Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 04 Dec 2007.

To cite this article: Hammed H. A. M. Hassan & Mohamed M. Abdel Rahman (2000) The Pyranoid C_6-Portion of the Natural $C_{12-\alpha,\beta}$-Unsaturated-δ-Lactones From D-Glucose, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:2, 201-216, DOI: 10.1080/00397910008087311

To link to this article: http://dx.doi.org/10.1080/00397910008087311

SYNTHETIC COMMUNICATIONS, 30(2), 201–216 (2000)

THE PYRANOID C_6-PORTION OF THE NATURAL C_{12}–α,β-UNSATURATED-δ-LACTONES From D-GLUCOSE

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Abstract: The transformation of D-glucose to 5,6-disubstituted 5,6-dihydro-2H-pyran-2-one **3**, an analogue of the (5*R*)-C_6-pyranoid part of the natural α,β-unsaturated-δ-lactones is described.

Introduction. Saturated and unsaturated-γ and δ-lactones are found as structural subunits in a wide variety of natural products[1] with diverse biological activities.[2] C_{12}-α,β–unsaturated-δ-lactones such as (+)-*anamarine* **1** and (+)-*olguine* **2** (scheme 1), isolated from an unclassified hyptis species (*Labiatae)*[3], are a classes of these biologically active compounds.

The natural pyranoid C_6-unit of these lactones could be obtained from a suitable six-carbon sugar as the shortest potential route. However, the C(5) of the pyranoid C_6-portion has the (*R*)-configuration, which requires the use of inaccessible L-sugars as starting materials. Consequently, as previously reported the stereoisomer (5*S*)-C_6-

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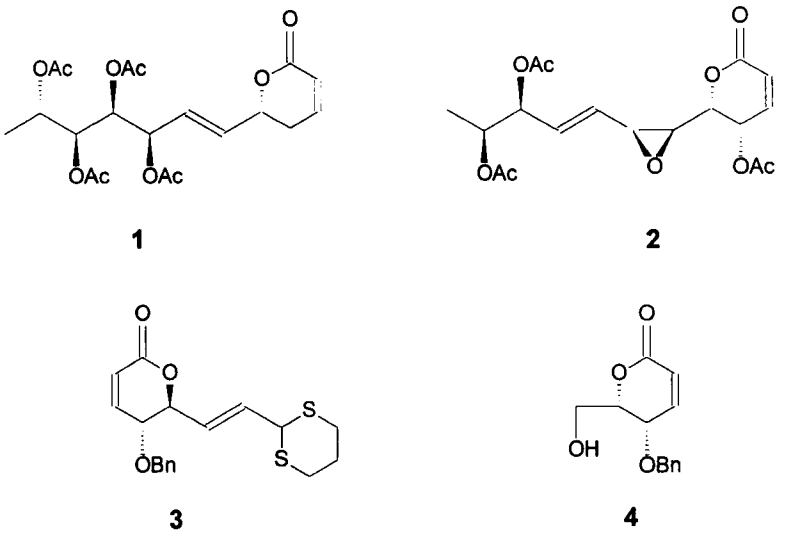


Scheme 1

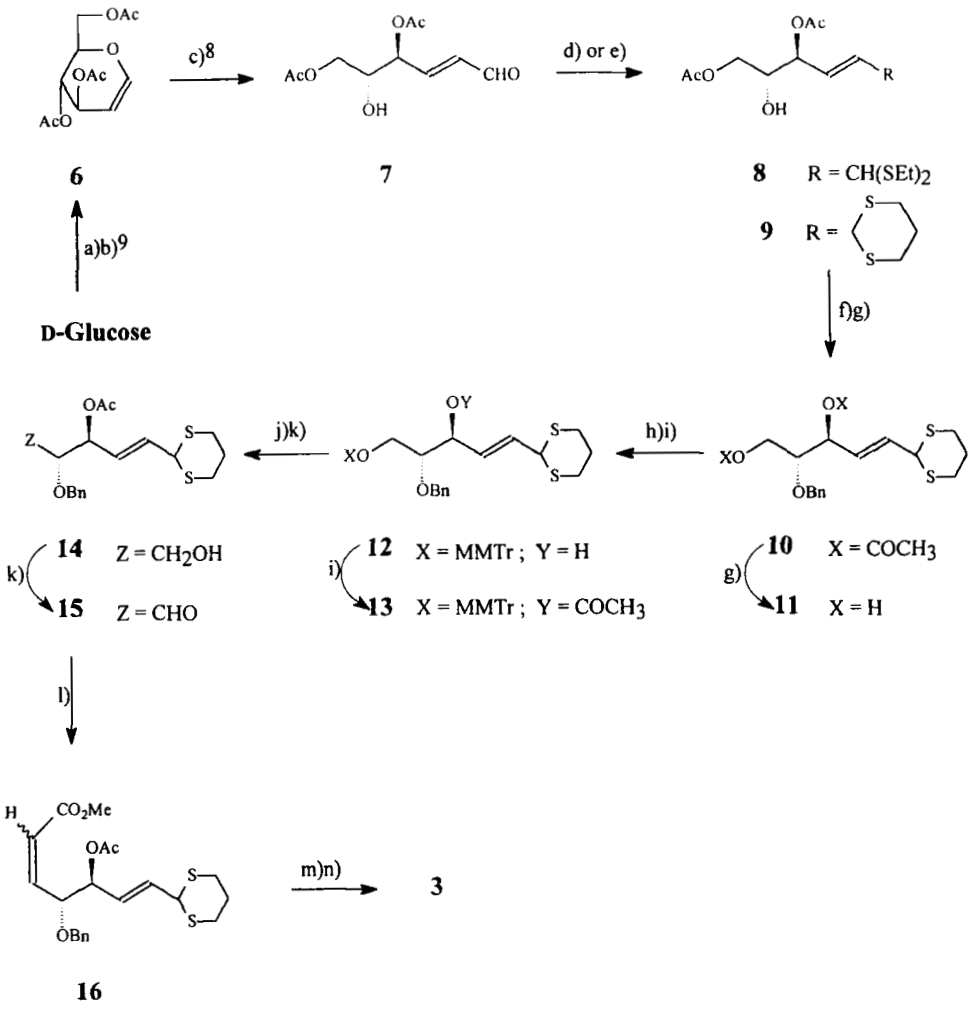
pyranoid part was prepared from either 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol **6**[4] or its derivative 3,4-di-*O*-acetyl-6-*O*-tosyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol[5] using standard procedures.[6] In an alternative approach, the natural (5*R*) C_6-pyranoid unit **4** was synthesised from (*R,R*)-tartaric acid.[7] In the present paper, we report the synthesis of 5,6-disubstituted-5,6-dihydro-2H-pyran-2-one **3**, a dihydropyranone analogue containing the (6*R*)-C_6 pyranoid portion (pyranone numbering) from D-glucose. The strategy for the present method follows the finding that[8] mercuric ion assisted acid hydrolysis of the dihydropyrane **6** gives *trans* enals of D-erythro or 4*S*,5*R*-configuration **7**. The next step is to proceed with protection of the C-1 aldehyde function, followed by a selective oxidation of the OH-6 function to the corresponding α-oxygenated aldehyde **15**. By converting aldehyde **15** to the elongated (*Z*)-δ-oxygenated-α,β–unsaturated ester **16**, the

cyclization of the latter was expected to offer an efficient method[7] for the synthesis of the (6*R*)-disubstituted dihydropyranone **3**.

Results. D-Glucose was used as a cheap starting material for the synthesis of 3,4,6-tri-*O*-acetyl-D-glucal **6** (70% yield) by a known procedure[9] (scheme 2). The known 4,6-di-*O*-acetyl-2,3-dideoxy-aldehydo-D-erythro-*trans*-hex-2-enose **7** was prepared by acidic ring opening of glucal-*O*-acetates **6** with 0.005M sulphuric acid in dioxane in the presence of mercuric sulphate in 90% yield.[8] Treatment of α,β-unsaturated aldehyde **7** with ethylthiol and a catalytic amount of $BF_3.OEt_2$ gave the desired dithioacetal **8** (72%) mixed with some inseparable side-reaction product.

The ^{1}H-NMR spectrum of **7** showed a triplet signal of six-proton intensity at δ1.25(J=8Hz), a quartet signal of four-proton intensity at δ2.8(J=8Hz) corresponding to two SEt groups and two doublets for the two olefin protons H-2 and H-3 at δ 5.8 and 6.3 ppm respectively, with a coupling constant ($^3J_{2,3}$=15Hz), proving the *trans* structure of the double bond.

More reproducible results regarding the reaction times, yields and purity were performed by using 1,3-propanedithiol instead of ethylthiol to protect the aldehyde function. Thus, treatment of **7** with 1,3-propandithiol/$BF_3.OEt_2$ for 2h afforded smoothly the trimethylene dithioacetal **9** in 90% yield as a single product. The OH-5 of the 2-substituted-1,3-dithiane **9** was protected as benzyl ether by subsequently treating with sodium hydride, benzyl bromide and a catalytic amount of Bu_4NI in DMF to afford **10** in good yield. Protection of OH-5 by benzyl group prior to the reaction with 1,3-propanedithiol was not successful.



Scheme 2

Key: a) Ac_2O, perchloricacid (70%); b) Br_2, red P, Zn dust; c) 0.005M H_2SO_4, $HgSO_4$, Dioxanc;d) EtSH, $BF_3.OEt_2$, $CHCl_3$; e) 1,3-propanedithiol, $BF_3.OEt_2$, $CHCl_3$, f) $PhCH_2Br$, NaH, Bu_4NI, DMF; g) NaOMe, MeOH; h) 4-methoxytrityl-chloride, Py; i) Ac_2O, Py; j) 0.01N HCl; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; l) Ph_3P=CH-CO_2Me, MeOH, r.t.; m) 0.5N LiOH, THF/MeOH (2:1); n) CF_3CO_2H/H_2O (90%).

The ^{1}H-NMR spectrum of **10** displayed a multiplet signal of five-proton intensity at δ7.31 and two doublets each of 1H intensity at δ4.80(J =11.7) and δ4.59(J =11.7) which correspond to the benzyl group, a multiplet signal at δ5.19 assigned to H-5, two singlet signals each of three-proton intensity at δ2.09 and δ2.06 corresponding to two acetyl protons, while the trimethylene protons of the 1,3-dithiane group at C-1 appeared as three multiplet signals at δ2.65, δ2.50 and δ1.95 ppm respectively. Furthermore, compound **10** exhibited in the ^{13}C-NMR spectrum signals at δ138.25, 128.77, 128.45, 126.95, 125.97 and 125.90 ppm corresponding to the six aromatic carbons, signals at δ133.61 and 131.84 are due to the olefinic carbons at C-3 and C-2 respectively, whereas other signals at δ171.02 (CO), 170.29(CO), 73.69, 71.01, 64.75, 62.25, 50.46, 36.20, 29.46, 28.57, 21.02 and 20.98 are consistent with the given formula **10**.

To convert **10** to our target α-oxygenated aldehyde **15** it was necessary to protect the secondary OH-4 selectively, followed by oxidation of the primary OH-6. Pursuing this, treatment of **10** with 0.05M $NaOCH_3$ solution afforded respectively (17%, R_f 0.3) of the unchanged **10**, (17%, R_f 0.23) of 6-hydroxyl-5-benzyloxy-4-acetyloxy-2-hexenal-trimethylene dithioacetal **14** and (29%, R_f 0.1) of the diol **11** as well as other undefined products. It is worth mentioning here that increasing the concentration of $NaOCH_3$ in solution to 0.25M diminished the yield of the diol **11** without isolation of any other defined products. However, a longer reaction time (48h) using dilute (0.05M) $NaOCH_3$ improved the yield of **11** up to 50%. De-*O*-acetylation of **10** using NH_4OH/MeOH (3:1, 2:1 and 1:1, respectively) failed.

Compound **11** exhibited ^{1}H-NMR signals at δ6.35(dd, J=14.1, 3.9Hz, H-3), δ5.95 (dd, J=14.1, 4.1Hz, H-2), 5.0(dt, J=6.0, 3.3 Hz, H-5), 4.52(dd, J=5.9, 3.3Hz, H-4)

and 3.80(m, 2H-6, H-1). The prominent feature was the disappearance of the signals at δ2.16 and δ 2.05ppm characteristic of the two acetyl protons.

The primary OH-6 group of **11** was selectively masked by the 4-methoxytrityl protective group (MMTr) to furnish the secondary (*E*)-allylic alcohol **12** in 63% yield, followed by protection of the secondary OH-4 of **12** by acetylation to furnish **13** in a moderate yield after purification on a column (46%). Compound **13** exhibits a unique pattern in the arrangement of the protecting groups because each can be removed selectively allowing further manipulations. Treatment of **11** with 0.01N HCl afforded **14** in 76% yield.

The ^{1}H-NMR spectrum of **14** exhibited a multiplet signal of 5-proton intensity at δ7.30 which corresponds to the aromatic protons, two doublet doublets at δ 7.0 (J=13.6, 5.8Hz) and δ 6.1(J=13.6, 5.2Hz) due to two olefinic protons H-3 and H-2 respectively, a doublet doublet of one-proton intensity at δ3.83(J=5.8, 3.2Hz) refers to H-4, and a singlet of three-proton intensity at δ2.11 due to acetyl protons. Despite the fact that the EI-MS of **14** did not show a molecular peak ion ($C_{18}H_{24}O_4S_2$, 368), it exhibited a unique fragmentation pattern for example (*m/z*= 277, 4.9%, *M*-Bn+2), a dehydration peak product (*m/z*=197, 41.19%), whereas the base peak appeared at *m/z*=91.

Oxidation of the primary alcohol **14** using Swern oxidation method[10] gave the aldehyde **15** in good yield (>60%). It is important to mention here that both pyridinium chlorochromate (PCC) and chromium trioxide-dipyridine complex[11] *in situ* oxidation methods afforded aldehyde **15** in low yield (<25%). Aldehyde **15** proved to be relatively unstable and easily hydratable, similar to other α-alkoxy

aldehydes analogues[12], and therefore it was used in the next step without purification. The crude Swern oxidation product was dissolved in dry methanol[7,13] and stirred with 1.5 molar equivalent of methoxycarbonymethylene triphenyl phosphorane (Ph_3P=CH-CO_2Me, *Aldrich*), at 0°C (30 min), then overnight at r.t., to give α,β-unsaturated ester **16** in 61% overall yield as a mixture of two possible stereoisomeric olefins (*Z*/*E* ratio 85:15 as judged from the ^{1}H-NMR analysis). The formation of **16** with high *Z*-stereoselectivity was not surprising when one takes into account the reported studies that have been devoted to the stereoselective *Wittig* olefination reactions of aldehydes with stabilized phosphoranes in methanol.[14]

The ^{1}H-NMR spectrum of **16** and its ^{13}C-NMR analysis confirmed the formation of this product. The unsaturated ester **16** exhibited in the ^{1}H-NMR spectrum two doublet doublets each of one-proton intensity at δ6.9(J =15.3, 5.7Hz) and δ5.90(J =15.3, 1.1Hz) corresponding to H-6 and H-7 for the *E*-isomer of **16**, whereas the *Z*-isomer of **16** showed two doublet doublets at δ6.24(J =11.7, 5.3Hz, H-6) and δ5.70(J =11.7, 0.9Hz, H-7). Moreover, the H-2 and H-3 protons appeared at δ6.07(dd, J =14.8, 5Hz) and δ 6.55(dd, J =14.8, 6.2Hz) respectively. The ^{13}C-NMR spectrum of **16** showed the olefinic carbon signals at 143.24, 142.91, 135.17, 131.97, and 131.67.

The unsaturated ester **16** was subjected to basic hydrolysis using 0.5N LiOH in THF/MeOH (2:1) to give the corresponding hydroxyacid, which is directly dissolved in 9:1 CF_3CO_2H/water (0°C for 3h, then r.t. overnight) to furnish **3** in 29% overall yield from **16**. Spectral data confirmed the formation of the lactone **3**. The ^{13}C-NMR showed a singlet at 162.51 corresponding to the carbonyl group, whereas the olefinic carbons appeared at 144.36, 142.64 and 132.22 ppm. Other signals at 128.62-125.35, 79.67, 71.50, 66.33, 64.44, 37.50, 29.44, 28.14 and 20.91ppm are consistent with the

indicated structure. Noteworthy in the ^{1}H-NMR spectrum of **3** is the appearance of H-5 and H-6 protcns as two doublet doublets at δ4.10(J=6, 2.1Hz) and δ4.51(J=6.1, 2.1Hz) respectively, confirming the indicated stereochemistry.

In conclusion, the synthesis of an analogue of (5*R*)-C_6-pyranoid part of the natural α,β-unsaturated δ-lactones has been successfully achieved from D-glucose.[15] Moreover, the lactone **3** can be a useful intermediate for the synthesis of a variety of biologically active compounds.

Experimental

General methods: All reactions were performed in closed and pre-heated flasks under N_2 atmosphere. Organic solvents were distilled prior to use. TLC was performed on silica gel 60 F_{254} (*Merck*). For normal column chromatography, silica gel 60 (0.063-0.200 mm, *Merck*) was used. Infrared (film, cm^{-1}) was measured using a *Perkin-Elmer* spectrometer model 1430. ^{1}H-NMR spectra were recorded for $CDCl_3$ solutions with a *Varian EM-390* spectrometer (90 MHz). The 200MHz ^{1}H-NMR and 50MHz ^{13}C-NMR spectra were recorded on a *Varian VXR* spectrometer while the 400MHz ^{1}H-NMR and 100MHz ^{13}C-NMR on a *Varian unity*. Mass spectra (electron impact), *VG micromass 16F* and *KRATOS* limited MS9/50 spectrometer. Microanalysis were performed on a *Carlo Elba EA* 1108 instrument.

4,6-Di-*O*-acetyl-2,3-dideoxy-aldehydo-D-erythro-trans-hex-2-enose 7.[7]

To a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal **6** (1g, 3.67 mmol) in 1,4-dioxane (5ml) and 0.005M H_2SO_4 (7ml) at 0°C, mercuric sulphate (11mg) is added. Stirring was continued for 20h at r.t., the mixture then was neutralised with $BaCO_3$ (200mg) and the resultant suspension filtered through a short column of celite (2g). The

filtrate was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (50ml). The organic solution was dried ($MgSO_4$) and evaporated to give **7** (1.1g) as a colourless oil which was used without further purification to the next step.

(4S,5R,E)-4,6-Diacetyloxy-5-hydroxy-2-hexenal diethyldithio acetal 8. A solution of **7** (100 mg, 0.43 mmol) in $CHCl_3$ was stirred at 0°C with 0.5 ml (6.75 mmol) of EtSH. After 1h, 100 μl of $BF_3.Et_2O$ was then injected to the white suspension and stirring was continued at r.t. for additional 3h. H_20 (30 ml) was added and the mixture was extracted with $CHCl_3$ (3x 25 ml). The organic phase was dried (Na_2SO4) and evaporated till dryness. Purification on silica gel (C_6H_6-EtOAc 5:1, *Rf* 0.3) afforded 101 mg (72%) of pure **8** as a dark thick oil. IR: 3450. 2960-2860, 1739, 1658, 1640, 1597, 1548, 1515, 1479, 1445, 1369, 1225, 1045, 944, 870, 817, 786, 740, 679. ^{1}H-NMR (90 MHz): 6.3 (dd, J=15,6Hz, H-3), 5.9 (dd, J=15,6Hz, H-2); 5.0(t, J=7Hz, H-4); 4.2 (m, 4H, 2x H-6, H-5, OH); 3.4(d, J=6Hz, H-1), 2.8 (q, 4H, J=8Hz, 2x CH_2), 2.05 (s, 6H, 2x CH_3), 1.25 (t, 6H, J=8, 2x CH_3). EI-MS: 224(*M-SEt*)(0.48), 173(3.7), 154(4.2), 141(6.3), 131 (3.1), 111(7.7), 105(4), 101(2.3), 97(4.8), 89(3.1), 85(2.4), 75(4.7), 69 (5.7), 61(4.3), 45(7.6), 43(100).

(4S,5R,E)-4,6-Diacetyloxy-5-hydroxy-2-hexenal trimethylenedithio acetal 9.

1,3-Propanedithiol (500μl, 5 mmol) was added to a cooled (0°C) solution of crude **7** (1.1g, 4.3 mmol) in 20 ml of $CHCl_3$. After 1h stirring at the same temperature, $BF_3.OEt_2$ (50μl) was injected and the solution was stirred at 0°C for further 1h. H_2O (30ml) was added and the resultant solution was evaporated under reduced pressure. The crude material was dissolved in 50 ml of dry CH_2Cl_2, filtered and evaporated till dryness to give 1.4g (≥90%) of the dithiane **9** as a colourless oil. It was passed to the

next step without further purification. IR: 3450, 2960-2820, 1739, 1650, 1420, 1270, 1170, 1050, 910, 770. ^{1}H-NMR (90MHz): 6.1(dd, J=15,6Hz, H-3), 5.8(dd, J=15,6Hz, H-2), 5.2(t, J=6Hz, H-4), 4.2(m, 1H, H-5), 3.7(m, 2x H-6), 3.6(d, J=7Hz, H-1), 2.94(m, 2H, 2x H_a), 2.73(m, 2H, 2x H_a), 2.2(m, 2H, 2x H_b), 2.16(s, 3H, CH_3), 2.05(s, 3H, CH_3).

(4R,5S,E)-4,6-Diacetyloxy-5-benzyloxy-2-hexenal trimethylenedithioacetal 10. A solution of the dithioacetal **9** (500 mg, 1.56 mmol) in 10 ml DMF was treated with 50 mg of NaH(moistened with mineral oil, 2 mmol). After 30 min stirring at 0°C, 240µl of benzylbromide (2 mmol) and a few crystals (5 mg) of Bu4NI were subsequently added. Stirring was continued overnight at r.t., then the mixture was poured into sat. NH_4Cl solution (25 ml), extracted with $CHCl_3$ (3x 15 ml), dried (Na_2SO_4) and evaporated till dryness to afford **10** as a colourless oil. Purification on silica gel (toluene-EtOAc 5:1, R_f 0.25) yielded 470 mg (72%) of pure (10). IR: 3100-2860, 1740, 1602, 1584, 1515, 1494, 1453, 1428, 1380, 1335, 1298, 1280, 1273, 1179, 1107, 1071, 910, 871, 801. ^{1}H-NMR (400 MHz): 7.36-7.28 (m, 5H, arom), 6.40(dd, J =14.1, 4.9Hz, H-3), 5.96(dd, J=14.1,4.9Hz, H-2); 5.19 (dt, J=6.01 and 3.34Hz, H-5), 4.80(d, 1H, J_{gem}=11.76, CH_2Ph), 4.59(d, 1H, J_{gem}=11.76, $PhCH_2$), 4.13(2d, J=5.12 and J=3.34Hz, 1H, H-4), 3.70 (m, 3H, 2x H-6), H-1), 2.65 (m, 2H, 2x H_a), 2.50 (m, 2H, 2x H_a), 2.15(s, 3H, CH_3), 2.07(s, 3H, CH_3), 1.95 (m, 2x H_b). ^{13}C-NMR (100 MHz): 171.02 (CO), 170.29(CO), 138.21, 128.772-125.97(arom), 133.61(C-3), 131.84(C-2), 73.69, 71.01, 64.75, 62.25, 50.46, 36.20, 29.46, 28.57, 21.02, 20.98.

(4S,5R,E)-4,6-Dihydroxy-5-benzyloxy-2-hexenal trimethylenedithioacetal 11. 400 mg (0.975 mmol) of **10** was stirred with 10 ml of 0.05M $NaOCH_3$ (prepared by

dissolving 100 mg of sodium in 100 ml of dry MeOH) for 18h at r.t. then the solvent was evaporated till dryness. The residue was purified on silica gel (toluene/EtOAc 4:1) to afford 56 mg(17%, R_f 0.3) of unchanged **10**, 60 mg(17%, R_f 0.23) of 6-hydroxy-5-benzyloxy-4-acetyloxy-2-hexenal trimethylenedithioacetal **14** and 90mg(29%, R_f 0.1) 0f **11** as a colourless oil. IR: 3410 (br), 3050-2860, 1680, 1658, 1600, 1531, 1515, 1480, 1460, 1445, 1425, 1375, 1331, 1067, 968, 876, 680. ^{1}H-NMR (400 MHz): 7.4-7.28(m, 5H,arom), 6.35(dd, J=14.1, 3.91Hz H-3), 5.95 (dd, J=14.1, 4.1Hz, H-2), 5.0 (dt, J=6.0, 3.3Hz, H-5), 4.80(d, 1H, J_{gem}=11.76, CH_2Ph), 4.64(d, 1H, J_{gem}=11.76, $PhCH_2$), 4.52 (dd, J=5.9, 3.3, H-4), 3.87-3.76(m, 3H, 2x H-6, H-1), 2.79(m, 2H, 2x H_a), 2.50(m, 2x H_a), 2.36(s, br 1H, OH, 1.95(m, 2H, 2x H_b), 1.23(s br, 1H, OH).

(4S,5R,E)-6-(4-Methoxytrityloxy)-5-benzyloxy-4-hydroxy-2-hexenal trimethylene dithio acetal 12. 100 mg (0.306 mmol) of the diol **11** dissolved in 6 ml of dry pyridine was stirred with 112 mg (0.364 mmol) of 4-methoxytriphenylmethylchloride at r.t. for 24h. The solvent was evaporated in the high vacuum and the crude product was purified by chromatography(toluene/EtOAc 3:1) to afford 129 mg (63%) of **12** as colourless oil. IR: 3450 (br), 3060-2860, 1670, 1610, 1510, 1490, 1470, 1426, 1300, 1040, 710, 600. ^{1}H-NMR (200 MHz): 7.45 (d, J=7Hz, $4H_{arom}$), 7.35-7.20(m, $13H_{arom}$), 6.85 (d, J=9Hz, $2H_{arom}$), 6.3 (dd, J=15, 5Hz, H-3); 6.0 (dd, J=13, 5Hz, H-2); 5.0 (dt, J=6, 3.3Hz, H-5), 4.6(s, 2H, CH_2Ph); 4.5 (m, H-4), 3.79(s, OCH_3), 3.3 (m, 3H, 2x H-6, H-1), 2.80(m, 2H, $2H_a$), 2.6(m, 2H, $2H_a$), 1.90(m, 2H, $2H_b$).

(4S,5R,E)-6-(4-Methoxytrityloxy)-5-benzyloxy-4-acetyloxy-2-hexenal trimethyl - ene dithio acetal 13. The foregoing alcohol **12** (100 mg, 0.167 mmol) dissolved in 2 ml of pyridine was treated with acetic anhydride (34μl, 0.334 mmol) and stirred at r.t.

for 3 days, then 2 ml of methanol was added and the solvent was evaporated till dryness. The resulting residue was purified by chromatography (toluene:EtOAc 3:1) to afford the title compound **13** in 46% yield (50 mg) as colourless oil. IR: 3080-2860, 1740, 1640, 1600, 1579, 1509, 1480, 1400, 1370, 1360, 1300, 1279, 1250, 1040, 1000, 940, 830, 730, 702. ^{1}H-NMR (200 MHz): 7.42 (d, J =8Hz, $4H_{arom}$), 7.32-7.20(m, $13H_{arom}$), 6.81(d, J=9Hz, $2H_{arom}$), 5.9(m, H-2, H-3). 4.9(m, H-5), 4.6(s, 2H, CH_2Ph), 4.5(m, H-4), 3.79(s, OCH_3), 3.21(m, 3H, 2x H-6, H-1), 2.80(m, 2H, 2x H_a), 2.46(m, 2H, 2x H_a), 2.15(s, 3H, CH_3), 1.80(m, 2H, 2x H_b).

(4S,5R,E)-6-Hydroxy-5-benzyloxy-4-acetyloxy-2-hexenal-trimethylenedithio acetal 14. 100 mg (0.14 mmol) of **13** dissolved in 10 ml of THF was treated with 10 drops of 0.01N HCl. The reaction was stirred at r.t. and TLC monitored it. After 2h powdered 1g $NaHCO_3$ and $MgSO_4$ were added and then the solid was filtered and washed with chloroform (25 ml). The combined filtrate was evaporated in *vacuum* and the residue was purified on silica gel (toluene-EtOAc 4:1, R*f* 0.23) to afford 43 mg (76%) of pure **14**. IR: 3450 (br), 3050-2860, 1740, 1660, 1600, 1560, 1530, 1515, 1483, 1460, 1450, 1426, 1375, 1331, 1076, 960, 829, 680, 600. ^{1}H-NMR (400 MHz): 7.33-7.25 (m, $5H_{arom}$), 7.0(dd, 1H, J=13.6, 5.8, H- 3), 6.1 (dd, 1H, J=13.6, 5.2Hz, H-2), 4.9 (dt, J=6.8, 3.2Hz, H- 5); 4.80(d, 1H, J_{gem}=11.76, CH_2Ph), 4.64(d, 1H, J_{gem} =11.76, $PhCH_2$), 3.7 (m, 2x H-6, H-1), 2.67 (m, 2H, 2x H_a), 2.52(m, 2H, 2x H_a), 2.31(s br, 1H, OH), 2.11(s, 3H, CH_3), 1.86(m, 2H, 2x H_b). EI-MS: 277(*M*-Bn+2), 197(41.2%), 106(8.2%), 91(100%), 69(7%), 43(26.7%).

(4S,5R,E,E/Z)-7-Methoxycarbonyl-5-benzyloxy-4-acetyloxy-2,6-heptadienal trimethylenedithioacetal 16. Dimethyl sulfoxide (25 µl, 0.35 mmol) was added to a solution of oxalyl dichloride (410 µl, 0.30 mmol) in dichloromethane (5 ml) at -78°C

and stirred for 20 min. A solution of alcohol **14** (100 mg, 0.27 mmol) in dichloromethane (3 ml) was added slowly and the mixture was further stirred at the same temperature for 40min. Et_3N (111 μl, 0.81 mmol) was injected dropwise and stirring was continued for 3h at -78°C→10°C and then concentrated under reduced pressure in a cold water bath to give the crude aldehyde **15** which was used immediately without isolation. A cooled (0°C) solution of Ph_3P=CH-CO_2Me (113 mg, 0.40 mmol) in MeOH (3 ml) was added to a solution of crude aldehyde **15** in the same solvent (3 ml). The mixture was stirred at r.t. for 30h then the solvent was evaporated under reduced pressure to give the crude olefins **16** (70 mg, 61% yield, Z:E ratio 5.5:1). The residue was purified on silica gel (toluene/hexane 5:1, R_f 0.31) to give (51 mg, 44%) of pure **16** as colourless thick oil. $C_{21}H_{26}O_5S_2$ requires:C, 59.71; H, 6.16; S, 15.16; Found: C, 60.0; H, 6.28; S, 14.60. IR: 3053-2860, 1730, 1660, 1600, 1510, 1470, 1200, 1040, 960, 710, 600. ^{1}H-NMR (400 MHz): 7.35 (m, $5H_{arom}$), 6.90 (dd,1H, J =15.32, 5.77Hz, H-6, *E*-isomer), 6.55(dd, 1H, J =14.87, 6.21, H-3), 6.24(dd, 1H, J =11.76, 5.32Hz, H-6, *Z*-isomer), 6.07 (dd, 1H, J =14.87, 5.0, H-2), 5.9(dd, J =15.32, 1.1Hz, H-7, E-isomer); 5.7 (dd, 1H, J = 11.76, 0.89Hz, H-7, Z-isomer), 5.03(dt, J =6.0, 3.3 Hz, H-5, 4.8(d, 1H, J =11.5, CH_2Ph), 4.5(d, 1H, J=11.5, CH_2Ph), 4.24(dd, 1H, J=6.21, 3.1Hz, H-4), 3.60(d, 1H, J=5.0Hz, H-1), 2.8(m, 2H, 2x H_a), 2.5(m, 2H, 2x H_a), 2.16(s, 3H, CH_3), 1.90(m, 2H, 2x H_b. ^{13}C-NMR: (100MHz): 171.078, 170.932, 167.130, 166.991, 143.246, 142.918, 138.893, 135.175, 131.974, 131.674, 129.504, 128.437-126.32, 73.749, 70.903, 66.599, 64.599, 64.639, 62.072, 51.567, 36.686, 29.567, 28.765, 20.582, 20.470.

[(5S, 6R, 3(Z), 2`(E)]-5-Benzyloxy-6-(2`-propenal trimethylene dithioacetal)-5,6-dihydropyran-2-One (3). Unsaturated ester **16** (50 mg, 0.118 mmol) dissolved in a mixture of THF/MeOH (2:1 v/v) (9 ml) was treated with a 0.5N aqueous solution of

LiOH (4.72 ml, 2.36 mmol) and stirring was continued at r.t. overnight. The solvent was removed under high vacuum, then 10 ml of H_2O was added to the residue and the aqueous solution was acidified to pH 2.5 with 2N HCl. The acidic aqueous solution was extracted with EtOAc (2x 15 ml), Et_2O(1x 20ml) and the organic solutions was subsequently dried ($MgSO_4$) and evaporated till dryness. The crude residue was dissolved in aqueous CF_3COOH (9:1, 10 ml) at 0°C and the solution was stirred at this temperature for 3h, then overnight at r.t.. The solution was neutralised by addition of solid anhydrous K_2CO_3 (100mg) and extracted with $CHCl_3$ (3x 15 ml). The organic extract was dried ($MgSO_4$) and evaporated till dryness to afford 27 mg (65% overall yield) of crude lactone **3** as a yellow oil which was purified on silica gel (toluene-EtOAc 5:1, *Rf* 0.26) to give 12 mg(29%) of pure **3**. IR: 3040-2871, 1740, 1725, 1625, 1602, 1327, 1311, 1180, 942, 818, 810. ^{1}H-NMR (400 MHz): 7.40-7.30(m, $5H_{arom}$), 7.02(dd, 1H, J=14.80, 5.2Hz, H-2`), 6.90(dd, 1H, J=10.20, 5.4Hz, H-4), 6.24(dd, 1H, J=14.80, 5.40Hz, H-1`), 6.02(d, 1H, J=10.22Hz, H-3), 4.82(d, 1H, J=11.6Hz, CH_2Ph), 4.70(dd, 1H, J=5.4, 2.1Hz, H-6), 4.59(d, 1H, J=11.6Hz, CH_2Ph), 4.10(dd, 1H, J=5.4, 2.1Hz, H-5), 3.60(m, 1H, H-3`), 2.80(m, 2H, 2x H_a), 2.50(m, 2H, 2x H_a), 1.80(m, 2H, 2x H_b). ^{13}C-NMR (100MHz): 162.51, 144.36, 142.64, 138.43, 132.22, 128.62, 127.53, 125.34, 79.67, 71.50, 66.33, 64.44, 37.50, 29.44, 28.14, 20.91. FAB-MS: (mass 348 calculated for $C_{18}H_{20}O_3S_2$): 367(M^++K)(3%), 347(1), 258(12), 200(4), 179(8), 158(100), 107(23), 91(12). EI-MS: 258(*M*-Bn+1)(1.0), 197(4.1), 179(1.3), 161(11.51), 106(13), 91(100).

ACKNOWLEDGMENT

We wish to thank Prof. Dr. *Ch. Tamm* for reading the manuscript and for his helpful comments.

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Received in the UK 12 October 1998