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TETRAHEDRON: *ASYMMETRY*

Camphor derived 1,4-oxathianes for carbonyl epoxidation

Varinder K. Aggarwal,[a,*] J. Gair Ford,[a] Ray V. H. Jones [b] and Robin Fieldhouse [b]

[a] *Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK*

[b] *Zeneca Process Technology Department, Earls Road, Grangemouth FK3 8XG, UK*

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Abstract

1,4-Oxathianes have been prepared in five steps from camphor and used to give stilbene oxides in excellent yield (81–100%) and with moderate enantioselectivity (54–64% ee).

1. Introduction

Methods for the asymmetric synthesis of epoxides continue to receive much attention.[1–9] The principle methods are undoubtedly the Sharpless epoxidation[6,8,10] and the Jacobsen/Katsuki epoxidation.[5,7] Also of note are the polyamino acid based methods originally developed by Julia,[11–16] the dioxirane methodology of Shi[17–19] and the metal catalysed methods of Enders,[20,21] Jackson[22] and Shibasaki.[23] As well as the synthesis of epoxides, the desymmetrisation of *meso* epoxides[5,24,25] and the resolution of racemic epoxides[5,6,26] have also become useful synthetic methods.

The reaction of sulfur ylides with aldehydes to furnish epoxides is a complementary route to epoxides. Recently, a number of sulfides have been developed which give epoxides with excellent enantiocontrol, making this method an attractive alternative to the oxidative methods cited above.[27–33] We recently reported a process operating under neutral conditions which allows the use of catalytic quantities of sulfides to produce epoxides in good yields and with excellent enantiomeric excesses (Scheme 1).[27,34] Our best results to date have been achieved using 1,3-oxathiane **1**, which can be used to catalyse the epoxidation of a number of aldehdyes with good enantiocontrol (Scheme 2).[27]

We questioned whether related 1,4-oxathianes (e.g. **2**) could be used in our catalytic cycle and recognised that they would offer greater stability to the reaction conditions than the corresponding 1,3-oxathianes. Increased stability would allow greater turnover and thereby lower sulfide loading. In this paper we describe the synthesis and ylide reactions of 1,4-oxathiane **2**.

* Corresponding author. E-mail: V.Aggarwal@sheffield.ac.uk

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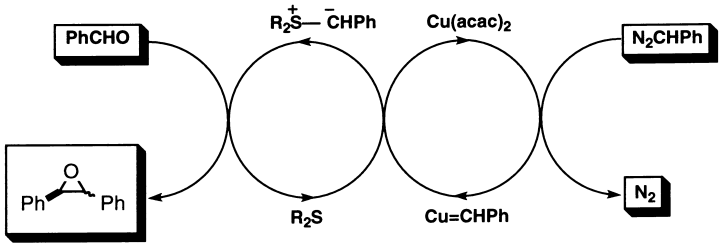
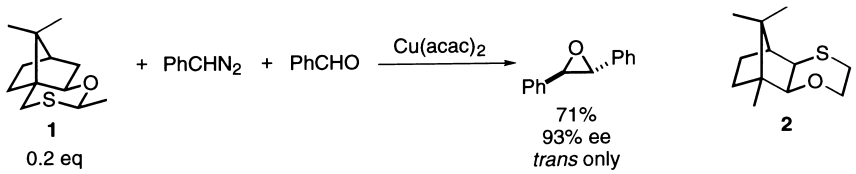


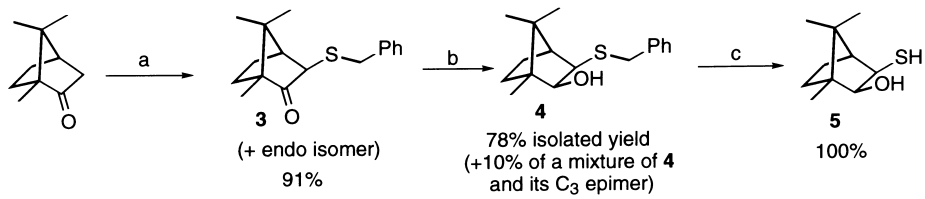
Scheme 1.



Scheme 2.

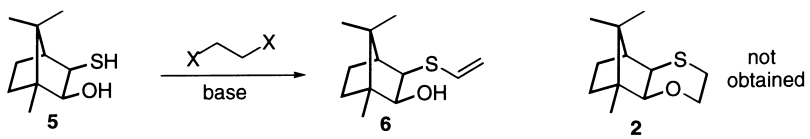
2. Results and discussion

The key intermediate in the synthesis of oxathiane **2** was hydroxy thiol **5** which was prepared using a combination of the procedures of Haynes and Ridley et al.[35] and Yang et al. as shown in Scheme 3. [36] Treatment of camphor with lithium diisopropylamide at −78°C generated the enolate which was cannulated into a solution of hexamethylphosphoramide and benzylthiotosylate to give the desired thioether **3** as a 97:3 mixture of *exo* and *endo* isomers which could not be separated at this stage (Scheme 3).[35] Treatment of **3** with diisobutylaluminium hydride at room temperature gave the corresponding *exo* alcohols, which could be readily separated by chromatography, in an overall yield of 88% (Scheme 3).[35] Debenzylation of **4** proceeded in quantitative yield to give the desired product **5** as a tractable white solid (Scheme 3).[36]



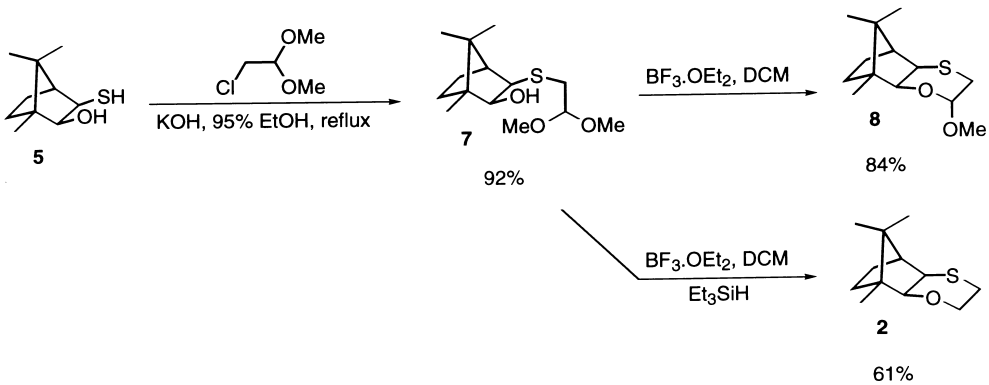
Scheme 3.

Attempts to dialkylate **5** using a variety of alkylating agents (X=Br, Cl), bases (Na_2CO_3, Et_3N, NaOMe, NaOH, Ag_2O, Bu^tOK), solvents, temperatures and additives (Bu_4NI, Bu_4NBr, Bu_4NCl, $CeCl_3$) all met with failure. In many cases the product of elimination **6** was obtained instead (Scheme 4).



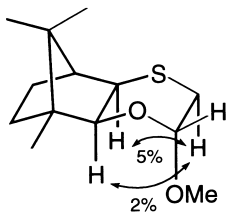
Scheme 4.

We therefore pursued an alternative route which proved more successful (Scheme 5). Reaction of hydroxythiol **5** with chloroacetaldehyde dimethyl acetal under basic conditions gave hydroxy acetal **7** which when treated with boron trifluoride etherate gave the cyclic acetal **8**.



Scheme 5.

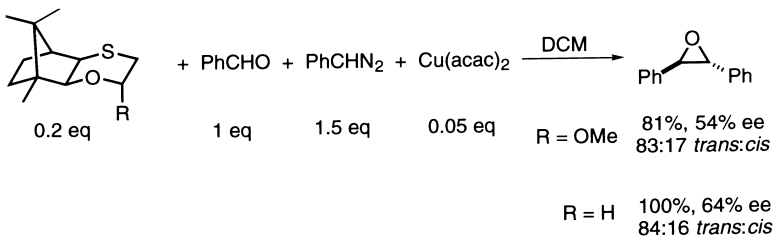
NOE studies on this compound showed that the methoxy group of the acetal moiety occupied the axial position as shown in Scheme 6. Irradiation of the axial proton adjacent to the sulfur gave the expected enhancements across the 1,4-oxathiane ring to the axial protons of the bornane skeleton. Irradiation of the acetal proton gave no such enhancements, indicating that this proton occupied the equatorial position. Enhancements between the axial protons on the camphor skeleton and the methoxy group were not reliable because of the relative proximity of their chemical shifts in the proton NMR spectra. The axial position of the methoxy group can be accounted for by the anomeric effect.[37–39]



Scheme 6.

Reaction of hydroxyacetal **7** with boron trifluoride etherate in the presence of triethylsilane gave oxathiane **2** directly.[40,41]

The 1,4-oxathianes **8** and **2** were tested in the catalytic cycle with benzaldehyde, using the standard conditions developed for the 1,3-oxathianes (Scheme 7).[27]

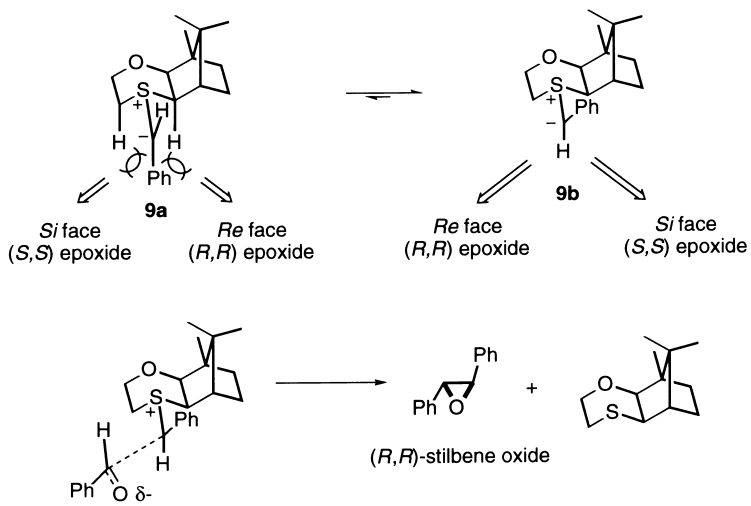


Scheme 7.

Significantly higher yields were obtained using the 1,4-oxathianes compared to the 1,3-oxathianes, suggesting that sulfide stability is an important factor. However, lower diastereoselectivity and enantioselectivity were observed. The diastereoselectivity is typical of simple, unhindered sulfides[42] which

do not have anomeric stabilisation.[43] The asymmetric induction observed is also similar to acyclic analogues of **2** (e.g. SMe ether of **5**).[44] This was surprising as greater selectivity was expected in ylide formation and conformation and greater face selectivity in reaction of the ylide was also expected from the conformationally more rigid sulfide.

The following model can be used to account for the sense of asymmetric induction observed (Scheme 8). Only one of the two sulfur lone pairs should be accessible, and hence only one diastereomer of the ylide should be formed upon reaction of the sulfide with the metal carbenoid. This ylide can adopt conformations **9a** or **9b**, but **9b** should be favoured due to 1,3-diaxial interactions in **9a**. The *Re* face should then be more accessible to the aldehyde due to the greater steric demands of the camphor skeleton hindering *Si* face attack. This would then lead to the formation of the (*R*,*R*) epoxide which was the major enantiomer obtained. The moderate enantioselectivity observed is probably due principally to incomplete facial selectivity.



Scheme 8.

3. Conclusions

1,4-Oxathianes **8** and **2** were prepared in five steps from camphor and were tested in the catalytic epoxidation cycle. It was found that epoxides were obtained in significantly higher yield but with lower diastereoselectivity and enantioselectivity compared to 1,3-oxathiane **1**. The higher yield is a result of the increased stability of the 1,4-oxathianes and their corresponding ylides to the reaction conditions, compared to the 1,3-oxathianes. The lower diastereoselectivity can be accounted for by the reduced stability of the ylide, resulting in less reversibility in betaine formation. The lower enantioselectivity is believed to arise from the lower face selectivity of the ylide.

4. Experimental

Proton and carbon-13 magnetic resonance spectra were recorded using a Bruker ACF-250 and a Bruker WH-400 (400 MHz) spectrophotometer supported by an Aspect 2000 data system. The chemical shifts were recorded on the δ scale and were measured relative to the residual signal of chloroform at δ 7.25.

All coupling constants are measured in hertz. The deuterated solvents used were as specified in the experimental sections. ^{13}C chemical shifts were measured from the central peak of chloroform at δ 77.0. Mass spectra were obtained using either a Kratos MS 25 or MS 80 instrument supported by a DS 55 data system operating in EI mode. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 157G grating FT-IR spectrophotometer. Optical rotations were measured using a Perkin–Elmer 141 polarimeter. $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excesses (ee) were determined by chiral HPLC using a Chiralcel OD column. Thin layer chromatography (TLC) was used routinely to monitor the progress and purity of compounds and was performed on Merck DC-alufolien Kieselgel 60 F254 sheets containing fluorescent indicator. TLC plates were visualised when possible with 254 nm ultraviolet light and by treatment with either a solution of phosphomolybdic acid (5 g dissolved in 100 mL of 95% ethanol), potassium permanganate (3 g potassium permanganate, 20 g potassium carbonate, 5 mL of a 5% w/v solution of sodium hydroxide dissolved in 300 mL of water), or anisaldehyde (9.2 mL of anisaldehyde, 3.75 mL of acetic acid, 12.5 mL of concentrated sulfuric acid dissolved in 338 mL of 95% ethanol) followed by warming of the TLC plate with a heat gun. Chromatographic purification of compounds was achieved by flash chromatography using Kieselgel 60 F254 and on C560, 40–63 micron. All solvents and reagents were purified according to standard procedures.

Compounds **3**, **4**[35] and **5**[36] were prepared as described in the literature.

*4.1. Preparation of (1*R,*2*S,*3*R,*4*S*)-3-(2,2-dimethoxyethylsulfanyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **7***

Potassium hydroxide (76 mg, 1.35 mmol) was added to a solution of hydroxy thiol **5** (102 mg, 0.55 mmol) and chloroacetaldehyde dimethylacetal (69 μL, 0.61 mmol) in 95% ethanol (1 mL) under nitrogen. The resulting mixture was heated under reflux for 20 h, after which time TLC analysis indicated that there was no starting material remaining. The ethanol was removed under reduced pressure and the residue loaded onto a silica gel column and eluted with 10% ethyl acetate in petrol to give the desired sulfide **7** as a clear oil (138 mg, 92%), $[\alpha]_D^{20}$ −8.1 (*c* 1.24 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3454.2 (OH), 2952, 1456, 1119; δ_H (250 MHz; $CDCl_3$) 0.76 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.02–1.26 (2H, m), 1.37–1.53 (1H, m), 1.62–1.91 (2H, m), 2.63 (1H, dd, *J* 14.0, 5.5, C*H*HS), 2.73 (1H, dd, *J* 14.0, 5.5, CH*H*S), 2.99 (1H, d, *J* 7.3, C*H*SR), 3.14 (1H, d, *J* 3.4, OH), 3.35 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.58 (1H, dd, *J* 7.3, 3.4, C*H*OH), 4.43 (1H, dd, *J* 5.5, 5.5, C*H*$(OMe)_2$); δ_C (63 MHz; $CDCl_3$) 11.71 (CH_3), 21.25 (CH_3), 21.34 (CH_3), 29.12 (CH_2), 33.26 (CH_2), 37.80 (CH_2), 46.73 (C), 49.55 (C), 53.21 (CH), 53.89 (CH_3), 53.93 (CH_3), 59.44 (CH), 79.16 (CH), 104.02 (CH); *m/z* (EI) 274 (M^+, 1.5%), 242 (M^+−MeOH, 1.5), 75 (100); Found: M^+, 274.1597. $C_{14}H_{26}O_3S$ requires 274.1603.

*4.2. Preparation of (1*R,*2*S,*4*R,*7*R,*8*S*)-4-methoxy-1,11,11-trimethyl-3-oxa-6-thiatricyclo[6.2.1.0^{2,7}]-undecane **8***

Boron trifluoride diethyl etherate (6 μL, 0.05 mmol) was added to an ice-cooled solution of sulfide **7** (12 mg, 0.04 mmol) in dichloromethane (100 μL) under nitrogen. The reaction was stirred for 1 h at 0°C, then warmed to room temperature and stirred for a further 2 h before loading directly onto a silica gel column and eluted with 5% ethyl acetate in petrol to give the desired sulfide **8** as a clear oil (9 mg, 84%), $[\alpha]_D^{20}$ −44.4 (*c* 5.41 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954, 1363, 1118, 1056; δ_H (250 MHz; $CDCl_3$) 0.82 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.02–1.21 (2H, m), 1.34 (3H, s, CH_3), 1.45–1.61 (1H, m), 1.67–1.88 (2H, m), 2.40 (1H, dd, *J* 14.0, 8.2, SC*H*H), 2.79 (1H, dd, *J* 14.0, 6.9, SCH*H*), 3.09 (1H, d, *J*

7.0, C*H*SR), 3.35 (3H, s, OCH_3), 3.45 (1H, d, *J* 7.0, C*H*OR), 4.82 (1H, dd, *J* 8.2, 7.0, C*H*OMe); δ_C (63 MHz; $CDCl_3$) 11.53 (CH_3), 21.70 (CH_3), 22.18 (CH_3), 29.22 (CH_2), 32.07 (CH_2), 33.63 (CH_2), 47.99 (C), 48.90 (C), 49.40 (CH), 51.62 (CH), 55.13 (CH_3), 75.59 (CH), 96.83 (CH); *m/z* (EI) 242 (M^+, 49%), 182 (32), 136 (100) 121 (80). Found: M^+, 242.1352. $C_{13}H_{22}O_2S$ requires 242.1341.

*4.3. Preparation of (1*R,*2*S,*7*R,*8*S*)-1,11,11-trimethyl-3-oxa-6-thiatricyclo[6.2.1.0^{2,7}]undecane **2***

Boron trifluoride diethyl etherate (0.04 mL, 0.33 mmol) was added to a solution of sulfide **7** (63 mg, 0.23 mmol) in dichloromethane (0.5 mL) under nitrogen. Triethylsilane (0.04 mL, 0.25 mmol) was added to the stirred solution after a few minutes, as TLC analysis indicated that no starting material remained. After a further 30 minutes, the reaction mixture was washed through a short pad of silica with 10% ethyl acetate in petrol, the solvents were removed under reduced pressure and the residue loaded onto a silica gel column and eluted with 5% ethyl acetate in petrol to give the desired 1,4-oxathiane **2** as a colourless oil (30 mg, 61%), $[\alpha]_D^{20}$ +46.98 (*c* 2.98 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2953, 1457, 1391, 1101; δ_H (250 MHz; $CDCl_3$) 0.82 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.01–1.18 (2H, m), 1.38 (3H, s, CH_3), 1.43–1.86 (3H, m), 2.56–2.90 (2H, m, CH_2S), 2.90–3.06 (1H, br d, *J* 6.7, C*H*SR), 3.20 (1H, d, *J* 6.7, C*H*OR), 3.46 (1H, ddd, *J* 10.7, 6.3, 4.9, OC*H*H), 3.96 (1H, ddd, *J* 10.7, 6.3, 4.9, OCH*H*); δ_C (63 MHz; $CDCl_3$) 11.72 (CH_3), 21.52 (CH_3), 22.13 (CH_3), 26.14 (CH_2), 29.13 (CH_2), 33.92 (CH_2), 47.84 (C), 48.19 (CH), 49.43 (C), 50.63 (CH), 62.73 (CH_2), 84.86 (CH); *m/z* (EI) 212 (M^+, 100%), 184 ($M^+ - C_2H_4$, 14), 108 (63), 102 (90).

4.4. General procedure for the epoxidation of benzaldehyde using catalytic quantities of sulfide

Using a syringe pump, phenyldiazomethane (0.75 mmol in 0.25 mL of dichloromethane) was added to a stirred solution of the desired sulfide (0.1 mmol), $Cu(acac)_2$ (0.025 mmol) and benzaldehyde (0.5 mmol) in dichloromethane (0.25 mL), under nitrogen at room temperature over a period of 3 h. After stirring for a further 1 h the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give *trans*-stilbene oxide. δ_H (250 MHz; $CDCl_3$) 3.85 (2H, s, C*H*), 7.35 (10 H, m, Ar*H*) (lit.,[34]).

Acknowledgements

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