Asymmetric Oxidations of Enolates Derived from Birch Reduction of Methyl 2-Methoxybenzoate and (*S*)-2-Methoxy-1-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]benzene

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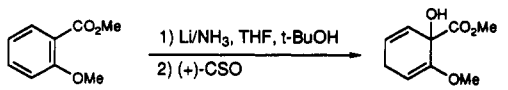
The alkylation of enolates generated by alkali metal in ammonia reduction of aromatic carboxylic acid derivatives is well-known,[1] but the oxidation of these enolates to give 6-hydroxy-1,4-cyclohexadienes has not been reported. The sensitivity of 6-hydroxy-1,4-cyclohexadienes to bis allylic oxidation[2] or dehydration to the starting aromatic compound places unusually demanding restrictions on the reactivity of the oxidant. (Camphorsulfonyl)oxaziridines have been used for the asymmetric oxidation of ketone, ester, and amide enolates.[3] Asymmetric oxidations of chiral imide[4a] and amide[3c,4b] enolates with oxaziridines[5] also have been reported. In this note we describe procedures for performing the asymmetric oxidation of achiral and chiral enolates prepared from *o*-anisic acid derivatives.

Results and Discussion

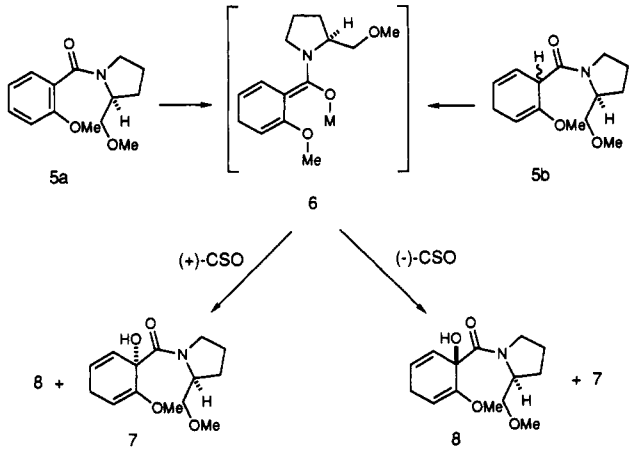
Methyl 2-methoxybenzoate (1) was reduced with lithium in NH_3–THF solution in the presence of *t*-BuOH (1 equiv). Piperylene was added to consume the excess lithium, and then 2 equiv of a solution of (+)-(2*R*,8a*S*)-(camphorsulfonyl)oxaziridine ((+)-CSO)[6] in DME was added to the enolate at −78 °C. After 5 min, excess NH_4Cl was added, and the reaction mixture was quickly submitted to workup by extraction and flash column chromatography on silica gel. These experimental conditions consistently provided 6-hydroxy-1,4-cyclohexadiene **2** in 50–60% isolated yields with 30% ee. Significant deviation from this protocol resulted in recovery of **1**, presumably by dehydration of **2** or elimination from a reaction intermediate.[5]



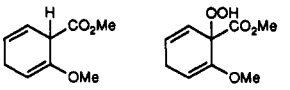
1 2 (30% ee)

We were curious to see what would be the stereoselectivity of enolate oxidation in an ammonia-free environment.[7] Birch reduction of **1** as previously described, followed by removal of ammonia and oxidation of the enolate with (+)-CSO at −78 °C, also provided **2** in 50–60% yield, but with only 5% ee.

Scheme I



Other methods of enolate oxidation were examined. Deprotonation of dihydrobenzoate **3**[1] with potassium bis(trimethylsilyl)amide at −78 °C, followed by oxidation with *m*-chloroperoxybenzoic acid provided racemic **2** in 30% yield, along with recovered starting material. Oxidation of the enolate with molecular oxygen gave *rac*-**2** (8%) and the hydroperoxide **4**.[8] Hydroperoxide **4** proved to be stable to silica gel chromatography and was isolated in 32% yield. Reduction of **4** with potassium iodide in MeOH–H_2O provided *rac*-**2** in 94% yield.



3 4

The poor enantioselectivity observed for formation of **2**[9] is consistent with literature reports of oxidations of achiral tetrasubstituted enolates with chiral oxaziridines.[3d] Significantly enhanced diastereoselectivities have been obtained from oxidations of chiral amide enolates with chiral oxaziridines (double asymmetric induction).[3c]

Birch reduction of chiral benzamide **5a**,[10] followed by oxidation of the resulting enolate **6** with (+)-CSO, provides dienol **7** with 86% de, but in only 16% isolated yield. The major byproduct of the enolate oxidation is recovered **5a** (47%). Removal of the ammonia prior to oxidation of the enolate generated from **5a** with (+)-CSO results in little change in reaction diastereoselectivity (85% de) but does afford a significantly enhanced yield of **7** (57%; 80% based on starting material consumed). Perhaps the best method for generation of **7** (93% de, 47% isolated yield; 73% based on recovered **5a** and **5b**) involves deprotonation of **5b**[7] with KH in THF at ambient temperature followed by oxidation with (+)-CSO at −78 °C.

The absence of a significant effect of ammonia on the stereoselectivity of enolate oxidation is remarkable in light of previously reported alkylation studies. It has been shown that removal of ammonia from solutions of the enolate **6** prior to alkylation resulted in complete inversion of the facial selectivity.[7]

(1) (a) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35. (b) For asymmetric reductive alkylation procedures, see: Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207.

(2) (a) Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6408. (b) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.

(3) (a) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402. (b) Davis, F. A.; Hague, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (c) Davis, F. A.; Ulatowski, T. G.; Hague, M. S. *J. Org. Chem.* **1987**, *52*, 5288. (d) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Hague, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

(4) (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (b) Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985**, *26*, 3539.

(5) For an excellent review of the utilization of oxaziridines in organic synthesis, see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(6) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

(7) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

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(9) It is noteworthy that alkylation of the enolate from Birch reduction of **1** with racemic 4-iodo-3-isopropyl-1-butene gave 3-carbomethoxy-3-(2′-isopropyl-3′-butenyl)-2-methoxy-1,4-cyclohexadiene with ~25% de; see: Schultz, A. G.; Geiss, W. *J. Org. Chem.* **1989**, *54*, 3158.

(10) Chiral benzamide **5a** has provided enolates that react with achiral alkylation reagents with outstanding stereocontrol; see ref 7.

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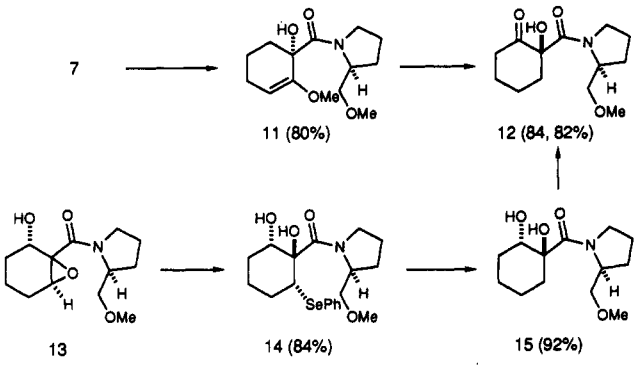
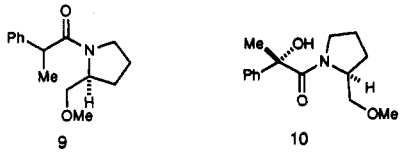
Scheme II



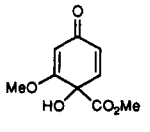
Davis and co-workers have reported that oxidations of the lithium enolate of amide **9** with (+)- or (-)-CSO gave (*S*)-**10** with 88–91% de.[3c] These observations suggested



that "the resident chirality of the enolate controls the sense of stereoselection".[3c] We were, therefore, surprised to find that oxidation of the enolate derived from **5** with racemic CSO or racemic 2-(phenylsulfonyl)-3-phenyloxaziridine afforded **7** with only 17% de, suggesting that (-)-CSO would provide a substantial inversion in the sense of stereoselection. In fact, oxidation of enolate **6** with (-)-CSO in the presence of NH_3 gave **8** with 33% de. Unfortunately, **8** could be obtained in only 11% yield (69% recovered **5a**). In contrast to the results with (+)-CSO, removal of the NH_3 prior to addition of (-)-CSO resulted in an inversion of stereoselection to give **7** (23% de, 25% isolated yield with 57% recovered **5a**).

The absolute configuration of **7** was determined by chemical interconversions as shown in Scheme II. Hydrogenation of **7** with the homogeneous hydrogenation catalyst $[Ir(cod)py(PCy_3)]PF_6$ in CH_2Cl_2[11,12] gave enol ether **11** in 80% yield; hydrolysis of **11** gave **12** in 84% isolated yield. This material was then compared to **12** prepared by another route. Epoxy alcohol **13**[13] was reacted with sodium phenylselenide to give diol **14** (84%). Hydrogenolysis of **14** with Raney nickel gave **15** (92%) and Swern oxidation of **15** gave a hydroxy ketone identical in all respects to **12** prepared from **5a** or **5b**.

It should be noted that hydroxy ketone **12**, diols **14** and **15**, and related materials are expected to have interesting utility in asymmetric synthesis. Furthermore, bis-allylic oxidation of **2** with *tert*-butyl hydroperoxide and pyridinium dichromate[2b] gave 4-hydroxy-2,5-cyclohexadien-1-one **16** in 77% yield.[14] Asymmetric oxidation of enolates such as **6** coupled with bis-allylic oxidation may be useful for asymmetric syntheses of the neolignans containing the 4-oxa-2,5-cyclohexadien-1-one ring system such as futoquinol[15a] and kadsurenone.[15b,c]



Experimental Section

General Procedures. ^1H NMR spectra were recorded at 200 MHz with tetramethylsilane as internal standard. Analytical TLC was performed on silica gel F-254 plates. Tetrahydrofuran (THF) was distilled under nitrogen from sodium/benzophenone. *tert*-Butyl alcohol was distilled under nitrogen from CaH_2. Potassium bis(trimethylsilyl)amide was purchased as a 0.5 M solution in toluene. Sodium bis(trimethylsilyl)amide was purchased as a 1.0 M solution in toluene. All other solvents and reagents were of reagent-grade quality and were utilized without further purification. Solutions were concentrated by a Buchi rotary evaporator. Residual solvent was removed by a mechanical vacuum pump. Diastereomer ratios were determined by analytical HPLC techniques on a Waters Associates 6000A instrument equipped with a R401 differential refractometer and Hewlett Packard Model 3394 integrator using a 25-cm Daicel OD chiral column.

6-Carbomethoxy-1-methoxy-1,4-cyclohexadien-6-ol (2). Method A. A stirred solution of **1** (2.0 g, 12 mmol) and *tert*-butyl alcohol (0.90 g, 12 mmol) in THF (20 mL) was cooled to -78 °C, and then ammonia (40 mL) was added. Lithium metal (252 mg, 36.0 mmol) was added, and the mixture was stirred for 15 min. Piperylene was added until the blue coloration disappeared. (+)-(2*R*,8a*S*)-(Camphorsulfonyl)oxaziridine[6] (5.0 g, 22 mmol) in DME (100 mL) was poured quickly into the stirred solution. After stirring for 5 min, excess solid ammonium chloride was added and the mixture was allowed to warm to room temperature. The solution was decanted, the residue was washed with methylene chloride, and the combined organic phases were concentrated at reduced pressure. Ether (100 mL) was added, and the solution was filtered. The filtrate was washed with water and brine and then dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane, 1:3) afforded **2** as an oil which slowly crystallized (1.28 g, 58%): mp 71–74 °C; $[\alpha]^{27}_D$ -14.5° (*c* 7.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.88–2.98 (m, 2 H), 3.60 (s, 3 H), 3.78 (s, 3 H), 3.91 (s, exchangeable with D_2O, 1 H), 5.01 (t, J = 3.6 Hz, 1 H), 5.65 (dt, J = 9.8 Hz, J = 2.1 Hz, 1 H), 6.12 (ddt, J = 9.8 Hz, J = 3.4 Hz, J = 1.1 Hz, 1 H); IR (CH_2Cl_2) 3500, 3040, 3020, 2940, 2820, 2800, 1750, 1680, 1640 cm^{-1}; CIMS m/z (relative intensity) 167 (M^+ + 1 - H_2O, 100).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.78; H, 6.75.

Chiral shift studies with 20% tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) indicated that **2** was obtained with 30% ee.

Method B. A stirred solution of **3**[7] (1 g, 6 mmol) in THF (20 mL) was cooled to -78 °C, and sodium bis(trimethylsilyl)amide (1.1 mL, 6.0 mmol) was added. A stream of oxygen was passed into the reaction mixture for 2 min. Excess solid ammonium chloride was added, and the mixture was allowed to warm to room temperature. Water (20 mL) and methylene chloride (50 mL) were added. The organic phase was washed with brine and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatogrpahy (silica gel, ethyl acetate/hexane, 1:1) afforded **2** (82 mg, 8%) and 6-carbomethoxy-6-hydroperoxy-1-methoxy-1,4-cyclohexadiene (**4**), a colorless oil (386 mg, 32%): ^1H NMR ($CDCl_3$) δ 2.9–3.0 (m, 2 H), 3.63 (s, 3 H), 3.81 (s, 3 H), 5.19 (t, J = 3.6 Hz, 1 H), 5.97 (dt, J = 9.8 Hz, J = 2 Hz, 1 H), 6.27 (dt, J = 9.8 Hz, J = 3.4 Hz, 1 H), 9.15 (s, exchangeable with D_2O, 1 H); IR (film) 3420, 3010, 2960, 1730, 1650 cm^{-1}; CIMS m/z (relative intensity) 201 (M^+ + 1, 7), 183 (3), 167 (100).

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(13) Epoxy alcohol **13** was prepared by stereoselective epoxidation of the corresponding chiral cyclohexenone, followed by ketone reduction with sodium borohydride. The molecular structure of **13** was determined by X-ray crystallographic studies; unpublished resutls of A. G. Taveras, RPI laboratories.

(14) Photorearrangements of enantiomerically enriched derivatives of **16** have been described; see: Schultz, A. G.; Harrington, R. E. *J. Org. Chem.* **1991**, *56*, 6391.

(15) (a) Matsui, K.; Munakata, K. *Tetrahedron Lett.* **1976**, 4371. (b) Chang, M. N.; Han, G.-Q.; Arison, B. H.; Springer, J. P.; Hwang, S.; Shen, T. Y. *Phytochemistry* **1985**, *24*, 2079. (c) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309.

A mixture of 4 (0.2 g, 1.0 mmol), potassium iodide (250 mg, 1.20 mmol), and water (5 mL) in methanol (10 mL) was stirred at room temperature for 15 min. The methanol was removed at reduced pressure, and ether (50 mL) was added. Water (10 mL) and then sodium thiosulfate were added to the stirred mixture until a colorless solution was obtained. The organic phase was washed with water and brine and then dried over magnesium sulfate. Concentration at reduced pressure provided 2 as a colorless solid (173 mg, 94%).

Method C. A stirred solution of 3 (0.1 g, 0.6 mmol) in THF (10 mL) was cooled to −78 °C, and then potassium bis(trimethylsilyl)amide (120 mL, 0.60 mmol) was added. After stirring at −78 °C for 5 min, solid *m*-chloroperoxybenzoic acid (155 mg, 0.90 mmol) was added. After 0.5 h, excess solid ammonium chloride was added, and the mixture was allowed to warm to room temperature, after which water (5 mL) and methylene chloride (20 mL) were added. The organic phase was washed with saturated sodium bicarbonate and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane, 1:3) afforded 2 (33 mg, 30%).

(2′*S*)-3-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-hydroxy-2-methoxy-1,4-cyclohexadiene (7). Method D. Diene 5b[7] (200 mg, 0.8 mmol) in THF (2 mL) was added at room temperature to a stirred suspension of KH (64 mg, 1.6 mmol) in THF (10 mL). After 1 h the mixture was cooled to −78 °C, (+)-CSO (367 mg, 1.60 mmol) was added, and the reaction stirred for 30 min and was quenched with pH 7.0 phosphate buffer. The mixture was diluted with water (5 mL) and washed with CH_2Cl_2 (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. A mixture of ether/hexane (1:1; 3 mL) was added to the residue, and the resulting precipitate (recovered imine) was filtered. Flash chromatography (ethyl acetate/hexane, 1:2) of the filtrate afforded a mixture of 7 and 8 as a colorless oil (100 mg, 47%; 27:1 mixture of 7 and 8): ^{1}H NMR ($CDCl_3$) δ 1.7–2.1 (m, 4 H), 2.81 (m, 1 H), 3.08 (m, 1 H), 3.34 (s, 3 H), 3.59 (s, 3 H), 3.18–3.70 (m, 4 H), 4.28–4.45 (m, 1 H), 5.01–5.08 (m, 1 H), 5.56 (dt, *J* = 9.8 Hz, *J* = 2 Hz, 1 H), 5.63 (s, exchangeable with D_2O, 1 H), 6.05–6.20 (m, 1 H); IR (film) 3340, 2930, 2880, 2830, 1625 cm^{-1}; CIMS *m*/*z* (relative intensity) 268 (M^+ + 1, 46), 250 (100).

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C, 62.76; H, 7.79.

Method E. A stirred solution of 5a (150 mg, 0.60 mmol) and *t*-BuOH (44 mg, 0.60 mmol) in THF (10 mL) was cooled to −78 °C, and then ammonia (40 mL) was added. Potassium metal (48 mg, 1.2 mmol) was added, and the mixture was stirred for 30 min. (+)-CSO (276 mg, 1.21 mmol) in DME (5 mL) was poured quickly into the stirred solution. After stirring for 5 min, excess solid ammonium chloride was added, and the mixture was allowed to warm to room temperature. Water was added, the mixture was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. A mixture of ether/hexane (1:1; 3 mL) was added to the residue, and the resulting precipitate was filtered. This was repeated until a white precipitate failed to appear. Flash chromatography (ethyl acetate/hexane, 1:3) afforded a mixture of 7 and 8 as a colorless oil (26 mg, 16%; 13:1 mixture of 7 and 8) and 5a (70 mg, 47%). Oxidation of 6 according to this procedure with (−)-CSO afforded a mixture of 8 and 7 (11%; 2:1 mixture of 8 and 7) and 5a (69%).

Method F. A stirred solution of 5a (150 mg, 0.60 mmol) and *t*-BuOH (44 mg, 0.60 mmol) in THF (10 mL) was cooled to −78 °C, and then ammonia (40 mL) was added. Potassium metal (48 mg, 1.2 mmol) was added, and the mixture was stirred for 30 min. Piperylene was added until the blue coloration disappeared, and the mixture was then warmed to room temperature to allow the ammonia to evaporate. The mixture was cooled to −78 °C, and (+)-CSO (276 mg, 1.21 mmol) in DME (5 mL) was poured quickly into the stirred solution. After stirring for 5 min, excess solid ammonium chloride was added and the mixture was allowed to warm to room temperature. Water was added, the mixture was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. A mixture of ether/hexane (1:1; 3 mL) was added to the residue, and the resulting precipitate was filtered. This was repeated until a white precipitate failed to appear. Flash chromatography (ethyl acetate/hexane, 1:3) afforded a mixture of 7 and 8 as a colorless oil (91 mg, 57%; 12:1 mixture of 7 and 8) and 5a (44 mg, 29%). Oxidation of 6 according to this procedure with (−)-CSO afforded a mixture of 7 and 8 (25%; 1.6:1 mixture of 7 and 8) and 5a (57%).

(2′*S*)-1-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-1-hydroxy-2-methoxycyclohex-2-ene (11). A solution of 7 (100 mg, 0.37 mmol) and $[Ir(cod)pyPCy_3]PF_6$ (15.0 mg, 0.02 mmol) was stirred under H_2 (1 atm) for 12 h. The reaction mixture was concentrated at reduced pressure, ether was added, and the solution was decanted. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane, 1:1) afforded 11 as a colorless oil (80 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 1.65–2.38 (m, 10 H), 3.15–3.32 (m, 1 H), 3.35 (s, 3 H), 3.53 (s, 3 H), 3.35–3.60 (m, 2 H), 3.61 (dd, *J* = 9.5 Hz, *J* = 3.1 Hz, 1 H), 4.22–4.40 (m, 1 H), 4.90–4.98 (m, 1 H), 5.07 (s, exchangeable with D_2O, 1 H); IR (film) 3360, 2935, 2830, 1620 cm^{-1}; CIMS *m*/*z* (relative intensity) 270 (M^+ + 1, 100), 252 (6).

Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61. Found: C, 62.04; H, 8.41.

(2*S*,2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-2-hydroxycyclohexan-1-one (12). A solution of 11 (0.04 g, 0.15 mmol) and 10% hydrochloric acid (1 mL) in methanol (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated at reduced pressure, and the residue was partitioned with methylene chloride (10 mL) and water (5 mL). The organic phase was washed with saturated sodium bicarbonate and water and then dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane, 1:2) afforded 12 as a colorless oil (32 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 1.45–2.2 (m, 9 H), 2.56–2.75 (m, 2 H), 2.85–3.01 (m, 1 H), 3.36 (s, 3 H), 3.3–3.8 (m, 4 H), 4.18–4.35 (m, 1 H), 4.56 (s, exchangeable with D_2O, 1 H); IR ($CDCl_3$) 3420, 2930, 2860, 1710, 1620 cm^{-1}; CIMS *m*/*z* (relative intensity) 256 (M^+ + 1, 100).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29. Found: C, 61.21; H, 8.35.

(1*S*,2*S*,2′*S*,6*R*)-1-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-2-hydroxy-6-(phenylseleno)cyclohexan-1-ol (14). Sodium borohydride (0.068 g, 1.8 mmol) was added to diphenyl diselenide (0.29 g, 0.93 mmol) in absolute ethanol (5 mL). After the exothermic reaction had subsided, epoxide 13[13] (0.20 g, 0.80 mmol) was added and the mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature, ethanol was evaporated, and the residue was partitioned between methylene chloride and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). Flash chromatography (ethyl acetate/hexanes, 1:1) gave 14 as a colorless oil which solidified upon exposure to vacuum (0.272 g, 84%). This material was recrystallized in 74% yield (ethyl acetate/hexanes) to give colorless needles: mp 115–118 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (m, 1 H), 1.70 (m, 8 H), 2.06 (m, 2 H), 3.17 (m, 2 H), 3.23 (s, 3 H), 3.58 (dd, *J* = 8.79 Hz, *J* = 3.30 Hz, 1 H), 3.70 (m, 1 H), 4.21 (m, 2 H), 5.15 (d, *J* = 3.01 Hz, exchangeable with D_2O, 1 H), 5.55 (s, exchangeable with D_2O, 1 H), 7.27 (m, 3 H), 7.52 (m, 2 H); IR (CH_2Cl_2) 3350, 2900, 1600, 1400, 700 cm^{-1}; EIMS *m*/*e* (relative intensity) 413 (M^+, 24), 368 (20), 256 (100), 157 (95).

Anal. Calcd for $C_{19}H_{27}NO_4Se$: C, 55.34; H, 6.60. Found: C, 55.30; H, 6.54.

(1*S*,2*S*,2′*S*)-1-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-2-hydroxycyclohexan-1-ol (15). Selenide 14 (0.598 g, 1.45 mmol) was stirred with activated Raney nickel (4.35 g) in THF (50 mL) at room temperature for 4 h. The mixture was filtered [**Caution**: activated Raney nickel is pyrophoric], and the solid was rinsed with ethanol. Flash chromatography (ethyl acetate) gave 15 as a colorless oil (0.345 g, 92%): ^{1}H NMR (DMSO-d_6) δ 1.2–2.0 (m, 12 H), 3.18 (m, 1 H), 3.23 (s, 3 H), 3.45 (dd, *J* = 9.07 Hz, *J* = 3.09 Hz, 1 H), 3.57 (m, 1 H), 3.71 (m, 1 H), 3.90 (m, 1 H), 4.10 (m, 1 H), 5.00 (s, 1 H), 5.25 (s, 1 H); IR (CH_2Cl_2) 3380, 2900, 1580, 1400 cm^{-1}; CIMS *m*/*z* (relative intensity) 258 (M^+ + 1, 100), 212 (4).

An acceptable elemental analysis could not be obtained.

(2*S*,2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-2-hydroxycyclohexan-1-one (12): Confirmation of the Structure of 12 Obtained from 5a. Methylene chloride (5 mL) and oxalyl chloride (0.184 g, 1.45 mmol) were cooled to −60 °C, and then dimethyl sulfoxide (0.330 g, 4.22 mmol) dissolved in methylene chloride (1 mL) was added. The mixture was stirred for 2 min, and then 15 (0.124 g, 0.482 mmol) in methylene chloride

(1 mL) was added. After 15 min, triethylamine (0.943 g, 9.32 mmol) was added, and stirring was continued for 5 min. The mixture was warmed to room temperature and then partitioned between water and methylene chloride. Flash chromatography (ethyl acetate/hexanes, 1:1) afforded ketone **12** as a colorless oil (0.1 g, 82%): ^{1}H NMR ($CDCl_3$) δ 1.45–2.20 (m, 9 H), 2.56–2.75 (m, 2 H), 2.8–3.05 (m, 1 H), 3.35 (s, 3 H), 3.3–3.8 (m, 4 H), 4.20–4.35 (m, 1 H), 4.61 (s, 1 H); IR (CH_2Cl_2) 3420, 2930, 2860, 1710, 1620; CIMS, *m/z* (relative intensity) 256 (M^+ + 1, 100).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29. Found: C, 60.98; H, 8.31.

4-Carbomethoxy-4-hydroxy-3-methoxy-2,5-cyclohexadien-1-one (16). A mixture of **2** (100 mg, 0.54 mmol), pyridinium dichromate (0.89 g, 2.2 mmol), *tert*-butyl hydroperoxide (0.2 g, 2.2 mmol), and Celite (100 mg) in benzene (20 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with methylene chloride (50 mL), filtered through Celite, and concentrated at reduced pressure. Flash chromatography (silica gel, ethyl acetate/hexane, 1:1) and crystallization (ethyl acetate/hexane, 1:10) provided **16** as colorless crystals (83 mg, 77%): mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3 H), 3.82 (s, 3 H), 4.15 (s, exchangeable with D_2O, 1 H), 5.62 (d, J = 1.4 Hz, 1 H), 6.28 (dd, J = 9.9 Hz, J = 1.5 Hz, 1 H), 6.50 (d, J = 9.9 Hz, 1 H); $[\alpha]^{28}_D$ −18.2° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3200, 3050, 2950, 1760, 1665, 1625, 1600 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 285 (3406), 234 (6744); CIMS *m/z* (relative intensity) 199 (M^+ + 1, 100).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.61; H, 5.22.

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Oxidative Ring-Closure of Substituted Bisallenes: Example of an Unsymmetrical Nazarov-Type Ring Closure

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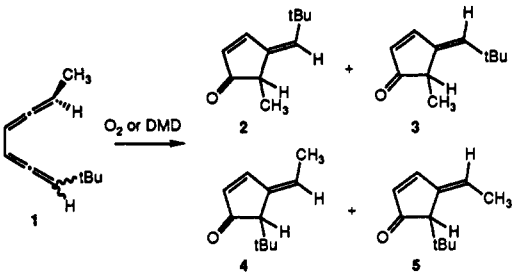
Introduction

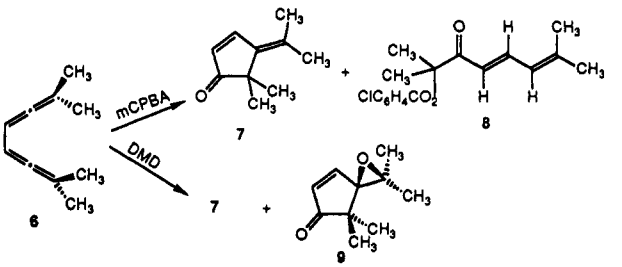
In an earlier study on the stereoselectivity of the (4 + 2) cycloaddition reactions of substituted bisallenes[1] it was observed that during the reaction of a 1:1 mixture of *erythro*- and *threo*-8,8-dimethyl-2,3,5,6-nonatetraene (**1**) with 0.5 molar equiv of *N*-phenylmaleimide exposed to the air a mixture of the 5-alkyl-4-alkylidenecyclopentenones **2–5** was formed. These observations have led to further studies on the oxidation and epoxidation of bisallenes. The recent article by Bartlett and Banavali on the "spontaneous oxygenation" of strained alkenes to produce epoxides[2] has helped to clarify the mechanism of the air oxidation of **1** and has prompted us to report our observations.

Results

Bisallene **1** on being stirred at room temperature in $CDCl_3$ solution exposed to the air for 24 h cleanly produces a mixture of **2–5** in a 24:25:32:19 ratio. Attempted chromatographic separation on silica gel resulted in the isolation of inseparable mixtures of **2** and **3** and **4** and **5**. The infrared spectra of the two mixtures displayed an intense band in the carbonyl region at 1690 cm^{-1}. The ultraviolet spectra showed a λ_{max} at 280 nm versus a calculated value of 276 nm for the dienone chromophore in **2–5**. The positions of the methyl groups in **2–5** were readily assigned on the basis of their chemical shifts in the NMR spectra, being at δ 1.33 and 1.21 in **2** and **3**, and at much lower field at δ 1.83 and 1.92 in **4** and **5**. The assignment of the stereochemistry about the exocyclic double bonds in **2–5** has been made on the basis of the relative magnitudes of the allylic coupling constants between the β and δ protons which are in general larger when syn compared to when anti.[3] In **3** and **5** the coupling constants are 1.58 and 1.63 Hz, while in **2** and **4** they are 0.48 and 0.62 Hz, respectively. The oxidation of **1** with dimethyldioxirane[4] (DMD) similarly produced a mixture of **2–5** in a 26:30:28:16 ratio which is considered to be within experimental error the same as that formed in the air oxidation of **1**.



Interestingly, 2,7-dimethyl-2,3,5,6-octatetraene (**6**) does not undergo air oxidation. Treatment with *m*-chloroperbenzoic acid resulted in the formation of a 29:71 mixture of **7** and **8**. The structure of **7** was readily apparent from its NMR spectrum which contained vinyl proton doublets and three singlets representing two different vinyl methyl and two identical saturated methyl groups. The structure of **8** was also readily apparent from its NMR spectrum which implicated the presence of a CH=CHCH= system, the presence of two vinyl methyl groups and two identical saturated methyl groups, and the presence of *m*-chlorophenyl group. The trans stereochemistry about the double bond is suggested by the magnitude of the vicinal coupling constant of 11.65 Hz. The reaction of **6** with 1 molar equiv of DMD produces a mixture of **7** and **9**, along with some unreacted **6**. Reaction of **6** with a excess of DMD cleanly produces only **9**, which does not react further with the DMD.



Discussion

By analogy with the observations of epoxide formation in the spontaneous oxygenation of strained alkenes,[2] the air oxidation of the very reactive bisallene **1** would also appear to involve epoxide formation.[5] The similarity of the product ratios derived from the air oxidation and the reaction of **1** with DMD supports this view. The formation of the four products indicates that both allene chromo-

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(2) Bartlett, P. D.; Banavali, R. *J. Org. Chem.* **1991**, *556*, 6043.
(3) Sternhall, S. *Rev. Pure Appl. Chem.* **1964**, *14*, 15.
(4) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
(5) The mechanistic details of the air oxidation of **1** to produce the epoxides have not been explored.

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