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Resolution of (1,1'-Binaphthalene)-2,2'-dithiol via Diastereoisomeric Dithioacetals Derived from *D*-Glucose.

Upul K. Bandarage, Gavin F. Painter and Robin A.J. Smith*

Department of Chemistry, University of Otago, PO Box 56, Dunedin, New Zealand

Abstract:. *The efficient resolution of (1,1'-binaphthalene)-2,2'-dithiol has been achieved by the preparation and separation of the chiral diastereoisomeric binaphthalene dithioacetals derived from 2,3,4,5,6-penta-O-methyl-D-glucose followed by transthioacetalization with ethane-1,2-dithiol.*

INTRODUCTION

In recent years many C_2 symmetric chiral auxiliaries have been prepared and used in asymmetric synthesis. Within this class, 2,2'-disubstituted-1,1'-binaphthalene compounds have taken a dominant role[1] and many have been resolved into their optically active forms. From the viewpoint of application to the development of asymmetric synthetic methodology it is highly desirable that both enantiomers of chiral auxiliaries are readily available in useful quantities. Herein we report an effective resolution of a significant compound in the biaryl series, (1,1'-binaphthalene)-2,2'-dithiol (**1**) *via* a dithioacetalization process. Optically active **1** was first prepared in 1957[2] by a procedure involving the resolution of the distrychnine salts of the corresponding disulfonic acid followed by reduction of the optically active acid chloride. This process is not amenable to sensible scale up and does not readily lead to significant amounts of both enantiomers. More recently, the asymmetric oxidations of thioethers related to **1** have been reported[3] which allows access to both enantiomers of **1**. This approach also presents some difficulties related to the necessary chromatography of a complex mixture of variously oxidized diastereoisomeric compounds and a subsequent multistep reaction sequence to the target chiral molecules. An alternative approach has exploited the ready availability of chiral (1,1'-binaphthalene)-2,2'-diol from several sources[4] including the resolution of derived thiophosphoroamides.[5] One enantiomer of the chiral diol was converted into *(R)*-**1** by a sequence involving the Newman-Kwart thermorearrangement of a bisthiocarbamate derivative.[5] This reaction has a history of being rather capricious although it has been researched in detail.[6] Close attention to experimental conditions was required in order to obtain useful chemical and enantiomeric efficiencies.

A direct resolution route from **1** is therefore attractive from the practical standpoint and was the driving motivation for this investigation. During the latter part of this work the report of an enzyme-based enantioselective hydrolysis of bisthioesters derived from **1** appeared[7] which complements our

totally chemical approach. The procedure reported in this paper is non enzymatic and the chiral source is derived from the common material *D*-glucose. Chromatographic separation of diastereoisomers is a requirement of the sequence but, as column and radial chromatographic techniques are readily amenable to scale up, this process seems to satisfy the criteria listed earlier.

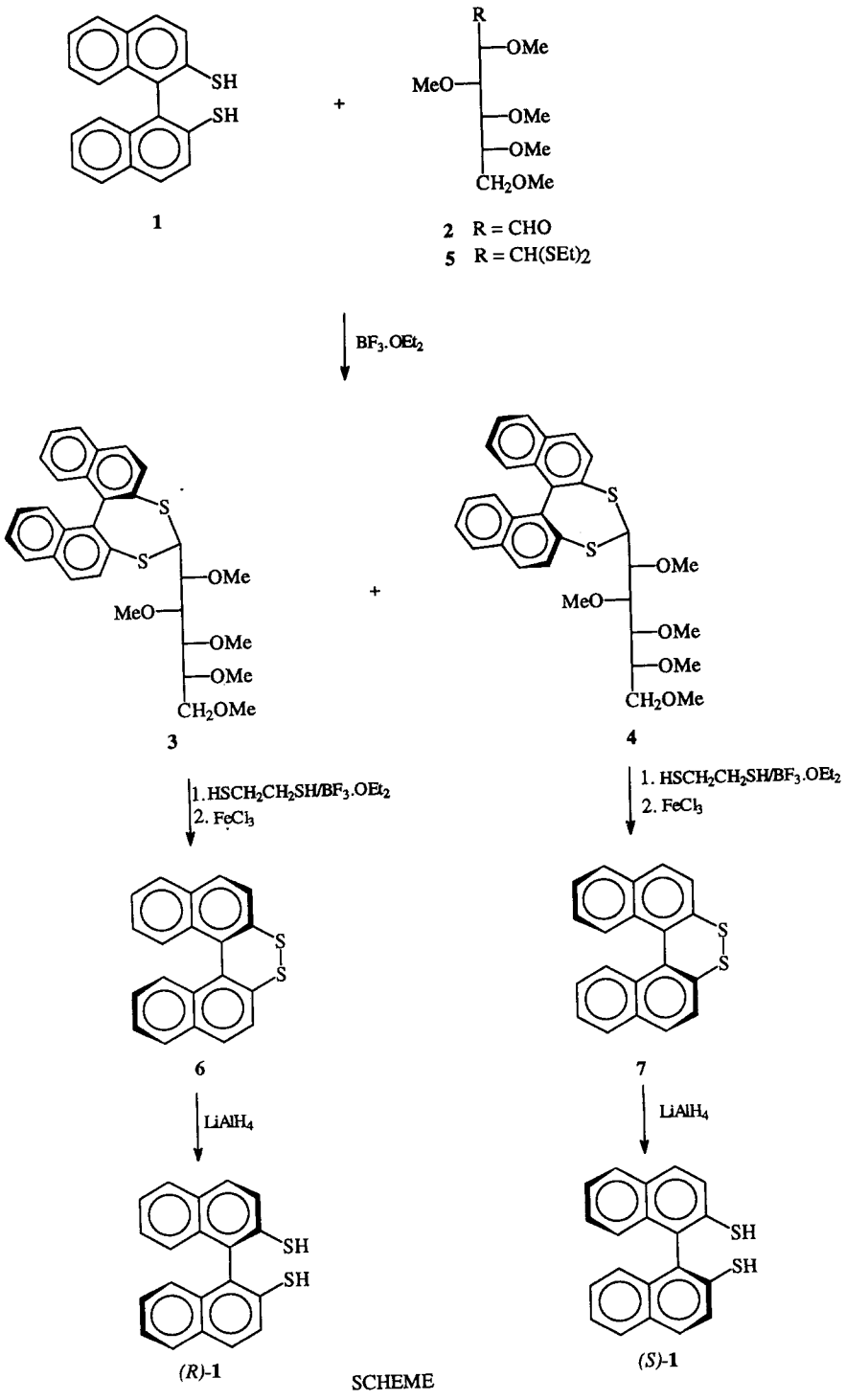
DISCUSSION

Reaction of racemic **1** with optically active ketones or aldehydes in the presence of Lewis acid catalysts gives two diastereoisomeric dithioacetals. In principle, the rate of the formation of these diastereoisomers could be different and lead to useful kinetic selectivities. However we did not observe any useful kinetic resolution of **1** using a selection of chiral ketones including 2- and 3-methylcyclohexanone, (-)-menthone, cholestan-2-one, and cholestan-3-one.[8] The diastereoisomeric mixtures obtained from these studies were inevitably chromatographically inseparable mixtures. In contrast, reaction of **1** with chiral aldehydes bearing polar groups at stereogenic centre(s) did show modest kinetic selection and, more usefully, were separable by chromatography. Specifically, the acyclic aldehyde, 2,3,4,5,6-penta-O-methyl-*D*-glucose (**2**), readily obtained from *D*-glucose by standard methodology,[9] reacted with racemic **1** in the presence of $BF_3.OEt_2$ to give two polar, separable, optically active dithioacetal diastereoisomers **3** and **4** in 1:1.4 ratio (Scheme). Subsequent refinements to the formation of **3** and **4** have involved transthioacetalization of the bisethylthioacetal **5** thus avoiding manipulation of the sensitive[10] aldehyde **2** (Scheme). The ^1H NMR spectrum of the less polar diastereoisomer **3** showed a characteristic ring methine doublet at δ5.20 with J=7.5 Hz while the other diastereoisomer, **4**, showed the corresponding doublet at δ5.11 with J=5.1Hz. These spectral features allowed for easy estimation of the stereoisomeric purity of various samples.

There are many methods available for the hydrolysis of thioacetals,[11] but in all cases the emphasis is on the isolation of the carbonyl component of the product mixture with maximum efficiency. Application of some of these procedures to **3** and **4** were unrewarding in terms of effective recovery of chiral forms of **1**. Eventually a transthioacetalization process with ethane-1,2-dithiol in the presence of excess $BF_3.OEt_2$ was discovered (Scheme) which gave the required enantiomers (*R*)-**1** and (*S*)-**1** in *ca* 70% yield. Reaction of **3** gave (-)-**1** which has been shown to have the (*R*) absolute configuration[12] and similarly **4** gave (*S*)-(+)-**1**. As also noted by other workers in this area,[5,7] the specific rotation values for enantiomeric forms of **1** were difficult to obtain accurately as some oxidation occurs in solution and the samples rapidly become contaminated with small amounts of the derived disulfides which show very large rotation values. To alleviate this difficulty, the crude enantiomeric dithiols were oxidized with $FeCl_3$ to the stable disulfides **6** and **7** allowing effective handling and purification. Hydride reduction serves to create the chiral dithiol from the disulfide as required (Scheme). In order to confirm the stereochemical integrity of the reaction sequence a sample of (+)-**1** was reacted completely with excess **2** in the presence of $BF_3.OEt_2$ and gave **4** with stereochemical purity in excess of 98% as indicated by ^1H NMR spectroscopy.

CONCLUSION

This resolution approach, involving successive transthioacetalization reactions is an attractive route to chiral dithiobinaphthalene species and utilizes a readily accessible chiral source material. Application of this procedure to other biaryldithiols is currently being examined.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CH2OMe
2 R = CHO
5 R = CH(SEt)2
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1. HSCH2CH2SH/BF3.OEt2
2. FeCl3
6
7
LiAlH4
(R)-1
(S)-1

SCHEME

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were obtained, in $CDCl_3$ solutions, on a Varian VXR 300 spectrometer operating at 299.904 MHz and 75.419 MHz respectively. Spectral data, relative to internal tetramethylsilane δ = 0 ppm, is presented as: Chemical shift (multiplicity, coupling constant, number of protons). Polarimetric readings were obtained on a Perkin-Elmer 141 polarimeter in $CHCl_3$ solutions. Melting points were determined either on a Gallenkamp heating block apparatus in open capillary tubes. Radial chromatography was carried out, under nitrogen, with a Harrison Research Chromatotron model 7924T using Silica gel 60 PF_{254} (Merck, Art 7749). Column chromatography was carried out at atmospheric pressure on Silica gel 60 (Merck Art 9385). Preparative thin layer chromatography was carried on 1.25mm thick layers of Silica gel 60 PF_{254} (Merck, Art 7747).

2,3,4,5,6-Penta-O-methyl-D-glucose diethylthioacetal (**5**)[13] (modified procedure)

Sodium hydride (60% dispersion, 1.09g, 27.3 mmol) was washed free of mineral oil under Argon with pentane (3x50cm^3) then suspended in N,N-dimethylformamide (50 cm^3). The suspension was cooled to -20°C and 1,1-bisethylthio-*D*-glucose[14] (1.00g, 3.49 mmol) was added in portions over 45 min. After the hydrogen evolution ceased (*ca* 40 min) the external temperature was adjusted to 0°C and iodomethane (2.00 cm^3, 33.5 mmol) was added dropwise over 5 min. The reaction mixture was allowed to slowly warm to room temperature with stirring over 3 hr then quenched with water (100 cm^3). The product was extracted with ether (2x100 cm^3) and the combined extract washed with water (5x200 cm^3) then dried ($MgSO_4$). Filtration and evaporation of solvents in vacuo gave pure **5** (1.21g, 97%) as a colourless oil. ^{1}H NMR δ(ppm):1.24 (t, J=7.4Hz, 3H, $SCH_2\underline{CH_3}$); 1.26 (t, J=7.4Hz, 3H, $SCH_2\underline{CH_3}$); 2.55-2.85 (m, 4H, $SC\underline{H_2}CH_3$); 3.37, 3.43, 3.47, 3.56, 3.61 (s, 15H, 5xOCH_3); 3.4-3.8 (m, 6H, OCH); 3.91 (d, J=3.9Hz, 1H, H-1). ^{13}C NMR δ(ppm): 14.41, 14.50 (2xCH_3); 25.04, 25.41 (2xSCH_2); 53.17 (SCHS); 57.43, 58.97, 60.28, 61.15, 61.20 (5xOCH_3); 70.35 (OCH_2); 79.80, 80.37, 82.66, 85.42 (4xOCH).

(R)-4[(1"R,2"S,3"R,4"R)-1",2",3",4",5"-Pentamethoxypentyl]-dinaphtho[2,1-d:1',2'-f][1,3]dithipin (**3**) *and (S)-4[(1"R,2"S,3"R,4"R)-1",2",3",4",5"-pentamethoxypentyl]-dinaphtho[2,1-d:1',2'-f][1,3]dithipin* (**4**)

(a) A solution of 2,3,4,5,6-penta-O-methyl-*D*-glucose[9](**2**) (0.5 g, 2 mmol) in dry CH_2Cl_2 (5 cm^3) was added to a stirred solution of (1,1'-binaphthalene)-2,2'-dithiol[6](**1**) (0.8 g, 2.5 mmol) and $BF_3.OEt_2$ (3 drops) in dry CH_2Cl_2 (10 cm^3) at room temperature under nitrogen. After stirring overnight under nitrogen at room temperature, the reaction mixture was poured into cold water (50 cm^3) and extracted with CH_2Cl_2 (3x25 cm^3). The combined extracts were washed successively with 10% NaOH (20 cm^3), water and dried ($MgSO_4$). Filtration and evaporation of solvents in vacuo gave a crude product whose ^{1}H NMR spectrum showed **3** and **4** in a 1:1.4 ratio. Separation by radial chromatography and elution with ether/hexane 1:4 gave **3** (0.43g, 39%) and **4** (0.32g, 29%). For a separation of the same mixture using column chromatography see (b) below. Compound **3** R_f 0.67(ether/hexane 2:1); $[\alpha]_{546}^{20}$ -145.4 , $[\alpha]_{589}^{20}$ -121.7 (*c* 4); ^{1}H NMR δ(ppm): 3.48, 3.49, 3.51, 3.54, 3.54 (s, 15H, 5xOCH_3); 3.45 - 3.93 (m, 6H, OCH); 5.20 (d, J=7.5 Hz, 1H, H-4); 7.11-7.26 (m, 4H, Ar); 7.42-7.51 (m, 2H, Ar); 7.78 (d, J=8.4Hz, 1H, Ar); 7.86 (d, J=8.4Hz, 1H, Ar); 7.92-7.99 (m, 4H, Ar). ^{13}C NMR δ(ppm): 57.59, 59.18, 60.70, 60.70, 61.41 (5xOCH_3); 67.22 (S-CH-S); 70.82 (CH_2O); 80.59, 80.90, 82.68, 84.53 (4xOCH); 126.32 (CH); 126.38 (CH); 126.50 (CH); 126.60 (CH); 127.52 (CH); 127.71 (CH); 128.18 (CH); 128.23 (CH); 128.54 (CH); 128.57 (C); 128.99 (CH); 131.66 (C); 132.33 (C); 132.36 (C); 132.47 (CH); 132.70 (CH); 133.91 (C);

133.96 (C); 142.30 (C), 142.73 (C). Anal: calcd. for $C_{31}H_{34}O_5S_2$: C, 67.65; H, 6.28; S, 11.44. Found: C, 67.65; H, 6.22; S, 11.65%. Compound **4** R_f 0.61(ether/hexane, 2:1); $[\alpha]_{546}^{20}$ +172.4 , $[\alpha]_{589}^{20}$ +143.3 (*c* 3); ^{1}H NMR δ(ppm): 3.30, 3.37, 3.50, 3.54, 3.55 (s, 15H, 5xOCH$_3$); 3.41-3.66 (m, 6H, OCH); 5.11 (d, J=5.1 Hz, 1H, H-4); 7.10-7.26 (m, 4H, Ar); 7.40-7.52 (m, 2H, Ar); 7.81-8.01 (m, 6H, Ar). ^{13}C NMR δ(ppm): 57.66, 59.05, 60.60, 60.97, 61.06 (5xOCH$_3$); 67.60 (S-CH-S); 70.59 (CH_2O); 80.24, 80.77, 82.36, 83.20 (4xOCH); 126.21 (CH); 126.37 (CH); 126.42 (CH); 126.56 (CH); 127.61 (CH); 127.66 (CH); 128.12 (CH); 128.15 (CH); 128.23 (CH); 129.07 (CH); 129.60 (C); 131.35 (C); 132.20 (CH); 132.20 (C); 132.34 (C); 133.65 (CH); 133.77 (C); 133.94 (C); 142.33 (C), 142.77 (C). Anal: calcd. for $C_{31}H_{34}O_5S_2$: C, 67.65; H, 6.28; S, 11.44. Found: C, 67.46; H, 6.19; S, 11.65%.

(b) A solution of **5** (0.23g, 0.65 mmol) and **1** (0.205g, 0.65 mmol) in dry CH_2Cl_2 (10 cm^3) was cooled to -30°C and deoxygenated by alternate evacuation and pressurization with argon (3x). $BF_3.OEt_2$ (0.8 cm^3, 6.5 mmol) was added dropwise over 5 min at -30°C then the temperature was allowed to rise to -15°C. The reaction mixture was stirred overnight and during this period the temperature rose to 15°C. Water (100 cm^3) was added and the product was extracted with ether (3x50 cm^3). The combined organic extract was washed successively with water (100 cm^3), 10% NaOH (2x150 cm^3) and water (2x100 cm^3) then dried ($MgSO_4$). Filtration and evaporation of the solvents in vacuo gave a crude product (0.297g) which was shown to be a 1:1 mixture of **3** and **4** by ^{1}H NMR. The mixture was adsorbed onto a column of silica gel (30g) from hexane/CH_2Cl_2 1:1 and developed with ether/hexane 1:3 (240 cm^3). Elution with ether/hexane 1:2 gave **3** (0.104g, 30%) as a white crystalline solid initially softening on heating at 65°C and completely molten at 75°C. Further elution with the same solvent mixture gave **4** (0.105g, 30%) also as a white solid m.p. over the range 68-80°C.

(R)-(-)-Dinaphtho[2,1-c:1',2'-e][1,2]dithiin (**6**)

A solution of **3** (0.24 g,0.43 mmol) in dry CH_2Cl_2 (5 cm^3) was added to a stirred solution of ethane-1,2-dithiol (0.08 g,0.85 mmol) and $BF_3.OEt_2$ (1 g, 7 mmol) in dry CH_2Cl_2 (10 cm^3) at room temperature under nitrogen. After 12 hr at room temperature the solvent and excess ethane-1,2-dithiol were evaporated in vacuo. The crude product was dissolved in ethanol (25 cm^3) and anhydrous $FeCl_3$ (1.5 g) was added. The mixture was heated for 30 min and then cooled to room temperature. Water (50 cm^3) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 cm^3). The organic phase was dried ($MgSO_4$), then filtered. Evaporation of the solvents gave a crude product which was separated by preparative layer or radial chromatography (CH_2Cl_2/hexane, 3:7) to give (R)-(-)-**6** (0.096 g,70%). The product was recrystallised from a large volume of glacial acetic acid to give bright yellow needles, m.p. 262°C (lit.[2] m.p. 262-263°C); $[\alpha]_{546}^{20}$ -771 , $[\alpha]_{589}^{20}$ - 731 (*c* 0.8) (lit.[2] $[\alpha]_{546}^{20}$ -777).

(S)-(+)-Dinaphtho[2,1-c:1',2'-e][1,2]dithiin (**7**)

Similar to that described above for **6**, reaction of **4** (0.24 g) gave **7** (0.092 g, 68%) which also recrystallised from glacial acetic acid to give bright yellow needles, m.p. 261°C (lit.[2] m.p. 262-263°C) $[\alpha]_{546}^{20}$ 751 , $[\alpha]_{589}^{20}$ +707 (*c* 0.8) (lit.[2] $[\alpha]_{546}^{20}$ +775).

(R)-(-)-(1,1'-Binaphthalene)-2,2'-dithiol (*(R)*-**1**)

$LiAlH_4$ (0.021g, 0.56 mmol) was added to a solution of **6** (0.090 g, 0.28 mmol) in dry ether (5 cm^3). The mixture was heated under reflux for 2 hr, during which time the colour of the solution change

from yellow to colourless. After cooling to room temperature excess $LiAlH_4$ was destroyed by dropwise addition of ethyl acetate followed by 10% hydrochloric acid (10 cm^3) and the product was extracted with ether (2 x 10 cm^3). The ethereal solution was dried ($MgSO_4$), filtered and evaporated to give a crude product which was separated by preparative layer chromatography (CH_2Cl_2/hexane, 1:1) to give (R)-**1** (0.089 g, 97%). m.p. *ca* 100°C (Lit.[2] m.p. *ca* 100°C), $[\alpha]_{546}^{20}$ -31.2 , $[\alpha]_{589}^{20}$ -30 (*c* 0.8) (Lit.[2] $[\alpha]_{546}^{20}$ -33).

*(S)-(+)-(1,1'-Binaphthalene)-2,2'-dithiol ((S)-***1**)

Similar reaction of **7** (0.90 g) gave (S)-**1** (0.085 g, 97%), m.p. *ca* 100°C (Lit.[2] m.p. *ca* 100°C), $[\alpha]_{546}^{20}$ +57 , $[\alpha]_{589}^{20}$ +54 (*c* 0.8) (Lit.[2] $[\alpha]_{546}^{20}$ +67).

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