Diversion from Bicyclo[4.2.0]octanol Formation Through the Use of Vinyl Electrophiles

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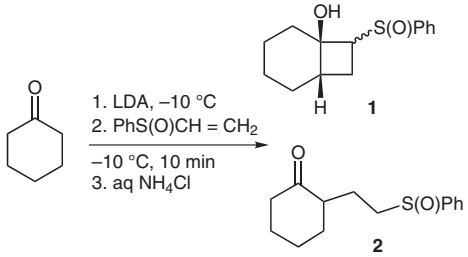
Abstract: Bicyclo[4.2.0]octanols can be obtained from the reaction of phenyl vinyl sulfoxide and the lithium enolate of cyclohexanone under controlled conditions. Diversion to alkylation or Michael–Michael-ring closure was observed when alternative vinyl electrophiles were used. Novel bicyclic disulfones and hydroxyhexahydronaphthalenes were isolated. The use of a vinyl sulfoxide electrophile is crucial to the formation of bicyclo[4.2.0]octanols from simple ketones.

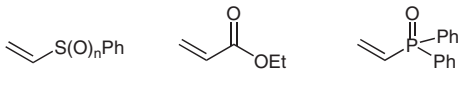
Key words: alkylations, bicyclic compounds, ketones, Michael additions, ring closure

Previously, the efficient assembly of bicyclo[n.2.0]alkan-1-ols was achieved by reaction of the lithium enolate of (simple) ketones and phenyl (or tolyl) vinyl sulfoxide (for example **1**, Scheme 1).[1–4] Controlled reaction conditions are required to favour bicyclo[n.2.0]alkanol formation over alkylation products such as **2**.[1] Notably alternate electrophiles have not been tested under the specific conditions required for bicyclo[n.2.0]alkanol formation. Now selected α,β-unsaturated electrophiles were considered in order to explore whether other novel functionality could be introduced to produce functionalized bicyclo[4.2.0]octan-1-ols in this process.



Scheme 1

Presently, the role of oxidation state and geometry at sulfur, and the polarity of the sulfur–oxygen bond in the electrophile were probed, using cyclohexanone as a representative ketone. Phenyl vinyl sulfide (**3**), phenyl vinyl sulfone (**5**), ethyl acrylate (**6**) and diphenylvinylphosphine oxide (**7**), were selected as electrophiles (Figure 1). Acrylonitrile was not considered due to its propensity to polymerise.



3 n = 0
4 n = 1
5 n = 2

6 **7**

Figure 1 α,β-Unsaturated electrophiles used in this work

In this study, the lithium enolate of cyclohexanone was generated from cyclohexanone or TMS cyclohexyl ether, either method giving similar results with phenyl vinyl sulfoxide (**4**) as previously described.[2] To allow for comparison, the lithium enolate of cyclohexanone was treated with electrophiles **3**, **5**–**7** under conditions that had previously given moderate to good yields of bicyclo[4.2.0]octan-1-ols with **4** (–30 °C, 5 min or –10 °C, 10 min).[1] A range of results was obtained (Table 1).

Reaction of the lithium enolate of cyclohexanone with phenyl vinyl sulfide (**3**), yielded only unreacted **3** (entry 1, Table 1). This result may not be unexpected. Although phenyl vinyl sulfide (**3**) has been used as an electrophile in reactions with nucleophiles such as alkyllithium bases[5] and the *t*-BuOK catalysed addition of some ketones and nitriles,[6] conjugate addition of lithium enolates to α,β-unsaturated sulfides is unreported.

Reaction of the lithium enolate of cyclohexanone with phenyl vinyl sulfone (**5**) under controlled conditions gave a complex mixture of products, including unreacted cyclohexanone (entry 4, Table 1). Signals attributable to phenyl vinyl sulfone (**5**) were not detected in the ^{1}H NMR (400 MHz) spectrum of the crude product mixture, indicating that the electrophile had been completely consumed in the reaction. Monoalkylated ketone **8**[7,8] (2.5%) and 2,4-bis(phenylsulfonyl)octahydronaphthalen-4a-ols **9**–**14** (46%) (Figure 2) were isolated in a 33:22:7:14:13:11 ratio of **9**:**10**:**11**:**12**:**13**:**14**.

In the course of this work, single crystals of bicyclic disulfones **9**, **10**, **11** and **12**, were obtained and the X-ray crystal structures determined. The ORTEP-3 diagrams are shown in Figure 3.[9] The relative stereochemistry of **9**, **10**, **11** and **12**, assigned using the X-ray crystal structures were consistent with the stereochemistry assigned by NMR spectroscopy.

Crystal packing of structures **9**–**12** is stabilized by O–H···O$_{(s)}$ and C–H···O$_{(s)}$ hydrogen bonding and by both face-to-face π···π and edge-to-face C–H···π phenyl–phenyl in-

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Table 1 Reaction of Electrophiles **3**–**7** with Enolate Precursors

Entry	Enolate Precursor	Electrophile	Temp (°C)	Time (min)	Product (Yield, %)
1	cyclohexanone	**3**	–30	5	**3** (95)
2	cyclohexanone	**4**	–30	5	**1** (42), **2** (3)
3	cyclohexanone	**4**	–10	10	**1** (74), **2** (4)
4	cyclohexanone	**5**	–10	10	**8** (2.5), **9** (15), **10** (10), **11** (3.5), **12** (6.5), **13** (6), **14** (5)
5	cyclohexanone	**6**	–30	5	**15** (14.5), **16** (6.5), **17** (36)
6	cyclohexenyloxy-TMS	**7**	–10	10	**18** (89)

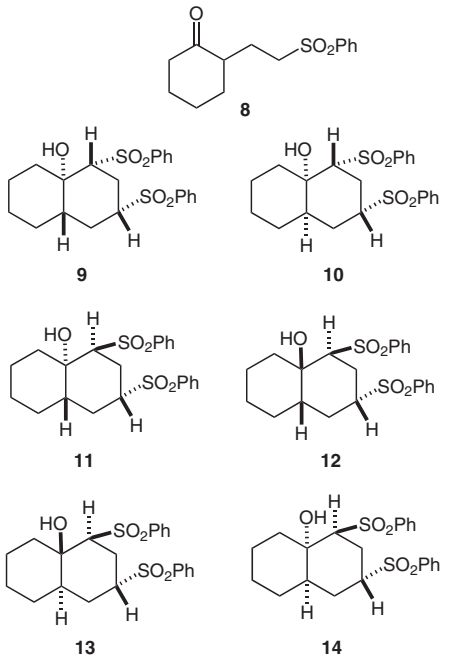


Figure 2 Products from the reaction of phenyl vinyl sulfone (**5**) with the enolate of cyclohexanone

teractions. In all four structures, the hexahydronaphthalene rings lie in a fused chair-chair conformation.

Since crystals suitable for X-ray structure determination could not be obtained for bicyclic disulfones **13** and **14**, the relative stereochemistry for these bicyclic disulfones was assigned from the ^{1}H NMR spectra coupling constants (H2 as pseudo equatorial and H4 as axial) and the construction of simple models.

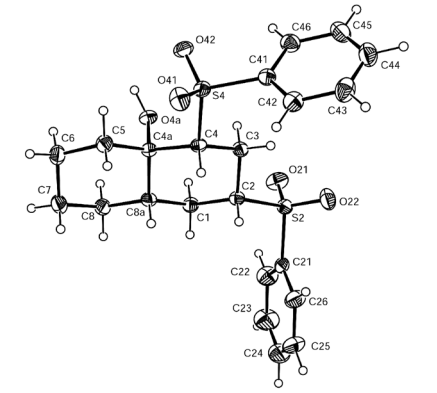
For bicyclic disulfone **13**, it was determined that H2 pseudo equatorial and H4 axial would be on opposite faces of the molecule. With a *trans* ring junction, the hydroxyl group must be on the same face as H2 and the relative stereochemistry was thus assigned as (2*RS*,4*SR*,4a*RS*,8a*RS*)-**13**. In bicyclic disulfone **14**, H2 equatorial and H4 axial would be on opposite faces of the molecule and with a *cis* ring junction the hydroxyl group must occupy the same face as H4. In the ^{1}H NMR spectrum, the chemical shift of H4 axial ($\delta = 4.01$) was consistent with deshielding of this proton as a result of proximity to the hydroxyl group and the axial phenyl sulfonyl group at C2. The relative stereochemistry was thus assigned as (2*RS*,4*SR*,4a*SR*,8a*RS*)-**14**. The absent isomers (2*RS*,4*RS*,4a*RS*,8a*SR* and 2*RR*,4*RR*,4a*RR*,8a*RR*) both have conformations which either have unfavourable 1,3-diaxial phenylsulfonyl interactions or hydroxy, phenylsulfonyl gauche interactions.

Alkylation of enolates by phenyl vinyl sulfone,[10] domino Michael reactions leading to tricyclo[3.2.1.0^{2,7}]octan-6-ones,[11] bicyclo[2.2.2]octan-2,5-diones,[12] decalones[13] and a hydrindanol[14] have been observed. Here we report the first example of a *Mi*chael–*Mi*chael-*R*ing *C*losure (MIMIRC) of phenyl vinyl sulfone to form a hydroxyhexahydronaphthalene, with determination of the diastereomers obtained.

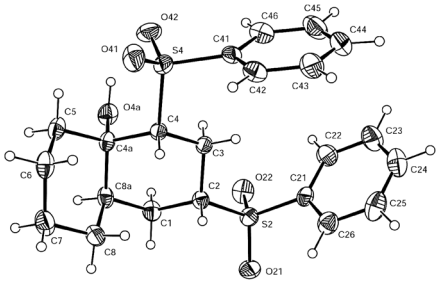
Next, the lithium enolate of cyclohexanone was reacted with ethyl acrylate under controlled conditions (entry 5, Table 1). ^{1}H NMR (400 MHz) spectroscopic analysis of the crude mixture obtained indicated that unreacted cyclohexanone was present, ethyl acrylate had been completely consumed and other products were present. Three diesters **15**–**17** were isolated from the crude product mixture in a combined unoptimised yield of 57%. Monoalkylation of cyclohexanone was not observed. Assignment of the relative stereochemistry of diesters **15**–**17** was based on ^{1}H NMR spectra coupling constants for individual protons and are shown in Figure 4.

Bicyclic esters **15**–**17** arose from a MIMIRC process, as observed with the reaction of the phenyl vinyl sulfone (**5**). However, the MIMIRC process was more selective when ethyl acrylate (**6**) was used as the electrophile instead of phenyl vinyl sulfone (**5**). The different distribution of isomers was attributed to the relative reactivity of the electrophile and subsequent steric interactions in the resultant products. Sequential MIMIRC of vinyl esters in the formation of polyfunctionalised cyclohexanols have been reported.[15] Here, we report the first 'unfunctionalised' example, with the formation of diesters **15**–**17**.

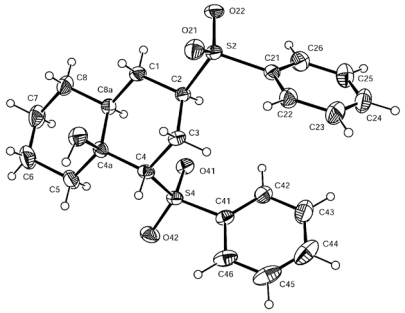
In a final example, the lithium enolate of cyclohexanone was reacted with diphenyl phosphine oxide (**7**),[16] under controlled conditions (entry 6, Table 1). The only product observed was phosphine oxide **18** (89%).[16] Phosphine oxide **18** arose from simple alkylation, and has been described previously as the product formed from the



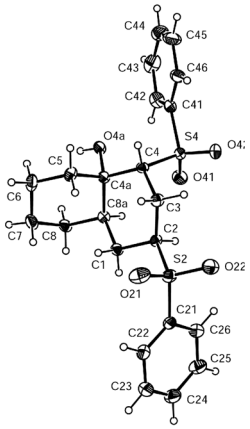
(2*RS*,4*RS*,4a*SR*,8a*SR*)-**9**



(2*RS*,4*RS*,4a*SR*,8a*RS*)-**10**

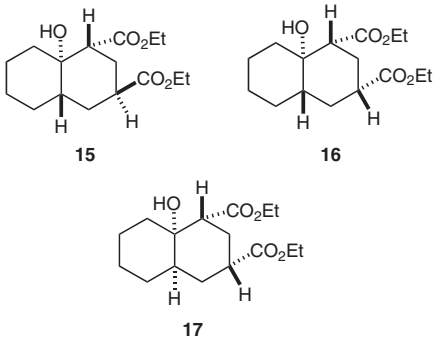


(2*RS*,4*SR*,4a*SR*,8a*SR*)-**11**



(2*SR*,4*RS*,4a*SR*,8a*RS*)-**12**

Figure 3 ORTEP-3 diagrams for the molecular structure of the bicyclic disulfones **9**–**12** shown with the assignment of the relative stereochemistry in each case. Displacement ellipsoids for the non-hydrogen atoms are drawn with 30% probability.



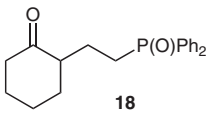
15 **16** **17**

Figure 4 Products from the reaction of ethyl acrylate (**6**) with the enolate of cyclohexanone

pyrrolidine enamine of cyclohexanone and diphenylvinylphosphine oxide.[17]

The results presented above highlight the critical role of the sulfoxide functional group in the formation of bicyclo[4.2.0]octan-1-ols from the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide (**4**). The recovery of phenyl vinyl sulfide (**3**) confirmed the requirement for the electrophile to at least be reactive to nucleophilic attack by a ketone enolate in conjugate addition.

Changing the oxidation state of sulfur from sulfoxide to sulfone dramatically diverted the reaction from bicyclooctanol formation to MIMIRC and generated the novel bicyclic disulfones **9**–**14**. Replacing sulfur with carbon or phosphorus also stopped bicyclo[4.2.0]octan-1-ol formation. In the reaction with the lithium enolate of cyclohexanone, ethyl acrylate (**6**) gave novel hydroxyhexahydronaphthalenes **15**–**17** resulting from MIMIRC whereas diphenylvinylphosphine oxide (**7**) gave a single product of monoalkylation **18** (Figure 5). These results imply that the different valence, hybridisation and geometry of sulfur with carbon and phosphorus and the polarity of the S–O bond must be important to the reaction intermediate(s) required for bicyclo[4.2.0]octanol formation. It was concluded that the sulfoxide functionality in α,β-unsaturated electrophile was essential to the formation of bicyclo[4.2.0]octan-1-ols from the lithium enolate of cyclohexanone. The crucial involvement of phenyl vinyl sulfoxide has implications for further applications of the cyclisation methodology for the formation of bicycloalkanols.



18

Figure 5 Product from the reaction of diphenylvinylphosphine oxide (**7**) with the enolate of cyclohexanone

The general experimental conditions, reaction with phenyl vinyl sulfoxide and instrumentation have been described elsewhere.[1–3] Solvents and commercially available reagents were purified in the standard manner. Diphenylvinylphosphine oxide **7** was prepared according to literature procedure.[16]

Data Collection, Structure Solution and Refinement

X-ray diffraction data were collected at 295(2) K on a Rigaku AFC7R diffractometer, MoK_α radiation (λ = 0.71069 Å), graphite monochromator, using $\omega/2\theta$ or ω scans. Absorption corrections were not applied. The structures were solved by direct methods and refined using full-matrix least squares on F^2. Non-hydrogen atoms were refined anisotropically. The carbon protons were included at calculated position and constrained as riding atoms with C–H 0.95 Å. The hydroxyl protons were located by difference methods and constrained as a riding atoms with O–H 0.90 Å. U_{iso}(H) values were set to 1.2 U_{eq} of the parent atom. Computation used the TeXsan[18] and SHELX-97[19] program systems, and ORTEP-3[20] software.

Crystal Data

9

$C_{22}H_{26}O_5S_2$, M = 434.6. Triclinic, space group P–1, a = 13.360(3), b = 14.369(6), c = 5.749(3) Å, α = 99.67(4), β = 102.41(3), γ = 96.69(2)°, V = 1049 Å^3. D_c (Z = 2) = 1.376 g cm^{-3}. Crystal size: 0.35 × 0.20 × 0.20 mm;. $2\theta_{max}$ = 55°; 5678 reflections collected, 4824 unique (R_{int} = 0.035). R = 0.040 [3428 reflections with I>2σ(I)], w$R(F^2)$ (all data) = 0.117. $|\Delta\rho_{max}|$ = 0.280 eÅ^{-3}.

10

$C_{22}H_{26}O_5S_2$, M = 434.6. Monoclinic, space group $P2_1/n$, a = 21.384(9), b = 9.560(4), c = 10.635(4) Å, β = 94.30(3), V = 2168 Å^3. D_c (Z = 4) = 1.325 g cm^{-3}. Crystal size: 0.40 × 0.30 × 0.30 mm;. $2\theta_{max}$ = 55°; 6041 reflections collected, 5007 unique (R_{int} = 0.064). R = 0.050 [2579 reflections with I>2σ(I)], w$R(F^2)$ (all data) = 0.154. $|\Delta\rho_{max}|$ = 0.401 eÅ^{-3}.

11

$C_{22}H_{26}O_5S_2$, M = 434.6. Monoclinic, space group $P2_1/n$, a = 15.672(6), b = 10.462(4), c = 13.148(5) Å, β = 97.46(3), V = 2137 Å^3. D_c (Z = 4) = 1.350 g cm^{-3}. Crystal size: 0.30 × 0.30 × 0.20 mm;. $2\theta_{max}$ = 55°; 5520 reflections collected, 4905 unique (R_{int} = 0.034). R = 0.046 [2762 reflections with I>2σ(I)], w$R(F^2)$ (all data) = 0.144. $|\Delta\rho_{max}|$ = 0.363 eÅ^{-3}.

12

$C_{22}H_{26}O_5S_2$, M = 434.6. Monoclinic, space group Cc, a = 5.865(3), b = 21.999(9), c = 15.908(5) Å, β = 93.05(3), V = 2049 Å^3. D_c (Z = 4) = 1.408 g cm^{-3}. Crystal size: 0.30 × 0.15 × 0.10 mm;. $2\theta_{max}$ = 55°; 2770 reflections collected, 2361 unique (R_{int} = 0.028). R = 0.036 [1762 reflections with I>2σ(I)], w$R(F^2)$ (all data) = 0.094. $|\Delta\rho_{max}|$ = 0.235 eÅ^{-3}.

Reaction of Enolate of Cyclohexanone with Phenyl Vinyl Sulfide (3)

The lithium enolate of cyclohexanone, generated from LDA (~2.0 M, 2.80 mL, 5.60 mmol) and cyclohexanone (0.50 g, 0.53 mL, 5.10 mmol) in THF (30 mL), was allowed to warm to –30 °C and to this was added phenyl vinyl sulfide (**3**; 0.69 g, 0.67 mL, 5.10 mmol) in one portion. The reaction mixture was stirred for 5 min and the temperature was maintained at –30 °C during this time. The reaction was quenched with aq sat. NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the crude mixture as an amber oil (674 mg). The mixture was analysed by ^{1}H NMR (200 MHz) spectroscopy and determined to contain unreacted phenyl vinyl sulfide **3** (>95%).

Reaction of Enolate of Cyclohexanone with Phenyl Vinyl Sulfone (5)

The lithium enolate of cyclohexanone, generated from LDA (~2.0 M, 4.70 mL, 9.40 mmol) and cyclohexanone (0.92 g, 0.97 mL, 9.40 mmol) in THF (50 mL), was allowed to warm to –10 °C. Phenyl vinyl sulfone (**5**; 1.58 g, 9.40 mmol) in THF (5 mL) was added rapidly and the reaction mixture stirred for 10 min. The temperature was maintained at –10 °C during this time. The reaction was quenched and worked up as described above to give the crude mixture as an amber oil (2.136 g). The crude reaction mixture, analysed by ^{1}H NMR (400 MHz), spectroscopy included a complex mixture of 2,4-bis(phenylsulfonyl)octahydronaphthalen-4a-ol (bicyclic disulfones **9**–**14**), the monoalkylated ketone **8**, and unreacted cyclohexanone. The crude product mixture was fractionated by silica column chromatography using a solvent gradient starting with 100% hexane and increasing to EtOAc–hexane (50:50). Five major fractions and other minor fractions (298 mg) containing complex mixtures of products were obtained. Fraction 1 contained a mixture of the monoalkylated ketone **8** and bicyclic disulfone **14** (90 mg, 47:53). Fraction 2 contained a mixture of monoalkylated ketone **8** and bicyclic disulfones **9**, **10** and **14** (197 mg, 10:50:16:24). Fraction 3 contained a mixture of bicyclic disulfones **9** and **10** (283 mg, 50:50). Fraction 4 contained a mixture of bicyclic disulfones **9**, **10**, **11** and **12** (153 mg, 20:20:20:40). Fraction 5 contained a mixture of bicyclic disulfones **9**, **11**, **12** and **13** (280 mg, 15:15:25:45). The yields of the major products contained in the major fractions were calculated (based on phenyl vinyl sulfone) to be: **9** (15%), **10** (10%), **11** (3.5%), **12** (6.5%), **13** (6%), **14** (5%), and the monoalkylated ketone **8** (2.5%). The bicyclic disulfones **9**–**14** were isolated and purified as follows.

Column fraction 1: Bicyclic disulfone **14** and monoalkylated ketone **8** were separated by semipreparative HPLC (EtOAc–hexane, 50:50, 3 mL/min).

(2*RS*,4*SR*,4a*SR*,8a*RS*)-2,4-Bis(phenylsulfonyl)octahydronaphthalen-4a-ol (14)

Compound **14** (22 mg) was isolated (t_R 8.6 min) as an analytically pure sample; white solid; mp 229–230 °C.

IR (KBr): 3434, 1302, 1146 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.47 (m, 3 H, 1 × H8, 2 × H7), 1.47–1.80 (m, 5 H, H3*eq*, 1 × H5, 2 × H6, 1 × H8), 1.80–2.07 (m, 3 H, 2 × H1, H8a), 2.36 (ddd, $J_{3ax,2eq}$ = 6 Hz, $J_{3ax,4ax}$ = 13.5 Hz, $J_{3,3}$ = 14.5 Hz, 1 H, H3*ax*), 2.46–2.59 (m, 1 H, 1 × H5), 2.97 (d, J = 1.5 Hz, 1 H, OH), 3.14 (dddd, $J_{2eq,1eq}$ = 2 Hz, $J_{2eq,3eq}$ = 2 Hz, $J_{2eq,1ax}$ = 6Hz, $J_{2eq,3ax}$ = 6 Hz, 1 H, H2*eq*), 4.01 (dd, $J_{4ax,3eq}$ = 3.5 Hz, $J_{4ax,3ax}$ = 13.5 Hz, 1 H, H4*ax*), 7.36–7.90 (m, 10 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C6), 22.1 (C3), 25.0 (C1), 25.2 (C7 or C8), 28.2 (C7 or C8), 37.3 (C5), 40.0 (C8a), 58.4 (C2), 64.7 (C4), 72.1 (C4a), 128.1, 128.2 (*o*-C_6H_5), 129.2, 129.4 (*m*-C_6H_5), 133.7, 133.8 (*p*-C_6H_5), 137.4, 139.3, (*i*-C_6H_5),

MS (ESMS +ve): m/z = 457 (MNa^+).

Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 60.78; H, 6.05.

2-[2′-(Phenylsulfonyl)ethyl]cyclohexanone (8)[7,8]

Compound **8** (17 mg) was isolated (t_R 9.4 min) and recrystallised; white solid; mp 72–73 °C (Et_2O) [Lit.[7] 71–72 °C (petroleum ether)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (dddd, $J_{3ax,4eq}$ = 4 Hz, $J_{3ax,4ax}$ = 13 Hz, $J_{3ax,2ax}$ = 13 Hz, $J_{3ax,3eq}$ = 13 Hz, 1 H, H3*ax*), 1.50–1.72 (m, 3 H, 1 × H1′, 1 × H4, 1 × H5), 1.80–1.89 (m, 1 H, 1 × H4), 1.93–2.12 (m, 3 H, 1 × H1′, H3*eq*, 1 × H5), 2.19–2.38 (m, 2 H, 2 × H6), 2.41–2.52 (m, 1 H,H2*ax*), 3.08 (ddd, $J_{2',1'}$ 6 Hz, $J_{2',1'}$ = 10 Hz, $J_{2',2'}$ = 14 Hz, 1 H, 1 × H2′), 3.25 (ddd, $J_{2',1'}$ = 6 Hz, $J_{2',1'}$ = 10 Hz, $J_{2',2'}$ = 14 Hz, 1 H, 1 × H2′), 7.51–7.59 (m, 2 H, *m*-C_6H_5), 7.60–7.67 (m, 1 H, *p*-C_6H_5), 7.84–7.92 (m, 2 H, *o*-C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (C1′), 25.1 (C4), 27.9 (C5), 34.4 (C3), 42.1 (C6), 48.9 (C2), 54.0 (C2′), 128.0 (*o*-C_6H_5), 129.2 (*m*-C_6H_5), 133.6 (*p*-C_6H_5), 139.1 (*i*-C_6H_5), 211.8 (C1).

Column fraction 3: Bicyclic disulfones **9** and **10** were separated by semipreparative HPLC (EtOAc–hexane, 30:70, 3 mL/min).

(2*RS*,4*RS*,4a*SR*,8a*RS*)-2,4-Bis(phenylsulfonyl)octahydronaphthalen-4a-ol (10)

Compound **10** was contained in the first fraction and obtained as an analytically pure sample (t_R 24.3 min); white solid; mp 234–235 °C.

IR (KBr): 3434, 1305, 1146 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.36 (m, 2 H, 1 × H6, 1 × H8), 1.39–1.76 (m, 7 H, H1*eq*, H3*eq*, 1 × H5, 1 × H6, 2 × H7, 1 × H8), 1.76–1.90 (m, 1 H, H8a), 2.11 (ddd, $J_{3ax,2ax}$ = 13 Hz, $J_{3ax,4ax}$ 13, $J_{3,3}$ 13, 1 H, H3ax), 2.25 (ddd, $J_{1ax,8aeq}$ = 5 Hz, $J_{1ax,2ax}$ = 13 Hz, $J_{1,1}$ = 13 Hz, 1 H, H1*ax*), 2.66–2.76 (m, 1 H, 1 × H5), 2.97 (dddd, $J_{2ax,1eq}$ = 4 Hz, $J_{2ax,3eq}$ = 4 Hz, $J_{2ax,1ax}$ = 13 Hz, $J_{2ax,3ax}$ = 13 Hz, 1 H, H2*ax*), 3.44 (dd, $J_{4ax,3eq}$ = 3.5 Hz, $J_{4ax,3ax}$ = 13.5 Hz, 1 H, H4*ax*), 7.44–7.84 (m, 10 H, C_6H_5), (OH not observed).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (C7), 23.7 (C3), 25.0 (C1), 25.5 (C6), 28.1 (C8), 38.4 (C5), 44.0 (C8a), 58.3 (C2), 60.8 (C4), 72.4 (C4a), 128.5, 129.0 (*o*-C_6H_5), 129.2, 129.4 (*m*-C_6H_5), 133.9, 134.2 (*p*-C_6H_5), 136.3, 138.3 (*i*-C_6H_5).

MS (ESMS +ve): *m*/*z* = 457 (MNa^+).

Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 60.78; H, 6.10.

(2*RS*,4*RS*,4a*SR*,8a*SR*)-2,4-Bis(phenylsulfonyl)octahydronaphthalen-4a-ol (9)

Compound **9** was contained in the second fraction and obtained as an analytically pure sample (t_R 24.7 min); white solid; mp 238–239 °C.

IR (KBr): 3452, 1306, 1146 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.44 (m, 4 H, 1 × H5, 1 × H7, 1 × H8, H8a), 1.44–1.84 (m, 7 H, 2 × H1, H3*eq*, 2 × H6, 1 × H7, 1 × H8), 2.10 (ddd, $J_{3ax,2ax}$ = 13 Hz, $J_{3ax,4ax}$ = 13 Hz, $J_{3,3}$ = 13 Hz, 1 H, H3*ax*), 2.46–2.58 (m, 1 H, 1 × H5), 2.85 (dddd, $J_{2ax,1eq}$ = 4 Hz, $J_{2ax,3eq}$ = 4 Hz, $J_{2ax,1ax}$ = 13 Hz, $J_{2ax,3ax}$ = 13 Hz, 1 H, H2*ax*), 2.91 (dd, $J_{4ax,3eq}$ = 3 Hz, $J_{4ax,3ax}$ = 13 Hz, 1 H, H4*ax*), 3.11 (d, *J* = 1.5 Hz, 1 H, OH), 7.42–7.83 (m, 10 H, 2 × C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (C6), 23.6 (C3), 25.4 (C7 or C8), 26.3 (C1), 28.0 (C7 or C8), 37.1 (C5), 44.5 (C8a), 61.7 (C2), 69.0 (C4), 71.4 (C4a), 128.3, 128.9 (*o*-C_6H_5), 129.2, 129.4 (*m*-C_6H_5), 133.8, 134.1 (*p*-C_6H_5), 136.5, 138.3 (*i*-C_6H_5).

MS (ESMS +ve): *m*/*z* = 457 (MNa^+).

Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 61.03; H, 6.13.

Column fraction 4: Bicyclic disulfones **11** and **12** were isolated from a mixture of **9**, **10**, **11**, and **12** by semipreparative HPLC (EtOAc–hexane, 30:70, 3 mL/min).

(2*RS*,4*SR*,4a*RS*,8a*SR*)-2,4-Bis(phenylsulfonyl)octahydronaphthalen-4a-ol (12)

Compound **12** was isolated from the first fraction as an analytically pure sample (t_R 32 minutes); white solid; mp 205–206 °C.

IR (KBr): 3450, 1304, 1144 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.54 (m, 5 H, 1 × H5, 1 × H6, 2 × H7, 1 × H8), 1.68–1.83 (m, 1 H, 1 × H6), 1.83–2.13 (m, 5 H, 2 × H1, 1 × H3, 1 × H5, 1 × H8), 2.17–2.30 (m, 1 H, 1 × H3), 2.37–2.49 (m, 1 H, H8a), 3.27 (dd, $J_{4eq,3eq}$ = 3 Hz, $J_{4eq,3ax}$ = 5 Hz, 1 H, H4*eq*), 3.49 (d, $J_{OH,5}$ = 1.5 Hz, 1 H, OH), 3.84 (dddd, $J_{2ax,3eq/1eq}$ = 4 Hz, $J_{2ax,3eq/1eq}$ = 5 Hz, $J_{2ax,3ax}$ = 12 Hz, $J_{2ax,1ax}$ = 12 Hz, 1 H, H2*ax*), 7.39–7.90 (m, 10 H, 2 × C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (C7), 21.0 (C6), 24.0 (C3), 26.0 (C1), 26.4 (C8), 33.3 (C5), 37.9 (C8a), 57.5 (C2), 68.2 (C4a), 73.7 (C4), 127.8, 128.7 (*o*-C_6H_5), 129.3 (*m*-C_6H_5), 133.8, 133.9 (*p*-C_6H_5), 137.3, 140.0, (*i*-C_6H_5).

MS (ESMS +ve): *m*/*z* = 457 (MNa^+).

Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 61.02; H, 6.05.

(2*RS*,4*SR*,4a*SR*,8a*SR*)-2,4-Bis(phenylsulfonyl)octahydronaphthalen-4a-ol (11)

Compound **11** was isolated from the second fraction as an analytically pure sample (t_R 36 min); white solid; mp 199–201 °C.

IR (KBr): 3453, 1304, 1144 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.85 (m, 10 H, 2 × H1, 1 × H3, 1 × H5, 2 × H6, 2 × H7, 2 × H8), 2.20 (dddd, $J_{8aax,1eq}$ = 4 Hz, $J_{8aax,8eq}$ = 4 Hz, $J_{8aax,1ax}$ 12 Hz, $J_{8aax,8ax}$ = 12 Hz, 1 H, H8a*ax*), 2.26–2.41 (m, 2 H, 1 × H3, 1 × H5), 3.14 (dd, $J_{4eq,3eq}$ = 2 Hz, $J_{4eq,3ax}$ = 5.5 Hz, 1 H, H4*eq*), 3.77 (dddd, $J_{2ax,1eq}$ = 3.5 Hz, $J_{2ax,3eq}$ = 3.5 Hz, $J_{2ax,1ax}$ = 13 Hz, $J_{2ax,3ax}$ = 13 Hz, 1 H, H2*ax*), 7.34–7.84 (m, 10 H, C_6H_5), (OH not observed).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C6), 22.8 (C3), 25.1 (C7), 26.3 (C1), 28.7 (C8), 37.6 (C5), 38.4 (C8a), 57.2 (C2), 68.2 (C4), 72.2 (C4a), 127.8, 128.9 (*o*-C_6H_5), 129.2, 129.3 (*m*-C_6H_5), 133.7, 133.8 (*p*-C_6H_5),138.7, 137.1, (*i*-C_6H_5).

MS (ESMS +ve): *m*/*z* = 457 (MNa^+).

Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 60.57; H, 6.13.

Column fraction 5: Semipreparative HPLC (EtOAc–hexane, 30:70) of a mixture of **9**, **11**, **12** and **13** gave bicyclic disulfone **13** (64 mg) (t_R 45 min).

(2*RS*,4*SR*,4a*RS*,8a*RS*)-2,4-Bis(phenylsulfonyl)octahydronaphthalen-4a-ol (13)

Purification by semipreparative HPLC (EtOAc–hexane, 50:50) gave an analytically pure sample of (t_R 13 min); white solid; mp 178–179 °C.

IR (KBr): 3454, 1305, 1143 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.39 (m, 2 H, 1 × H7, 1 × H8), 1.39–1.79 (m, 7 H, 1 × H1, 1 × H3, 2 × H6, 1 × H7, 1 × H8, H8a), 1.79–1.95 (m, 2 H, 1 × H1, 1 × H3), 2.12 (ddd, 1 H, $J_{5ax,6eq}$ = 4 Hz, $J_{5ax,6ax}$ = 13.5 Hz, $J_{5,5}$ = 13.5 Hz, H5*ax*), 2.25–2.36 (m, 1 H, H5*eq*), 3.26 (dd, $J_{4ax,3eq}$ = 6 Hz, $J_{4ax,3ax}$ = 12.5 Hz, 1 H, H4*ax*), 3.41 (dddd, $J_{2eq,1eq/3eq}$ = 4 Hz, $J_{2eq,1eq/3eq}$ = 7 Hz, $J_{2eq,1ax/3ax}$ = 8.5 Hz, $J_{2eq,1ax/3ax}$ = 13 Hz, 1 H, H2*eq*), 7.41–7.84 (m, 10 H, 2 × C_6H_5), (OH not observed).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (C6), 22.9 (C3), 24.9 (C1), 25.1 (C7 or C8), 28.8 (C7 or C8), 35.4 (C5), 37.4 (C8a), 57.0 (C2), 69.2 (C4), 73.4 (C4a), 128.3, 128.8 (*o*-C_6H_5), 129.2, 129.3 (*m*-C_6H_5), 133.8, 133.9 (*p*-C_6H_5), 136.7, 138.8 (*i*-C_6H_5).

MS (ESMS +ve): *m*/*z* = 457 (MNa^+).

Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 60.80; H, 6.03. Found: C, 60.84; H, 6.16.

Reaction of Enolate of Cylohexanone with Ethyl Acrylate (6)

The lithium enolate of cyclohexanone, generated from LDA (~1.6 M, 3.50 mL, 5.60 mmol) and cyclohexanone (0.50 g, 0.53 mL, 5.10 mmol) in THF (30 mL), was allowed to warm to –30 °C. Ethyl acrylate (**6**; 0.51 g, 5.10 mmol) was added rapidly and the mixture was stirred for 5 min. The temperature was maintained at –30 °C during this time. The reaction was quenched and worked up as described above to give the crude product mixture (725 mg) as an amber oil. Purification by silica gel column chromatography (EtOAc–hexane, 5:95) gave three major fractions and recovered cyclohexanone (130 mg, 26%). Fraction 1 contained the diester **15** (102 mg, 13%). Purification by silica column chromatography (EtOAc–hexane, 10:90) gave **15** as a white solid; mp 32.5–34 °C.

(1*RS*,3*SR*,4a*SR*,8a*SR*)-8a-Hydroxydecahydronaphthalene-1,3-dicarboxylic Acid Diethyl Ester (15)
IR (KBr): 3500, 2933, 1727, 1705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.30 (m, 10 H, 2 × CH_3, H4a*ax*, 1 × H5, 1 × H7, 1 × H8), 1.32–1.48 (m, 2 H, 1 × H5, 1 × H6), 1.48–1.56 (m, 1 H, 1 × H8), 1.58–1.70 (m, 3 H, H4*eq*, 1 × H6, 1 × H7), 1.77 (ddd, $J_{4ax,3eq}$ = 5.5 Hz, $J_{4ax,4aax}$ = 12 Hz, $J_{4,4}$ = 13.5 Hz, 1 H, H4*ax*), 1.98–2.12 (m, 2 H, 2 × H2), 2.53 (dd, $J_{1ax,2eq}$ = 5 Hz, $J_{1ax,2ax}$ = 12 HZ, 1 H, H1*ax*), 2.69 (dddd, $J_{3eq,2eq}$ = ~2.5 Hz, $J_{3eq,4eq}$ = ~2.5 Hz, $J_{3eq,2ax}$ = ~5 Hz, $J_{3eq,4ax}$ = ~5, 1 H, H3*eq*), 3.10 (s, 1 H, OH), 4.20–4.05 (m, 4 H, 2 × OCH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (2 × CH_3), 21.4 (C6), 26.0 (C7), 26.2 (C2), 27.9 (C5), 28.7 (C4), 37.2 (C8), 38.3 (C3), 40.1 (C4a), 48.5 (C1), 60.3, 60.5 (2 × OCH_2), 69.7 (C8a),174.8 (C3-C=O), 176.4 (C1-C=O).

MS (ESMS +ve): *m*/*z* = 305 (MLi^+).

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, C, 64.33; H, 9.06.

Fraction 2 contained a mixture of the diesters **15** and **16** (62 mg, 8%). Purification by silica gel column chromatography (EtOAc–hexane, 10:90) gave a 20:80 mixture of the diester **15** and **16** as a colourless oil, which was inseparable by HPLC,

15 and (1*RS*,3*RS*,4a*SR*,8a*SR*)-8a-Hydroxydecahydronaphthalene-1,3-dicarboxylic Acid Diethyl Ester (16) (20:80)
IR (Nujol): 3510, 2933, 1731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.86 (m, 17 H, 2 × CH_3, 2 × H4, H4a*ax*, 2 × H5, 2 × H6, 2 × H7, 2 × H8), 1.93 (dddd, $J_{2eq,4}$ = 2 Hz, $J_{2eq,1ax}$ = 4 Hz, $J_{2eq,3ax}$ = 4 Hz, $J_{2,2}$ = 13 Hz, 1 H, H2*eq*), 2.09 (ddd, $J_{2ax,1ax}$ = 13 Hz, $J_{2ax,3ax}$ = 13 Hz, $J_{2,2}$ = 13 Hz, 1 H, H2*ax*), 2.26 (dd, $J_{1ax,2eq}$ = 4 Hz, $J_{1ax,2ax}$ = 13 Hz, 1 H, H1*ax*), 2.38 (dddd, $J_{3ax,2eq}$ = 4 Hz, $J_{3ax,4eq}$ = 4 Hz, $J_{3ax,2ax}$ = 12 Hz, $J_{3ax,4ax}$ = 12 Hz, 1 H, H3*ax*), 4.05–4.20 (m, 4 H, 2 × OCH_2), (OH not observed).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (2 × CH_3), 21.4 (C5 or C6 or C7), 26.0 (C5 or C6 or C7), 27.6 (C2), 27.9 (C5 or C6 or C7), 30.4 (C4), 37.1 (C8), 42.3 (C3), 43.7 (C4a), 51.6 (C1), 60.4, 60.7 (2 × OCH_2), 69.3 (C8a), 174.5 (C3-C=O), 175.7 (C1-C=O).

MS (ESMS +ve): *m*/*z* = 305 (MLi^+).

HRMS: *m*/*z* calcd for $C_{16}H_{26}O_5$: 298.17802; found: 298.17863

Fraction 3 contained the diester **17** (274 mg, 36%). Purification by silica column chromatography (EtOAc–hexane, 10:90) gave diester **17** as a colourless oil,

(1*RS*,3*RS*,4a*RS*,8a*SR*)-8a-Hydroxydecahydronaphthalene-1,3-dicarboxylic Acid Diethyl Ester (17)
IR (Nujol): 3519, 1738, 1716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.78 (m, 16 H, 2 × CH_3, H4*eq*, H4a*eq*, 2 × H5, 2 × H6, 2 × H7, 2 × H8), 1.88–1.98 (m, 1 H,H2*eq*), 2.12 (ddd, $J_{2ax,1ax}$ = 13 Hz, $J_{2ax,3ax}$ = 13 Hz, $J_{2,2}$ = 13 Hz, 1 H,H2*ax*), 2.25 (ddd, $J_{4ax,4aeq}$ = 5 Hz, $J_{4ax,3ax}$ = 13 Hz, $J_{4,4}$ = 13 Hz, 1 H, H4*ax*), 2.51 (dddd, $J_{3ax,2eq}$ = 4 Hz, $J_{3ax,4eq}$ = 4 Hz, $J_{3ax,2ax}$ = 13 Hz, $J_{3ax,4ax}$ = 13 Hz, 1 H, H3*ax*), 2.88 (dd, $J_{1ax,2eq}$ = 4 Hz, $J_{1ax,2ax}$ = 13 Hz, 1 H, H1*ax*), 4.10 (q, *J* = 7 Hz, 2 H, OCH_2), 4.16 (q, *J* = 7 Hz, 2 H, OCH_2), (OH not observed).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (2 × CH_3), 23.5 (C5 or C6 or C7), 25.8 (C5 or C6 or C7), 27.4 (C2), 28.0 (C5 or C6 or C7), 29.2 (C4), 36.9 (C3), 38.6 (C8), 41.4 (C4a), 42.5 (C1), 60.2, 60.6 (2 × OCH_2), 70.3 (C8a), 174.8 (C3-C=O), 175.6 (C1-C=O).

MS (ESMS +ve): *m*/*z* = 305 (MLi^+).

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.39; H, 8.98.

Reaction of Enolate of Cyclohexanone with Diphenylvinylphosphine Oxide (7)
The lithium enolate of cyclohexanone generated as outlined previously[2] using MeLi in Et_2O (~1.4 M, 0.46 mL, 0.64 mmol) and cyclohex-1-enyloxytrimethylsilane (130 mg, 0.15 mL, 0.76 mmol) in anhyd THF (7 mL). The solution was warmed to –10 °C and diphenylvinylphosphine oxide (**7**;[16] 145 mg, 0.64 mmol) in THF (1.5 mL) was added dropwise over 20 seconds and the reaction mixture was stirred for 10 min. The temperature was maintained at –10 °C during this time. The reaction was quenched and worked up as described above to give the crude product mixture as an amber oil (235 mg). The oil, analysed by ^1H NMR (400 MHz) was determined to contain the alkylated ketone 269 (89%) with the remainder attributable to EtOAc, unreacted cyclohexanone and polymeric material. Recrystallisation gave 2-[2′-(diphenylphosphoryl)ethyl]cyclohexanone (**18**)[17] as a white solid; mp 110–112 °C (Et_2O) [Lit.[17] 109–110 °C (EtOAc)].

^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.42 (m, 1 H, 1 × H3),1.51–1.71 (m, 3 H, 1 × H1′, 1 × H4, 1 × H5), 1.73–2.10 (m, 4 H, 1 × H1′, 1 × H3, 1 × H4, 1 × H5), 2.10–2.27 (m, 2 H,1 × H2′, 1 × H6), 2.27–2.35 (m, 1 H,1 × H6), 2.35–2.54 (m, 2 H, 1 × H2′, H2), 7.38–7.52 (m, 6 H, *m*- and *p*-C_6H_5), 7.66–7.74 (m, 2 H, *o*-C_6H_5), 7.75–7.82 (m, 2 H, *o*-C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.17 (d, $J_{C,P}$ = 3.5 Hz, C1′), 25.03 (C4), 27.33 (d, $J_{C,P}$ = 72 Hz, C2′), 28.06 (C5), 34.36 (C3), 42.24 (C6), 51.05 (d, $J_{C,P}$ = 12.5 Hz, C2), 128.57, 128.62 (d, $J_{C,P}$ = 11.5 Hz, *o*-C_6H_5), 130.62, 130.89, (d, $J_{C,P}$ = 9 Hz, *m*-C_6H_5), 131.58, 131.66, (d, $J_{C,P}$ = 2.5 Hz, *p*-C_6H_5), 132.53, 133.50 (d, $J_{C,P}$ = 87.5 Hz, *i*-C_6H_5), 212.9 (C1).

^{31}P NMR MHz, $CDCl_3$): δ = 33.48 (P=O).

MS (ESMS +ve): *m*/*z* = 333 (MLi^+).

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