Pergamon

Tetrahedron Vol. 50, No. 30, pp. 8929-8940, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00504-4

Stereoselective Dioxygenation of Enoates

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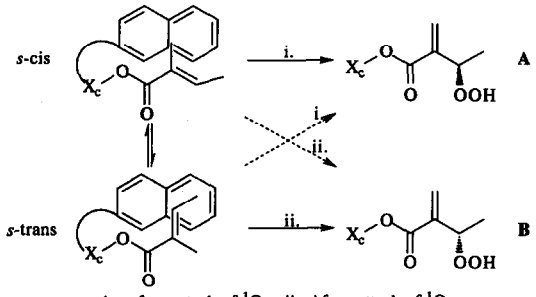
Abstract: The auxiliary-directed reaction of singlet oxygen with tiglate esters furnishes an asymmetric synthesis of 3-hydroperoxy-2-methylidene butenoates. Although previous reports have suggested that *s*-cis enoate conformers undergo preferential oxygenation relative to the *s*-trans conformers, our results suggest that both conformers are reactive and that the modest stereoselectivity is based upon a conformational equilibrium favoring the *s*-trans conformer.

As a part of a program developing new methodology for the synthesis of peroxide-containing natural products, we became interested in the asymmetric dioxygenation of enoates with singlet oxygen ($^1O_2$). Unlike the poorly regioselective reaction of simple alkenes with $^1O_2$, the ene-like dioxygenation of α-alkyl-α,β-unsaturated carbonyl groups occurs regiospecifically to afford good yields of 3-hydroperoxy-2-alkylidene aldehydes, ketones, esters, or acids.[1,2] However, the reaction between an achiral oxidant ($^1O_2$) and a prochiral substrate (enoate) is inherently limited to the synthesis of racemic hydroperoxides. We now report the asymmetric synthesis of 3-hydroperoxy-2-methylidene butenoates based upon reaction between $^1O_2$ and 2-methyl-2-butenoate (tiglate) esters of chiral auxiliaries. (Scheme 1)

The single reported attempt at asymmetric dioxygenation of an enoate employed a maleate chiral auxiliary and proceeded without stereoselectivity.[3] Previous research in our group involving diastereoselective dioxygenation of chiral alkenes demonstrated the critical importance of controlling both the approach of $^1O_2$ and the conformation of the alkene.[4] Scheme 1 illustrates this strategy for an auxiliary tethered enoate. The ability of cyclohexyl- or borneol-based chiral auxiliaries to control the interaction of reagents with tethered substrates has been extensively exploited for asymmetric synthesis and we now report the application of these auxiliaries to the stereoselective dioxygenation of tiglate esters.[5]



i. *re* face attack of $^1O_2$; ii. *si* face attack of $^1O_2$

Scheme 1

Several classes of chiral auxiliaries were compared for their ability to control the stereoselectivity of singlet oxygenation. (Figure 1) Naphthylborneol[6] (**1**), *trans*-2-arylcyclohexanols[5] (**2**), and 8-phenylmenthol[7] (**3a**) were synthesized according to reported procedures. The synthesis of 8-naphthylmenthol (**3b**) involved a slight modification of the procedure reported for 8-phenylmenthol.[8] Esterification of the auxiliaries was accomplished in good yield through carbodiimide-mediated coupling between the acid and alcohol (**2**) or through reaction of the corresponding lithium alkoxides with the anhydride of 2-methyl-2-butenoic acid. (**1, 3ab**).

Our previous investigations into dioxygenation of auxiliary-tethered alkenes had demonstrated that the formation of the major hydroperoxide diastereomer could be attributed to attack of $^1O_2$ on the most accessible face of the most populated alkene conformer.[4] Unfortunately, preliminary modeling of enoates **1 - 3** indicated that dioxygenation stereoselectivity might be inherently limited by the nearly equal conformational energies of the *s*-cis and *s*-trans enoate conformers. Both molecular modeling and semi-empirical calculations predicted the *s*-trans conformer to be favored by only 0.2 - 0.5 kcal/mol.[9] However, previous investigations based upon oxygenation of rigid alkenes suggested that *s*-trans unsaturated carbonyl groups were incapable of undergoing an ene dioxygenation; later workers found the *s*-trans conformers to in fact undergo dioxygenation but at a considerably reduced rate relative to the *s*-cis conformers.[1,10] We initially hypothesized that the higher reactivity of the *s*-cis conformer, coupled with selective facial shielding of the enoate by a chiral auxiliary, should lead to diastereoselective formation of a single major product. (**A** in Scheme 1)

Modeling also suggested that the different auxiliaries might vary widely in the ability of their aromatic sidechain to shield one face of the tethered enoate.[9] (Figure 1) The

extensive tilting predicted for both the enoate and the naphthalene sidechains of the borneol enoate (**1**) left both faces of the enoate open towards attack of a small electrophile such as $^1O_2$. The trans-2-aryl cyclohexyl enoates **2** were also predicted to undergo oxygenation with poor stereoselectivity; the "widening V" relationship of the arene and enoate sidechains would result in a distance of > 5 Å between the aromatic ring and the developing hydroperoxide stereocenter. The 8-arylmenthyl auxiliaries **3**, in contrast, were predicted to hold the enoate and arene sidechains nearly parallel at a distance of 3.5 - 4.5 Å and were anticipated to be quite effective in controlling the approach of $^1O_2$. These predictions are in accordance with previous conformational and structural studies of 8-arylmenthyl esters;[5,11] in particular, a recent crystal structure of the closely related *trans*-2-[1-(2-naphthyl)-1-methylethyl]cyclohexyl crotonate shows the crotonate and arene sidechains to be coplanar at a distance of 3.4 - 4 Å.[12]

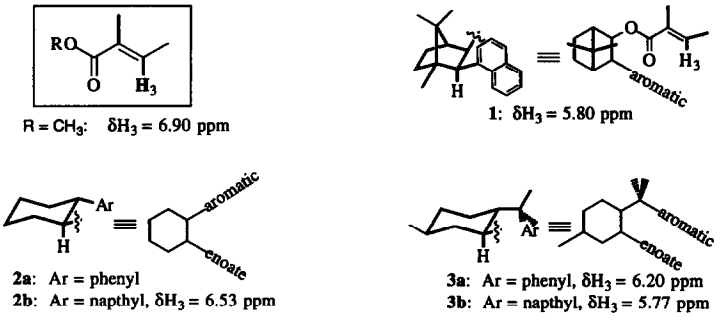
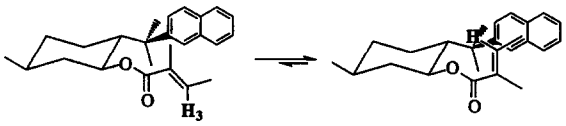


Figure 1

The modeling results were supported by the magnitude of aromatic-induced shifts in the ^1H NMR spectra. (Figure 1) The signal corresponding to the enoate hydrogen (H_3) is shifted significantly upfield in **3a** relative to **2b**, and, as predicted by our modeling studies, further still in the case of **3b**.[13] A variable temperature NMR study of **3b** revealed, as expected, the presence of two conformers. The chemical shift of the enoate hydrogen, 5.77 ppm at room temperature, moved upfield upon cooling, eventually reaching 5.0 ppm. (Table 1) Modeling predicted the enoate hydrogen of the *s*-trans conformer to experience a greater degree of aromatic-induced shielding and our observations can be interpreted in terms of a conformational equilibrium that is shifted toward the *s*-trans conformer at lower temperature. The corresponding variable temperature NMR experiment for **1** displayed a much smaller (≤ 0.2 ppm) change in the

chemical shift of the enoate hydrogen over the same temperature range, illustrating the different nature of the arene/enoate interaction for **1** and **3b**.

Table 1. Low Temperature NMR Experiment



Temp, °C	25	0	- 20	- 40	- 60	- 80
δH_3	5.77	5.50	5.41	5.30	5.18	5.00

Oxidations were performed under visible irradiation in a jacketed Pyrex cell containing an oxygen-aspirated solution of substrate (0.1 M) and sensitizer (TPP or Rose Bengal, typically 0.001 M). Reactions were followed by TLC and stopped after the disappearance of the enoate (typically 0.5 - 2 h). The ratio of stereoisomers (Scheme 1, **A : B**) could be ascertained through ^1H NMR on the crude mixture of hydroperoxides or through HPLC analysis of the corresponding alcohols obtained upon Ph_3P reduction.[14] As predicted, the naphthylborneol (**1**) and naphthylcyclohexyl (**2ab**) auxiliaries proved completely ineffective for controlling the stereochemistry of dioxygenation. (Table 2) The

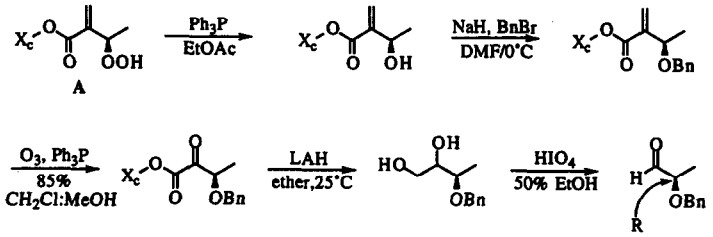
Table 2

Compound	Sensitizer/solv.	Temp.	Yield	A : B
1	TPP/CH_2Cl_2	25°C	84%	1 : 1
2a	TPP/CCl_4	25°	---	1 : 1
2b	TPP/CCl_4	25°	70	1 : 1
3a	TPP/CCl_4	25°	98	1 : 2.0
3b	TPP/CH_2Cl_2	25°	82	1 : 2.3
3b	TPP/CCl_4	25°	87	1 : 2.3
3b	RB/CH_3OH	25°	69	1 : 2.5
3b	RB/CH_3CN	25°	94	1 : 2.3
3b	RB/CH_3OH	- 30°	89	1 : 3.0
3b	TPP/CH_2Cl_2	- 45°	83	1 : 3.3
3b	TPP/CH_2Cl_2	- 60°	86	1 : 4.5

TPP: 5,10,15,20-tetraphenyl-21H,23H-porphine; RB: Rose Bengal

8-naphthylmenthyl enoate (**3b**), in contrast, underwent oxidation with modest but consistent selectivity at room temperature under a variety of conditions. Diastereoselectivity improved at reduced temperatures and a ratio of 4.5 : 1 was obtained at - 60 °C.

The absolute stereochemistry of the newly formed hydroperoxides was determined as illustrated in Scheme 2. The alcohols derived upon Ph_3P reduction of the crude hydroperoxides were separated by preparative HPLC. The minor alcohol was protected as the benzyl ether and cleaved to the ketoester upon ozonolysis. Lithium aluminum hydride reduction followed by periodate cleavage of the resulting diols afforded 2*R*-(benzyloxy)propanal with a rotation of $[\alpha]_D = +30.8$.[15] A subsequently obtained crystal structure of the minor alcohol, shown in Figure 2, verified the stereochemical relationship between the newly formed stereocenter and the chiral auxiliary.



Scheme 2

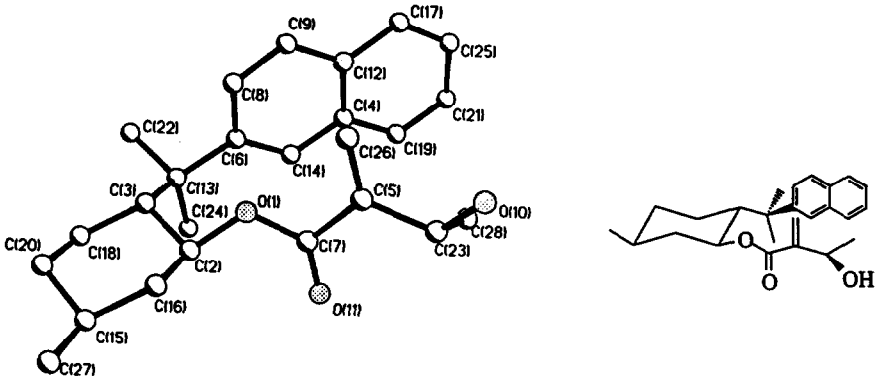
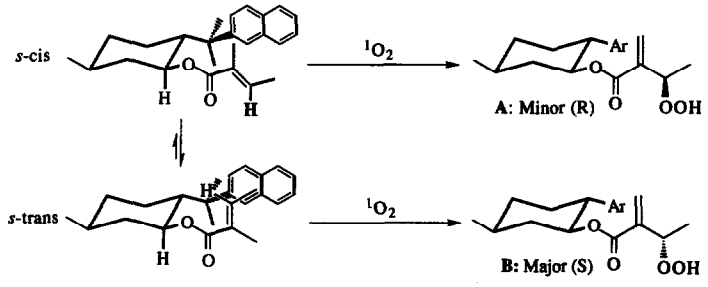


Figure 2. Ball and stick ORTEP drawing of the crystal structure for the minor alcohol.

Based upon existing models for diastereoselection in reactions of 8-phenylmenthol esters, the minor (R) hydroperoxide is derived from reaction between $^1O_2$ and the minor *s*-cis enoate conformer.[5] (Scheme 3) Contrary to literature precedent, the *s*-trans conformer is apparently quite reactive as the source of the major (S) hydroperoxide product. This stereochemical correlation between enoate conformer and hydroperoxide product assumes complete control of the approach of oxygen towards a particular ester conformer. The assumption of an *s*-anti ester conformation (C-O-C(=O)-C) and an eclipsing interaction between the carbonyl bond and ring hydrogen (H-C-O-C(O)) is supported by modeling studies and the crystal structure shown in Figure 2, by structural and conformational studies on other 8-arylmenthyl esters, and by the stereochemical outcome of both nucleophilic and electrophilic attack on 8-arylmenthyl enoates.[9,11,12,16,17] The ability of the naphthyl group of the auxiliary to completely block one face of the enoate towards attack by $^1O_2$ is in accordance with our previous observations regarding the ability of an arene to control approach of $^1O_2$ to a tethered alkene.[4] Our stereochemical rationale also agrees both qualitatively and quantitatively with the diastereoselection reported for the dihydroxylation of 8-arylmenthyl tiglates with OsO_4.[17] Several other groups have also reported reaction between $^1O_2$ and chiral alkenes to occur through attack on the least hindered face of the most populated conformer.[18,19] Considering the NMR and modeling results, the observed temperature-dependent stereoselection is most easily interpreted based upon *differing populations* rather than *differing reactivities* of the two enoate conformers.[20]



Scheme 3

In summary, we have demonstrated that moderate diasteroselectivity can be achieved in the dioxygenation of 8-naphthylmenthyl enoates. The stereoselective shielding induced by the auxiliary appears to be compromised by a lack of conformational bias between *s*-cis and *s*-trans enoate conformers, providing indirect evidence for the similar

reactivity of *s*-cis and *s*-trans enoate conformers towards reaction by $^1O_2$. Attempts to further improve stereoselection through conformational control are currently in progress and will be reported in due course.

Acknowledgment

We gratefully acknowledge the American Cancer Society (CN-33 and CN-33a) for financial support, Professor Richard Shoemaker for valuable assistance with NMR studies and Dr. Charles Ross for acquiring and refining the crystal structure of the minor alcohol.

EXPERIMENTAL

All reagents and solvents were used as supplied commercially, except THF, which was distilled from Na/Ph_2CO. ^1H and ^{13}C NMR spectra were recorded on 300-, 360-, or 500-MHz spectrometers in $CDCl_3$; individual peaks are reported as (multiplicity, number of hydrogens, coupling constant (Hz), assignment). Infrared spectra were recorded on neat films. Optical rotations were obtained in a 1-dm cell in $CHCl_3$ unless otherwise noted. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. Semipreparative and analytical HPLC was performed with Rainin Dynamax Si columns, 2.1 x 25-cm and 0.5 cm x 25-cm respectively, with refractive index detection. All hydroperoxides were handled and stored in the presence of approximately 0.1% butylated hydroxytoluene (BHT), added from a 1 M stock solution in CH_2Cl_2. Progress of reactions involving peroxides was monitored by TLC, using an N,N'-dimethyl-*p*-phenylenediamine indicator; hydroperoxides yield an immediate reddish-pink spot.[21]

Photooxygenations:

Oxidation of the esters was carried out in a jacketed Pyrex cell into which was placed a solution of substrate (0.1M) and sensitizer (5,10,15,20-tetraphenyl-21H,23H-porphine (TPP) or Rose Bengal, typically 0.001M). The solution was aspirated with oxygen and photolyzed with a 200 W illuminator (Dolan-Jenner Industries) at a distance of 1-10 cm. Reactions were followed by TLC and stopped after the disappearance of the enoate (typically 0.5 - 2 hours). Product ratios were obtained by ^1H NMR integration of the crude products and by analytical HPLC analysis of the alcohols obtained by PPh_3 reduction of the peroxides.

2-methyl-2-butenoic acid, bicyclo [2.2.1] heptane-1,7,7, trimethyl-2-exo-(1-napthalenyl)-3-exo-ester- (1):

To a 0 °C solution of napthylborneol (39 mg, 0.14 mmol) in 0.4 mL THF was added a slight excess of *n*-butyl lithium (0.3 mL, 1.6 M in hexane) until the presence of free alkyl lithium was indicated (1,10-phenanthroline), whereupon a slight excess of tiglic

anhydride (35 mg, 0.19 mmol)was rapidly added. The solution was stirred for 30 min and quenched with H_2O (1 mL). The solution was extracted with methylene chloride (3 x 1 mL) and dried over anhydrous $NaSO_4$. Removal of solvent at reduced pressure followed by flash chromatography on silica gel (10% EA/hex) afforded 42.3 mg (84.6%) of the ester: R_f : 0.6 (10% EA/hex); $[\alpha]_D$ = - 192.3 (c = 0.98); ^1H NMR (500 MHz) δ 7.30 - 8.02 (7H, naphthyl); 5.80 (q, 1H, J = 4.1, C=C**H**-CH_3), 5.45 (d, 1H, J = 8.8, **CH**-OR), 4.09 (d, 1H, J = 8.8 , **CH**-nap), 2.03 (d, 1H, J = 5, **CH**), 1.50 - 1.90 (4H, -CH_2-), 1.36 (d, 3H, J = 7, C=CHCH_3), 1.34 (s, 3H, C(CH_3)$_2$), 1.28 (s, 3H, C(CH_3)$_2$), 1.02 (s, 3H, -CH_3), 1.00 (s, 3H, -CH_3); ^{13}C NMR (75.6 MHz) 167.1, 136.1, 133.4, 128.6, 128.1, 126.8, 126.3, 125.9, 124.9, 124.2, 123.4, 79.9, 55.4, 51.0, 49.2, 48.2, 42.5, 23.9, 23.8, 21.6, 14.8, 13.8, 10.9; IR: 2954, 2873, 1705, 1651, 1442, 1257, 1153, 1137, 1074, 785 cm^{-1}.

2-methylene-3-hydroperoxy butanoic acid, bicyclo [2.2.1] heptane-1,7,7 trimethyl-2-exo-(1-napthalenyl)-3-exo-ester:

The ester **1** (82 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2 mL) containing 1.0 mM TPP in a water-cooled pyrex cell into which oxygen was bubbled. The reaction was photolyzed at a distance of 1 cm for 80 min. The solvent was removed *in vacuo*. Flash chromatography on silica gel (4.5% EA/hex) gave 75 mg (84%) of two hydroperoxides as an inseparable 1 : 1 mixture: R_f: 0.11 (10% EA/Hex.); ^1H NMR (300MHz) δ 7.25 - 8.05 (7H, naphthyl), 5.57 (dd, 1H, J = 6.7, 8.58, **CH**-OR), 5.42 (s, 0.5H, C=CH_2), 5.33 (s, 0.5H, C=CH_2), 5.27 (s, 0.5H, C=CH_2), 5.19 (s, 0.5H, C=CH_2), 4.06/4.18 (dq, 1H, J = 37.1, 6.8, -**CH**-OOH), 4.11 (d, 1H, J = 8.8, **CH**-nap), 1.20 - 2.10 (5H,bicycloheptane), 1.34 (s, 3H, C-(CH_3)$_2$), 1.31 (s, 3H, C-(CH_3)$_2$), 1.03 (s, 3H, R_3C-CH_3), 0.79/0.50 (d, 3H, J = 6.4, CH(OOH)-CH_3, 1 : 1 ratio of diasteromers); ^{13}C NMR (75.6 MHz) δ = 140.4, 135.7, 133.5, 128.8, 127.1, 126.6, 126.1, 125.1, 124.5, 123.6, 80.5, 80.2, 78.9, 55.6, 51.2, 49.3, 48.3, 42.5, 33.9, 25.6, 24.9, 23.4, 21.5, 18.1, 17.7, 14.8; IR: 3406, 2970, 2876, 1714, 1630, 1394, 1290, 1174, 1086, 787 cm^{-1}.

2-methyl-2-butenoic acid, 1-(*trans*-2-napthylcyclohexyl) ester (2b):

To a solution of *trans*-2-naphthyl-1-cyclohexanol (453 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added 4-dimethyl amino pyridine (DMAP, 61 mg, 0.5 mmol) and 2-methyl-2-butenoic acid (200 mg, 2.00 mmol). After 5 minutes, dicyclohexyl carbodiimide (DCC) (520 mg, 2.5 mmol) was added. The solution was stirred at 25 °C for 10 hours. The solvent was removed at reduced pressure and dry ethyl ether (50 mL) was added. The solution was filtered to remove the insoluble urea. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (10% EA/hex) afforded 421 mg (88.5%) of the ester: R_f : 0.33 (10% EA/hex); ^1H NMR (500 MHz) δ 7.77 (d, 1H, J = 6.9), 7.76 (d, 1H, J = 6.9), 7.75 (d, 1H, J = 8.5), 7.63 (s, 1H), 7.42 (t, 1H, J = 6.9), 7.39 (t, 1H, J = 7.3), 7.36 (dd, 1H, J = 8.1, 1.2), 6.53 (bq, 1H, J = 7.3, C=C**H**-CH_3),

5.09 (dt, 1H, J = 10.5, 4.4, -CH-OR), 2.91 (dt, 1H, J = 10.9, 3.6, -CH-Nap), 1.57 (d, 3H, J = 7.3, -C=CH-CH_3), 1.55 (s, 3H, CH_3-C=CH-); ^{13}C NMR (75.6 MHz) δ 167.4, 141.0, 136.4, 133.6, 132.4, 128.7, 127.8, 127.6, 127.5, 126.1, 126.0, 125.7, 125.1, 76.1, 50.0, 34.0, 32.4, 26.0, 24.8, 14.1, 11.8; IR: 2943, 2922, 1697, 1649, 1632, 1600, 1450, 1267, 1128, 1144, 1117, 820, 750, 733 cm^{-1}; Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.82: H, 7.76. Found: C, 82.04: H, 7.69.

2-methylene-3-hydroperoxy butanoic acid, 1-(*trans*-2-napthylcyclohexyl) ester:

The ester **2b** (50 mg, 0.16 mmol) was dissolved in CCl_4 (1 mL) containing 1.0 mM TPP in a water-cooled pyrex cell into which oxygen was bubbled. The solution was photolyzed at a distance of 1 cm for 35 min. The solvent was removed *in vacuo*. Flash chromatography on silica gel (40% EA/hex) gave 38 mg (70%) of the peroxide: R_f: 0.10 (10% EA/hex); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06/8.07 (s, 1H, -OOH, 1 : 1 ratio of diasteromers), 7.35 - 7.80 (7H, naphthyl), 6.041/6.037 (s, 1H, C=CH_2, 1 : 1 ratio of diasteromers), 5.989/5.986 (s, 1H, C=CH_2, 1 : 1 ratio of diasteromers), 5.17 (dt, 1H, J = 10.5, 4.5, CH-OR), 4.68 (bq, 1H, J = 6.4, CH(OOH)-CH_3) 2.92 (dt, 1H, J = 11.5, 3.1, CH-nap), 1.40 - 2.39 (8H), 0.99/0.84 (d, 3H, J = 6.4, CH-(OOH)-CH_3, 1 : 1 ratio of diasteromers); ^{13}C NMR (125.8 MHz) δ 166.1, 141.7, 141.3, 141.2, 134.1, 133.1, 128.7, 128.2, 126.9, 126.6, 126.4, 126.1, 125.4, 80.1, 77.7, 50.8, 50.7, 32.9, 26.5, 25.4, 18.8; IR: 3371, 2931, 1709, 1450, 1265, 1173, 1086, 816, 746 cm^{-1}.

2-methyl-2-butenoic acid, 5--methyl-2-(1-methyl-1-phenylethyl) cyclohexyl ester, [1R-(1α, 2β, 5α] (3a):

To a 0 °C solution of 5-methyl-2-(1-methyl-1-phenylethyl) cyclohexanol (248 mg, 1.07 mmol) in THF (10 mL) was added *n*-butyl lithium (1.5 M, 1.43 mL, 2.15 mmol/hexane) until the presence of free alkyl lithium was indicated (1,10-phenanthroline). After five minutes, a solution of 2-methyl-2-butenoic anhydride (375 mg, 2.06 mmol in 3 mL THF, 0.69 mM) was added. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (5% EA/hex) gave 313 mg (93%) of the ester: R_f: 0.46 (10% EA/hex); $[\alpha]_D$ = - 39.4 (c = 0.31); ^1H NMR (300 MHz) δ 7.07 - 7.30 (5H, phenyl), 6.20 (bq, 1H, J = 6.9, C=CH-CH_3), 4.91 (dt, 1H, J = 10.7, 4.3, CH-OR), 2.07 (dt, 1H, J = 12.2, 3.3, CH-C(CH_3)$_2$-Ph), 1.62 (d, 3H, J = 6.9, C=C-CH_3), 1.60 (s, 3H, CH_3-C=CH-), 1.31 (s, 3H, CH-C(CH_3)$_2$-Ph), 1.21 (s, 3H, CH-C(CH_3)$_2$-Ph), 0.90-1.70 (7H), 0.87 (d, 3H, J = 6.4, CH-CH_3); ^{13}C NMR (75.6 MHz) δ 167.7, 152.4, 137.4, 129.2, 128.6, 126.1, 125.4, 74.8, 51.2, 42.6, 40.4, 35.3, 32.0, 28.2, 27.4, 26.2, 22.5, 14.9, 12.3; IR: 2954, 2923, 2869, 1698, 1456, 1261, 1141, 1128, 733, 700 cm^{-1}; Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21: H, 9.62. Found: C, 79.98: H, 9.44.

2-methylene-3-hydroperoxy butanoic acid, 5-methyl-2-(1-methyl-1-phenylethyl) cyclohexyl ester, [1R-(1α, 2β, 5α]:

The ester **3a** (283 mg, 0.90 mmol) was dissolved in CCl_4 (10 mL) containing 1.0 mM TPP in a water-cooled Pyrex Cell into which oxygen was bubbled. The reaction was photolyzed for 75 minutes at a distance of 1 cm. The solvent was removed *in vacuo*. Flash chromatography on silica gel (10% EA/hex) gave 304 mg (97.5%) of the hydroperoxide: R_f : 0.19 (10% EA/hex); ^1H NMR (300 MHz) δ 8.13 (s, 1H, CH-OOH, minor), 8.05 (s, 1H,CH-OOH, major), 7.07-7.31 (5H, phenyl), 5.71 (s, 1H, C=CH_2, minor), 5.70 (s, 1H, C=CH_2, major), 5.61 (s, 1H, C=CH_2, minor), 5.59 (s, 1H, C=CH_2, major), 4.92 (dt, 1H, J = 10.5, 4.1, CH-OR), 4.74 (q, 1H, J = 6.7, CH-OOH, major), 4.69 (q, 1H, J = 6.7, CH-OOH, minor) 2.12 (dt, 1H, J = 12.2, 3.3, CH-$C(CH_3)_2$-Ph), 1.31 (s, 3H, CH-$C(CH_3)_2$-Ph), 1.26 (d, 3H, J = 6.4, CH(OOH)-CH_3), 1.21 (s, 3H, CH-$C(CH_3)_2$-Ph), 0.88 (d, 3H, J = 6.7, CH-CH_3), 0.75 - 1.95 (7H); ^{13}C NMR (125.8 MHz) δ 128.7, 128.7, 126.1, 126.0, 125.9, 125.7, 125.6, 80.1, 79.8, 75.8, 75.7, 51.0, 42.3, 35.2, 31.9, 28.6, 27.3, 25.9, 22.4, 19.3, 18.8; IR : 3415, 2956, 2924, 1705, 1369, 1294, 1176, 1109, 1086, 700 cm^{-1}.

2-methyl-2-butenoic acid, 5-methyl-2-[1-methyl-1-(2-naphthalenyl) ethyl] cyclohexyl ester, [1R-(1α, 2β, 5α)]- (3b):

To a 0 °C solution of 5-methyl-2-[1-methyl-1-(2-naphthalenyl)ethyl] cyclohexanol (116 mg, 0.41 mmol) in THF (10 mL) was added *n*-butyl lithium (1.5 M, 0.6 mL, 0.9 mmol/hexane) until the presence of free alkyl lithium was detected (1,10-phenanthroline). After ten minutes, a solution of 2-methyl-2-butenoic anhydride (77 mg, 0.42 mmol in 2 mL THF, 0.21 mM) was added. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (5 - 20% EA/hex) gave 137 mg (93%) of the ester: R_f: 0.49 (10% EA/hex); $[\alpha]_D$ = - 46.1 (c = 1.8); ^1H NMR (300 MHz) δ 7.75 (d, 1H, J = 7.3), 7.74 (d, 1H, J = 8.9), 7.77 (dd, 1H, J = 7.7), 7.54 (s, 1H), 7.49 (dd, 1H, J = 8.9, 2.0), 7.39 (t, 1H, J = 7.7), 7.36 (t, 1H, J = 6.9), 6.73 (dt, 1H, J = 12.1, 3.6, CH-C(CH_3)-Nap), 5.77 (bq, 1H, J = 6.9, C=CH-CH_3), 4.94 (dt, 1H, J = 10.5, 4.4, CH-OR), 1.40 (s, 3H, C-$(CH_3)_2$), 1.26 (s, 3H, C-$(CH_3)_2$), 1.31 (s, 3H, CH_3-C=CH-CH_3), 1.08 (d, 3H, J = 7.3, C=C-CH_3), 0.80-1.83 (7H), 0.86 (d, 3H, J = 6.9, CH-CH_3); ^{13}C NMR (75.6 MHz) δ 149.4, 136.7, 133.7, 131.5, 128.0, 127.9, 127.3, 127.2, 125.6, 125.0, 124.9, 122.8, 77.1, 73.8, 50.3, 41.9, 39.7, 34.7, 31.4, 28.6, 26.6, 23.9, 21.8, 13.6, 11.3; IR : 2952, 2922, 1697, 1456, 1263, 1142, 1134, 816, 746, 733 cm^{-1}. Anal. Calcd. for $C_{25}H_{32}O_2$: C, 82.35: H, 8.84. Found: C, 82.12: H, 8.72.

2-methylene-3-hydroperoxy butanoic acid, 5-methyl-2-[1-methyl-1-(2-naphthalenyl)ethyl] cyclohexyl ester, [1R-(1α, 2β, 5α)]-:

The ester **3b** (44.5 mg, 0.12 mmol) was dissolved in CCl_4 (10 mL) containing 1.0 mM TPP. Photooxygenation was performed as for ester **3a.** The solution was stabilized with a small amount of butylated hydroxytolulene (BHT) and concentrated. Flash chromatography on silica gel (5 - 10% EA/hex) gave 39.5 mg (82 %) of the peroxide: R_f:

0.14 (10% EA/hex); ^{1}H NMR (500 MHz) δ 7.36 - 7.77 (7H, naphthyl), 5.52 (s, 1H, C=C**H**$_2$, minor), 5.30 (s, 1H, C=C**H**$_2$, major), 5.20 (s, 1H, C=C**H**$_2$, minor), 5.07 (s, 1H, C=C**H**$_2$, major), 4.97 (dt, 1H, J = 10.9, 4.4, C**H**-OR), 4.49 (q, 1H, J = 6.5, C**H**-OOH, major), 4.13 (q, 1H, J = 6.5, C**H**-OOH, major), 2.25 (dt, 1H, J = 12.1, 3.6, C**H**-C(CH$_3$)$_2$-Nap), 1.41 (s, 3H, C-(C**H**$_3$)$_2$), 1.27 (s, 3H, C-(C**H**$_3$)$_2$), 0.98 (d, 3H, J = 6.5, CH(OOH)C**H**$_3$), 0.88 (d, 3H, J = 6.5, CH-C**H**$_3$), 0.8 - 1.8 (7H); ^{13}C NMR (125.8 MHz): δ = 128.0, 127.8, 127.5, 127.4, 127.3, 127.1, 125.7, 125.2, 125.1, 125.0, 124.6, 122.7, 79.0, 74.8, 50.0, 41.69, 41.65, 39.7, 34.6, 31.3, 28.7, 26.5, 23.8, 21.7, 17.9; IR : 3408, 3056, 2954, 2924, 1703, 1371, 1292, 1274, 1176, 1085 cm^{-1}.

2-methylene-3-hydroxy butanoic acid, 5-methyl-2-[1-methyl-1-(2-naphthalenyl)ethyl] cyclohexyl ester, [1R-(1α, 2β, 5α)-3R]- (A):

The mixture of peroxides was dissolved in 10% EA/hex and triphenylphospine (1.5eq) was added. The resulting alcohols were separated by HPLC (10% EA/hex): R$_f$: 0.21 (10% EA/hex); ^{1}H NMR (300 MHz) δ 7.3 - 7.8 (7H, naphthyl), 5.46 (s, 1H, C=C**H**$_2$), 5.07 (s, 1H, C=C**H**$_2$), 5.00 (dt, 1H, J = 11.0, 4.3, C**H**-OR), 3.56 (q, 1H, J = 6.4, C**H**-OH), 2.20 (dt, 1H, J = 11.9, 3.6, C**H**-C-(CH$_3$)$_2$-Ar), 1.42 (s, 3H, C-(C**H**$_3$)-Ar), 1.28 (s, 3H, C-(C**H**$_3$)-Ar), 0.92 (d, 3H, J = 6.4, CH-(OH)-C**H**$_3$), 0.88 (d, 3H, J = 6.7, CH-(OH)-C**H**$_3$), 0.8 - 1.95 (7H); ^{13}C NMR (75.6 MHz) δ 166.2, 150.2, 144.3, 134.1, 132.0, 128.6, 128.1, 127.8, 126.4, 125.8, 123.5, 123.3, 74.9, 66.6, 50.8, 42.3, 35.2, 32.0, 30.4, 29.8, 27.0, 23.7, 22.5, 22.1; IR: 2954, 2925, 2869,1704,1294, 1275, 1167, 1089, 818, 746 cm^{-1}; Anal. Calcd. for C$_{25}$H$_{32}$O$_3$: C, 78.89: H, 8.47. Found: C, 78.70: H, 8.56.

2-methylene-3-hydroxy butanoic acid, 5-methyl-2-[1-methyl-1-(2-naphthalenyl)ethyl] cyclohexyl ester, [1R-(1α, 2β, 5α)-3S]- (B).

^{1}H NMR (300 MHz) δ 7.3 - 7.8 (7H, naphthyl), 5.21 (s, 1H, C=C**H**$_2$), 4.98 (dt, 1H, J = 10.7, 4.5, C**H**-OR), 4.95 (s, 1H, C=C**H**$_2$), 3.97 (q, 1H, J = 6.4, C**H**-OH), 2.21 (dt, 1H, J = 12.4, 1.9, C**H**-C-(CH$_3$)$_2$-Ar), 1.42 (s, 3H, C-(C**H**$_3$)-Ar), 1.28 (s, 3H, C-(C**H**$_3$)-Ar), 1.03 (d, 3H, J = 6.4, CH-(OH)-C**H**$_3$), 0.88 (d, 3H, J = 6.4, CH-(OH)-C**H**$_3$), 0.8 - 1.95 (7H); ^{13}C NMR (125.8 MHz) δ 166.2, 150.2, 144.3, 128.4, 128.4, 128.1, 127.9, 126.3, 125.8, 125.7, 123.8, 123.4, 78.0, 77.5, 77.4, 74.9, 67.2, 50.8, 42.4, 35.2, 32.0, 29.4, 27.1, 24.3, 22.4, 22.2; The coordinates for the crystal structure shown in Figure 2 have been deposited in the Cambridge Crystallographic Database.

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(*Received in USA* 17 *March* 1994; *revised* 6 *June* 1994; *accepted* 7 *June* 1994)