^{1}H NMR (CCl_4) δ 7.10 (1 H, s), 6.76 (1 H, s), 5.53 (1 H, ddd, J = 5.8, 2.4, 1.9 Hz), 5.17 (1 H, ddd, J = 5.8, 2.0, 1.0 Hz), 3.20 (1 H, br d, J = 16 Hz), 2.58 (1 H, br d, J = 16 Hz), 2.08 (3 H, s), 1.37 (3 H, s), 1.27 (3 H, s), and 0.84 (3 H, s); LRMS, m/z (relative intensity) 296 (17), 294 (M^+, 16), 281 (6), 279 (6), 240 (5), 238 (5), 215 (22), 200 (41), 185 (22), 173 (100), 159 (20), 158 (12), 155 (8), 145 (8), 115 (8), 91 (9), and 77 (11).

Cupalaurenol acetate (6): $[\alpha]^{19}_D$ + 65.1° (c 1.0, $CHCl_3$); UV (EtOH) λ_{max} 205 (ε 21 000), 225 (sh) (10 000), and 280 nm (3000); IR (CCl_4) 3040, 2960, 2920, 2860, 1760, 1480, 1370, 1210, 1180, 1140, and 905 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.28 (1 H, s), 7.00 (1 H, s), 5.50 (1 H, br d, J = 5.8 Hz), 5.25 (1 H, br d, J = 5.8 Hz), 3.26 (1 H, br d, J = 16 Hz), 2.69 (1 H, br d, J = 16 Hz), 2.21 (3 H, s), 2.05 (3 H, s), 1.40 (3 H, s), 1.33 (3 H, s), and 0.87 (3 H, s); LRMS, m/z (relative intensity) 338 (8), 336 (9), 279 (4), 257 (7), 240 (7), 238 (7), 215 (26), 200 (27), 185 (11), 173 (100), and 159 (15). Found: C, 60.57; H, 6.34; Br, 23.65. Calcd for $C_{17}H_{21}BrO_2$: C, 60.54; H, 6.28; Br, 23.69.

Oxidation of 3 to Laurequinone (7). To a solution of 34.7 mg of **3** in 80% acetic acid (1 mL) was added several drops of 1% chromium trioxide solution in acetic acid. The mixture was allowed to stand at 20 °C for 3 h and extracted with chloroform (3 × 5 mL) after addition of water (5 mL). The organic layer was separated by TLC (silica gel, 1:3 hexane–$CHCl_3$) to give 12.2 mg of **7** as a yellow oil, $[\alpha]^{18}_D$ −49.3° (c 0.30, $CHCl_3$) [lit.[7] $[\alpha]^{24}_D$ −53.5° (c 0.91, $CHCl_3$)]. The IR and ^{1}H NMR spectra were virtually identical with those of an authentic sample.

Conversion of 3 to 2. A procedure developed by Musliner and Gates[8] was adapted. Thus, a mixture of 42.9 mg of **3**, 182 mg of anhydrous potassium carbonate, and 53.7 mg of 1-phenyl-5-chlorotetrazole in dry acetone (15 mL) was heated at reflux for 20 h. The reaction mixture was filtered to remove inorganic solid and separated by preparative TLC (silica gel, 1:3 hexane–$CHCl_3$) to give 64 mg of the tetrazoyl ether **8** as an oil: IR (CCl_4) 3060, 2960, 2930, 2860, 1505, 1430, 1295, 1145, 1130, 1110, and 1095 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.92–7.40 (7 H, m), 2.13 (3 H, s), 1.52 (3 H, s), 1.26 (3 H, s), 0.53 (1 H, s), and 0.43 (1 H, br s). The ether **8** (64 mg) in ethanol (5 mL) was hydrogenated over 10% Pd/C (20 mg) for 32 h. After removing the catalyst by filtration, the reaction mixture was separated by preparative TLC (silica gel, 4:1 hexane–$CHCl_3$) to yield 26.8 mg of an oil. Further purification of the oil on a Lobar Si-60 column (5:1 hexane–$CHCl_3$) gave 16.2 mg of **2**; $[\alpha]^{20}_D$ −7.4° (c 0.27, $CHCl_3$). The IR and ^{1}H NMR spectra were identical with those of cyclolaurene isolated from *A. dactylomela*.

Conversion of 5 to Cuparene (9). A solution of **5** (44.2 mg) in acetone (25 mL) was similarly treated with 1-phenyl-5-chlorotetrazole (54.3 mg) and potassium carbonate (62 mg) to give 64 mg of the tetrazoyl ether of **5** as an oil: IR (CCl_4) 3050, 2970, 1600, 1505, 1455, 1360, 1300, 1145, and 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0–7.4 (7 H, m), 5.62 (1 H, br d, J = 6.1 Hz), 5.40 (1 H, br d, J = 6.1 Hz), 3.35 (1 H, br d, J = 15.6 Hz), 2.83 (1 H, br d, J = 15.6 Hz), 2.17 (3 H, s), 1.45 (3 H, s), 1.33 (3 H, s), and 0.92 (3 H, s). Hydrogenolysis of the ether in the same manner gave, after TLC separation, 18.7 mg of cuparene (**9**) as an oil: $[\alpha]^{20}_D$ +66.8° (c 0.37, $CHCl_3$); IR (CCl_4) 2960, 1520, 1465, 1380, 1200, 1125, and 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (2 H, d, J = 8.4 Hz), 7.10 (2 H, d, J = 8.4 Hz), 2.23 (3 H, s), 1.63 (6 H, m), 1.23 (3 H, s), 1.01 (3 H, s), and 0.55 (3 H, s).

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Notes

A Two-Dimensional ^{1}H NMR Investigation of the Ring A Conformation in 3-Keto Triterpenoids: Observation of an Unusually Large Vicinal Coupling Constant

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The potential of two-dimensional (2D) NMR experiments such as J-resolved spectroscopy (2D-J) and J-correlated spectroscopy (COSY) in the structural and stereochemical analysis of proteins,[1] polysaccharides,[2] and nucleic acids,[3] where the spectra contain many overlapping but isolated spin systems, is now well documented. However, their applications to complex natural products containing extended spin systems such as steroids and triterpenoids have been limited.[4] In the present communication, we record the first application of homonuclear 2D-J and COSY experiments to determine the ring A conformation of a 3-keto triterpenoid, viz., 3-ketours-12-en-24-oic acid methyl ester (**1**) (Chart I), a derivative of biologically active β-bosewellic acid.[5]

(1) For a review, see: Wider, G.; Macura, S.; Kumar Anil; Ernst, R. R.; Wüthrich, K. *J. Magn. Reson.* **1984**, *56*, 207.

(2) (a) Hall, L. D.; Morris, G. A.; Sukumar, S. *J. Am. Chem. Soc.* **1980**, *102*, 1745. (b) Bruch, R. C.; Bruch, M. D. *J. Biol. Chem.* **1982**, *257*, 3409. (c) Gagnaire, D. Y.; Taravel, F. R.; Vignon, M. R. *Macromolecules* **1982**, *15*, 126. (d) Bernstein, M. A.; Hall, L. D. *J. Am. Chem. Soc.* **1982**, *104*, 5553. (e) Prestegard, J. H.; Koerner, T. A. W., Jr.; Demou, P. C.; Yu, R. K. *J. Am. Chem. Soc.* **1982**, *104*, 4993. (f) Schraml, J.; Hirch, J.; Petrakova, E.; Krahe, E.; Bliefert, C. *Collect. Czech. Chem. Commun.* **1984**, *49*, 1605.

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(5) The potent antiinflammatory and antiarthritic activity of the Indian Ayurvedic drug obtained from *Boswellia serrata* has been shown to be due to β-boswellic acid and related triterpene acids present in it.[11]

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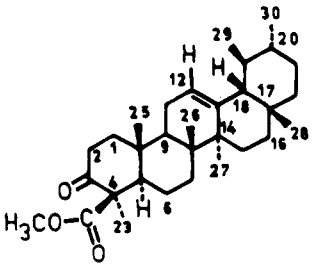
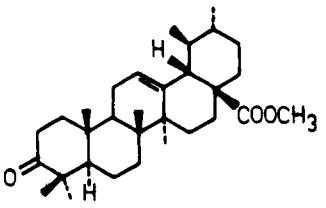
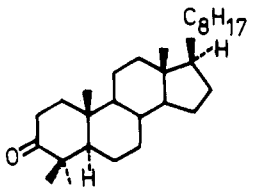
Chart I



1



2



3

One of the major stereochemical problems that has been the subject of continuing interest over the past three decades is the conformational anaysis of ring A or 3-keto triterpenoids and 4,4-dimethyl-3-keto steroids.[6] However, a consensus regarding the exact conformation of ring A in these molecules in solution is lacking yet.

We have initiated a systematic and indepth study of the above problem based on high-field ^1H NMR spectroscopy. Recently, we proposed a high-field ^1H NMR approach involving a concerted use of spin–spin coupling constants, obtained from first order one-dimensional spectra, and NOE's obtained through NOE difference spectroscopy and showed unequivocally that ring A in 3-ketours-12-en-28-oic acid methyl ester (2) exists in half-chair conformation.[7] The required coupling constants in this case were measured directly from the first-order resonances present in the 1D spectrum.

We now turned our attention from 2, which bears a 4β-CH_3 group, to 1, which bears a 4β-$COOCH_3$ group, with a view to examine the steric effect of 4β-functional group on the ring A conformation. This hitherto unexplored aspect of ring A conformation, it was felt, would provide a deeper understanding of the "4,4-dimethyl effect".[8] The surprising 1D spectral complexity of ring A methylene proton resonances in 1, as against their simplicity in the 1D spectrum of 2, is overcome by the judicious use of the inherent high-resolution of 2D-J[9] and correlative ability

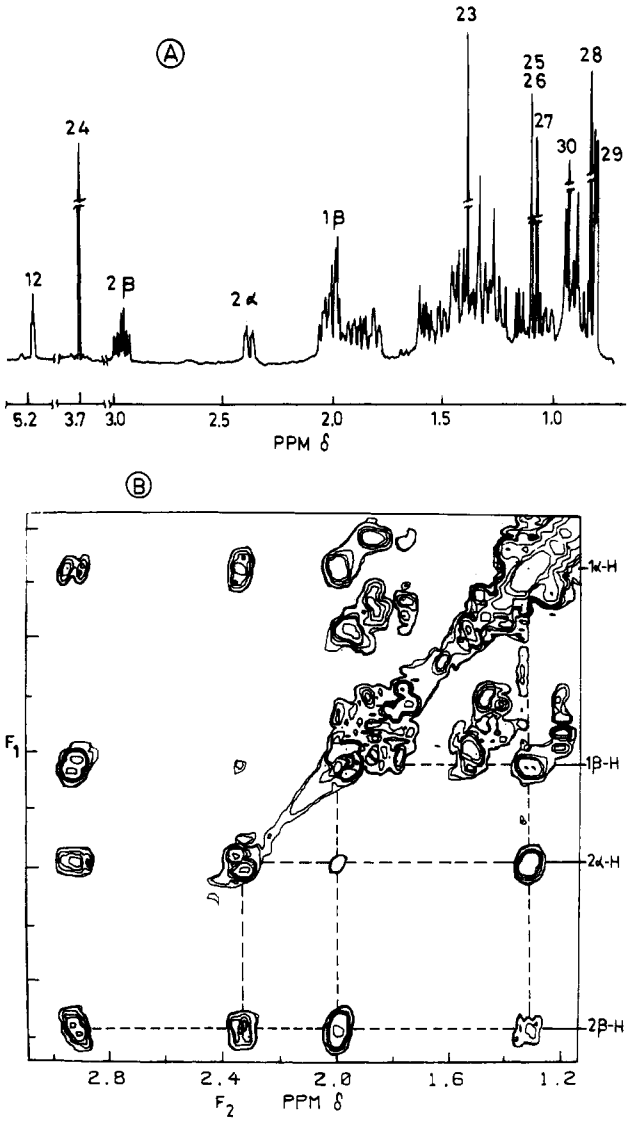


Figure 1. (A) 1D ^1H NMR spectrum at 500 MHz of 1 ($CDCl_3$, 25 °C). (B) A fragment of the contour plot of homonuclear COSY spectrum at 500 MHz of 1 ($CDCl_3$, 25 °C) showing spin-coupling of 1α-H, 1β-H, 2α-H, and 2β-H.

of COSY techniques in the present work.

The 500-MHz 1D ^1H NMR spectrum of 1 is shown in Figure 1A. The assignments of methyl resonances[10] were made by using $Eu(fod)_3$ as the lanthanide shift reagent and reported elsewhere.[11] The resonances centered at δ 2.95 and 2.37 could tentatively be assigned to 2β(a)-H and 2α(e)-H on the basis of their chemical shift and coupling constants. This assignment gains support from the fact that the resonance at δ 2.37 undergoes greater lanthanide-induced shift than that at δ 2.95, and hence the former is equatorial.

The assignments of all four ring A methylene protons were confirmed by the use of COSY. A fragment of contour plot of the homonuclear COSY spectrum is shown in Figure 1B. The coupling network involving 1α-H, 1β-H, 2α-H, and 2β-H is clearly disclosed by the appearance of a pair of six cross-peaks.

The next objective was to determine accurately the coupling constants for the ring A methylene protons. The

(6) As a leading reference, see: Dougherty, D. A.; Mislow, K.; Huffman, J. W.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 1585.
(7) Loganathan, D.; Chari, K. V. R.; Trivedi, G. K., submitted for publication.
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(9) Nagayama, K.; Bachmann, P.; Wüthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1978**, *31*, 133.
(10) No NMR data of 1 is available in literature.
(11) Loganathan, D. Ph.D. Thesis, Indian Institute of Technology, Bombay, 1984.

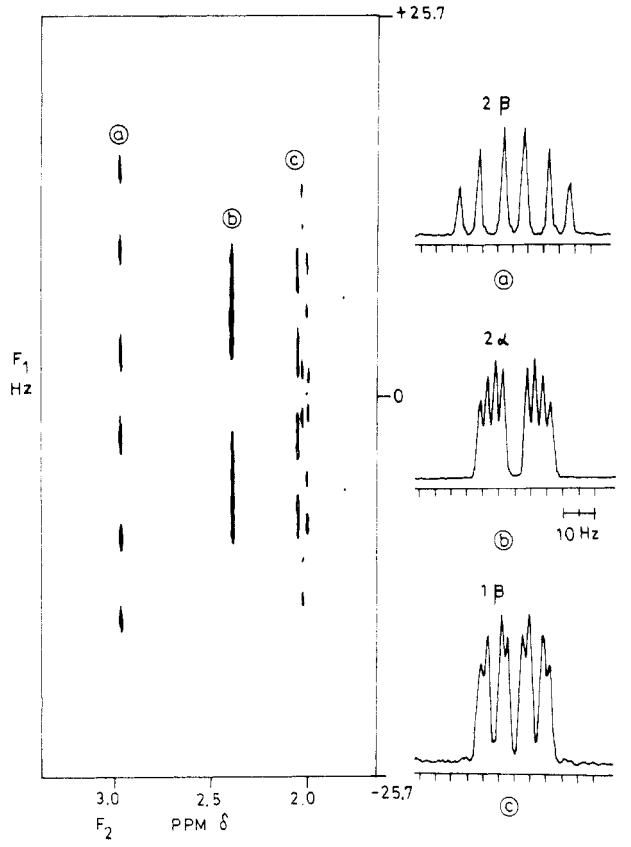

Figure 2. A fragment of contour plot of homonuclear 2D-J spectrum at 500 MHz of 1 ($CDCl_3$, 24 °C) shown along with individual proton multiplets (J spectra).

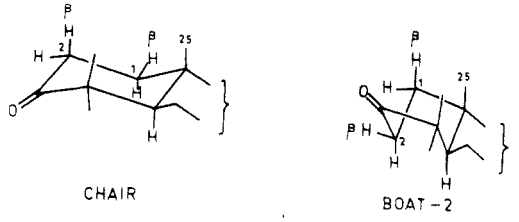

Figure 3. Alternative conformations of ring A in 1.

2D-J experiment served this objective most elegantly. A fragment of contour plot of 500-MHz homonuclear 2D-J spectrum is shown in Figure 2. Guided by the chemical shift data of 1α-H, 1β-H, 2α-H, and 2β-H, obtained from the COSY experiment, individual slices of the 2D-J spectrum along the J axis were taken and the resultant "J spectra" are seen inset in Figure 2. Incidentally, 2α-H resonance appearing at δ 2.37 is completely resolved and first order in the 2D-J spectrum (see its order in the 1D spectrum) which enabled the direct and accurate measurement of its coupling constants. Table I lists all the geminal and vicinal coupling constants.

The implications of the unusually large J_{vic} value of 14.8 Hz are worth looking into. Use of the modified Karplus equation[12] in eq 1 shows that 14.8 Hz corresponds to a dihedral angle ($\phi_{1\alpha,2\beta}$) of 166 ± 2°. Knowing well that even

$$J_{vic} = \begin{cases} 10\cos^2\phi - 0.28 & 0° \le \phi \le 90° \\ 16\cos^2\phi - 0.28 & 90° \le \phi \le 180° \end{cases} \quad (1)$$

in simple cyclohexanone, which exists in total chair conformation, the $\phi_{2(a)\text{-}H,3(a)\text{-}H}$ is only about 170°,[13] the above result leads to a near total chair conformation for the ring A in 1. The only other alternative conformation that has a $\phi_{1\alpha,2\beta}$ value of about 170° is the so-called boat-2 form (see Figure 3) in which 1β-H is closer to 25-CH_3 than 2β-H. However, irradiation of 25-CH_3 signal resulted in a larger enhancement in the NOE difference spectrum of 1 for 2β-H than that of 1β-H, thus ruling out the boat-2 form for ring A.

Table I. ^{1}H NMR Chemical Shifts[a] and Coupling Constants[b] of Ring A Methylene Protons in 1

proton	δ ($CDCl_3$)	
1α	1.34	
1β	2.02	
2α	2.37	
2β	2.93	
proton pair	**J_{gem}, Hz**	**J_{vic}, Hz**
1α,1β	13.4	
1α,2α		4.8
1α,2β		14.8
1β,2α		2.4
1β,2β		6.7
2α,2β	14.8	

[a] Obtained from COSY [b] Obtained from 2D-J.

Incidentally, Burkert and Allinger[14] have reported a $J_{1\alpha(a),2\beta(a)}$ value of 13.7 Hz for the ring A protons of 4,4-dimethyl-3-ketoandrostanone (3) on the basis of the iterative computer simulation of higher order spectra. These authors argued that the larger coupling constant of 13.7 Hz, which is even larger than in 4-*tert*-butylcyclohexanone, requires an anti-periplanar arrangement between 1(a)-H and 2(a)-H. Therefore, these authors concluded that ring A in 3 exists in chair conformation. This observation is rather surprising in view of the potential 1,3-diaxial methyl repulsion being very much present in the ring A of 3.

The present observation of $J_{1\alpha,2\beta}$ value of 14.8 Hz in the case of 1 could possibly be rationalized in terms of the planarity of its 4β-$COOCH_3$ group. Thus, the latter poses lesser hinderance to 25-CH_3 compared to that of 4β-CH_3 as in 2 and 3. This appears to result in a more perfect chair conformation for ring A in 1 than that was assigned to the ring A in 3 by Burkert and Allinger, as evident from the increase of about 1 Hz in $J_{1\alpha,2\beta}$. However, at this juncture, it seems more reasonable to believe that the range of 13.7–14.8 Hz represents the domain of chair conformations for ring A involving minor deformations within the chair form.

In compound 2, on the other hand, the ring A is forced to adapt a half-chair conformation[15] in view of the transmission effect of 8β-CH_3. Even though compound 1 also bears an 8β-CH_3, the transmission effect is not felt by its ring A due to the steric relief provided by the planar 4β-$COOCH_3$.

In conclusion, we have shown through the concerted use of vicinal coupling constants and NOE's that the ring A of 3-ketours-12-en-24-oic acid methyl ester (1) exists in a near total chair conformation in solution. The possible implications of an unusually large vicinal coupling constant observed during the present two-dimensional ^{1}H NMR investigation are worth looking into.

Experimental Section

All ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer operating in the Fourier transform mode under ASPECT 2000 control. A $CDCl_3$ solution (0.05 M) of the sample with 0.1% Me_4Si as an internal standard was used in a 5-mm

(12) Williamson, K. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 4623.
(13) Lambert, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 1836.
(14) Burkert, U.; Allinger, N. L. *Tetrahedron* **1978**, *34*, 307.
(15) In the case of 2, the observed value of $J_{1\alpha,2\beta}$ is 10.7 Hz.

NMR tube. Chemical shifts (δ) are expressed in ppm. NOE difference spectra were recorded according to the method of Hall and Sanders.[4a]

Homonuclear proton COSY experiments were carried out with the pulse sequence D–$\pi/2$–t_1–Δ_1–$\pi/2$–Δ_2–t_2, where t_1 is the incremental delay, D the recycle delay (1 s), Δ_1 the initial delay (0.025 s), and Δ_2 the refocusing delay (0.025 s). t_1 was incremented 256 times at regular intervals. The digital resolution along both axes was 7.5 Hz/point.

Homonuclear proton 2D–J experiments were carried out with the pulse sequence D–$\pi/2$–$t_{1/2}$–π–$t_{1/2}$–t_2. The initial delay $t_{1/2}$ was incremented 64 times at regular intervals. The digital resolution along f_1 and f_2 axes were 0.4 and 1.9 Hz/point, respectively. In both homonuclear proton COSY and 2D–J experiments sine-bell and sine-square-bell window functions were used along f_1 and f_2 axes, respectively, for resolution enhancement.

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Homolytic Reactions of Phenyl Tribromomethyl Sulfone and Olefins

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During a study of 1,1-elimination of phenyl tribromomethyl sulfone (1) by metals and by organometallic bases in efforts to generate (eq 1) and capture bromo(phenylsulfonyl)methylene (3), addition of 1 to varied olefins was observed.[1] Reactions of 1 with terminal olefins 4 (1) at reflux under nitrogen in benzene or (2) upon irradiation (400-W mercury lamp) in benzene at 20–25 °C have now been found to involve directed homolytic addition to give the corresponding phenyl 1,1,3-tribromoalkyl sulfones (5, eq 2). Thus 2-methyl-1-butene (4a), 1-octene (4b), and vinyltrimethylsilane (4c) are readily converted thermally or photolytically to 5a (93%, 90%), 5b (80%), and 5c (46%, 81%).[2,3] The likely overall mechanism of addition involves homolytic cleavage of a C–Br bond in 1 followed by the chain sequence illustrated (eq 3–4). The free-radical behavior of 1 thus parallels that of various polyhalides (for example, CBr_4, $BrCCl_3$, ICF_3, $SiCl_4$, and SO_2Cl_2, etc.) with olefins.[4] Reaction of 4 with an olefin is the first example of such addition of an α-sulfonyl-α-alkyl free radical to a carbon–carbon doubl bond. All attempts however to effect thermal or photolytic additions of dibromomethyl phenyl sulfone ($C_6H_5SO_2CHBr_2$) to various olefins were unsuccessful.

The strained cyclic olefins, norbornene and cyclopentene, undergo addition of 1 to yield 2-bromo-3-[dibromo(phenylsulfonyl)methyl]norbornane (9, 94–98%) and dibromo(2-bromocyclopentyl)methyl phenyl sulfone (10, 63–83%), respectively. Adducts 9 and 10 are sharp-melting, give only single peaks upon HPLC analysis, and are presumably single enantiomeric pairs. The structures of 9 and 10 as anti are suggested by steric considerations, ^{1}H NMR evidence, and the facts that bromotrichloromethane, p-toluenesulfonyl chloride, and 1-iodoperfluoropropane undergo homolytic addition to norbornene in which the trichloromethyl ($Cl_3C\cdot$), the p-toluenesulfonyl (p-$CH_3C_6H_4SO_2\cdot$), and the perfluoro-1-propyl ($CF_3CF_2CF_2\cdot$) radicals attack the carbon–carbon double bond stereospecifically exo.[5] Eclipsing of the bromine (Br) and the

(1) Abstracted from the M.S. Thesis of D. L. Fields, The Ohio State University, Columbus, Ohio, 1984.

(2) Photolyses and thermolyses of 1 in styrene, methyl acrylate, and ethyl vinyl ether, respectively, result in extensive telomerization and polymerization.

(3) Preparative addition reactions of 1 to olefins are simple experimentally and can be followed with ease by monitoring the disappearance of 1 by TLC. Photolysis is of advantage over thermolysis for effecting addition of 1 to low-boiling olefins and in general occurs more rapidly and gives cleaner products. The reaction times vary specifically according to the olefin, the experimental method, and the reactant concentrations. Adducts 5 are usually stable crystalline products which are readily handled. Their structures are assigned from their elemental analyses, from their MS, ^{1}H NMR and IR spectra, and upon consideration of their origins.

(4) For summaries on this subject see: (a) Davies, D. I.; Parrott, M. J. "Free Radicals in Organic Synthesis"; Springer-Verlag: Berlin, 1978. (b) Nonhebel, D. C.; Walton, J. C. "Free-radical Chemistry"; Cambridge University Press; New York, 1974. (c) Cadogan, J. I. G. "Principles of Free Radical Chemistry"; The Chemical Society Monographs for Teachers No. 24; The Chemical Society: London, 1973. (d) Huyser, E. S. "Free-Radical Chain Reactions"; Wiley-Interscience: New York, 1970. (e) Pryor, W. A. "Free Radicals"; McGraw-Hill Book Company: New York, 1965. (f) Sosnovsky, G. "Free Radical Reactions in Preparative Organic Chemistry"; The Macmillan Company: New York, 1964.

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