Pergamon

Tetrahedron, Vol. 52, No. 36, pp. 11857-11866, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00677-1

Asymmetric Induction in the Coupling of 5,6-Dihydro-1,4-dithiins with Chiral Aldehydes. A New Synthetic Approach to Polyhydroxylated Compounds[¶]

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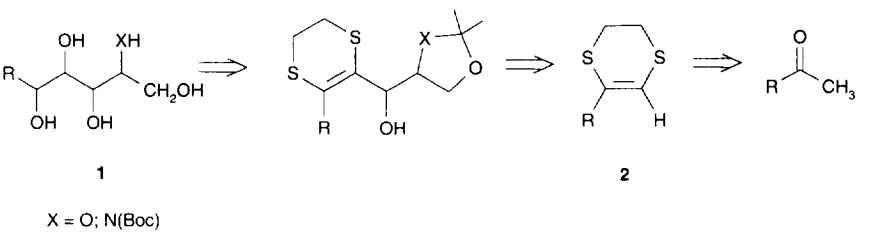
Abstract: A new strategy is designed to synthesize polyhydroxyl compounds (and/or carbohydrates) by coupling of 5,6-dihydro-1,4-dithiins - carrying a vinylic hydrogen atom - with chiral aldehydes and, in sequence, stereoselective removal of the dithiodimethylene dithiin bridge and stereospecific hydroxylation of the resulting polyhydroxyl alkenes. In this paper the study of both coupling and desulfurization steps is reported by the use of 2-phenyl-5,6-dihydro-1,4-dithiin (**5**) as a model compound in the reactions with three chiral aldehydes, **3a,b** and **4**.

Seeking new non natural polyhydroxylated compounds has become one of the major interests[1,2] of synthetic organic chemists in the last decade. This is due to the importance of such compounds considering their own biological role[1,2] as well as their possible exploitation as substrates in the preparation of more complex biologically active compounds such as macrolide antibiotics[3,4], nucleosides[5], polytoxine-like compounds[6], Lewis[x] sialyl acids[7] and many other substances containing modified carbohydrates.

Pursuing our current interest in the chemistry of 5,6-dihydro-1,4-dithiins[8], seen as *cis* or *trans* double bond mimics[9], and their coupling reactions with various electrophiles[10] we have now designed a new rather general strategy to achieve polyhydroxylated compounds, as **1,** by mean of 5,6-dihydro-1,4-dithiins, as **2,** and protected chiral aldehydes as **3a,b** and **4**. This is depicted in the retro-synthesis pathway of Scheme 1.

The results we wish to report in this paper deal with the coupling of 2-phenyl-5,6-dihydro-1,4-dithiin (**5**) (exploited as a non C-2 functionalized model building block which permitted our attention to be



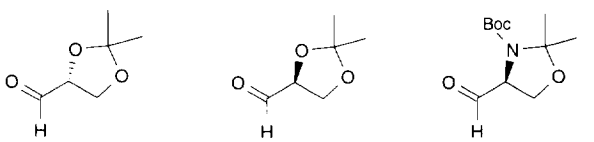
1 **2**

X = O; N(Boc)

Scheme 1. - Conversion of simple carbonyl compounds into polyhydroxylated compounds *via* 5,6-dihydro-1,4-dithiins

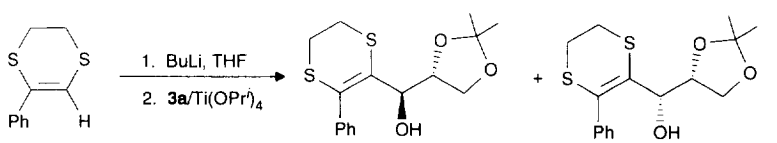
focused only on the asymmetric induction in its coupling reactions) with (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehydes (**3a,b**) and *N*(Boc)-*N,O*-protected (*S*)-serinal **4**, as well as with the diastereoselective reductive desulfurization of the resulting coupling products to prepare *E* or *Z* polyhydroxyalkenes (as **12**, **13a,b**, and **14**).

Under our typical conditions, **5** in anhydrous THF was first treated with BuLi at -78° C for a few minutes. Freshly prepared[11] protected aldehyde **3a** and $Ti(OPr^i)_4$ were then added to the resulting pale orange suspension and, after 30 min at -78° C and some hours at -20° C, the usual work-up afforded a 70:30 mixture



3a **3b** **4**

of the two possible *anti* (1'*R*,2'*R*) **6** and *syn* (1'*S*,2'*R*) **7** diastereomers with a quite satisfactory 90% overall yield. The mixture, after chromatography on silica gel, afforded the pure products: **6**-*anti*, m.p. 159-162° C (hexane/Et_2O), $[\alpha]_D^{25}$ = 7.5° (c= 2.0, $CHCl_3$) -whose structure, including absolute configuration at C-1', was determined by X-ray crystallographic analysis (Figure 2)- and **7**-*syn*, m.p. 86-87° C (hexane/CH_2Cl_2), $[\alpha]_D^{25}$ = 72.0° (c= 2.8, $CHCl_3$) (*anti* : *syn* d.e. = 40%.).



5 **6** **7**

anti (1'*R*, 2'*R*) *syn* (1'*S*, 2'*R*)

Attempts to improve the *anti* : *syn* diastereomer ratio coming from the coupling reaction were made by usyng other common coupling catalysis agents[12], although the results obtained were rather unsatisfactory as is shown in Table 1.

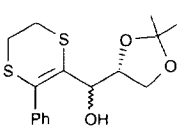
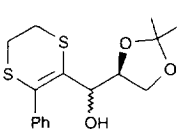
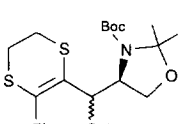
Table 1. - Coupling reactions of 5 with the protected aldehyde 3a and miscellaneous catalysts

Catalyst (20%)[a]	(*R*,*R*) : (*S*,*R*) ratio[b] **6**-*anti* : **7**-*syn*	Yield (%)
$Ti(OPr^i)_4$	70 : 30	90
$Zr(OPr^i)_4$	78 : 22	65
ZnI_2	--	85[c]
$ZnBr_2$	55 : 45	75
$MgBr_2$	47 : 53	70

[a] Moles. [b] Determined by GC/MS analysis. [c] A desulfurized compound (structure yet undetermined) was obtained.

The coupling reaction of **5** with other chiral aldehydes, namely (*S*)-2,3-*O*-isopropylideneglyceral[13] (**3b**) and *N*(Boc)-*N*,*O*-protected (*S*)-serinal[14] **4**, in the presence of $Ti(OPr^i)_4$ led to the results shown in Table 2.

Table 2. - $Ti(OPr^i)_4$ Catalyzed coupling reactions of 5 with protected aldehydes 3a,b, and 4

Protected aldehyde	Products	*anti* : *syn* ratio[a]	Yield (%)
(*R*)-glyceral (**3a**)		**6** (1'*R*,2'*R*) : **7** (1'*S*,2'*R*) 70 : 30	90
(*S*)-glyceral (**3b**)		**8** (1'*S*,2'*S*) : **9** (1'*R*,2'*S*) 70 : 30	88
N(Boc)-(*S*)-serinal (**4**)		**10** (1'*S*,2'*S*) : **11** (1'*R*,2'*S*) 40 : 60	80

[a] Determined by GC/MS analysis.

Obviously, the behaviour of the protected (*S*)-glyceral **3b** in the coupling reaction totally parallels the one of its enantiomer **3a**: *anti* (1'*S*,2'*S*) **8** [m.p. 161-163° C (hexane/Et_2O), $[\alpha]_D^{25}$ = -7.3° (c= 2.0, $CHCl_3$)] and *syn* (1'*R*,2'*S*) **9** [m.p. 86-87° C (hexane/CH_2Cl_2), $[\alpha]_D^{25}$ = -74.0° (c= 2.0, $CHCl_3$)] diastereomers were in fact obtained in a 70:30 ratio (*anti* : *syn* d.e. = 40%).

In the case of *N*(Boc)-*N*,*O*-protected (*S*)-serinal **4** the *anti* : *syn* ratio is instead inverted leading to a 60:40 *syn* (1'*R*,2'*S*) **11** [m.p. 120-121° C (hexane/CH_2Cl_2), $[\alpha]_D^{25}$ = -138.0° (c= 1.2, $CHCl_3$)] -whose structure, including absolute configuration at C-1', was determined by X-ray crystallographic analysis (Figure 3)- to *anti* (1'*S*, 2'*S*) **10** [oily, $[\alpha]_D^{25}$ = -25.5° (c= 2.0, $CHCl_3$)] diastereomer mixture (*syn* : *anti* d.e. = 20%).

This evidence can be accounted for by considering the nucleophile attack at the formyl carbon to occur according to a modified Cram transition state model, as is reported in the literature for the nucleophilic additions to formyl groups at C-4 in rigid 1,3-dioxolane rings[15]. In this view the steric environment for the coupling of **3a** should be that depicted in Figure 1*a* where the nucleophile attack leading to the *anti* diastereomer appears favoured by the formation of a six-term transition state including Ti(IV). When instead the nucleophile attack at the formyl group in **4** is concerned, the same model does not appear suitable (Figure 1*b*) to justify the prevalence of the *syn* coupling product **11**. Actually the coordination of Ti(IV) atom by the carbamic nitrogen atom and the carbonyl group in **4** could lead to the latter, although such a coordination can be expected to be scarcely effective. Therefore, the prevalence of the *syn* diastereomer **11** should be

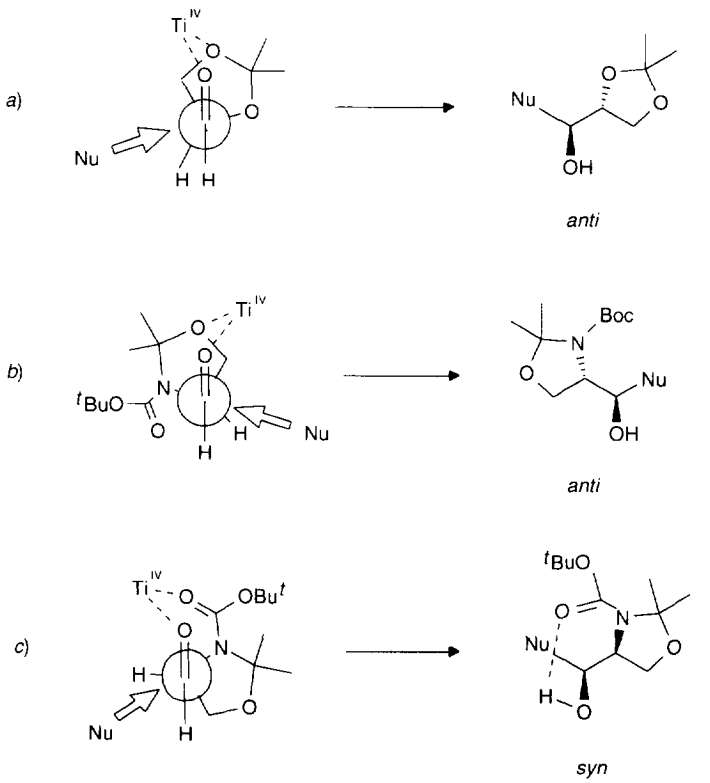


Figure 1 - Modified Cram transition state models for nucleophile attacks to the chiral aldehydes 3a and 4

likely accounted for by the preferred coordination of Ti (IV) atom with both the carbonyl oxygens present in **4**, as is shown in Figure 1*c*. In our opinion the involvement of a seven-member ring in the transition state does

not appear untenable, should one consider that the preferred conformation of the final *syn* product **11**, as shown by the X-ray analysis, is indeed stabilized by a seven-member ring forming hydrogen bond: as a matter of fact, the hydroxyl group in the *syn* diastereomer **11** forms a strong intramolecular H bond (Figure 3) with the carboxy O(3) atom (*vide infra*).

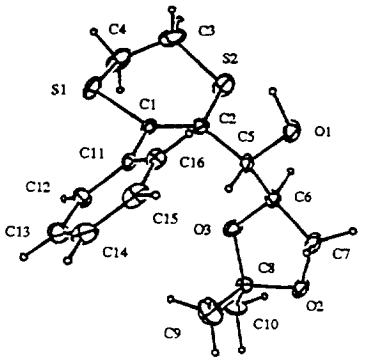


Figure 2 - Ortep view of compound 6-*anti* (absolute configuration)
Relevant geometrical parameters (Å, °): S(1)-C(1) 1.765(3), S(1)-C(4) 1.788(6), S(2)-C(2) 1.757(4), S(2)-C(3) 1.796(6), O(2)-C(7) 1.435(5), O(2)-C(8) 1.418(5), O(3)-C(6) 1.418(5), O(3)-C(8) 1.431(5), C(1)-C(2) 1.347(5), C(3)-C(4) 1.461(9), C(6)-C(7) 1.542(6), C(1)-S(1)-C(4) 105.2(2), C(2)-S(2)-C(3) 103.9(2), C(7)-O(2)-C(8) 106.2(3), C(6)-O(3)-C(8) 109.6(3), S(1)-C(1)-C(2) 126.0(3), S(2)-C(2)-C(1) 126.8(3), S(2)-C(3)-C(4) 114.5(4), S(1)-C(4)-C(3) 113.9(4), O(3)-C(6)-C(7) 104.2(3), O(2)-C(7)-C(6) 102.6(4), O(2)-C(8)-O(3) 104.6(3).

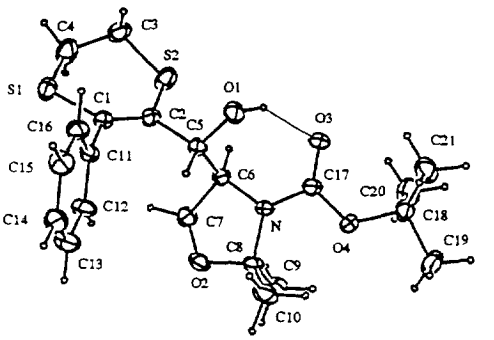
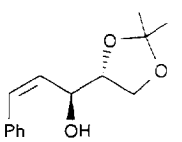


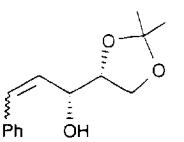
Figure 3 - Ortep view of compound 11-*syn* (absolute configuration)
Relevant geometrical parameters (Å, °): S(1)-C(1) 1.767(4), S(1)-C(4) 1.789(6), S(2)-C(2) 1.770(4), S(2)-C(3) 1.781(5), O(2)-C(7) 1.425(5), O(2)-C(8) 1.429(5), N-C(6) 1.470(5), N-C(8) 1.494(5), N-C(17) 1.342(5), C(1)-C(2) 1.334(5), C(3)-C(4) 1.491(7), C(6)-C(7) 1.530 (6), C(1)-S(1)-C(4) 106.2(2), C(2)-S(2)-C(3) 102.4(2), C(7)-O(2)-C(8) 109.0(3), C(6)-N-C(8) 111.4(3), C(6)-N-C(17) 119.6(3), C(8)-N-C(17) 126.4(3), S(1)-C(1)-C(2) 127.6(3), S(2)-C(2)-C(1) 124.5(3), S(2)-C(3)-C(4) 113.2(4), S(1)-C(4)-C(3) 114.5(4), O(2)-C(8)-N 101.1(3).

The subsequent step completing our synthetic pathway to achieve polyhydroxylated compounds consisted of the diastereoselective removal of the dithiodimethylene bridge from the dithiin moiety of the coupling products. This was done according to our previous reports[9] on sulfur removal from 2,3-disubstituted 5,6-dihydro-1,4-dithiins: the *anti* compound **6** (1'*R*, 2'*R*) was indeed treated with Ni-Raney W2 in glacial acetic acid at room temperature for 25 min and, provided that under such conditions the isopropylidene protection is totally unaffected by the acidic medium, the *anti* (1*Z*, 3*S*, 4*R*) isopropylidene protected polyhydroxyalkene **12** could be obtained in 80% yield without any traces of its *E* isomer. By the same procedure the *O*-isopropylidene protected polyhydroxyalkenes **13a** and **14** could be obtained by stereoselective desulfurization of the parent dithiins **7** and **8** respectively.

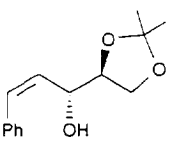
The dithiin **7** was also treated[9] with $LiAlH_4/Ti(OPr^i)_4$/quinoline (16 : 8 : 0.15) in ethanol at 50° C for 90 min and under such conditions led to the sole *syn* (1*E*,3*R*,4*R*) *O*-isopropylidene protected polyhydroxyalkene **13b** in 72% yield.



12



13a (*Z*)
13b (*E*)



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X-Ray analysis of 6-anti and 11-syn structures

The absolute configurations (Figures 2 and 3) were assigned to both compounds **6** and **11** on the basis of the Hamilton's test[16] applied to the values of the conventional R and weighed R_w indices (Table 3).

The puckering amplitude of the dithiin ring, defined according to Cremer and Pople[17], turned out to be nearly the same in both molecules [0.515(5) Å in **6** and 0.557(5) Å in **11**] although resulting from different steric situations: in the compound **6**, in fact, the dithiin ring assumes a cyclohexene-like half-chair conformation with C(3) and C(4) atoms displaced on opposite sides, by 0.430(6) Å and 0.336(6) Å respectively, out of the best plane passyng through the other intraring atoms; otherwise, the compound **11** exhibits an approximate half-boat conformation where only C(3) is significantly [0.746(5) Å] out of the plane formed by the remaining intraring atoms. In both compounds, as expected, the S-C_{sp2} bonds [average value =1.765(4) Å] are shorter than the S-C_{sp3} bonds [average value = 1.788(6) Å]. Relief from the steric hindrance between the side chains at C(1) and C(2) is achieved by enlargement of the valence angles C(11)-C(1)-C(2) and C(5)-C(2)-C(1) as well as displacement out of the double-bond plane of C(5) [0.040(4) Å] and C(11) [-0.080(4) Å] in the case of **6** and of C(11) [0.056(4) Å] in the case of **11**, respectively.

It is noteworthy that, as already mentioned above, the *syn* diastereomer **11**, coming from *N*(Boc)-*N,O*-protected (*S*)-serinal **4**, exhibits a strong intramolecular hydrogen bond between the carbonyl oxygen O(3) (Figure 3) and O(1)-H atoms [O(1)···O(3) = 2.784(4) Å, H···O(3) = 1.95(2) Å, O(1)-H···O(3) = 144(1)°]. Otherwise, the *anti* diastereomer **6** coming from the protected (*R*)-glyceral **3a** still exhibits a strong and almost linear, but intermolecular, hydrogen bond between the hydroxyl group O(1)-H and O(2) at 0.5-x, 1-y, 0.5+z, [O(1)·····O(2) = 2.978(5) Å, H·····O(2) = 1.87(7) Å, O(1)-H·····O(2) = 172(7)°]. In our opinion this can also account for the pretty high value of the melting point of the compound **6**.

All the other geometrical parameters for both compounds fall within the expected ranges.

The synthetic strategy described by this paper should represent, in our opinion, a significant approach to the synthesis of polyhydroxylated compounds. It permits, in fact, the achievement of a wide range of chiral polyhydroxylated olefins, promptly and in quite satisfactory yields accompanied by significant diastereomeric excesses. The possibility to control the stereochemistry of the double bond in the desulfurization step further increases the number of different polyhydroxylated compounds that can derive from either *syn* or *anti* hydroxyl addition on it.

Successful work is already in progress in our laboratory by replacing our model 5,6-dihydro-1,4-dithiin **5** with the one coming from commercially available methyl piruvate to accomplish the synthesis of natural and non natural carbohydrates.

EXPERIMENTAL SECTION

All chemicals were purchased (Aldrich, Fluka, Sigma) at the highest purity available and used without further purification. Solvents were dried and distilled (CH_2Cl_2 from P_2O_5, THF from $LiAlH_4$) immediately before use. Melting points were determined in open capillary tubes and are uncorrected. TLCs were run on Merck silica gel 60 F_{254} plates developed with Seebach reagent or UV visualized. Column chromatography was performed on Macherey-Nagel MN-kieselgel 60 (70-230 mesh). Optical rotations were measured on a Perkin-Elmer 141 polarimeter (1.0 dm cell) for

$CHCl_3$ solutions, unless otherwise specified. ^1H NMR Spectra were recorded on a Bruker AC 270 instrument (270 MHz) on $CDCl_3$ solutions. 400 MHz Spectra were recorded on a Bruker WH 400 instrument. Chemical shifts are given in ppm downfield from TMS internal standard; coupling constants are given in Hz. GC/MS analyses were performed on a Hewlett-Packard 5980 GS / 5971 MS instrument.

Coupling reaction of the model 5,6-dihydro-1,4-dithiin 5 with the protected aldehyde 3a. Typical procedure.

To a magnetically stirred solution of 2-phenyl-5,6-dihydro-1,4-dithiin (**5**) (0.5 g; 2.6 mmol) in anhydrous THF (5 cm^3) at -78° C and under argon (or nitrogen) atmosphere, 1.6 M BuLi in hexane (1.9 cm^3; 3.0 mmol) is added. After a few minutes freshly prepared protected aldehyde **3a** (0.4 g; 3.1 mmol) and $Ti(OPr^i)_4$ (0.2 cm^3; 0.6 mmol) dissolved in the same solvent (2 cm^3) are also added in one portion to the resulting pale orange suspension, stirring being gently continued for 30 min at -78° C and then overnight at -20° C. The reaction mixture is finally treated with 10% aq NH_4Cl (30 cm^3) and shaken with $CHCl_3$ (3x30 cm^3). The combined organic layers, washed with H_2O until neutral, dried (Na_2SO_4), and evaporated under reduced pressure, give a crude residue that by chromatography on silica gel ($CHCl_3$) affords the pure diastereomers **6**-*anti* and **7**-*syn* (0,7 g; 90% overall yield):

6-*anti*: 2-phenyl-3-[(1'*R*,2'*R*)-1'-(2',3'-*O*-isopropylidene-1',2',3'-trihydroxypropyl)]-5,6-dihydro-1,4-dithiin (0.5 g, 63% yield); m.p. 159-162° C (hexane/Et_2O); $[\alpha]_D^{25}$ = + 7.5° (c=2.0); MS: m/e 324 $[M]^+$, 223 $[M-101]^+$; ^1H NMR: δ 1.28 (*s*, 3H, CH_3); 1.32 (*s*, 3H, CH_3); 2.04 (*d*, 1H, $J_{OH,1'}$=5.3, OH); 3.12-3.36 (*m*, 4H, 2 CH_2S); 3.90 (*dd*, 1H, $J_{3'a,2'}$=6.1, $J_{3'a,3'b}$=8.6, H-3'a); 4.04 (*dd*, 1H, $J_{3'b,2'}$=5.9, $J_{3'b,3'a}$=8.6, H-3'b); 4.18 (*ddd*, 1H, $J_{2',1'}$=7.2, $J_{2',3'b}$=5.9, $J_{2',3'a}$=6.1, H-2'); 4.32 (*dd*, 1H, $J_{1',2'}$=7.2, $J_{1',OH}$=5.3, H-1'); 7.32 (*m*, 5H, aromatic H); IR (KBr): cm^{-1} 3600 (OH *str.*). (Found: C, 59.47; H, 6.12. $C_{16}H_{20}O_3S_2$ requires C, 59.23; H, 6.21%.)

7-*syn*: 2-phenyl-3-[(1'*S*,2'*R*)-1'-(2',3'-*O*-isopropylidene-1',2',3'-trihydroxypropyl)]-5,6-dihydro-1,4-dithiin (0.2 g, 27% yield); m.p. 86-87° C (hexane/CH_2Cl_2); $[\alpha]_D^{25}$ = +72° (c=2.8); MS: 324 $[M]^+$, 223 $[M-101]^+$; ^1H NMR: δ 1.18 (*s*, 3H, CH_3); 1.34 (*s*, 3H, CH_3); 2.49 (*d*, 1H, $J_{OH,1'}$= 3.7, OH); 3.18-3.35 (*m*, 4H, 2 CH_2S); 3.50 (*dd*, 1H, $J_{3'a,2'}$=6.0, $J_{3'a,3'b}$=8.0, H-3'a); 3.97 (*dd*, 1H, $J_{3'b,2'}$=6.0, $J_{3'b,3'a}$=8.0, H-3'b); 4.25-4.36 (*m*, 2H, H-3' e H-2'); 7.30-7.39 (*m*, 5H, aromatic H); IR (KBr): cm^{-1} 3615 (OH *str.*). (Found: C, 59.35; H, 6.18. $C_{16}H_{20}O_3S_2$ requires C, 59.23; H, 6.21%.)

Under the same conditions the model dithiin **5**, by reaction with the protected aldehydes **3b** and **4** respectively, afforded the following coupling products:

8-*anti* (from **3b**): 2-phenyl-3-[(1'*R*,2'*S*)-1'-(2',3'-*O*-isopropylidene-1',2',3'-trihydroxypropyl)]-5,6-dihydro-1,4-dithiin (62% yield); m.p. 161-163° C (hexane/Et_2O); $[\alpha]_D^{25}$ = -7.3° (c=2.0); ^1H NMR spectrum identical with that of **6**.

9-*syn* (from **3b**): 2-phenyl-3-[(1'*S*,2'*S*)-1'-(2',3'-*O*-isopropylidene-1',2',3'-trihydroxypropyl)]-5,6-dihydro-1,4-dithiin (26% yield); m.p. 86-87° C (hexane/CH_2Cl_2); $[\alpha]_D^{25}$ = -74.0° (c=2.0); ^1H NMR spectrum identical with that of **7**.

10-*anti* (from **4**): 2-phenyl-3-[(1'*S*,2'*S*)-1'-(2'-*N*,3'-*O*-isopropylidene-2'-*N*-Boc-amino-1',3'-dihydroxypropyl]-5,6-dihydro-1,4-dithiin (32% yield); oily; $[\alpha]_D^{25}$ = -25.5° (c=2.0); ^1H NMR: δ 1.36 (*s*, 3H, CH_3); 1.47 (*s*, 3H, CH_3); 1.48 (*s*, 9H, Bu^t); 3.20-3.40 (*m*, 4H, 2 CH_2S); 3.75 (*dd*, 1H, $J_{3'a,3'b}$=8.9, $J_{3'a,2'}$ =6.1, H-3'a); 3.93 (*dd*, 1H, $J_{3'b,3'a}$=8.9, $J_{3'b,2'}$ =7.4, H-3'b); 3.98-4.10 (*m*, 1H, H-2'); 4.15(*br s*, 1H, OH); 4.45 (*d*, 1H, $J_{1',2'}$=6.5, H-1'); 7.15-7.33 (*m*, 5H, aromatic H). (Found: C, 59.62; H, 6.86; N, 3.27. $C_{21}H_{29}O_4NS_2$ requires C, 59.54; H, 6.90; N, 3.31%.)

11-*syn* (from **4**): 2-phenyl-3-[(1'*R*,2'*S*)-1'-(2'-*N*,3'-*O*-isopropylidene-2'-*N*-Boc-amino-1',3'-dihydroxypropyl]-5,6-dihydro-1,4-dithiin (48% yield); m.p. 120-121° C (hexane/CH_2Cl_2); $[\alpha]_D^{25}$ = -138.0° (c=1.2); ^1H NMR: δ 1.25 (*s*, 3H, CH_3); 1.43 (*s*, 3H, CH_3); 1.46 (*s*, 9H, Bu^t); 3.15-3.42 (*m*, 4H, 2 CH_2S); 3.90 (*m*, 2H, H-3'a e H-3'b); 4.32 (*m*, 1H, H-2'); 4.45 (*d*, 1H, $J_{1',2'}$=7.6, H-1'); 5.18 (*br s*, 1H, OH); 7.28-7.42 (*m*, 5H, aromatic H). (Found: C, 59.65; H, 6.87; N, 3.34. $C_{21}H_{29}O_4NS_2$ requires C, 59.54; H, 6.90; N, 3.31%.)

Desulfurization of the coupling product 6 with Ni-Raney W2 in acetic acid. Typical procedure.

To a magnetically stirred suspension of Ni-Raney W2 (1.0 g; wet) in glacial acetic acid (2 cm^3) at room temperature the coupling product **6** (0.1 g; 0.3 mmol) dissolved in the same solvent (1 cm^3) is added in one portion. The suspension is stirred for 25 min and then filtered, the solid material being washed with H_2O (30 cm^3) and $CHCl_3$ (4x10 cm^3). The filtrate is treated with saturated aq Na_2CO_3 (30 cm^3), washed with H_2O until neutral, dried (Na_2SO_4), and evaporated under reduced pressure to give a crude product that by chromatography on silica gel (hexane/Et_2O 1:1) affords unreacted starting product **6** (20 mg; 0.06 mmol) and *Z* alkene **12**-*anti*, (1*Z*,3*S*,4*R*)-1-phenyl-4,5-*O*-isopropylidene-3,4,5-trihydroxypent-1-ene (0.07 g; 80% yield); oily; $[\alpha]_D^{25}$ = +32.5° (c=2.5); MS: m/e 234 $[M]^+$; ^1H NMR (400 MHz): δ 1.36 (*s*, 3H, CH_3); 1.43 (*s*, 3H, CH_3); 2.18 (*br s*, 1H, OH); 3.98 (*dd*, 1H, $J_{5a,4}$ =6.5, $J_{5a,5b}$ =8.2, H-5a); 4.08 (*dd*, 1H, $J_{5b,4}$ =6.5, $J_{5b,5a}$ =8.2, H-5b); 4.21 (*ddd*, 1H, $J_{4,5b}$ =6.5, $J_{4,5a}$ =6.5, $J_{4,3}$ =4.5, H-4); 4.75 (*dd*, 1H, $J_{3,4}$ =4.5, $J_{3,2}$ =9.3, H-3); 5.62 (*dd*, 1H, $J_{2,3}$ =9.3, $J_{2,1}$ =11.7, H-2); 6.73 (*d*, 1H, $J_{1,2}$ =11.7, H-1); 7.28-7.40 (*m*, 5H, aromatic H). (Found: C,71.89; H, 7.70. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.)

Under the same conditions the following protected polyhydroxy alkenes were obtained from their parent coupling products **7** and **8**, respectively:

13a-*syn* (from **7**-*syn*): (1*Z*,3*R*,4*R*)-1-phenyl-4,5-*O*-isopropylidene-3,4,5-trihydroxypent-1-ene (82% yield); oily; $[\alpha]_D^{25}$ = + 6.0° (c=1.7); MS: m/e 234 $[M]^+$; ^1H NMR: δ 1.36 (*s*, 3H, CH_3); 1.42 (*s*, 3H, CH_3); 3.70 (*dd*, 1H, $J_{5a,5b}$ =9.0, $J_{5a,4}$ =6.1, H-5a); 3.98 (*dd*, 1H, $J_{5b,5a}$ =9.0, $J_{5b,4}$ =6.3, H-5b); 4.13 (*ddd*, 1H, $J_{4,5a}$ =6.1, $J_{4,5b}$ =6.3, $J_{4,3}$ = 5.9, H-4); 4.48 (*dd*, 1H, $J_{3,4}$ =5.9, $J_{3,2}$ =9.4, H-3); 5.68 (*dd*, 1H, $J_{2,3}$ =9.4, $J_{2,1}$ =11.5, H-2); 6.74 (*d*, 1H, $J_{1,2}$ =11.5, H-1); 7.29-7.43 (*m*, 5H, aromatic H). (Found: C,71.68; H, 7.77. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.)

14-*anti* (from **8**-*anti*): (1*Z*,3*R*,4*S*)-1-phenyl-4,5-*O*-isopropylidene-3,4,5-trihydroxypent-1-ene (85% yield); oily; $[\alpha]_D^{25}$ = -31.7° (c=1.5); MS: m/e 234 $[M]^+$; ^1H NMR spectrum identical with that of **12**.

Cross-over desulfurization of the coupling product 7 with $LiAlH_4$/$Ti(OPr^i)_4$.

To a magnetically stirred suspension of $Ti(OPr^i)_4$ (5 cm^3; 1.7 mmol) in anhydrous THF (5 cm^3), at room temperature and under dry argon atmosphere, a suspension of $LiAlH_4$ (0.13 g; 3.4 mmol) in the same solvent (5 cm^3) is added dropwise. After 30 min stirring, a solution of the coupling product **7** (70 mg; 0.22 mmol) and quinoline ($3.7x10^{-3}$ cm^3; $3.2x10^{-2}$ mmol) in the same solvent (1 cm^3) is added dropwise to the suspension at 50° C. After 90 min (GC/MS monitoring) the reaction mixture is treated with water until neutral, dried (Na_2SO_4), and evaporated under reduced pressure to give a crude product that by chromatography on silica gel (hexane:Et_2O 9:1) affords unreacted starting product **7** (7.0 mg; 0.02 mmol) and *E*-alkene **13b**-*syn*, (1*E*,3*R*,4*R*)-1-phenyl-4,5-*O*-isopropylidene-3,4,5-trihydroxypent-1-ene (40 mg; 72% yield); oily; $[\alpha]_D^{25}$ = +46° (c=4.9, acetone); MS: m/e 234 $[M]^+$; ^1H NMR (400 MHz): δ 1.38 (*s*, 3H, CH_3); 1.48 (*s*, 3H, CH_3); 2.42 (*br s*, 1H, OH); 3.83 (*dd*, 1H, $J_{5a,4}$ =6.1, $J_{5a,5b}$ =8.4, H-5a); 4.01 (*dd*, 1H, $J_{5b,4}$ =5.6, $J_{5b,5a}$ =8.4, H-5b); 4.13 (*m*, 1H, H-4); 4.21 (*br t*, 1H, $J_{3,4}$ =6.4, $J_{3,2}$ =6.8, H-3); 6.13 (*dd*, 1H, $J_{2,3}$ =6.8, $J_{2,1}$ =16.0, H-2); 6.70 (*d*, 1H, $J_{1,2}$ =16.0, H-1); 7.28-7.40 (*m*, 5H, aromatic H). (Found: C,71.91; H, 7.77. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.)

X-Ray analysis of compounds 6-anti and 11-syn.

Crystal data and relevant details of the structure determinations for the compounds **6** and **11** are presented in Table 3. Both compounds were recrystallized from hexane. X-Ray data were collected at room temperature on Enraf-Nonius CAD4-F automatic diffractometer on line with a Micro Vax Digital computer usyng the ω/θ scan mode. Unit cell

parameters were achieved by least-squares fitting of the setting values of 25 strong reflections in the θ range 27° ≤ θ ≤ 30°. Three monitoring reflections, taken every 500, showed insignificant intensity fluctuations in the case of both **6** and **11**. Intensities were corrected for Lorenz and polarization factors whereas absorptions were neglected.

Both structures were resolved by direct methods usyng MULTAN 82 programs[18]. The refinement of positional and anisotropic thermal parameters for non-hydrogen atoms performed by full-matrix (on *F*) least-squares cycles.

Table 3. - Main crystallographic data for compounds 6 and 11

	6-*anti*	**11**-*syn*
Crystal size/mm	0.15x0.15x0.30	0.20x0.20x0.40
Formula	$C_{16}H_{20}O_3S_2$	$C_{21}H_{29}NO_4S_2$
Fw	324.5	423.6
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a /Å	10.325(2)	11.904(3)
b /Å	11.247(3)	13.465(2)
c /Å	13.816(3)	13.934(3)
V /Å^3	1604(1)	2233(1)
Z	4	4
D_c/g cm^{-3}	1.34	1.26
λ (Cu-Kα) /Å	1.54056	1.54056
θ_{max} (°)	75	75
Absorption coefficient (μ), cm^{-1}	30.2	23.2
No. of indep. refl.	1917	2625
No. of refl. above 3σ(I)	1702	2326
No. of refined parameters	190	253
Goodness of fit	1.490	1.022
R	0.049	0.047
R_w	0.063	0.055
R (inverted structure)	0.059	0.054
R_w (inverted structure)	0.073	0.062

H-atoms were generated at their expected positions by taking into account the indications of the difference Fourier map for methyl and hydroxyl groups. All the H-atoms were included, but unrefined, in the last refinement cycles with the isotropic thermal parameter slightly larger than the B_{eq} of the carrier atoms. The refined parameters for both compounds **6** and **11** included an overall scale factor and positional and anisotropic thermal parameters of the non-hydrogen atoms. The weighing scheme was $w^{-1} = [\sigma^2(F_o) + (0.02\,F_o)^2 + q\,]$ where σ is derived from counting statistics and $q = 2$ for **6** and $q = 1$ for **11**, respectively. For both compounds the absolute value of the highest positive or negative peak in the final difference Fourier maps was not larger than 0.4 e Å^{-3}. Neutral atomic scattering factors and anomalous dispersion corrections were taken from literature[19]. All the crystallographic calculations were performed by usyng the E.-N. (SDP) programs set[20].

Lists of structure factors and final atomic parameters, and complete sets of bond lenghts and angles for both compounds **6** and **11** as well, have been deposited at the Dipartimento di Chimica, Università di Napoli Federico II and are available on request from F. G.

ACKNOWLEDGEMENTS

Financial support from National Research Council (CNR) to R.C. is gratefully acknowledged. ^{1}H NMR Spectra and X-ray analyses were performed at Centro Interdipartimentale di Metodologie Chimico-fisiche, Università di Napoli Federico II. The skillfull participation of the student Ornella Giordano in this work is also acknowledged.

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(*Received in UK* 10 *June* 1996; *revised* 17 *July* 1996; *accepted* 18 *July* 1996)