Controlled diastereoselection in 2-lithio-1,3-dithiane additions onto α-substituted γ-lactols. Model studies toward bryostatins from (*R*)-pantolactone

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Homochiral α-substituted γ-lactols **3** and **4** derived from (*R*)-pantolactone **1** were used in 2-lithio-1,3-dithiane additions to afford very high controls in diastereoselectivities arising from 1,2-asymmetric inductions. Thus non-chelation controlled nucleophilic addition on **3** gave the *anti* diastereomer **5** as the major product (92% de), while the chelation controlled addition on **4** furnished the *syn* diastereomer **7** (96% de) as the almost exclusive product. The stereochemical outcomes of these reactions were proven unambiguously by locking the conformation of the *syn*- and *anti*-triol adducts **7** and **8** through their respective acetonides and by nuclear Overhauser enhancement measurements. The lack of 1,3-dioxolane formation in the case of the *anti*-triol **8** was taken as a further confirmation of the absolute configuration at the newly created stereocenter.

Key words: byrostatin, pantolactone, α-hydroxylactol, dithiane.

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Les γ-lactols homochirals **3** et **4** α-substitués dérivés de la (*R*)-pantolactone **1** ont été utilisés dans des réactions d'additions avec le carbanion lithié du 1,3-dithiane pour fournir un très haut contrôle diastéréosélectif provenant d'une induction asymétrique-1,2. Le stéréocontrôle de l'addition nucléophilique sur **3** en l'absence de phénomène de chélatation a donné le diastéréomère *anti* **5** comme produit majeur tandis que la chélatation comme moyen de stéréocontrôle de l'addition nucléophilique sur **4** a conduit presque exclusivement au diastéréomère *syn* **7** comme produit final. Les résultats stéréochimiques de ces réactions ont été prouvés de façon non-ambigüe en fixant la conformation des adduits *syn*- et *anti*-triol **7** et **8** par la formation de leurs dérivés acétals respectifs et par des mesures d'effets nOe. L'absence de formation de 1,3-dioxolane dans le cas du triol-*anti* **8** a été considérée comme preuve supplémentaire de la configuration absolue au nouveau centre stéréogénique formé.

Mots clés : byrostatine, pantolactone, α-hydroxylactol, dithiane.

Introduction

During synthetic endeavors (1–3) toward the construction of the antineoplastic macrolides bryostatins (4), chiral fragments containing quaternary *gem*-dimethyl carbon centers were required. Within the chiral pool, (*R*)-pantolactone **1** was sought as a useful chiral template. As such, **1** has scarcely been utilized for the enantiomeric synthesis of complex natural products (5, 6). On the other hand, **1** and its (*S*)-enantiomer (7) have received increased interest as chiral auxiliaries in asymmetric Diels–Alder cycloadditions (7, 8) and in diastereoselective ketene protonations (9).

Although there have been numerous examples of 1,2-induction in acyclic stereoselections (10), examples of similar or remote inductions in γ- or δ-lactols have received limited attention (11). We wish to describe herein the results obtained with 2-lithio-1,3-dithiane additions onto α-substituted γ-lactols. The effects of 1,2-chelation and non-chelation on the diastereoselectivities will be evaluated. The above findings should provide important clues for the choice of (*R*)-pantolactone derived chiral templates.

Results and discussion

2-Lithio-1,3-dithiane additions onto 3 and 4

To evaluate the extent of the asymmetric induction onto homochiral α-substituted γ-lactols, we required derivatives **3** and **4**. The silyl ether protecting group was chosen because it has been clearly established as a non-chelating group in nucleophilic addition assisted by Lewis acid (12). Thus, we anticipated good *syn*/*anti* complementary diastereoselection upon addition of 2-lithio-1,3-dithiane on **3** and **4** since the α-hydroxylactol derivative **4**, as opposed to **3**, should allow strong 1,2-chelation. First, protection of the hydroxyl group of (*R*)-pantolactone **1** as its *tert*-butyldimethylsilyl ether in the usual manner (TBDMSi-Cl, CH_2Cl_2, DMAP) furnished the crystalline lactone **2** in 95% yield. Reduction of the lactone with diisobutylaluminum hydride (DIBAH, THF, −78°C) afforded the lactol **3** (87%) as an anomeric mixture (2.3:1). When the above reduction was attempted in toluene, over-reduction occurred to a large extent. Attempts to reduce the α-hydroxylactone **1** to the γ-lactol **4** under a similar set of conditions (DIBAH/THF or toluene) inevitably gave the triol as the major product. Reduction with slightly acidic (H_2SO_4) sodium borohydride (13) also gave the triol as the major product. Finally, controlled reduction to the lactol **4** was achieved using borane–THF complex (83%) (14) (Scheme 1).

Metalation of 1,3-dithiane according to Seebach and Corey (15) (*n*-BuLi, THF, −20°C, 2 h) and subsequent addition of the resulting 2-lithio-1,3-dithiane onto **3** afforded a mixture of *anti* and *syn* adducts **5** and **6** with very high diastereoselectivity in favour of the predicted *anti* diastereomer **5** (73% yield) (Scheme 2). Due to the complexity of the ^{1}H NMR spectrum of the crude reaction mixture, the ratio of **5** to **6** was assessed from the ^{1}H NMR spectra of the unprotected triols **7** and **8** obtained by acidic methanolysis of the crude mixture (MeOH, TsOH, ~quant.). The relative integration for the dithianyl protons (identified as H1′) at 4.04 ppm ($J_{1',1}$ = 8.8 Hz) for the *syn* diastereomer **7** and at 4.55 ppm ($J_{1',1}$ = 2.7 Hz) for the *anti* and major diastereomer **8** indicated an *anti* to *syn* (**5**,**8**:**6**,**7**) ratio (*vide infra*) of 96:4 (92% de). The same ratio was obtained from the integrations of the chemical shifts of the H2 protons at 3.79 ppm ($J_{1,2}$ ~ 0 Hz) for **7** and at 3.58 ppm ($J_{1,2}$ = 8.4 Hz) for **8**. The small coupling constant (~0 Hz) between H1 and H2 in **7** (*syn*) and the larger one (8.4 Hz) for the same protons in **8** (*anti*) was diagnostic of the absolute stereochemistries of the diastereomers based upon previous empirical rules with aldol adducts (16). For instance, when seen as a Newman projection,

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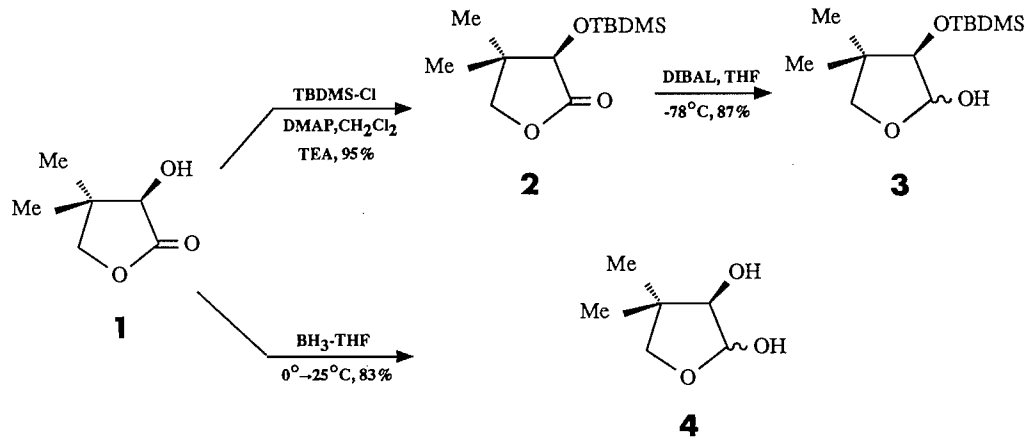
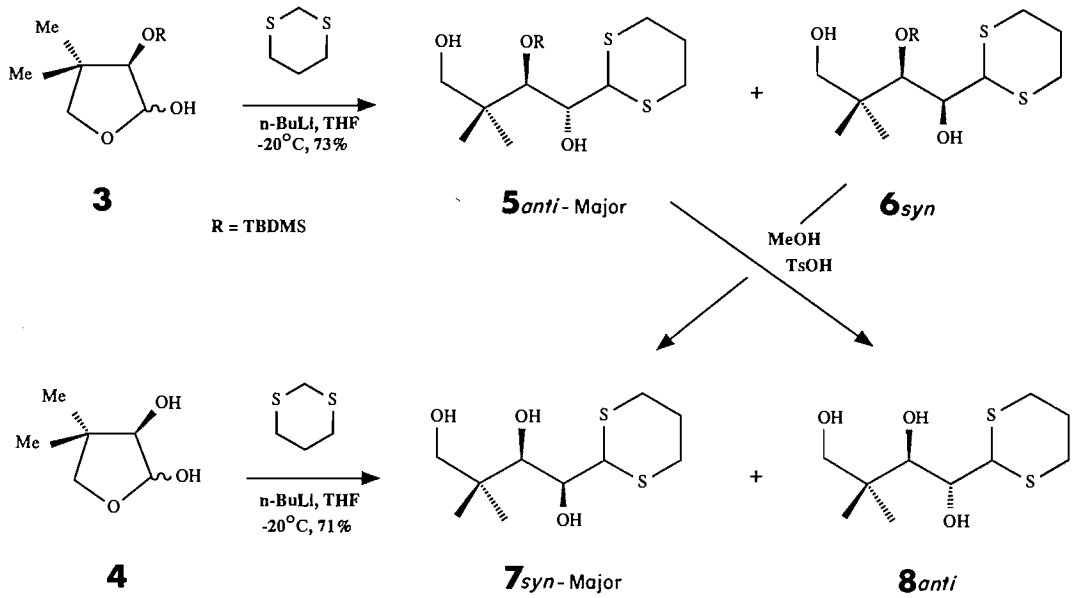


SCHEME 1



SCHEME 2

the conformer **7**-*A* should be preferred over conformer **7**-*B* because of a dominant unfavourable interaction between the dithiane residues (Di) and the neopentyl group (R), thus bringing the H1 and H2 protons into a *gauche* relationship (<~60°, $J_{1,2} \sim 0$ Hz). Likewise the conformer **8**-*A* should be favoured over **8**-*B* for similar reasons, thus bringing the H1 and H2 protons into an *anti* relationship (<~180°, $J_{1,2} = 8.4$ Hz). A third rotamer for each of the above Newman projections was not accounted for, since they would be equivalent to the unfavourable rotamers **7**-*B* and **8**-*B* with the dithianyl and neopentyl groups in *gauche* relationships (Fig. 1).

When the above 2-lithio-1,3-dithiane addition was effected onto the unprotected α-hydroxylactol **4**, a high stereocontrol for the reversed diastereofacial selectivity was achieved based on α-chelation (1,2-induction) (Scheme 2). Indeed, the *syn* diastereomer **7** was obtained as the major product (71%) after silica gel chromatography, together with a small amount of the *anti* diastereomer **8**. The ratio of *syn*-**7** to *anti*-**8** was also determined from the ^{1}H NMR spectrum of the crude reaction mixture, which indicated a ratio of *syn*/*anti* of 98:2 (96% de) (Table 1).

Determination of the absolute stereochemistries of 7 and 8

The coupling constants between the protons at the two

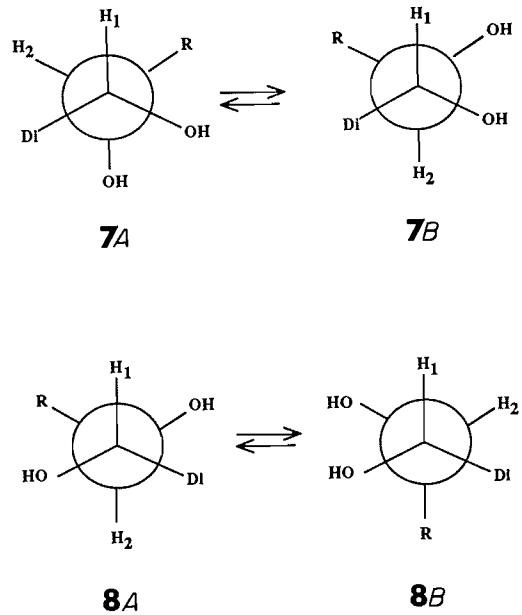
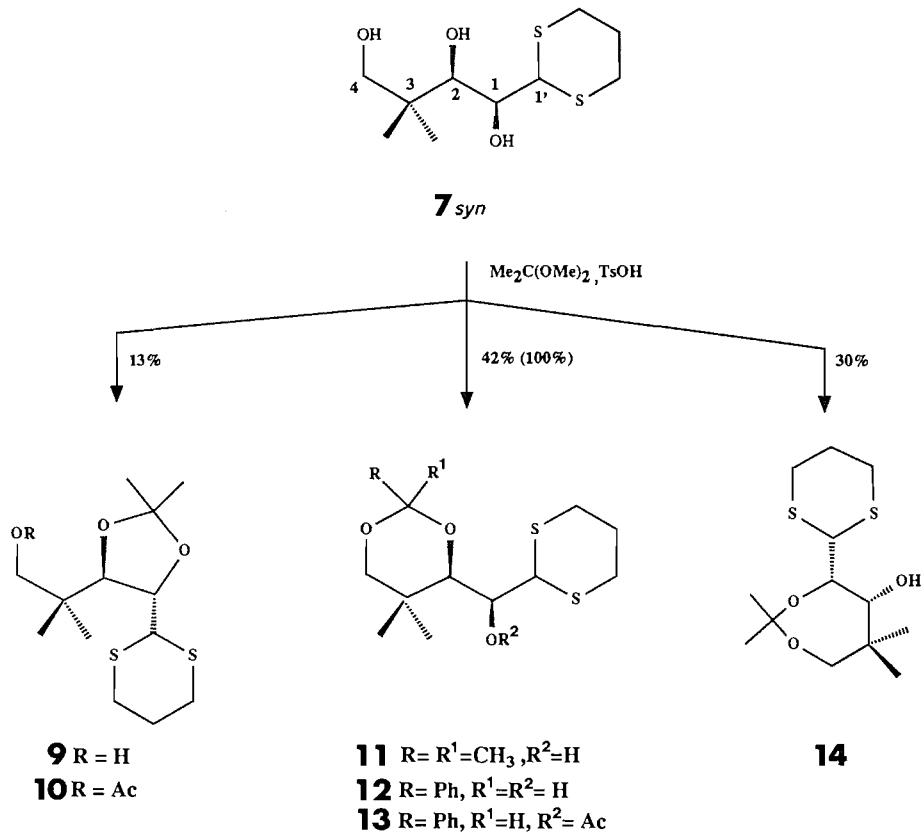


FIG. 1



SCHEME 3

TABLE 1. Results of the addition of 2-lithio-1,3-dithiane onto **3** and **4**

			δ ppm (Hz)[a]		
γ-Lactol	Yields	*anti*/*syn*	*H1'*	H1 ($J_{1',1}$)	H2 ($J_{1',2}$)
3	**5(8)** (73%)	96 : 4	4.55[b]	3.93 (2.7)	3.58 (8.4)
4	**7** (71%)	2 : 98	4.04	3.93 (8.8)	3.79 (~0)

[a]Taken at 300 MHz in $CDCl_3$.
[b]For free *anti*-triol **8**.

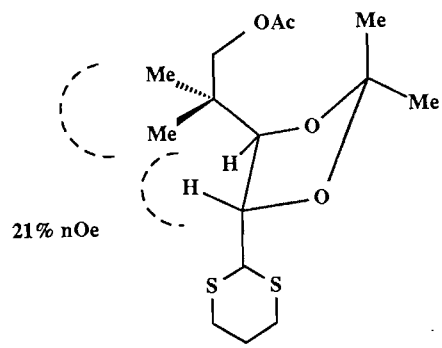


FIG. 2

stereocenters did not allow unambiguous determination of the absolute chirality at the newly created stereogenic center. Therefore, to obtain confirmation of the diastereofacial selectivities, a series of transformations was initiated in order to lock the conformation of the acyclic adducts. To achieve this goal, we elected to tether the C-1 and C-2 hydroxyl groups through formation of their respective 1,3-dioxolanes, following Gerlach's strategy (17). It was expected that proton nuclear Overhauser enhancement (nOe) studies would provide definitive establishment of the C-1 chirality.

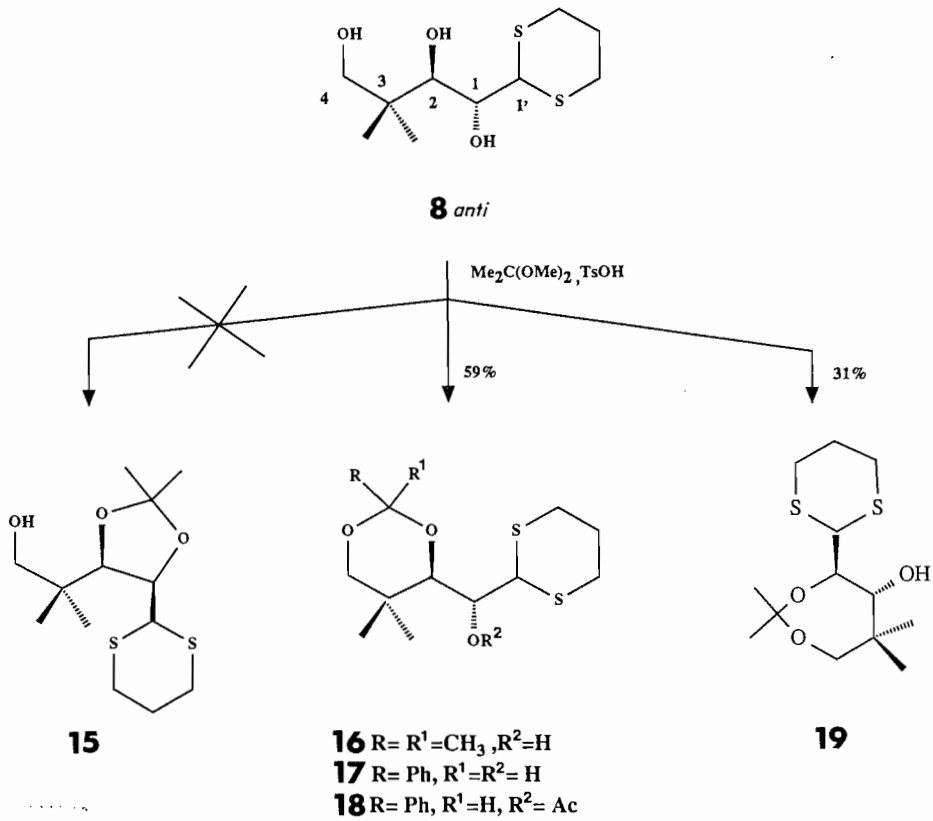
Thus, the anticipated *syn* adduct **7** was first subjected to standard acetonation conditions (2,2-dimethoxypropane, TsOH, benzene, 25°C, 18 h). An unexpected mixture of acetonides was obtained. Further studies revealed that three regioisomeric acetonides **9**, **11**, and **14**, which could be separated by silica gel chromatography, were produced in 13%, 42%, and 30% yields respectively (Scheme 3). Equilibration to the expected thermodynamic 1,3-dioxolane **9** was apparently slow under the above experimental conditions. However, later experimentation demonstrated that this equilibration was significantly faster when acetone and TsOH alone were used. In this case, exclusive formation of **9** occurred in only 3 h at room temperature (Scheme 3). The regioselectivity of the 1,3-dioxolane **9** was confirmed by acetylation of the remaining primary hydroxyl group (Ac_2O, pyridine, 92%). This resulted in an expected downfield shift (~0.5 ppm) of the diastereotopic C-4 methylene protons of **10** (3.97 and 3.86 ppm) relative to those of **9** (3.47 and 3.42 ppm). ^{1}H NMR nOe experiments demonstrated that, for the acetylated 1,3-dioxolane **10**, there was a 21% intensity enhancement between the H-1 proton (dd at 4.14 ppm) and the *gem*-dimethyl protons (2 s at 0.96 and 0.99 ppm). This observed nOe is only consistent with the proposed (1*S*,2*R*)-1,2-*syn* stereochemistry. No nOe should result in the *anti* configuration (Fig. 2).

The identity of the 1,3-dioxane acetonide **11** was determined by comparing its ^{1}H NMR spectral data to those of its related benzylidene acetal **12**. The pertinent ^{1}H NMR data are given in

TABLE 2. Selected chemical shifts (ppm) and coupling constants (Hz) for the acetals

Parent triol	Acetal	H1′[a]	H1	H2
syn-**7**	**9**	4.12 ($J_{1',1}$ 4.6)	4.11 (4.6, ~0)	4.12 ($J_{1,2}$ ~0)
	11	4.12 ($J_{1',1}$ 6.6)	3.80 (6.6, ~0)	3.93 ($J_{1,2}$ ~0)
	12	4.23 ($J_{1',1}$ 6.6)	3.90 (6.6, ~0)	3.95 ($J_{1,2}$ ~0)
	14	4.38 ($J_{1',1}$ 10.2)	3.98 (10.2, ~0)	3.55 ($J_{1,2}$ ~0)
anti-**8**	**16**	4.52 ($J_{1',1}$ 1.9)	3.82 (1.9, 8.9)	3.70 ($J_{1,2}$ 8.9)
	17	4.59 ($J_{1',1}$ 1.8)	3.96 (1.8, 9.0)	3.74 ($J_{1,2}$ 9.0)
	19	4.45 ($J_{1',1}$ 2.7)	3.97 (2.7, 9.2)	3.35 ($J_{1,2}$ 9.2)[b]

[a]H1′ refers to the 2-dithianyl proton.
[b]Observed $J_{2,OH}$ = 5.6 Hz.

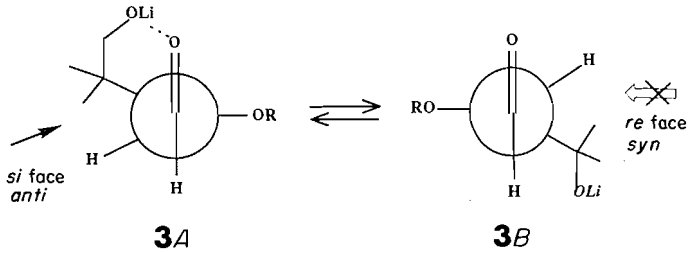


SCHEME 4

Table 2. The six-membered benzylidene acetal **12** formed between the C-2 and C-4 hydroxyl groups of the *syn*-triol **7** was the sole product obtained upon *trans*-acetalization of **7** with benzaldehydedimethylacetal (TsOH, benzene, 1 h, 25°C, 87%). The structure of **12** was further confirmed by acetylation of the remaining secondary C-2 hydroxyl group (Ac_2O, DMAP, pyridine, 86%).

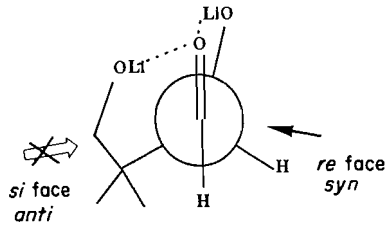
When the expected *anti*-triol **8** was exposed to the same acetonide-forming conditions described above for the *syn*-triol **7** (2,2-dimethoxypropane, TsOH, 18 h, 90%), only two products were obtained in a ratio of 2:1 (Scheme 4). They were assigned structures **16** (59%) and **19** (31%) following similar arguments and derivatization (Ac_2O, pyridine) to those described above. No 1,3-dioxolane product corresponding to **15** was obtained. The only valid explanation for the lack of formation of the five-membered acetonide **15** is that it would require an unfavourable *cis* orientation of both the *gem*-dimethyl and the 1,3-dithiane substituents. Inspection of Dreiding models illustrates that this situation would be extremely sterically demanding, hence this product was not formed. This offers further evidence for the absolute stereochemistry at C-1.

Again, the structure of the 1,3-dioxane acetonide **16** was confirmed by comparison of its coupling patterns and chemical shifts to the analogous six-membered benzylidene acetal **17** ($PhCH(OMe)_2$, TsOH, benzene, 84%). Table 2 gives the relevant ^1H NMR data. Acetylation of the benzylidene acetal **17**



3A 3B

FIG. 3



4

FIG. 4

(Ac_2O, DMAP, pyridine, 74%), as described above for **12**, demonstrated that the secondary C-1 hydroxyl group was, as expected, free.

Rationale for the observed diastereoselection

Felkin–Anh modification (18) of the Cram model (19) can provide a satisfactory explanation for the observed diastereoselection in the non-chelated situation with **3**. Indeed, as shown by the Newman projections (Fig. 3), conformer **3**-*A* of the protected γ-lactol **3** should be favoured over conformer **3**-*B* for the nucleophilic attack on the *si* face of the carbonyl following the Bürgi–Dunitz (20) trajectory. The *re*-face attack on conformer **3**-*B* is hindered by the neo-pentyl function. If one would consider the bulky neopentyl group as the one perpendicular to the carbonyl group, the reversed diastereoselection would have been obtained. It is also conceivable that the high diastereoselection obtained through conformer **3**-*A* might have been assisted by an added interplay of 1,4-chelation with the neopentylic alkoxide. The above results indicate that the more polar silyloxy protecting group might override the bulkier neopentyl group in its perpendicular arrangement to the carbonyl group in order to maximize electronic effect (σ*-orbital energies).

This situation may be contrasted to the one obtained from the unprotected γ-lactol **4** in which strong 1,2-chelation (and possibly added 1,4-chelation) surely favours *re*-face attack to provide the *syn*-triol adduct **7** as the almost exclusive diastereomer formed (Fig. 4).

In conclusion, good yields and a high degree of diastereoselection have been obtained in 2-lithio-1,3-dithiane additions onto both α-protected and α-unprotected γ-lactols. The absolute stereochemistry of the diastereomers has been unequivocally established using nOe measurements on locked conformers using acetal formations. These model studies are being used for the construction of bryostatin fragments (2). Moreover, it is also of interest to mention that there are only limited examples of diastereoselections in α-substituted γ-lactols. An interplay of 1,2- and possibly 1,4-chelation has been invoked to explain the stereochemical outcome of the nucleophilic additions observed during this study. Further work is in progress to delineate the above factors.

Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 or a Varian Gemini 200 spectrometer at 300 and 200 MHz respectively for protons and at 75.4 and 50.3 MHz respectively for carbons. The proton chemical shifts (δ) are given relative to internal Me_4Si (δ = 0) for $CDCl_3$ solutions. The carbon chemical shifts are given relative to deuterochloroform at 77.0 ppm. The analyses were done as a first-order approximation. Optical rotations were measured on a Perkin Elmer 241 polarimeter and were run at room temperature (~25°C). IR spectra were taken in chloroform using a Perkin Elmer 783 spectrophotometer. Mass spectra were recorded on a VG 7070-E spectrometer for CI and EI. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. (Ont.) or M-H-W Laboratories (Phoenix, AZ). Thin-layer chromatography (TLC) was performed using silica gel 60-F254 plates and column chromatography on silica gel 60 (230–400 mesh, E. Merck No. 9385). The developed plates were sprayed or dipped with a solution of ceric sulfate (1%) and ammonium molybdate (2.5%) in 10% aqueous sulfuric acid and heated at ~150°C. Purifications by Chromatotron were performed on a Harrison Research Chromatotron model 7924 using silica gel 60-F254 rotors (1, 2, or 4 mm thickness). (*R*)-(−)-Pantolactone (Aldrich) was dried in a Dean–Stark apparatus using benzene as solvent. All solvents and reagents used were reagent grade and, when required, further purifications were accomplished following published procedures (21). Titrations of the organolithium reagents were done using diphenylacetic acid (22).

(R)-[(tert-Butyldimethylsilyl)oxy]pantolactone 2

To a solution of dry (*R*)-pantolactone (**1**) (2.00 g, 15.4 mmol) in dichloromethane (40 mL) was added triethylamine (2.69 mL, 19.3 mmol), *tert*-butyldimethylsilyl chloride (2.79 g, 18.5 mmol), and DMAP (0.39 g, 3.2 mmol). After stirring for 1 day at room temperature, the mixture was diluted with ether (100 mL) and washed with 0.2 N HCl, saturated aqueous $NaHCO_3$, and brine (50 mL of each). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The white amorphous residue was recrystallized in hexanes, yielding 3.76 g (95%) of the silyl ether **2** as white needles melting at 95.6–96.3°C; $[\alpha]_D$ +33.8° (*c* 1.0 in $CHCl_3$); IR (CH_2Cl_2) ν_{max}: 3050, 2959, 2858, 2302, 1791, 1252, 1132 cm^{-1}; ^1H NMR (300 MHz) δ: 3.97 (d, A of AB, J = 8.9 Hz, 1H, H4), 3.97 (s, 1H, H2), 3.86 (d, B of AB, J = 8.9 Hz, 1H, H4'), 1.12 (s, 3H, *gem* CH_3), 1.03 (s, 3H, *gem* CH_3), 0.91 (s, 9H, $C(CH_3)_3$), 0.18 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$); ^{13}C NMR (50.4 MHz) δ: 176.9 (C1), 76.5 (C2), 75.5 (C4), 40.7 (C3), 25.4 ($C(CH_3)_3$), 22.7, 18.8 (*gem* CH_3's), 18.0 ($SiC(CH_3)_3$), −4.8, −5.7 ($Si(CH_3)_2$); MS (EI) *m/z*: 187 (M^+−57, 20%), 143 (M^+−101, 35%). HRMS calcd. for $C_8H_{15}O_3Si$ (M^+−$C(CH_3)_3$): 187.0791; found: 187.0796.

(R)-[(tert-Butyldimethylsilyl)oxy]pantolactol 3

The silylated γ-lactone **2** (1.91 g, 7.81 mmol) was dissolved in THF (30 mL) and cooled to −78°C. Diisobutylaluminum hydride (1.0 M in THF, 10.9 mL, 10.9 mmol) was added over a 15 min period via a pressure-equalizing addition funnel. This mixture was stirred for 3 h and then quenched by addition of Glauber's salt ($Na_2SO_4 \cdot 10H_2O$, ~6 g). After warming to ambient temperature, the Glauber's salt was removed by filtration under suction. The filter cake was returned to the flask and refluxed with 50 mL of ethyl acetate (5 min), and filtered. This procedure was repeated with another 50 mL of ethyl acetate. The filtrates were combined and washed with 0.2 N HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield a white amorphous solid. Purification by silica gel flash chromatography (2:8 ether/hexanes) and recrystallization from hexanes afforded 1.67 g (87%) of the silylated γ-lactol **3** as white needles melting at 48.5–51.5°C. When different,

data for the minor anomer (2.3:1 anomeric ratio) are given in brackets; $[\alpha]_D$ −13.3° (*c* 2.0 in $CHCl_3$); IR (CH_2Cl_2) ν_{max}: 3591, 3050, 2959, 2931, 2859, 1472, 1256, 1048 cm^{-1}; ^1H NMR (300 MHz) δ: 5.12 (app t, OH coupling, 1H, H1), 5.35 (dd, *J* = 4.2, 9.8 Hz, 1H, H1), (3.82) (d, *J* = 9.8 Hz, 1H, H2), 3.76 (d, A of AB, *J* = 8.2 Hz, 1H, H4), 3.64 (d, <1 Hz, 1H, H2), 3.63 (d, B of AB, *J* = 8.2 Hz, 1H, H4′), (3.60) (s, 2H, H4), 1.03 (s, 3H, *gem* CH_3), 0.97 (s, 3H, *gem* CH_3), 0.88 (0.92) (s, 9H, $C(CH_3)_3$), 0.07, 0.05 (0.10, 0.08) (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50.4 MHz) δ: 98.0 (104.6) (C1), 79.2 (85.5) (C2), 76.3 (78.4) (C4), 42.0 (42.1) (C3), 25.6 ($C(CH_3)_3$), 25.4, 19.9 (23.6, 19.9) (gem CH_3's), 18.0 (17.9) ($SiC(CH_3)_3$), −5.4 (−4.8) ($Si(CH_3)_2$). MS (CI ether) *m/z*: 247 (M^++1, 1%), 229 ((M^++1)-18, 100%), 189 (M^+−57, 23%). Anal. calcd. for $C_{12}H_{26}O_3Si$: C 58.49, H 10.63, Si 11.40; found: C 58.45, H 10.59, Si 11.33.

(R)-(−)-Pantolactol ***4***

Over a period of 1 h, borane–tetrahydrofuran complex (1.0 M in THF) was added to (*R*)-(−)-pantolactone (**1**) (6.00 g, 46.1 mmol) in THF (100 mL) at 0°C. After stirring for 12 h at room temperature, the reaction was quenched by careful addition of water until the evolution of hydrogen had ceased. The solvent was then removed *in vacuo* to leave a colourless syrup. Several coevaporations with 60 mL of a 2% acetic acid in methanol solution were accomplished, followed by silica gel flash chromatography (7:3 ether/hexanes). This yielded the hydroxy γ-lactol **4** (5.00 g, 82%) as a colourless oil. When different, the data for the minor anomer (1.4:1 anomeric ratio) are given in brackets; $[\alpha]_D$ −2.7° (*c* 2.2 in $CHCl_3$); IR (thin film) ν_{max}: 3395, 2971, 2881, 1471, 1382, 1031 cm^{-1}; ^1H NMR (200 MHz) δ: 5.41–5.47 (5.21–5.26) (m, 1H, H1), (3.82) (d, A of AB, *J* = 8.4 Hz, 1H, H4), 3.73) (d, B of AB, *J* = 8.4 Hz, 1H, H4′), 3.66 (d, A of AB, *J* = 8.1 Hz, 1H, H4), 3.62–3.69 (m, 1H, H2), 3.45 (d, B of AB, *J* = 8.1 Hz, 1H, H4′), 2.85–2.91 (2.51–2.61) (br s, 1H, OH exchangeable), 1.06, 1.04 (1.10, 1.06) (s, 6H, *gem* CH_3's); ^{13}C NMR (50.4 MHz) δ: 97.5 (103.4) (C1), 78.2 (84.1) (C2), 77.2 (78.5) (C4), 41.5 (41.6) (C3), 25.4, 19.5 (23.7, 19.3) (*gem* CH_3's); MS (CI ether) *m/z*: 133 (M^++1, 15%), 131 (M^+−1, 8%), 115 ((M^++1)-18, 96%). Anal. calcd. for $C_6H_{12}O_3$: C 54.53, H 9.15; found: C 54.34, H 8.97.

*(1R,2R)-1,2-*anti*-3,3-Dimethyl-1-(1,3-dithian-2-yl)-2-[(*tert*-butyldimethylsilyl)oxy]-1,4-butanediol* ***5***

To 1,3-dithiane (1.26 g, 10.5 mmol, purified by vacuum sublimation) in THF (30 mL) at 20°C was added *n*BuLi (1.5 M in hexane, 7.00 mL, 10.5 mmol) and the solution was stirred for 2 h, whereupon a solution of the silylated γ-lactol **3** (1.03 g, 4.18 mmol) in THF (5 mL) was added via canula. The mixture was stirred a further 2 h and then placed in the refrigerator (−10°C) for 18 h, whereupon it was quenched by addition of 2 mL of saturated aqueous NH_4Cl and allowed to warm to room temperature. The solution was then diluted with ethyl acetate (80 mL) and extracted with 0.2 N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide a syrup. Further purification by flash chromatography (4:6 ether/hexanes) yielded 1.12 g (73%) of the diol adduct **5** as a colourless syrup; $[\alpha]_D$ −6.2° (*c* 1.8 in $CHCl_3$); ^1H NMR (300 MHz) δ: 4.30 (d, *J* = 5.9 Hz, 1H, H1′), 3.90 (dd, *J* = 5.1, 5.9 Hz, 1H, H1), 3.84 (d, *J* = 5.1 Hz, H2), 3.61 (d, A of AB, *J* = 11.3 Hz, 1H, H4), 3.35 (d, B of AB, *J* = 11.3 Hz, 1H, H4′), 2.66–2.96 (m, 4H, $CH_2(CH_2S)_2$), 2.41–3.00 (br s, 2H, OH exchangeable), 1.88–2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.04, 0.93 (s, 6H, *gem* CH_3's), 0.92 (s, 9H, $C(CH_3)_3$), 0.18, 0.11 (s, 6H, $Si(CH_3)_2$); MS (CI ether) *m/z*: 367 (M^++1, 1%), 329 (M^+−37, 83%).

*(1S,2R)-1,2-*syn*-3,3-Dimethyl-1-(1,3-dithian-2-yl)-1,2,4-butanetriol* ***7***

This material was prepared using a procedure similar to the one described above for the conversion of **3** to **5**. Thus, the 2-hydroxy γ-lactol (**4**) (0.44 g, 3.33 mmol) when treated with 2-lithio-1,3-dithiane (11.7 mmol) yielded, after purification by flash chromatography (6:4 ether/hexanes), 0.60 g (71%) of the *syn*-triol adduct **7** as a white solid melting at 63.0–64.5°C; $[\alpha]_D$ −36.4° (*c* 2.5 in $CHCl_3$); ^1H NMR (300 MHz) δ: 4.04 (d, *J* = 8.8 Hz, 1H, H1′), 3.93 (d, *J* = 8.8 Hz, 1H, H1), 3.79 (s, 1H, H2), 3.63 (d, A of AB, *J* = 11.4 Hz, 1H, H4), 3.34 (d, B of AB, *J* = 11.4 Hz, 1H, H4′), 2.71–3.00 (br s, 3H, OH exchangeable), 2.62–2.93 (m, 4H, $CH_2(CH_2S)_2$), 1.99–2.07 (m, 2H, $CH_2(CH_2S)_2$), 1.00, 0.95 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 253 (M^++1, 92%), 235 ((M^++1)-18, 73%), 149 (M^+−103, 68%), 133 (M^+−119, 64%).

*(1R,2R)-1,2-*anti*-3,3-Dimethyl-1-(1,3-dithian-2-yl)-1,2,4-butanetriol* ***8***

The silyl ether **5** (0.96 g, 2.62 mmol) was dissolved in methanol (30 mL), catalytic TsOH (~10 mg) was added, and the solution was stirred at ambient temperature for 5 h. At this point, TLC (ether) indicated the reaction to be complete and it was subsequently processed by addition of an excess of Dowex 1-X8 resin in the ^-OH form, filtration, and removal of solvent *in vacuo* to yield a resinous material. This was further purified by flash chromatography (7:3 ether/hexanes) to provide a quantitative yield (0.66 g) of the triol adduct **8** as a solid melting at 108.0–109.1°C; $[\alpha]_D$ −33.3° (*c* 2.5 in $CHCl_3$); ^1H NMR (300 MHz) δ: 4.55 (d, *J* = 2.7 Hz, 1H, H1′), 3.93 (dd, *J* = 2.7, 8.4 Hz, 1H, H1), 3.58 (d, *J* = 8.4 Hz, 1H, H2), 3.54 (d, A of AB, *J* = 11.3 Hz, 1H, H4), 3.45 (d, B of AB, *J* = 11.3 Hz, 1H, H4′), 2.86–3.01 (m, 4H, $CH_2(CH_2S)_2$), 2.52–2.79 (br, s, 3H, OH exchangeable), 1.85–2.14 (m, $CH_2(CH_2S)_2$), 1.04, 0.93 (s, 6H, *gem* CH_3's); MS (EI) *m/z*: 149 (M^+−103, 6%); MS (CI ether) *m/z*: 253 (M^++1, 24%), 235 ((M^++1)-18, 11%), 149 (M^+−103, 20%), 133 (M^+−119, 27%).

Acetonide formation on the syn*-triol* ***7***

Triol **7** (0.89 g, 3.53 mmol) was dissolved in 10 mL of a 40% 2,2-dimethoxypropane in benzene solution containing a catalytic amount of TsOH (~15 mg) and the solution was stirred at ambient temperature. After overnight contact, the reaction mixture was neutralized by the addition of triethylamine and the solvent was evaporated under vacuum. The residue was diluted in ethyl acetate (40 mL) and washed with 0.2 N HCl, saturated aqueous $NaHCO_3$, and brine (30 mL portions). Drying over Na_2SO_4 and concentration *in vacuo* afforded a colourless oil. Purification by preparative TLC (1:1 ether/hexanes) yielded three products: 0.13 g (13%) of **9**, 0.43 g (42%) of **11**, and 0.31 g (30%) of **14** (five, six-, and seven-membered ring acetonides, respectively) as colourless oils. The order of polarity in the above solvent was (R_F): **14**(0.33), **9**(0.38), **11**(0.50). Submitting triol **7** (55.6 mg, 0.221 mmol) to the acetonide-forming conditions acetone/catalytic TsOH (25°C) afforded the thermodynamic 1,3-dioxolane acetonide **9** as the exclusive product after 3 h (85%).

*(1S,2R)-1,2-*syn*-1,2-O-Isopropylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-4-butanol* ***9****:* ^1H NMR (300 MHz) δ: 4.12 (d, *J* = 4.6 Hz, 1H, H1′), 4.13 (s, 1H, H2), 4.11 (d, *J* = 4.6 Hz, 2H, H1), 3.47 (d, A of AB, *J* = 11.2 Hz, 1H, H4), 3.42 (d, B of AB, *J* = 11.2 Hz, 1H, H4′), 2.77–3.00 (m, 4H, $CH_2(CH_2S)_2$), 1.95–2.20 (br, s, 1H, OH exchangeable), 1.92–2.17 (m, 2H, $CH_2(CH_2S)_2$), 1.46, 1.40 (s, 6H, $(RO)_2C(CH_3)_3$), 0.98, 0.93 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 293 (M^++1, 53%), 2.75 ((M^++1)-18, 1%), 235 ((M^++1)-58, 58%).

*(1S,2R)-1,2-*syn*-4-Acetoxy-1,2-O-isopropylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-butane* ***10***

To the acetonide **9** (52.5 mg, 0.180 mmol) in pyridine (5.0 mL) was added acetic anhydride (1.0 mL) and the solution was stirred at room temperature for 4 h. At this point, methanol (1.0 mL) was added and allowed to react for 1 h to destroy the excess acetic anhydride. The solvent was then removed *in vacuo*. The remaining oil was dissolved in 50 mL of ethyl acetate and washed with 30 mL portions of 0.2 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Further purification by preparative TLC (2:8 ether/hexanes) afforded the acetate **10** as a colourless oil (55 mg, 92%); ^1H NMR (300 MHz) δ: 4.14 (dd, *J* = 3.2, 7.5 Hz, 1H, H1), 4.06 (d, *J* = 3.2 Hz, 1H, H2), 4.05 (d, *J* = 7.5 Hz, 1H, H1′), 3.97 (d, A of AB, *J* = 11.0 Hz, 1H, H4), 3.86 (d, B of AB, *J* = 11.0 Hz, 1H, H4′), 2.71–3.01 (m, 4H, $CH_2(CH_2S)_2$), 2.08 (s, 3H, OAc), 1.91–2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.45, 1.37 (s, 6H,

$(RO)_2C(CH_3)_2$), 0.99, 0.96 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 335 ($M^+ + 1$, 45%), 276 (($M^+ + 1$)-59, 100%).

*(1S,2R)-1,2-*syn*-2,4-O-Isopropylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-1-butanol* ***11****:* ^{1}H NMR (300 MHz) δ: 4.12 (d, *J* = 6.6 Hz, 1H, H1′), 3.93 (s, 1H, H2), 3.80 (d, *J* = 6.6 Hz, 1H, H1), 3.65 (d, A of AB, 1H, *J* = 11.4 Hz, H4), 3.27 (d, B of AB, *J* = 11.4 Hz, 1H, H4′), 2.85–3.00 (br s, 1H, OH exchangeable), 2.71–2.88 (m, 4H, $CH_2(CH_2S)_2$), 1.83–2.16 (m, 2H, $CH_2(CH_2S_2)$, 1.47, 1.42 (s, 6H, $(RO)_2C(CH_3)_2$), 1.12, 0.78 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 293 ($M^+ + 1$, 80%), 275 (($M^+ + 1$)-18, 2%), 235 (($M^+ + 1$)-58, 100%).

*(1S,2R)-1,2-*syn*-1,4-O-Isopropylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-2-butanol* ***14****:* ^{1}H NMR (300 MHz) δ: 4.38 (d, *J* = 10.2 Hz, 1H, H1′), 3.98 (d, *J* = 10.2 Hz, 1H, H1), 3.55 (s, 1H, H2), 3.66 (d, A of AB, *J* = 12.5 Hz, 1H, H4), 2.96 (d, B of AB, *J* = 12.5 Hz, 1H, H4′), 2.82–2.87 (m, 4H, $CH_2(CH_2S)_2$), 2.41–2.60 (br, s, 1H, OH exchangeable), 1.79–2.10 (m, 2H, $CH_2(CH_2S)_2$), 1.41, 1.38 (s, 6H, $(RO)_2C(CH_3)_2$), 0.99, 0.87 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 293 ($M^+ + 1$, 96%), 275 (($M^+ + 1$)-18, 6%), 235 (($M^+ + 1$)-58, 95%).

*(1S,2R)-1,2-*syn*-1,4-O-Benzylidiene,3,3-dimethyl-1-(1,3-dithian-2-yl)-1-butanol* ***12***

To the triol **7** (98.5 mg, 0.39 mmol) in benzene (10 mL) was added benzaldehyde dimethylacetal (234 μL, 1.56 mmol) and a catalytic amount of TsOH (~10 mg). After stirring for 1 h at ambient temperature, the reaction mixture was neutralized with triethylamine and the solvent removed under vacuum. The residue was diluted in ethyl acetate (40 mL) and washed successively with 0.2 N HCl, saturated aqueous $NaHCO_3$, and brine (30 mL of each), dried over Na_2SO_4, and concentrated under reduced pressure. The oil was further purified by Chromatotron chromatography (2:8 ether/hexanes), providing the benzylidene acetal **12** as a colourless oil (115 mg, 87%); ^{1}H NMR (300 MHz) δ: 7.33–7.53 (m, 5H, aromatic), 5.63 (s, 1H, CHPh), 4.23 (d, *J* = 6.6 Hz, 1H, H1′), 3.95 (s, 1H, H2), 3.90 (d, *J* = 6.6 Hz, 1H, H1), 3.73 (d, A of AB, *J* = 11.1 Hz, 1H, H4), 3.66 (d, B of AB, *J* = 11.1 Hz, 1H, H4′), 2.80–3.02 (br s, 1H, OH exchangeable), 2.74–2.91 (m, 4H, $CH_2(CH_2S)_2$), 1.84–2.15 (m, 2H, $CH_2(CH_2S)_2$), 1.25, 0.85 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 341 ($M^+ + 1$, 79%), 323 (($M^+ + 1$)-18, 4%), 235 (($M^+ + 1$)-106, 59%).

*(1S,2R)-1,2-*syn*-1-Acetoxy-2,4-O-Benzylidene-3,3-dimethyl-1-(1,3-dithian-2-yl)-butane* ***13***

The alcohol **12** (61.2 mg, 0.180 mmol) was stirred at room temperature in pyridine (5.0 mL) containing acetic anhydride (1.0 mL) and DMAP (8.2 mg, 0.067 mmol). After 5 h, the excess acetic anhydride was quenched by addition of methanol (1 mL) for 1 h and the solution was concentrated under reduced pressure. The remaining syrup was taken up in ethyl acetate (30 mL) and washed with 0.2 N HCl, saturated aqueous $NaHCO_3$, and brine (20 mL of each). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Further purification was accomplished by Chromatotron chromatography (1:9 ether/hexanes) to yield 59.3 mg (86%) of the acetate **13** as a colourless oil; ^{1}H NMR (300 MHz) δ: 7.32–7.52 (m, 5H aromatic), 5.60 (dd, *J* = 1.3, 10.1 Hz, 1H, H1), 5.48 (s, 1H, CHPh), 4.35 (d, *J* = 1.3 Hz, 1H, H1′), 3.91 (d, *J* = 10.1 Hz, 1H, H2), 3.70 (d, A of AB, *J* = 10.7 Hz, 1H, H4), 3.63 (d, B of AB, *J* = 10.7 Hz, 1H, H4′), 2.88–3.00 (m, 2H, $CH_2(CH_2S)_2$), 2.48–2.63 (m, 2H, $CH_2(CH_2S)_2$), 2.11 (s, 3H, OAc), 1.96–2.10 (m, 2H, $CH_2(CH_2S)_2$), 1.15, 0.91 (s, 6H, *gem* CH_3's).

Acetonide formation on the anti*-triol* ***8***

The acetonides on triol **8** were prepared in a manner similar to the one described above for the conversion of **7** to **9**, **11**, and **14** (40% 2,2-dimethoxypropane in benzene, 25°C, 18 h). Thus, 155 mg (0.613 mmol) of triol **8** yielded two products. They were identified as the six-membered (**16**) and seven-membered (**19**) ring acetonides (**16** less polar than **19**). The yields for **16** and **19** were 59% and 31%, respectively, and both products were obtained as colourless oils.

*(1R,2R)-1,2-*anti*-2,4-O-Isopropylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-1-butanol* ***16****:* ^{1}H NMR (300 MHz) δ: 4.52 (d, *J* = 1.9 Hz, 1H, H1′), 3.82 (dd, *J* = 1.9, 8.9 Hz, 1H, H1), 3.70 (d, *J* = 8.9 Hz, 1H, H2), 3.56 (d, A of AB, *J* = 11.6 Hz, 1H, H4), 3.20 (d, B of AB, *J* = 11.6 Hz, 1H, H4′), 2.79–3.02 (m, 4H, $CH_2(CH_2S)_2$), 1.96–2.41 (br s, 1H, OH exchangeable), 1.81–2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.39, 1.36 (s, 6H, $(RO)_2C(CH_3)_2$), 1.07, 0.92 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 293 ($M^+ + 1$, 15%), 275 (($M^+ + 1$)-18, 1%), 235 (($M^+ + 1$)-58, 52%).

*(1R,2R)-1,2-*anti*-1,4-O-Isopropylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-2-butanol* ***19****:* ^{1}H NMR (300 MHz) δ: 4.45 (d, *J* = 2.7 Hz, 1H, H1′), 3.97 (dd, *J* = 2.7, 9.2 Hz, 1H, H1), 3.56 (d, A of AB, *J* = 12.5 Hz, 1H, H4), 3.35 (dd, *J* = 5.6, 9.2 Hz, 1H, H2), 3.04 (d, B of AB, *J* = 12.5 Hz, 1H, H4′), 2.81–3.01 (m, 4H, $CH_2(CH_2S)_2$), 2.19 (d, *J* = 5.6 Hz, 1H, OH exchangeable), 1.91–2.15 (m, 2H, $CH_2(CH_2S)_2$), 1.39, 1.35 (s, 6H, $(RO)_2C(CH_3)_2$), 0.98 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 293 ($M^+ + 1$, 35%), 275 (($M^+ + 1$)-18, 3%), 235 (($M^+ + 1$)-58, 95%).

*(1R,2R)-1,2-*anti*-2,4-O-Benzylidene,3,3-dimethyl-1-(1,3-dithian-2-yl)-1-butanol* ***17***

This material was prepared and purified in the same manner as described above for the conversion of **7** to **12**. Thus, the triol **8** (81.2 mg, 0.322 mmol) yielded the benzylidene acetal **17** as a colourless oil (92 mg, 84%); ^{1}H NMR (300 MHz) δ: 7.33–7.49 (m, 5H, aromatic), 5.44 (s, 1H, CHPh), 4.59 (d, *J* = 1.8 Hz, 1H, H1′), 3.96 (dd, *J* = 1.8, 9.0 Hz, 1H, H1), 3.74 (d, *J* = 9.0 Hz, 1H, H2), 3.65 (d, A of AB, *J* = 11.3 Hz, 1H, H4), 3.60 (d, B of AB, *J* = 11.3 Hz, 1H, H4′), 2.81–2.99 (m, 4H, $CH_2(CH_2S)_2$), 1.80–2.16 (m, 2H, $CH_2(CH_2S)_2$), 1.51–1.80 (br s, 1H, OH exchangeable), 1.21, 0.97 (s, 6H, *gem* CH_3's); MS (CI ether) *m/z*: 341 ($M^+ + 1$, 37%), 323 (($M^+ + 1$)-18, 3%), 235 (($M^+ + 1$)-106, 23%).

*(1R,2R)-1,2-*anti*-1-Acetoxy-2,4-O-Benzylidene-3,3-dimethyl-1-(1,3-dithian-2-yl)-butanol* ***18***

This material was prepared and purified in the same manner as described above for the conversion of **12** to **13**. Thus, 42.0 mg (0.123 mmol) of the alcohol **17** yielded the acetate **18** as a colourless oil (34.6 mg, 74%); ^{1}H NMR (300 MHz) δ: 7.35–7.50 (m, 5H, aromatic), 5.47 (s, 1H, CHPh), 5.44 (dd, *J* = 2.2, 9.2 Hz, 1H, H1), 4.55 (d, *J* = 2.2 Hz, 1H, H1′), 3.74 (d, *J* = 9.2 Hz, 1H, H2), 3.61 (s, 2H, H4,4′), 2.76–2.98 (m, 4H, $CH_2(CH_2S)_2$), 2.14 (s, 3H, OAc), 1.85–2.12 (m, 2H, $CH_2(CH_2S)_2$), 1.18, 0.78 (s, 6H, *gem* CH_3's).

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