47. Studied Directed toward the Synthesis of Phomenoic Acid

Part 2[1])

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

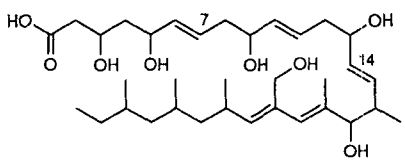
by **Hammed H. A. M. Hassan** and **Christoph Tamm***

Institut für Organische Chemie der Universität, St. Johanns-Ring 19, CH–4056 Basel

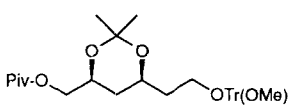
(15.XII.95)

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.

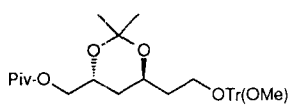
Introduction. – In the preceding communication [1], we have presented a general concept for the stereocontrolled total synthesis of phomenoic acid (**1**), a secondary metabolite of *Phoma lingam* TODE, and described the enantioselective synthesis of the key intermediates **2** and **3** and their enantiomers.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



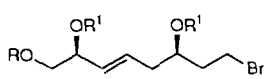
1 Phomenoic Acid



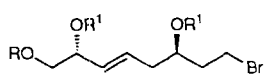
(2*S*,4*S*) - **2**



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



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



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

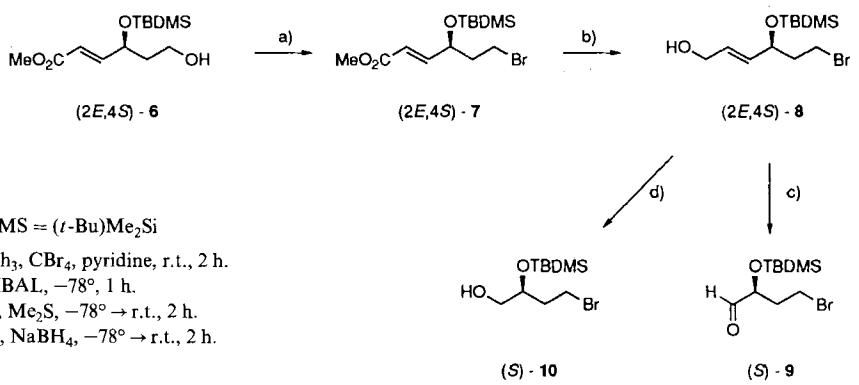
Tr(OMe) = (4-methoxyphenyl)(diphenyl)methyl

[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**.

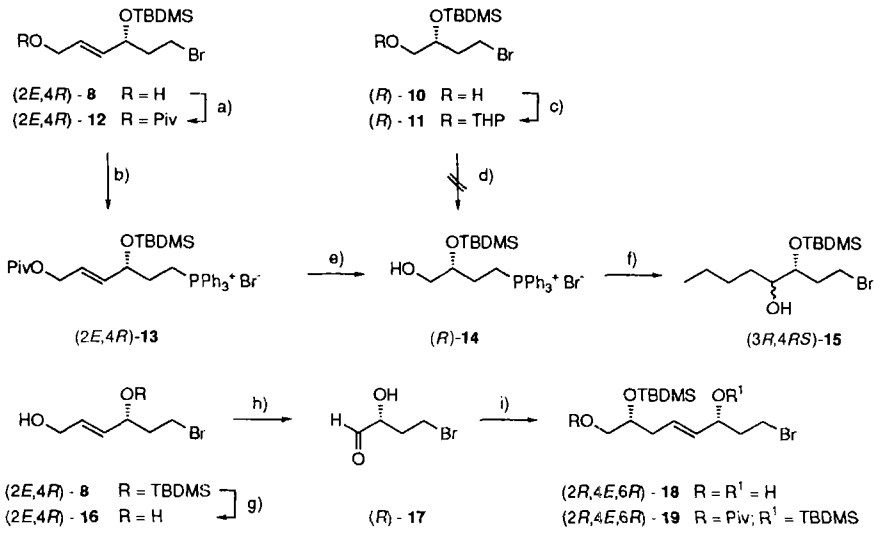
Results and Discussion. – For the synthesis of the aldehyde (*S*)-**9**, ester (2*E*,4*S*)-**6** was transformed to the bromo derivative (2*E*,4*S*)-**7** by treatment with PPh_3 and CBr_4 (*Scheme 1*). Ozonolysis of **7** to form **9** proceeded with limited success, probably due to the conjugation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

Scheme 1



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] inspite 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 (2*E*,4*R*)-**8**. At first, the OH group was protected by the pivaloyl group to afford fully protected bromo derivative (2*E*,4*R*)-**12** (74%). Because of the relatively high molecular weight and stability of **12**, phosphonium salt (2*E*,4*R*)-**13** was prepared by heating (2*E*,4*R*)-**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 (2*E*,4*R*)-**13** led to the alcohol (*R*)-**14**. The latter tended to hydrate very rapidly.

Scheme 2

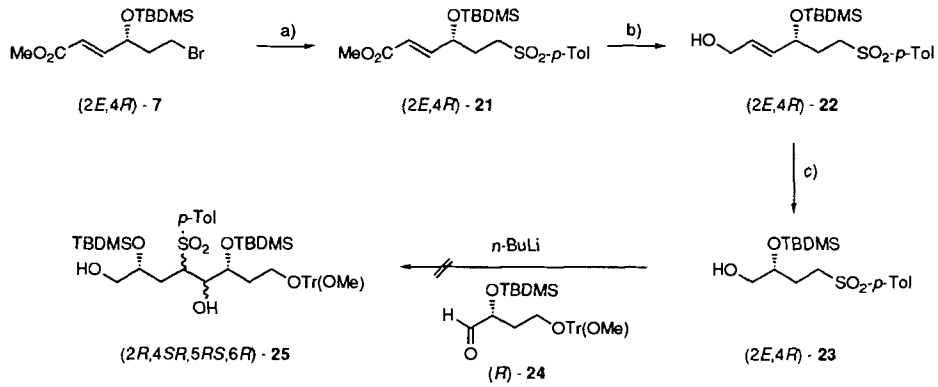


TBDMS = (*t*-Bu)Me_2Si, THP = tetrahydro-2*H*-pyran-2-yl

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° → r.t., 2 h. f) BuLi, (*R*)-**9**, −78° → −40°. g) TBAF, r.t., 13 h. h) O_3, Me_2S, −78° → r.t., 2 h. i) BuLi, (*R*)-**14**, −78° → −40° → 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 (2*R*,4*E*,6*R*)-**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 (2*E*,4*R*)-**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 inspite of the possibility of racemization [3]. Treatment of (2*E*,4*R*)-**8** with Bu_4NF in THF afforded bromo diol (2*E*,4*R*)-**16** (63%). Ozonolyis 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 (2*R*,4*E*,6*R*)-**18**, which corresponds to the C(7)-to-C(14) segment of phomenoic 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 (2*E*,4*R*)-**7** was converted to the corresponding sulfone (2*E*,4*R*)-**21** by treatment with sodium 4-toluenesulfinate in DMF according to *Ferraboschi et al.* [7] (37%; *Scheme 3*). Reduction of (2*E*,4*R*)-**21** with DIBAL in hexane gave the alcohol (2*E*,4*R*)-**22** (63%). Ozonolysis of the

Scheme 3



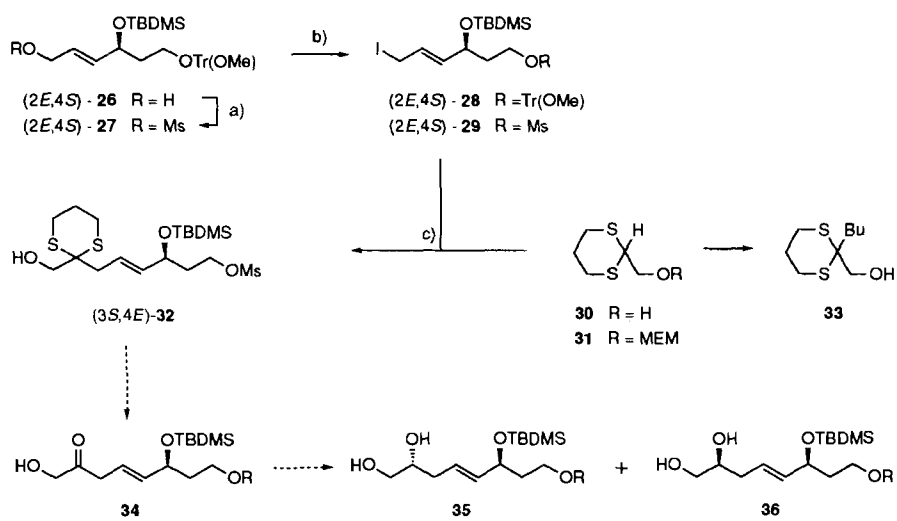
TBDMS = (*t*-Bu)Me_2Si

a) *p*-Tol-SO_2Na, reflux, 3 h. b) DIBAL, −50°, 1 h. c) O_3, $NaBH_4$, −78° → r.t., 2 h.

latter and subsequent reduction of the ozonide with $NaBH_4$ 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 (2*R*,4*RS*,5*RS*,6*R*)-**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)Me_2Si, Tr(OMe) = (4-methoxyphenyl)(diphenyl)methyl, MEM = $MeOCH_2CH_2OCH_2$

a) MsCl, Et_3N, −20°, 45 min. b) LiI/acetone, −30°, 5 h. c) BuLi, (2*E*,4*S*)-**29**, −78° → −40°, 4 h.

1,3-dithiane **31** was prepared by treating 2-hydroxyacetaldehyde with propane-1,3-dithiol and $BF_3 \cdot Et_2O$ 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 (2*E*,4*R*)-6-Bromo-4-[(*tert*-butyl)dimethylsilyloxy]hex-2-enoate* ((2*E*,4*R*)-**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 1N 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. $[\alpha]_D = +10.95$ ($c = 2.0$, Et_2O). IR (film): 3040–2860, 1730, 1660, 1470, 1430, 1360, 1250, 1160, 1100, 970, 835, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.92 (*s*, *t*-Bu); 1.99 (*m*, CH_2(5)); 3.44 (*m*, 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}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, $[M + NH_4]^+$), 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**. $[\alpha]_D = -9.1$ ($c = 2.0$, Et_2O). IR (film): 2960–2860, 1730, 1660, 1470, 1430, 1360, 1265, 1250, 1165, 1100, 970, 840, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.88 (*s*, *t*-Bu); 2.01 (*m*, CH_2(5)); 3.41 (*m*, 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}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, $[M + NH_4]^+$), 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).

*(2*E*,4*R*)-6-Bromo-4-[(*tert*-butyl)dimethylsilyloxy]hex-2-enol* ((2*E*,4*R*)-**8**). A 1.5M 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 1N 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. $[\alpha]_D = +10.6$ ($c = 1.0$, Et_2O). IR (film): 3350 (br.), 2980–2850, 1680, 1460, 1360, 1250, 1080, 1000, 970, 840, 770. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.85 (*s*, *t*-Bu); 1.95 (*m*, CH_2(5)); 3.42–3.61 (*m*, CH_2(6), OH); 4.13 (*t*, $J = 6$, 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}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, $[M + NH_4]^+$), 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**. $[\alpha]_D = -9.6$ ($c = 2.0$, Et_2O). IR (film): 3350 (br.), 2960–2860, 1680, 1460, 1360, 1250, 1080, 1000, 870, 830, 770. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.80 (*s*, *t*-Bu); 1.80–2.10 (*m*, CH_2(5), OH); 3.40 (*t*, $J = 6$, CH_2(6)); 3.90 (*d*, $J = 4$, CH_2(1)); 4.20 (*m*, H–C(4)); 5.60 (*m*, H–C(2), H–C(3)). CI-MS (NH_3): 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**). O_3 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 O_3 with N_2, Me_2S (10.3 µl, 0.138 mmol) was added. The mixture was stirred at r.t. for 2 h and then concentrated to ¼ of its volume, diluted with Et_2O (10 ml), and washed once with brine. Drying and evaporation afforded (*R*)-**9** (14 mg; 52%). Colorless oil. $[\alpha]_D = +1$ ($c = 1.0$, CH_2Cl_2). IR (film): 2960–2850, 1740, 1470, 1250, 1110, 830, 770. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.85 (*s*, *t*-Bu); 1.80–2.10 (*m*, CH_2(3)); 3.20 (*t*, $J = 5$, CH_2(4), OH); 4.12 (*m*, CH_2(2)); 9.62 (*s*, CHO). CI-MS (NH_3): 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. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.80 (*s*, *t*-Bu); 1.90–2.10 (*m*, CH_2(3)); 3.20 (*t*, $J = 6$, CH_2(4), OH); 4.15 (*m*, CH_2(2)); 9.60 (br. *s*, CHO). CI-MS (NH_3): 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**). O_3 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 O_3 with N_2, $NaBH_4$ (10 mg 0.264 mmol) was added, and the mixture was warmed to r.t. and stirred for 2 h. After concentrating to ½ of the volume, Et_2O (10 ml) was added and the mixture washed once with brine. Drying and evaporation afforded (*R*)-**10** (29 mg; 80%). Colorless oil. $[\alpha]_D = +2.0$ ($c = 1.0$, Et_2O). IR (film): 3400 (br.), 2960–2850, 1460, 1360, 1250, 1110, 1050, 830, 770. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.80 (*s*, *t*-Bu); 1.95 (*m*, CH_2(3), OH); 3.30–3.70 (*m*, CH_2(4), CH_2(1)); 4.20 (*m*, CH_2(2)). CI-MS (NH_3): 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. $[\alpha]_D = -2.6$ ($c = 1.0$, Et_2O). ^{1}H-NMR (60 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.85 (*s*, *t*-Bu); 1.30 (br. *s*, OH); 1.80–2.10 (*m*, CH_2(3)); 3.30–3.70 (*m*, CH_2(4), CH_2(1)); 4.20 (*m*, H–C(2)). CI-MS (NH_3): 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·H_2O (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 $NaHCO_3$ and stirring continued for 2 h. A few drops of H_2O were added and the mixture extracted with Et_2O (3 × 10 ml). The org. extracts were dried, concentrated, and purified on silica gel (Et_2O/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. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.83 (*s*, *t*-Bu); 1.83–2.18 (*m*, CH_2(3), CH_2(3′), CH_2(4′), CH_2(5′)); 3.27–3.57 (*m*, CH_2(4)); 3.68–3.91 (*m*, H–C(2), CH_2(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 µl, 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 (Et_2O/petroleum ether 1:9; R_f 0.44): (2*E*,4*R*)-**12** (61 mg; 74%). Colorless oil. $[\alpha]_D = +12.5$ ($c = 1.0$, Et_2O). IR (film): 2980–2860, 1730, 1480, 1360, 1280, 1250, 1150, 1080, 970, 830, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.81 (*s*, (*t*-Bu)Si); 1.11 (*s*, Me_3C); 1.82–1.91 (*m*, CH_2(5)); 3.33–3.51 (*m*, CH_2(6)); 4.25 (*m*, H–C(4)); 4.45 (*d*, $J = 5$, CH_2(1)); 5.64 (*m*, H–C(2), H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): −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**). Ph_3P (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 (Et_2O, 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.81 (*s*, (*t*-Bu)Si); 1.10 (*s*, Me_3C); 1.66–1.99 (*m*, CH_2(2)); 3.50–3.70 (*m*, CH_2(1)); 4.50 (*m*, CH_2(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**). O_3 was bubbled through a stirred soln. of (3*R*,4*E*)-**13** (15 mg, 0.022 mmol) in AcOEt at −78° until a blue color appeared. After flushing off excess O_3 with N_2, $NaBH_4$ 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 H_2O, dried, and evaporated *in vacuo* to afford (*R*)-**14** (5 mg; 44%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.79 (*s*, *t*-Bu); 2.05 (br. *s*, OH); 2.30 (*t*, *J* = 8, CH_2(2)); 3.60–3.80 (*m*, CH_2(1), CH_2(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 ((3*R*,4*RS*)-**15**). A soln. of BuLi (0.05 mmol) in THF/Et_2O 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/Et_2O 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 H_2O, extracted with Et_2O (3 × 5 ml), dried, and evaporated. Purification on silica gel (Et_2O/petroleum ether 1:1, R_f 0.23) gave (3*R*,4*RS*)-**15** (78%). Colorless oil. $[\alpha]_D = +13.2$ (*c* = 0.5, CH_2Cl_2). IR (film): 3350 (br.), 2960–2860, 1470, 1370, 1250, 1050, 830, 770. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.80 (*s*, *t*-Bu); 1.40–1.90 (*m*, CH_2(2), CH_2(5), CH_2(6), CH_2(7), CH_3(8)); 3.45–3.55 (*m*, CH_2(1)); 3.85 (*m*, H–C(4)). ^{13}C-NMR (101 MHz, $CDCl_3$): −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 (NH_3): 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 ((2*E*,4*R*)-**16**). Bu_4NF (82 mg, 0.259 mmol) was added in portions over 20 min to a stirred soln. of (2*E*,4*R*)-**8** (55.6 mg, 0.179 mmol) in THF (3 ml). After stirring at r.t. for 13 h, H_2O (5 drops) was added, followed by extraction with Et_2O. The org. layer was washed with H_2O and brine, dried, and evaporated. The crude product was purified on silica gel (CH_2Cl_2/MeOH 19:1) to give (2*E*,4*R*)-**16** (22 mg; 63%). Colorless oil. $[\alpha]_D = -4$ (*c* = 1.0, CH_2Cl_2). IR (film): 3400 (br.), 2960–2870, 1470, 1380, 1100, 1000, 970, 880. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.84–1.99 (*m*, CH_2(5)); 3.36 (*t*, *J* = 8, CH_2(6)); 4.16 (br. *s*, OH); 4.35 (br. *s*, OH); 4.45–4.74 (*m*, CH_2(1), H–C(4)); 5.76–5.93 (*m*, H–C(2), H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.9; 24.3; 59.2; 62.6; 130.4; 133.2.

(R)-4-Bromo-2-hydroxybutanal ((*R*)-**17**). A soln. of (2*E*,4*R*)-**16** (19.1 mg, 0.097 mmol) in AcOEt (2 ml) was treated with O_3 at −78°, until a pale blue color developed. After flushing off excess O_3 with N_2, Me_2S (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 H_2O (0.5 ml), dried, and evaporated *in vacuo* to give crude (*R*)-**17** which was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.00–2.39 (*m*, CH_2(3)); 3.31 (*m*, CH_2(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 ((2*R*,4*E*,6*R*)-**18**). To a soln. of BuLi (1.6M in hexane; 60 μl, 0.058 mmol) in THF/Et_2O 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 /Et_2O 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 H_2O (3 ml) and extracted with Et_2O (4 × 5 ml). The org. extracts were combined, dried, and evaporated. Prep. TLC (CH_2Cl_2/MeOH 29:1) afforded only a very small amount of (2*R*,4*E*,6*R*)-**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 ((2*E*,4*R*)-**21**). A mixture of (2*E*,4*R*)-**7** (55 mg, 0.159 mmol) and 4-$MeC_6H_4SO_2Na$ (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 H_2O (5 ml) and extracted with Et_2O (3 × 10 ml). The combined org. layers were dried, evaporated, and purified on silica gel (Et_2O/petroleum ether 1:1; R_f 0.40) to give (2*E*,4*R*)-**21** (24 mg; 37%). $[\alpha]_D = +2.0$ (*c* = 1.0, CH_2Cl_2). IR (film): 3060–2860, 1730, 1600, 1440, 1300, 1150, 1090, 830, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.85 (*s*, *t*-Bu); 1.79–2.00 (*m*, CH_2(5)); 2.45 (*s*, MeC_6H_4); 3.00–3.22 (*m*, CH_2(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 ((2*E*,4*R*)-**22**). A 1.5M soln. of DIBAL (100 μl, 0.145 mmol) in hexane was added to a soln. of (2*E*,4*R*)-**22** (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. NH_4Cl soln. (1 ml) was added, followed by Et_2O (5 ml). The org. layer was separated, washed with 1N HCl and brine, dried, and evaporated. Purification on silica gel (Et_2O/petroleum ether 1:1; R_f 0.20) gave (2*E*,4*R*)-**22** (12 mg; 62%). Colorless oil. $[\alpha]_D = +4.7$ (*c* = 0.4, Et_2O). IR (film): 3400 (br.), 2960–2860, 1600, 1450, 1310, 1250, 1150, 840, 770. ^{1}H-NMR

(300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.85 (*s*, *t*-Bu); 1.20 (br. *s*, OH); 1.85–1.90 (*m*, $CH_2(5)$); 2.46 (*s*, MeC_6H_4); 3.12 (*t*, $J = 7$, $CH_2(6)$); 4.15 (*d*, $J = 6$, $CH_2(1)$); 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 ¼ 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. $[\alpha]_D = +5$ ($c = 0.30$, CH_2Cl_2). IR (film): 3400 (br.), 2960–2860, 1600, 1450, 1300, 1250, 1100, 830, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.82 (*s*, *t*-Bu); 1.71–1.98 (*m*, $CH_2(3)$); 2.40 (br. *s*, OH); 2.46 (*s*, MeC_6H_4); 3.24 (*m*, $CH_2(4)$); 3.70 (*m*, $CH_2(1)$); H–C(2)); 7.36–7.76 (*m*, arom. H). CI-MS (NH_3): 376 (30, $[M + NH_4]^+$), 359 (100, $[M + H]^+$), 329 (10), 287 (9), 132 (18), 106 (9).

(2E,4S)-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}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.86 (*s*, *t*-Bu); 1.85 (*m*, $CH_2(5)$); 2.91 (*m*, $CH_2(6)$); 2.96 (*s*, Me); 3.74 (*s*, MeO); 4.25 (*m*, $CH_2(1)$, 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).

(2E,4S)-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 → 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), *(3S,4E)-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}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.79 (*s*, *t*-Bu); 1.76 (*m*, $CH_2(5)$); 3.09 (*t*, $J = 4$, $CH_2(6)$); 3.48 (*d*, $J = 5$, $CH_2(1)$); 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}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.82 (*s*, *t*-Bu); 1.83 (*m*, $CH_2(2)$); 2.93 (*s*, Me); 3.78 (*d*, $J = 8$, $CH_2(6)$); 4.21 (*m*, $CH_2(1)$, 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 $BF_3 \cdot Et_2O$ (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°. $[\alpha]_D = -4$ ($c = 2.0$, CH_2Cl_2). IR (film): 3450, 2960–2820, 1420, 1270, 1170, 1050, 910, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.04 (*m*, $CH_2(5)$); 2.73, 2.94 (2*m*, $CH_2(4)$, $CH_2(6)$); 2.83 (*t*, $J = 7$, H–C(2)); 3.90 (*m*, CH_2OH). ^{13}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. $[\alpha]_D = -1.4$ ($c = 1.0$, Et_2O). IR (film): 2930–2800, 1450, 1410, 1290, 1160, 1100, 1030, 900. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.02 (*m*, $CH_2(5)$); 2.87 (*m*, $CH_2(4)$, $CH_2(6)$); 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}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, $[M + NH_4]^+$), 239 (19, $[M + H]^+$), 163 (100), 133 (17), 94 (14).

(3S,4E)-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 H_2O (3 ml) and extracted with petroleum ether (3 × 5 ml). The extracts were washed with H_2O (3 × 5 ml), dried, and evaporated. Prep. TLC (silica gel; CH_2Cl_2; R_f 0.12) gave (3*S*,4*E*)-**32** (1.1 mg; 39%). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.0 (2*s*, Me_2Si); 0.82 (*s*, *t*-Bu); 1.80–1.97 (*m*, CH_2(6), CH_2(7), OH); 2.48 (*m*, CH_2(5′)); 2.70 (*m*, 4 H, CH_2(4′), CH_2(6′)); 2.92 (*s*, Me); 3.05 (*m*, CH_2OH); 4.22 (*m*, H–C(3), CH_2(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).

REFERENCES

[1] H. H. A. M. Hassan, Ch. Tamm, *Helv. Chim. Acta* **1994,** *77,* 838.
[2] M. Schlosser, H. B. Tuong, B. Schaub, *Tetrahedron Lett.* **1985,** *26,* 311.
[3] K. Y. Ko, W. D. Frazee, E. L. Eliel, *Tetrahedron* **1984,** *40,* 1333.
[4] Y. Guindon, D. Delorme, C. V. Lau, R. Zamboni, *J. Org. Chem.* **1988,** *53,* 267; P. Yadagiri, S. Lumin, J. R. Falck, *Tetrahedron Lett.* **1989,** *30,* 429.
[5] A. Maercker, 'Organic Reactions', J. Wiley & Sons, Inc., New York–London–Sydney, 1965, Vol. 14, p. 271.
[6] M. Julia, J. M. Paris, *Tetrahedron Lett.* **1973,** 4833.
[7] P. Ferraboschi, D. Brembilla, P. Grisenti, E. Santiello, *Synlett* **1991,** 310.
[8] T. Mandai, K. Hara, T. Nakajiama, M. Kawada, J. Otera, *Tetrahedron Lett.* **1983,** *24,* 4993.
[9] E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed.* **1965,** *4,* 1075; E. J. Corey, J. L. Gras, P. Ulrich, *Tetrahedron Lett.* **1976,** 809.
[10] J. E. McMurry, M. D. Erion, *J. Am. Chem. Soc.* **1985,** *107,* 2712.
[11] V. Martischonok, G. G. Melikyan, A. Minerf, O. Vosliowsky, H. J. Bestmann, *Synthesis* **1991,** 560.
[12] V. K. Singh, *Synthesis* **1992,** 605.