An Elimination Approach to the Synthesis of (+)-Scorodonin†

Zhang, Yan(张艳) Wu, Yikang*(伍贻康)

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

1,2-Elimination of optically-active vinyl sulfoxide-allylic acetates led to corresponding allenynes in excellent yields. When the chirality of the sulfinyl group "matched" that at the allylic position, the chirality at the allylic stereogenic center could be efficiently transferred to the allenic axis.

Keywords elimination, natural products, allenes, alkynes, sulfoxides

Introduction

Scorodonin (**1**) is a natural antibiotic isolated from *Marasmius scorodonius*.[1] Preliminary biotesting has shown that this compound can inhibit the growth of bacteria, yeasts and filamentous fungi, and the incorporation of thymidine and uridine into DNA and RNA in cells of the ascitic form of Ehrlich carcinoma. Recently, we reported the first synthesis of this natural product, with the key allenic axis formed in 63% *ee* via a coupling reaction between an optically-active bromoallene (95% *ee*) and a zincated terminal alkyne.[2] Because the chirality transfer in this case was not as good as that in the similar couplings in our synthesis of Nemotin[3] (**2**) and Phomallenic acid C[4] (**3**) (Figure 1), alternative approaches were also sought. Herein we wish to report an elimination approach to the construction of an allenyne intermediate, from which using our earlier procedures it would be possible to obtain the antipode of the natural Scorodonin.

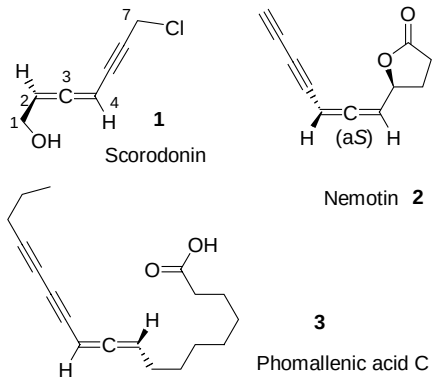


Figure 1 The structures of natural Scorodonin (**1**), Nemotin (**2**), and Phomallenic acid C (**3**).

Results and discussion

1,2-Elimination of optically-active sulfoxide-allylic acetates leading to corresponding allenes was initially developed by Satoh and co-workers.[5] Although this approach is not so atom-economic as elimination of similar iodides,[6] it does enjoy a distinct advantage—the diastereomers of the elimination precursors (sulfoxide-allyl alcohols, *vide infra*) are often separable by chromatography on silica gel because of the sulfoxide chirality. This benefit is particularly evident when both epimers of the allylic stereogenic center are needed in the studies, such as the present one.

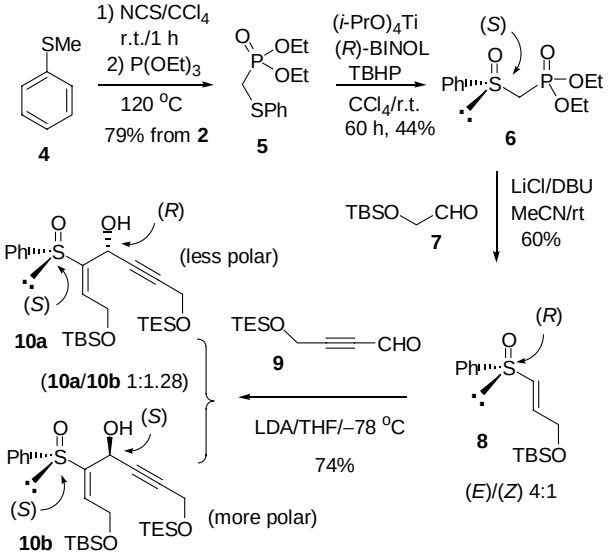
The optically-active sulfinyl functionality required for chromatographic separation of the two allylic epimers and consequent definition of the absolute stereochemistry of the allenic axis at a later stage of the synthesis was prepared according to the literature procedures. In the event, treatment of thioanisole (**4**) with NCS (*N*-chloro-succinimide) in CCl_4 at ambient temperature followed by heating with $P(OEt)_3$ gave the desired phenylthiomethylphosphate **5** in 79% overall yield (Scheme 1).[7] Asymmetric oxidation of the **5** was realized under the conditions of $(i\text{-PrO})_4$Ti/(*R*)-BINOL (1,1'-bi-2-naphthol)/TBHP (*tert*-butylhydroperoxide) as reported by Naso and coworkers.[8]

Condensation of the resulting optically-active sulfoxide **6** (88.5% *ee*) with the known aldehyde **7**[9] in the presence of LiCl/DBU/MeCN delivered the α,β-unsaturated sulfoxide **8**[10] in 60% yield as a 4∶1 mixture of the (*E*)/(*Z*) isomers. As in the next step of reaction both isomers reacted in the same way leading to a single double bond isomer, it was not necessary to isolate the two C-C double bond isomers at this stage.

The mixture of the (*E*)/(*Z*) isomers was deprotonated with LDA (lithium diisopropylamide) in THF at −78

* E-mail: yikangwu@sioc.ac.cn
Received May 4, 2010; revised and accepted July 16, 2010.
Project supported by the National Basic Research Program of China (973 Program) (No. 2010CB833200), the National Natural Science Foundation of China (Nos. 20921091, 20672129, 20621062, 20772143) and the Chinese Academy of Sciences ("Knowledge Innovation", KJCX2.YW.H08).
† Dedicated to the 60th Anniversary of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Scheme 1



℃ to generate the corresponding carbanion, which on reaction with aldehyde **9** [could be readily prepared from TES (triethylsilyl) protected proparyl alcohol and DMF (*N*-dimethylformamide)] afforded a pair of separable epimers (**10a** and **10b**) in a 1∶1.28 ratio. The configurations of the newly formed allylic stereogenic centers in **10a** and **10b** were not experimentally determined at this stage, but deduced later from the end products with the aid of the rules embedded in Satoh's work.[5]

The hydroxyl groups in **10a** and **10b** were then converted into better leaving groups, respectively, by acetylation with Ac_2O in the presence of pyridine and DMAP (4-dimethylaminopyridine) (Scheme 2). The resulting **11a** and **11b** were then converted, respectively, into corresponding allenes using the conditions of Satoh.[5] Thus, treatment of the acetates **11a** or **11b** with *i*-PrMgBr in THF led to clean formation of the corresponding allene. The reaction proceeded very fast even at −100 ℃ (Table 1), requiring less than 15 min to go to completion.

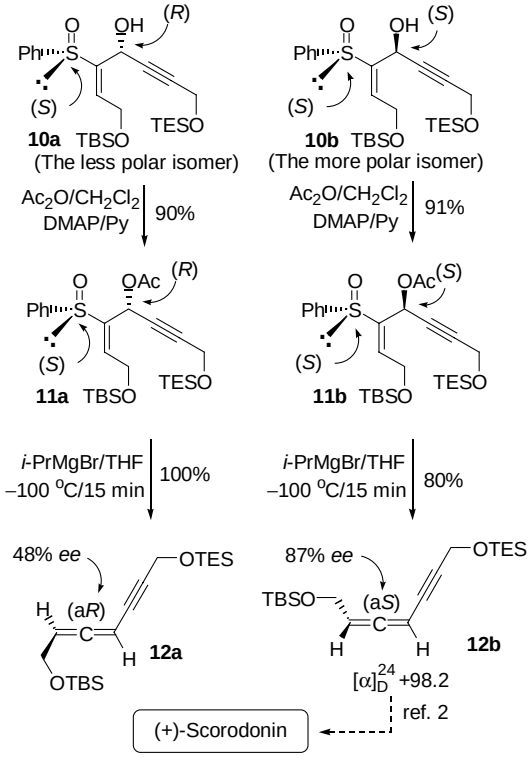
It is well established that the chiralty of the newly formed allenic axis is dictated by the allylic stereogenic center. However, the relative configuration of the sulfinyl group with respect to that of the allylic stereogenic center appeared also to have a substantial influence. With **11b** as the substrate, which led to the (a*S*) allene in the end, the efficiency for the chirality transfer from the allylic position to the allenic axis was excellent at a wide range of temperatures (Table 1, Entries 1—5). In the beginning we expected similar efficiency with the other isomer (**11a**) because at a glance the configuration of the sulfinyl group did not seem to have any direct relation to the elimination. Interestingly, the efficiency for the chirality transfer in the case of **11a**, which was of (*R*) configuration at the allylic position, turned out to be much lower than observed with **11b** (Table 1, Entry 6). Satoh *et al.*[5] had also mentioned similar cases in their work, though without any explanation or comments. It seems that there exists a delicate interaction between the configurations of the sulfinyl group and the allylic stereogenic center. When the configuration at these two positions matches with each other, the chirality at the allylic carbon can be transferred to the allenic axis in a highly stereoselective manner.

Table 1 Reaction of **11** with *i*-PrMgBr in THF leading to **12**

Entry	Substrate	Temperature	Product (yield, *ee*)	Eff.[a]
1	**11b**	−30 ℃	**12b** (93%, 85% *ee*)	96%
2	**11b**	−45 ℃	**12b** (93%, 84% *ee*)	94%
3	**11b**	−60 ℃	**12b** (93%, 82% *ee*)	93%
4	**11b**	−78 ℃	**12b** (90%, 84% *ee*)	95%
5	**11b**	−100 ℃	**12b** (80%, 87% *ee*)	98%
6	**11a**	−100 ℃	**12a** (100%, 48% *ee*)	54%

[a] Efficiency for the chirality transfer, defined as *ee* value of the product **12**/the *ee* value of the starting **11** employed.

Scheme 2



It should be noted that because **12a** (the antipode of **12b**) was an advanced intermediate in our previous synthesis of (−)-Scorodonin, from **12b** following the procedure in that work would lead to (+)-Scorodonin of the same enantiopurity (87% *ee*), the antipode of **1**. If using the (*R*) sulfoxide instead of the (*S*) one (**6**) as used in this work in the beginning, the same route should allow for synthesis of natural Scorodonin.

Conclusion

An elimination approach to the synthesis of the

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chiral allene-alkyne assembly of the natural antibiotic Scorodonin was developed. Starting from the (*S*)-sulfoxide of 88.5% *ee*, (a*S*)-allenyne was obtained in 87% *ee*. The stereoselectivity is substantially higher than that (63% *ee*) of the bromoallene-alkyne coupling approach adopted in our previous synthesis. Following the procedures of deprotection and chlorination of **12a** described in that work, it should be possible to obtain (+)-Scorodonin from **12b**. Similarly, using a (*R*)-sulfoxide instead of the (*S*) one may eventually give the natural Scorodonin in significantly improved enantioselectivity.

Experimental

Dry THF was distilled over Na/Ph_2CO under N_2 prior to use. Dry CH_2Cl_2, dry DMF, and dry MeCN were distilled over CaH_2 under N_2 prior to use. Addition of air/moisture sensitive reagents was done using syringe techniques. PE (for chromatography) stands for petroleum ether (b.p. 60—90 ℃). Column chromatography was performed on silica gel (300—400 mesh) under slightly positive pressure. NMR spectra were recorded on a Varian Mercury or a Bruker Avance NMR spectrometer operating at 300, 400, or 500 MHz for ^{1}H as indicated for each individual compound below with Me_4Si as the internal standard. IR spectra were measured on a FT-IR 440 or a Nicolet Avatar 360 infrared spectrometer. ESI-MS data were acquired on a HP5989A mass spectrometer. HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on Perkin-Elmer Polarimeter 341 or an Agilent Technologies P-1030 Polarimeter.

Diethyl (*S*)-phenylsulfinylmethylphosphate (6) NCS (3.725 g, 27.9 mmol) was added to a solution of **4** (3.0 mL, 25.4 mmol) in CCl_4 (25 mL) stirred at ambient temperature. Stirring was continued for 11 h. The white solids were filtered off. The filtrate was concentrated on a rotary evaporator. To the residue was added triethyl phosphite (5.3 mL, 30.48 mmol). The mixture was stirred in a 120 ℃ oil bath for 48 h. After being cooled to ambient temperature, the mixture was chromatographed [*V*(EtOAc) ∶ *V*(PE)＝1 ∶ 1] on silica gel to give the intermediate diethyl phenylthiomethylphosphate (5.2 g, 79% from **4**) as a yellowish oil.

A solution of (*i*-PrO)$_4$Ti (80 μL, 0.27 mmol) in CCl_4 (6.0 mL) was added to a solution of (*R*)-BINOL ([α]$_D^{25}$ +33.4 (*c* 1.0, THF), 145 mg, 0.51 mmol) in CCl_4 (40 mL) stirred at ambient temperature. To the resulting solution was added H_2O (91 μL, 5.0 mmol). Stirring was continued at ambient temperature for 1 h before a solution of the above mentioned diethyl phenylthiomethylphosphate (2.6 g, 10 mmol) in CCl_4 (6.0 mL) was introduced. The mixture was stirred for another 30 min. *tert*-Butylhydroperoxide (>65% aq. solution, 1.72 mL, 12.2 mmol) was added. Stirring was then continued at ambient temperature for 3 d. The mixture was loaded onto a silica gel column, first eluting with Et_2O to recover the unreacted starting phenylthiomethylphosphate (1.196 g, 46%), then with EtOAc/MeOH (*V* ∶ *V*＝10 ∶ 1) to obtain the known **6** (1.214 g, 44%) as a yellowish liquid. [α]$_D^{23}$ +98.6 (*c* 1.0, $CHCl_3$) [Lit.[8] [α]$_D$ +98.1 (*c* 1.0, $CHCl_3$)], 88.5% *ee* [t_R(major)＝11.40 min, t_R(minor)＝13.06 min] as determined by HPLC on a CHIRALPAK OJ-H column (0.46 cm×25.0 cm) eluting with *n*-hexane/*i*-PrOH (*V* ∶ *V*＝80 ∶ 20) at a flow rate of 0.7 mL/min with the UV detector set to 214 nm. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.73—7.70 (m, 2H), 7.53—7.50 (m, 3H), 4.18—4.05 (m, 4H), 3.39 (t, *J*＝14.6 Hz, 1H), 3.27 (dd, *J*＝15.4, 14.6 Hz, 1H), 1.30 (dt, *J*＝0.5, 7.1 Hz, 3H), 1.27 (dt, *J*＝0.5, 7.1 Hz, 3H).

(*R*,*E*)-3-*tert*-Butyldimethylsilyloxy-prop-1-enylphenylsulfoxide (8) A solution of **6** (1.26 g, 4.56 mmol), DBU (0.744 mL, 4.98 mmol), LiCl (228 mg, 5.38 mmol) and aldehyde **7** (722 mg, 4.15 mmol) in dry MeCN (25 mL) was stirred at ambient temperature overnight. Removal of the volatiles on a rotary evaporator left a residue, which was chromatographed [*V*(PE) ∶ *V*(Et_2O) ∶ *V*(CH_2Cl_2)＝9 ∶ 2 ∶ 1] on silica gel to give pure (*E*)-isomer (accounted for the majority of the product) along with a mixture of the (*E*)/(*Z*) isomers (737 mg altogether, 2.49 mmol, 60%) as colorless oils. Data for the (*E*)-isomer (the less polar component): [α]$_D^{24}$ +118.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65—7.60 (m, 2H), 7.53—7.42 (m, 3H), 6.67 (dtd, *J*＝14.9, 3.4, 0.3 Hz, 1H), 6.49 (dt, *J*＝14.9, 1.9 Hz, 1H), 4.37 (dd, *J*＝3.6 2.2 Hz, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.8, 138.1, 133.4, 130.9, 129.2, 124.4, 62.0, 25.7, 25.6, 18.2, −5.6; FT-IR (film) *v*: 3311, 2926, 2881, 1616, 1442, 1089, 1028, 932, 757, 692 cm^{-1}; ESI-MS *m*/*z*: 297.0 ([M＋H]$^+$); ESI-HRMS calcd for $C_{15}H_{25}SiO_2S$ 297.1339 ([M＋H]$^+$), found 297.1341.

(3*R*)-7-*tert*-Butyldimethylsilyloxy-5-((*S*)-phenylsulfinyl)-1-triethylsilyloxy-hept-5-en-2-yn-3-ol (10a) and (3*S*)-7-*tert*-butyldimethylsilyloxy-5-((*S*)-phenylsulfinyl)-1-triethylsilyloxy-hept-5-en-2-yn-3-ol (10b) *n*-BuLi (2.5 mol•L^{-1}, in hexanes, 8.8 mL, 22 mmol) was added dropwise to a solution of $Et_3SiOCH_2C{\equiv}CH$ (3.4 mL, 20 mmol) in dry THF (40 mL) stirred at 0 ℃. Stirring was continued at the same temperature for 15 min. Then the bath temperature was cooled to −78 ℃ before dry Me_2NCHO (2.32 mL, 30 mmol) was introduced dropwise. The stirring was continued while bath was allowed to warm slowly to ambient temperature. 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 on a rotary evaporator and column chromatography [*V*(EtOAc) ∶ *V*(PE)＝1 ∶ 100] on silica gel gave the aldehyde **9** (3.8 g, 19 mmol, 95%) as a colorless oil. The NMR for **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.23 (s, 1H), 4.49 (s, 2H), 0.97 (t, *J*＝8.0 Hz, 9H), 0.65 (q, *J*＝7.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 176.4, 94.8, 84.1, 51.1, 6.5, 4.2.

n-BuLi (2.5 mol•L^{-1}, in hexanes, 0.40 mL, 1.0 mmol) was added dropwise to a solution of dry *i*-Pr_2NH (0.14 mL, 1.01 mmol) in dry THF (3.0 mL) stirred at 0 ℃. Stirring was continued at the same temperature for 15 min. The bath temperature was cooled to −78 ℃ before a solution of **8** (200 mg, 0.676 mmol) in dry THF (1.0 mL) was introduced. The mixture was stirred at −78 ℃ for another 15 min. A solution of the above mentioned aldehyde **9** (200 mg, 1.01 mmol) in dry THF (1.0 mL) was then added. The stirring was continued at the same temperature for 1 h. Aq. sat. NH_4Cl (10 mL) was added, followed by water (10 mL). The mixture was extracted with Et_2O (20 mL×3), washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography [*V*(PE) ∶ *V*(CH_2Cl_2) ∶ *V*(Et_2O) = 3 ∶ 3 ∶ 1] on silica gel afforded **10a** and **10b** (247 mg altogether, 74% in total) as colorless oils.

Data for **10a** (the less polar isomer): $[\alpha]_D^{27}$ +23.0 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.71—7.65 (m, 2H), 7.49—7.43 (m, 3H), 6.60 (t, *J*=4.9 Hz, 1H), 5.06 (d, *J*=7.6 Hz, 1H), 4.63 (dd, *J*=15.6, 4.9 Hz, 1H), 4.57 (dd, *J*=15.6, 5.1 Hz, 1H), 4.19—4.08 (m, 2H), 3.99 (d, *J*=7.6 Hz, 1H), 0.93 (t, *J*=8.2 Hz, 9H), 0.90 (s, 9H), 0.58 (q, *J*=7.7 Hz, 6H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 143.7, 142.5, 135.2, 131.4, 129.0, 126.0, 84.6, 81.9, 60.5, 57.5, 51.0, 25.7, 18.2, 6.6, 4.2, −5.4, −5.6; FT-IR (film) *v*: 3346, 2955, 2929, 2857, 2080, 1442, 1259, 1084, 1020, 836, 780 cm^{-1}; ESI-MS *m*/*z*: 495.1 ([M+H]$^+$); ESI-HRMS calcd for $C_{25}H_{43}Si_2O_4S$ 495.2415 ([M+H]$^+$), found 495.2415.

Data for **10b** (the more polar isomer): $[\alpha]_D^{24}$ −16.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.67—7.61 (m, 2H), 7.50—7.44 (m, 3H), 6.57 (t, *J*=4.9 Hz, 1H), 5.03 (dt, *J*=6.2, 1.6 Hz, 1H), 4.67 (dd, *J*=6.5, 4.9 Hz, 1H), 4.63 (dd, *J*=6.5, 5.4 Hz, 1H), 4.41 (d, *J*=6.4 Hz, 1H), 4.08 (d, *J*=1.7 Hz, 2H), 0.91 (t, *J*=7.7 Hz, 9H), 0.90 (s, 9H), 0.55 (q, *J*=8.0 Hz, 6H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 143.8, 141.8, 137.0, 131.3, 129.0, 125.6, 83.9, 82.2, 60.6, 56.5, 50.9, 25.8, 18.2, 6.6, 4.2, −5.4, −5.5; FT-IR (film) *v*: 3344, 3053, 2954, 2861, 2081, 1645, 1463, 1257, 1084, 1019, 836, 746, 688 cm^{-1}; ESI-MS *m*/*z*: 495.1 ([M+H]$^+$); ESI-HRMS calcd for $C_{25}H_{43}Si_2O_4S$ 495.2415 ([M+H]$^+$), found 495.2420.

(3*S*)-3-Acetyloxy-7-*tert*-butyldimethylsilyloxy-5-((*S*)-phenylsulfinyl)-1-triethylsilyloxy-hept-5-en-2-yne (11b) To a solution of **10b** (70 mg, 0.142 mmol) in dry CH_2Cl_2 (1.5 mL) stirred in an ice-water bath were added in turn Ac_2O (44 μL, 0.426 mmol), pyridine (36 μL, 0.65 mmol) and DMAP (1.7 mg, 0.0142 mmol). The stirring was then continued at ambient temperature for 2 h. The mixture was diluted with Et_2O (30 mL), 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 on a rotary evaporator and column chromatography [*V*(PE) ∶ *V*(EtOAc)=6 ∶ 1] on silica gel afforded the acetate **11b** (69 mg, 0.129 mmol, 91%, which is more polar than **11a**) as a colorless oil. The epimer **11a** was prepared from **10a** in a similar manner.

Data for **11a** (less polar than **11b**): $[\alpha]_D^{27}$ +43.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.68—7.64 (m, 2H), 7.47—7.44 (m, 3H), 6.80 (t, *J*=5.2 Hz, 1H), 6.25 (t, *J*=1.9 Hz, 1H), 4.73—4.59 (m, 2H), 4.27 (d, *J*=1.9 Hz, 2H), 1.57 (s, 3H), 0.95 (t, *J*=7.8 Hz, 9H), 0.92 (s, 9H), 0.60 (q, *J*=8.1 Hz, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 168.4, 143.0, 139.4, 139.0, 131.4, 129.0, 126.0, 86.3, 78.6, 60.4, 57.3, 51.1, 25.8, 19.9, 18.2, 6.6, 4.3, −5.36, −5.38; FT-IR (film) *v*: 3400, 2955, 2930, 2858, 2081, 1751, 1370, 1219, 1086, 1015, 837, 748 cm^{-1}; ESI-MS *m*/*z*: 537.1 ([M+H]$^+$); ESI-HRMS calcd for $C_{27}H_{44}Si_2O_5SNa$ 559.2340 ([M+Na]$^+$), found 559.2337.

Data for **11b** (more polar than **11a**): $[\alpha]_D^{27}$ +29.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.68—7.64 (m, 2H), 7.48—7.43 (m, 3H), 6.72 (t, *J*=5.3 Hz, 1H), 6.19 (d, *J*=2.0 Hz, 1H), 4.63 (ddd, *J*=21.6, 16.0, 4.8, 2H), 4.00 (d, *J*=1.8 Hz, 2H), 1.95 (s, 3H), 0.92 (s, 9H), 0.90 (t, *J*=7.9 Hz, 9H), 0.54 (q, *J*=7.7 Hz, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 168.3, 142.3, 139.2, 139.2, 131.4, 129.0, 125.8, 85.5, 78.5, 60.5, 57.3, 50.8, 25.8, 20.4, 18.2, 6.5, 4.2, −5.38, −5.41; FT-IR (film) *v*: 3393, 2955, 2928, 2856, 1752, 1372, 1257, 1219, 1084, 1020, 837, 779 cm^{-1}; ESI-MS *m*/*z*: 537.1 ([M+H]$^+$); ESI-HRMS calcd for $C_{27}H_{45}Si_2O_5S$ 537.2521 ([M+H]$^+$), found 537.2519.

(3a*S*)-1-(*tert*-Butyldimethylsilyloxy)-7-triethylsilyloxy-hepta-2,3-dien-5-yne (12b) A solution of **11b** (25 mg, 0.0466 mmol) in dry THF (1.0 mL) was added to a solution of *i*-PrMgBr (2.5 mol•L^{-1}, 0.11 mL, 0.28 mmol) in dry THF (1.5 mL) stirred at −100 ℃ (Et_2O-liq. N_2 bath) under argon. The mixture was stirred at the same temperature for 15 min. Aq. sat. NH_4Cl was added. The mixture was extracted with Et_2O (5 mL×3). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and column chromatography [*V*(Et_2O) ∶ *V*(PE) = 1 ∶ 75] on silica gel afforded the known allene **12b**[2] (13 mg, 0.0373 mmol, 80%) as a colorless oil. $[\alpha]_D^{24}$ +98.2 (*c* 0.6, $CHCl_3$), of 87% *ee* [t_R(major)=11.65 min, t_R(minor)=10.92 min] as determined by HPLC on a CHIRALPAK OD column (0.46 cm×25.0 cm) eluting with *n*-hexane at a flow rate of 0.7 mL/min with the UV detector set to 214 nm. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 5.50 (dt, *J*=6.4, 6.2 Hz, 1H), 5.49 (dt, *J*=5.0, 3.4 Hz, 1H), 4.41 (s, 2H), 4.23 (dd, *J*=5.1, 3.6 Hz, 2H), 0.98 (t, *J*=7.9 Hz, 9H), 0.90 (s, 9H), 0.65 (q, *J*=7.9 Hz, 6H), 0.09 (s, 6H).

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(E1005042 Pan, B.)

