

47. Studied Directed toward the Synthesis of Phomenoic Acid

Part 2¹⁾

Stereocontrolled Synthesis of the C(7)-to-C(14) Segment

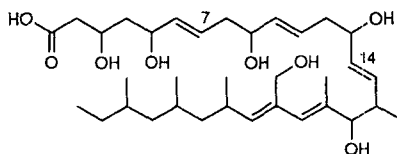
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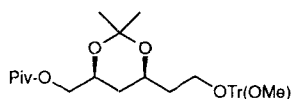
(15.XII.95)

Starting from the esters (2*E*,4*S*)-**6** and (2*E*,4*R*)-**6**, bromo aldehydes (*S*)-**9** and (*R*)-**9** as well as bromo alcohols (*S*)-**10** and (*R*)-**10**, respectively, were prepared. Bromo alcohol (*R*)-**8** was converted to the diol (2*E*,4*R*)-**16**. Ozonolysis of the latter led to aldehyde (*R*)-**17**, which was transformed, by a *Wittig* reaction, to (2*R*,4*E*,6*R*)-**18**, corresponding to the C(7)-to-C(14) segment of phomenoic acid (**1**). Attempts to improve the yields by applying a *Julia* coupling of (*R*)-**23**, which was prepared from (2*E*,4*R*)-**7**, with (*R*)-**24** were unsuccessful. Finally, the coupling of the iodo derivative (2*E*,4*S*)-**28** with the lithiated derivative of 1,3-dithiane **30** by the *Corey-Seebach* 'Umpolung' led to (3*S*,4*E*)-**32** which is a derivative of the C(7)-to-C(14) segment of **1**, suitable for further transformations.

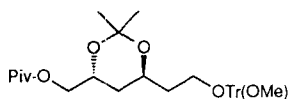
Introduction. – In the preceding communication [1], we have presented a general concept for the stereocontrolled total synthesis of phomenoic acid (**1**), a secondary metabolite of *Phoma lingam* TODE, and described the enantioselective synthesis of the key intermediates **2** and **3** and their enantiomers. They correspond to the C(1)-to-C(6)



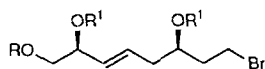
1 Phomenoic Acid



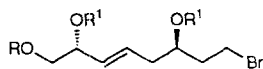
(2*S*,4*S*) - **2**



(2*R*,4*S*) - **3**



(2*S*,4*E*,6*S*) - **4**



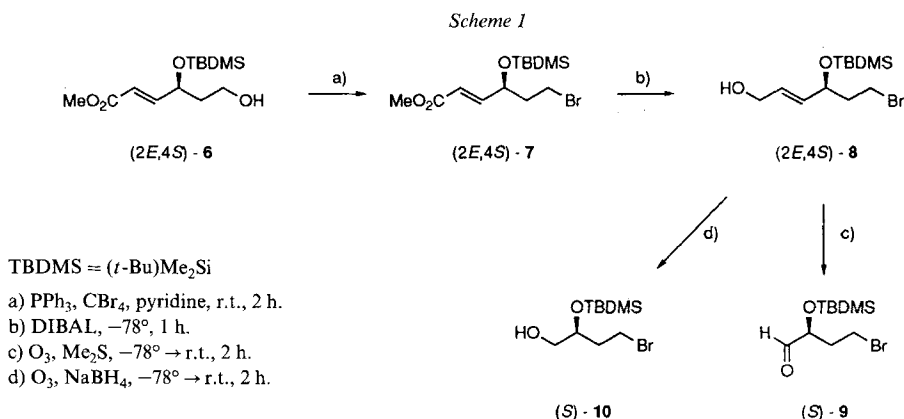
(2*R*,4*E*,6*S*) - **5**

Tr(OMe) = (4-methoxyphenyl)(diphenyl)methyl

¹⁾ Part 1: [1].

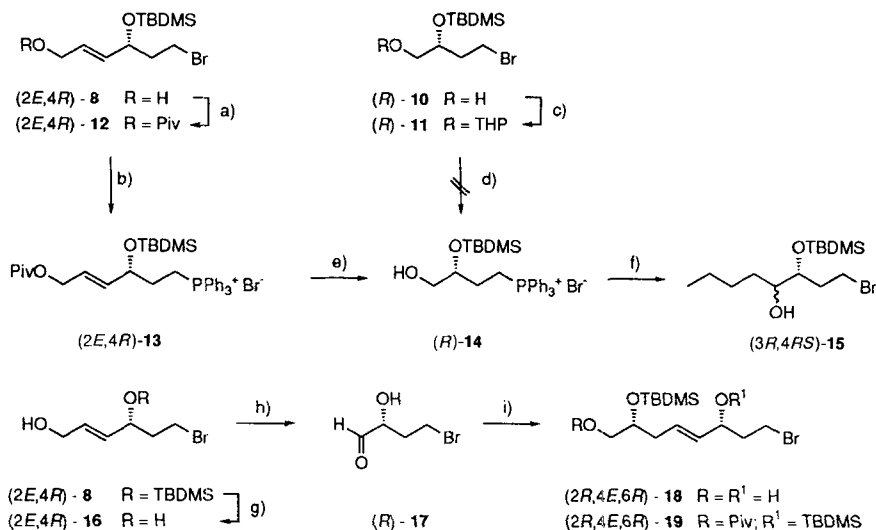
segment of the microbial metabolite [1]. This communication deals with our efforts directed to the stereocontrolled synthesis of the C(7)-to-C(14) moiety, especially of the multifunctionalized compounds **4** and **5**, and their enantiomers. According to our strategy, both enantiomers of aldehyde **9** and alcohol **10** are important intermediates, and they can be prepared starting from the known unsaturated hydroxy ester **2**.

Results and Discussion. – For the synthesis of the aldehyde (*S*)-**9**, ester (*2E,4S*)-**6** was transformed to the bromo derivative (*2E,4S*)-**7** by treatment with PPh_3 and CBr_4 (Scheme 1). Ozonolysis of **7** to form **9** proceeded with limited success, probably due to the conjugation of the ester $\text{C}=\text{O}$ group with the olefinic $\text{C}=\text{C}$ bond. To overcome this difficulty, (*2E,4S*)-**7** was first reduced to the alcohol (*2E,4S*)-**8** with DIBAL in hexane (yield 88%). Subsequent ozonolysis, followed by reduction of the ozonide obtained with Me_2S , yielded the desired aldehyde (*S*)-**9**. Alcohol (*S*)-**10** was prepared by ozonolysis of (*2E,4S*)-**8** and subsequent treatment of the ozonide with NaBH_4 . The same reduction sequence was applied to the enantiomeric ester (*2E,4R*)-**6** to yield the products (*R*)-**9** and (*R*)-**10** in 63 and 67% overall yields, respectively.



Having prepared compounds (*R*)-**9** and (*S*)-**9** as well as (*R*)-**10** and (*S*)-**10**, respectively, the next goal was the synthesis of the intermediates **18** and **19** (Scheme 2). The availability of the bromo derivatives **10** prompted us to apply the Wittig-Schlosser reaction to form the (*E*)-alkenes [2] in spite of the known possibility that α -hydroxy aldehydes can racemize [3], and/or of the difficulty of the anion-ylide addition to α -hydroxy aldehydes [4]. As outlined in Scheme 2, the primary OH group of (*R*)-**10** was protected by the THP group by treatment with 3,4-dihydro-2*H*-pyran and TsOH to afford (*R*)-**11** (66%). Transformation of either (*R*)-**10** or (*R*)-**11** to ylide (*R*)-**12** by treatment with PPh_3 in benzene [5] was unsuccessful. Therefore, it was decided to reverse the reaction sequence by starting with allylic alcohol (*2E,4R*)-**8**. At first, the OH group was protected by the pivaloyl group to afford fully protected bromo derivative (*2E,4R*)-**12** (74%). Because of the relatively high molecular weight and stability of **12**, phosphonium salt (*2E,4R*)-**13** was prepared by heating (*2E,4R*)-**12** with PPh_3 in MeCN at 60° for 48 h. However, the yield of **13** was poor after purification on a silica column (12%). Ozonolysis of (*2E,4R*)-**13** led to the alcohol (*R*)-**14**. The latter tended to hydrate very rapidly.

Scheme 2

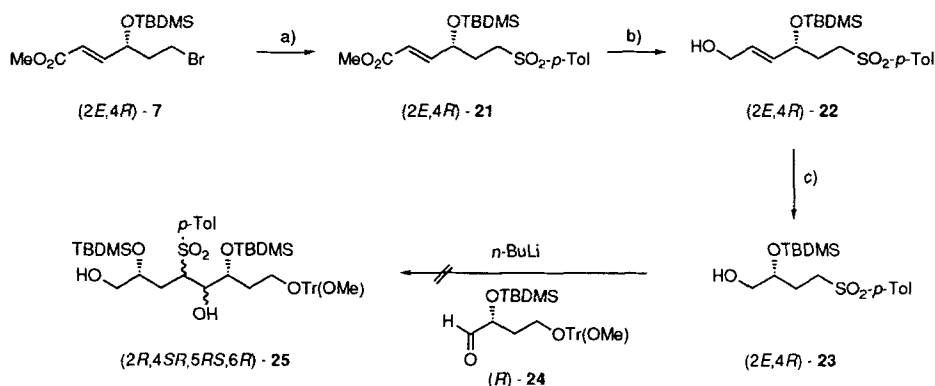


TBDMS = (*t*-Bu) Me_2Si , THP = tetrahydro-2*H*-pyran-2-yl

a) Pivaloyl chloride, pyridine, r.t., 24 h. b) PPh_3 , reflux, 48 h. c) 2,3-Dihydro-4*H*-pyrane, TsOH, 20°, 5 h. d) PPh_3 . e) O_3 , NaBH_4 , $-78^\circ \rightarrow \text{r.t.}$, 2 h. f) BuLi, (*R*)-**9**, $-78^\circ \rightarrow -40^\circ$. g) TBAF, r.t., 13 h. h) O_3 , Me_2S , $-78^\circ \rightarrow \text{r.t.}$, 2 h. i) BuLi, (*R*)-**14**, $-78^\circ \rightarrow -40^\circ \rightarrow \text{r.t.}$

Therefore, it was immediately subjected to *Wittig* reaction. Treatment of (*R*)-**14** in THF with 2 equiv. of BuLi in hexane in THF/ Et_2O at 0° and then with 1 equiv. of aldehyde (*R*)-**9** led only to the addition of BuLi to finally give butyl derivative **15** (80%) and not the desired product (*2R,4E,6R*)-**19** which corresponds to the required building block. Extensive variation of the reaction conditions failed to yield the needed compound. Also the reaction of (*R*)-**9** with (*2E,4R*)-**13** was unsuccessful. The reason for the negative results of the *Wittig* coupling may be due to steric hindrance of the protecting (*t*-Bu) Me_2Si group in α -position to the C=O group in aldehyde (*R*)-**9**. Removal of the (*t*-Bu) Me_2Si group of (*R*)-**9** was considered to be a solution of the problem in spite of the possibility of racemization [3]. Treatment of (*2E,4R*)-**8** with Bu_4NF in THF afforded bromo diol (*2E,4R*)-**16** (63%). Ozonolysis of the latter, followed by treatment of the ozonide with Me_2S , provided the α -hydroxy aldehyde (*R*)-**17**. Because of the instability of the product obtained, it was immediately subjected to the *Wittig* coupling. Subsequent treatment of phosphonium salt (*R*)-**14** in THF with 2 equiv. of BuLi in hexane in THF/ Et_2O and 1 equiv. of (*R*)-**17** in THF afforded (*2R,4E,6R*)-**18**, which corresponds to the C(7)-to-C(14) segment of phenomenic acid (**1**) as a suitable derivative for further transformations. However, the yield was very low, even after extended variation of the reaction conditions. Therefore, we investigated the *Julia* coupling [6] as an alternative to the *Wittig* reaction for the formation of an (*E*)-alkene. For this purpose, the bromo ester (*2E,4R*)-**7** was converted to the corresponding sulfone (*2E,4R*)-**21** by treatment with sodium 4-toluenesulfinate in DMF according to Ferraboschi *et al.* [7] (37%; Scheme 3). Reduction of (*2E,4R*)-**21** with DIBAL in hexane gave the alcohol (*2E,4R*)-**22** (63%). Ozonolysis of the

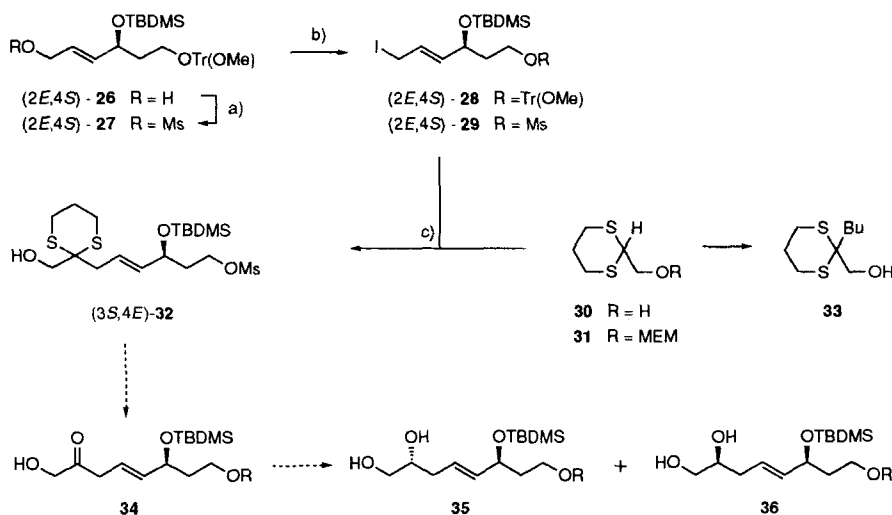
Scheme 3

TBDMS = (*t*-Bu) $_2$ Sia) *p*-Tol-SO₂Na, reflux, 3 h. b) DIBAL, –50°, 1 h. c) O₃, NaBH₄, –78° → r.t., 2 h.

latter and subsequent reduction of the ozonide with NaBH₄ yielded sulfone (*R*)-**23** (78%). However, after subsequent treatment of (*R*)-**23** in THF with 2 equiv. of BuLi and 1 equiv. of aldehyde (*R*)-**24** [1], no formation of the desired product (*2R,4R,5R,6R*)-**25** was observed.

The failure of the *Wittig* and *Julia* olefinations led us to explore the application of organometallic reagents which contain two heteroatomic moieties on their carbanionic center [8], such as 2-lithio-1,3-dithiane (*Corey-Seebach* reagent) [9]. The required starting

Scheme 4

TBDMS = (*t*-Bu) $_2$ Si, Tr(OMe) = (4-methoxyphenyl)(diphenyl)methyl, MEM = MeOCH₂CH₂OCH₂a) MsCl, Et₃N, –20°, 45 min. b) LiI/acetone, –30°, 5 h. c) BuLi, (*2E,4S*)-**29**, –78° → –40°, 4 h.

1,3-dithiane **31** was prepared by treating 2-hydroxyacetaldehyde with propane-1,3-dithiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CHCl_3 to give 1,3-dithiane-2-methanol (**30**) followed by treatment of the latter with (2-methoxyethoxy)methyl (MEM) chloride and BuLi in DMF (Scheme 4). At first, the coupling of 1,3-dithiane **30** was examined with BuLi. The addition product **33** was obtained in good yield. However, the reaction with the protected 1,3-dithiane **31** under the same conditions failed, probably due to the difficulty of generating the lithiated anion. The analogous coupling of 1,3-dithiane **30** with the iodo derivative (3*S*,4*E*)-**29** furnished (3*S*,4*E*)-**32** (39%) which represents a derivative of the C(7)-to-C(14) segment of phomenoic acid (**1**). The iodo derivative (3*S*,4*E*)-**29** was prepared from the known alcohol (2*E*,4*S*)-**26** [1] via methanesulfonate (2*E*,4*S*)-**27** by reacting the latter with LiI in acetone [10]. The yield of (2*S*,4*S*)-**28** obtained was low, because, in the courses of the reaction, Tr(OMe) was partly exchanged by Ms, thus forming (3*S*,4*E*)-**29** probably due to the liberation of methanesulfinic acid. Completion of the synthesis of stereoisomers (2*R*,4*E*,6*S*)-**35** and (2*S*,4*E*,6*S*)-**36** requires only the hydrolysis of 1,3-dithiane (3*S*,4*E*)-**32** to hydroxy ketone (4*E*,6*S*)-**34** with HgCl_2/HgO [11] and subsequent enantioselective catalytic reduction [12].

Financial support of these investigations by the Swiss National Science Foundation is gratefully acknowledged.

Experimental Part

General. See [1].

Methyl (2E,4R)-6-Bromo-4-[(tert-butyl)dimethylsilyloxy]hex-2-enoate ((2E,4R)-7). To a stirred soln. of (2*E*,4*R*)-**6** (250 mg, 0.912 mmol), dissolved in Et_2O (20 ml), PPh_3 (1.35 g, 5.16 mmol), CBr_4 (1.735 g, 5.16 mmol), and pyridine (0.1 ml) were subsequently added. Stirring was continued at r.t. for 2 h, followed by evaporation of the solvent. The residue was dissolved in CH_2Cl_2 , washed once with 1*N* HCl, brine, and then dried. Evaporation and purification on silica gel (CH_2Cl_2) afforded (2*E*,4*R*)-**7** (180 mg; 60%). Colorless oil. $[\alpha]_{\text{D}}^{20} = +10.95$ ($c = 2.0$, Et_2O). IR (film): 3040–2860, 1730, 1660, 1470, 1430, 1360, 1250, 1160, 1100, 970, 835, 770. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.0 (2*s*, Me_2Si); 0.92 (*s*, *t*-Bu); 1.99 (*m*, $\text{CH}_2(5)$); 3.44 (*m*, $\text{CH}_2(6)$); 3.75 (*s*, MeOH); 4.50 (*m*, H–C(4)); 6.05 (*dd*, $J = 2$, 16 H–C(2)); 6.90 (*dd*, $J = 5$, 18, H–C(13)). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): –5.2; –4.7; 17.9; 25.6; 29.9, 40.1; 51.6; 69.7; 120.6; 150.0; 167.1. CI-MS (NH_3): 356/354 (100, $[M + \text{NH}_4]^+$), 339 (M^+), 337 (29), 312 (33), 310 (18), 205 (12), 156 (12), 154 (12), 144 (20), 132 (42); 110 (22), 91 (57).

Similarly, enantiomer (2*E*,4*S*)-**7** was obtained in 80% yield starting from (2*E*,4*S*)-**6**. $[\alpha]_{\text{D}}^{20} = -9.1$ ($c = 2.0$, Et_2O). IR (film): 2960–2860, 1730, 1660, 1470, 1430, 1360, 1265, 1250, 1165, 1100, 970, 840, 770. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.0 (2*s*, Me_2Si); 0.88 (*s*, *t*-Bu); 2.01 (*m*, $\text{CH}_2(5)$); 3.41 (*m*, $\text{CH}_2(6)$); 3.72 (*s*, MeO); 4.46 (*m*, H–C(4)); 6.00 (*dd*, $J = 2$, 15, H–C(2)); 6.88 (*dd*, $J = 5$, 15, H–C(3)). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): –5.2; –4.8; 25.6; 28.9; 40.0; 44.4; 51.5; 69.6; 120.6; 150.0; 183.5. CI-MS (NH_3): 356/354 (10, $[M + \text{NH}_4]^+$), 339 (M^+), 337 (48), 307 (19), 305 (19), 281 (47), 279 (45), 229 (21), 207 (100), 205 (77), 156 (28), 154 (28), 132 (37), 127 (28), 125 (18), 106 (30), 91 (56).

(2E,4R)-6-Bromo-4-[(tert-butyl)dimethylsilyloxy]hex-2-enol ((2E,4R)-8). A 1.5*M* soln. of DIBAL in hexane (365 μl , 0.519 mmol) was added dropwise over 30 min to a soln. of (2*E*,4*R*)-**7** (150 mg, 0.442 mmol) in hexane (5 ml) at -78° . After stirring for 1 h, 5 drops of MeOH were added and the mixture warmed to r.t. NH_4Cl Soln. (sat., 5 ml) was added, followed by Et_2O (10 ml). The org. layer was washed once with 1*N* HCl and brine. Drying and evaporation afforded crude (2*E*,4*R*)-**8** which was purified on silica gel (Et_2O /petroleum ether 1:1): (2*E*,4*R*)-**8** (90 mg; 65%). Yellow oil. $[\alpha]_{\text{D}}^{20} = +10.6$ ($c = 1.0$, Et_2O). IR (film): 3350 (br.), 2980–2850, 1680, 1460, 1360, 1250, 1080, 1000, 970, 840, 770. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 0.0 (2*s*, Me_2Si); 0.85 (*s*, *t*-Bu); 1.95 (*m*, $\text{CH}_2(5)$); 3.42–3.61 (*m*, $\text{CH}_2(6)$, OH); 4.13 (*t*, $J = 6$, $\text{CH}_2(1)$); 4.33 (*m*, H–C(4)); 5.66 (*dd*, $J = 6$, 16, H–C(2)); 5.79 (*dd*, $J = 3$, 15, H–C(3)). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): –5.2; –4.7; 18.1; 25.8; 40.8; 63.0; 69.7; 70.7; 129.4; 133.9. CI-MS (NH_3): 328/326 (12, $[M + \text{NH}_4]^+$), 311/309 (3, M^+), 293 (77), 291 (75), 249 (17), 247 (46), 196 (26), 194 (26), 178 (12), 176 (11), 161 (7), 159 (8), 132 (100).

Similarly, enantiomer (2*E*,4*S*)-**8** was obtained in 88% yield starting from (2*E*,4*S*)-**7**. $[\alpha]_D = -9.6$ ($c = 2.0$, Et₂O). IR (film): 3350 (br.), 2960–2860, 1680, 1460, 1360, 1250, 1080, 1000, 870, 830, 770. ¹H-NMR (60 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.80 (*s*, *t*-Bu); 1.80–2.10 (*m*, CH₂(5), OH); 3.40 (*t*, $J = 6$, CH₂(6)); 3.90 (*d*, $J = 4$, CH₂(1)); 4.20 (*m*, H–C(4)); 5.60 (*m*, H–C(2), H–C(3)). CI-MS (NH₃): 309 (18, $[M - 1]^+$), 307 (15), 293 (57), 291 (56), 251 (5), 229 (59), 213 (12); 211 (18), 196 (14), 194 (5), 139 (15), 137 (15), 97 (21), 75 (100).

(2*R*)-4-Bromo-2-[(*tert*-butyl)dimethylsilyloxy]butanal ((*R*)-**9**). O₃ was bubbled through a stirred soln. of (2*E*,4*R*)-**8** (30 mg, 0.096 mmol) in MeOH (5 ml) at -78° until saturation. After flushing off excess O₃ with N₂, Me₂S (10.3 μ l, 0.138 mmol) was added. The mixture was stirred at r.t. for 2 h and then concentrated to $\frac{1}{4}$ of its volume, diluted with Et₂O (10 ml), and washed once with brine. Drying and evaporation afforded (*R*)-**9** (14 mg; 52%). Colorless oil. $[\alpha]_D = +1$ ($c = 1.0$, CH₂Cl₂). IR (film): 2960–2850, 1740, 1470, 1250, 1110, 830, 770. ¹H-NMR (60 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.85 (*s*, *t*-Bu); 1.80–2.10 (*m*, CH₂(3)); 3.20 (*t*, $J = 5$, CH₂(4), OH); 4.12 (*m*, CH₂(2)); 9.62 (*s*, CHO). CI-MS (NH₃): 300 (10, $[M + NH_4]^+$), 298 (10), 283 (16), 281 (15), 267 (62), 265 (61), 225 (30), 223 (39), 179 (10), 169 (9), 167 (10), 139 (19), 103 (19), 73 (100).

Starting from (2*E*,4*S*)-**8**, following the same procedure as described above, (*S*)-**9** was obtained in 61% yield as a colorless oil. IR (film): 2960–2860, 1740, 1470, 1250, 1110, 950, 830, 770. ¹H-NMR (60 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.80 (*s*, *t*-Bu); 1.90–2.10 (*m*, CH₂(3)); 3.20 (*t*, $J = 6$, CH₂(4), OH); 4.15 (*m*, CH₂(2)); 9.60 (br. *s*, CHO). CI-MS (NH₃): 300 (88, $[M + NH_4]^+$), 298 (87), 282 (15), 280 (15), 267 (7), 265 (6), 256 (21), 254 (60), 225 (17), 223 (18), 200 (22), 179 (10), 171 (31), 132 (100).

(2*R*)-4-Bromo-2-[(*tert*-butyl)dimethylsilyloxy]butan-1-ol ((*R*)-**10**). O₃ was bubbled through a stirred soln. of (2*E*,4*R*)-**8** (40 mg, 0.128 mmol) in MeOH (5 ml) at -78° until a blue color appeared. After flushing off excess O₃ with N₂, NaBH₄ (10 mg 0.264 mmol) was added, and the mixture was warmed to r.t. and stirred for 2 h. After concentrating to $\frac{1}{2}$ of the volume, Et₂O (10 ml) was added and the mixture washed once with brine. Drying and evaporation afforded (*R*)-**10** (29 mg; 80%). Colorless oil. $[\alpha]_D = +2.0$ ($c = 1.0$, Et₂O). IR (film): 3400 (br.), 2960–2850, 1460, 1360, 1250, 1110, 1050, 830, 770. ¹H-NMR (60 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.80 (*s*, *t*-Bu); 1.95 (*m*, CH₂(3), OH); 3.30–3.70 (*m*, CH₂(4), CH₂(1)); 4.20 (*m*, CH₂(2)). CI-MS (NH₃): 302 (9, $[M + NH_4]^+$), 300 (8), 285 (100, M^+), 283 (98), 267 (28), 265 (24), 234 (38), 220 (35), 203 (76), 132 (95).

Starting from (2*E*,4*S*)-**8** and following the same procedure given above, (*S*)-**10** was obtained in 85% yield. $[\alpha]_D = -2.6$ ($c = 1.0$, Et₂O). ¹H-NMR (60 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.85 (*s*, *t*-Bu); 1.30 (br. *s*, OH); 1.80–2.10 (*m*, CH₂(3)); 3.30–3.70 (*m*, CH₂(4), CH₂(1)); 4.20 (*m*, H–C(2)). CI-MS (NH₃): 302 (36, $[M + NH_4]^+$), 300 (35), 285 (25, M^+), 283 (24), 266 (64), 256 (72), 234 (97), 221 (52), 203 (9), 196 (17), 194 (17), 132 (100).

(2*R*)-4-Bromo-2-[(*tert*-butyl)dimethylsilyloxy]-1-(*tetrahydro*-2*H*-pyran-2-yloxy)butane ((*R*)-**11**). Compound (*R*)-**10** (32 mg, 0.113 mmol) and TsOH·H₂O (8.5 mg, 0.05 mmol) were stirred in 3,4-dihydro-2*H*-pyran (3 ml) at 20° for 5 h. The mixture was carefully neutralized by addition of a few crystals of NaHCO₃ and stirring continued for 2 h. A few drops of H₂O were added and the mixture extracted with Et₂O (3 $\times$ 10 ml). The org. extracts were dried, concentrated, and purified on silica gel (Et₂O/petroleum ether 1:1; R_f 0.66) to afford (*R*)-**11** (28 mg; 66%) as a mixture of diastereoisomers. IR (film): 2940–2840, 1440, 1350, 1230, 1200, 1150, 1120, 1080, 1035, 1010, 960, 870, 810, 730. ¹H-NMR (300 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.83 (*s*, *t*-Bu); 1.83–2.18 (*m*, CH₂(3), CH₂(3'), CH₂(4'), CH₂(5')); 3.27–3.57 (*m*, CH₂(4)); 3.68–3.91 (*m*, H–C(2), CH₂(6')); 4.58 (*m*, H–C(2')). FAB-MS (+ KCl): 409 (4, $[M + K]^+$), 305 (3), 287 (3), 221 (20), 185 (3), 169 (3), 85 (100).

(2*E*,4*R*)-6-Bromo-4-[(*tert*-butyl)dimethylsilyloxy]hex-2-enyl 2,2-Dimethylpropanoate ((2*E*,4*R*)-**12**). Pivaloyl chloride (63 μ l, 0.52 mmol) was added to a stirred soln. of (2*E*,4*R*)-**8** (65 mg, 0.209 mmol) in pyridine (3 ml). After stirring at r.t. for 24 h, the solvent was removed *in vacuo* and the crude material purified on silica gel (Et₂O/petroleum ether 1:9; R_f 0.44): (2*E*,4*R*)-**12** (61 mg; 74%). Colorless oil. $[\alpha]_D = +12.5$ ($c = 1.0$, Et₂O). IR (film): 2980–2860, 1730, 1480, 1360, 1280, 1250, 1150, 1080, 970, 830, 770. ¹H-NMR (300 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.81 (*s*, (*t*-Bu)Si); 1.11 (*s*, Me₃C); 1.82–1.91 (*m*, CH₂(5)); 3.33–3.51 (*m*, CH₂(6)); 4.25 (*m*, H–C(4)); 4.45 (*d*, $J = 5$, CH₂(1)); 5.64 (*m*, H–C(2), H–C(3)). ¹³C-NMR (75 MHz, CDCl₃): -4.95 ; -4.85 ; 18.1; 25.8; 27.2; 29.8; 38.7; 40.7; 41.2; 63.9; 69.6; 70.7; 124.8; 136.5; 178.1. FAB-MS (+ KCl): 433 (1, $[M + K]^+$), 431 (1), 395 (1), 393 (0.2), 293 (8), 291 (5), 263 (6), 261 (5), 249 (4), 247 (3), 57 (100).

{(3*R*,4*E*)-3-[(*tert*-Butyl)dimethylsilyloxy]-6-(2,2-dimethylpropanoyl)hex-4-enyl}triphenylphosphonium Bromide ((3*R*,4*E*)-**13**). Ph₃P (43.8 mg, 0.166 mmol) and (2*E*,4*R*)-**12** (55 mg, 0.139 mmol) in MeCN (3 ml) were heated to reflux for 48 h. The solvent was evaporated *in vacuo*. The semi-solid residue obtained was purified on silica gel (Et₂O, then AcOEt/MeOH 4:1) to give (3*R*,4*E*)-**13** as a hygroscopic oil (11 mg; 12%). IR (film): 3060–2860, 1730, 1590, 1480, 1440, 1370, 1280, 1250, 1150, 1120, 1000, 830, 780. ¹H-NMR (300 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.81 (*s*, (*t*-Bu)Si); 1.10 (*s*, Me₃C); 1.66–1.99 (*m*, CH₂(2)); 3.50–3.70 (*m*, CH₂(1)); 4.50 (*m*, CH₂(6), H–C(3)); 5.69 (*dd*, $J = 6$, 14, H–C(4)); 5.88 (*m*, H–C(5)); 7.35–7.80 (*m*, 15 arom. H). FAB-MS: 575 (100, $[M - Br]^+$), 289 (9), 279 (9), 262 (15), 183 (6), 159 (7).

{(R)-3-[(tert-Butyl)dimethylsilyloxy]-4-hydroxybutyl}triphenylphosphonium Bromide ((R)-14). O₃ was bubbled through a stirred soln. of (3R,4E)-13 (15 mg, 0.022 mmol) in AcOEt at –78° until a blue color appeared. After flushing off excess O₃ with N₂, NaBH₄ was added, the soln. warmed to r.t. and stirred for 2 h. The mixture was concentrated to ½ of its volume, washed once with H₂O, dried, and evaporated *in vacuo* to afford (R)-14 (5 mg; 44%). ¹H-NMR (300 MHz, CDCl₃): 0.0 (2s, Me₂Si); 0.79 (s, *t*-Bu); 2.05 (br. s, OH); 2.30 (t, *J* = 8, CH₂(2)); 3.60–3.80 (m, CH₂(1), CH₂(4)); 4.06 (m, H–C(3)); 7.29–7.95 (m, 15 arom. H). FAB-MS: 465 (67, [M – Br]⁺), 435 (4), 421 (8), 349 (16), 273 (50), 262 (15), 185 (9), 183 (10), 109 (14), 95 (29), 55 (100).

(3R,4RS)-1-Bromo-3-[(tert-butyl)dimethylsilyloxy]octan-4-ol ((3R,4RS)-15). A soln. of BuLi (0.05 mmol) in THF/Et₂O 5:3 (0.3 ml) was added dropwise to a stirred soln. of (R)-14 (5 mg, 9.7 μmol) in THF (0.5 ml) at 0°. The clear, red soln. was stirred at 0° for 20 min. After cooling to –78°, (R)-9 (6.4 mg, 0.022 mmol) was added. The mixture was stirred for 10 min, then warmed to –40° and, after 20 min, BuLi (0.05 mmol) in THF/Et₂O 5:3 (0.5 ml) was added to the yellow soln. The resulting red mixture was stirred for 30 min at –30° and for 1 h at r.t. The mixture was poured in H₂O, extracted with Et₂O (3 × 5 ml), dried, and evaporated. Purification on silica gel (Et₂O/petroleum ether 1:1, R_f 0.23) gave (3R,4RS)-15 (78%). Colorless oil. [α]_D²⁰ = +13.2 (*c* = 0.5, CH₂Cl₂). IR (film): 3350 (br.), 2960–2860, 1470, 1370, 1250, 1050, 830, 770. ¹H-NMR (400 MHz, CDCl₃): 0.0 (2s, Me₂Si); 0.80 (s, *t*-Bu); 1.40–1.90 (m, CH₂(2), CH₂(5), CH₂(6), CH₂(7), CH₃(8)); 3.45–3.55 (m, CH₂(1)); 3.85 (m, H–C(4)). ¹³C-NMR (101 MHz, CDCl₃): –4.7; –4.4; 15.3; 25.8; 27.9; 33.5; 39.3; 41.8; 60.0; 63.0; 65.8; 68.9. CI-MS (NH₃): 343 (1, [M + H]⁺), 341 (2), 313 (4), 311 (4), 269 (36), 267 (100), 231 (7), 135 (7), 132 (5), 99 (9), 62 (42), 81 (7).

(2E,4R)-6-Bromohex-2-ene-1,4-diol ((2E,4R)-16). Bu₄NF (82 mg, 0.259 mmol) was added in portions over 20 min to a stirred soln. of (2E,4R)-8 (55.6 mg, 0.179 mmol) in THF (3 ml). After stirring at r.t. for 13 h, H₂O (5 drops) was added, followed by extraction with Et₂O. The org. layer was washed with H₂O and brine, dried, and evaporated. The crude product was purified on silica gel (CH₂Cl₂/MeOH 19:1) to give (2E,4R)-16 (22 mg; 63%). Colorless oil. [α]_D²⁰ = –4 (*c* = 1.0, CH₂Cl₂). IR (film): 3400 (br.), 2960–2870, 1470, 1380, 1100, 1000, 970, 880. ¹H-NMR (300 MHz, CDCl₃): 1.84–1.99 (m, CH₂(5)); 3.36 (t, *J* = 8, CH₂(6)); 4.16 (br. s, OH); 4.35 (br. s, OH); 4.45–4.74 (m, CH₂(1), H–C(4)); 5.76–5.93 (m, H–C(2), H–C(3)). ¹³C-NMR (75 MHz, CDCl₃): 19.9; 24.3; 59.2; 62.6; 130.4; 133.2.

(R)-4-Bromo-2-hydroxybutanal ((R)-17). A soln. of (2E,4R)-16 (19.1 mg, 0.097 mmol) in AcOEt (2 ml) was treated with O₃ at –78°, until a pale blue color developed. After flushing off excess O₃ with N₂, Me₂S (21.3 μl, 0.291 mmol) was added and the soln. warmed to r.t. and stirred for another 2 h. The mixture was concentrated to ½ of its volume, washed once with H₂O (0.5 ml), dried, and evaporated *in vacuo* to give crude (R)-17 which was used without further purification. ¹H-NMR (300 MHz, CDCl₃): 2.00–2.39 (m, CH₂(3)); 3.31 (m, CH₂(4), OH); 4.40 (m, H–C(2)); 9.75 (s, CHO).

(2R,4E,6R)-8-Bromo-2-[(tert-butyl)dimethylsilyloxy]oct-4-ene-1,6-diol ((2R,4E,6R)-18). To a soln. of BuLi (1.6M in hexane; 60 μl, 0.058 mmol) in THF/Et₂O 5:3 (250 μl), (R)-14 (16 mg, 0.029 mmol) in THF (0.5 ml) was added dropwise at 0°. The yellow soln. was stirred for 20 min at 0°, followed by cooling to –78° and treatment with (R)-17 (6 mg, 0.036 mmol). After stirring for 10 min, the mixture was warmed to –40°. After 20 min, more BuLi (30 μl, 0.029 mmol) in THF/Et₂O 5:3 (0.2 ml) was added. The mixture was stirred for 30 min at –40° followed by stirring at r.t. After 12 h, it was poured in to H₂O (3 ml) and extracted with Et₂O (4 × 5 ml). The org. extracts were combined, dried, and evaporated. Prep. TLC (CH₂Cl₂/MeOH 29:1) afforded only a very small amount of (2R,4E,6R)-18 which was only characterized by MS. FAB-MS (+ KCl): 457 (5), 391 (3, [M + K]⁺), 239 (37), 165 (21), 139 (24), 115 (51), 81 (38), 79 (55), 41 (100).

Methyl (2E,4R)-4-[(tert-butyl)dimethylsilyloxy]-6-(4-tolylsulfonyl)hex-2-enoate ((2E,4R)-21). A mixture of (2E,4R)-7 (55 mg, 0.159 mmol) and 4-MeC₆H₄SO₂Na (28.4 mg, 0.159 mmol) in DMF (5 ml) was refluxed for 3 h. After cooling to r.t., the mixture was diluted with H₂O (5 ml) and extracted with Et₂O (3 × 10 ml). The combined org. layers were dried, evaporated, and purified on silica gel (Et₂O/petroleum ether 1:1; R_f 0.40) to give (2E,4R)-21 (24 mg; 37%). [α]_D²⁰ = +2.0 (*c* = 1.0, CH₂Cl₂). IR (film): 3060–2860, 1730, 1600, 1440, 1300, 1150, 1090, 830, 770. ¹H-NMR (300 MHz, CDCl₃): 0.0 (2s, Me₂Si); 0.85 (s, *t*-Bu); 1.79–2.00 (m, CH₂(5)); 2.45 (s, MeC₆H₄); 3.00–3.22 (m, CH₂(6)); 3.79 (s, MeO); 4.46–4.50 (m, H–C(4)); 5.95 (dd, *J* = 3, 16, H–C(2)); 6.77 (dd, *J* = 3, 16, H–C(3)); 7.35–7.80 (m, 4 arom. H). FAB-MS (+ KCl): 451 (35, [M + K]⁺), 413 (28, M⁺), 381 (10), 355 (10), 283 (25), 249 (11), 157 (10), 139 (12), 125 (16), 77 (12), 73 (100).

(2E,4R)-4-[(tert-butyl)dimethylsilyloxy]-6-(4-tolylsulfonyl)hex-3-en-1-ol ((2E,4R)-22). A 1.5M soln. of DIBAL (100 μl, 0.145 mmol) in hexane was added to a soln. of (2E,4R)-21 (20 mg, 0.048 mmol) in hexane (2 ml) at –50°. After stirring for 1 h, MeOH (5 drops) was added and the mixture warmed to r.t. Sat. NH₄Cl soln. (1 ml) was added, followed by Et₂O (5 ml). The org. layer was separated, washed with 1N HCl and brine, dried, and evaporated. Purification on silica gel (Et₂O/petroleum ether 1:1; R_f 0.20) gave (2E,4R)-22 (12 mg; 62%). Colorless oil. [α]_D²⁰ = +4.7 (*c* = 0.4, Et₂O). IR (film): 3400 (br.), 2960–2860, 1600, 1450, 1310, 1250, 1150, 840, 770. ¹H-NMR

(300 MHz, CDCl_3): 0.0 (2s, Me_2Si); 0.85 (s, *t*-Bu); 1.20 (br. s, OH); 1.85–1.90 (m, $\text{CH}_2(5)$); 2.46 (s, MeC_6H_4); 3.12 (t, $J = 7$, $\text{CH}_2(6)$); 4.15 (d, $J = 6$, $\text{CH}_2(1)$); 4.30 (m, H-C(4)); 5.60 (dd, $J = 2, 14$, H-C(2)); 5.77 (m, H-C(3)); 7.36–7.76 (m, 4 arom. H). FAB-MS (+ KCl): 423 (9, $[M + K]^+$), 385 (3, $[M + H]^+$), 327 (15), 255 (18), 253 (20), 157 (24), 73 (100).

(*R*)-2-[*(tert*-Butyl)dimethylsilyloxy]-4-(*tolylsulfonyl*)butan-1-ol ((2*R*)-23). O_3 was bubbled through a stirred soln. of (2*E*,4*R*)-22 (10 mg, 0.026 mmol) in AcOEt (3 ml) at -78° , until a blue color appeared. Excess O_3 was removed by flushing with N_2 , followed by addition of NaBH_4 (10 mg). The mixture was warmed to r.t. and stirred for 2 h. The mixture was concentrated to $\frac{1}{4}$ of its volume, then Et_2O (5 ml) was added. The org. layer was separated, washed with brine, dried, and evaporated: pure (*R*)-23 (7 mg; 78%). Colorless oil. $[\alpha]_D^{25} = +5$ ($c = 0.30$, CH_2Cl_2). IR (film): 3400 (br.), 2960–2860, 1600, 1450, 1300, 1250, 1100, 830, 770. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.0 (2s, Me_2Si); 0.82 (s, *t*-Bu); 1.71–1.98 (m, $\text{CH}_2(3)$); 2.40 (br. s, OH); 2.46 (s, MeC_6H_4); 3.24 (m, $\text{CH}_2(4)$); 3.70 (m, $\text{CH}_2(1)$); H-C(2)); 7.36–7.76 (m, arom. H). CI-MS (NH_3): 376 (30, $[M + \text{NH}_4]^+$), 359 (100, $[M + H]^+$), 329 (10), 287 (9), 132 (18), 106 (9).

(2*E*,4*S*)-4-[*(tert*-Butyl)dimethylsilyloxy]-6-[(4-methoxyphenyl)(diphenyl)methoxy]hex-2-enyl Methanesulfonate ((2*E*,4*S*)-27). MsCl (6.6 μl , 86 μmol) was added to a soln. of (2*E*,4*S*)-26 [1] (30 mg, 58 μmol) and Et_3N (11.9 μl , 86 μmol) in CH_2Cl_2 (2 ml) at -20° . The mixture was stirred for 45 min, then H_2O (2 ml) was added. The org. layer was separated and washed with sat. NH_4Cl soln., sat. KHCO_3 soln., and brine. Drying and evaporated *in vacuo* gave crude (2*E*,4*S*)-27, which was used without further purification. IR (film): 3080–2860, 1610, 1580, 1510, 1470, 1370, 1260, 1170, 1040, 970, 930, 840, 750, 710. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.0 (2s, Me_2Si); 0.86 (s, *t*-Bu); 1.85 (m, $\text{CH}_2(5)$); 2.91 (m, $\text{CH}_2(6)$); 2.96 (s, Me); 3.74 (s, MeO); 4.25 (m, $\text{CH}_2(1)$, H-C(4)); 5.82 (m, H-C(2), H-C(3)); 6.78 (d, $J = 9$, 2 arom. H); 7.10–7.52 (m, 12 arom. H).

(2*E*,4*S*)-4-[*(tert*-Butyl)dimethylsilyloxy]-1-iodo-6-[(4-methoxyphenyl)(diphenyl)methoxy]hex-2-ene ((2*E*,4*S*)-28). Dry LiI (19.9 mg, 0.23 mmol) was added to a soln. of (2*E*,4*S*)-27 in acetone (5 ml) at -30° . After stirring for 5 h, the mixture was poured into H_2O (3 ml) and extracted with Et_2O (3×5 ml). The combined extracts were washed with H_2O and brine, dried, and evaporated. Prep. TLC (silica gel; petroleum ether/ Et_2O 9:1 $\rightarrow$ 1:1; R_f 0.36) gave (2*E*,4*S*)-28 (2 mg; 8%) as a colorless oil, as well as unreacted (2*E*,4*S*)-27 (3.5 mg; 11%). On eluting with CH_2Cl_2 (silica gel; R_f 0.46), (3*S*,4*E*)-4-[*(tert*-butyl)dimethylsilyloxy]-6-iodohex-4-enyl methanesulfonate ((3*S*,4*E*)-29; 2.7 mg; 16%) was obtained.

(2*E*,4*S*)-28: IR (film): 3060–2860, 1600, 1500, 1450, 1250, 1180, 1070, 1040, 830, 770. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.0 (2s, Me_2Si); 0.79 (s, *t*-Bu); 1.76 (m, $\text{CH}_2(5)$); 3.09 (t, $J = 4$, $\text{CH}_2(6)$); 3.48 (d, $J = 5$, $\text{CH}_2(1)$); 3.72 (m, H-C(4)); 3.75 (s, MeO); 5.60 (m, H-C(2), H-C(3)); 6.82 (d, $J = 6$, 2 arom. H); 7.11–7.41 (m, 12 arom. H). FAB-MS (+ KCl): 289 (2), 273 (100), 259 (3), 243 (2), 239 (2), 229 (2), 215 (2), 195 (3), 165 (7), 105 (7), 73 (22).

(3*S*,4*E*)-29: IR (film): 3000–2800, 1660, 1580, 1480, 1430, 1330, 1230, 1150, 1070, 950, 900, 820, 750. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.0 (2s, Me_2Si); 0.82 (s, *t*-Bu); 1.83 (m, $\text{CH}_2(2)$); 2.93 (s, Me); 3.78 (d, $J = 8$, $\text{CH}_2(6)$); 4.21 (m, $\text{CH}_2(1)$, H-C(3)); 5.56–5.80 (m, H-C(4), H-C(5)). FAB-MS (+ KCl): 473 (10, $[M + K]^+$), 435 (4, $[M + H]^+$), 377 (9), 303 (10), 289 (7), 273 (79), 211 (11), 207 (17), 195 (7), 171 (11), 153 (48), 127 (6), 115 (10), 97 (19), 73 (100).

1,3-Dithian-2-methanol (30). A mixture of 2-hydroxyacetaldehyde (3.0 g, 50 mmol) and propane-1,3-dithiol (8.1 ml, 75 mmol) in CHCl_3 (30 ml) was treated carefully with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (6.45 ml, 50 mmol) at -20° . After stirring for 14 h, the mixture was washed with 10% aq. KOH (3×5 ml) and H_2O (2×5 ml), dried, and evaporated. FC (AcOEt /petroleum ether 1:1) gave 30 (7.5 g; 100%). Colorless solid. M.p. 35° . $[\alpha]_D^{25} = -4$ ($c = 2.0$, CH_2Cl_2). IR (film): 3450, 2960–2820, 1420, 1270, 1170, 1050, 910, 770. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 2.04 (m, $\text{CH}_2(5)$); 2.73, 2.94 (2m, $\text{CH}_2(4)$, $\text{CH}_2(6)$); 2.83 (t, $J = 7$, H-C(2)); 3.90 (m, CH_2OH). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 25.4; 26.6; 46.2; 63.1. EI-MS (70 eV): 150 (18, M^+), 119 (100), 91 (6), 85 (4), 75 (8).

2-[(2-Methoxyethoxy)methoxy]methyl-1,3-dithian (31). A 1.6M soln. of BuLi (4.2 ml, 6.66 mmol) was added to a soln. of 30 (1.0 g, 6.66 mmol) in dry 1,2-dimethoxyethane (DME, 10 ml) at 0° . After stirring for 20 min, (2-methoxyethoxy)methyl chloride (0.76 ml, 6.66 mmol) in DME (1 ml) was added. The mixture was stirred at r.t. for 2 h, evaporated, and purified by FC (AcOEt /petroleum ether 1:3; R_f 0.24) to give 31 (1.5 g; 92%). Yellow oil. $[\alpha]_D^{25} = -1.4$ ($c = 1.0$, Et_2O). IR (film): 2930–2800, 1450, 1410, 1290, 1160, 1100, 1030, 900. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 2.02 (m, $\text{CH}_2(5)$); 2.87 (m, $\text{CH}_2(4)$, $\text{CH}_2(6)$); 3.40 (s, MeO); 3.56 (m, CH_2O); 3.75 (m, CH_2O); 3.84 (d, $J = 6$, SCHCH_2); 4.24 (t, $J = 6$, H-C(2)); 4.78 (s, OCH_2O). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 25.8; 29.1; 46.2; 59.0; 67.0; 69.6; 71.7; 95.6. CI-MS (NH_3): 256 (23, $[M + \text{NH}_4]^+$), 239 (19, $[M + H]^+$), 163 (100), 133 (17), 94 (14).

(3*S*,4*E*)-3-[*(tert*-Butyl)dimethylsilyloxy]-6-[2-(hydroxymethyl)-1,3-dithian-2-yl]hex-4-enyl Methanesulfonate ((3*S*,4*E*)-32). A 1.6M soln. of BuLi in hexane (7.7 μl , 12 μmol) was added to a stirred soln. of (2*E*,4*S*)-30 (1.4 mg, 9 μmol) in THF (0.5 ml) at -78° . The mixture was warmed to r.t. over 2 h. After cooling to -78° , again (3*S*,4*E*)-29 (2.7 mg, 6 μmol) in THF (50 μl) was added over 10 min. The mixture was stirred for 1 h at -78° , then warmed to -40° and kept at this temp. for 4 h. After warming to r.t. and stirring for further 12 h, the reaction was

quenched with cold H₂O (3 ml) and extracted with petroleum ether (3 × 5 ml). The extracts were washed with H₂O (3 × 5 ml), dried, and evaporated. Prep. TLC (silica gel; CH₂Cl₂; R_f 0.12) gave (3*S*,4*E*)-**32** (1.1 mg; 39%). ¹H-NMR (300 MHz, CDCl₃): 0.0 (2*s*, Me₂Si); 0.82 (*s*, *t*-Bu); 1.80–1.97 (*m*, CH₂(6), CH₂(7), OH); 2.48 (*m*, CH₂(5′)); 2.70 (*m*, 4 H, CH₂(4′), CH₂(6′)); 2.92 (*s*, Me); 3.05 (*m*, CH₂OH); 4.22 (*m*, H–C(3), CH₂(1)); 5.50 (*m*, H–C(4), H–C(5)). FAB-MS (+ KCl): 416 (15, [M + K – Ms]⁺), 273 (15), 213 (12), 211 (28), 171 (7), 149 (8), 107 (6), 97 (41), 89 (8), 73 (100).

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