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DiTOX-Mediated Synthesis of 2-Bromo-4-deoxypyranoside Derivatives

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Abstract: Stereocontrolled cycloaddition of Danishefsky's diene to *syn*-2-formyl-2-methyl-1,3-dithiane 1-oxide is used as the basis for a short stereoselective synthesis of a 2-bromo-4-deoxymannose derivative.

Introduction

1,3-Dithiane 1-oxide (DiTOX) derivatives can act as combined chiral auxiliaries and asymmetric building blocks. Previously we have shown that 2-acyl substituted derivatives undergo a variety of transformations with excellent diastereoselectivities.[1] Asymmetric sulfur oxidation allows access to both diastereoisomers of the acyl dithiane unit with excellent enantioselectivities.[2] A chelation control model of these systems allows us to predict the stereochemical outcome of the reactions studied.

In previous reports we have demonstrated the very high diastereoselectivity attainable in the formation of a new chiral centre using a DiTOX stereocontrolling element. We describe here the introduction of several new asymmetric centres, controlled by a single DiTOX unit, in the synthesis of 2-bromo-4-deoxy-ketopyranose derivatives.

Discussion

Asymmetric hetero-Diels-Alder reactions have provided key processes for the synthesis of optically active dihydropyrones.[3] Cycloaddition reactions of aldehydes attached to chiral auxiliaries are well known,[4] and those using sulfoxide containing auxiliaries have been discussed in several reviews.[5] Ghosh has described asymmetric hetero-Diels Alder reaction of 2-formyl-2-methyl-1,3-dithiane to Danishefsky's diene (*E*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene) in the presence of a chiral Lewis acid,[6] and we have previously reported the diastereoselective cycloaddition of 2-formyl-2-methyl-1,3-dithiane 1-oxides with the same diene.[7] The products, 2-(4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methyl-1,3-dithiane 1-oxides **1** were obtained with up to exclusive diastereoselectivity and 80% yield depending on the conditions employed. Optimum conditions were found to comprise *syn*-2-formyl-2-methyl-1,3-dithiane 1-oxide, low temperature, THF solvent and magnesium bromide as Lewis acid (Scheme 1). The dihydropyrone product appeared to be amenable to further manipulation as a pyranoside precursor, and it is progress in this area which we report here.

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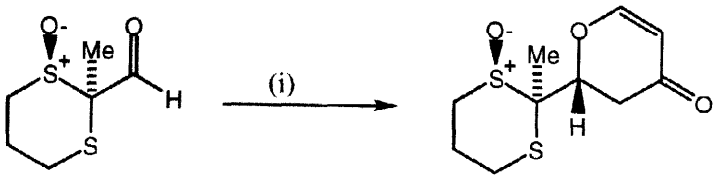
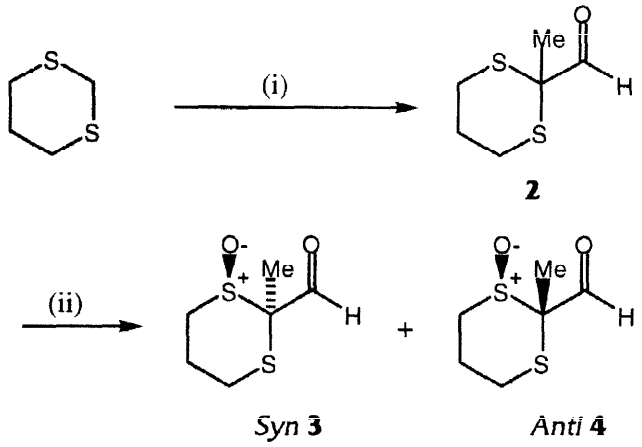


1

(i) (a) $MgBr_2$ (1.1 eq.), THF, 20 °C, 15 min
(b) Danishefsky's diene (1.1 eq.), –78 °C, 1 h; –20 °C, 16 h (c) 0.005 M HCl/THF (1:4)

Scheme 1

The *syn*-2-formyl-2-methyl-1,3-dithiane 1-oxide substrate was prepared in two steps from 1,3-dithiane (Scheme 2). One-pot methylation and subsequent formylation was achieved with methyl iodide and *N,N*-dimethylformamide employing butyllithium as base to give **2** in 67% yield. Oxidation to mono-sulfoxide was accomplished with sodium periodate to give a mixture of *syn* **3** & *anti* **4** diastereoisomers in 39 & 45% respectively, easily separated by simple chromatographic procedures.



2

Syn **3** *Anti* **4**

(i) (a) *n*-BuLi, THF, –20 °C; (b) MeI, –20 °C; (c) *n*-BuLi, THF, –20 °C;
(d) DMF, –20 °C; (ii) $NaIO_4$, $MeOH/H_2O$, 20 °C

Scheme 2

The key cycloaddition reaction was conducted in THF at –78 °C. *Syn*-2-formyl-2-methyl-1,3-dithiane 1-oxide **3** was stirred with magnesium bromide at room temperature for 15 minutes before cooling to –78 °C. Danishefsky's diene was introduced over 15 minutes, and after 3 hours the mixture was allowed to reach room temperature. Mild acidic work-up gave **1** as a single diastereoisomer in 61% yield (structure confirmed by single crystal X-ray analysis).

The next synthetic manipulation undertaken was reduction of the enone to the allylic alcohol. In simple acyclic 2-acyl DiTOX systems, we have observed very high diastereoselectivity in reduction of the carbonyl group to alcohol using diisobutylaluminium hydride or diisobutylaluminium hydride/zinc chloride,[8] a system also known to be successful with related dihydropyrone substrates.[9] Unfortunately, this system did not prove to be useful in reduction of **1**. We were therefore pleased to find that sodium borohydride accomplished the reduction, without the need for cerium chloride,[10] to give a single diastereoisomer **5** which was protected as its acetate **6** (Scheme 3). The stereochemistry of **5**, which was confirmed by single crystal X-ray analysis (Figure 1), is that resulting from the expected axial attack on a conformation of **1** in which the DiTOX unit is in an equatorial position (Figure 2).

Our next objective was to functionalize selectively the glycal carbon-carbon double bond. Attempts to dihydroxyiate **6** under conditions which had proved successful in our hands in simpler acyclic systems [11] yielded a complex mixture of products. Epoxidation with mCPBA was also unsuccessful, leading only to the *bis*-sulfone.

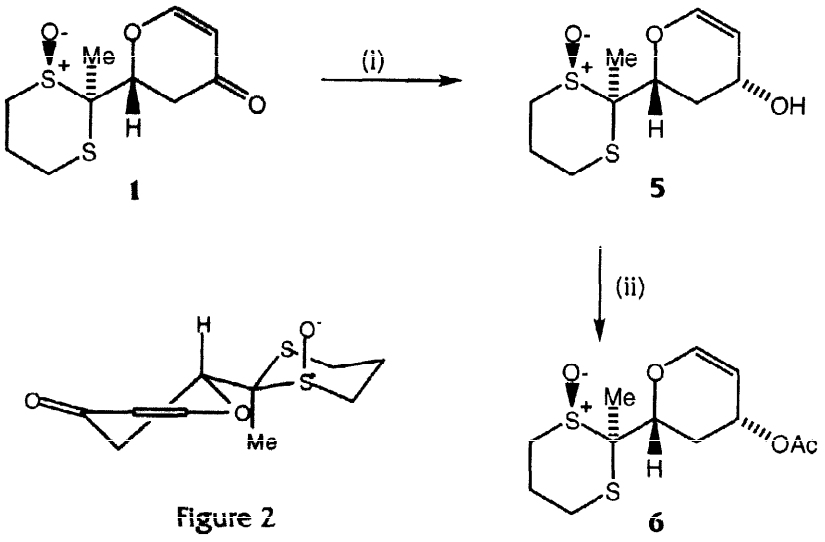


Figure 2

(i) $NaBH_4$, EtOH, 0 °C;
(ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 20 °C

Scheme 3

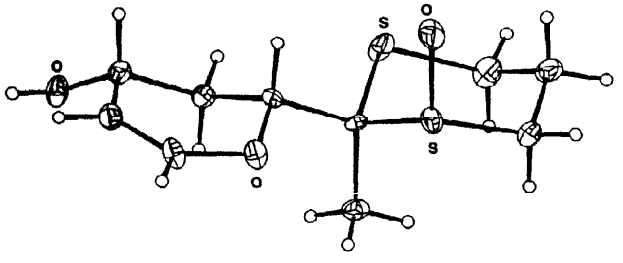
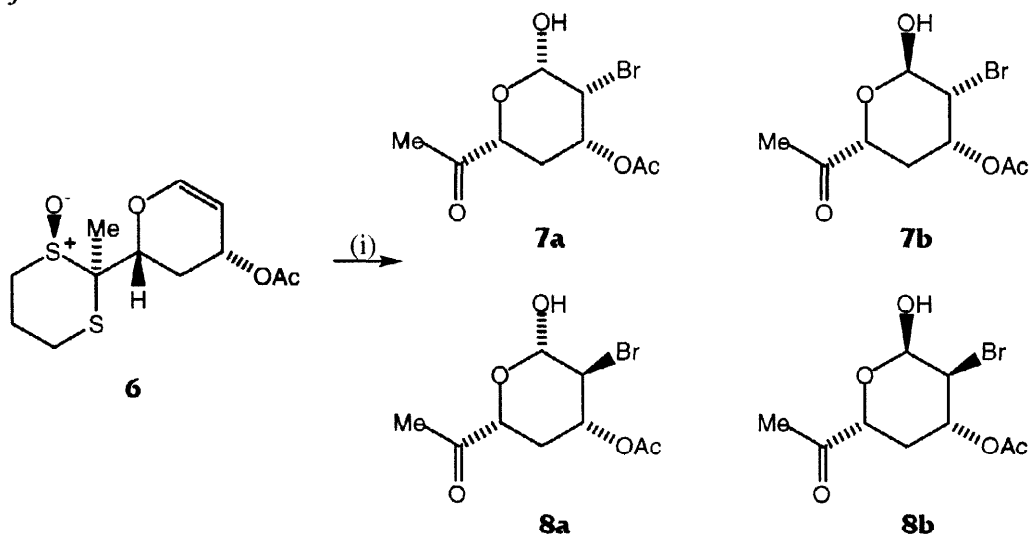


Figure 1

Glycals have been diastereoselectively halohydroxylated with NBS[12] and N-bromoacetamide[13] with varying degress of success. Wong has produced 2-deoxy-2-bromosugars from glycals with chloroperoxidase to give single isomers in some cases.[14] Previously we have shown that DiTOX units can be hydrolysed to give the correponding ketones by treatment with N-bromosuccinimide in aqueous acetone.[15] We were interested to find that under these conditions we could both hydrolyse the thioacetal of **6** and functionalize the glycal double bond in one step. Thus, treatment of **6** with eight equivalents of NBS at 0 °C very rapidly gave a mixture of four diastereoisomeric pyranose derivatives as two pairs of anomers, a 2-bromo-4-deoxymannose/talose derivative **7a/b** and a 2-bromo-4-deoxy glucose/galactose derivative **8a/b**, the mannose/talose derivative **7a/b** being the major products (scheme 4).

The two pairs of inseparable anomers were isolated in 90% yield. Structural assignments and ratios of isomers were determined on the basis of ^1H, ^{13}C and 2D-COSY NMR spectroscopy, and integration of the signal corresponding to the 3-H proton. The ratio **7a/b**:**8a/b** was found to be 16:1 and the anomeric ratio of **7a**:**7b** was 1:2.4 (α:β). The **7a/b**:**8a/b** ratio is a result of facially selective

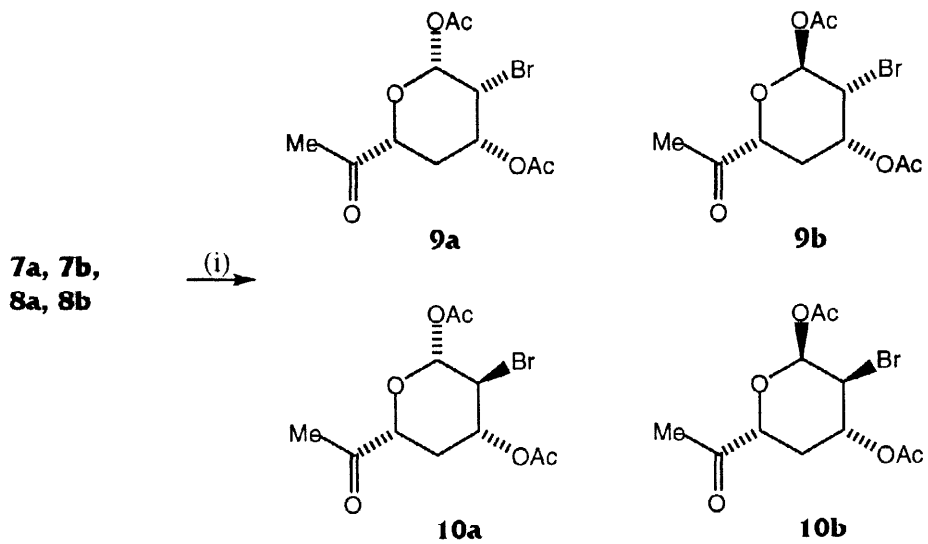
bromonium ion formation, while the anomeric ratio may be affected by neighbouring group participation by the 3-position acetate. Halogenation has been used for oxidative coupling of glycals to give oligosaccharides. In these cases, diaxial opening is observed to give the α-anomer exclusively.[16]



(i) NBS (8 eq.), acetone/H_2O (97:3), 0 °C

Scheme 4

When the 1-position hydroxyls were protected as their acetates **9a/b** and **10a/b** (Scheme 5) we observed an expected change in anomeric ratio, which increased to a 1:5 ratio of **9a**:**9b**, determined by integration of the signals corresponding to the 1-H and 3-H protons in the ^1H NMR spectrum. The stereochemistry of **9a** and **9b** was confirmed by nOe experiments and C-1 ^{13}C-^1H carbon coupling constants.[17] For example, in **9b**, irradiation of the 5-H proton gave a positive nOe with the 3-H but not the 1-H proton, while in **9a**, irradiation of the 1-H proton gave a positive nOe with the 2-H, 3-H and 5-H protons. For **9b**, the H–C-1 coupling constant was found to be 180 Hz, while for **9a** it was 162 Hz, again confirming the β configuration of **9b**.



(I) Ac_2O (1.1 eq), pyridine (5 eq), DMAP (0.1 eq), CH_2Cl_2

Scheme 5

Interestingly, and consistent with the assigned structures, the pattern of C-1 ^{13}C chemical shifts observed was more similar to that of α/β-D-mannose than to that of α/β-D-glucose or α/β-D-galactose, in that the C-1 ^{13}C chemical shift of the anomer with an axial OAc substituent **9b** appears at lower field than does that of the anomer with an equatorial OAc substituent **9a**.

Conclusions

The 1,3-dithiane 1-oxide unit has been shown to induce extremely high stereoselectivity in the cycloaddition of Danishefsky's diene to *syn*-2-formyl-2-methyl-1,3-dithiane 1-oxide. The product dihydropyrone is used as the basis for a short synthesis of a 2-bromo-4-deoxymannose derivative.

Acknowledgments

This investigation has enjoyed the support of the EPSRC and SmithKline Beecham Pharmaceuticals. We are indebted to the EPSRC service at the University of Wales, Cardiff for single crystal X-ray structure determination.

Experimental Section

General experimental details

Purification of Reagents

Commercially available reagents were used as supplied unless otherwise stated. Butyllithium was purchased from the Aldrich chemical company in 100 mL bottles as a 2.5 M solution in hexane; the molarity was determined by titration against a solution of diphenylacetic acid. Lithium hexamethyldisilazide was purchased from the Aldrich chemical company in 100 mL bottles as a 1 M solution in THF. *N*-Bromosuccinimide was recrystallized from water.

Purification of Solvents

Petroleum ether refers to petroleum ether, b.p. 40-60 °C, unless otherwise stated. Ethyl acetate and petroleum ether were distilled prior to use. Tetrahydrofuran was freshly distilled under argon from the sodium/benzophenone ketyl radical before use.

Preparation of glassware

All organometallic reactions were carried out in round bottom flasks which were either baked at 150 °C for a minimum of four hours or dried in a Bunsen burner flame. The flasks were allowed to cool in a desiccator over self indicating silica gel, and were purged with argon prior to being stoppered with septum caps. Other apparatus such as syringes, needles, cannulas and magnetic stirrer bars were also dried as above and allowed to cool in a desiccator. Reactions were maintained under a slight static positive pressure of nitrogen and reagents and solvents introduced *via* syringe or using cannula techniques, through a septum cap.

Normal work-up procedures

After reaching room temperature, the reaction mixture was poured onto saturated aqueous ammonium chloride and extracted into dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulphate and the solvents removed under reduced pressure to yield the crude products.

Purification of Products

Flash column chromatography was carried out using Merck art. 9385 Kieselgel 60 (230-400 mesh) or ICN Silica 32-63 60 Å, using hand-bellows or an air line to apply pressure to the column. Mixtures of ethyl acetate and petroleum ether (bp 40-60 °C) were used as eluent, unless otherwise stated. Thin layer chromatography was carried out using glass-backed plates coated with a 0.25 mm layer of silica gel 60H containing fluorescer, using mixtures of ethyl acetate and petroleum ether (bp 40-60 °C) as eluent unless otherwise stated. UV-inactive compounds were visualized by spraying with either dodecamolybdophosphoric acid (15% w/v in ethanol), or a solution of potassium

permanganate (10 g) and sodium carbonate (5 g) in water (2000 ml) followed in both cases by charring where appropriate.

Spectroscopy and other data

Infrared spectra were recorded in the range 4000-600 cm^{-1}, and were calibrated against the 1602 cm^{-1} absorption of polystyrene. Solid samples were run as Nujol mulls and liquids as thin films. ^1H NMR spectra were recorded using Bruker ACE200, or Bruker AMX400 instruments using deuteriochloroform solutions and tetramethylsilane as internal reference. ^{13}C NMR spectra were recorded using a Bruker AMX400 instrument using deuteriochloroform solutions and tetramethylsilane or chloroform as internal reference. Mass spectra were obtained on VG Micromass 7070E or AEI MS 902 mass spectrometers. Microanalyses were performed using a Carlo Erba elemental analyser at the University of Liverpool, Department of Chemistry microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

Procedures

2-Methyl-2-formyl-1,3-dithiane 2

To a stirring solution of 1,3-dithiane (20.0 g, 167 mmol) in THF (300 mL) at –20 °C was added a 2.4 M solution of n-butyllithium in hexanes (1.1 eq, 76.4 mL, 183 mmol). After 1 hour, methyl iodide (1.1 eq, 11.42 mL, 183 mmol) was added and the solution allowed to reach room temperature over 1 hour before recooling to –20 °C prior to further addition of a 2.4 M solution of *n*-butyllithium in hexanes (1.1 eq, 76.4 mL, 183 mmol). The reaction mixture was stirred at this temperature for 1 hour and dimethylformamide (1.1 eq, 14.1 mL, 183 mmol) added. The reaction mixture was allowed to reach room temperature over 1 hour. Normal work-up procedure and distillation (81-83 °C, 1.7 mmHg) gave **2** as a pale orange oil (18.2 g, 67%). ν_{max} (film) 1715 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.50 (3H, s), 1.62-1.89 (1H, m), 2.01-2.19 (1H, m), 2.56-2.66 (2H, m), 2.99-3.14 (2H, m), and 9.05 (1H, s); *m/z* 162.01716 (M^+), $C_6H_{10}S_2O$ requires 162.01732. Found: C, 44.59; H, 6.45; $C_6H_{10}S_2O$ requires C, 44.41, H, 6.21%.

***Syn* & *anti*-2-methyl-2-formyl-1,3-dithiane 1-oxide 3 & 4**

To a mechanically stirring solution of **(1)** (5.00 g, 30.9 mmol) in methanol (150 mL) at 0 °C was added an aqueous solution of sodium metaperiodate (1.1 eq, 7.26 g, 34.0 mmol) dropwise over 30 minutes. Stirring was continued overnight at 20 °C. The white precipitate was removed by filtration and washed with dichloromethane. The filtrate was reduced in volume by evaporation to approximately 10% of the original and partitioned between water and dichloromethane. The aqueous layer was washed twice with dichloromethane, the combined organic layers dried over $MgSO_4$ and the solvents removed under reduced pressure to yield a crude mixture of diastereoisomeric sulfoxides. Separation by column chromatography using 25% ethyl acetate/ dichloromethane as eluent yielded both the less polar *syn* **3** and more polar *anti* **4** diastereoisomers as pale yellow oils.

For *syn* **3**: (2.126 g, 39%), ν_{max} (film) 1713 and 1052 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.85 (3H, s), 2.23-2.57 (3H, m), 2.85-3.00 (1H, m), 3.19-3.26 (1H, m), 3.45-3.63 (1H, m), and 9.64 (1H, s); *m/z* 178.01232 (M^+), $C_6H_{10}O_2S_2$ requires 178.01224. Found: C, 40.30; H, 5.72; $C_6H_{10}O_2S_2$ requires C, 40.42, H, 5.65%.

For *anti* **4**: (2.494 g, 45%), ν_{max} (film) 1706 and 1033 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.66 (3H, s), 1.76-1.89 (1H, m), 2.26-2.84 (3H, m),3.06-3.40 (2H, m), and 9.39 (1H, s); *m/z* 178.01232 (M^+), $C_6H_{10}O_2S_2$ requires 178.01224. Found: C, 40.10; H, 5.72; $C_6H_{10}O_2S_2$ requires C, 40.42, H, 5.65%.

2-(2-(*Syn*-1-oxo-2-methyl-1,3-dithianyl))-2,3-dihydropyranone 1

To a stirring solution of **3** (3.50 g, 19.7 mmol) in THF (160 mL) at room temperature was added magnesium bromide (1.1 eq, 4.22 g, 22.9 mmol). After 15 minutesutes at room temperature the solution was cooled to –78 °C and Danishefsky's diene (1.3 eq, 4.96 mL, 26.0 mmol) added by syringe pump over 15 minutes. The solution was allowed to reach room temperature overnight. The solvent was removed on a rotary evaporator and THF:0.005 M HCl (4:1, 160 mL) added to the oil.

The mixture was stirred for 1.5 hours, extracted into dichloromethane, washed with saturated aqueous sodium hydrogen carbonate, dried over $MgSO_4$ and the solvents removed under reduced pressure. Column chromatography using 25-75% ethyl acetate/dichloromethane as eluent gave **1** as a colourless crystalline solid (3.10 g, 61%), mp 172-173 °C, ν_{max} (Nujol) 1667 and 1039 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, s), 1.81-1.89 (1H, m), 2.47-2.70 (4H, m), 2.75-2.82 (1H, m), 2.89-2.96 (1H, m), 3.10-3.15 (1H, m), 4.80 (1H, dd, J = 15.0 & 3.4 Hz), 5.48 (1H, dd, J = 6.0 & 1.2 Hz), and 7.39 (1H, d, J = 6.0 Hz); δ_C (100 MHz, $CDCl_3$) 14.6, 15.6, 23.7, 35.6, 41.1, 63.1, 77.9, 107.6, 162.1, and 190.7. *m/z* 246.03874 (M^+), $C_{10}H_{14}O_3S_2$ requires 246.03842. Found: C, 48.72; H, 5.73; $C_6H_{10}O_2S_2$ requires C, 48.76, H, 5.73%.

2-(2-(*Syn*-1-oxo-2-methyl-1,3-dithianyl))-2,3-dihydro-1-hydroxypyran 5

To a stirring solution of sodium borohydride (1.1 eq, 0.084 g, 2.24 mmol) in EtOH (40 mL) at 0 °C was added **1** (0.50 g, 2.03 mmol). After 4 hours the solution was poured onto 10 mL ice/water, extracted into dichloromethane, dried over $MgSO_4$ and the solvents removed under reduced pressure. Column chromatography using 100% ethyl acetate to 10% EtOH/ ethyl acetate as eluent gave **5** as a colourless crystalline solid (0.378 g, 75%). mp 176-178 °C. ν_{max} (Nujol) 3375, 1645 and 1031 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.62 (3H, s), 1.60-1.73 (1H, m), 1.75-1.80 (1H, m), 2.24 (1H, dd, J = 12.8 & 6.8 Hz), 2.44-2.57 (2H, m), 2.71 (1H, td, J = 14.0 & 2.8 Hz), 2.90 (1H, br s), 2.90-2.97 (1H, m), 3.03-3.07 (1H, m), 4.27 (1H, d, J = 12.4 Hz), 4.51 (1H, t, J = 8.2 Hz), 4.81 (1H, d, J = 6.0 Hz), and 6.34 (1H, d, J = 6.0 Hz); δ_C (100 MHz, $CDCl_3$) 14.2, 15.1, 23.8, 31.4, 40.9, 62.9, 64.0, 73.9, 106.8, and 143.8. *m/z* 248.05431 (M^+), $C_{10}H_{16}O_3S_2$ requires 248.05408. Found: C, 48.42; H, 6.52; $C_6H_{16}O_2S_2$ requires C, 48.36, H, 6.49%.

2-(2-(*Syn*-1-oxo-2-methyl-1,3-dithianyl))-2,3-dihydro-1-acetoxypyran 6

To a stirring solution of **5** (0.300 g, 1.20 mmol) in dichloromethane (15 mL) at room temperature was added pyridine (5.0 eq, 0.48 mL, 5.95 mmol), acetic anhydride (1.1 eq, 0.12 mL, 1.32 mmol) and DMAP (0.07 eq, 0.01 g, 0.08 mmol). After 30 minutes, normal work-up procedure and column chromatography using 100% ethyl acetate as eluent gave **6** as a colourless crystalline solid (0.272 g, 78%). mp 162-164 °C. ν_{max} (Nujol) 1727, 1647 and 1030 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.62 (3H, s), 1.74-1.83 (2H, m), 2.05 (3H, s), 2.32-2.37 (1H, m), 2.47-2.59 (2H, m), 2.68-2.76 (1H, m), 2.87-2.94 (1H, m), 3.05-3.09 (1H, m), 4.35 (1H, dd, J = 12.4 & 1.2 Hz), 4.79 (1H, dt, J = 6.4 & 1.8 Hz), 4.42-5.47 (1H, m), and 6.44 (1H, d, J = 6.0 Hz); δ_C (100 MHz, $CDCl_3$) 14.5, 15.2, 21.1, 23.9, 27.5, 40.9, 63.8, 65.7, 73.9, 102.4, 145.8, and 170.5. *m/z* 290.06460 (M^+), $C_{12}H_{18}O_4S_2$ requires 290.06467.

(±)-α/β-1-Hydroxy-*cis*-(2-bromo-3-acetoxy-5-acetyl)-tetrahydropyran 7a & 7b

To a stirring solution of NBS (8 eq, 0.49g, 2.75 mmol) in acetone/water (97:3, 4 mL) at 0 °C was added **6** (0.100 g, 0.34 mmol). After 10 minutes, the solution was poured onto 5 mL saturated sodium sulfite, extracted into dichloromethane, dried over $MgSO_4$ and the solvents removed under reduced pressure. Column chromatography using 10% ethyl acetate / dichloromethane as eluent gave **7b & 7a** (2.4:1) as an inseparable colourless oil (0.087 g, 90%). ν_{max} (film) 3424, 1780 and 1740 cm^{-1}, *m/z* 298.02988 ($M+NH_4^+$), $C_9H_{17}{}^{79}BrNO_5$ requires 298.02901.

For **7b**: δ_H (400 MHz, $CDCl_3$, COSY) 2.11 (3H, s), 2.26 (3H, s), 1.91-2.10 (2H, m, H-C(4)), 4.06 (1H, br s, OH-C(1)), 4.41-4.42 (1H, m, H-C(2)), 4.54 (1H, dd, J = 11.4 & 3.3 Hz, H-C(5)), 5.28 (1H, ddd, J = 11.1, 4.6 & 3.7 Hz, H-C(3)), and 5.58 (1H, s, H-C(1)).

For **7a**: δ_H (400 MHz, $CDCl_3$, COSY) 2.13 (3H, s), 2.30 (3H, s), 1.91-2.10 (2H, m, H-C(4)), 3.90 (1H, br s, OH-C(1)), 3.97 (1H, dd, J = 11.9 & 3.0 Hz, H-C(5)), 4.62-4.63 (1H, m, H-C(2)), 4.65 (1H, bs, H-C(1)), and 4.98 (1H, ddd, J = 11.6, 3.3 & 3.3 Hz, H-C(3)).

(±)-α/β-1-Acetoxy-*cis*-(2-bromo-3-acetoxy-5-acetyl)-tetrahydropyran 9a & 9b

To a stirring solution of **(7a & 7b, 8a & 8b)** (0.020 g, 0.07 mmol) in dichloromethane (1 mL) at room temperature was added pyridine (5 eq, 0.03 mL, 0.20 mmol), acetic anhydride (1.1 eq, 0.007 mL, 0.08 mmol) and DMAP (0.1 eq, 0.001 g, 0.008 mmol). After 4 hours, normal work-up

procedure and purification by preparative TLC using 50% ethyl acetate/ petroleum ether as eluent gave **9b & 9a** (5:1) as an inseparable colourless oil (0.018 g, 78%). ν_{max} (film) 1746 and 1724 cm^{-1}; *m/z* 340.03971 ($M+NH_4^+$), $C_{11}H_{19}{}^{79}BrNO_6$ requires 340.03957.
For **9b**: δ_H (400 MHz, $CDCl_3$) 2.12 (3H, s), 2.08-2.21 (2H, m, H-C(4)), 2.15 (3H, s), 2.28 (3H, s), 4.32 (1H, dd, J = 10.2 & 4.8 Hz H-C(5)), 4.36-4.38 (1H, m, H-C(2)), 5.15-5.20 (1H, m, H-C(3)), and 6.40 (1H, d, J = 2.0 Hz, H-C(1)).
For **9a**: δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s), 2.08-2.21 (2H, m, H-C(4)), 2.21 (3H, s), 2.29 (3H, s), 4.04 (1H, dd, J = 11.2 & 3.6 Hz H-C(5)), 4.54-4.55 (1H, m, H-C(2)), 4.95 (1H, ddd, J = 11.0, 3.4 & 3.6 Hz H-C(3)), and 5.64 (1H, d, J = 1.6 Hz, H-C(1)).

References

1 Page, P. C. B.; M^{c}Kenzie, M. J.; Buckle, D. R. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2673, and references contained therein.
2 Page, P. C. B.; Wilkes, R. D.; Witty, M. J. *Org. Prep. Proc. Intl.*, **1994**, 702, and references contained therein.
3 Boger, D. L.; Weinreb, S. M. in 'Hetero Diels-Alder Methodology in Organic Synthesis,' Academic Press Inc., San Diego, 1987, pp. 105-119; Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **1986**, *108*, 7060.
4 Danishefsky, S. J.; Kobayashi, S.; Kerwin, J. F. *J. Org. Chem.*, **1982**, *47*, 1981; Danishefsky, S. J.; Chao, K.-H.; Schulte, G. J. *ibid.*, **1985**, *50*, 4650; Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.*, **1985**, *107*, 1246; Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *ibid.*, **1985**, *107*, 1256; Mulzer, J.; Meyer, F.; Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503.
5 De Lucchi, O.; Pasquato, L. *Tetrahedron*, **1988**, *44*, 6755; Arai, Y.; Koizumi, T. *Sulfur Reports*, **1993**, *15*, 41; Carreño, M. C. *Chem. Rev.*, **1995**, *95*, 1717.
6 Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427.
7 Page, P. C. B.; Prodger, J. C. *Synlett*, 1991, 84.
8 Page, P. C. B.; Prodger, J. C. *Synlett*, 1990, 460.
9 Danishefsky, S. J.; Kerwin, J. F. *J. Org. Chem.*, **1982**, *47*, 1597.
10 Danishefsky, S. J.; Berkowitz, D. B.; Schulte, G. K. *J. Am. Chem. Soc.*, **1992**, *114*, 4518; Crimmins, M. T.; O'Mahony, R. *J. Org. Chem.*, **1989**, *54*, 1157; Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.*, **1981**, *103*, 5454.
11 Page, P. C. B.; M^{c}Kenzie, M. J.; Buckle, D. R., ms in preparation.
12 Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.*, **1987**, *109*, 8117; Still, W. C.; Hamann, P. R.; Bhagwat, S. S. *J. Am. Chem. Soc.*, **1985**, *107*, 6372; Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495; Kirby, A. J.; Ryder, H.; Matassa, V. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 617.
13 Marzabadi, C. H.; Spilling, C. D. *J. Org. Chem.*, **1993**, *58*, 3761.
14 Wong, C.-H.; Liu, K. K.-C. *J. Org. Chem.*, **1992**, *57*, 3748.
15 Corey, E. J.; Erickson, B. W. *J. Org. Chem.*, **1971**, *36*, 3553.
16 Tatsuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.*, **1977**, *99*, 5826; Danishefsky, S. J., Friesen, R. W. *J. Am. Chem. Soc.*, **1989**, *111*, 6656.
17 For major component **9b**, irradiation of H-5 gave an nOe to H-3 but not to H-1. H-1 is therefore equatorial and the structure is as shown. Anomeric carbon atoms: For **9a**, δ_C = 90. 5 ppm, J_{CH} = 162 Hz; for **9b**, δ_C = 93. 9 ppm, J_{CH} = 181 Hz. *Prog. NMR Spectroscopy*, **1981**, *14*, 249, section 17.