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Sulfoxide-directed desymmetrisation of cyclohexa-1,4-dienes

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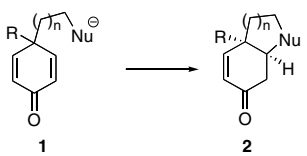
Abstract—Cyclohexa-2,5-dien-1-ylmethanol derivatives have been subjected to a short sequence featuring esterification to introduce a malonate side-chain, oxidation of the doubly allylic position and stereoselective cyclisation. When used in conjunction with a chiral sulfoxide, the cyclisation is diastereoselective (2:1) favouring one of the diastereotopic double-bonds.

1. Introduction

The stereoselective formation of quaternary stereogenic centres, particularly all-carbon quaternary stereogenic centres, is a significant challenge for the modern synthetic chemist.[1] As an alternative to the direct formation of such a stereogenic centre using carbon–carbon bond forming reactions, the indirect approach of desymmetrising a suitable precursor is attractive.[2] Cyclohexa-1,4-dienes are attractive substrates for such reactions, and have been desymmetrised by way of free-radical,[3] and anionic[4] cyclisation reactions as well as by asymmetric oxidation[5] and cycloaddition.[6] In a prototype reaction, the cyclisation of compound **1** leads to the formation of two new stereogenic centres, one of which is quaternary. The double-bonds in diene **1** are enantiotopic, and so preferential attack on one of them would result in the enantioselective formation of the cyclised product **2** (Scheme 1).

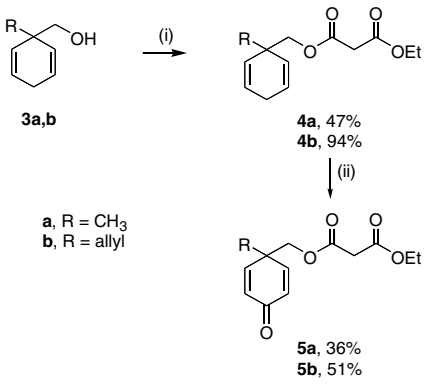
There are a wide range of possible substrates for such a reaction, these differing mainly in the choice of nucleophile and tether length, but also in the method used for inducing asymmetry. For our preliminary studies we were attracted to the use of chiral sulfoxides,[7] since these can readily be formed with high enantiomeric excess.[8] This would constitute a diastereoselective approach, and so a single enantiomer of the sulfoxide would not actually be necessary in order to prove the validity of the method.[9]



Scheme 1.

2. Discussion

Initially we chose to prepare achiral substrates which would allow us to test the key bond-forming reactions without the added stereochemical complexities, and for this purpose selected a malonate-type nucleophile for cyclisation. The formation of substrates **5a** and **5b** was straightforward as shown in Scheme 2. Compounds



Scheme 2. Reagents and conditions: (i) Ethyl malonyl chloride, Et_3N, DMAP, CH_2Cl_2; (ii) PDC, *t*-BuOOH in decane, celite, benzene.

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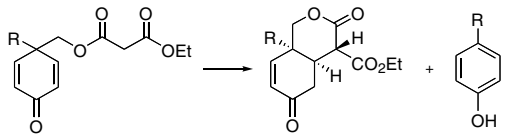
3a[10] and **3b** were prepared by Birch reduction/alkylation[11] of benzoic acid followed by reduction. Reaction of alcohols **3a** and **3b** thus formed with ethyl malonyl chloride gave mixed malonate esters **4a** and **4b** in moderate yields. The allylic oxidation[12] of these compounds under standard conditions was a clean reaction, and completely chemoselective, but unfortunately the isolated yields of dienones **5a** and **5b** after chromatography were relatively poor. Nevertheless, this method allowed the formation of sufficient quantities of these compounds for evaluation in the key cyclisation reaction. Cyclisation of **5a** or **5b** could give rise to the formation of four diastereomeric products. In the event, we have only ever observed the formation of a single diastereoisomer (Table 1). Using sodium ethoxide in ethanol, the desired product **6a** was accompanied by significant amounts of phenol **7a**. This is presumably formed by transesterification of **5a** followed by deformylation. Similar results were obtained with substrate **5b**. Using potassium *t*-butoxide as base in THF, only the desired product **6a** was formed from **5a**, although with **5b**, compound **7b** was also formed under these conditions (Table 1). The stereochemistry of compounds **6a** and **6b** were deduced by extensive 2D NMR spectroscopy, and are supported by the crystal structure determination of a related compound (vide infra).

Although the relative stereochemistry of compounds **6a** and **6b** can easily be rationalised by the geometry shown in structure **8** in Scheme 3, the actual scenario may not be as straightforward. While this attack will most likely give stereoisomer **9**, this will be followed by rapid proton transfer under the reaction conditions to give malonate anion **10**. The observed stereochemistry will then be defined upon protonation during work-up.

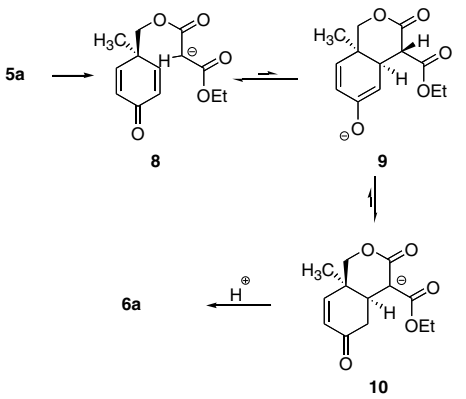
Table 1. Cyclisation of compounds **5a** and **5b**



5a,b **6a,b** **7a,b**

Substrate	R	Conditions[a]	Yield of **6** (%)	Yield of **7** (%)
5a	CH_3	NaOEt, EtOH	35	35
5a	CH_3	KO*t*-Bu, THF	92	0
5b	Allyl	NaOEt, EtOH	31	27
5b	Allyl	KO*t*-Bu, THF	38	8

[a] All reactions were carried out at 25 °C.

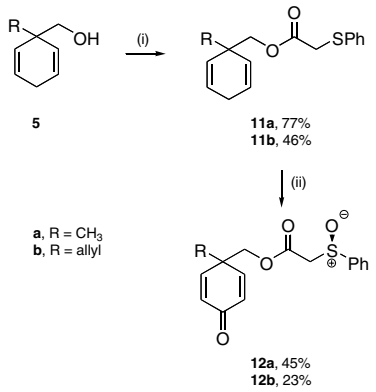


Scheme 3. Proposed reaction geometry and proton transfer.

With these results in hand, our attention then turned to the preparation of a chiral sulfoxide in order to carry out an auxiliary-controlled cyclisation reaction. Coupling of alcohols **3a** and **3b** with phenylsulfanylacetyl chloride[13] gave esters **11a** and **11b** in moderate yield. Oxidation as before also gave clean oxidation of the sulfide to the required sulfoxides **12a** and **12b** with no evidence for over oxidation to the sulfone (Scheme 4).

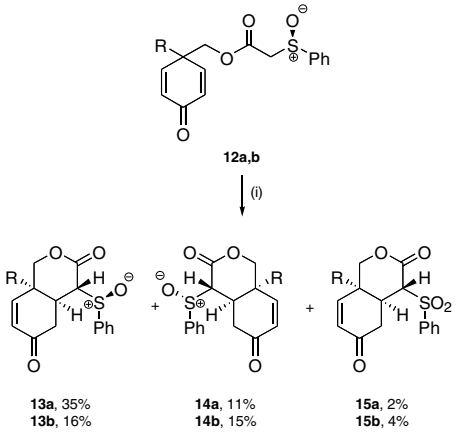
With these two key substrates in hand, the cyclisation step was attempted next (Scheme 5). Cyclisation of compounds **12a** and **12b** both proceeded cleanly to give a mixture of three compounds (2:1 mixture of the main two compounds in both cases, plus small variable amounts of a very minor component). These were separated by column chromatography, although significant losses occurred so that the isolated yields do not necessarily reflect the stereoselectivity of the reaction.

Sufoxides **14a** and **13b** and sulfone **15a** were characterised by single crystal X-ray diffraction (Figs. 1–3).[14] Isolation of the sulfones was somewhat surprising given the



5 **11a**, 77% **11b**, 46% **12a**, 45% **12b**, 23%

Scheme 4. Reagents and conditions: (i) Phenylsulfanylacetyl chloride, Et_3N, DMAP, CH_2Cl_2; (ii) PDC, *t*-BuOOH in decane, Celite, benzene.



12a,b **13a**, 35% **13b**, 16% **14a**, 11% **14b**, 15% **15a**, 2% **15b**, 4%

Scheme 5. Reagents and conditions: (i) KO*t*-Bu, THF, 25 °C.

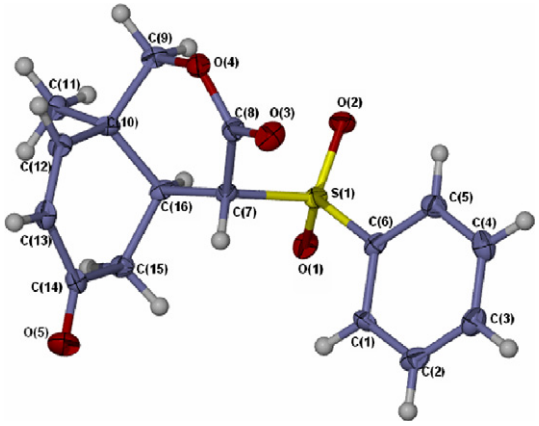


Figure 1. Structure of compound **15a** from X-ray crystallographic data.

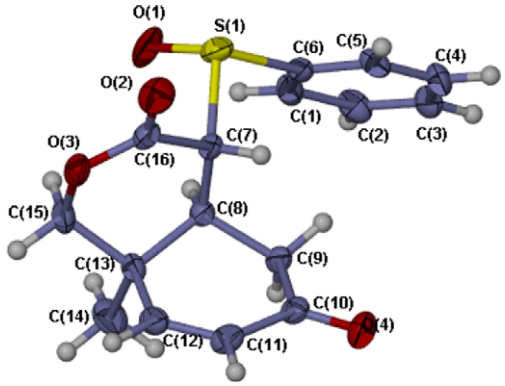


Figure 2. Structure of compound **14a** from X-ray crystallographic data.

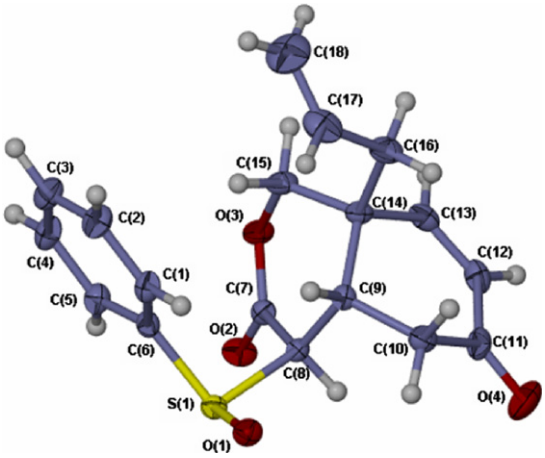
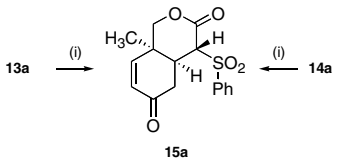


Figure 3. Structure of compound **13b** from X-ray crystallographic data.

lack of sulfone impurities in sulfoxides **12a** and **12b**, and we speculate that some oxidation of the cyclised sulfoxides is occurring upon chromatography. Although the similarity in spectroscopic data between **13a** and **13b** and between **14a** and **14b** strongly supports the assignment of diastereoisomers at sulfur, this was confirmed for **13a** and **14a** by oxidation of both compounds to give sulfone **15a** (Scheme 6). Furthermore, when this oxidation was carried out to approximately 50% conversion, there was no isomerisation of the residual starting material, confirming that both sulfoxides are stereochemically stable under the conditions used for oxidation.



Scheme 6. Reagents and conditions: (i) Oxone®, H_2O, MeOH.

In summary, we have demonstrated for the first time that chiral sulfoxides can be used to direct the cyclisation of enolate nucleophiles onto cyclohexadienones.

3. Experimental

3.1. Cyclisation of sulfoxide 12a

In a flame-dried flask and under a nitrogen atmosphere, potassium *t*-butoxide (7 mmol, 0.78 g, 2 equiv) was added to a cooled solution of sulfoxide **12a** (1.059 g, 3.48 mmol) in dry THF (130 ml) at 0 °C. The mixture was stirred at this temperature for 5.5 h, and then at room temperature for 17.5 h. The resulting mixture was quenched with saturated NH_4Cl solution (50 ml), and the organic material was extracted into CH_2Cl_2 (3×50 ml). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to afford 592 mg of a crude mixture of compounds **15a**, **14a**, and **13a** as a golden solid. Purification by flash chromatography (eluting with CH_2Cl_2–ethyl acetate 9.3:0.7) afforded, on order of elution, pure products **15a**, **14a** and **13a**.

3.2. (*S*$_{SR}$,4*SR*,4a*RS*,8a*SR*)-4-Benzenesulfinyl-8a-methyl-1,4a,5,8a-tetrahydro-4*H*-isochromene-3,6-dione (13a)

Off-white solid (372 mg, 35%), mp 132–134 °C (Found: MH^+ 305.0843. $C_{16}H_{17}SO_4$ requires M, 305.0842); ν_{max} (CH_2Cl_2)/cm^{-1} 3055, 2985, 1724, 1686, 1424, 1265, 1050, 738; δ_H (400 MHz; $CDCl_3$) 7.61–7.50 (5H, m, $5 \times$ aromatic CH), 6.54 (1H, dd, *J* 10.3, 1.8 C*H*=CH–C=O), 6.03 (1H, d, *J* 10.3, CH=C*H*–C=*O*), 3.86 (1H, d, *J* 5.6, CH–SO), 3.75 (1H, d, *J* 11.3, one of O–CH_2), 2.90–2.84 (3H, m, one of O–CH_2, ring junction CH and one of CH_2–C=O), 2.47 (1H, dd, *J* 18.7, 4.0, one of CH_2–C=O), 1.09 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 195.2 (C=O), 163.6 (O–C=O), 152.2 (C*H*=CH–C=O), 139.3 (C_q–S), 132.7 (*p*-aromatic CH), 132.1 (CH=C*H*–C=O), 129.5 ($2 \times o$-aromatic CH), 125.1 ($2 \times m$-aromatic CH), 74.5 (O–CH_2), 66.5 (CH–SO), 40.6 (*C*H_2–C=O), 36.2 (C_q ring), 36.1 (ring junction CH), 20.7 (CH_3); *m*/*z* (APCI) 305 (MH^+, 100%), 247 (19), 179 (34).

3.3. (*S*$_{SR}$,4*RS*,4a*SR*,8a*RS*)-4-Benzenesulfinyl-8a-methyl-1,4a,5,8a-tetrahydro-4*H*-isochromene-3,6-dione (14a)

Yellow solid (118 mg, 11%), mp 108–110 °C (Found: MNH_4^+ 322.1111. $C_{16}H_{20}SO_4N$ requires M, 322.1108);

ν_{max} ($CDCl_3$)/cm^{-1} 1737, 1685, 1445, 1404, 1247, 1060, 909, 733; δ_H (400 MHz; $CDCl_3$) 7.61–7.56 (2H, m, 2 × aromatic CH), 7.55–7.50 (3H, m, 3 × aromatic CH), 6.63 (1H, dd, *J* 10.2, 1.8, C*H*=CH–C=O), 5.98 (1H, d, *J* 10.2, CH=C*H*–C=O), 4.32 (1H, d, *J* 11.2, one of O–CH_2), 4.05 (1H, d, *J* 11.2, one of O–CH_2), 3.25 (1H, d, *J* 5.1, CH–SO), 2.91–2.85 (1H, m, ring junction CH), 2.36 (1H, dd, *J* 17.3, 5.2, one of CH_2–C=O), 1.23 (3H, s, CH_3), 0.93 (1H, dd, *J* 17.3, 2.7, one of CH_2–C=O); δ_C (100 MHz; $CDCl_3$) 195.0 (C=O), 167.0 (O–C=O), 152.9 (C*H*=CH–C=O), 140.2 (C_q–S), 132.3 (*p*-aromatic CH), 131.7 (CH=C*H*–C=O), 129.8 (2 × *o*-aromatic CH), 124.0 (2 × *m*-aromatic CH), 74.7 (O–CH_2), 69.4 (CH–SO), 39.8 (CH_2–C=O), 36.5 (C_q ring), 33.6 (ring junction CH), 20.4 (CH_3); *m*/*z* (APCI) 305 (MH^+, 39%), 235 (35), 197 (10), 180 (12), 179 (100), 149 (10), 125 (37).

3.4. (4*RS*,4a*SR*,8a*RS*)-4-Benzenesulfonyl-8a-methyl-1,4a,5,8a-tetrahydro-4*H*-isochromene-3,6-dione (15a)

Off-white solid (21 mg, 2%), mp 185–186 °C (Found: MNH_4^+ 338.1062. $C_{16}H_{20}O_5NS$ requires M, 338.1057); ν_{max} (CH_2Cl_2)/cm^{-1} 3056, 2940, 1737, 1680, 1319, 1265, 1149, 736; δ_H (400 MHz; $CDCl_3$) 7.80 (2H, app. dd, *J* 8.4, 1.2, 2 × *o*-aromatic CH), 7.66 (1H, app. tt, *J* 7.4, 1.2, *p*-aromatic CH), 7.56–7.50 (2H, m, 2 × *m*-aromatic CH), 6.63 (1H, dd, *J* 10.3, 2.0, C*H*=CH–C=O), 6.03 (1H, d, *J* 10.3, CH=C*H*–C=O), 4.51 (1H, d, *J* 11.3, one of O–CH_2), 4.17 (1H, d, *J* 11.3, one of O–CH_2), 3.72 (1H, d, *J* 5.4, CH–SO_2), 3.3 (1H, app. tt, *J* 5.0, 2.5, ring junction CH), 2.95 (1H, dd, *J* 17.5, 5.0, one of CH_2–C=O), 2.56 (1H, dd, *J* 17.5, 2.5, one of CH_2–C=O), 1.34 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 194.8 (C=O), 162.4 (O–C=O), 152.0 (C*H*=CH–C=O), 136.0 (C_q–S), 135.0 (CH=C*H*–C=O), 132.0 (*p*-aromatic CH), 129.4 (2 × *o*-aromatic CH), 129.3 (2 × *m*-aromatic CH), 75.2 (O–CH_2), 69.6 (CH–SO_2), 40.5 (*C*H_2–C=O), 38.4 (ring junction CH), 36.9 (C_q ring), 20.3 (CH_3); *m*/*z* (APCI) 321 (MH^+, 100%), 319 (11), 121 (16).

Acknowledgements

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14. CCDC Nos. 634105, 634104 and 634106 contain the supplementary crystallographic data for compounds **14a**, **15a** and **13b**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Figures 1–3 are Pov-Ray representations with thermal ellipsoids at the 50% probability level.