368 (90), 260 (17), 259 (68), 217 (47), 203 (11), 190 (19), 189 (100), 177 (60), 176 (15). Anal. Calcd for $C_{22}H_{24}O_3S$: C, 71.71; H, 6.56. Found C, 71.64; H, 6.58.

2-Methyl-2-(phenylthio)-5-(1-methylethenyl)cyclohexanone (11). To a stirred solution of 0.210 g (30 mg-atoms) of Li in 200 mL of liquid NH_3 at -78 °C was added dropwise a solution of 1.5 g (10.0 mmol) of (-)-carvone (**9**) in 10 mL of THF. After the solution was stirred at this temperature for 10 min, the excess Li was destroyed with isoprene and the NH_3 was evaporated, initially under a stream of N_2, and finally under vacuum at 40 °C for 15 min. The solid mass was blanketed with dry N_2 and dissolved in 40 mL of dry THF at -78 °C. This solution was transferred under N_2 pressure through a steel cannula to a solution of 5.0 g (20.0 mmol) of phenyl benzenethiosulfonate (Fluka) in 20 mL of THF at room temperature. After being stirred for 1 h, the reaction was quenched with 10% aqueous HCl, extracted with ether, washed with brine, and dried (Na_2SO_4). Evaporation and chromatography afforded 1.59 g (61%) of **11** as an yellow oil. IR 1702 cm^{-1}; ^1H NMR δ 1.23 (s, 3 H), 1.78 (s, 3 H), 3.37 (t, 1 H, J = 14 Hz), 4.89 (s, 2 H), 7.22-7.39 (m, 5 H); MS m/z (relative intensity) 262 (22), 261 (89), 260 (42), 243 (11), 218 (12). These properties agree with those reported for material prepared by a different route.[9]

1-(Phenylthio)-4a-methyl-*trans*-octahydro-2(1*H*)-naphthalenone (8). Reduction of 0.164 g (1.00 mmol) of 4a-methyl-*trans*-octahydro-2(1 *H*)-naphthalenone **7**[8] with Li in NH_3 and reaction with phenyl benzenethiosulfonate as described for the preparation of **11** gave 0.149 g (54%) of **8** as a pale yellow oil: IR 1715 cm^{-1}; ^1H NMR δ 1.04 (s, 3 H), 3.51 (d, 1 H, J = 18 Hz), 7.21-7.45 (m, 5 H); MS m/z (relative intensity) 275 (31), 274 (91), 219 (22), 218 (71), 217 (44), 185 (27), 109 (100). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.41; H, 8.08. Found C, 74.27; H, 8.09.

4-*tert*-Butylcyclohexene-1-carboxaldehyde. A solution of 0.80 g (3.80 mmol) of (methoxymethylene)diphenylphosphine oxide in 5 mL of THF was added to a solution of 3.8 mmol of LDA in 5 mL of THF at -78 °C. The resulting solution was stirred at -78 °C for 30 min, and a solution of 0.500 g (1.90 mmol) of 2-(phenylthio)-4-*tert*-butylcyclohexanone[5] in 5 mL of THF was added dropwise over 15 min. The reaction mixture was stirred at -78 °C until TLC showed that consumption of the starting material was complete. The reaction was warmed to room temperature and stirred until TLC showed disappearance of the initial 1,2 adduct. The solution was diluted with water and extracted with ether, and the organic layer was washed with brine and dried (Na_2SO_4). Concentration afforded 0.299 g (54%) of crude enol ether, which was used without purification. A solution of 0.250 g (0.86 mmol) of the enol ether in 2 mL of acetonitrile and 0.934 g (3.5 mmol) of $HgCl_2$ in 3 mL of acetonitrile/water (4:1) was heated to 50 °C and stirred for 4 h. After being cooled, the reaction mixture was filtered through a Florisil column. The filtrate was diluted with water and extracted with ether, and the organic layer was washed with saturated aqueous NH_4Cl and brine and dried (Na_2SO_4). Concentration and chromatography on silica gel gave 0.135 g (94%) of aldehyde as an oil: ^1H NMR δ 0.91 (s, 9 H), 6.83 (m, 1 H), 9.43 (s, 1 H); MS m/z (relative intensity) 166 (6), 123 (19), 110 (47), 109 (30), 95 (39), 81 (31), 67 (22), 57 (100). This compound has been reported previously.[2d,10]

3-Methylcyclohexene-2-carboxaldehyde. From 0.264 g (1.20 mmol) of 2-(phenylthio)-6-methylcyclohexanone,[5] using the procedure described for the preparation of 4-*tert*-butylcyclohexene-1-carboxaldehyde, there was obtained 0.076 g (51%) of aldehyde, the spectral properties of which (IR, ^1H NMR) agree with those reproted.[11]

***trans*-4a-Methyl-1,1a,4,4a,5,6,7,8-octahydronaphthalene-2-carboxaldehyde (4).** To a solution of 1.85 g (5.32 mmol) of (methoxymethyl)triphenylphosphonium chloride in 2 mL of dry toluene at room temperature was added 1.5 mL of 3.55 M potassium *tert*-amylate in toluene (5.3 mmol). After the mixture was stirred for 10 min, a solution of 0.728 g (2.66 mmol) of phenylthio ketone **6**[5] in 2 mL of dry toluene was added in one portion. The solution was stirred for 1 h at room temperature, heated at reflux for 16 h, and cooled. The solution was diluted with water and extracted with ether, and the organic layer was washed with brine and dried (Na_2SO_4). Concentration afforded 0.394 g (65%) of crude enol ether, which was use in the next step without purification. A mixture of 0.260 g (0.86 mmol) of enol ether, 1.02 g (4.30 mmol) of $HgCl_2$ in 15 mL of THF/H_2O (4:1), and 1 drop of concentrated HCl was warmed at 50 °C for 4 h. After being cooled to ambient temperature, the reaction mixture was filtered through a Florisil column. The filtrate was diluted with water, extracted with ether, washed with saturated aqueous NH_4Cl and brine, and dried (Na_2SO_4). Removal of the solvent and distillation (bath temperature 65 °C (0.8 mm)) gave 0.136 g (89%) of aldehyde **4** as an air-sensitive oil: IR 1683 cm^{-1}; ^1H NMR δ 0.78 (s, 3 H), 6.72 (br s, 1 H) 9.41 (s, 1 H); MS m/z (relative intensity) 178 (78), 163 (20), 149 (26), 109 (38), 81 (100).

***trans*-4a-Methyl-1a,3,4,4a,5,6,7,8-octahydronaphthalene-2-carboxaldehyde (5).** Wittig reaction of 0.348 g (1.22 mol) of phenylthio ketone **8** followed by hydrolysis as described for the synthesis of **4** gave 0.120 g (53%) of **5** as white, air-sensitive crystals that melted below room temperature: IR 1689 cm^{-1}; ^1H NMR δ 0.76 (s, 3 H), 6.44 (br s, 1 H), 9.40 (s, 1 H); MS m/z (relative intensity) 178 (47), 163 (27), 160 (37), 149 (31), 147 (22), 109 (75), 67 (100).

2-Methyl-5-(1-methylethenyl)cyclohexene-1-carboxaldehyde (10). Wittig reaction of 0.278 g (1.07 mmol) of phenylthio ketone **11** followed by hydrolysis as described for the synthesis of **4** gave 0.125 g (71%) of **10** as an oil: IR 1672 cm^{-1}; ^1H NMR δ 1.75 (s, 3 H), 2.15 (s, 3 H), 4.71 (d, 2 H, J = 10 Hz), 10.15 (s, 1 H); MS m/z (relative intensity) 164 (32), 149 (26), 135 (24), 121 (36), 107 (41). This compound has been described previously.[12]

1-Methoxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxaldehyde (12). Wittig reaction of 0.059 g (0.16 mmol) of phenylthio ketone **14** followed by hydrolysis as described for the preparation of **4** provided crude aldehyde **12**, which was purified by chromatography on silica gel to give 0.024 g (56%) of **12** as an air-sensitive oil: IR 1682 cm^{-1}; ^1H NMR δ 1.13, 1.43 (s, 3 H each), 3.77 (d, 1 H, J = 3.6 Hz), 3.82 (s, 3 H), 6.46 (t, 2 H, J = 8.1 Hz), 6.84 (br s, 1 H) 7.08 (t, 1 H, J = 8.1 Hz), 9.50 (s, 1 H); HRMS calcd for $C_{17}H_{20}O_2$ 272.1406, found 272.1386.

Acknowledgment. We thank the National Institute on Drug Abuse for support of this work under Grant DA-03590. We also thank Grace R. Zoorob for assistance in preparing starting materials and Dr. Qingmei Zha, Brown University, for the high-resolution mass spectral determination.

Supplementary Material Available: ^1H NMR spectra of **4**, **5**, and **12** (3 pages). Ordering information is given on any current masthead page.

(8) Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.
(9) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554.
(10) Muzart, J.; Pale, P.; Pete, J. P. *J. Chem. Soc., Chem. Commun.* **1981**, 668.
(11) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.
(12) deBotton, M. *Bull. Soc. Chim. Fr.* **1973**, 2472.

A Short Synthesis of Two Chiral Anthracycline AB Synthons

Herbert L. Holland* and Peter Viski

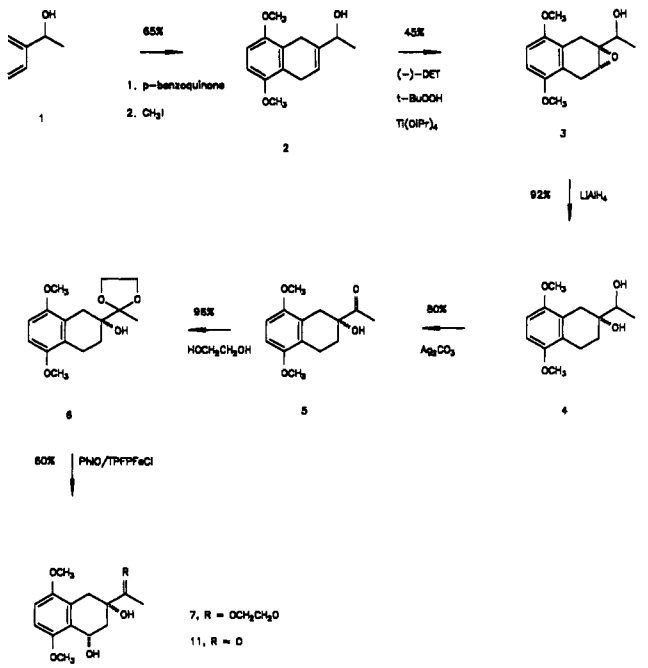
Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada

Received February 19, 1991

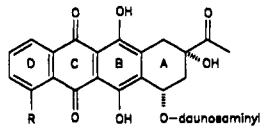
The potent antitumor activity of the anthracyclines and their use in cancer chemotherapy has promoted a continued interest in the synthesis of this class of compounds. Anthracyclines with high antineoplastic activity, exemplified by daunomycin and its 4-demethoxy derivative,

0022-3263/91/1956-5226$02.50/0 © 1991 American Chemical Society

Scheme I



share the ring A functionality shown below, namely cis-7,9-dihydroxylation and a 9-acetyl or 9-hydroxyacetyl group, with the 7*S*,9*S* absolute stereochemistry.



R = H, 4-Demethoxydaunomycin

R = OCH_3, daunomycin

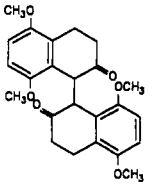
Many synthetic methods for the production of anthracyclines have been developed, and work in this area has been reviewed recently.[1-3] Chiral syntheses of anthracyclines have focused on the production of a chiral synthon for the AB portion of the target molecule, and high-yield methods have been developed for the addition of the CD portion of the anthracyclines via Friedel–Crafts alkylation of intermediates such as the hydroxy ketone **5**.[4] Compounds such as **5** are currently available in enantiomerically pure form by resolution,[5] by stereospecific dihydroxylation,[4] or Sharpless oxidation[6] of 2-substituted 3,4-dihydronaphthalenes. Introduction of the necessary benzylic hydroxyl group is then typically carried out by a bromination/solvolysis procedure following construction of the ABCD ring system.[7] As discussed elsewhere,[8] the latter approach is not without its problems: the reaction is not stereoselective and is difficult to perform on a large scale.

An alternative approach to the asymmetric synthesis of anthracyclines has been to construct an AB synthon such as **7** or **11** that possesses all the necessary chirality. Molecules of this type are currently only available by lengthy procedures involving a chiral precursor such as a carbohydrate[9] or via resolution of a synthetic intermediate.[10] We now report a short and efficient synthesis of chiral anthracycline AB synthons both with (**7**) and without (**5**) the benzylic hydroxyl group.

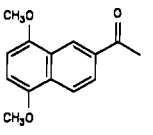
Our approach, outlined in Scheme I, utilizes Sharpless oxidation of the racemic allylic alcohol **2**, readily available in a one-pot procedure from the alcohol **1** and *p*-benzoquinone. Low-temperature oxidation of **2** in the presence of diethyl D-tartrate proceeds with kinetic resolution, giving a single enantiomer of the epoxide **3** in ca. 50% yield, together with ca. 50% of unreacted material, which was also found to be stereochemically homogeneous (ee ≥95%) and which could be recycled in the Sharpless oxidation following oxidation (CrO_3/pyridine) and immediate hydride reduction. Opening of the epoxide ring of **3** by hydride gave the chiral diol **4** in 92% isolated yield.

The absolute stereochemistry of **3** and **4** at C-2 (naphthalene numbering) follows from their conversion to the known hydroxy ketone (*R*)-**5** (see below): the configuration of the carbinol carbon of **2** and **3** has not been determined directly and is therefore not specified in Scheme I. However, the following factors suggest that diol **4** has the 2*R*,1′*R* absolute configuration: diol **4** produced by our route differs (mp, $[\alpha]_D$) from that described by Rao et al.[6] as the 2*R*,1′*S* enantiomer; and the 2*R*,1′*R* diol is that which would be expected to form from **2** and D-DET on the basis of the known stereoselectivity of the Sharpless reaction.[6,11] Preparation of **3** and **4** as racemates can be achieved readily via peracid oxidation of **2**, which proceeds to furnish a single diastereomer of the epoxide **3** and, following reduction, the diol **4**.

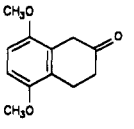
Oxidation of **4** was performed using silver carbonate[6] and gave the keto alcohol (*R*)-**5** as a single enantiomer in 80% isolated yield, representing an overall 22% yield of (*R*)-**5** from *p*-benzoquinone. A minor product obtained from the oxidation of **5** was tentatively identified by spectral data (see Experiment Section) as the dimeric β-tetralone **8** (M^+ 410), the ^{13}C NMR spectral data being particularly illustrative of the presence of a symmetrical dimer. Interestingly, **8** is produced in enantiomerically enriched form, although whether this phenomenon is attributable to inherent chirality at C-1 or to restricted rotation about the C-1–1″ bond has not been investigated.



8



9



10

(1) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790–807.
(2) Krohn, K. *Tetrahedron* **1990**, *46*, 291–318.
(3) See also the collected papers on anthracycline synthesis: *Tetrahedron* **1984**, *40*, 4539–4683.
(4) See, for example: Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213–6215.
(5) Del Nero, S.; Gandolfi, C.; Lombardi, P.; Arcamone, F. *Chem. Ind.* **1981**, 810–811.
(6) Rao, A. V. R.; Yadav, J. S.; Bal Reddy, K.; Mehendale, A. R. *Tetrahedron* **1984**, *40*, 4643–4647.
(7) See, for example: Wong, C. M.; Popein, D.; Schwenk, R.; Te Raa, J. *Can. J. Chem.* **1971**, *49*, 2712–2718.
(8) Dominquez, D.; Arkdecky, R.; Cava, M. P. *J. Am. Chem. Soc.* **1983**, *105*, 1608–1613.
(9) Florent, J.-C.; Genot, A.; Monneret, C. *Tetrahedron Lett.* **1985**, *26*, 5295–5298.
(10) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625–4632.
(11) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.

Stereoselective introduction of the benzylic hydroxyl group was achieved following conversion of **5** to the ketal, and oxidation of the latter using iodosobenzene in the presence of [5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphine]iron(III) chloride (TPFPPFeCl). This reagent has been developed as a model system for the enzymic hydroxylation reaction and has previously been used successfully for benzylic hydroxylation.[12] When performed on ketal **6**, the benzylic hydroxylation reaction proceeded to give the cis diol **7** as the major product in isolated yields of 30–60% in repeated runs at temperatures between 10 and 20 °C: the yield was found to highly temperature dependant, being maximal at 20 °C. Direct hydroxylation of ketone **5** was unsuccessful, producing a complex mixture of products. When applied to the diol **4**, the PhIO/TPFPPFeCl system led to the formation of the β-tetralone **10** as the only isolable reaction product. The superiority of this direct method for the stereoselective introduction of the benzylic hydroxyl group into **6** is demonstrated by the results of the attempted hydroxylation of **5** and **6** by the conventional bromination/solvolysis sequence, which in our hands gave only naphthalene **9**.

We therefore offer the route shown in Scheme I as the most direct method to the chiral anthracycline synthons **5** and **7** and suggest the PhIO/TPFPPFeCl oxidant as a possible means of stereospecific introduction of the benzylic hydroxyl group into 7-deoxyanthracyclines.

Experimental Section

Techniques and Procedures. The techniques used were those previously described.[13] Only hitherto unreported spectroscopic data are listed below.

3-Methylenepent-1-en-4-ol (1). This was prepared from commercial 2-chloro-1,3-butadiene in 70% yield.[14,15] The product, a mixture of **1** (80%) and hexa-1,2-dien-5-ol (20%), was used directly in the next stage.

5,8-Dimethoxy-2-(1′-hydroxyethyl)-1,4-dihydronaphthalene (2). This was prepared from *p*-benzoquinone and crude **1** by the published procedures,[16] with the following modification: the intermediate hydroquinone was not isolated, but the crude product from the Diels–Alder reaction was methylated directly to give **2**, isolated following chromatography in an overall yield of 65% based on *p*-benzoquinone. Analytical and spectral data were identical with those reported.[15]

(±)-5,8-Dimethoxy-2,3-epoxy-2-(1′-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene ((±)-3). A solution of the alkene **2** in CH_2Cl_2 was treated at 0 °C with a solution of 1.1 equiv of *m*-CPBA in CH_2Cl_2, and the resulting mixture was stirred for 12 h at ambient temperature. The usual workup afforded epoxide (±)-**3** (90%):[16] ^1H NMR as reported;[16] ^{13}C NMR δ 18.7 (C-2′), 23.8 and 24.0 (C-1, -4), 54.2 (C-3), 55.6 (2 C, OCH_3), 62.5 (C-2), 107.6 (2 C, C-6, -7), 121.6 and 121.8 (C-4a, -8a), 150.7 and 150.9 (C-5, -8); IR (KBr) 3520, 2970, 2827, 1605, 1480 cm^{-1}; MS (EI) *m/z* (relative intensity) 250 (20), 205 (100), 188 (24).

(±)-5,8-Dimethoxy-2-hydroxy-2-(1′-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene ((±)-4). A solution of the epoxide (±)-**3** (0.5 g) in dry THF (10 mL) was added slowly at 0 °C to a stirred suspension of $LiAlH_4$ (0.05 g) in dry THF (5 mL). The reaction mixture was allowed to warm to room temperature and then cooled to 0 °C and quenched by the cautious addition of ice–water. The resulting suspension was poured into water and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to give the diol (±)-**4** (92%) as a pale yellow oil that slowly crystallized on standing, mp 71–74 °C: ^1H NMR δ 1.23 (3 H, d, *J* = 6.4 Hz, C-2′ CH_3), 1.5–2.0 (2 H, m, C-3 CH_2), 2.4–3.0 (4 H, m, C-1, -4 CH_2's), 3.75, 3.77 (each 3 H, s, OCH_3), 3.6–3.8 (1 H, q, *J* = 6.4 Hz, C-1′ H), 6.62 (2 H, s, C-6,7 H's); ^{13}C NMR δ 17.1 (C-2′), 19.8 (C-3), 27.3 (C-4), 33.1 (C-1), 55.6 (2 C, OCH_3), 72.2 (C-2), 72.8 (C-1′), 107.1 (2C, C-6, -7), 124.2 and 126.1 (C-4a, -8a), and 151.3 and 151.9 (C-5, -8); IR (film) 3450, 2936, 2833, 1595, 1480 cm^{-1}; MS (EI) *m/z* (relative intensity) 252 (45), 207 (100), 189 (38).

(2*R*)-(+)-5,8-Dimethoxy-2,3-epoxy-2-(1′-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene ((+)-3). Diethyl D-tartrate (4.2 g) was added at −75 °C to a solution of titanium(IV) isopropoxide (5.7 g) in CH_2Cl_2 (200 mL) under an atmosphere of argon. A solution of the olefin **2** (5 g) in a small amount of CH_2Cl_2 was then added, and the resulting mixture was stirred at −75 °C for 30 min. *tert*-Butyl hydroperoxide (3.7 mL of 3 M solution in 2,2,4-trimethylpentane) was then added over a period of 15 min, and the reaction mixture was stirred at −75 °C for 1 h and then allowed to reach 0 °C over a further period of 2 h. The mixture was poured into a solution of ferrous sulfate (10 g) and tartaric acid (4 g) in water (100 mL), and the resulting mixture was stirred for 30 min. The product was then isolated by extraction with ether. The combined organic phase was concentrated to a volume of 100 mL and then stirred at 0 °C with a solution of sodium hydroxide (4 g) in water (100 mL) for 1 h. The organic phase was separated, dried, and evaporated to give an oil that could be used directly in the preparation of (−)-**4** without further purification. For characterization the epoxide (+)-**3** (2.3 g, 43%, mp 65–67 °C) was isolated by chromatography using ether as eluant. The compound had ^1H NMR as reported[16] and ^{13}C NMR and IR as above, $[\alpha]_D$ +51.6° (*c* = 1.3). Also obtained was unreacted **2** (2.4 g), $[\alpha]_D$ −19.2° (*c* = 0.5), ee ≥95%.

(2*R*)-5,8-Dimethoxy-2-hydroxy-2-(1′-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene ((−)-4). The crude product of the above reaction (5.2 g) was dissolved in dry THF (50 mL), and the solution was added dropwise to a stirred suspension of $LiAlH_4$ (0.1 g) in THF (10 mL). The reaction mixture was allowed to warm to room temperature before being cooled to 0 °C and quenched with ice–water (20 mL). Water (500 mL) was then added, and the mixture was extracted with ether. The extract was dried, evaporated, and chromatographed using ether as eluant to give **2** (2.5 g), followed by the diol (−)-**4** (2.3 g, 43% from **2**) as a light yellow oil that crystallized on standing, mp 74–77 °C (white crystals from ether/hexane). ^1H and ^{13}C NMR, IR, and MS data as reported above, $[\alpha]_D$ −34.3° (*c* = 1.2), ee ≥95%. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.56; H, 7.80.

1-[2′-((2′*R*)-5′,8′-Dimethoxy-2′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalenyl)]ethanone (5). This was prepared in 80% yield by Ag_2CO_3 oxidation of the diol **4** using the procedure described:[6] mp 128–130 °C (lit.[6] mp 128–129 °C); ^1H NMR and IR spectral data as described;[6] ^{13}C NMR δ 19.2 (C-3′), 23.9 (C-2), 29.7, 32.4 (C-1′, -4′), 55.5, 55.6 (OCH_3), 76.4 (C-2′), 107.1, 107.4 (C-6′, -7′), 122.8, 125.6 (C-4a′, -8a′), 151.1, 151.6 (C-5′, -8′), 212.3 (C-1); MS (EI) *m/z* (relative intensity) 250 (40), 232 (5), 207 (100), 189 (37); ee ≥95%. Also isolated from the reaction mixture by column chromatography was a low yield (10%) of material, mp 249–251 °C, tentatively characterized as 1,1′-bi(5,8-dimethoxy-2-oxo-1,2,3,4-tetrahydronaphthalenyl) (**8**): ^1H NMR δ 2.1–2.3, 2.7–2.9, 3.0–3.2, 3.3–3.5 (each 1 H, m, methylene H's), 3.67, 3.81 (each 3 H, s, OCH_3), 4.19 (1 H, s, CH), 6.68, 6.76 (2 H, ABq, aromatic H's); ^{13}C NMR δ 18.7 (CH_2), 35.5 (CH_2), 48.9 (CH), 54.1, 55.0 (OCH_3), 107.5, 108.6 (aromatic CH), 123.7, 126.2 (aromatic C), 149.4, 150.5 (aromatic CO), 208.1 (C=O); MS (EI) *m/z* 410 (26), 205 (88), 189 (19), 177 (28), 164 (19) relative to 78 (100); MS (FAB) *m/z* 413 (10) relative to 206 (100); $[\alpha]_D$ −9.6° (*c* = 0.5); ee (^1H NMR using the CH singlet) 33%.

2-Methyl-2-[2′-((2′*R*)-5′,8′-dimethoxy-2′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalenyl)]-1,3-dioxolane (6). A solution of the ketone **5** (2 g) and *p*-toluenesulfonic acid (0.05 g) in ethylene glycol (3 mL) and benzene (50 mL) was refluxed for 6 h. The mixture was cooled, washed sequentially with water, 10% aqueous Na_2CO_3, and water, dried over $MgSO_4$, and evaporated. The residue was crystallized from acetonitrile to give ketal **6** (2.15 g, 96%): mp 125–127 °C; ^1H NMR δ 1.44 (3 H, s, CH_3), 1.6–2.1 (2 H, m, CH_2), 2.6–3.1 (2 H, m, CH_2), 3.78, 3.80 (each 3 H, s, OCH_3), 4.06 (4 H, s, OCH_2CH_2O), 6.64 (2 H, s, aromatic H's); ^{13}C NMR δ 19.4 (CH_3), 19.6 (C-3′), 27.1, 30.7 (C-1′, -4′), 55.5, 55.7 (OCH_3), 65.56, 65.62 (OCH_2CH_2O), 74.4 (C-2′), 106.8, 107.0 (C-

(12) Watanabe, Y.; Ishimura, Y. *J. Am. Chem. Soc.* **1989**, *111*, 410–411.
(13) Holland, H. L.; Chernishenko, M. J.; Conn, M.; Munoz, A.; Manoharan, T. S.; Zawadski, M. *Can. J. Chem.* **1990**, *68*, 696–700.
(14) Nunomoto, S.; Yamashita, Y. *J. Org. Chem.* **1979**, *44*, 4788–4791.
(15) Kondo, S.; Dobashi, S.; Matsumoto, M. *Chemistry Lett.* **1976**, 1077–1080.
(16) Del Nero, S.; Lombardi, P. *Gazz. Chim. Ital.* **1983**, *113*, 125–127.

6′,-7′), 112.5 (C-2), 124.5, 126.3 (C-4a′,-8a′), and 151.1 and 152.0 (C-5′,-8′); IR (KBr) 3441, 2940, 2830, 1600, 1480 cm^{-1}; MS (EI) m/z (relative intensity) 294 (100), 261 (20), 206 (90), 189 (56); $[\alpha]_D$ −57.8° (c = 1.2); ee ≥95%. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.46; H, 7.69.

2-Methyl-2-[3′-((1′*S*,3′*S*)-1′,3′-dihydroxy-5′,8′-dimethoxy-1′,2′,3′,4′-tetrahydronaphthalenyl)]-1,3-dioxolane (7). The ketal **6** (0.1 g) was dissolved in CH_2Cl_2 (10 mL) at 20 °C, and [5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphine]iron-(III) chloride (30 mg) was added, followed by iodosobenzene (0.156 g). The resulting reaction mixture was stirred at 20 °C for 1 h and then filtered. The filtrate was concentrated and the resulting oil purified by preparative TLC using ether as eluant to give the title compound in 60% yield: mp 138–140 °C (lit.[10] mp 141–143 °C); NMR and IR data as reported;[10] MS (EI) m/z 310 (6), 266 (3) relative to 205 (100); $[\alpha]_D$ +5.0° (c = 1.2, $CHCl_3$) (lit.[9] $[\alpha]_D$ +5.3° ($CHCl_3$)); ee ≥95%.

Iodosobenzene Oxidation of 2(*R*)-(−)-5,8-Dimethoxy-2-hydroxy-2-(1′-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene ((−)-4). Oxidation of **4** by the procedure described above gave as the only isolable product 5,8-dimethoxy-β-tetralone (**10**), obtained in isolated yields of 60–80%, mp 96–98 °C (lit.[6] mp 97–98 °C); ^1H NMR and IR as reported.[4]

Iodosobenzene Oxidation of 1-[2′-((2′*R*)-5′,8′-Dimethoxy-2′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalenyl)]ethanone (5). Treatment of **5** (100 mg) with iodosobenzene under the conditions described above for the preparation of **7** gave a complex reaction mixture, TLC analysis of which suggested the formation of the 1,3-diol **11** as only a minor product. In view of its complexity, this reaction was not investigated further.

Attempted Bromination/Solvolysis of 1-[2′-((2′*R*)-5′,8′-Dimethoxy-2′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalenyl)]-ethanone (5) and 2-Methyl-2-[2′-(5′,8′-dimethoxy-2′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalenyl)]-1,3-dioxolane (6). Treatment of the ketone **5** or the ketal **6** with *N*-bromosuccinimide gave only 1-[2′-(5,8-dimethoxynaphthalenyl)]ethanone (**9**), described below for reaction of **5** with NBS. A solution of **5** (0.1 g) and NBS (0.07 g) in CCl_4 (50 mL) containing one drop of 3.0 M *tert*-butyl hydroperoxide solution was refluxed under argon for 1 h. TLC monitoring of the reaction indicated the formation of a single major product, which could be isolated by filtration following reduction of the reaction volume to 5 mL. This product remained unchanged after treatment of the reaction mixture with refluxing aqueous methanol and was identified as 1-[2′-(5,8-dimethoxynaphthalenyl)]ethanone (**9**) by comparison with reported physical and spectral data:[17] mp 110–112 °C (lit.[17] mp 111–112 °C); ^1H NMR δ 2.6 (3 H, s, C-1 CH_3), 3.87, 3.90 (each 3 H, s, OCH_3), 6.65, 6.72 (2 H, ABq, C-6′,-7′ H's), 7.96 (1 H, d of d, C-3′H), 8.16 (1 H, d, C-4′H), 8.74 (1 H, d, C-1′H); MS (EI) m/z (relative intensity) 230 (85), 215 (100), 189 (14).

Acknowledgment. This work was funded by the Natural Sciences and Engineering Research Council of Canada Strategic Grant no. STRIN 041 to H.L.H.

(17) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1982**, *23*, 4373–4376.

Dependence of Isotropic Hyperfine Coupling in the Fluoromethyl Radical Series on Inversion Angle

Christopher J. Cramer

U.S. Army Chemical Research Development and Engineering Center, Research Directorate, Physics Division, Chemometric and Biometric Modeling Branch, Aberdeen Proving Ground, Maryland 21010-5423

Received September 25, 1990 (Revised Manuscript Received May 13, 1991)

Electron spin resonance (ESR) has proven a powerful tool in the study of organic radicals.[1] By analysis of hyperfine coupling constants (hfs), insights into hybridization, bonding, and molecular geometry may be obtained.[2] However, first-order theoretical models[3] are not always successful in describing these properties.[4] An alternative that is rapidly becoming more available to the experimental chemist is direct calculation of electronic structure and properties for comparison to experiment. Such a symbiosis of spectroscopic and computational techniques has been applied not only to radicals as simple as methyl[5] and the methane cation radical,[6] but as well to larger open-shell systems, like the 7-norbornyl radical, the cubane cation radical, and the benzene and toluene radicals and radical anions.[7,8]

The accurate ab initio prediction of isotropic hfs for open-shell molecules has been a long-standing goal for a number of investigators. While semiempirical techniques are extremely rapid, they only rarely provide results of better than qualitative accuracy.[9] Unrestricted Hartree–Fock (UHF) methods,[10] which do not take additional account of correlation effects, often give poor hfs values due, inter alia, to unrealistic spin polarizations, sometimes occurring in the core s orbitals[11] and sometimes in the valence orbitals.[12] Configuration interaction (CI) and coupled cluster (CCD) methods have proven extremely succesful for very small molecules but rapidly become unwieldly and expensive when multiple heavy atoms are present.[2d,13] We apply here a method for calculating hfs from Z-vector derived[14] MP2[15] spin density matrices that

(1) (a) Matsushita, M.; Momose, T.; Shida, T.; Teki, Y.; Takui, T.; Itoh, K. *J. Am. Chem. Soc.* **1990**, *112*, 4700. (b) Muto, H.; Nunome, K.; Fukaya, M. *J. Phys. Chem.* **1990**, *94*, 418. (c) Jeevarajan, A. S.; Carmichael, I.; Fessenden, R. W. *Ibid.* **1990**, *94*, 1372. (d) Gilbert, B. C.; Whitwood, A. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1921. (e) Dowd, P. *Acc. Chem. Res.* **1972**, *5*, 242. (f) Griller, D.; Ingold, K. U. *Ibid.* **1980**, *13*, 193.

(2) (a) Weltner, W. *Magnetic Atoms and Molecules*; Scientific and Academic Editions: New York, 1983. (b) Symons, M. *Chemical and Biochemical Aspects of Electron Spin Resonance*: John Wiley & Sons: New York, 1978. (c) Ayscough, P. B. *Electron Spin Resonance in Chemistry*; Methuen: London, 1967.

(3) (a) Morton, J. R.; Preston, K. F. *J. Magn. Res.* **1978**, *30*, 577. (b) Morton, J. R. *Chem. Rev.* **1964**, *64*, 453.

(4) (a) Mackey, J. H.; Wood, D. E. *J. Chem. Phys.* **1970**, *52*, 4914. (b) Knight, L. B., Jr.; Ligon, A.; Cobranchi, D. P.; Earl, E.; Feller, D.; Davidson, E. R. *Ibid.* **1986**, *85*, 5437. (c) Benzel, M. A.; Maurice, A. M.; Belford, R. L.; Dykstra, C. E. *J. Am. Chem. Soc.* **1983**, *105*, 3802.

(5) (a) Nakatsuji, H.; Izawa, M. *J. Chem. Phys.* **1989**, *91*, 6205. (b) Sekino, H.; Bartlett, R. J. *Ibid.* **1985**, *82*, 4225. (c) Carmichael, I. *Chem. Phys.* **1987**, *116*, 351. (d) Chipman, D. M. *J. Chem. Phys.* **1983**, *78*, 3112. (e) Fessenden, R. W. *J. Phys. Chem.* **1967**, *71*, 74. (f) Moss, R. E. *Mol. Phys.* **1966**, *10*, 339. (g) Botschwina, P.; Flesch, J.; Meyer, W. *Chem. Phys.* **1983**, *74*, 321. (h) Hameka, H. F.; Turner, A. G. *J. Magn. Reson.* **1985**, *64*, 66.

(6) (a) Knight, L. B., Jr.; Steadman, J.; Feller, D.; Davidson, E. R. *J. Am. Chem. Soc.* **1984**, *106*, 3700. (b) Garcia de la Vega, J. M.; Paniagua, M.; Segovia, A.; Sieiro, C. *J. Mol. Struct.* **1986**, *142*, 323.

(7) (a) Kochi, J. K.; Bazukis, P.; Krusic, P. J. *J. Am. Chem. Soc.* **1978**, *95*, 1516. (b) Knight, L. B., Jr.; Arrington, C. A.; Gregory, B. W.; Cobranchi, S. T. *J. Am. Chem. Soc.* **1987**, *109*, 5521.

(8) Hameka, H. F. *J. Magn. Reson.* **1987**, *75*, 9.

(9) (a) INDO: Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory*; McGraw-Hill: New York, 1970. (b) MNDO: Glidewell, C. *Inorg. Chim. Acta* **1984**, *83*, L81. (c) MINDO/3: Pandey, P. K. K.; Chandra, P. *Can. J. Chem.* **1979**, *57*, 3126.

(10) (a) Claxton, T. A.; Chen, T.; Symons, M. C. R.; Glidewell, C. *Faraday Discuss. Chem. Soc.* **1984**, *78*, 121. (b) Chipman, D. M. *J. Chem. Phys.* **1983**, *78*, 4785.

(11) (a) Chipman, D. M. *Phys. Rev. A* **1989**, *39*, 475. (b) Poling, S. M.; Davidson, E. R.; Vincow, G. *J. Chem. Phys.* **1971**, *54*, 3005.

(12) Edlund, O.; Lund, A.; Shiotani, M.; Sohma, J.; Thuomas, K.-Å, *Mol. Phys.* **1976**, *32*, 49.

(13) (a) Carmichael, I. *J. Phys. Chem.* **1987**, *91*, 6443. (b) Feller, D.; Davidson, E. R. *J. Chem. Phys.* **1984**, *80*, 1006. (c) Knight, L. B., Jr.; Steadman, J.; Feller, D.; Davidson, E. R. *J. Am. Chem. Soc.* **1984**, *106*, 3700. (d) Nakatsuji, H.; Izawa, M. *J. Chem. Phys.* **1989**, *91*, 6205. (e) Chipman, D. M. *Ibid.* **1979**, *71*, 761. (f) Carmichael, I. *J. Phys. Chem.* **1990**, *93*, 190.

(14) Handy, N. C.; Schaeffer, H. F., III. *J. Chem. Phys.* **1980**, *72*, 5031.

(15) (a) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (b) Carsky, P.; Hess, B. A., Jr.; Schaad, C. J. *J. Comput. Chem.* **1984**, *5*, 280.

This article not subject to U.S. Copyright. Published 1991 by the American Chemical Society