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An enantioselective total synthesis of natural antibiotic marasin†

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Synthetic studies directed toward the allenediyne antibiotic marasin are presented. Different approaches to the installation of the optically active chiral allenediyne motif were explored en route to the synthesis of the natural product. The stereoselectivity for the construction of the chiral allenediyne motif was dependent on not only the reaction employed but also the substrate structure.

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Introduction

Marasin (**1**, Fig. 1) is an allenediyne active[1a] against numerous bacteria including *Mycobacterium tuberculosis*. Both (a*R*)-(−)- and (a*S*)-(+)-**1** occur in nature, with the former isolated from *Marasmius ramealis*[1a] as well as *Cortinellus berkeleyanus*,[2] and the latter from *Aleurodiscus roseus*.[3] To date only two syntheses of marasin are documented in the literature. The first one was disclosed by Graaf[4] and co-workers, which used a ferrocene-derived chiral catalyst-mediated coupling of a zincated allene with a bromodiyne as the key step and eventually resulted in (a*R*)-(−)-marasin in 0.5% e.e. The second one was a biosynthesis, completed by Davies and Hodge[5] in 2005. In continuation of our studies on structurally similar allenediynes including nemotin[6] (**2**) and phomallenic acids[7] (**3**), we have also made efforts in developing an enantioselective chemical synthetic route to this rather unstable bioactive allenediyne. Herein we wish to detail the results.

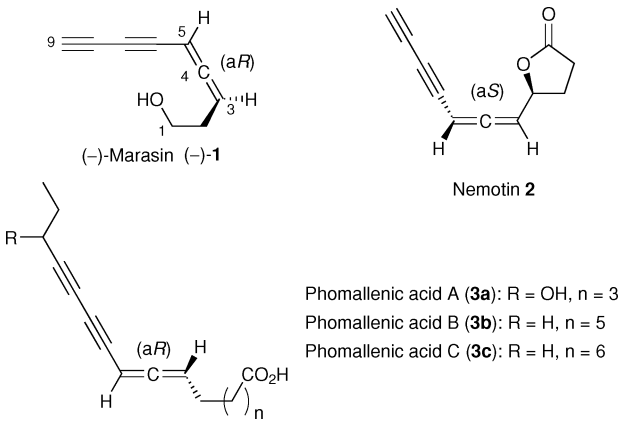
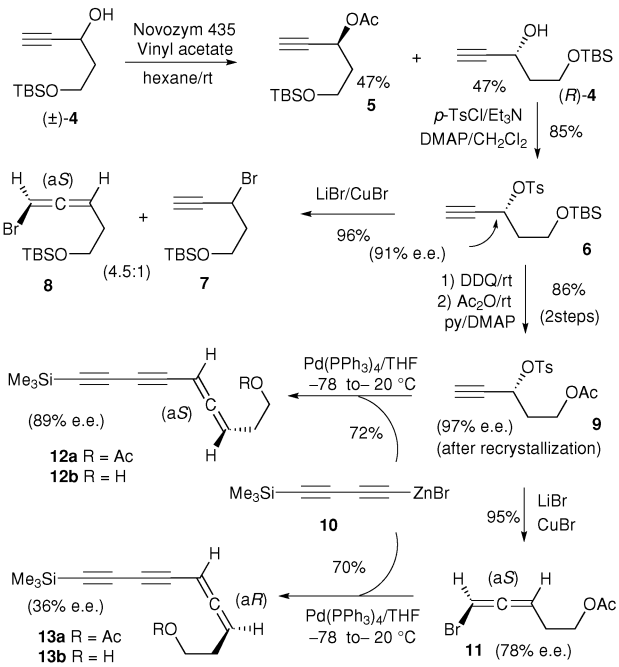


Fig. 1 The structures for (−)-marasin ((−)-**1**), nemotin (**2**) and phomallenic acids (**3a–c**).

Results and discussion

Our initial plan was to use the coupling of a bromoallene with a diyne as the tool to install the key allenediyne motif as shown in Scheme 1. The known racemic propargyl alcohol (±)-**4**[8] was resolved into (*R*)-**4**[9] and optically active acetate **5**[10] using Novozyme 435/vinyl acetate.[11] The (*R*)-**4**[9] was then transformed into the corresponding bromoallene **8** as in our previous[6,7] work, with an intension to apply the same coupling reaction to incorporate the diyne subunit. Unfortunately, in the present case, the desired bromoallene **8** turned out to be inseparable from the proparyl bromide formed concurrently (**8** : **7** = 4.5 : 1 as determined by ^{1}H NMR) by chromatography. To get around this problem, we tried to replace the TBS (*tert*-butyldimethylsilyl) protecting group with an acetyl one, which according to our experience[12] of similar compounds often facilitated the chromatographic separation on silica gel.



Scheme 1

An immediate advantage of using an acetyl group was that tosylate **9** was a solid, which could be recrystallized to give higher enantiopurity (97% e.e.). On treatment with LiBr/CuBr[13] tosylate **9** was converted to bromoallene **11**, which indeed could be isolated in pure form as hoped. Further coupling of **11** with the zincated diyne **10** (prepared[6,14] *in situ* from bis-trimethylsilylbutadiyne *via* reaction with MeLi and $ZnBr_2$) gave (a*R*)- allenediyne **13a** in 70%

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all new compounds, chiral HPLC chromatograms, and experimental details for **5**, **17**, **18**, **22**, (±)-**25**, **26**, **29**, **30**, *ent*-**30**, **31**, *ent*-**31**, *ent*-**33**, *ent*-**34**, *ent*-**35**, (*Z*)-**39**, (*S*)-**41b**. See DOI: 10.1039/c0ob00151a

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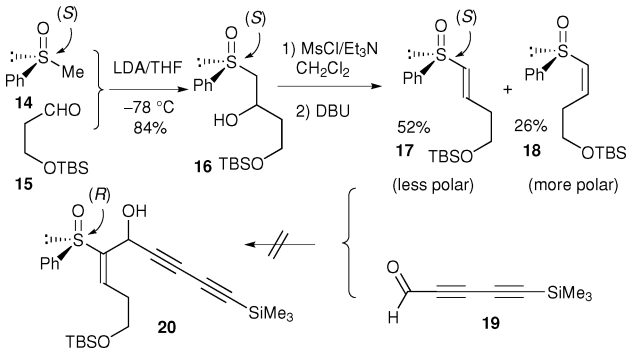
yield.[14c] However, the e.e. value was only 36% (determined on **13b** obtained by DIBAL-H reduction) if the coupling was performed at temperatures below –20 °C. At 0 °C, the allenediyne obtained was entirely racemic. Direct coupling of tosylate **9** with diyne anion **10** appeared to be much better in this case, giving the (a*S*)-isomer **12a** in 89% e.e. (determined on **12b**‡ obtained *via* DIBAL-H reduction of **12a**) and 72% yield.

While working on the direct coupling-based strategy, we also examined some other alternatives that might lead to the desired chiral allenediyne motif. One of the potentially applicable methodologies is that developed by Satoh[15] and coworkers, which introduces allenic axes *via* elimination of vinyl sulfoxide-allyl acetates. In the present context, it would require a precursor such as **20** (Scheme 2) before attempting the key elimination. Here, an optically-active sulfinyl group was preferred because it would assist clean separation of the two diastereomers of the allyl alcohols generated in a non-stereoselective addition (*vide infra*).



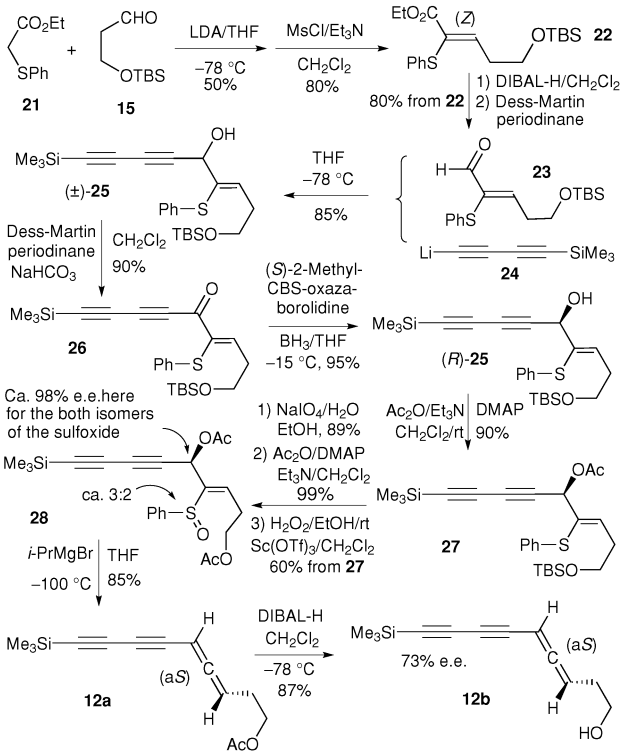
Scheme 2

In execution of this plan, the known optically-active sulfoxide **14**[16] was treated with LDA (lithium diisopropylamide) followed by aldehyde **15**[17] to afford the alcohol **16** as a pair of diastereomers (38 : 46, separable on silica gel). Activation of the hydroxyl group with MsCl (methanesulfonyl chloride) followed by DBU (1,8-diaza-bicyclo[5.4.0]undec-7-ene) mediated β-elimination afforded **17** in 53% yield, along with 26% of the (*Z*)-isomer **18**. However, the subsequent reaction of **17** with **19**[18] in the presence of LDA led to a complex mixture. Because the highly unstable nature of aldehyde **19** made extensive screening of suitable reaction conditions experimentally unfeasible, later we abandoned this plan and switched to another route that could avoid involvement of **19**.

As shown in Scheme 3, condensation of aldehyde **15** with ethyl phenylthioacetate **21**[19] yielded an intermediate alcohol, which was directly mesylated and eliminated to give **22** as the major product. It may be noteworthy here that use of a sulfinyl (sulfoxide) instead of a PhS- group in **21** failed to give the corresponding condesation product because a SPAC[20] reaction (Sulfoxide Piperidine and Carbonyl reaction) occurred.

The ester group was then transformed into an aldehyde group by a DIBAL-H reduction followed by a Dess–Martin oxidation. The resulting enal **23** was directly treated with lithiated diyne **24**

‡ Desilylation of **12b** to yield marasin was not attempted in this work.



Scheme 3

prepared[14] *in situ* from bis-trimethylbutadiyne to afford racemic propargyl alcohol **25**.

Conversion of the racemic **25** into a single (*R*) isomer was realized by a two-step sequence. The racemic alcohol was first transformed into the corresponding ketone **26** through reaction with Dess–Martin periodinane. The ketone carbonyl group was then stereoselectively reduced with BH_3 in the presence of (*S*)-2-methyl-CBS-oxazaborolidine (CBS[21] reduction). Further exposure of the (*R*)-**25** to Ac_2O/Et_3N/DMAP gave the acetate **27** in 90% yield.

Oxidation of the PhS- group in **27** into a sulfinyl one was first attempted using $NaIO_4/EtOH/H_2O$. However, only the TBS protecting group was cleaved.[22] To make full use of this unexpected product, the newly-freed hydroxyl group was acetylated with Ac_2O/Et_3N/DMAP in CH_2Cl_2 and the resulting acetate was re-submitted to a sulfur oxidation.

With $H_2O_2/Sc(OTf)_3$[23] as the reagents, the oxidation of the sulfur atom occurred smoothly. The sulfoxide **28** was formed as a 3 : 2 (the less polar component : the more component) mixture of diastereomers differing only at the configuration at the sulfur center. Although the absolute configuration of the sulfur atom was not determined, both isomers were of *ca.* 98% e.e. as measured by chiral HPLC. Both isomers on treatment with *i*-PrMgBr in THF at –100 °C underwent smooth elimination to yield (a*S*)-allenediyne **12a**, but with different stereoselectivity as noted[15] earlier by Satoh. The more polar isomer of **28** (**28b**) led to formation of **12a** in 85% yield within 20 min. Because the polarity of **12a** was not large enough for facile HPLC analysis, the terminal acetyl protecting group was cleaved with DIBAL-H in CH_2Cl_2 at –78 °C to give alcohol **12b**, which was determined to be of 72.5% e.e. If starting with the less polar isomer of **28** (**28a**) under otherwise identical conditions, the **12b** was of only 49% e.e.

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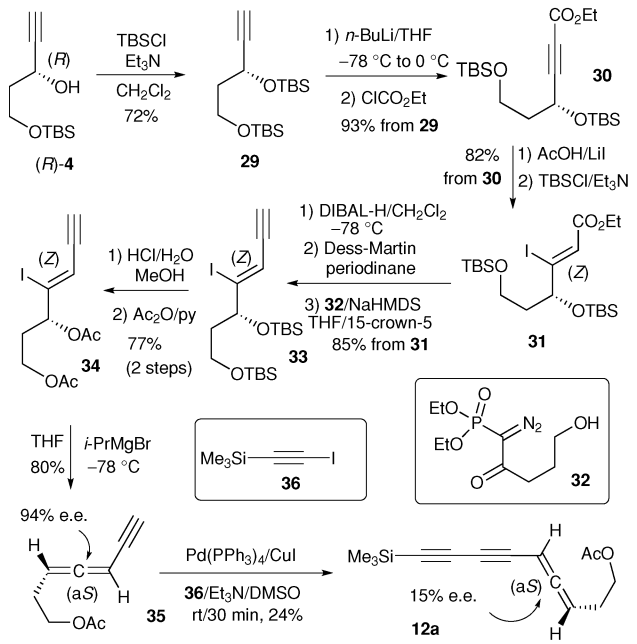
As the efficiency for the chirality transfer in the above case was only 74% (= 73% e.e. (for the product **12**)/98% e.e. (for the precursor **28**)), which was apparently not as good as those observed earlier with the corresponding elimination of iodides[24] in our recent work, we next examined another route with an iodide to replace the sulfinyl group in the elimination precursor.

The initial synthetic efforts along this line are depicted in Scheme 4. From the preceding attempts we were already aware that the diyne species such as **10**, **19**, and **24** were difficult to handle. One of the possible means to get around this problem is to incorporate the diyne subunit in steps, with only one triple bond at a time. To execute this plan, (*R*)-**4** was treated with $TBSCl/Et_3N$ to give **29**. Deprotonation of **29** with *n*-BuLi in THF followed by acylation with $ClCO_2Et$ introduced an ester group at the terminal alkyne.



Scheme 4

The iodine atom was then incorporated using the method of Ma and Lu[25] to obtain a (*Z*)-iodoalkene. Because under the iodination conditions some of the TBS protecting group was lost, the product mixture was treated with $TBSCl/Et_3N$ to resume full protection of the hydroxyl groups.

Installation of a terminal alkyne started with a reduction of **31** with DIBAL-H followed by an oxidation with Dess–Martin periodinane. The resulting intermediate aldehyde was then treated with a carbenoid generated *in situ* from **32**, a stable/convenient precursor to enynes recently developed by us,[26] to give the iodoenyne **33**.

The TBS protecting groups in **33** were then replaced with acetyl groups through an acid-mediated desilylation followed by acetylation with Ac_2O/py. Further treatment of the resulting diacetate **34** with *i*-PrMgBr at –78 °C afforded allenyne **35** in 80% yield. The e.e. value of this allene was determined to be 94%, which indicated that the chirality transfer from the allylic acetate to the allenic axis in this case was highly stereospecific.

In parallel to the transformations in Scheme 4, starting from (*S*)-**4**, which was obtained through hydrolysis of the acetyl group in **5** with $K_2CO_3/MeOH$), the antipode of **35** (*ent*-**35**) was also synthesized, though of only 81% e.e. because the enantiopurity of the starting **5** was not as high as that of (*R*)-**4**.

Up to this point, it seemed that appending another triple bond onto the terminal alkyne *via* an alkyne–alkyne coupling followed by removal of the acetyl protecting group would finish the whole synthesis. Unfortunately, this seemingly simple coupling turned out to be extremely difficult. Using $Me_3SiC{\equiv}C–X$ (X = Br or I) to couple with **35** or its zinc or copper salt, or with the copper or zinc salt of $Me_3SiC{\equiv}CH$ to couple with a brominated (at the terminal alkyne) **35** we tried a range of coupling conditions without success. The tested palladium catalyst included $Pd(PPh_3)_4$, $Pd_2(dba)_3$ (dba = dibenzylidenacetone), and $Pd(dppe)Cl_2$ (dppe = 1,2-bis(di-phenylphosphino)-ethane), with Et_3N or *i*-Pr_2NH or DABCO (1,4-diazabicyclo[2.2.2]octane) or pyrrolidine as the base and DMSO or THF or toluene–THF as the solvent at temperatures ranging from –20 °C through 0 °C up to ambient temperature in the presence or absence of CuI and/or LiBr.[27] In most cases no reaction occurred at low temperatures (< rt), while a complex mixture was normally obtained at ambient temperature. The best result along this route was observed with the coupling between **35** and $Me_3SiC{\equiv}C–I$[28] (**36**) under the conditions of $Pd(PPh_3)_4/CuI/Et_3N/DMSO$/rt, with an isolated yield of 24% for **12a**. However, chiral HPLC analysis revealed that the e.e. value of the **12a** thus obtained was only 15% (measured after deacetylation into **12b**). Racemization apparently occurred during the alkyne-alkyne coupling. It is noteworthy that to our knowledge no such coupling between an alkyne and an allenyne has ever been documented to date, not even a racemic version.

As the late-stage installation of the second triple bond onto the substrate structure through an alkyne–allenyne coupling was unfeasible, we decided to return to the earlier strategy—to introduce diyne subunit in one step. However, construction of the allenediyne *via* elimination of a vinyl iodide instead of a sulfoxide was still preferred because of the high enantioselectivity observed in the formation of **35** and some[24] other cases.

The synthesis was then started as shown in Scheme 5. The reaction of the iodinated Horner reagent **38**[29] (prepared *in situ* from **37**) with aldehyde **15** gave the desired α,β-unsaturated ester **39**. The configuration of the main isomer of **39** was not established experimentally at this stage but deduced later as (*Z*) on the basis of the results of the elimination reaction leading to the formation of the allenic axis and the literature[29] precedents.

The ester **39** was transformed into the corresponding aldehyde through a DIBAL-H reduction followed by a Dess–Martin oxidation. The diyne subunit was then introduced *via* addition of the lithiated diyne **24** to aldehyde **40**. The resulting racemic alcohol **41a** was converted into a single (*S*)-isomer in the same manner as used in the transformation of racemic **25** into (*R*)-**25** (Scheme 3), but using (*R*)-2-methyl-CBS-oxazaborolidine as the catalyst instead of the (*S*)-one.

The resulting (*S*)-**41a**, which was of 89% e.e. as determined on the corresponding diol (*S*)-**41b**, was treated with $K_2CO_3/MeOH$ to remove the TMS protecting group on the alkyne terminal. Acetylation of the intermediate alcohol with $Ac_2O/Et_3N/DMAP$ delivered the elimination precursor **43** in 79% yield. Finally, under

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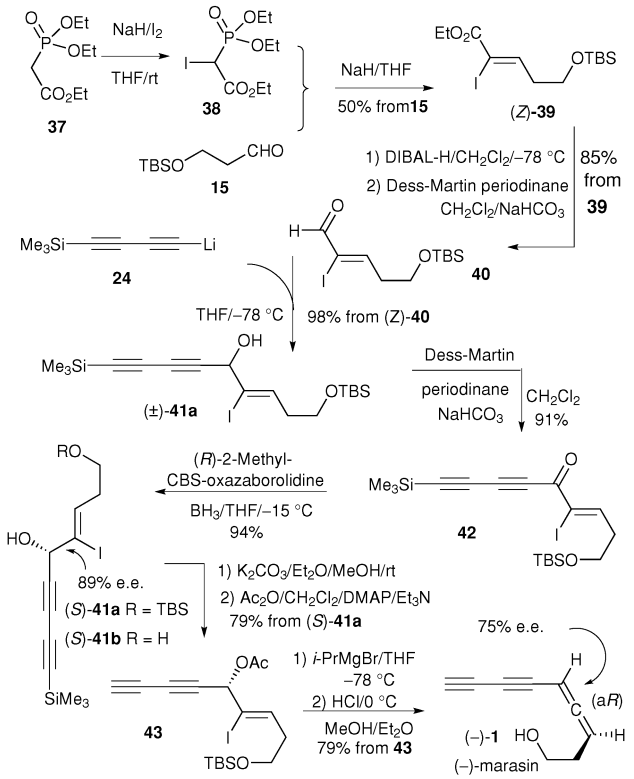

Scheme 5

the same conditions as for converting **34** into **35** followed by an acid-mediated hydrolysis of the TBS group afforded the end product (a*R*)-marasin (75% e.e.).

Conclusions

A synthesis of the natural antibiotic marasin has been achieved with an enantioselectivity much higher than that reported for the previous chemical synthesis. En route to the total synthesis, different approaches to the construction of the chiral allenediyne motif were examined. Among these, coupling of an optically active bromoallene (78% e.e., prepared from the corresponding propargyl tosylate) with a zincated diyne gave the expected allenediyne in 36% e.e. Direct coupling of the tosylate precursor (97% e.e.) with the same diyne species led to the allenediyne of higher enantiopurity (89% e.e.), but of different axial configuration. Installation of the same allenediyne arrangement through elimination of a diyne-containing allyl acetate–vinyl sulfoxide (98% e.e.) afforded the allenediyne in 73% e.e., with a chirality transfer efficiency of 74% (= 73% e.e. (for the allenediyne)/98% e.e. (for the precursor)). With an iodine to replace the chiral sulfinyl in the elimination substrate, the chirality was more efficiently transferred from the allylic acetate to the allenix axis, with the efficiency being 84% (= 75% e.e./89% e.e.). If the substrate for the elimination reaction contained one less triple bond, the corresponding allenyne could be built with much better enantiopurity (94% e.e.). However, subsequent attachment of another acetylene unit *via* alkyne–alkyne coupling under a variety sets of conditions was unsuccessful because of the substrate instability.

Experimental

General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using a Varian Mercury or a Bruker Avance instrument operating at the frequencies indicated in each case. The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR. EIMS and EI-HRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. Dry THF and dry Et_2O were distilled from Na/Ph_2CO under argon prior to use. Dry CH_2Cl_2 and dry *i*-Pr_2NH were distilled over CaH_2 prior to use. Novozyme 435 (demobilized on resin as white pellets of 0.3–0.9 mm in diameter) was purchased from Novozymes A/S (www.novozymes.com). Unless otherwise specified, all other solvents and reagents were commercially available and used as received without any further purification. PE (chromatography solvent) stands for petroleum ether (60–90 °C).

(*R*)-5-*tert*-Butyldimethylsilyl-3-tosyloxy-pentyne (6). To a solution of (*R*)-**4** (214 mg, 1.0 mmol) in dry CH_2Cl_2 (8 cm^3) stirred in an ice-water bath were added in turn *p*-TsCl (228 mg, 1.2 mmol), Et_3N (2.0 cm^3, 1.5 mmol) and DMAP (12 mg, 0.1 mmol). The mixture was then stirred at ambient temperature overnight before being diluted with Et_2O (40 cm^3), washed with aq. sat. NH_4Cl (twice), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20 : 1 PE/EtOAc) on silica gel gave **6** (313 mg, 0.85 mmol, 85%) as a colorless oil, which was of 91% e.e. (t_R (major) = 10.68 min, t_R (minor) = 9.43 min) as determined by chiral HPLC analysis on a CHIRALPAK AS column (4.6 × 25 cm) eluting with 98 : 2 *n*-hexane/*i*-PrOH at a flow rate of 0.8 cm^3 min^{-1} with the UV detector set to 214 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 5.24 (dt, J = 1.5, 7.2 Hz, 1H), 3.68 (t, J = 5.7 Hz, 2H), 2.44 (s, 4H, -PhCH_3 and the acetylenic proton), 2.42 (d, J = 1.5 Hz, 1H), 2.12–1.88 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.8, 133.7, 129.6, 128.0, 78.9, 76.3, 68.4, 57.9, 38.7, 25.7, 21.6, 18.1, –5.5, –5.6; FT-IR (film) 3282, 2955, 2930, 2857, 2884, 1595, 1370, 1190, 1178, 1098 cm^{-1}; ESI-MS *m*/*z* 391.2 ([M+Na]$^+$); ESI-HRMS calcd. for $C_{18}H_{28}SiO_4SNa$ 391.1370 ([M+Na]$^+$), found 391.1363.

(*R*)-3-Tosyloxy-pent-1-yn-5-yl acetate (9). A solution of **6** (240 mg, 0.65 mmol) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 16 mg, 0.065 mmol) in 9 : 1 MeCN–H_2O (6.5 cm^3) was stirred at ambient temperature for 2 h before being diluted with EtOAc (40 cm^3), washed in turn with aq. sat. $NaHSO_3$, aq. sat. $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left an oily residue, which was directly dissolved in dry CH_2Cl_2 (5 cm^3). The resulting solution was then cooled in an ice-water bath. Ac_2O (0.2 cm^3, 1.95 mmol), pyridine (0.054 cm^3, 0.65 mmol), and DMAP (8 mg, 0.065 mmol) were added. The mixture was stirred at ambient temperature for 2 h before being diluted with Et_2O (40 cm^3), washed in turn with aq. sat. $CuSO_4$, aq. sat. NH_4Cl, aq. sat. $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (6 : 1 PE/EtOAc) on silica gel gave acetate **9** (166 mg, 0.559 mmol, 86% from **6**) as a

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colorless oil, which solidified on standing. Recrystallization from petroleum ether twice raised the e.e. value to 96.5% (t_R (major) = 40.03 min, t_R (minor) = 33.58 min) as determined by chiral HPLC on a CHIRALPAK AS column (4.6 × 25 cm) eluting with 95 : 5 *n*-hexane/*i*-PrOH at a flow rate of 0.8 cm^3 min^{-1} with the UV detector set to 214 nm. $[\alpha]_D^{28}$ +51.7 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.18 (dt, *J* = 2.1, 7.8 Hz, 1H), 4.18-4.07 (m, 2H), 2.46 (d, *J* = 2.1 Hz, 1H), 2.43 (s, 3H), 2.19–2.08 (m, 2H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 145.1, 133.3, 129.7, 128.0, 78.1, 76.8, 67.6, 59.4, 34.6, 21.6, 20.7; FT-IR (film) 3278, 2965, 2115, 1738, 1598 cm^{-1}; ESI-MS *m*/*z* 319.1 ([M+Na]$^+$); ESI-HRMS calcd. for $C_{14}H_{16}SO_5Na$ 319.0611 ([M+Na]$^+$), found 319.0617.

(a*S*)-1-Trimethylsilyl-9-acetoxynona-5,6-diene-1,3-diyne (12a) derived from tosylate 9. MeLi (1.5 M, in Et_2O, 0.4 cm^3, 0.6 mmol) was added to a solution of bis-trimethylsilylbutadiyne (117 mg, 0.6 mmol) in dry THF (4 cm^3) stirred at −10 °C under argon. The flask was wrapped up with aluminium foil to exclude light. Stirring was then continued at ambient temperature for 50 min. At 0 °C, a solution of anhydrous $ZnBr_2$ in dry THF (1 M, 0.6 cm^3, 0.6 mmol) was added. The resulting solution was stirred at ambient temperature for 10 min before being added to another flask containing $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) stirred in a −78 °C bath under argon. The mixture was stirred at −78 °C for 10 min. A solution of tosylate **9** (148 mg, 0.5 mmol) in dry THF (2 cm^3) was introduced. Stirring was continued while the bath temperature was allowed to warm slowly to −20 °C, when TLC showed completion of the reaction. Aq. sat. NH_4Cl was added, followed by Et_2O. The phases were separated. The organic layer was concentrated on a rotary evaporator. The residue was chromatographed (15 : 1 PE/Et_2O) on silica gel to give **12a** (88 mg, 0.36 mmol, 72%) as a yellowish oil (determination of the e.e. value was performed on the corresponding **12b** as given below). $[\alpha]_D^{26}$ +264.5 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.47 (q, *J* = 6.8 Hz, 1H), 5.42–5.39 (m, 1H), 4.13 (t, *J* = 6.4 Hz, 2H), 2.38 (dq, *J* = 6.6, 3.0 Hz, 2H), 2.05 (s, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.1, 170.9, 90.1, 89.9, 87.8, 75.7, 74.9, 69.9, 62.6, 27.4, 20.8, −0.51; FT-IR (film) 2960, 2202, 2103, 1947, 1743, 1365, 1237, 1047, 846, 761 cm^{-1}; EI-MS *m*/*z* (%) 246 (M$^+$, 50), 231 (12),189 (22), 171 (43), 129 (17), 121 (30), 75 (25), 73 (48), 43 (100); EI-HRMS calcd. for $C_{14}H_{18}O_2Si$ 246.1076 (M$^+$), found 246.1082.

(a*S*)-9-Trimethylsilylnona-3,4-diene-6,8-diyn-1-ol derived originally from tosylate 9 (12b). DIBAL-H (1.0 M, in cyclohexane, 1.1 cm^3, 1.1 mmol) was added to a solution of acetate **12a** (derived from direct coupling of tosylate **9** with diyne **10** described above, 90 mg, 0.366 mmol) in dry CH_2Cl_2 (2.0 cm^3) stirred at −78 °C under argon. After completion of the addition, the mixture was stirred at the same temperature for 15 min. MeOH (0.3 cm^3) was carefully added to quench the excess hydride, followed by 10% aq. sodium potassium tartrate. The mixture was stirred at ambient temperature until a two-phase clear system was formed. Et_2O was added. The phases were separated. The organic layer was concentrated on a rotary evaporator. The residue was chromatographed (4 : 1 PE/Et_2O) on silica gel to afford allendiynol **12b** (67 mg, 0.328 mmol, 90%) as a yellowish oil. $[\alpha]_D^{27}$ +244.4 (*c* 0.95, $CHCl_3$), 89% e.e. (t_R (major) = 14.86 min, t_R (minor) = 14.09 min) as determined by chiral HPLC analysis on a CHIRALPAK OJ-H column (0.46 × 25 cm) eluting with 98 : 2 *n*-hexane/*i*-PrOH at a flow rate of 0.7 cm^3 min^{-1} with the UV detector set to 214 nm. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.51 (q, *J* = 6.8 Hz, 1H), 5.45–5.38 (m, 1H), 3.71 (br t, *J* = 6.1 Hz, 2H), 2.38-2.26 (m, 2H), 2.03 (br s, 1H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.0, 90.6, 89.9, 87.8, 75.3, 74.8, 70.1, 61.4, 31.3, −0.50; FT-IR (film) 3292, 2958, 2202, 2085, 1948, 1252, 1047, 867, 758 cm^{-1}; EI-MS *m*/*z* (%) 204 (M$^+$, 4), 190 (19), 189 (100), 164 (14), 131 (13), 115 (19), 75 (16), 43 (16); EI-HRMS calcd. for $C_{12}H_{16}OSi$ 204.0970 (M$^+$), found 204.0964.

(a*S*)-1-Bromo-5-acetoxypenta-1,2-diene (11). A solution of tosylate **9** (100 mg, 0.34 mmol) in dry THF (1.0 cm^3) was added to a solution of $CuBr{\cdot}SMe_2$ (139 mg, 0.68 mmol), LiBr (60 mg, 0.68 mmol) in dry THF (1.5 cm^3) stirred at ambient temperature. Stirring was then continued for 4 h at the same temperature. Et_2O (30 cm^3) was added. The mixture was washed with aq. sat. NH_4Cl (twice) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20 : 1 PE/Et_2O) on silica gel gave bromoallene **11** (66 mg, 0.322 mmol, 95%) as a colorless oil. $[\alpha]_D^{25}$ +74.7 (*c* 1.2, $CHCl_3$); 78% e.e. (t_R (major) = 11.68 min, t_R (minor) = 12.48 min) as determined by chiral HPLC on a CHIRALPAK AS column (0.46 × 25 cm) eluting with 98 : 2 *n*-hexane/*i*-PrOH at a flow rate of 0.8 cm^3 min^{-1} with the UV detector set to 214 nm. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.00 (dt, *J* = 5.9, 2.3 Hz, 1H), 5.39 (q, *J* = 6.4 Hz, 1H), 4.18 (t, *J* = 6.3 Hz, 2H), 2.49 (dq, *J* = 2.4, 6.4 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 171.0, 96.5, 73.0, 62.4, 27.6, 20.9; FT-IR (film) 3278, 2965, 2115, 1738, 1598 cm^{-1}; EI-MS *m*/*z* (%) 205 (M$^+$ (^{81}Br), 0.06), 204 (M$^+$ (^{79}Br), 0.01), 125 (M–Br, 22), 83 (4), 73 (5), 66 (5), 65 (52), 43 (100); EI-HRMS calcd. for $C_7H_9O_2$ 125.0603 ([M–Br]$^+$), found 125.0607.

(a*R*)-1-Trimethylsilyl-9-acetoxynona-5,6-diene-1,3-diyne (13a) derived from bromoallene 11. Using the same procedure for conversion of **9** into **12a** given above (except with bromoallene **11** to replace tosylate **9** as the starting material), **11** was converted into **13a** in 70% yield (36% e.e. as measured by chiral HPLC on the corresponding **13b** obtained *via* a DIBAL-H reduction as described for conversion of **12a** into **12b** given above). $[\alpha]_D^{27}$ −99 (*c* 0.3, $CHCl_3$). For other spectroscopic data, *cf.* those reported above for its antipode **12a**.

(5*R*,6*Z*)-9-(*tert*-Butyldimethylsilyloxy)-6-phenylthio-1-trimethylsilylnon-6-ene-1,3-diyn-5-ol ((*R*)-25). To a solution of ketone **26** (100 mg, 0.226 mmol) in dry THF (1.5 cm^3) stirred at −15 °C under argon was added a solution of (*S*)-2-methyl-CBS-oxazaborolidine (1 M, in toluene, 0.566 cm^3, 0.566 mmol). The mixture was stirred at the same temperature for 15 min before $BH_3{\cdot}Me_2S$ (2 M, in THF, 0.905 cm^3, 1.81 mmol) was introduced. Stirring was then continued at −15 °C for 1 h. MeOH (0.5 cm^3) was added, followed by Et_2O (30 cm^3). The mixture was washed in turn with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (30 : 1 PE/EtOAc) on silica gel afforded (*R*)-**25** (95 mg, 0.214 mmol, 95%) as a yellowish oil. $[\alpha]_D^{24}$ +147.3 (*c* 1.0, $CHCl_3$). For other spectroscopic data, *cf.* those for racemic **25** given in the ESI†.

(5*R*,6*Z*)-5-Acetoxy-9-(*tert*-butyldimethylsilyloxy)-6-phenylthio-1-trimethylsilylnon-6-ene-1,3-diyne (27). To a solution of (*R*)-**25** (86 mg, 0.194 mmol) in dry CH_2Cl_2 (5 cm^3) stirred in an

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ice-water bath were added Ac_2O (0.059 cm^3, 0.582 mmol), Et_3N (0.081 cm^3, 0.582 mmol), and DMAP (2.4 mg, 0.019 mmol). The mixture was stirred at ambient temperature for 40 min before being diluted with Et_2O (20 cm^3), washed in turn with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (60 : 1 PE/EtOAc) on silica gel provided acetate **27** (85 mg, 0.175 mmol, 90%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.14 (m, 5H), 6.76 (t, J = 6.5 Hz, 1H), 5.91 (s, 1H), 3.71 (t, J = 6.3 Hz, 2H), 2.70–2.56 (m, 2H), 1.92 (s, 3H), 0.91 (s, 9H), 0.19 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 141.3, 134.4, 129.7, 129.0, 126.5, 88.7, 86.9, 72.4, 72.0, 66.7, 61.6, 33.6, 25.9, 20.5, 18.3, –0.58, –5.4; FT-IR (film) 3068, 2956, 2929, 2857, 2118, 1751, 1577, 1371, 1252, 1218, 1099, 844, 776 cm^{-1}; ESI-MS m/z 509.2 ([M+Na]$^+$); ESI-HRMS calcd. for $C_{26}H_{38}Si_2O_3SNa$ 509.1972 ([M+Na]$^+$), found 509.1974.

(5*R*,6*Z*)-5-Acetoxy-9-(*tert*-butyldimethylsilyloxy)-6-phenylsulfinyl-1-trimethylsilylnon-6-ene-1,3-diyne (28a and 28b). $NaIO_4$ (62 mg, 0.29 mmol) was added to a solution of **27** (28 mg, 0.0575 mmol) in a mixture of THF (0.6 cm^3), EtOH (0.1 cm^3), and H_2O (0.3 cm^3) stirred at ambient temperature. Stirring was continued overnight. The solids were filtered off (washing with Et_2O). The filtrate and washings were combined, washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5 : 1 PE/EtOAc) on silica gel gave the intermediate alcohol (**27a**, 19 mg, 0.0510 mmol, 89% from **27**) as a colorless oil, which was directly dissolved in dry CH_2Cl_2 (1.0 cm^3) and cooled in an ice-water bath. To this solution were added Ac_2O (0.015 cm^3, 0.153 mmol), Et_3N (0.021 cm^3, 0.153 mmol) and DMAP (0.6 mg, 0.005 mmol). The mixture was stirred at ambient temperature for 40 min before being diluted with Et_2O (10 cm^3), washed with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20 : 1 PE/EtOAc) on silica gel gave the intermediate phenylthio ether-diacetate (**27b**, 21 mg, 0.0507 mmol, 99% from **27a**) as a colorless oil, which was dissolved in CH_2Cl_2–EtOH (10 : 1 v/v, 0.3 cm^3) and added to a solution of $Sc(OTf)_3$ (4.9 mg, 0.01 mmol) in CH_2Cl_2–EtOH (10 : 1 v/v, 0.2 cm^3) and aq. H_2O_2 (50%, 0.010 cm^3, 0.15 mmol) stirred at ambient temperature. The mixture was stirred at ambient temperature overnight. Water was added, followed by Et_2O. The phases were separated. The organic layer was washed with water (several times), aq. sat. Na_2SO_3, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1 : 1 PE/EtOAc) on silica gel gave the less polar isomer (**28a**, 9 mg, 0.0209 mmol, 41% from **27b**) and the more polar isomer of **28** (**28b**, 6 mg, 0.0139 mmol, 27% from **27b**) as colorless oils, along with unreacted phenylthio ether-diacetate (**27b**, 4 mg, 0.00965 mmol, 19% of the starting **27b**).

Data for the less polar isomer of **28** (**28a**, which differs from **28b** only in the configuration of the sulfoxide): $[\alpha]_D^{25}$ –132.6 (c 1.0, $CHCl_3$); 98% e.e. (t_R (major) = 17.69 min, t_R (minor) = 12.35 min) as determined by chiral HPLC on a CHIRALPAK OD column (0.46 × 25 cm) eluting with 80 : 20 n-hexane/i-PrOH at a flow rate of 0.7 cm^3 min^{-1} with the UV detector set to 214 nm. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62-7.57 (m, 2H), 7.56–7.46 (m, 3H), 6.70 (t, J = 7.7 Hz, 1H), 6.10 (s, 1H), 4.35–4.24 (m, 2H), 3.16–3.07 (m, 1H), 3.01–2.92 (m, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 168.7, 143.0, 141.6, 139.4, 131.2, 129.4, 124.3, 89.2, 86.5, 72.2, 71.4, 62.1, 58.5, 28.5, 20.8, 20.7, –0.65; FT-IR (film) 3059, 2960, 2923, 2109, 1747, 1650, 1443, 1367, 1251, 1217, 1047, 956, 848, 757, 602 cm^{-1}; ESI-MS m/z 453.1 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{22}H_{26}SiO_5SNa$ 453.1162 ([M+Na]$^+$), found 453.1166.

Data for the more polar isomer of **28** (**28b**): $[\alpha]_D^{25}$ +156.6 (c 1.0, $CHCl_3$); 97.8% e. e.. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.52 (m, 2H), 7.51–7.41 (m, 3H), 6.84 (t, J = 7.7 Hz, 1H), 6.39 (s, 1H), 4.38–4.27 (m, 2H), 3.18–3.09 (m, 1H), 3.05–2.96 (m, 1H), 2.13 (s, 3H), 1.41 (s, 3H), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 168.4, 142.5, 141.9, 141.0, 130.5, 129.1, 124.0, 89.2, 86.6, 72.5, 71.6, 62.2, 57.2, 28.6, 20.8, 19.8, –0.64; FT-IR (film) 3059, 2961, 2925, 2108, 1747, 1444, 1368, 1218, 1083, 1049, 848, 753 cm^{-1}; ESI-MS m/z 453.0 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{22}H_{26}SiO_5SNa$ 453.1162 ([M+Na]$^+$), found 453.1168.

(a*S*)-1-Trimethylsilyl-9-acetoxynona-5,6-diene-1,3-diyne (12a) derived from sulfoxide 28b. A solution of the more polar isomer of **28** (**28b**, 20 mg, 0.0465 mmol) in dry THF (1 cm^3) was added to a solution of i-PrMgBr (2.5 M, in Et_2O, 0.11 cm^3, 0.28 mmol) in dry THF (1 cm^3) stirred at –100 °C under argon. The mixture was stirred at the same temperature for 20 min. Aq. sat. NH_4Cl was added. The mixture was extracted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (15 : 1 PE/Et_2O) on silica gel gave **12a** (10 mg, 0.0406 mmol, 87%) as a colorless oil. $[\alpha]_D^{25}$ +156.6 (c 0.39, $CHCl_3$). The e.e. value was 73% as determined on the corresponding **12b** as described above.

If using **28a** (the less polar isomer of **28**) to replace **28b**, the product **12a** was of much lower enantiopurity as indicated by the specific rotation ($[\alpha]_D^{25}$ +81.4 (c 0.351, $CHCl_3$)).

(2*Z*,5*R*)-5,7-Di-*tert*-butyldimethylsilyloxy-4-iodohept-2-en-1-yne (33). DIBAL-H (1.0 M, in cyclohexane, 0.46 cm^3, 0.46 mmol) was added to a solution of **31** (110 mg, 0.208 mmol) in dry CH_2Cl_2 (2 cm^3) stirred at –78 °C under argon. Stirring was continued at the same temperature for 1 h. 1 N HCl (0.5 cm^3) was added, followed by EtOAc (10 cm^3). The phases were separated. The organic layer was washed with 1 N HCl. The combined aqueous layers were back-extracted with EtOAc (4 × 5 cm^3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue (the intermediate alcohol) was dissolved in dry CH_2Cl_2 (2 cm^3). $NaHCO_3$ (35 mg, 0.416 mmol) was added, followed by Dess–Martin periodinane (106 mg, 0.25 mmol). The mixture was stirred at ambient temperature for 1 h. Aq. sat. Na_2SO_3 (2 cm^3) was added. The mixture was stirred until all solids dissolved before being extracted with Et_2O (2 × 10 cm^3), washed with aq. sat. NH_4Cl, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (80 : 1 PE/Et_2O) on silica gel gave the intermediate aldehyde (90 mg, 0.186 mmol, 89% from **31**) as a yellowish-green oil.

NaHMDS (2.0 M, in THF, 0.12 cm^3, 0.24 mmol) was added to a solution of carbine precursor **32** (64 mg, 0.24 mmol) in dry THF (1.5 cm^3) stirred at –78 °C under argon. Stirring was continued at the same temperature for 40 min (a yellow color developed). A solution of the above obtained intermediate aldehyde (90 mg, 0.186 mmol) in dry THF (1.0 cm^3) was introduced. After stirring

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at −78 °C for another 10 min, 15-crown-5 (0.037 cm^3, 0.185 mmol) was added. The color of the system darkened. The mixture was stirred at −78 °C for another 2 h before the bath was allowed to warm to ambient temperature. Aq. sat. NH_4Cl (5 cm^3) was added, followed by Et_2O (30 cm^3). The phases were separated. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (300 : 1 PE/EtOAc) on silica gel gave the iodoenyne **33** (86 mg, 0.179 mmol, 96% from the intermediate aldehyde, 85% from **31**) as a colorless oil. $[\alpha]_D^{23}$ +19.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.40 (d, J = 1.2 Hz, 1H), 4.16 (dd, J = 7.2, 4.6 Hz, 1H), 3.74–3.55 (m, 2H), 3.35 (d, J = 2.2 Hz 1H), 1.91–1.64 (m, 2H), 0.92 (s, 9H), 0.90 (s, 9H), 0.09–0.05 (several singlets, 12H altogether); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 127.5, 115.9, 83.2, 82.7, 75.4, 58.4, 40.4, 25.9, 25.8, 18.14, 18.12, −4.5, −5.1, −5.3, −5.4; FT-IR (film) 3301, 2955, 2929, 2885, 2858, 1472, 1256, 1097 cm^{-1}; EI-MS *m*/*z* (%) 423 ([M–C_4H_9]$^+$ 8), 395 (15), 295 (16), 267 (8), 219 (29), 189 (59), 147 (100), 133 (16); EI-HRMS calcd. for $C_{19}H_{37}Si_2O_2I$ 480.1377 ([M]$^+$), found 480.1363.

(2*Z*,5*R*)-5,7-Diacetoxy-4-iodohept-2-en-1-yne (34). Conc. HCl (0.8 cm^3, 9.6 mmol) was added to a solution of **33** (250 mg, 0.52 mmol) in THF (4 cm^3) stirred in an ice-water bath. Stirring was continued at the same temperature for 1.5 h. EtOAc (30 cm^3) was added. The phases were separated. The organic layer was washed with aq. sat. $NaHCO_3$ and brine (twice). The aqueous layers were back-extracted with EtOAc (2 × 10 cm^3). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was dissolved in dry CH_2Cl_2 (5 cm^3) and cooled in an ice-water bath. To this solution were added in turn Ac_2O (0.31 cm^3, 3.12 mmol), pyridine (0.087 cm^3, 1.04 mmol), and DMAP (6 mg, 0.052 mmol). The mixture was stirred at ambient temperature for 2 h before being diluted with Et_2O (40 cm^3), washed in turn with aq. sat. $CuSO_4$, aq. sat. NH_4Cl, aq. sat. $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5 : 1 PE/Et_2O) on silica gel afforded diacetate **34** (135 mg, 0.402 mmol, 77%) as a colorless oil. $[\alpha]_D^{22}$ +22.8 (*c* 1.1, $CHCl_3$); 95% e.e. (t_R (major) = 22.94 min, t_R (minor) = 15.85 min) as determined by chiral HPLC analysis on a CHIRALPAK AS column (0.46 × 25 cm) eluting with 90 : 10 *n*-hexane/*i*-PrOH at a flow rate of 0.8 cm^3 min^{-1} with the UV detector set to 214 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.48 (d, J = 1.4 Hz, 1H), 5.08 (t, J = 6.7 Hz, 1H), 4.18–4.00 (m, 2H), 3.43 (d, J = 1.7 Hz, 1H), 2.17–1.90 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 169.5, 120.2, 118.3, 84.5, 82.5, 75.2, 59.6, 33.5, 21.0, 20.8; FT-IR (film) 3273, 2949, 2110, 1741, 1370, 1229, 1047 cm^{-1}; ESI-MS *m*/*z* 358.8 ([M+Na]$^+$); MALDI-HRMS calcd. for $C_{11}H_{13}O_4INa$ 358.9751 ([M+Na]$^+$), found 358.9749.

(a*S*)-Hepta-3,4-diene-6-yn-1-yl acetate (35). A solution of **34** (101 mg, 0.3 mmol) in dry THF (1.0 cm^3) was added to a solution of *i*-PrMgBr (2 M, in Et_2O, 0.9 cm^3, 1.8 mmol) in dry THF (5 cm^3) stirred at −78 °C under argon. Stirring was continued at −60 °C for 4.5 h. Aq. sat. NH_4Cl (10 cm^3) was added, followed by Et_2O (50 cm^3). The phases were separated. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20 : 1 PE/Et_2O) on silica gel gave **35** (36 mg, 0.24 mmol, 80%) as a colorless oil, along with unreacted **34** (16 mg, 0.048 mmol, 16%). Data for **35**: $[\alpha]_D^{23}$ +199.8 (*c* 0.78, $CHCl_3$); 94% e.e. (t_R (major) = 15.20 min, t_R (minor) = 20.14 min) as determined by chiral HPLC analysis on a CHIRALPAK AS column (0.46 × 25 cm) eluting with 90 : 10 *n*-hexane/*i*-PrOH at a flow rate of 0.8 cm^3 min^{-1} with the UV detector set to 214 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.45 (dq, J = 1.1, 6.4 Hz, 1H), 5.41–5.36 (m, 1H), 4.16 (t, J = 6.6 Hz, 2H), 2.86 (br t, J = 1.7 Hz, 1H), 2.45–2.08 (m, 2H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.5, 171.0, 89.6, 78.4, 75.5, 62.8, 27.4, 20.9; FT-IR (film) 3259, 2963, 2875, 2111, 1956, 1740, 1367, 1238, 1044 cm^{-1}; EI-MS *m*/*z* (%) 150 (M$^+$, 0.8), 109 (12), 108 (38), 90 (21), 89 (41), 63 (8), 51 (10), 43 (100); EI-HRMS calcd. for $C_9H_{10}O_2$ 150.0681 (M$^+$), found 150.0677.

(a*S*)-Nona-3,4-diene-6,8-diyn-1-yl acetate (12a) derived from 35. A solution of **35** (15 mg, 0.10 mmol) and 1-iodo-2-trimethylsilylacetylene **36** (34 mg, 0.15 mmol) in DMSO (0.6 cm^3) was added to a solution of $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), CuI (1.9 mg, 0.01 mmol) and Et_3N (0.042 cm^3, 0.3 mmol) in DMSO (0.3 cm^3) stirred at ambient temperature under argon. Stirring was continued at the same temperature for 30 min. Aq. sat. NH_4Cl was added. The mixture was extracted with Et_2O (3 × 3 cm^3), washed with aq. sat. NH_4Cl, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20 : 1 PE/Et_2O) on silica gel delivered **12a** (6 mg, 0.0244 mmol, 24%) as a colorless oil. $[\alpha]_D^{27}$ +44.1 (*c* 0.3, $CHCl_3$); 14.8% e.e.

(*Z*)-9-*tert*-Butyldimethylsilyloxy-6-iodo-1-trimethylsilylnon-6-ene-1,3-diyn-5-ol ((±)-41a). DIBAL-H (1.0 M, in cyclohexane, 0.66 cm^3, 0.66 mmol) was added to a solution of (*Z*)-**39** (107 mg, 0.278 mmol) in dry CH_2Cl_2 (3 cm^3) stirred at −78 °C under argon. Stirring was continued at the same temperature for 1 h. 1 N HCl (0.6 cm^3) was added, followed by EtOAc (10 cm^3). The phases were separated. The organic layer was washed with 1 N HCl. The combined aqueous layers were back-extracted with EtOAc (4 × 5 cm^3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue (the intermediate alcohol) was dissolved in dry CH_2Cl_2 (3 cm^3). $NaHCO_3$ (46 mg, 0.54 mmol) was added, followed by Dess–Martin periodinane (127 mg, 0.30 mmol). The mixture was stirred at ambient temperature for 0.5 h. Aq. sat. Na_2SO_3 (2 cm^3) was added. The mixture was stirred until all solids dissolved before being extracted with Et_2O (2 × 20 cm^3), washed with aq. sat. NH_4Cl, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (30 : 1 PE/EtOAc) gave the intermediate aldehyde (80 mg, 0.235 mmol, 85% from (*Z*)-**39**) as a colorless oil.

To a solution of bis-trimethylsilyl-butadiene (370 mg, 1.9 mmol) in dry THF (10 cm^3) stirred at −10 °C under argon was added MeLi (1.5 M, in Et_2O, 1.12 cm^3, 1.68 mmol). The flask was wrapped up with aluminium foil to exclude light. Stirring was then continued at ambient temperature for 50 min to yield a solution of the lithiated diyne **24**. The bath was cooled down to −78 °C and the cold solution of **24** was added dropwise to (*via* a cannula) another flask containing a solution of the above obtained aldehyde **40** (380 mg, 1.12 mmol) in dry THF (5 cm^3) stirred at −78 °C under argon. The mixture was stirred at −78 °C for another 2 h before being diluted with Et_2O, washed with aq. sat. NH_4Cl (twice), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation

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and column chromatography (15 : 1 PE/Et_2O) on silica gel gave racemic **41** (510 mg, 1.10 mmol, 98% from aldehyde **40**, 83% from ester **39**) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.21 (dt, J = 0.6, 6.6 Hz, 1H), 4.83 (d, J = 7.3 Hz, 1H), 3.68 (t, J = 6.5 Hz, 2H), 2.62 (d, J = 7.6 Hz, 1H), 2.39 (q, J = 6.5 Hz, 2H), 0.89 (s, 9H), 0.19 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.0, 108.9, 88.9, 86.9, 75.1, 71.7, 70.0, 61.0, 39.2, 25.9, 18.3, –0.56, –5.3; FT-IR (film) 3378, 2956, 2929, 2857, 2222, 2107, 1645, 1252, 1097, 844, 777 cm^{-1}; ESI-MS m/z 484.9 ([M+Na]$^+$); ESI-HRMS calcd. for $C_{18}H_{31}O_2Si_2INa$ 485.07995 ([M+Na]$^+$), found 485.08008.

(*Z*)-9-*tert*-Butyldimethylsilyloxy-6-iodo-1-trimethylsilylnon-6-ene-1,3-diyn-5-one (42). Dess–Martin periodinane (149 mg, 0.35 mmol) was added to a solution of (±)-**41** (135 mg, 0.292 mmol) in dry CH_2Cl_2 (2 cm^3) stirred at ambient temperature, followed by $NaHCO_3$ (22 mg, 0.526 mmol). Stirring was continued at the same temperature for 30 min. Aq. Na_2SO_3 (2 cm^3) was added. The mixture was stirred until all solids dissolved before being extracted with Et_2O (2 × 20 cm^3), washed with aq. NH_4Cl, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography (50 : 1 PE/Et_2O) on silica gel afforded ketone **42** (122 mg, 0.265 mmol, 91%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (t, J = 6.5 Hz, 1H), 3.81 (t, J = 6.1 Hz, 2H), 2.68 (q, J = 6.3 Hz, 2H), 0.90 (s, 9H), 0.22 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 158.2, 111.5, 97.6, 85.5, 77.6, 68.1, 60.2, 41.0, 25.8, 18.2, –0.83, –5.4; FT-IR (film) 2956, 2852, 2220, 2099, 1647, 1597, 1253, 1096, 847 cm^{-1}; ESI-MS m/z 482.9 ([M+Na]$^+$); ESI-HRMS calcd. for $C_{18}H_{29}O_2Si_2INa$ 483.0643 ([M+Na]$^+$), found 483.0632.

(6*Z*,5*S*)-9-*tert*-Butyldimethylsilyloxy-6-iodo-1-trimethylsilylnon-6-ene-1,3-diyn-5-ol ((*S*)-41a). To a solution of ketone **42** (290 mg, 0.63 mmol) in dry THF (5 cm^3) stirred at –15 °C under argon was added a solution of (*R*)-2-methyl-CBS-oxazaborolidine (1 M, in toluene, 1.26 cm^3, 1.26 mmol). The mixture was stirred at the same temperature for 15 min before BH_3·Me_2S (2 M, in THF, 0.79 cm^3, 1.58 mmol) was introduced. The mixture was stirred at –15 °C for 1 h. MeOH (1.0 cm^3) was added, followed by Et_2O (50 cm^3). The mixture was washed in turn with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$, and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (15 : 1 PE/Et_2O) on silica gel afforded (*S*)-**41a** (275 mg, 0.595 mmol, 94%) as a colorless oil. $[\alpha]_D^{24}$ –31.5 (*c* 1.0, $CHCl_3$). For other spectroscopic data, *cf.* those for racemic **41** given above. The e.e. value was determined on the corresponding (*S*)-**41b** as described in the ESI.†

(6*Z*,5*S*)-5-Acetoxy-9-*tert*-butyldimethylsilyloxy-6-iodonon-6-ene-1,3-diyne (43). K_2CO_3 (81 mg, 0.587 mmol) was added to a solution of (*S*)-**41a** (270 mg, 0.587 mmol) in Et_2O–MeOH (1 : 1 v/v, 2.0 cm^3) stirred at ambient temperature. The mixture was stirred for another 10 min before being diluted with Et_2O (50 cm^3), washed with aq. sat. NH_4Cl and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was dissolved in dry CH_2Cl_2 (5.0 cm^3) and cooled in an ice-water bath. To this solution were added Ac_2O (0.182 cm^3, 1.76 mmol), Et_3N (0.245 cm^3, 1.76 mmol), and DMAP (7 mg, 0.0587 mmol). The mixture was stirred at ambient temperature for 40 min before being diluted with Et_2O (50 cm^3), washed in turn with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (25 : 1 PE/Et_2O) on silica gel afforded **43** (200 mg, 0.463 mmol, 79% from (*S*)-**41a**) as a colorless oil, which turned yellow on standing. $[\alpha]_D^{23}$ +7.7 (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.35 (t, J = 6.6 Hz, 1H), 5.98 (s, 1H), 3.70 (t, J = 6.4 Hz, 2H), 2.42 (q, J = 6.5 Hz, 2H), 2.29 (d, J = 1.1 Hz, 1H), 2.14 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 139.4, 101.2, 71.4, 70.9, 70.0, 69.7, 67.1, 60.8, 39.3, 25.8, 20.8, 18.2, –5.4; FT-IR (film) 3291, 2954, 2929, 2858, 2071, 1752, 1645, 1471, 1370, 1255, 1218, 1098, 1015, 837, 777 cm^{-1}; ESI-MS m/z 455.1 ([M+Na]$^+$); ESI-HRMS calcd. for $C_{17}H_{25}O_3SiINa$ 455.0510 ([M+Na]$^+$), found 455.0514.

(3a*R*)-Nona-3,4-diene-6,8-diyn-1-ol ((a*R*)-1, (a*R*)-Marasin). A solution of **43** (100 mg, 0.23 mmol) in dry THF (1.0 cm^3) was added to a solution of *i*-PrMgBr (2.5 M, in Et_2O, 0.9 cm^3, 2.3 mmol) in dry THF (10 cm^3) stirred at –78 °C under argon. Stirring was continued at –60 °C for 12 h. Aq. sat. NH_4Cl (10 cm^3) was added, followed by Et_2O (50 cm^3). The phases were separated. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was dissolved in Et_2O–MeOH (1.0 cm^3 each) and cooled in an ice-water bath. Conc. HCl (6 drops from a pipette) was added. The mixture was stirred at the same temperature for 40 min before being diluted with Et_2O (30 cm^3), washed with aq. sat. $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2 : 1 PE/Et_2O) on silica gel gave (a*R*)-**1** (marasin, 24 mg, 0.182 mmol, 79% from **43**) as a colorless oil (neat marasin turned yellow rapidly on standing, but could be kept for much longer time in a freezer as a dilute solution in EtOH). $[\alpha]_D^{23}$ –266.0 (*c* 0.19, CH_2Cl_2) (lit.[2] $[\alpha]_D^{24}$ –360 (*c* 0.07, CH_2Cl_2)); $[\alpha]_D^{23}$ –271.2 (*c* 1.1, EtOH) (lit.[1a] $[\alpha]_D^{25}$ –325 (EtOH)); 75% e.e. (t_R (major) = 15.25 min, t_R (minor) = 14.39 min) as determined by chiral HPLC analysis on a CHIRALPAK OJ-H column (0.46 × 25 cm) eluting with 90 : 10 *n*-hexane/*i*-PrOH at a flow rate of 0.7 cm^3 min^{-1} with the UV detector set to 214 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (q, J = 6.9 Hz, 1H), 5.44–5.41 (m, 1H), 3.75 (t, J = 6.3 Hz, 2H), 2.40 (s, 1H), 2.40–2.32 (m, 2H), 1.77 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.1, 90.9, 75.0, 74.2, 70.7, 68.7, 68.1, 61.5, 31.3; FT-IR (film) 3294, 2207, 1950, 1046 cm^{-1}; UV ν_{max} (EtOH) 278, 263, 249, 237, 212 nm; EI-MS m/z (%) 132 (M$^+$, 14), 131 (76), 103 (100), 78 (62), 77 (62), 76 (47), 75 (79), 74 (65); EI-HRMS calcd. for C_9H_8O 132.0575 (M$^+$), found 132.0576.

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