $CHCl_3$); IR (neat): 3450, 2935, 2856, 1735, 1710, 1452, 1262, 1158, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.49 (s, 2H), 4.24-4.18 (m, 1H),), 4.15 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.49 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.44 (dd, *J* = 9.6, 6.1 Hz, 1H), 3.02 (d, *J* = 3.9 Hz, 1H), 2.52 (d, *J* = 6.2 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 159.0, 129.7, 129.1, 113.5, 72.8, 72.7, 66.9, 60.4, 54.9, 38.1, 13.9; MS (ESI): *m/z* 291 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{20}NaO_5$ 291.1203, Found 291.1227.

General procedure for the esterification: To a solution of an alcohol **18** (1.0 eq) in CH_2Cl_2 (10 mL/mmol) were added DCC (1.2 eq), DMAP (0.2 eq) and (*R*)- or (*S*)-methoxyphenylacetic acid (1.5 eq). The mixture was stirred overnight at room temperature and the cloudy solution was filtered on cotton. The filtrate was diluted with H_2O (10 mL), the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2) and the combined organic layer was washed with saturated aqueous solutions of $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was characterised by ^1H NMR spectroscopy.

(*R*)-Ethyl 3-((*R*)-2-methoxy-2-phenylacetoxy)-4-((4-methoxybenzyl)oxy)butanoate (60)

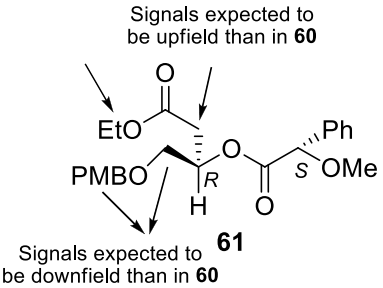


60

Following the procedure detailed above alcohol **18** (27.0 mg, 0.1 mmol), was reacted with (*R*)-methoxyphenylacetic acid (24.0 mg, 0.15 mmol) to afford ester **60** (35 mg, 85% yield). TLC: R_f 0.4 (20% EtOAc/hexane); IR (neat): 2935, 2854, 1740, 1448, 1272, 1172, 1052, 803

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2H), 7.28-7.22 (m, 3H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.41-5.36 (m, 1H), 4.69 (s, 1H), 4.21 (d, *J* = 11.5 Hz, 1H), 4.18 (d, *J* = 11.5 Hz, 1H), 4.02-3.95 (m, 2H), 3.72 (s, 3H), 3.40 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.34 (s, 3H), 3.32 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.60 (d, *J* = 6.2 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 3H).

(*R*)-Ethyl 3-((*S*)-2-methoxy-2-phenylacetoxy)-4-((4-methoxybenzyl)oxy)butanoate (61)



Following the procedure detailed above alcohol **18** (27.0 mg, 0.1 mmol), was reacted with (*S*)-methoxyphenylacetic acid (24.0 mg. 0.15 mmol) to afford ester **61** (34 mg, 83% yield). TLC: R_f 0.5 (20% EtOAc/hexane); IR (neat): 2937, 2850, 1738, 1457, 1270, 1162, 1055, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44-7.40 (m, 2H), 7.36-7.30 (m, 3H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.46-5.41 (m, 1H), 4.74 (s, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 3.90 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.82-3.76 (m, 4H), 3.59 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.55 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.38 (s, 3H), 2.58 (d, *J* = 6.2 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H).

Note: A comparison of the NMR of esters **60** and **61** unambiguously proves the configuration of the newly created stereocenter in compound **18** as '*R*' based on the report of Trost and co-workers.

(*R*)-Ethyl 4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy)butanoate (19)

To a stirred solution of alcohol **18** (13.4 g, 50.0 mmol) and *i*-Pr_2NEt (21 mL, 120 mmol) in CH_2Cl_2 (200 mL) cooled to 0 °C was added MOMCl (4.5 mL, 60.0 mmol) at 0 °C and resulting reaction mixture was stirred at room temperature. After stirring for 4 h, the reaction was quenched with an aqueous saturated solution of NH_4Cl (100 mL) and extracted with

$CHCl_3$ (50 mL x 3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 5% EtOAc/hexane (v/v) as the eluent to afford the MOM ether **19** (14.8 g, 95% yield) as a colourless oil. TLC: R_f 0.6 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +72.0 (*c* 1, $CHCl_3$); IR (neat): 2937, 2855, 1735, 1448, 1276, 1044, 1161, 805 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.70 (s, 2H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.21-4.16 (m, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.55 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.49 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.32 (s, 3H), 2.64-2.55 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 159.0, 129.9, 129.0, 113.5, 96.2, 73.2, 72.7, 71.3, 60.2, 55.3, 55.0, 37.6, 14.0; MS (ESI): *m/z* 313 $[M+H]^+$. HRMS (ESI): calcd. for $C_{16}H_{25}O_6$ 313.1646, Found 313.1662.

(*R*)-4-((4-Methoxybenzyl)oxy)-3-(methoxymethoxy)butanal (20)

To a stirred solution of ester **19** (3.12 g, 10.0 mmol) in anhydrous CH_2Cl_2 (60 mL) cooled to –78 °C was added DIBAL-H (1.25 M in toluene 8 mL) dropwise over a period of 10 minutes, TLC examination soon after addition revealed consumption of starting material, the reaction mixture was quenched at –78 °C by adding a saturated solution of sodium potassium tartrate (20 mL). The reaction mixture was warmed to room temperature and stirred for 2 h. The organic layer was separated and extracted with $CHCl_3$ (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residual oil was purified by flash chromatography on silica gel using 3% EtOAc/hexane (v/v) as the eluent to afford aldehyde **20** (2.62 g, 98% yield) as a colourless oil. TLC: R_f 0.5 (20% EtOAc/hexane); IR (neat): 2933, 2856, 2239, 1725, 1448, 1276, 1161, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.77 (t, *J* = 2.5 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.26 (quint, *J* = 5.3 Hz, 1H), 3.80 (s,

3H), 3.55 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.51 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.35 (s, 3H), 2.70-2.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.6, 159.2, 129.8, 129.2, 113.7, 96.1, 73.0, 71.7, 71.3, 55.5, 55.2, 46.5.

(5*R*,7*R*,10*R*,11*R*)-11-((*tert*-butyldimethylsilyl)oxy)-5-(((4-methoxybenzyl)oxy)methyl)-15,15-dimethyl-14,14-diphenyl-10-(phenylthio)-2,4,13-trioxa-14-silahexadec-8-yn-7-ol (21) and (5*R*,7*S*,10*R*,11*R*)-11-((*tert*-butyldimethylsilyl)oxy)-5-(((4-methoxybenzyl)oxy)methyl)-15,15-dimethyl-14,14-diphenyl-10-(phenylthio)-2,4,13-trioxa-14-silahexadec-8-yn-7-ol (22)

To a solution of compound **15** (2.8 g, 5.0 mmol) in anhydrous THF (30 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexane, 2 mL, 5 mmol) dropwise and stirred at the same temperature for 40 min. A solution of aldehyde **20** (1.4 g, 5.5 mmol) in THF (2 mL) was added to the above lithio alkyne. The reaction mixture was warmed gradually to 0 °C over a period of 1 h. The reaction mixture was quenched at 0 °C with an aqueous saturated solution of NH_4Cl (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude compound. Purification by flash chromatography on silica gel using 15% EtOAc/hexane (v/v) as the eluent furnished alcohol **21** and **22** as an inseparable epimeric mixture in equimolar amounts as a yellow oil (3.82 g, 93% yield). TLC: R_f 0.2 (20% EtOAc/hexane); IR (neat): 3452, 2933, 2856, 2250, 1510, 1455, 1279, 1027, 11612, 810 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.63 (m, 8H), 7.54-7.50 (m, 4H), 7.45-7.34 (m, 12H), 7.30-7.19 (m, 10H), 6.89-6.85 (m, 4H), 4.71-4.60 (m, 4H), 4.49-4.42 (m, 4H), 4.58-4.52 (m, 2H), 4.36-4.33 (m, 2H), 4.05-3.94 (m, 5H), 3.90-3.85 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 (m, 2H), 3.50-3.42 (m, 4H), 3.36 (s, 3H), 3.33 (s, 3H), 2.0 (dt, *J* = 14.2, 5.4 Hz, 1H), 1.96-1.90 (m, 1H), 1.89-1.83 (m, 1H), 1.78 (dt, *J* = 14.5, 5.0 Hz, 1H), 1.04 (s, 18H), 0.85 (s, 18H), 0.05 (s, 6H), –0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 135.4, 133.1, 133.0, 131.6, 131.5, 129.7, 129.6, 129.2, 129.1, 128.6, 127.6, 113.6, 96.7, 96.0, 85.2, 85.1, 84.0, 83.9, 75.1, 75.0, 74.2, 72.9, 72.8, 72.2, 71.9, 64.7, 64.6,

60.2, 59.4, 55.6, 55.5, 55.1, 43.3, 43.2, 40.3, 39.6, 26.7, 25.6, 19.0, 17.9, –4.5, –4.6, –4.7, –4.8; MS (ESI): *m/z* 851 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{47}H_{64}NaO_7SSi_2$ 851.3803, Found 851.3805.

(5*R*,10*R*,11*R*)-11-((*tert*-Butyldimethylsilyl)oxy)-5-(((4-methoxybenzyl)oxy)methyl)-15,15-dimethyl-14,14-diphenyl-10-(phenylthio)-2,4,13-trioxa-14-silahexadec-8-yn-7-one (23)

To a solution of the epimeric mixture of alcohols **21** and **22** (3.3 g, 4.0 mmol) in anhydrous CH_2Cl_2 (30 mL) cooled to 0 °C was added Dess-Martin periodinane (2.2 g, 5.2 mmol) in one portion and the reaction mixture stirred at the same temperature for 1 h. The reaction was quenched at 0 °C by the addition of a 1:1 mixture of saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ (10 mL). The reaction mixture was stirred at room temperature for 1 h. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude compound. Purification by flash chromatography on silica gel using 2-5% EtOAc/hexane (v/v) as the eluent afforded propargylic ketone **23** (3.1 g, 95% yield) as a yellow oil. TLC: R_f 0.5 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +89.0 (*c* 1, $CHCl_3$); IR (neat): 2935, 2852, 2245, 1705, 1510, 1420, 1270, 1168, 805 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.67-7.61 (m, 4H), 7.54 (d, *J* = 8 Hz, 2H), 7.44-7.34 (m, 6H), 7.31-7.21 (m, 5H), 6.87 (d, *J* = 8 Hz, 2H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 5.8 Hz, 1H), 4.27-4.21 (m, 1H), 4.08-4.03 (m, 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.80 (s, 3H), 3.62 (d, *J* = 9.0 Hz, 1H), 3.51 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.45 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.30 (s, 3H), 2.85-2.73 (m, 2H), 1.02 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.6, 159.1, 135.4, 134.6, 133.0, 132.9, 132.2, 130.0, 129.8, 129.7, 129.2, 128.9, 127.8, 127.7, 127.5, 113.7, 96.4, 92.2, 83.6, 74.4, 72.9, 72.4, 71.4, 64.2, 55.5, 55.2, 48.2, 43.7, 26.7, 25.6, 19.1,

179, –4.6, -4.8; MS (ESI): *m/z* 849 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{47}H_{62}NaO_7SSi_2$ 849.3647, Found 849.3622.

(5*R*,7*R*,10*R*,11*R*)-11-((*tert*-Butyldimethylsilyl)oxy)-5-(((4-methoxybenzyl)oxy)methyl)-15,15-dimethyl-14,14-diphenyl-10-(phenylthio)-2,4,13-trioxa-14-silahexadec-8-yn-7-ol (22)

To a solution of ketone **23** (826 mg, 1 mmol) in ethyl acetate (15 mL) was added sodium formate (1.36 g, 20.0 mmol), (*R*,*R*)-Noyori catalyst (7.0 mg, 0.01 mmol), distilled H_2O (15 mL), finally catalytic amounts of hexadecyltrimethylammonium bromide and the reaction mixture was stirred at room temperature for 24 h. The layers were separated, the aqueous layer was extracted with ethyl acetate (10 mL x 3) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude compound. Purification by flash chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent provided alcohol **22** (695 mg, 84% yield) as a yellow coloured oil. TLC: R_f 0.2 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +68.0 (*c* 1, $CHCl_3$); IR (neat): 3445, 2930, 2848, 2239, 1423, 1279, 1158, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68-7.62 (m, 4H), 7.52 (d, *J* = 8 Hz, 2H), 7.46-7.32 (m, 6H), 7.30-7.18 (m, 5H), 6.88 (d, *J* = 8 Hz, 2H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.60-4.50 (m, 1H), 4.43 (s, 2H), 4.37-4.32 (m, 1H), 4.05-3.86 (m, 3H), 3.80 (s, 3H), 3.62 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.50-3.40 (m, 2H), 3.35 (s, 3H), 2.93 (d, *J* = 6.2 Hz, 1H), 2.01-1.83 (m, 1H), 1.82-1.71 (m, 1H), 1.00 (s, 9H), 0.83 (s, 9H), 0.04 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 135.6, 135.5, 133.2, 133.1, 131.6, 129.7, 129.6, 129.1, 128.6, 127.6, 126.7, 113.7, 96.8, 85.1, 84.0, 75.0, 74.3, 72.9, 72.2, 64.7, 59.5, 55.7, 55.2, 43.3, 39.6, 26.7, 25.7, 19.1, 18.0, –4.5, –4.7; MS (ESI): *m/z* 851 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{47}H_{64}NaO_7SSi_2$ 851.3803, Found 851.3807.

(2*E*,5*Z*,6*R*,8*R*)-5-((2*R*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(phenylthio)butylidene)-9-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)non-2-ene-1,6-diol (26)

To a solution of mixture of alkyne **22** (528.0 mg, 0.64 mmol) and homoallyl alcohol (92.0 mg, 1.24 mmol) in acetone (1 mL) was added $[CpRu(CH_3CN)_3]PF_6$ (28.0 mg, 0.064 mmol) and stirred at room temperature for 2 h. Acetone was evaporated the residue taken in to Et_2O (2 mL) and H_2O (2 mL). The aqueous layer was extracted with Et_2O (2 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography using 30% EtOAc/hexane (v/v) as the eluent to afford readily separable regioisomers **26** and **27** in (1:1 ratio) in a combined yield of 25% (143 mg). TLC: R_f 0.3 (40% EtOAc/hexane); $[\alpha]^{25}_D$ = +44.0 (*c* 1, $CHCl_3$); IR (neat): 3449, 2933, 2856, 2239, 1610, 1524, 1448, 1345, 1266, 1162, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74-7.66 (m, 4H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.45-7.35 (m, 6H), 7.25-7.20 (m, 5H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.62 (dt, *J* = 15.2, 4.7 Hz, 1H), 5.59 (dt, *J* = 15.2, 5.3 Hz, 1H), 5.43 (d, *J* = 11.1 Hz, 1H), 4.62 (d, *J* = 6.5 Hz, 1H), 4.53- 4.49 (m, 2H), 4.40 (s, 2H), 4.30 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.07 (d, *J* = 4.1 Hz, 2H), 4.02 (dd, *J* = 10.0, 5.8 Hz, 1H), 3.84-3.75 (m, 6H), 3.55 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.34 (d, *J* = 5.0 Hz, 1H), 3.24 (s, 3H), 2.81 (dd, *J* = 16.9, 5.2 Hz, 1H), 2.67 (dd, *J* = 16.9, 5.9 Hz, 1H), 1.54-1.47 (m, 1H), 1.36-1.30 (m, 1H), 1.08 (s, 9H), 0.84 (s, 9H), –0.03 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 140.2, 135.6, 134.5, 133.3, 133.2, 131.2, 130.9, 129.8, 129.7, 129.2, 128.8, 128.6, 127.7, 127.4, 126.6, 113.7, 96.7, 75.2, 73.8, 72.9, 72.8, 66.1, 65.3, 63.6, 55.5, 55.2, 51.7, 37.5, 34.3, 26.9, 25.8, 19.2, 18.0, –4.3, –4.8; MS (ESI): *m/z* 923 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{51}H_{72}NaO_8SSi_2$ 923.4378, Found 923.4372.

(2*E*,5*Z*,7*R*,9*R*)-5-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-((*tert*-butyldiphenylsilyl)oxy)-1-(phenylthio)propyl)-10-((4-methoxybenzyl)oxy)-9-(methoxymethoxy)deca-2,5-diene-1,7-diol (27)

TLC: R_f 0.3 (40% EtOAc/hexane); $[\alpha]^{25}_D$ = +32.0 (*c* 1, $CHCl_3$); IR (neat): 3448, 2935, 2846, 2299, 1615, 1528, 1438, 1335, 1246, 1130, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (d,

J = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.50-7.46 (m, 2H), 7.45-7.34 (m, 6H), 7.26-7.19 (m, 5H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.86 (d, *J* = 11.1 Hz, 1H), 5.48-5.41 (m, 1H), 5.21-5.15 (m, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 2H), 4.47 (d, *J* = 11.7 Hz, 2H), 4.35 (dd, *J* = 10.9, 2.2 Hz, 1H), 4.19-4.16 (m, 1H), 4.10-4.07 (m, 1H), 3.94-3.89 (m, 1H), 3.84-3.78 (m, 6H), 3.56 (dd, *J* = 10.0, 4.7 Hz, 1H), 3.47 (d, *J* = 5.0 Hz, 2H), 3.37 (s, 3H), 2.56-2.50 (m, 1H), 2.47-2.41 (m, 1H), 1.39-1.36 (m, 2H), 1.06 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), –0.14 (s, 3H); MS (ESI): *m/z* 923 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{51}H_{72}NaO_8SSi_2$ 923.4378, Found 923.4364.

(*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)butan-1-one (33)

To a stirred solution of 4-benzyl-2-thioxothiazolidine (2.3 g, 11.0 mmol) in anhydrous CH_2Cl_2 (22 mL) cooled to 0 ºC was added Et_3N (2.0 mL, 14.3 mmol) followed by *n*-butyryl chloride (1.25 mL, 12 mmol). The reaction mixture was stirred for 1 h at room temperature and quenched with an aqueous saturated solution of NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness under reduced pressure, and purified by silica gel chromatography using 1% EtOAc/hexane (v/v) as the eluent to afford compound **33** (2.9 g , 95% yield) as a solid. M.P. = 101 ºC. TLC: R_f 0.80 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = –204.0 (*c* 1, CHCl3); IR (KBr): 2958, 2925, 1694, 1162, 1062, 1034 cm-1; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-725 (m, 5H), 5.40-5.35 (m, 1H), 3.41-3.31 (m, 2H), 3.22 (dd, *J* = 13.1, 3.6 Hz, 1H), 3.15-3.10 (m, 2H), 2.88 (d, *J* = 11.6 Hz, 1H), 1.80-1.65 (m, 2H), 098 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 173.8, 136.4, 129.3, 128.7, 127.0, 68.4, 40.2, 36.6, 31.8, 18.0, 13.5; MS (ESI): *m/z* 280 $[M+H]^+$. HRMS (ESI): calcd. for $C_{14}H_{18}NO_2S_2$ 280.0825, Found 280.0824.

(2*R*,3*R*)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-2-ethyl-3-hydroxy-4-(phenylthio)butan-1-one (35)

To a solution of thiazolidine thione **33** (2.79 g, 10.0 mmol) in CH_2Cl_2 (60 mL) cooled to 0 °C, maintained under N_2 atmosphere was added, titanium (IV) chloride (20.0 mmol, 2.2 mL) dropwise and the mixture stirred for 5 min. To the resulting yellow slurry diisopropylethylamine (1.9 mL, 11.0 mmol) was added. The dark red titanium enolate was stirred for 20 min at 0 °C and then was cooled to –78 °C. Freshly prepared 2-phenylthio acetaldehyde **34** (1.67 g, 11.0 mmol) was added dropwise. The resulting mixture was stirred for 1 h at –78 °C and then was warmed to 0 °C. The reaction was quenched with an aqueous saturated solution of NH_4Cl (60 mL) and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness under reduced pressure and purified by silica gel chromatography using 8% EtOAc/hexane (v/v) as the eluent to furnish the yellow coloured compound **35** (3.62 g, 84% yield). TLC: R_f 0.20 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +62.0 (*c* 1, $CHCl_3$); IR (neat): 3448, 2933, 2856, 2239, 1710, 1448, 1276, 1161, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.43-7.20 (m, 10H), 5.41-5.32 (m, 1H), 4.85 (dt, *J* = 9.4, 4.7 Hz, 1H), 4.16-4.07 (m, 1H), 3.36 (dd, *J* = 11.5, 6.9 Hz, 1H), 3.28-2.98 (m, 4H), 2.96-2.87 (m, 2H), 1.95-1.65 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 175.8, 136.1, 135.2, 129.2, 129.1, 128.8, 128.6, 127.0, 126.0, 69.5, 68.6, 48.9, 38.4, 36.7, 32.2, 21.4, 11.3; MS (ESI): *m/z* 454 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{22}H_{25}NNaO_2S_3$ 454.0940, Found 454.0930.

(2*R*,3*R*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2-ethyl-4-(phenylthio)butan-1-one (36)

To a stirred solution of alcohol **35** (6.4 gm, 15.0 mmol) in CH_2Cl_2 (60 mL) cooled at –78 °C was added 2,6-lutidine (3.8 mL, 33.0 mmol), followed by addition of TBSOTf (3.7 mL, 16.5 mmol). After 1 h, the reaction was quenched by addition of an aqueous saturated solution of $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (40 mL x 2).The combined organics were washed with 10% $NaHSO_4$ (40 mL), dried

and concentrated under reduced pressure. The crude product was purified by column chromatography using 2% EtOAc/hexane (v/v) as the eluent to provide the product **36** (7.6 g, 94% yield) as bright yellow oil. TLC: R_f 0.6 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +98.9 (*c* 1, $CHCl_3$); IR (neat): 3061, 3027, 2955, 2930, 2882, 2856, 1688, 1564, 1461, 1340, 1258, 1191, 1161, 837,776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.22 (m, 10H), 5.35-5.29 (m, 1H), 4.93-4.88 (m, 1H), 4.33 (dd, *J* = 12.3, 6.7 Hz, 1H), 3.32-3.23 (m, 3H), 3.16 (dd, *J* = 13.7, 5.3 Hz, 1H), 3.04-2.98 (m, 1H), 2.86 (d, *J* = 12.3 Hz, 1H), 1.90-1.70 (m, 2H), 0.94-0.85 (m, 12H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 175.5, 136.7, 136.6, 129.5, 129.3, 128.9, 128.8, 127.1, 126.0, 72.0, 69.2, 50.0, 40.6, 36.5, 31.7, 25.9, 23.5, 18.1, 11.0, –4.0, –4.4; MS (ESI): *m/z* 568 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{28}H_{39}NNaO_2S_3Si$ 568.1804, Found 568.1809.

(2*R*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-ethyl-4-(phenylthio)butanal (37)

DIBAL-H (1.25 M in toluene, 8 mL, 10 mmol,) was added dropwise to a solution of TBS compound **36** (2.72 g, 5.0 mmol) in anhydrous CH_2Cl_2 (40 mL) cooled to –78 °C and stirred for 30 minutes at the same temperature. The yellow colour of reaction mixture turned to colourless and TLC examination revealed consumption of starting material. The reaction mixture was then quenched by adding saturated aqueous sodium potassium tartrate solution (25 mL) at –78 ºC followed by vigorous stirring for 1 h at room temperature. The aqueous phase was then extracted with CH_2Cl_2 (30 mL x 3) and the combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to yield aldehyde **37** (1.54 g, 89% yield) as a colourless oil. TLC: R_f 0.7 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +32.9 (*c* 1, $CHCl_3$); IR (neat): 3060, 2930, 2874, 1720, 1687, 1583, 1438, 1362, 1341, 1258, 1137, 1035, 793 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.75 (d, *J* = 1.5 Hz, 1H), 7.36-7.18 (m, 5H), 4.20 (dt, *J* = 6.7, 3.0 Hz, 1H), 3.05-3.0 (m, 2H), 2.60-2.52

(m, 1H), 1.84-1.72 (m, 1H), 1.55-1.40 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3, 135.6, 129.6, 128.9, 126.4, 70.8, 57.4, 38.5, 25.6, 17.8, 16.6, 12.2, –4.3, –4.9; (ESI): *m/z* 361 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{30}NaO_2SSi$ 361.1628, Found 361.1623.

(4*S*,5*R*,*Z*)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-6-(phenylthio)hex-2-enoate (39)

To the suspension of NaH (60% in Nujol, 480 mg, 12 mmol) in anhydrous THF (30 mL) cooled to –78 ºC was added Ando's reagent **38** (3.84 g, 12.0 mmol) in anhydrous THF (20 mL) after 15 minutes, the aldehyde **37** (3.38 g, 10.0 mmol) in THF (5 mL) was added and the resulting mixture was gradually warmed to –20 ºC over 1-2 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2).The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. After determining *Z*/*E* ratio of the crude mixture by ^{1}H NMR the product was purified by silica gel chromatography using 1% EtOAc/hexane (v/v) as the eluent to afford compound **39** (3.59 g, 88% yield). TLC: R_f 0.6 (2% EtOAc/hexane); $[\alpha]^{25}_D$ = +18.7 (*c* 1, $CHCl_3$); IR (neat): 2959, 2930, 2857, 1720, 1645, 1585, 1472, 1414, 1388, 1255, 1185, 1094, 1040, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.28-7.24 (m, 2H), 7.18-7.14 (m, 1H), 6.06 (dd, *J* = 11.7, 10.8 Hz, 1H), 5.86 (d, *J* = 11.7 Hz, 1H), 4.20-4.14 (m, 2H), 3.86-3.81 (m, 1H), 3.76-3.69 (m, 1H), 3.14 (dd, *J* = 13.1, 6.2 Hz, 1H), 2.97 (dd, *J* = 13.1, 6.2 Hz, 1H), 1.68-1.60 (m, 1H), 1.35-1.25 (m, 4H), 0.88 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.03 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 151.1, 136.8, 129.4, 128.7, 125.8, 121.1, 74.1, 59.8, 44.1, 39.0, 25.8, 21.4, 18.0, 14.2, 11.6, –4.6, –4.1; (ESI): *m/z* 431 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{22}H_{36}NaO_3SSi$ 431.2047, Found 431.2053.

(5*S*,6*R*)-5-Ethyl-6-((phenylthio)methyl)-5,6-dihydro-2H-pyran-2-one (7)

To a stirred solution of ester **38** (818 mg, 2 mmol) in methanol (20 mL) cooled to 0 °C was added 1 N HCl in methanol (2 mL, 2 mmol) and the reaction mixture stirred at room temperature for 1 day. Methanol was evaporated under reduced pressure to afford a residue which was diluted with EtOAc (10 mL). The organic layer was washed with aqueous saturated solution of $NaHCO_3$ (5 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to provide the lactone **7** (357 mg, 72% yield) as a colourless oil. TLC: R_f 0.4 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +36.5 (*c* 1, $CHCl_3$); IR (neat): 3066, 3022, 2945, 2872, 2850, 1690, 1620, 1451, 1330, 1250, 1189, 1166, 837 cm^1; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.36 (m, 2H), 7.33-7.20 (m, 3H), 7.02 (dd, *J* = 9.7, 6.2 Hz, 1H), 6.03 (d, *J* = 9.7 Hz, 1H), 4.54-4.48 (m, 1H), 3.35 (dd, *J* = 13.8, 5.7 Hz, 1H), 3.11 (dd, *J* = 13.9, 9.1 Hz, 1H), 2.62-2.55 (m, 1H), 1.70-1.61 (m, 1H), 1.55-1.45 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 150.3, 134.3, 130.0, 129.1, 126.9, 120.7, 78.2, 36.4, 34.1, 20.1, 10.6; (ESI): *m/z* 271 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{16}NaO_2Si$ 271.0764, Found 271.0775.

(4*S*,5*R*,6*R*,*Z*)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-4-ethyl-6-(phenylthio)-8-(trimethylsilyl)oct-2-en-7-ynoate (40)

Compound **40** was prepared following the procedure detailed earlier for the preparation of compound **14**. The sulfide **39** (6.12 g, 15.0 mmol) afforded the compound **40** (5.89 g, 78% yield) as a yellow oil. TLC: R_f 0.6 (2% EtOAc/hexane); $[\alpha]^{25}_D$ = +52.1 (*c* 1, $CHCl_3$); IR (neat): 2959, 2931, 2898, 2857, 2171, 1721, 1643, 1466, 1414, 1252, 1183, 1101, 1031, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.52-7.47 (m, 2H), 7.28-7.22 (3H), 6.0 (dd, *J* = 11.6, 10.8 Hz, 1H), 5.86 (d, *J* = 11.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.0-3.91 (m, 1H), 3.90-3.85 (m, 2H), 1.99-1.92 (m, 1H), 1.34-1.27 (m, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 0.94 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.19 (s, 3H), 0.11 (s, 9H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ

165.8, 149.8, 135.0, 132.7, 128.4, 127.1, 121.7, 105.1, 90.2, 76.9, 59.8, 46.6, 44.2, 26.0, 22.7, 18.4, 14.2, 11.4, –0.2, –3.6, –4.3; (ESI): *m/z* 505 $[M+H]^+$. HRMS (ESI): calcd. for $C_{27}H_{45}O_3SSi_2$ 505.2622, Found 505.2628.

(4*S*,5*R*,6*R*,*Z*)-Ethyl 4-ethyl-5-hydroxy-6-(phenylthio)oct-2-en-7-ynoate (41)

A buffered solution prepared from TBAF (1 M in THF, 20 mL, 20 mmol) was added to a solution of the compound **40** (5.04 g, 10.0 mmol) in THF (60 mL) cooled to 0 ºC and the reaction mixture stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (60 mL) and washed with saturated aqueous solution of NH_4Cl (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to furnish the crude product which was purified by flash chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent delivered alcohol **41** (2.86 g, 90% yield) as a colourless oil. TLC: R_f 0.2 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +62.7 (*c* 1, $CHCl_3$); IR (neat): 3299, 2964, 2930, 2874, 1716, 1644, 1261, 1183, 1094, 1029, 800, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57-7.53(m, 2H), 7.35-7.30 (m, 3H), 6.17 (dd, *J* = 11.6, 10.6 Hz, 1H), 5.90 (d, *J* = 11.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.90-3.83 (m, 1H), 3.78 (dd, *J* = 7.7, 2.4 Hz, 1H), 3.70-3.66 (m, 1H), 2.90 (bs, 1H), 2.48 (d, *J* = 2.7 Hz, 1H), 1.80-1.71 (m, 1H), 1.50-1.41 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 149.6, 133.8, 131.7, 128.8, 128.3, 121.5, 80.6, 74.9, 74.6, 59.9, 45.3, 42.3, 21.2, 14.1, 11.5; (ESI): *m/z* 319 $[M+H]^+$. HRMS (ESI): calcd. for $C_{18}H_{23}O_3S$ 319.1362, Found 319.1373

(5*S*,6*R*)-5-Ethyl-6-((*R*)-1-(phenylthio)prop-2-yn-1-yl)-5,6-dihydro-2H-pyran-2-one (42)

To a solution of the δ-hydroxy ester **41** (6.36 g, 2.0 mmol) in benzene (20 mL) and Ti(O-*i*Pr)$_4$ (0.06 mL, 0.20 mmol) was added and the yellow solution was refluxed for 3 h. The solution was cooled to room temperature and and a few drops of H_2O were added to quench Ti(O-

*i*Pr)$_4$. The resulting suspension was filtered through a pad of Celite and washed with EtOAc (20 mL) the filtrate was evaporated and the residue was purified by column chromatography using 35% EtOAc/hexane (v/v) as the eluent to yield alcohol **42** (424 mg, 78% yield) as a colourless oil. TLC: R_f 0.3 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +43.7 (*c* 1, $CHCl_3$); IR (neat): 2963, 1722, 1411, 1261, 1093, 1030, 864, 800, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H), 7.37-7.32 (m, 3H), 7.05 (dd, *J* = 9.7, 6.4 Hz, 1H), 6.07 (d, *J* = 9.7 Hz, 1H), 4.29 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.97 (dd, *J* = 10.2, 2.6 Hz, 1H), 2.66-2.60 (m, 1H), 2.44 (d, *J* = 2.6 Hz, 1H), 1.85-1.77 (m, 1H), 1.58-1.52 (m, 1H), 0.97 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 150.3, 135.2, 133.5, 128.9, 128.8, 120.7, 79.0, 78.9, 75.0, 40.3, 37.3, 20.3, 10.8; (ESI): *m/z* 295 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{16}NaO_2S$ 295.0763, Found 295.0783.

(2*R*,3*S*)-3-Ethyl-6-isopropoxy-2-((*R*)-1-(phenylthio)prop-2-yn-1-yl)-3,6-dihydro-2H-pyran (30)

DIBAL-H (1.25 M in toluene, 1.6 mL, 2 mmol) was added dropwise to a solution of lactone **42** (544 mg, 2 mmol) in CH_2Cl_2 (10 mL) cooled to –78 °C and the mixture stirred for 30 min at the same temperature. The reaction mixture was quenched by adding saturated aqueous sodium potassium tartrate solution (5 mL), diluted by CH_2Cl_2 (10 mL) and stirred vigorously for 1 h. The aqueous phase was extracted with CH_2Cl_2 (10 mL x 3), the combined organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the product used in the next step without further purification and characterisation.

The crude lactol obtained above was dissolved in *iso*-propanol (20 mL), PPTS (50 mg, 0.2 mmol) was added and the reaction mixture stirred for 24 h. Solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with aqueous saturated solution of $NaHCO_3$ (10 mL), brine (20 mL), dried over

anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford a crude compound that was purified by column chromatography using 1% EtOAc/hexane (v/v) as the eluent afforded pyran **30** (499 mg, 79% yield for 2 steps) as a inseparable mixture of anomers. TLC: R_f 0.8 (4% EtOAc/hexane); IR (neat): 3294, 3045, 2964, 2930, 2878, 2825, 1689, 1581, 1474, 1186, 1109, 1046, 1023, 964, 850, 740, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.60-7.55 (m, 4H), 7.35-7.26 (m, 6H), 6.16 (dd, *J* = 10.0, 6.0 Hz, 1H), 6.08 (dd, *J* = 10.2, 5.6 Hz, 1H), 5.72 (dd, *J* = 10.0, 2.7 Hz, 1H), 5.62 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.19 -5.17 (m, 1H), 5.15 (d, *J* = 2.7 Hz, 1H), 4.26-4.17 (m, 2H), 4.06-3.98 (m, 2H), 3.94 (dd, *J* = 10.5, 2.4 Hz, 1H), 3.67 (dd, *J* = 10.5, 2.4 Hz, 1H), 2.35 (d, *J* = 2.4 Hz, 1H), 2.30 (d, *J* = 2.4 Hz, 1H), 2.29-2.26 (m, 1H), 2.25-2.19 (m 1H), 1.79-1.61 (m, 2H), 1.45-1.40 (m, 2H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.8, 133.6, 133.3, 133.1, 132.9, 128.7, 128.6, 127.8, 127.7, 127.6, 97.7, 92.2, 80.2, 80.0, 75.8, 74.1, 73.9, 71.3, 70.9, 68.0, 41.6, 41.2, 37.7, 37.2, 23.6, 23.5, 22.1, 21.7, 20.9, 20.6, 11.3, 11.2; (ESI): *m/z* 339 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{24}NaO_2S$ 339.1389, Found 339.1410.

(Bromoethynyl)cyclohexane (44)

To a solution of commercially available ethynylcyclohexane **43** (3.24 gm, 30.0 mmol) in anhydrous acetone (60 mL) was added NBS (5.8 g, 33.0 mmol) and $AgNO_3$ (51.0 mg, 0.3 mmol). The reaction mixture was stirred at ambient temperature for 2 h, monitoring the progress by TLC. When the starting alkyne had disappeared on TLC, the mixture was filtered through a pad of Celite and filtrate evaporated. The residue was purified by small pad of silica gel using hexane as the eluent to afford bromoethynyl cyclohexane **44** (5.1 g 92% yield) as red coloured oil. TLC: R_f 0.7 (hexane); IR (neat): 2930, 2855, 2225, 1709, 1418, 1260, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.43-2.36 (m, 1H), 1.82-1.75 (m, 2H), 1.64-

1.74 (m, 2H), 1.54-1.40 (m, 3H), 1.35-1.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.3, 39.6, 32.2, 30.0, 25.7, 24.6.

6-Cyclohexyl-2-methylhexa-3,5-diyn-2-ol (46)

To a mixture of MeOH (10 mL) and H_2O (5 mL) were added *n*-butylamine (11.8 mL, 120.0 mmol), 2-methyl-3-butyne-2-ol **45** (5.04 g, 60.0 mmol), copper(I) chloride (594 mg, 6 mmol) and hydroxylaminehydrochloride (832 mg, 12 mmol) in order. The solution of bromoethynyl cyclohexane **44** (7.4 g, 40.0 mmol) in MeOH (5 mL) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 24 h and quenched with H_2O (10 mL). The mixture was extracted with ether (20 mL x 2), the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent to furnish product **46** (6.54 g, 86% yield). TLC: R_f 0.2 (10% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.50-2.43 (m, 1H), 2.02-1.94 (bs, 1H), 1.83-1.76 (m, 2H), 1.73-1.66 (m, 2H), 1.55-1.42 (m, 9H), 1.35-1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 85.6, 80.3, 67.3, 65.5, 64.1, 32.0, 31.1, 25.6, 24.6.

Compound 32: **Buta-1,3-diyn-1-ylcyclohexane (32)**

To a solution of alkynol **46** (1.12 g, 5.87 mmol) in PhH (290 mL), was added powdered KOH (726.0 mg, 12.9 mmol) in one portion. The reaction mixture was then heated to reflux under N_2 atmosphere. After 4 h, the reaction was cooled to room temperature and reaction solution was filtered through a pad of silica gel, eluting with 5% EtOAc/hexane (v/v) to afford the title compound as a pale yellow oil **32** (720 mg, 93% yield), which turned orange on standing. TLC: R_f 0.6 (10% EtOAc/hexane); IR (neat): 3307, 2930, 2855, 2225, 1709, 1448, 613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43-2.41 (m, 1H), 2.0 (d, *J* = 1.0 Hz, 1H), 1.84-1.76 (m. 2H), 1.73-1.66 (m, 2H), 1.52-1.43 (m, 3H), 1.35-1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.9, 68.4, 64.9, 64.5, 31.8, 29.1, 25.6, 24.5.

Ethyl 5-cyclohexylpenta-2,4-diynoate (47)

A solution of *n*-BuLi (2 M in hexane, 10 mL, 20 mmol) was added dropwise to a solution of alkyne **32** (2.64 g, 20.0 mmol) in anhydrous THF (100 mL) cooled to –78 ºC. After stirring for 1 h, ethyl chloroformate (2.3 mL, 24.0 mmol) was added at –78 ºC. The reaction mixture was stirred at –78 ºC for 1 h and then warmed gradually to 0 ºC over a period of 30 min. The reaction was quenched with an aqueous saturated solution of NH_4Cl (10 mL). The aqueous layer was separated and extracted with Et_2O (10 mL x 2). The combined organic layer was washed with brine (10 mL) and dried over $NaSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography using 2% EtOAc/hexane as an eluent to afford the desired product **47** (3.83 g, 94% yield). TLC: R_f 0.6 (5% EtOAc/hexane); IR (neat): 2933, 2856, 2239, 1710, 1448, 1276, 1161, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.23 (q, *J* = 7.0 Hz, 2H), 2.56-2.50 (m, 1H), 1.84-1.77 (m, 2H), 1.73-1.66 (m, 2H), 1.54-1.46 (m, 3H), 1.36-1.28 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 91.2, 71.6, 65.9, 63.5, 62.1, 31.5, 29.4, 25.4, 24.4. 13.9; MS (ESI): *m/z* 205 $[M+H]^+$. HRMS (ESI): calcd. for $C_{13}H_{17}O_2$ 205.1223, Found 205.1230.

Ethyl 7-cyclohexyl-3-oxohepta-4,6-diynoate (48)

To a solution of diisopropylamine (11 mL, 78 mmol) in anhydrous THF (70 mL) cooled to 0 ºC was added a solution of *n*-BuLi (2.5 M in hexane, 30.6 mL, 77.0 mmol) dropwise at 0 °C. After stirring for 20 min at the same temperature, the reaction mixture was cooled to –78 °C and ethyl acetate, (7.3 mL, 75.0 mmol) freshly distilled over P_2O_5, was added dropwise very slowly. The reaction mixture was cooled to -85 °C (EtOAc/N_2 liq) and the solution of ester **47** (6.1 g, 30.0 mmol) in anhydrous THF (10 mL) was added at such a rate that the internal temperature did not rise above –78 °C. After stirring for 1 h, glacial acetic acid (5.15 mL, 90.0 mmol) was added. The resulting suspension was warmed to 0 °C and hydrolyzed with H_2O (15 mL x 3). The pH of the aqueous phase was adjusted to pH ≈ 3 by adding aqueous 3

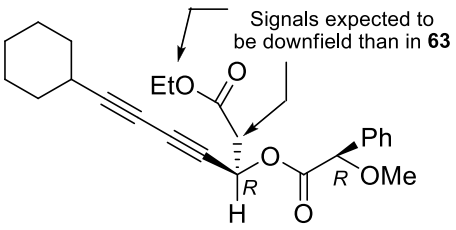
M HCl solution and the layers were separated. The aqueous phase was extracted with Et_2O (60 mL x 4) and the combined organic layer was washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using 2% EtOAc/hexane as an eluent furnished the β-keto ester **48** (6.71 g, 91%) as a yellow oil. TLC: R_f 0.7 (5% EtOAc/hexane); IR (neat): 2961, 2929, 2854, 2225, 1736, 1646, 1260, 1094, 1030, 800 cm^{-1}; Keto form: ^1H NMR (500 MHz, $CDCl_3$): δ 4.23 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 2H), 2.60-2.51 (m, 1H), 1.86-1.78 (m, 2H), 1.74-1.66 (m, 2H), 1.56-1.46 (m, 3H), 1.37-1.32 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H);

^1H NMR (500 MHz, $CDCl_3$, Enol form): δ 11.79 (s, 1H), 5.39 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.60-2.51 (m, 1H), 1.86-1.78 (m, 2H), 1.74-1.66 (m, 2H), 1.56-1.46 (m, 3H), 1.37-1.32 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 171.8, 165.7, 154.1, 98.4, 95.7, 92.3, 78.4, 78.3, 71.9, 68.5, 64.0, 63.3, 61.6, 60.6, 51.0, 31.6, 31.4, 29.7, 29.6, 25.5, 25.4, 14.0, 13.9; MS (ESI): *m/z* 269 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{18}NaO_3$ 269.1148, Found 269.1160.

(*R*)-Ethyl 7-cyclohexyl-3-hydroxyhepta-4,6-diynoate (49)

The compound **49** was prepared following procedure documented for compound **22**. The ketone (246 mg, 1 mmol) **48** delivered alcohol **49** (193 mg, 78% yield) as a yellow coloured oil. TLC: R_f 0.3 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +22.3 (*c* 1.0, $CHCl_3$); IR (neat): 3436, 2931, 2855, 2253, 1735, 1261,1030, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.80 (q, *J* = 6.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.10 (d, *J* = 6.4 Hz, 1H), 2.73 (d, *J* = 6.0 Hz, 2H), 2.50-2.42 (m, 1H), 1.82-1.75 (m, 2H), 1.72-1.66 (m, 2H), 1.54-1.40 (m, 3H), 1.35-1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 85.7, 74.8, 70.1, 64.1, 61.1, 59.0, 41.6, 31.9, 29.3, 25.5, 24.5, 14.0; MS (ESI): *m/z* 249 $[M+H]^+$. HRMS (ESI): calcd. for $C_{15}H_{21}O_3$ 249.1485, Found 249.1503.

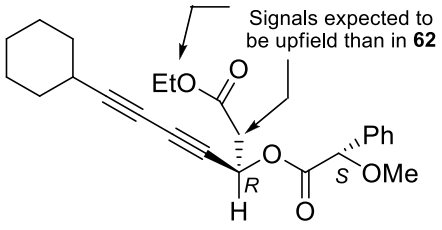
(*R*)-Ethyl 7-cyclohexyl-3-((*R*)-2-methoxy-2-phenylacetoxy)hepta-4,6-diynoate (62)



62

The compound **62** was prepared following procedure documented for compound **60**. The alcohol **49** (24.0 mg, 0.1 mmol) delivered ester **62** (32 mg, 82% yield). TLC: R_f 0.7 (5% EtOAc/hexane); IR (neat): 2931, 2855, 2253, 1735, 1261,1030, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.32 (m, 5H), 5.83 (dd, *J* = 8.5, 5.5 Hz, 1H), 4.77 (s, 1H), 4.12-4.02 (m, 2H), 3.42 (s, 3H), 2.86 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.77 (dd, *J* = 16.1, 5.2 Hz, 1H), 2.49-2.42 (m, 1H), 1.81-1.60 (m, 4H), 1.54-1.40 (m, 3H), 1.35-1.25 (m, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

(*R*)-Ethyl 7-cyclohexyl-3-((*S*)-2-methoxy-2-phenylacetoxy)hepta-4,6-diynoate (63)



63

The compound **63** was prepared following procedure documented for compound **61**. The alcohol (24.0 mg, 0.1 mmol) **49** delivered ester **63** (31 mg, 80% yield). TLC: R_f 0.7 (5% EtOAc/hexane); IR (neat): 2931, 2855, 2253, 1735, 1261,1030, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.30 (m, 5H), 5.80 (dd, *J* = 8.6, 5.4 Hz, 1H), 4.76 (s, 1H), 3.91 (dq, *J* = 10.6 Hz, 7.1 Hz, 1H), 3.80 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.42 (s, 3H), 2.74 (dd, *J* = 16.1, 8.5 Hz, 1H), 2.67 (dd, *J* = 16.1, 5.3 Hz, 1H), 2.49-2.42 (m, 1H), 1.81-1.60 (m, 4H), 1.54-1.40 (m, 3H), 1.35-1.25 (m, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). Note: A comparison of the NMR signals of the esters **62** and **63** confirms the assignment of configuration to the carbinol stereocenter.

The observed chemical shifts are in complete agreement with the model proposed by Trost and co-workers.

(*R*)-7-Cyclohexyl-1-ethoxy-1-oxohepta-4,6-diyn-3-yl 4-nitrobenzoate (64)

To a solution of the mixture of compound **49** (124.0 mg, 0.5 mmol) and 4-nitrobenzoic acid (92.0 mg, 0.55 mmol) in anhydrous CH_2Cl_2 (3 mL) was added EDC.HCl (191 mg, 1 mmol) and DMAP (12.0 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 mL x 3). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, to afford the residue which was purified by flash column chromatography on silica gel using 5-8% EtOAc/hexane (v/v) as the eluent to yield compound **64** (182 mg, 92% yield). TLC: R_f 0.8 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +52.5 (*c* 1.0, $CHCl_3$); IR (neat): 2933, 2856, 2254, 1737, 1561,1346, 1266, 1178, 1020, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 6.04 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.17 (q, *J* = 6.7 Hz, 2H), 3.05 (dd, *J* = 15.8, 8.3 Hz,1H), 2.94 (dd, *J* = 15.8, 5.2 Hz, 1H), 2.52-2.40 (m, 1H), 1.84-1.59 (m, 4H), 1.55-1.38 (m, 3H), 1.35-1.20 (m, 6H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 168.3, 163.0, 150.6, 134.6, 130.8, 123.5, 86.8, 71.7, 70.7, 63.8, 61.9, 61.1, 39.7, 31.7, 29.3, 25.5, 24.5, 14.0; MS (ESI): *m/z* 420 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{22}H_{23}NNaO_6$ 420.1418, Found 420.1434. The optical purity of ester **64** was determined to be 97.7% ee by chiral HPLC. The enantiomeric ratio was determined by HPLC, injection Volume-20 μL, Mobile Phase-10% *iso*-propanol in hexane, Column-CHIRAL PAK IC (250mm x 4.6 mm, 5u), Flow rate-1 mL/min, detection-210 nm. Minor isomer 16.205 min & major isomer 19.11 min.

(*R*,4*Z*,6*Z*)-Ethyl 7-cyclohexyl-3-hydroxyhepta-4,6-dienoate (50)

Nitrogen was passed through a suspension of (2 g, 30 mmol) Zn dust suspended in H_2O (12 mL) and stirred for 15 min at room temperature $Cu(OAc)_2.H_2O$ (0.2 g, 1.0 mmol) was added and stirring continued for 15 min. Later $AgNO_3$ (0.2 g, 1.1 mmol) was introduced (exothermic reaction) and the suspension stirred for further 30 min. The activated zinc dust was collected by filtration and carefully washed with H_2O (12 mL x 2), MeOH (12 mL x 2), acetone (12 mL x 2), and Et_2O (12 ml). The moist Zn/Cu/Ag mixture was immediately transferred into MeOH/H_2O (1:1, 6 mL), the alkyne **49** (99.0 mg, 0.4 mmol) was added followed by the addition of TMSCl (0.5 mL, 4.0 mmol). The reaction was stirred at ambient temperature for 24 h. Et_2O (10 mL) was added, the reaction mixture was passed through a short plug of silica gel eluting with Et_2O (30 mL). The combined organic layer was washed with H_2O (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to afford a residue that was purified by flash column chromatography on silica gel using 5-8% EtOAc/hexane (v/v) as the eluent provided (*Z*,*Z*)-diene alcohol **50** (87 mg, 87% yield). TLC: R_f 0.3 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +34.6 (*c* 1.0, $CHCl_3$); IR (neat): 2933, 2856, 2254, 1737, 1645, 1346, 1266, 1178, 1020, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.35 (t, *J* = 11.3 Hz, 1H), 6.14 (t, *J* = 11.7 Hz, 1H), 5.44-5.37 (m, 2H), 5.05-4.97 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.92-2.79 (bs, 1H), 2.56 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.51 (dd, *J* = 16.1, 4.2 Hz, 1H), 2.47-2.38 (m, 1H), 1.75-1.57 (m, 4H), 1.35-1.23 (m, 6H), 1.21-1.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 140.5, 130.8, 125.2, 120.7, 64.1, 60.5, 41.6, 36.2, 32.9, 32.8, 25.7, 25.5, 13.9; MS (ESI): *m/z* 275 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{24}NaO_3$ 275.1618, Found 275.1636.

(*R*,4*Z*,6*Z*)-Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-7-cyclohexylhepta-4,6-dienoate (51)

To the stirred solution of alcohol **50** (252 mg, 1 mmol) in anhydrous DMF (2 mL) cooled to 0 ^oC and maintained under nitrogen atmosphere were added imidazole (136 mg, 2 mmol) and TBSCl (165.0 mg, 1.1 mmol) sequentially. The mixture was warmed to room temperature

and stirred for 2.5 h. It was diluted with ether (10 mL) and washed with H_2O (20 mL x 2). The aqueous layer was extracted with ether (25 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residual oil was purified by flash chromatography on silica gel using 2-3% EtOAc/hexane (v/v) as the eluent to afford TBS ether **51** (347 mg, 95% yield) as a colourless oil. TLC: R_f 0.8 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +91.8 (*c* 1.0, $CHCl_3$); IR (neat): 2934, 2854, 1735, 1642, 1270, 1025, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.23 (t, *J* = 11.0 Hz, 1H), 6.13 (t, *J* = 11.0 Hz, 1H), 5.42-5.30 (m, 2H), 5.10-5.02 (m, 1H), 4.15-4.05 (m, 2H), 2.54 (dd, *J* = 14.3, 8.5 Hz, 1H), 2.49-2.41 (m, 1H), 2.37 (dd, *J* = 14.3, 4.3 Hz, 1H), 1.75-1.56 (m, 4H), 1.35-1.22 (m, 6H), 1.19-1.03 (m, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 140.1, 132.7, 123.5, 120.9, 65.8, 60.2, 43.7, 36.3, 33.0, 25.8, 25.7, 25.6, 17.9, 14.1, –4.4, –5.2; MS (ESI): *m/z* 389 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{38}NaO_3Si$ 389.2482, Found 389.2512.

(*R*,4*Z*,6*Z*)-3-((*tert*-Butyldimethylsilyl)oxy)-7-cyclohexylhepta-4,6-dienal (31)

To a stirred solution of ester **51** (1.83 g, 5.0 mmol in anhydrous CH_2Cl_2 (30 mL) cooled to –78 °C. DIBAL-H (1.25 M in toluene, 4.0 mL, 5 mmol) was added very slow dropwise. After stirring at –78 °C for 5 min saturated solution of Rochelle's salt (15 mL) was added. The mixture was allowed to warm to room temperature and stirred for 1 h. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure and residue was purified by flash column chromatography on silica gel using 2% EtOAc/hexane (v/v) as the eluent to afford **31** (1.54 g, 92% yield). TLC: R_f 0.7 (5% EtOAc/hexane); IR (neat): 2935, 2840, 2742, 1720, 1644, 1272, 1032, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (t, *J* = 2.8 Hz, 1H), 6.26 (t, *J* = 11.0 Hz, 1H), 6.09 (t, *J* = 11.0 Hz, 1H), 5.44-5.34 (m, 2H), 5.15-5.10 (m, 1H), 2.64 (ddd, *J* = 15.5, 8.0, 2.8 Hz, 1H), 2.48-2.38

(m, 2H), 1.75-1.56 (m, 4H), 1.35-1.03 (m, 6H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 140.8, 132.5, 123.6, 120.5, 64.7, 51.6, 36.4, 33.1, 33.0, 25.8, 25.7, 25.6, 17.9, –4.2, –5.0.

(1*R*,4*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-10-cyclohexyl-1-((2*R*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-1-(phenylthio)deca-7,9-dien-2-yn-4-ol (52) and (1*R*,4*S*,6*R*,7*Z*,9*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-10-cyclohexyl-1-((2*R*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-1-(phenylthio)deca-7,9-dien-2-yn-4-ol (53)

To a solution of terminal alkyne **30** (1.58 g, 5.0 mmol) in anhydrous THF (30 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexane, 2 mL, 5 mmol) dropwise and the reaction mixture was stirred at the same temperature for 40 min. A solution of aldehyde **31** (1.67 g, 5.20 mmol) in anhydrous THF (2 mL) was added to the above lithio alkyne. The reaction mixture was warmed gradually to 0 °C and stirred for a period of 1 h. The reaction mixture was quenched at 0 °C with an aqueous saturated solution of NH_4Cl (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (10 mL x 3) and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude compound. Purification by flash chromatography on silica gel using 5% EtOAc/hexane (v/v) as the eluent furnished alcohols **52** and **53** (2.90 g, 91% yield) as an epimeric mixture in equimolar amounts as a yellow oil. TLC: R_f 0.2 (5% EtOAc/hexane); IR (neat): 3447, 3050, 2975, 2930, 2852, 1640, 1575, 1460, 1375, 1320, 1245, 1170, 1090, 1015, 820 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.53 (m, 4H), 7.32-7.23 (m, 6H), 6.26-6.18 (m, 2H), 6.13 (dd, *J* = 10.0, 5.0 Hz, 1H), 6.09-5.97 (m, 3H), 5.71 (dd, *J* = 10.0, 2.6 Hz, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 5.40-5.32 (m, 4H), 5.18-5.16 (m, 1H), 5.13 (d, *J* = 2.0 Hz,1H), 5.01-4.90 (m, 2H), 4.52-4.44 (m, 2H), 4.26-4.21 (m, 1H), 4.17 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.08-3.92 (m, 3H), 3.68 (dd, *J* = 10.5, 2.9 Hz, 1H), 3.11 (d, *J* = 5.9 Hz, 1H), 2.99 (d, *J* = 5.9 Hz, 1H), 2.47-2.37 (m, 2H), 2.29-2.18 (m, 2H), 1.81-1.40 (m, 24H), 1.32-1.23 (m, 8H), 1.18 (dd, *J* = 9.7, 6.0 Hz, 6H), 1.11-1.04 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 6H),

0.95 (t, *J* = 7.4 Hz, 6H), 0.87 (s, 18H), 0.08-0.01 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.4, 134.2, 133.6, 133.4, 133.2, 133.0, 132.9, 132.8, 128.5, 127.6, 127.5, 123.4, 123.3, 120.8, 92.2, 87.2, 87.0, 81.1, 80.8, 71.7, 68.0, 67.9, 67.5, 66.9, 60.8, 60.0, 45.3, 44.2, 42.0, 41.9, 37.3, 36.4, 33.1, 25.9, 25.7, 23.5, 20.9, 20.7, 17.9, 11.2, –4.0, –4.9; (ESI): *m/z* 661 $[M+Na]^+$.

(1*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-10-cyclohexyl-1-((2*R*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-1-(phenylthio)deca-7,9-dien-2-yn-4-one (54)

The compound **54** was prepared following procedure documented for compound **23**. The epimeric mixture of alcohols **52** and **53** (1.27 g, 2 mmol) delivered ketone **54** (1.18 g, 93%). TLC: R_f 0.4 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +87.6 (*c* 1, $CHCl_3$); IR (neat): 2930, 2850, 1690, 1510, 1425, 1250, 1160, 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.57 (m, 2H), 7.36-7.30 (m, 3H), 6.21 (t, *J* = 11.1 Hz, 1H), 6.13 (dd, *J* = 10.0, 6.0 Hz, 1H), 6.07 (t, *J* = 11.1 Hz, 1H), 5.73 (dd, *J* = 10.0, 1.8 Hz, 1H), 5.38 (t, *J* = 9.7 Hz, 1H), 5.28 (t, *J* = 9.7 Hz, 1H), 5.15 (d, *J* = 1.8 Hz, 1H), 5.09-5.03 (m, 1H), 4.26-4.19 (m, 2H), 4.12 (d, *J* = 10.5 Hz, 1H), 2.62 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.48-2.33 (m, 2H), 2.26-2.18 (m, 1H), 1.75-1.58 (m, 10H), 1.50-1.41 (m, 2H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.82 (s, 9H), 0.0 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4, 140.5, 134.0, 132.9, 132.5, 132.4, 128.9, 128.3, 125.8, 123.6, 120.8, 92.3, 88.3, 85.2, 71.1, 68.2, 65.1, 53.6, 41.9, 37.3, 36.4, 33.1, 33.0, 25.8, 25.7, 25.6, 23.5, 21.0, 20.8, 17.9, 11.2, –4.3, –5.0; (ESI): *m/z* 659 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{38}H_{56}NaO_4SSi$ 659.3560, Found 659.3572.

1*R*,4*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-10-cyclohexyl-1-((2*R*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-1-(phenylthio)deca-7,9-dien-2-yn-4-ol (53)

The compound **53** was prepared following procedure documented for compound **22**. The ketone **54** (636 mg, 1 mmol) afforded alcohol **53** (515 mg, 81% yield). TLC: R_f 0.2 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +71.3 (*c* 1, $CHCl_3$); IR (neat): 3042, 2980, 2927, 2854, 1648, 1582, 1466, 1380, 1318, 1257, 1184, 1091, 1018, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-

7.52 (m, 2H), 7.35-7.24 (m, 3H), 6.28-6.10 (m, 2H), 6.00 (t, *J* = 11.0 Hz, 1H), 5.72 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.42-5.30 (m, 2H), 5.13 (d, *J* = 2.0 Hz, 1H), 4.98-4.86 (m, 1H), 4.53-4.40 (m, 1H), 4.30-4.14 (m, 2H), 4.06 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.03 (d, *J* = 5.7 Hz, 1H), 2.50-2.36 (m, 1H), 2.32-2.21 (m, 1H), 1.80-1.58 (m, 10H), 1.50-1.40 (m, 1H), 1.34-1.26 (m, 4H), 1.20-1.11 (m, 5H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 134.2, 133.5, 133.0, 132.9, 128.5, 127.5, 125.7, 123.3, 120.8, 92.2, 87.2, 80.8, 71.8, 68.0, 66.9, 60.0, 44.2, 42.0, 37.3, 36.4, 33.1, 33.0, 25.9, 25.7, 23.5, 20.9, 20.7, 17.9, 11.3, –4.1, –4.9; (ESI): *m/z* 661 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{38}H_{58}NaO_4SSi$ 661.3717, Found 661.3723.

(5*R*,7*R*)-5-((1*Z*,3*Z*)-4-Cyclohexylbuta-1,3-dien-1-yl)-9,9-diethyl-7-((*R*)-3-((2*R*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-3-(phenylthio)prop-1-yn-1-yl)-2,2,3,3-tetramethyl-4,8-dioxa-3,9-disilaundecane (29)

To a stirred solution of alcohol **53** (636 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) cooled to 0 °C was added imidazole (150.0 mg, 2.2 mmol) followed by TES-Cl (0.18 mL, 1.10 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched by the addition of H_2O (2 mL) and diluted with CH_2Cl_2 (8 mL). The layers were separated, and the organic layer was washed with H_2O (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using pure hexane to afford pure silyl ether **29** (706 mg, 94% yield) as a gummy oil. TLC: R_f 0.6 (2% EtOAc/hexane); $[\alpha]^{25}_D$ = +93.5 (*c* 1, $CHCl_3$); IR (neat): 2957, 2928, 2854, 2254, 1652, 1583, 1464, 1379, 1320, 1252, 1184, 1092, 1017, 935, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.30-7.21 (m, 3H), 6.20 (t, *J* = 11.2 Hz, 1H), 6.15 (dd, *J* = 10.0, 6.0 Hz, 1H), 6.06 (t, *J* = 11.2 Hz, 1H), 5.72 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.37-5.26 (m, 2H), 5.13 (d, *J* = 2.0 Hz, 1H), 4.74-4.68 (m, 1H), 4.37-4.33 (m, 1H), 4.26-4.20 (m, 1H), 4.15 (dd, *J* = 10.6, 2.8 Hz, 1H), 4.05 (dd, *J* = 10.6, 1.3 Hz, 1H), 2.47-2.37 (m, 1H), 2.28-2.22 (m, 1H), 1.78-1.40 (m, 10H),

1.32-1.25 (m, 5H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.12-0.98 (m, 2H), 0.96-0.88 (m, 12H), 0.85 (s, 9H), 0.60-0.52 (m, 6H), 0.01 (s, 3H), –0.01 (s, 3H)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139,6, 134.4, 134.1, 132.9, 132.8, 128.5, 127.7, 125.7, 123.1, 121.3, 92.2, 87.8, 80.3, 71.5, 67.9, 64.9, 59.0, 47.8, 41.9, 37.3, 36.3, 33.2, 33.1, 26.0, 25.9, 25.8, 23.5, 20.9, 20.7. 18.0, 11.2, 6.8, 5.0, –3.9, –4.7; (ESI): *m/z* 775 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{44}H_{72}NaO_4SSi_2$ 775.4582, Found 775.4565.

(1*E*,4*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-10-cyclohexyl-1-((2*S*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-4-((triethylsilyl)oxy)deca-1,7,9-trien-3-one (55)

To a solution of **29** (376.0 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) cooled to −40 °C was added *m*-CPBA (121.0 mg, 0.5 mmol) and the reaction mixture stirred at the same temperature for another 30 min. Toluene (5 mL) and 2-mercapto-1-methyl-imidazole (86.0 mg, 0.75 mmol) were added. The reaction mixture was stirred at 70 °C for 4 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The combined organic layer was washed successively with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 2% ethyl acetate/hexane (v/v) as the eluent to afford the product **55** (280 mg, 85% yield for 2 steps) as a liquid. TLC: R_f 0.7 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +67.4 (*c* 1, $CHCl_3$); IR (neat): 2957, 2928, 2854, 1739, 1694, 1633, 1465, 1378, 1257, 1182, 1095, 1182, 1095, 947, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (dd, *J* = 15.6, 3.6 Hz, 1H), 6.70 (dd, *J* = 15.6, 2.2 Hz, 1H), 6.22 (t, *J* = 11.0 Hz, 1H), 6.16-6.08 (m, 2H), 5.76-5.72 (m, 1H), 5.40-5.20 (m, 2H), 5.11 (d, *J* = 2.2 Hz, 1H), 4.83-4.74 (m, 2H), 4.43 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.99-3.91 (m, 1H), 2.48-2.35 (m, 1H), 2.06-1.96 (m, 1H), 1.93-1.85 (m, 1H), 1.77-1.58 (m, 6H), 1.48-1.21 (m, 5H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.16 (d, *J* = 10.6 Hz, 3H), 1.14-1.01 (m, 2H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.91-0.84 (m, 12H), 0.66-0.58 (m, 6H), 0.04 (s, 3H), 0.03 (s, 3H)); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 200.5, 145.5, 139.9, 133.7, 132.7, 125.7, 123.6, 123.5, 121.1, 93.1, 74.7, 69.7, 68.8, 65.2, 44.1, 38.8, 36.3, 33.1, 33.0, 25.8, 25.7, 23.6, 22.1, 18.0, 11.4, 6.7, 5.0, –3.6, –4.8; (ESI): *m/z* 683 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{38}H_{68}NaO_5Si_2$ 683.4497, Found 683.4485.

(3*R*,4*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-10-cyclohexyl-3-((*E*)-2-((2*S*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)vinyl)-3-hydroxy-4-((triethylsilyl)oxy)deca-7,9-dienenitrile (56)

To a solution of acetonitrile (82 mg, 2 mmol) in anhydrous THF (10 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexane, 0.8 mL, 4.0 mmol) dropwise and the reaction mixture was stirred at the same temperature for 40 min. A solution of ketone **55** (330 mg, 0.5 mmol) in anhydrous THF (2 mL) was added dropwise to the above lithio acetonitrile and the reaction mixture was stirred at –78 °C for a period of 1 h. The reaction mixture was quenched at –78 °C with an aqueous saturated solution of NH_4Cl (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (10 mL x 3) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the mixture of diastreomers. Purification by flash chromatography on silica gel using 4% EtOAc/hexane (v/v) as the eluent afforded less polar major component alcohol **56** (238 mg) and more polar minor component alcohol **57** (59 mg) in a combined yield of 90%. TLC: R_f 0.2 (5% EtOAc/hexane); $[\alpha]^{25}_D$= +48.5 (*c* 1, $CHCl_3$); IR (neat): 3442, 2957, 2252, 1649, 1465, 1380, 1254, 1183, 1095, 1012, 835, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.22 (t, *J* = 11.5 Hz, 1H), 6.13 (dd, *J* = 10.0, 5.0 Hz, 1H), 6.07-6.00 (m, 2H), 5.90 (dd, *J* = 15.5, 1.5 Hz, 1H), 5.72 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.33 (t, *J* = 10.0 Hz, 1H), 5.27 (t, *J* = 10.0 Hz, 1H), 5.05 (d, *J* = 2.4 Hz, 1H), 4.76-4.68 (m, 1H), 4.66-4.62 (m, 1H), 3.99-3.90 (m, 1H), 3.84 (t, *J* = 4.2 Hz, 1H), 3.48 (bs, 1H), 2.60 (d, *J* = 16.3 Hz, 1H), 2.55 (d, *J* = 16.3 Hz, 1H), 2.46-2.35 (m, 1H), 2.11-2.01 (m, 1H), 1.98-1.88 (m, 1H), 1.78-1.52 (m, 7H), 1.43-1.21 (m, 4H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.16-1.10 (m, 2H), 0.97 (t, *J* = 7.8 Hz,

9H), 0.92-0.86 (m, 12H), 0.72 -0.60 (m, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 133.3, 133.1, 130.4, 130.0, 125.6, 123.5, 120.5, 117.3, 93.2, 75.2, 74.4, 69.6, 68.9, 67.1, 41.9, 39.2, 36.3, 33.0, 32.9, 26.8, 25.8, 25.6, 23.7, 22.1, 21.7, 17.9, 11.4, 6.8, 5.1, –3.5, –4.6; (ESI): *m/z* 724 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{40}H_{71}NNaO_5Si_2$ 724.4763, Found 724.4775.

(3*S*,4*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-10-cyclohexyl-3-((*E*)-2-((2*S*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)vinyl)-3-hydroxy-4-((triethylsilyl)oxy)deca-7,9-dienenitrile (57)

TLC: R_f 0.3 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +36.8 (*c* 1, $CHCl_3$); IR (neat): 3447, 2956, 2250, 1640, 1460, 1365, 1258, 1190, 1082, 1010, 828, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (t, *J* = 11.5 Hz, 1H), 6.15 (dd, *J* = 10.0, 5.6 Hz, 1H), 6.07-5.98 (m, 2H), 5.88 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.72 (dd, *J* = 11.0, 2.8 Hz, 1H), 5.41 (t, *J* = 10.6 Hz, 1H), 5.27 (t, *J* = 10.0 Hz, 1H), 5.08 (d, *J* = 2.6 Hz, 1H), 4.81-4.72 (m, 1H), 4.68-4.64 (m, 1H), 4.30 (bs, 1H), 3.97-3.89 (m, 2H), 2.73 (d, *J* = 16.2 Hz, 1H), 2.54 (d, *J* = 16.2 Hz, 1H), 2.49-2.36 (m, 1H), 2.04-1.88 (m, 2H), 1.78-1.50 (m, 6H), 1.41-1.20 (m, 5H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.12-1.04 (m, 2H), 1.01-0.94 (m, 9H), 0.92-0.86 (m, 12H), 0.71-0.61 (m, 6H), 0.14 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.8, 133.5, 133.1, 131.3, 129.1, 125.5, 123.4, 120.5, 117.5, 93.6, 75.2, 74.4, 69.9, 68.9, 68.1, 42.7, 39.1, 36.4, 33.1, 33.0, 28.7, 25.9, 25.7, 23.7, 22.3, 21.7, 18.0, 11.5, 6.8, 5.1, –3.9, –4.4; (ESI): *m/z* 724 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{40}H_{71}NNaO_5Si_2$ 724.4763, Found 724.4752.

2-((4*R*,5*R*)-5-((*R*,3*Z*,5*Z*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-cyclohexylhexa-3,5-dien-1-yl)-4-((*E*)-2-((2*S*,3*S*,6*R*)-3-ethyl-6-methoxy-3,6-dihydro-2H-pyran-2-yl)vinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetonitrile (58)

To a solution of compound **56** (35.0 mg, 0.05 mmol) in *iso*-propanol (2 mL) was added PPTS (1.20 mg, 0.005 mmol) and the mixture stirred at room temperature for 4 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using

20% EtOAc/hexane (v/v) as the eluent to furnish the deprotected diol compound as colourless oil, which was utilised in next step without characterisation. To a solution of the diol in anhydrous CH_2Cl_2 (1.0 mL) cooled to 0 °C, was added neat 2,2-dimethoxypropane (2,2-DMP) (20.0 µL, 0.15 mmol) followed by catalytic amount of (±)-camphorsulphonic acid (1 mg, 0.005 mmol) and the mixture stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with H_2O (2 mL), brine (2 mL), and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using 5% EtOAc/hexane (v/v) as the eluent to furnish the title compound **58** as colourless oil (23 mg, 78% yield for 2 steps). TLC: R_f 0.6 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +38.9 (*c* 0.5, $CHCl_3$); IR (neat): 2975, 2258, 1620, 1440, 1355, 1248, 1190, 1082 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.18 (t, *J* = 11.4 Hz, 1H), 6.13 (dd, *J* = 10.0, 5.6 Hz, 1H), 6.06 (t, *J* = 11.4 Hz, 1H), 5.90 (dd, *J* = 15.4, 4.4 Hz, 1H), 5.74 (dd, *J* = 10.0, 2.6 Hz, 1H), 5.65 (dd, *J* = 15.4, 1.8 Hz, 1H), 5.37-5.31 (m, 2H), 4.85 (d, *J* = 2.6 Hz, 1H), 4.74 (t, *J* = 9.0 Hz, 1H), 4.58-4.54 (m, 1H), 4.34 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.34 (s, 3H), 2.70 (d, *J* = 16.8 Hz, 1H), 2.61 (d, *J* = 16.8 Hz, 1H), 2.45-2.36 (m, 1H), 1.93-1.88 (m, 1H), 1.72-1.58 (m, 8H), 1.54-1.40 (m, 10H), 1.31-1.28 (m, 2H), 0.91-0.84 (m, 12H), 0.08 (s, 3H), 0.3 (s, 9H); (ESI): *m/z* 622 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{35}H_{57}NNaO_5Si$ 622.3904, Found 622.3904.

Allyl ((3*R*,4*R*,6*R*,7*Z*,9*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-10-cyclohexyl-3-((*E*)-2-((2*S*,3*S*,6*R*)-3-ethyl-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)vinyl)-3,4-dihydroxydeca-7,9-dien-1-yl)carbamate (59)

To a solution of **56** (175.0 mg, 0.25 mmol) in anhydrous Et_2O (12 mL) cooled to 0 °C was added $LiAlH_4$ (19.0 mg, 0.5 mmol) and the mixture stirred while warming to room temperature for 4 h. The reaction was quenched with H_2O (1 mL) at 0 °C and the precipitated solid was filtered through Celite and washed with MeOH (5 mL). To the combined filtrate and washings $NaHCO_3$ (168 mg, 2 mmol) and allyl chloroformate (40 µL, 0.38 mmol) were

added the mixture stirred at room temperature for 2 h. Methanol was evaporated and the residue was diluted with EtOAc (5 mL) and H_2O (5 mL). The layers were separated, the aqueous layer was extracted with EtOAc (5 mL x 2) and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude compound which was purified by flash column chromatography on silica gel using 8% EtOAc/hexane (v/v) as the eluent to yield carbamate **59** (143 mg, 85% for 2 steps) as a colourless oil. TLC: R_f 0.4 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +39.7 (*c* 0.3, $CHCl_3$); IR (neat): 3449, 2922, 2832, 1725, 1524, 1633, 1465, 1382, 1260, 1080, 947, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.24 (t, *J* = 11.5 Hz, 1H), 6.10 (dd, *J* = 10.0, 5.0 Hz, 1H), 5.90-5.81 (m, 3H), 5.71 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.57-5.47 (m, 2H), 5.44-5.23 (m, 3H), 5.18 (dq, *J* = 2.6, 1.3 Hz, 1H), 5.04 (d, *J* = 2.6 Hz, 1H), 4.99-4.91 (m, 1H), 4.64-4.57 (m, 1H), 4.53 (d, *J* = 5.2 Hz, 2H), 4.0-3.88 (m, 2H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.42-3.30 (m, 1H), 3.22-3.12 (m, 1H), 2.84 (bs, 1H), 2.48-2.32 (m, 1H), 2.02-1.86 (m, 2H), 1.76-1.56 (m, 8H), 1.54-1.42 (m, 1H), 1.38-1.22 (m, 4H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.10-1.02 (m, 2H), 0.92-0.84 (m, 12H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 140.5, 133.2, 133.1, 132.3, 130.3, 129.6, 125.6, 123.5, 120.5, 117.4, 93.6, 77.1, 73.7, 69.9, 69.4, 68.0, 65.3, 39.1, 38.0, 37.0, 36.7, 36.4, 33.1, 33.0, 25.9, 25.8, 25.7, 23.8, 22.3, 21.8, 17.9, 11.4, –4.4, –5.2; (ESI): *m/z* 698 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{38}H_{65}NNaO_7Si$ 698.4423, Found 698.4430.

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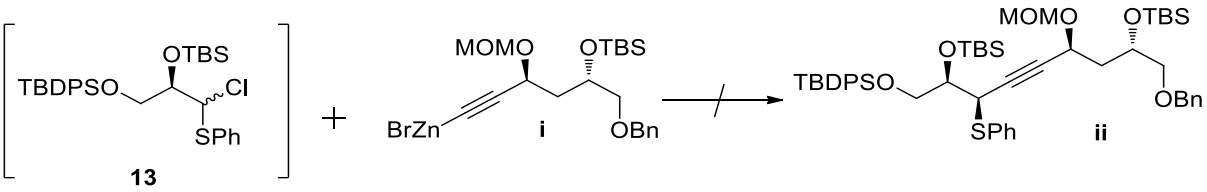
[14] It is to be noted that our initial attempt of reacting the chloro sulfide **13** with the alkynylzinc bromide **i** failed to furnish the expected product **ii**, instead a complex mixture of products resulted. So chloro sulfide **13** was reacted with alkynylzinc bromide derived from TMS-acetylene.



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