26. Synthesis of Enantiomerically Pure Substituted Cyclopentenes from (−)-Quinic Acid

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Summary

The synthesis of a large variety of enantiomerically pure substituted reactive cyclopentenes **16**, **23**, **24** and **28** have been synthesized from the readily available (−)-quinic acid **1**. The straightforward strategy involves a high-yielding intramolecular aldolization-dehydration of acyclic 1,6-dialdehydes **13**, **18**, **19** and **27** obtained by oxidative cleavage of cyclohexanediols **5**, **7**, **11** and **12**, using either lead tetraacetate or triphenylbismuth carbonate. Neither sulfoxide formation nor racemization of the intermediate dialdehydes at the oxygenated chiral centre was observed. Transformation of the thioacetal **25** to the corresponding ketone **26** using phenylselenic anhydride is also described.

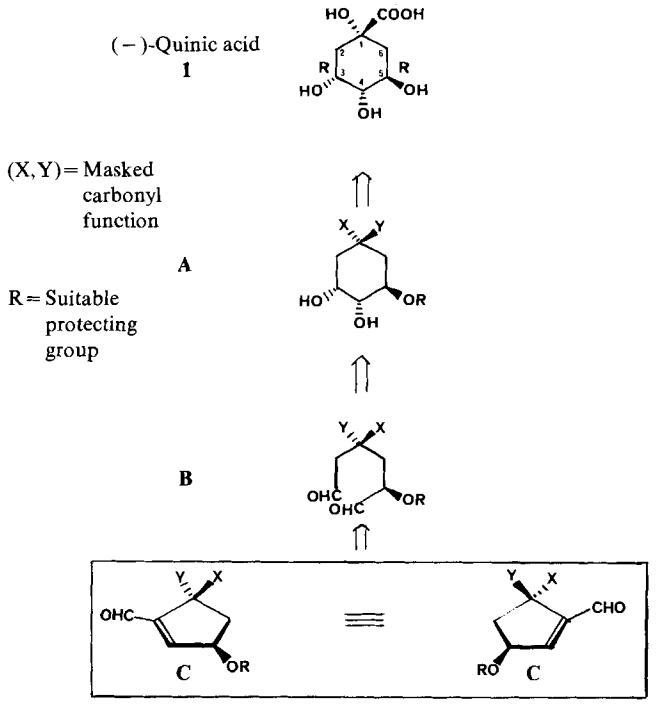
1. Introduction. – The isolation of many cyclopentanoid natural products [1] has engendered an explosive synthetic effort [2]. Many of the available routes require resolution of racemates [3] and separation of diastereoisomeric mixtures [4], and we felt that there remains still a need of an additional, short, convergent and chirally selective method for the synthesis of cyclopentanoid natural products.

For the total synthesis of substituted chiral cyclopentanoids, the chiral, substituted cyclopentenes of type **17**, **25**, **29**, cyclopentenone **26**, and their progenitors **16**, **23**, **24** and **28** would be ideal intermediates. We now describe the preparation of such reactive molecules from (−)-quinic acid (**1**) and in the next article [5] their use for the synthesis of highly substituted cyclopentane nuclei, including 11-α-hydroxy-13-oxa-prostanoic acid [6].

(−)-Quinic acid was chosen because, besides its availability in optically pure form, its quaternary C-atom may be regarded as a masked carbonyl group, and both C(3) and C(5) possess the required (*R*) absolute configuration and functionalities *(Scheme)*.

The strategy devised for the synthesis of 2-substituted cyclopentenes, depicted retrosynthetically in the *Scheme*, involves an intramolecular aldolisation-dehydration of an acyclic 1,6-dialdehyde **B**, which in turn may be derived *a priori* from cyclohexanediol of type **A**, by oxidative cleavage. It was imperative at the outset, to choose appropriate protecting groups, readily introduced, resisting the conditions

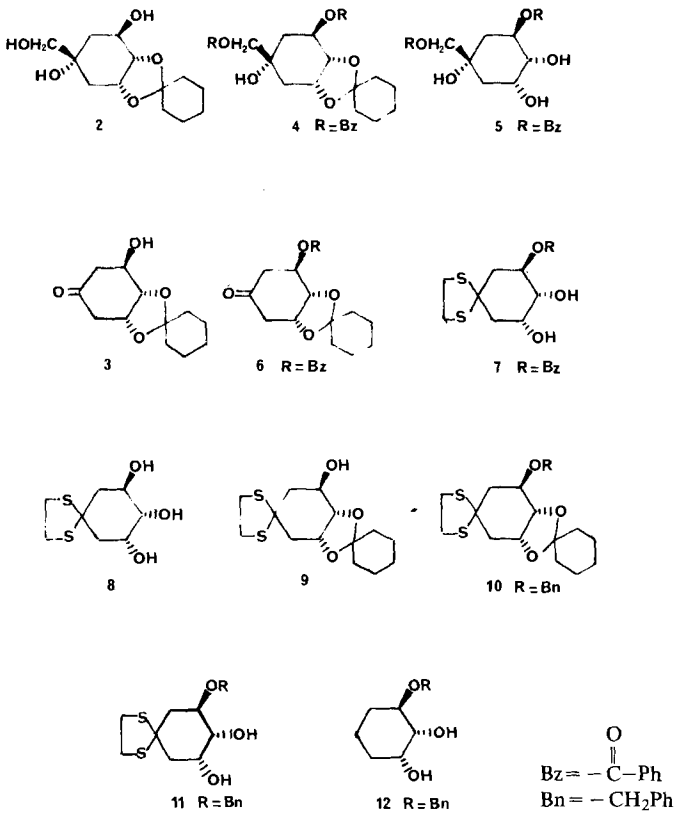
Scheme



of the oxidative ring-contraction and finally easily removed in a stepwise manner at any moment of the reaction sequence. Therefore the initial goal was the preparation of conveniently protected cyclohexane derivatives from triol **2** and hydroxy ketone **3**.

2. Results. – (–)-Quinic acid (**1**) was readily transformed into the cyclohexylidene acetal **2** [7] which on treatment with benzoyl chloride in pyridine gave the dibenzoate **4**. Acid hydrolysis, using ethanolic hydrochloric acid furnished the triol **5** selected as the first candidate for oxidative ring-contraction. The second approach consisted of elaborating from the accessible ketone **3** the corresponding elusive acetals or dithioacetals.

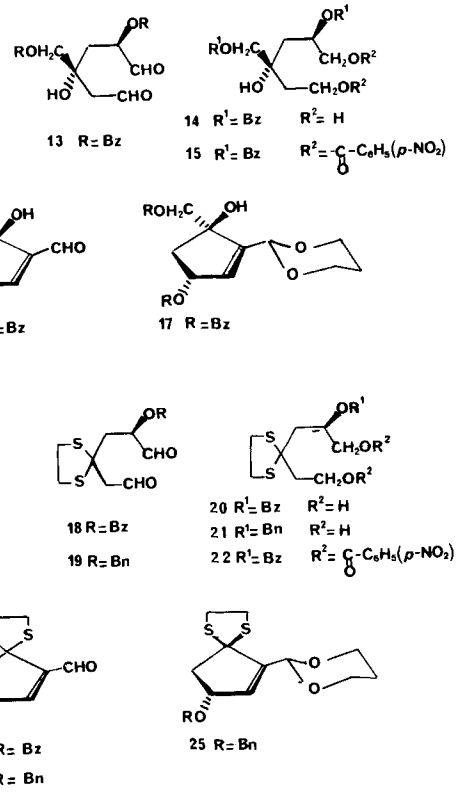
The unprotected hydroxy ketone **3** as reasonably expected was unstable under either acidic or even mildly basic conditions, and prone to β-elimination. However, the benzoate **6** could be prepared in high yield. Acetalization of either the hydroxy ketone **3** or its benzoate **6** using ethane-1,2-diol, propane -1,3-diol, or 2,2-dimethylpropane-1,3-diol and acid catalyst resulted only in aromatization of the ring, and was therefore temporarily abandoned. However, the reaction of **3** or **6** in anhydrous chloroform with ethane-1,2-dithiol in the presence of boron trifluoride etherate yielded the corresponding dithioacetals **8** and **7** in excellent yields, with simultaneous removal of the cyclohexylidene acetal group.



The cyclohexylidene protecting group being needed for the preparation of the dithioacetal **11**, the triol **8** was retransformed into its cyclohexylidene derivative by reaction of 1,1-dimethoxycyclohexane in the presence of a catalytic amount of sulfuric acid in *N,N*-dimethylformamide. Benzylation of the free hydroxyl group of **9** using sodium hydride and benzyl bromide in *N,N*-dimethylformamide yielded **10** in high yield. Acid hydrolysis of the latter using aqueous acetic acid led to compound **11**.

A third type of diol **12** was prepared by *Raney* nickel desulfurization [8] of **11** in boiling ethanol, giving **12** in good yield.

The key step in our sequence *(Scheme)* was the oxidative ring-contraction which has ample precedent [9]. Success, however, depended largely upon the following criteria: *a)* efficient cleavage of the *cis*-vicinal diols (without sulfoxide formation); *b)* intramolecular aldolisation-dehydration with the preservation of the protecting groups; *c)* absence of partial racemisation of the intermediate dialdehydes **13**, **18**, **19** and **27** at the oxygenated chiral centre; *d)* ready removal of the protecting groups. Having in hand several *cis*-cyclohexanediols **5**, **7**, **11** and **12**, we first examined the cyclohexanetriol **5**.



Lead-tetraacetate oxidation of the triol **5** in anhydrous chloroform gave an unstable dialdehyde **13**, which could not be isolated but was characterized as the di-*O*-*p*-nitrobenzoate **15** of **14** obtained after sodium borohydride reduction. Attempts to cyclize the acyclic dialdehyde **13** using the logical base catalysts, diazabicyclononane [10], pyrrolidine or piperidine acetate [11], (−)-(*S*)-proline [12] were unsuccessful. However, treatment of the acyclic dialdehyde **13** with dried lithium iodide [13] in anhydrous diethyl ether under N_2, gave a complex mixture of unstable products from which after addition *in situ* of 1,3-propanediol in anhydrous toluene and a catalytic amount of *p*-toluenesulfonic acid, the acetal **17** could be isolated on silica gel chromatography in 15% yield from **13**. The successful conversion **13** → **17**, albeit in low yield established the validity of our overall strategy.

To understand better the structural requirements for the oxidative ring-contraction, we next examined the oxidation of the dithioacetals **7** and **11**, and the cyclization of the resultant dialdehydes **18** and **19**. Oxidation of **7** and **11** in anhydrous toluene at room temperature using acetic-acid-free lead tetraacetate [14] or triphenylbismuth carbonate [15] in anhydrous dichloromethane furnished the dialdehydes **18** and **19** in excellent yields. These particularly unstable dialdehydes were *in situ* cyclized under N_2 with a catalytic amount of pyrrolidine acetate in

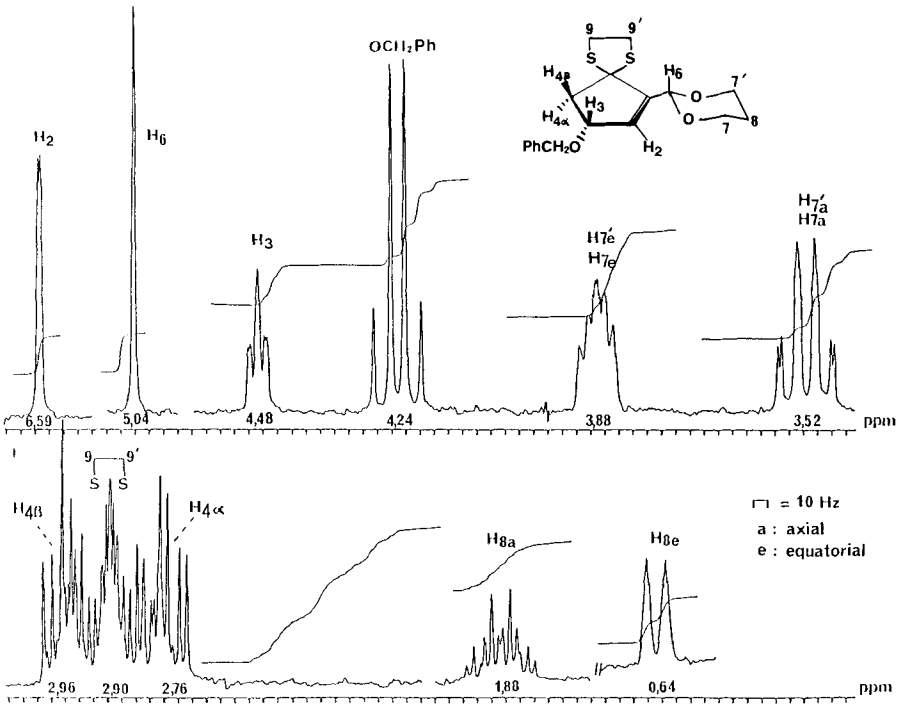


Figure. *^{1}H-NMR. spectrum* (400 MHz, C_6D_6) *of* **25**

Table 1. *^{1}H-NMR. data of* **25** (400 MHz, C_6D_6)[a])

δ (ppm)	H	J (Hz)		
0.64	H_e–C(8) (br. *d*)	$J(8a) = -12.5$	$J(7a) = J(7'a) = 2.5$	
1.88	H_a–C(8) (*q* × *t*)	$J(8e) = -12.5$	$J(7a) = J(7'a) = 12.5$	$J(7e) = J(7'e) = 5$
2.76	H_α–C(4) (*d* × *d*; *AB*)	$J(4\beta) = -13.5$	$J(3) = 5$	
2.90	2 H–C(9) 2 H–C(9′) (*m*)			
2.96	H_β–C(4) (*d* × *d*, *AB*)	$J(4a) = -13.5$	$J(3) = 6.5$	
3.52	H_a–C(7) H_a–C(7′) (2 *t* × *d*)	$J(8a) = 12.5$	$J(8e) = 2.5$	$J(7e) = -12.5$
3.88	H_e–C(7) H_e–C(7′) (*m*)			
4.24	O–CH_2–Ph (*AB*)	$\|J(\text{gem})\| = 12$		
4.48	H–C(3) (*t* × *d*)	$J(4a) = 5$	$J(4\beta) = 6.5$	$J(2) = 2$
5.04	H–C(6) (br. *s*)	$J(2) \simeq 0.5$		
6.59	H–C(2) (br. *d*)	$J(3) = 2$	$J(2) \simeq 0.5$	
7.33	5 arom. H			

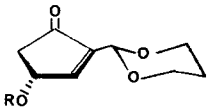
[a]) Attributions have been made using appropriate decoupling experiments; *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet, br. = broad, δ (TMS) = 0 ppm, a = axial, e = equatorial.

Table 2. *^{13}C-NMR. data of* **25** (15.08 MHz, $CDCl_3$)

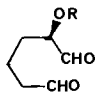
C-atoms	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(7')	C(8)	C(9)	C(9')
δ(ppm)	[a])	146.3	131.6	80.3	53.8	97.3	67.3	67.3	25.8	41.3[b])	40.5[b])

O–CH_2 (70.9); arom. C (138.2, 128.2, 127.6, 127.5)

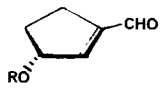
[a]) Do not appear on the spectrum.
[b]) Interchangeable values.



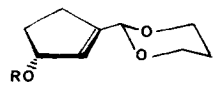
26 R=Bn



27 R = Bn



28 R=Bn



29 R=Bn

anhydrous toluene at 0° into the cyclopentenes **23** and **24** in virtually quantitative yields. No sulfoxide formation was detected during the oxidation.

Acetalization of **24** using 1,3-propanediol in anhydrous toluene containing a catalytic amount of *p*-toluenesulfonic acid provided **25** in 80% yield. That a single product was indeed formed, was demonstrated by the ^{1}H-NMR. (400 MHz) and ^{13}C-NMR. spectra *(Figure, Table 1* and *2)*, and the absolute configuration of the asymetric C-atom of **25** was established by X-ray crystallographic analysis [16].

Likewise, the cyclohexanediol **12**, under identical conditions, afforded the acyclic dialdehyde **27**, the cyclopentenecarbaldehyde **28** and the corresponding acetal **29** in high overall yield. It is interesting to note the ready cyclisation of two types of dialdehydes; dithioacetals **18** and **19** and unsubstituted **27**, whereas the transformation of the dialdehyde **13** to the corresponding cyclopentenecarbaldehyde **16** procededed sluggishly.

Finally, the removal of the ethylene dithioacetal protection in **25** was accomplished routinely by treatment with phenylselenic anhydride [17] and propylene oxide to give cyclopentenone **26** in 70% yield.

In conclusion, a variety of enantiomerically pure active cyclopentenes are thus readily available. These key intermediates are useful synthons for the synthesis of biologically active cyclopentanoid natural products [18].

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Experimental Part

General remarks. Melting points (m.p.) were obtained with a *Reichert* melting point apparatus and are uncorrected. Specific rotations were determined at 25° with a *Quik Roussel & Jouan* Polarimeter. IR. spectra (cm^{-1}) were recorded with a *Perkin Elmer 257* spectrometer. The ^{1}H-NMR. spectra were obtained with a *Varian T60* or *EM 306L* (60 MHz), a *Cameca TSN 250* (250 MHz) and a *Bruker WN 400* (400 MHz) spectrometers with tetramethylsilane (TMS) as an internal standard. The ^{13}C-NMR. spectra were recorded on a *Bruker HX 90* (22.63 MHz) or *WP60* (15.08 MHz) (TMS = 0 ppm). MS. (*m/z*) were obtained with a *MS 50* mass spectrograph.

Starting material. The (1*R*,2*S*,3*R*,5*R*)-1,2-*O*-cyclohexylidene-5-hydroxymethyl-1,2,3,5-cyclohexanetetrol (**2**) and the (3*R*,4*S*,5*R*)-3,4-*O*-cyclohexylidene-3,4,5-trihydroxycyclohexanone (**3**) were obtained from (−)-quinic acid (**1**) [7].

(*1R,2S,3R,5R*)-*3-O-Benzoyl-5-benzoyloxymethyl-1,2-cyclohexylidene-1,2,3,5-cyclohexanetetrol* (**4**). To a solution of **2** (3 g, 11.6 mmol) in 20 ml of dry pyridine were added at 0° 3.1 ml (2.3 equiv.) of benzoyl chloride. The mixture was stirred for 12 h at r.t., then diluted with 50 ml of water and extracted with CH_2Cl_2. The org. layer was dried (Na_2SO_4) and evaporated under reduced pressure. Crystallization from EtOH gave **4** (90%); m.p. 142°; $[\alpha]_D^{25} = -35°$ ($c = 0.9$, $CHCl_3$).

$C_{27}H_{30}O_7$ (466.534) Calc. C 69.51 H 6.58% Found C 69.61 H 6.29%

(*1R,2R,3R,5S*)-*3-O-Benzoyl-5-benzoyloxymethyl-1,2,3,5-cyclohexanetetrol* (**5**). To a solution of 25 ml EtOH and 2 ml HCl (12N) was added **4** (2.37 g, 5.1 mmol). The mixture was stirred for 2.5 h at 70°. Then solid $NaHCO_3$ was added and the solvent was evaporated under reduced pressure. The salts were filtered off and washed with $CHCl_3$. Crystallization from ethanol and ethyl acetate afforded **5** (90%); m.p.: 183–184°; $[\alpha]_D^{25} = -40°$ ($c = 0.90$, $CHCl_3$).

$C_{21}H_{22}O_7$ (386.39) Calc. C 65.27 H 5.74% Found C 65.30 H 5.85%

(*2R,4S*)-*2-Benzoyloxy-4-benzoyloxymethyl-4-hydroxy-1,6-hexanedial* (**13**). To a solution of **5** (386 mg, 1 mmol) in 30 ml of anh. $CHCl_3$ was added $Pb(OAc)_4$ (660 mg, 1.5 mmol). The mixture was stirred for 2 h at r.t. in absence of light. Then ethylene glycol was added to destroy excess $Pb(OAC)_4$ and the mixture was diluted with CH_2Cl_2. The org. layer was washed successively with water, saturated $NaHCO_3$-solution and water, then dried (Na_2SO_4) and evaporated under reduced pressure to give the dialdehyde **13** as an unstable oil (90%). – IR. (neat): 3400, 1700–1715, 1600. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.1–2.45 (*m*, 2 H–C(5)); 3.8 (*m*, 2 H–C(3)); 4.36 (*m*, 3 H and OH); 5.2 (*m*, CH_2–O–C–Ph); 5.4 (*m*, H–C(2)); 7.1 (*m*, 6 H, arom. H); 7.65 (*m*, 4 H, arom. H); 9.5 (*m*, CHO). (O)

(*3S,5R*)-*5-Benzoyloxy-3-benzoyloxymethyl-1,3,6-hexanetriol* (**14**). To a solution of **13** (380 mg, 1 mmol) in dimethoxyethane (7 ml) was added $NaBH_4$ (150 mg, 4 mmol). After stirring for 45 min, the reaction was quenched with acetic acid and water. The mixture was extracted with CH_2Cl_2 and the org. layer washed with a solution of $NaHCO_3$ and then with water. After drying (Na_2SO_4) and evaporation of the solvents, **14** (322 mg) was obtained and crystallized from ether/light petroleum (80%); m.p. 79–80°; $[\alpha]_D^{25} = +12°$ ($c = 1.25$, $CHCl_3$).

$C_{21}H_{24}O_7$ (388.40) Calc. C 64.93 H 6.23% Found C 64.74 H 6.36%

Di-O-p-*nitrobenzoate* **15** *of* **14**. To a solution of **14** (320 mg, 0.82 mmol) in anh. pyridine (7 ml) was added *p*-nitrobenzoyl chloride (360 mg, 1.9 mmol). The reaction was stirred at r.t. then diluted with 10 ml of water and extracted with $CHCl_3$. The org. layer was dried (Na_2SO_4), and evaporated to give **15** as a solid which was crystallized from EtOH (79%); m.p. 152–153°; $[\alpha]_D^{25} = -6°$ ($c = 1.03$, $CHCl_3$).

$C_{35}H_{30}O_{13}N_2$ (686.63) Calc. C 61.22 H 4.37 N 4.08% Found C 61.41 H 4.44 N 4.21%

(*3R,5S*)-*3-Benzoyloxy-5-benzoyloxymethyl-5-hydroxy-1-cyclopentene-1-carbaldehyde propylene acetal* (**17**). – *Cyclization of* **13**. Dried LiI (2 mmol) was added under N_2 to the crude dialdehyde **13** (300 mg, 0.78 mmol) dissolved in 20 ml of anh. Et_2O. After stirring for 12 h at r.t., the mixture was extracted with CH_2Cl_2. The org. extract was washed with water then dried (Na_2SO_4) and evaporated under reduced pressure to give an unstable oil which contained **16** and which was directly used.

Acetalization of **16**. To a mixture of the crude aldehyde **16** dissolved in 10 ml of anh. toluene, were added a large excess of 1,3-propanediol (3 ml) and a catalytic amount of *p*-toluenesulfonic acid. The reaction was monitored by TLC. ($CHCl_3$/ether 3:1). After 24 h at r.t. the mixture was diluted with CH_2Cl_2 and solid $NaHCO_3$ was added. The inorganic salts were filtered off and the filtrate was washed with water. The org. layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a coloured oil which was purified by silica gel chromatography ($CHCl_3$/ether/light petroleum 1:1:0,5). Compound **17** was isolated in 15% yield from the dialdehyde **13**; $[\alpha]_D^{25} = +54°$ ($c = 0.9$, $CHCl_3$). – ^{1}H-NMR. (250 MHz, $CDCl_3$): 1.48 (br. *d*, $J(8a) = -12.5$, 1 H, H_e–C(8)); 2.19 (*m*, 1 H, H_a–C(8)); 2.25 (*d*×*d*, *AB*, $J(4\beta) = -14$, $J(3) = 4$, 1 H, H_α–C(4)); 2.97 (*d*×*d*, *AB*, $J(4\alpha) = -14$, $J(3) = 7.5$, 1 H,

H_β–C(4)); 3.85 (*m*, 3 H, H_a–C(7), H_a–C(7'), OH–C(–5)); 4.19 (*m*, 2 H, H_e–C(7), H_e–C(7')); 4.5 (*s*, 2 H, CH_2OOCPh); 5.36 (*s*, 1 H, H–C(6)); 5.82 (*m*, $J(4a)=4$, $J(4\beta)=7.5$, $J(2)=1$, 1 H, H–C(3)); 6.26 (br. *s*, 1 H, H–C(2)); 7.5 (*m*, 6 H, arom. H); 8.05 (*m*, 4 H, arom. H).

$C_{24}H_{24}O_7$ (424.456) Calc. C 67.91 H 5.70%
Calc. (1/2 H_2O) C 66.50 H 5.75% Found C 66.46 H 5.75%

(*3R,4R,5R*)-*5-O-Benzoyl-3,4-O-cyclohexylidene-3,4,5-trihydroxycyclohexanone* (**6**). To a solution of **3** (2 g; 8.8 mmol) in 10 ml of anh. pyridine was added at 0° benzoyl chloride (2.5 ml). The mixture was stirred for 24 h and then poured into ice-water. The white precipitate was filtered off and recrystallized from EtOH in 80% yield; m.p. 120–121°; $[\alpha]_D^{25}=+69°$ ($c=1.3$ $CHCl_3$).

$C_{19}H_{22}O_5$ (330.37) Calc. C 69.07 H 6.71% Found C 68.83 H 6.56%

(*3R,4S,5R*)-*5-O-Benzoyl-3,4,5-trihydroxycyclohexanone ethylene dithioacetal* (7). To a solution of **6** (1.05 g, 3.2 mmol) in 10 ml of anh. $CHCl_3$ were added 2 ml of 1,2-ethanedithiol and 0.4 ml of boron trifluoride etherate. During the course of the reaction the dithioacetal **7** precipitated as a white solid. After 3 h at r.t., the mixture was diluted with methanol and neutralized with solid $NaHCO_3$. The inorg. salts were filtered off and the solvents were removed under reduced pressure. The residue was dissolved in hot light petroleum and filtered to furnish on cooling **7** as a white solid (80%); m.p.: 115–116°; $[\alpha]_D^{25}=0°$ ($c=1.47$ $CHCl_3$).

$C_{15}H_{18}O_4S_2$ (326.441) Calc. C 55.19 H 5.56 S 19.64% Found C 55.11 H 5.64 S 19.68%

(*2R*)-*2-Benzoyloxy-4-oxo-1,6-hexanedial 4-ethylene dithioacetal* (**18**). – *Oxidation of* **7** *with* $Pb(OAc)_4$. $Pb(OAc)_4$ (800 mg, 1.8 mmol), free of acetic acid, was added to a mixture of **7** (362 mg, 1 mmol) in 20 ml of anh. toluene. After stirring for 1.5 h in absence of light, the excess of $Pb(OAc)_4$ was destroyed by adding ethylene glycol (2 ml). The mixture was diluted with CH_2Cl_2 and washed successively with water, sat. $NaHCO_3$-solution and water. The org. layer was dried (Na_2SO_4) and concentrated under reduce pressure to give 300 mg of an unstable syrup. – IR. (neat): 1720. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.3 (*m*, 4 H, CH_2, H–C(3), H–C(5)); 3.35 (*m*, 4 H, CH_2–S); 5.9–6.3 (*m*, 1 H, H–C(2)); 7.2–7.35 (*m*, 3 H, arom. H); 7.9–8.26 (*m*, 2 H, arom. H); 9.65–9.8 (*m*, 2 H, 2 CHO).

Oxidation of **7** *with triphenylbismuth carbonate.* Triphenylbismuth carbonate (750 mg, 1.5 mmol) was added to a solution of **7** (326 mg, 1 mmol) in 10 ml of anh. CH_2Cl_2. The mixture was heated under reflux for 4.5 h. Then, after evaporation of the solvent, the crude mixture was separated by a short column chromatography (AcOEt/light petroleum 3:7) to give the dialdehyde **18** (80%). Its IR. and ^{1}H-NMR. spectra were identical with those obtained with $Pb(OAc)_4$.

(*5R*)-*5-Benzoyloxy-1,6-dihydroxy-3-hexanone ethylene dithioacetal* (**20**) *and its di-*O-p-*nitrobenzoate* (**22**). To a solution of the dialdehyde **18** (100 mg, 0.31 mmol) in 3 ml of dimethoxyethane was added $NaBH_4$ (30 mg). After stirring for 15 min, the excess hydride was destroyed by adding a few drops of acetic acid and water. After extraction with CH_2Cl_2, the organic layer was dried (Na_2SO_4) and concentrated to give **20** as a syrup which was purified on preparative silica gel plates (AcOEt/light petroleum 1:1).

The di-*O-p*-nitrobenzoate **22** was obtained by adding to the resulting **20** anh. pyridine (2 ml) and *p*-nitrobenzoyl chloride (80 mg). After extraction with $CHCl_3$, the org. layer was dried (Na_2SO_4) and evaporated under reduced pressure. The di-*O-p*-nitrobenzoate **22** was crystallized from ether/light petroleum; m.p. 128–129°.

$C_{29}H_{26}N_2O_{10}S_2$ (626.675) Calc. C 55.58 H 4.18 S 10.23% Found C 55.28 H 4.44 S 10.39%

(*3R*)-*3-Benzoyloxy-5-oxo-1-cyclopentene-1-carbaldehyde 5-ethylene dithioacetal* (**23**). To the crude dialdehyde **18** (250 mg, 0.76 mmol), dissolved under N_2 in 10 ml of dry toluene was added at 0° 0.2 ml of a solution of pyrrolidine acetate (1N in dry benzene). After 12 h at 0° and then extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to give **23** as an unstable oil which must be rapidly used. – IR. (neat): 1712, 1690. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.55 (*d*×*d*, *AB*, 1 H, H_a–C(4)); 3.3 (*d*×*d*, *AB*, 1 H, H_β–C(4)); 3.2 (*m*, 4 H, CH_2–S); 5.75–6 (*m*, 1 H, H–C(3)); 6.7 (*d*, 1 H, H–C(2)); 7.2–7.5 (*m*, 3 H, arom. H); 7.8–8.1 (*m*, 2 H, arom. H); 9.5 (*s*, 1 H, CHO).

(*3R,4S,5R*)-*3,4,5-Trihydroxycyclohexanone ethylene dithioacetal* (**8**). To a solution of **3** (124 g, 0.55 mol) in 600 ml of dry $CHCl_3$ were added at 0°, 1,2-ethanedithiol (248 ml) and boron trifluoride etherate (24.8 ml). The reaction mixture was stirred for 3 h at r.t. and the reaction monitored by TLC. ($CHCl_3$/ether 3:1). The dithioacetal **8** precipited during the reaction. The mixture was diluted with MeOH and neutralized by addition of solid $NaHCO_3$. The salts were filtered off and the solvents evaporated under reduced pressure. The resultant solid was recrystallized from acetone/light petroleum to give **8** (114 g, 94%); m.p.: 129–130°; $[\alpha]_D^{25} = -41°$ ($c = 1.4$, MeOH). – ^{13}C-NMR. ((D$_5$)pyridine): 38.8 (2 CH_2S); 46.2 (C(2)); 47 (C(6)); 65.4 (C(1)); 69.5 (C(3)); 70.55 (C(5)); 75.2 (C(4)).

$C_8H_{14}O_3S_2$ (222.332) Calc. C 43.22 H 6.35 S 28.84% Found C 42.97 H 6.40 S 29.08%

(*3R,4R,5R*)-*3,4*-O-*Cyclohexylidene-3,4,5-trihydroxycyclohexanone ethylene dithioacetal* (**9**). To a solution of **8** (114 g, 0.51 mol) in 400 ml of anh. DMF were added 1,1-dimethoxycyclohexane (100 ml) and conc. sulfuric acid (7.5 ml). The mixture was stirred at r.t. and the MeOH liberated during the course of the reaction removed *i.v.* After 24 h, the mixture was diluted with CH_2Cl_2 and neutralized with solid $NaHCO_3$. The inorg. salts were filtered off and the org. layer washed with water, dried (Na_2SO_4) and evaporated. The resulting solid was recrystallized from hexane to give **9** (95%); m.p. 138–140°; $[\alpha]_D^{25} = -44°$ ($c = 1.02$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 38.0 (CH_2–S); 38.2 (CH_2–S); 41.6 (C(6)); 46.5 (C(2)); 63 (C(1)); 71.5 (C(5)); 73.7 (C(3)); 79.7 (C(4)).

$C_{14}H_{22}O_3S_2$ (302.462) Calc. C 55.59 H 7.33 S 21.20% Found C 55.28 H 7.29 S 20.21%

(*3R,4S,5R*)-*5*-O-*Benzyl-3,4*-O-*cyclohexylidene-3,4,5-trihydroxycyclohexanone ethylene dithioacetal* (**10**). In a three-necked round-bottom flask was introduced under N_2 sodium hydride dispersion 50% in oil (37 g, 0.77 mol). The hydride was washed with light petroleum, then anh. DMF (100 ml) was added. To this suspension was added dropwise a solution of **9** (139 g, 0.46 mol) in anh. DMF (50 ml). After H_2-evolution, benzyl bromide (70 ml) was added dropwise at 0° and the mixture stirred for 4 h at r.t. The excess hydride was destroyed at 0° by slow addition of MeOH, and the mixture neutralized by adding aq. solution of HCl. The mixture was poured into ice-water and extracted with CH_2Cl_2. The org. layer was dried (Na_2SO_4) and evaporated to give **10** as a yellow oil which was crystallized from EtOH (95%); m.p.: 68–69°; $[\alpha]_D^{25} = -50°$ ($c = 1.06$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 38.1 (2 CH_2–S); 41.8 (C(6)); 44.3 (C(2)); 62.8 (C(1)); 71,55 (O–CH_3–Ph); 74 (C(3)); 78.1 (C(4)); 78.55 (C(5)).

$C_{21}H_{28}O_3S_2$ (392.587) Calc. C 64.25 H 7.19 S 16.34% Found C 64.15 H 6.96 S 16.52%

(*3R,4S,5R*)-*5*-O-*Benzyl-3,4,5-trihydroxycyclohexanone ethylene dithioacetal* (**11**). To a solution of acetic acid (500 ml) and water (220 ml) was added 175 g (0.45 mol) **10**. The mixture was heated under reflux for 3 h. After evaporation of the solvent a solid was obtained which was recrystallized from EtOH (90%); m.p.: 135–136°; $[\alpha]_D^{25} = -72°$ ($c = 1.03$, $CHCl_3$). – ^{13}C-NMR. ((D$_5$)pyridine): 38.2 (CH_2S); 39.5 (CH_2–S); 40.6 (C(6)); 46.4 (C(2)); 65.4 (C(1)); 69.2 (C(3)); 71.45 (O–CH_2–Ph); 72.35 (C(4)). – MS.: 312, 91, 65, 61.

$C_{15}H_{30}O_3S_2$ (312.247) Calc. C 57.66 H 6.45 S 20.43% Found C 57.65 H 6.53 S 20.23%

(*1R,2S,3R*)-*3*-O-*Benzyl-1,2,3-cyclohexanetriol* (**12**). A large excess of *Raney*-Nickel was added to a solution of **11** (6.2 g, 19.8 mmol) in EtOH (100 ml). The stirred mixture was heated under reflux for 12 h, then filtered through a cake of *Celite* and the residue washed with hot EtOH. After evaporation of the solvent the oily residue was dissolved in $CHCl_3$, filtered and crystallized from light petroleum (70%); m.p. 59–60°; $[\alpha]_D^{25} = -83°$ ($c = 1,3$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 18.45 (C(5)); 28.4 (C(6)); 29.8 (C(4)); 69.4 (C(2)); 71.1 (O–CH_2–Ph); 75.05 (C(3)); 78.5 (C(1)). – MS.: 222, 107, 91.

$C_{13}H_{18}O_3$ (222.287) Calc. C 70.24 H 8.16% Found C 70.12 H 8.11%

(*2R*)-*2-Benzyloxy-4-oxo-1,6-hexanedial 4-ethylene dithioacetal* (**19**). To a solution of **11** (7 g, 22.4 mmol) in anh. toluene (180 ml) was added $Pb(OAc)_4$ (14 g, 31.5 mmol) free of acetic acid. The mixture was stirred in absence of light at r.t. for 1.25 h. The excess $Pb(OAC)_4$ was destroyed by adding ethylene glycol (5 ml), and the mixture was diluted with CH_2Cl_2 and washed successively with water, sat. $NaHCO_3$-solution and water. The org. layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **19** as an unstable syrup **19** (90%) which must be utilized in situ; $[\alpha]_D^{25} = -11°$ ($c = 1.4$, $CHCl_3$). – IR. (neat): 1720.

(*5R*)-*5-Benzyloxy-1,6-dihydroxy-3-hexanone ethylene dithioacetal* (**21**). The reduction of **19** was realized as described for **18** using with $NaBH_4$ in dimethoxyethane. The resulting diol **21** was obtained as a syrup; $[\alpha]_D^{25} = -20°$ ($c = 1.4$, $CHCl_3$).

$C_{15}H_{22}O_3S_2$ (314.473) Calc. C 57.29 H 7.05 S 20.39% Found C 57.03 H 6.47 S 20.18%

(*3R*)-*3-Benzyloxy-5-oxo-1-cyclopentene-1-carbaldehyde 5-ethylene dithioacetal* (**24**). To a solution of crude dialdehyde **19** (7 g, 22.4 mmol) in 80 ml of anh. toluene was added at 0°, 0.8 ml of a 2N solution of pyrrolidine acetate in benzene. After one night at 0°, the mixture was extracted with CH_2Cl_2. The org. layer was dried (Na_2SO_4) and evaporated under reduced pressure to give 6.2 g (95%) of the α,β-unsaturated aldehyde **24** which may be used without purification. – IR. (neat): 1690, 1600. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.4 ($d\times d$, *AB*, $J(4\beta) = -13$, $J(3) = 6$, 1 H, H_α–C(4)); 3.0 ($d\times d$, *AB*, $J(4\alpha) = -13$, $J(3) = 6$, 1 H, H_β–C(4)); 3.45 (*m*, 4 H, CH_2–S); 4.4 (*s*, 2 H, OCH_2–Ph); 4.7 ($t\times d$, 1 H, H–C(3)); 6.65 (*d*, 1 H, H–C(2)); 7.2 (*s*, 5 H, arom. H); 9.5 (*s*, 1 H, CHO).

(*3R*)-*3-Benzyloxy-5-oxo-1-cyclopentene-1-carbaldehyde 1-propylene-acetal 5-ethylene-dithioacetal* (**25**). To a solution of **24** (6.2 g, 21.2 mmol) in 100 ml of anh. toluene were added 15 ml of 1,3-propanediol and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred for 36 h and the water formed was removed from time to time under reduced pressure. The reaction was quenched by dilution with CH_2Cl_2 and addition of solid $NaHCO_3$. The inorg. salts were filtered off and the org. layer was washed with water, dried (Na_2SO_4) and evaporated. The resultant coloured oil was purified on silica gel column chromatography (ether/light petroleum 1:1) to give **25** which was crystallized from ether/light petroleum (1:1) (85%); m.p. 70–71°; $[\alpha]_D^{25} = +86°$ ($c = 1.12$, $CHCl_3$). – ^{1}H-NMR. (400 MHz, C_6D_6): 0.64 (br. *d*, $J(8a) = -12.5$, 1 H, H_e–C(8)); 1.88 ($qa\times t$, $J(8e) = -12.5$, $J(7a) = 12.5$, $J(7e) = 5$, 1 H, H_a–C(8)); 2.76 ($d\times d$, *AB*, $J(4\beta) = -13.5$, $J(3) = 5$, 1 H, H_α–C(4)); 2.9 (*m*, 4 H, CH_2–S); 2.96 ($d\times d$, *AB*, $J(4\alpha) = -13.5$, $J(3) = 6.5$, 1 H, H_β–C(4)); 3.52 ($2\,t\times d$, 2 H, H_a–C(7), H_a–C(7′)); 3.88 (*m*, 2 H, H_e–C(7), H_e–C(7′)); 4.24 (*AB*, 2 H, OCH_2–Ph); 4.48 ($t\times d$, $J(4\alpha) = 5$, $J(4\beta) = 6.5$, $J(2) = 2$, 1 H, H–C(3)); 5.04 (*d*, $J(2) = 0.5$, 1 H, H–C(6)); 6.59 ($d\times d$, $J(3) = 2$, $J(6) = 0.5$, 1 H, H–C(2)); 7.32 (*m*, 5 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 25.8 (C(8)); 40.5 (CH_2–S); 41.3 (CH_2–S); 53.8 (C(4)); 67.3 (C(7), C(7′)); 80.4 (C(3)); 97.3 (C(6)); 131.6 (C(2)); 146.3 (C(1)). – MS.: 350, 289, 259, 244, 243, 242, 91, 87, 77, 65.

$C_{18}H_{22}O_3S_2$ (350.506) Calc. C 61.68 H 6.32 S 18.29% Found C 61.44 H 6.28 S 18.37%

(*2R*)-*2-Benzyloxy-1,6-hexanedial* (**27**). To a solution of **12** (2.34 g, 10.5 mmol) in 120 ml of anh. $CHCl_3$ was added $Pb(OAc)_4$ (5.7 g, 13 mmol). The mixture was stirred in absence of light during 1.5 h. Then excess $Pb(OAc)_4$ was destroyed by addition of ethylene glycol and the mixture was diluted with CH_2Cl_2. The org. layer was washed successively with water, sat. $NaHCO_3$-solution and water. After drying (Na_2SO_4), the solvents were evaporated under reduce pressure to give 2.1 g (89%) of the unstable dialdehyde **27**. – IR. (neat): 1720. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.7 (*m*, 4 H, CH_2); 2.4 (*m*, 2 H, CH_2); 3.7 (*m*, 1 H, H–C(2)); 4.5 (*s*, 2 H, OCH_2–Ph); 7.3 (*s*, 5 H, arom. H); 9.5 (*m*, 2 H, CHO).

(*3R*)-*3-Benzyloxy-1-cyclopentene-1-carbaldehyde* (**28**). The dialdehyde **27** was cyclized as described for **19**. After workup and evaporation **28** was obtained as a relatively unstable yellow oil (80%). – IR. (neat): 1690. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.6–2.7 (*m*, 4 H, CH_2); 4.6 (*s*, 2 H, OCH_2–Ph); 4.8 (*m*, 1 H, H–C(3)); 6.8 (*m*, 1 H, H–C(2)); 7.3 (*s*, 5 H, arom. H).

(*3R*)-*3-Benzyloxy-1-cyclopentene-1-carbaldehyde propylene acetal* (**29**). To a solution of **28** (1.5 g, 7.42 mmol) in 100 ml of anh. toluene were added 10 ml of 1,3-propanediol and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred under reduced pressure at 30° for 4 h (TLC. AcOET/light petroleum 1:1). The reaction was quenched by dilution with CH_2Cl_2, and addition of solid $NaHCO_3$. The salts were filtered off and the org. layer washed with water, dried (Na_2SO_4) and evaporated. The oily product obtained was purified on silica gel column to give **29** as an oil (77%); $[\alpha]_D^{25} = +74°$ ($c = 1.4$, $CHCl_3$). – ^{1}H-NMR. (400 MHz, C_6D_6): 0.62 (br. *d*, 1 H, H_e–C(8)); 1.82 ($qa\times t$, 1 H, H_a–C(8)); 1.92 (*m*, $J(4\beta) = -13.5$, $J(5\beta) = 5$, $J(5\alpha) = 9$, $J(3) = 4$, 1 H, H_α–C(4)); 2.02 (*m*, $J(4\alpha) = -13.5$, $J(5\beta) = 9$, $J(5\alpha) = 4.5$, $J(3) = 7$, 1 H, H_β–C(4)); 2.46 (*m*, $J(5\beta) = -16.5$, $J(4\beta) = 9$, $J(4\alpha) = 5$, $J(2) = 2$, $J(3) = 0.5$, 1 H, H–C(5)); 2.72 (*m*, $J(5\alpha) = 16.5$, $J(4\beta) = 4.5$, $J(4\alpha) = 9$, $J(3) = 2$, $J(2) = 2$, 1 H, H_β–C(5)); 3.37 (*m*, 2 H, H_a–C(7), H_a–C(7′)); 3.82 (*m*, 2 H, H_e–C(7), H_e–C(7′)); 4.52 (*m*, $J(4\alpha) = 4$, $J(4\beta) = 7$, $J(2) = 2$, $J(5\beta) = 2$, $J(5\alpha) = 2$, 1 H, H–C(3)); 4.95 (br. *d*, $J(2) = 1$, 1 H,

H–C(6)); 6.23 (*m*, $J(6)=1$, $J(3)=2$, $J(5\alpha)=2$, $J(5\beta)=2$, 1 H, H–C(2)); 7.32 (*m*, 5 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 25.8 (C(8)); 29.5 (C(4)); 30.3 (C(5)); 67.1 (C(7), C(7')); 84.2 (C(3)); 99.4 (C(6)); 128.2 (C(2)); 1.19 (C(1)). – MS.: 260, 169, 153, 91, 87.

$C_{16}H_{20}O_3$ (260.334) Calc. C 73.81 H 7.74% Found C 73.81 H 7.71%

(3R)-*Benzyloxy-5-oxo-1-cyclopentene-1-carbaldehyde 1-propylene acetal* (**26**). To a solution of **25** (350 mg, 1 mmol) in 10 ml of anh. CH_2Cl_2 were added phenylselenic anhydride (1 mmol) and a few drops of propylene oxide. The mixture was stirred for 12 h at r.t. Solid $NaHCO_3$ was added and the mixture separated on silica gel column (ether/light petroleum 1:1). The α,β-unsaturated ketone **26** was isolated (70%) and recrystallized from ether/light petroleum; m.p. 42–43°; $[\alpha]_D^{25}=+42°$ ($c=1$, $CHCl_3$). – IR. ($CDCl_3$): 1705, 1640. – ^{1}H-NMR. (250 MHz, $CDCl_3$): 1.4 (br. *d*, $J(8a)=-13$, 1 H, H_e–C(8)); 2.15 (*qa*×*t*, $J(8e)=-12.5$, $J(7a)=12.5$, $J(7e)=5$, 1 H, H_a–C(8)); 2.43 (*d*×*d*, *AB*, $J(4\beta)=-18.5$, $J(3)=2$, 1 H, H–C(4)); 2.75 (*d*×*d*, *AB*, $J(4\alpha)=-18.5$, $J(3)=6$, 1 H, H_β–C(4)); 3.9 (2 *t*×*d*, 2 H, H_a–C(7), H_a–C(7')); 4.18 (*m*, 2 H, H_e–C(7), H_e–C(7')); 4.6 (*s*, 2 H, OCH_2–Ph); 4.7 (*m*, 1 H, H–C(3)); 5.3 (*s*, 1 H, H–C(6)); 7.32 (*s*, 5 H, arom. H); 7.72 (*d*, $J(3)=2$, 1 H, H–C(2)). – ^{13}C-NMR. ($CDCl_3$): 25.8 (C(8)); 42.8 (C(4)); 67.4 (C(7), C(7')); 71.7 (O–CH_2–Ph); 74.9 (C(3)); 94.9 (C(6)); 145.1 (C(1)); 157.7 (C(2)); 202.8 (C(5)). – MS.: 274, 198, 183, 168, 167, 91, 87, 77, 65.

$C_{16}H_{18}O_4$ (274.316) Calc. C 70.05 H 6.61% Found C 70.14 H 6.60%

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