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AUXILIARY-DIRECTED DIOXYGENATION STEREOSELECTIVE SYNTHESIS OF A DIENE HYDROPEROXIDE

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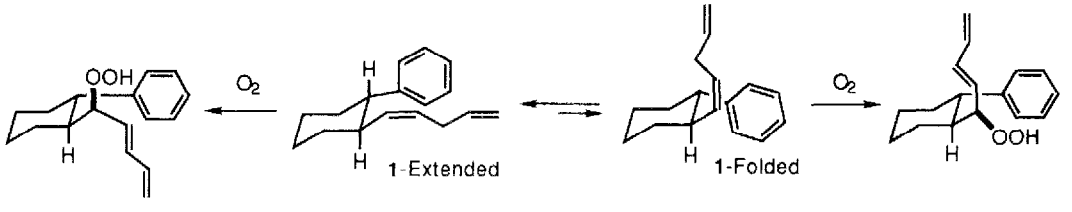
Summary *The presence of a chiral auxiliary is shown to induce highly stereoselective peroxidation of a tethered 1,4-diene*

The dioxygenation of 1,4-dienes to conjugated diene hydroperoxides is an important biological process For example, cyclooxygenase-catalyzed dioxygenation of arachidonic acid is responsible for the synthesis of prostaglandins while lipoxygenase-catalyzed dioxygenations produce a variety of hydroperoxyeicosatetraenoic acids (HPETEs), precursors of the inflammatory leukotrienes and lipoxins [1,2,3,4] Our interests were aroused by the contrast between the high enantioselectivity associated with enzymatic peroxidations of fatty acid dienes and the complete lack of stereoselectivity observed in corresponding chemical peroxidations with singlet or triplet oxygen [1,2] Despite the importance of HPETEs and other diene hydroperoxides, there have been very few studies of stereoselective chemical peroxidation and only one study involving oxygenation of 1,4-dienes [5,6] In this manuscript, we describe the use of a chiral auxiliary to direct the stereoselective chemical peroxidation of a 1,4-diene

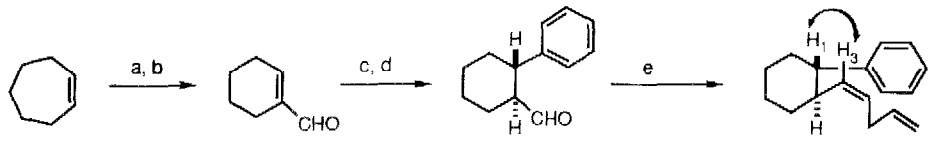
In order to perform stereoselective diene peroxidation under irreversible conditions, the auxiliary must control both the conformation of the diene and the approach of molecular oxygen to the diene For these reasons, we selected the phenylcyclohexyl auxiliary (**1**) shown in Scheme 1 Preliminary molecular modelling studies identified two low-energy conformations of the disubstituted olefin sidechain, "chain-extended" or "chain-folded", the extended conformer was favored by 1 5 kcal/mole [7] Previous workers have demonstrated the ability of the equatorial aromatic in 2-phenylcyclohexyl systems to effectively block the "back" face of a neighboring trigonal center [8] Together, these observations implied that oxygenation of the disubstituted olefin should proceed with high selectivity towards hydroperoxide introduction on the nonshielded face of the "chain-extended" conformer



Scheme 1

The synthesis of diene **1** is presented in Scheme 2 Cyclohexenecarboxyaldehyde was obtained through ozonolysis of cycloheptene followed by dehydrative aldol cyclization Conjugate addition of phenylmagnesium

bromide afforded 2-phenylcyclohexanecarboxaldehyde as a cis/trans mixture, base-catalyzed epimerization furnished the desired trans isomer Wittig olefination then accomplished formation of the desired 1,4-diene **1**

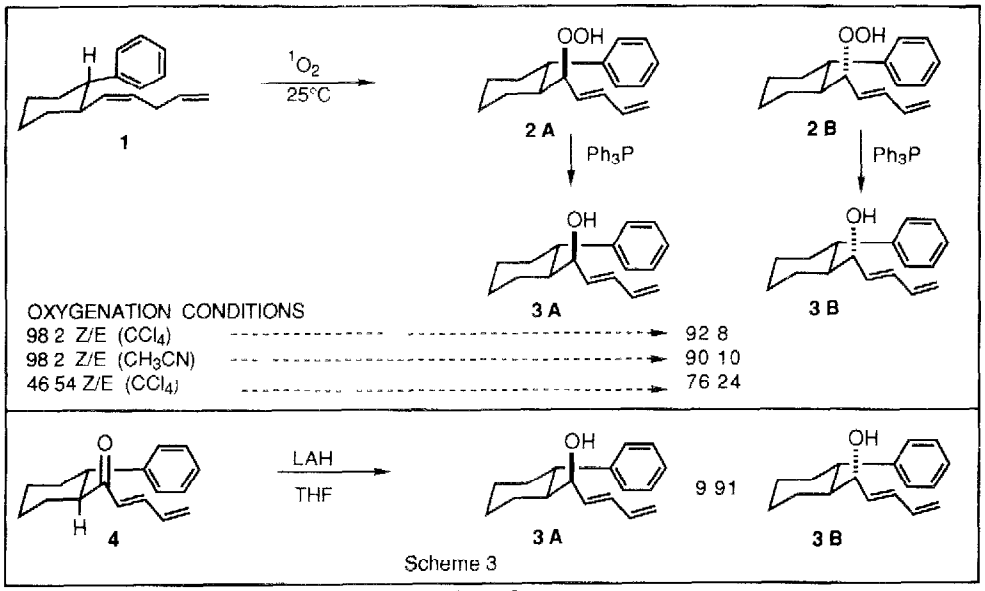


a O_3 then Me_2S b c PhMgBr, cat CuBr, TMSCl THF/HMPA
d KOtBu/THF e $Ph_3P^+CH_2CH_2CH{=}CH_2$ LiN(TMS)$_2$, THF/HMPA

Scheme 2

as an inseparable 98 2 *Z/E* mixture [9] The substantial NOE (5%) between H_1 and H_3 in this conformationally mobile system provides strong evidence for the presence of the "chain-extended" conformer while the strength and selectivity of the aromatic shielding can be seen in the resonance of H_3 at 5 1 ppm and the observation of the bisallylic methylene hydrogens as individual ABX systems at 2 5 and 2 65 ppm in the ^1H NMR spectrum

Chemical peroxidations were initially performed through photosensitized oxygenation [10] (Scheme 3) Although the reaction between **1** and $^1O_2$ could in theory deliver several regioisomers, oxygenation actually proceeded to afford, at 10-20% conversion, predominantly the epimers **2A** and **2B** in an 92 8 ratio Products were quantified by HPLC of the corresponding alcohols **3A** and **3B** after reduction with Ph_3P [11] Comparison of the products obtained in CCl_4 (tetraphenylporphyrin sensitizer) and in CH_3CN (Rose Bengal sensitizer) indicated only a minimal contribution from solvent polarity In contrast to the high stereoselectivity observed in the oxygenation of *Z*-**1** oxidation of a 46 54 Z/E mixture of diene **1**, obtained through the Schlosser modification of the Wittig reaction, afforded **3A** and **3B** in a 76 24 ratio Although the disubstituted olefin of both the E and Z isomers is effectively shielded by the neighboring aromatic, the reduced preference

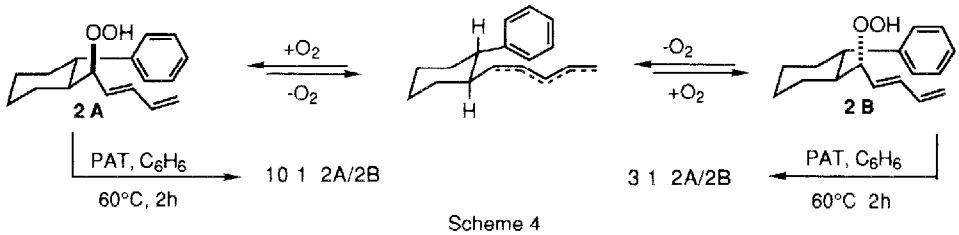


Scheme 3

New compounds were characterized by ^1H, ^{13}C and IR Accurate analyses were obtained for diene **1** and alcohol **3A**

of *E*-**1** for the "extended" conformer over the 'folded" conformer (0 5 kcal, based upon modelling) reduces the stereoselectivity of dioxygenation [7] GC analysis of recovered 1,4-diene indicated that there was no signficant difference in the consumption of the E and Z isomers over the course of the reaction Our stereochemical assignments were substantiated by reduction of ketone **4**, obtained upon oxidation of either **3A** or **3B**, to a 9 91 mixture of the alcohols **3A** and **3B** Hydride delivery would be expected to occur opposite the shielding aromatic ring to predominantly afford the minor oxygenation product and in fact, the major reduction product coelutes with the minor oxygenation product (**3B**)

Recent studies have indicated that lipoxygenase-mediated peroxidation of 1,4-dienes occurs via a highly constrained pentadienyl radical and we were also interested in using **1** to probe stereoselective oxygen attack on the delocalized pentadienyl radical [12] Direct radical autoxidation of 1,4-dienes is thought to involve abstraction of a bisallylic hydrogen to furnish an intermediate pentadienyl radical [1] However, direct autoxidation of diene **1** to the corresponding pentadienyl radical proved to be extremely sluggish even in the presence of radical initiators Fortunately, diene hydroperoxides are known to undergo radical equilibration via an intermediate pentadienyl radical [13] (Scheme 4) We have found in preliminary studies that treatment of either the major (**2A**) or minor (**2B**) diene hydroperoxides with 0 2 equiv of phenylazotriphenylmethane under O_2 atmosphere at 60°C for 2 h provides a mixture enriched in **2A** [14] We are currently investigating the origin of this thermodynamic stereochemical control



Scheme 4

In summary, we have shown that a chiral auxiliary is able to induce diastereoselective peroxidation of a nonconjugated diene in a predictable manner based upon control of diene conformation and oxidant approach Experiments probing the nature of the phenyl/dienyl interaction and the use of chiral auxiliaries for practical synthesis of optically active hydroperoxides are in progress

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9 Diene **1** To a 0 °C solution of (3-butenyl)triphenylphosphonium bromide (2 6673 g, 6 7 mmol) and HMPA (2 4 ml, 13 8 mmol) in dry THF (9 mL) was added dropwise LiN(TMS)2 (7 5 mL , 1 0M solution in THF) The resulting red solution was stirred for 30 min and cooled to -78 °C whereupon a solution of aldehyde (0 8546 g 4 5 mmol) and HMPA (1 5 ml , 8 6 mmol) in dry THF (4 5 mL) was added dropwise The solution was stirred for 10 min at -78°C -20°C for 20 minutes, and then quenched with H_2O Extraction (40% ethyl acetate/hexane) and drying over Na_2SO_4 was followed by flash chromatography (1% ethyl acetate/hexane) to afford 0 6270 g (61%) of a colorless oil, 1-(trans-2-phenylcyclohexyl)-1Z,4-pentadiene (**1**), as a 98 2 mixture of 1Z 1E isomers (GC analysis) Aldehyde (0 1350 g, 15%) was also recovered R_f=0 72 in 10% ethyl acetate/hexane, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7 24-7 11 (m, 5H, phenyl), 5 51 (m, 1H, C**H**=CH_2, collapses to dd, J=17 3, 9 2 Hz when δ 2 55 irradiated), 5 08 (m, 2H, CH-C**H**=C**H**-CH_2, collapses to δ 5 11, d, J=10 8 Hz and δ 5 06, J=11 0 Hz when δ 2 55 irradiated) 4 84 (dd 2H, J=13 3, 1 6 Hz, CH=CH_2), 2 62 (m, 1H, CH-HC**H**-CH, collapses to ABX J=15 0, 6 5 Hz when δ 5 05 irradiated), 2 49 (m, 2H, R_2**H**-CH=CH, and CH-**H**CH-CH, simplifies when either δ 5 05 or 2 65 irradiated), 2 27 (dt, 1H, J=11 2, 3 3 Hz, C**H**-Ph), 1 94-1 17 (m, 8H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 146 25, 137 12, 135 41 128 00, 127 64, 125 78, 125 67, 114 49, 50 23 41 74, 34 90, 33 79, 31 73, 26 64, 25 96 IR (neat) 3026, 3023, 2925, 2852, 1493, 1446, 910, 754, 737, 698 cm^{-1} UV λ_{max} 280 nm (ε=9,200, hexane) Anal Calcd for $C_{17}H_{22}$ C 90 20, H, 9 80 Found C, 90 17, H 9 89

10 Gollnick, K Kuhn, H J in *Singlet Oxygen* H Wasserman and R W Murray, editors , Academic New York 19 79, pp 287-427

11 Photooxygenation The diene (51 mg, 0 23 mmol) was dissolved in CCl_4 (0 46 mL) containing 2 5 mM TPP in a water-cooled Pyrex cell into which oxygen was bubbled The reaction was photolyzed with a 150 W illuminator (Edmund Scientific) at a distance of 10 cm for 15 min The solution was stabilized with a small amount of butylated hydroxytoluene (BHT) and concentrated Flash chromatography followed by NP-HPLC (5-10% Ethyl acetate/hexane) allowed separation of the hydroperoxides **2A** and **2B**

MAJOR HYDROPEROXIDE (**2a**) R_f=0 32 in 10% ethyl acetate/hexane, ^{1}H NMR (300 MHz $CDCl_3$) δ 7 56 (s, 1H, CHOO**H**), 7 36-7 18 (m, 5H, phenyl), 6 31 (dt, 1H, J=16 8 10 4 Hz, CH-C**H**=CH_2), 6 07 (dd, 1H, J=14 5, 10 5 Hz, CH=C**H**-CH=CH_2), 5 72 (dd, 1H, J=15 3, 7 5 Hz, CHOOH-C**H**=CH), 5 17 (d 1H J=16 9 Hz, CH=C**H**$_2$), 5 09 (d 1H, J=10 3 Hz, CH=C**H**$_2$), 4 08 (dd, 1H, J=7 4, 2 1 Hz C**H**OOH), 2 69 (dt, 1H, J= 3 9, 11 5 Hz, C**H**-Phenyl), 1 88-1 24 (m 9H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 145 70, 136 15, 133 65, 131 68, 128 55, 127 63, 126 23, 117 87 86 16, 47 78, 46 57, 35 68, 26 54, 25 54

ALCOHOLS Alternatively, a portion of the photooxygenation concentrate was dissolved in 1 mL of ethyl acetate and triphenylphosphine was added (0 1 mL of a 0 1*M* solution in ethyl acetate) The resulting solution was stirred until the hydroperoxides were no longer detectable by TLC typically 5 min Following removal of Ph_3PO by flash chromatography, the ratio of alcohols **3A** and **3B** was determined by comparison of the peaks at 7 1 and 10 3 min in the NP-HPLC (10% EA/hexane, 1 mL/min, 4 6mm x 25 cm Rainin Microsorb 5um Si, RI detection) The accuracy of the RI detection method was confirmed by UV detection (254 nm) or by ^{1}H NMR analysis of the crude alcohols

3A R_f=0 31 in 10% ethyl acetate/hexane ^{1}H NMR (500 MHz, $CDCl_3$) δ 7 31-7 18 (m, 5H, phenyl) 6 29 (dt, 1H, J=17 0 10 2 Hz, CH-C**H**=CH_2), 6 07 (dd, 1H, J=15 3 10 5 Hz, CH=C**H**-CH=CH_2), 5 67 (dd, 1H, J=15 3, 5 2 Hz, CHOH-C**H**=CH), 5 13 (d, 1H, J=16 9 Hz, CH=C**H**$_2$), 5 02 (d, 1H, J=10 1 Hz, CH=C**H**$_2$), 3 89 (s, 1H, C**H**OH-CH), 2 64 (dt, 1H J=11 6, 3 0 Hz, C**H**-Ph), 1 87-1 76 (m, 4H), 1 66 (m, 1H, R_2**H**-CHOH) 1 37-1 21 (m, 5H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 145 81, 136 47 136 26, 130 17, 128 56, 127 70, 126 19 116 54 71 88, 48 39, 46 54, 35 71, 26 71, 26 30, 24 89 IR (neat) 3417, 2927, 2852, 1448 1088, 1070, 1005, 901, 756, 700 cm^{-1}, UV λ_{max} 228 nm (ε=34,000, Hexane), Anal Calcd for $C_{17}H_{22}O$ C, 84 25, H, 9 15 Found C 84 12, H 9 20

3B R_f=0 25 in 10% ethyl acetate/hexane, ^{1}H NMR (360 MHz, $CDCl_3$) δ 7 32-7 16 (m, 5H, phenyl) 6 32 (dt, 1H, J=17 0,10 3 Hz, CH-C**H**=CH_2), 5 97 (dd, 1H, J=15 4, 10 4 Hz, CHOH-CH=C**H**-CH), 5 67 (dd, 1H, J=15 4, 7 2 Hz, CHOH-C**H**=CH), 5 15 (d, 1H J=17 0 Hz CH=C**H**$_2$), 5 07 (d, 1H, J=10 1 Hz, CH=C**H**$_2$), 3 89 (dd, 1H, J=7 0, 3 3 Hz, C**H**OH), 2 24 (dt, 1H, J=1 6, 1 3 Hz, C**H**-Ph), 2 06-1 11 (m, 10H), ^{13}C NMR (75 MHz $CDCl_3$) δ 145 58, 136 43, 132 64, 132 39, 128 54, 127 50, 126 16, 117 20, 73 16 48 34 47 21 36 47 26 72, 25 94 25 65

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14 A third isomer, the primary hydroperoxide arising from terminal oxygenation of the pentadienyl radical, was present as 30 50% of all equilibrations Equilibrations were quenched by addition of a slight excess of triphenylphosphine and were analyzed as the corresponding alcohols as in footnote 11

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