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CONTROLLED ENDOCYCLIC AND EXOCYCLIC γ- METALATIONS OF β-SUBSTITUTED CYCLOHEXENYL SULFONES. REGIOSPECIFIC SYNTHESES OF γ-OXYGENATED CYCLOHEXENYL SULFONES.[1]

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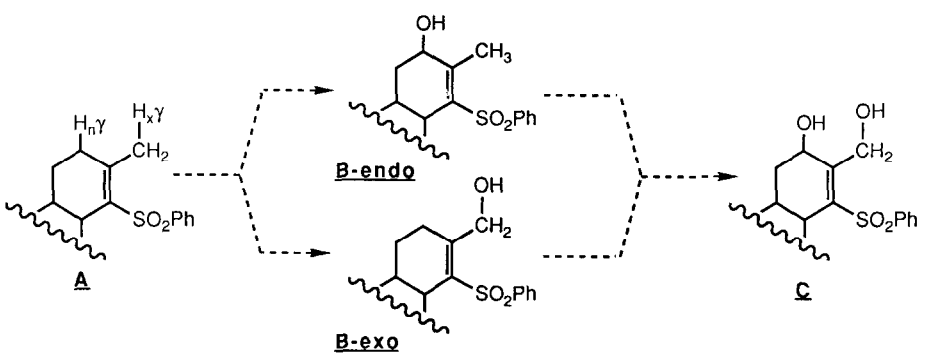
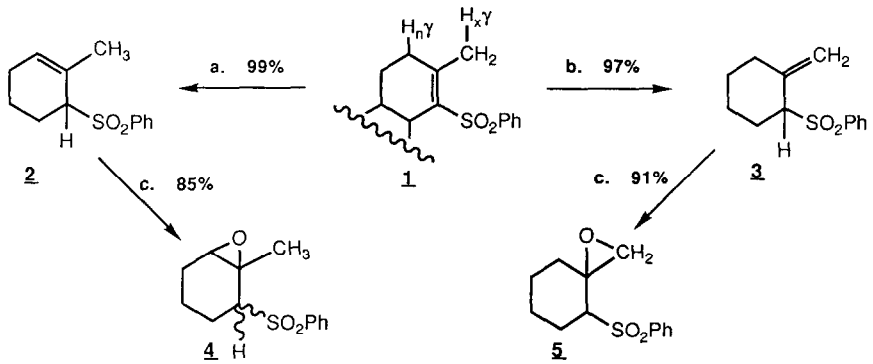
Abstract: β-Substituted cyclohexenyl sulfones may be regiospecifically isomerized to either endocyclic or exocyclic allyl sulfones. Epoxidation of these materials followed by a second metalation yields γ-hydroxy cyclohexenyl sulfones **6** and **7**. Subjection of either of these materials to a second oxidation/isomerization sequence smoothly provides the bis γ-hydroxylated cyclohexenyl sulfone **10** in excellent overall yield.

In conjunction with a synthetic project, we required methodology to specifically convert a β-methyl cyclohexenyl sulfone (**A**) to mono (**B-endo**, and **B-exo**) and dioxygenated (**C**) γ-hydroxy cyclohexenyl sulfone derivatives.



Based upon our previous experience,[2] we wished to prepare β-epoxy sulfones as progenitors for the γ-oxygenated targets. This required development of conditions for regiospecific metalation at both the endocyclic ($H_{n\gamma}$) and exocyclic ($H_{x\gamma}$) gamma positions. Reaction of 2-methyl-1-cyclohexenyl phenyl sulfone **1** with 1.0 equivalent of potassium t-butoxide in THF containing 0.1 equivalent of t-butanol for 3 h at 25°C smoothly provides endocyclic allyl sulfone **2** in 99% yield. Alternatively, treatment of **1** with 1.1 equivalents of n-butyllithium at -78°C for 1 h followed by quenching with saturated ammonium chloride yields

exocyclic allyl sulfone **3** in 97% with no trace of **2** being detected. Epoxidation of these two olefins using mCPBA in methylene chloride for 18 h afforded the expected β-epoxy sulfones **4** (85%; 2:1 diastereomers) and **5** (91%; single unassigned diastereomer).

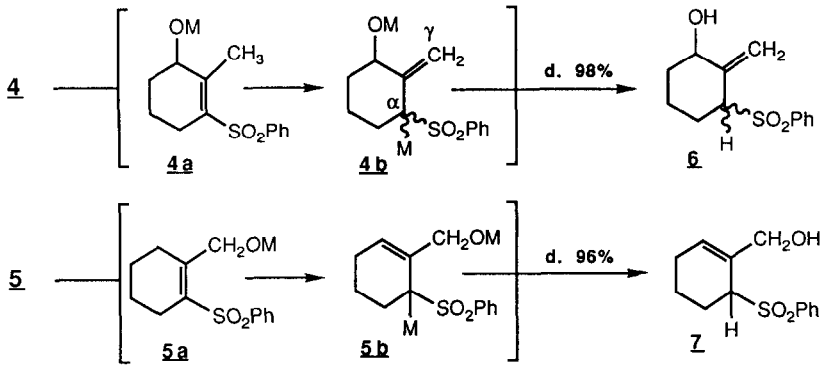


(a) 1.0eq. KOt-Bu, 0.1eq. t-BuOH, THF, RT (b) i. 1.1eq. n-BuLi, THF, -78°C ii. aq.NH_4Cl
(c) MCPBA, CH_2Cl_2, RT

Treatment of epoxide **4** with 1.0 equivalent of n-butyllithium at -78°C, stirring at 0°C for 2 h, followed by quenching with saturated ammonium chloride affords **4a** (M=H) in 96% yield[3]. Further treatment of **4a** (M=H)[5] with an additional 2.1 equivalents of n-butyllithium at -78°C stirring at 0°C for 2 h, and quenching with saturated ammonium chloride provides **6** in near quantitative yield. Alternatively, initial reaction of **4** with 2.1 equivalents of n-butyllithium under the same conditions directly afforded **6** in 98% yield.

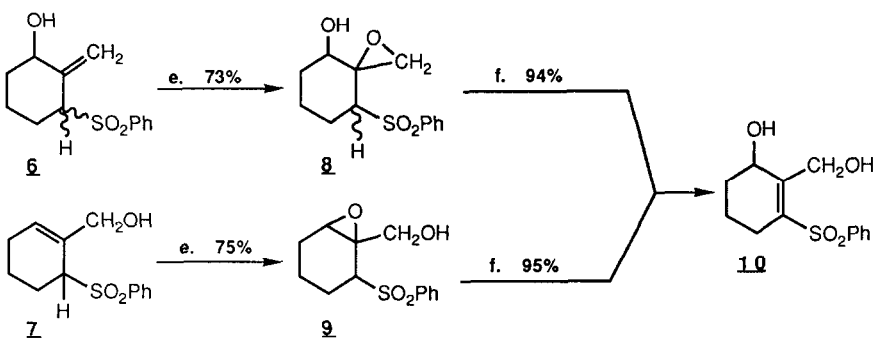
In a parallel fashion, treatment of epoxide **5** with 1.0 equivalent of n-butyllithium at -78°C, stirring at 0°C for 2 h, followed by quenching with saturated ammonium chloride affords **5a** (M=H)[5] in 95% yield. Further treatment of **5a** (M=H) with an additional 2.1 equivalents of n-butyllithium at -78°C, stirring at 0°C for 2 h, and quenching with saturated ammonium chloride provides **7** in 97% yield. Once again, simply directly reacting epoxide **5** with 2.1 equivalents of n-butyllithium under the above conditions provided **7** in 96% yield.

In both instances, conjugate-addition of the organometallic reagent to the initially formed γ-oxido vinyl sulfone intermediates (**4a**, **5a**) was a formal possibility, but our previous experiences have shown that β-substituted vinyl sulfones undergo γ-metalation in preference to *intermolecular* conjugate-addition upon exposure to organolithium reagents.[4]



(d) i. 2.1eq. n-BuLi, THF, -78°C to 0°C ii. aq.NH_4Cl

Epoxidation of allylic alcohols **6** and **7** using mCPBA in methylene chloride for 20 h at room temperature afforded β-epoxy cyclohexyl sulfones **8** (70%; single unassigned diastereomer) and **9** (73%; 3:2 ratio of two diastereomers). Reaction of either epoxide with 2.2 equivalents of n-butyllithium at -78°C for 2h, slowly warming up to room temperature, and quenching with saturated ammonium chloride provided the target dihydroxylated vinyl sulfone **10** in excellent yield[5].



(e) MCPBA, CH_2Cl_2 , RT; (f) i. 2.2eq. n-BuLi, THF, -78°C to RT, ii. aq.NH_4Cl

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References and notes

[1] Syntheses via vinyl sulfones 43. For a review on this subject, see Braish,T.F., Fuchs, P. L., Chem Rev., **1986**, 86, 903.

[2] (a) Conrad, P.C.; Fuchs, P.L. J. Am. Chem. Soc., **1978**, 100, 346; (b) Saddler, J.C.; Conrad, P.C.; Fuchs, P.L. Tetrahedron Letter, **1978**, 5079; (c) Barton, D.L.; Conrad, P.C.; Fuchs, P.L. Tetrahedron Letter, **1980**, 21, 1811; (d) Braish, T.F.; Fuchs, P.L. Chem. Rev., **1986**, 86, 903; (e) Donaldson, R.E.; Fuchs, P.L J. Am. Chem. Soc., **1981**, 103, 2108; (f) Saddler, J.C.; Donaldson, R.E.; Fuchs, P.L. J. Am. Chem. Soc., **1981**,103, 2110; (g) Saddler, J.C.; Fuchs, P.L. J. Am. Chem. Soc., **1981**, 103, 2112.

[3] (a) Compound **4a** may also be prepared in three steps in 48% overall yield from 2-methyl-cyclohexane-1,3-dione. The first step involves treatment of the dione with 1.5 equivalents of methanesulfonyl chloride in pyridine at room temperature for 2 h to form the β-mesyloxy enone (61%). This enone is reacted with 3.0 equivalents sodium benzenesulfinate in a mixture of NMP and benzene at reflux for 2 h to produce the β-phenylsulfonyl enone (84%). Reduction of this enone with 1.0 equivalent of sodium borohydride in the presence of 1.0 equivalent of cerium trichloride heptahydrate in a mixture of methanol and methylene chloride at -20°C for 30 min provided 93% of **4a** (M=H).

(b)For a general procedure for syntheses of 3-hydroxy-2-substituted-1-(phenylsulfonyl) cyclohexenes from β-diketones , see J. E. Toth, Ph.D. Thesis, Purdue University ,1986.

[4] (a) Hamann, P.R.; Toth, J.E.; Fuchs, P.L. J. Org. Chem., **1984**, 49, 3865; (b) Toth, J.E.; Hamann, P.R.; Fuchs, P.L. J. Org. Chem., **1988**, 53. 4694.

[5] **4a**(M=H); ^{1}H-NMR(200MHz, $CDCl_3$) δ7.88-7.46(5H, m), 4.01(1H, m), 2.54(1H, s), 2.52- 2.25(2H, m), 2.21(3H, s), 1.78-1.55(4H, m); ^{13}C-NMR(50MHz, $CDCl_3$) δ147.73(e), 141.24(e), 136.72(e), 133.38(o), 129.29(o), 127.31(o), 70.34(o), 30.73(e), 26.67(e), 18.11(e), 17.50(o); HRMS (EI) calculated for M^+ $C_{13}H_{16}O_3S_1$ 252.0820, found 252.0818, **5a**(M=H); ^{1}H-NMR (200MHz, $CDCl_3$) δ7.92-7.47(5H, m), 4.37(2H, d, J=7.26Hz), 3.07(1H, t, J=7.26Hz), 2.41-2.21(4H, m), 1.62-1.51(4H, m); ^{13}C-NMR(50MHz, $CDCl_3$) δ151.30(e), 140.67(e), 135.89(e), 133.56(o), 129.41(o), 127.37(o), 62.43(e), 31.44(e), 26.13(e), 21.88(e), 21.32(e); HRMS (EI) calculated for M^+ $C_{13}H_{16}O_3S_1$ 252.0820, found 252.0818, **10**; ^{1}H-NMR(200MHz, $CDCl_3$) δ7.92-7.50(5H, m), 4.76(2H, dd, J=22.62, 15.08Hz), 4.45(1H, s), 2.95(2H, broad), 2.45-2.16(2H, m), 1.92-1.58(4H, m); ^{13}C-NMR(50MHz, $CDCl_3$) δ148.71(e), 140.05(e), 138.60(e), 133.82(o), 129.50(o), 127.55(o), 67.95(o), 60.71(e), 30.32(e), 26.94(e), 18.12(e); HRMS (CI) calculated for $(M+H)^+$ $C_{13}H_{17}O_4S_1$ 269.0848, found 269.0846.

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