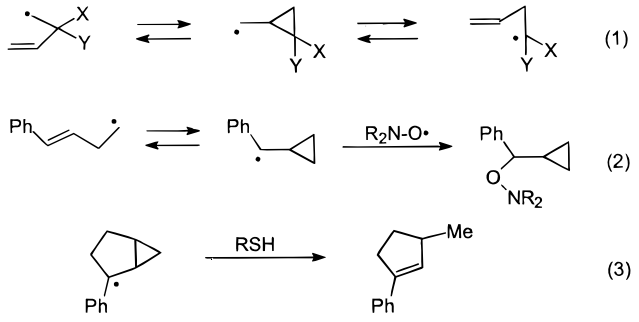
Cyclopropane Formation vs the Homoallyl−Homoallyl Radical Rearrangement in 7-Oxygen-Substituted Norborn-5-en-2-yl Radicals

A. Srikrishna,* R. Viswajanani, T. Jagadeeswar Reddy, D. Vijaykumar, and P. Praveen Kumar

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

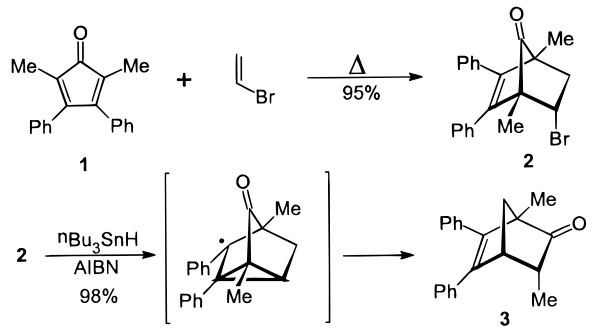
Received February 11, 1997

The homoallyl−homoallyl radical rearrangement *via* the cyclopropylcarbinyl radical (eq 1) plays an important role in mechanistic organic chemistry.[1] Although considerable amount of work was done from the point of view of its use as a radical clock, isolation of products resulting from the trapping of the intermediate cyclopropylmethyl radical is not that common. Trapping of the phenyl-substituted cyclopropylmethyl radical is known only under nitroxyl radical trap conditions (eq 2),[2] whereas under the conventional radical conditions it is known to generate mainly the open form, *e.g.* as depicted in eq 3, the phenyl-substituted bicyclic radical generates predominantly (>90%) the cyclopropane cleaved product.[3] The formation of the cyclopropane products *via* 3-*exo*-trig cyclization of homoallyl radicals are reported only in a very few specially designed substrates.[4] In this context, we have investigated the radical reactions of phenyl-substituted norbornenes, and herein we describe our novel findings on the formation of either the rearranged or the cyclopropane products from 7-oxygen-substituted norbornenes.

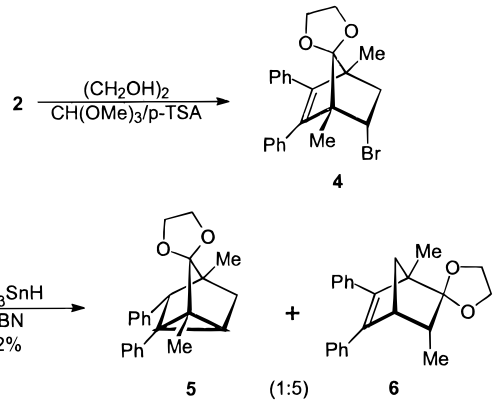


The Diels−Alder reaction of hemicyclone **1** with vinyl bromide gave a ≈9:1 mixture of *endo* and *exo* adducts, in 95% yield, which on crystallization furnished the *endo* adduct **2**, mp 102−104 °C.

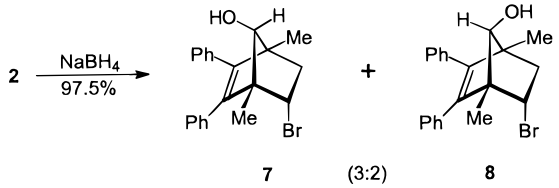
Refluxing a 0.02 M benzene solution of the adduct **2** with 1.1 equiv of tri-*n*-butyltin hydride and a catalytic amount of azobis(isobutyronitrile) (AIBN) furnished only the homoallyl−homoallyl rearrangement product **3**, mp 110 °C, in 98% yield, without formation of any cyclopropane compound. The structure of the rearranged product **3** was established from its spectral data, in particular the presence of one *tertiary* and one *secondary* methyl



group. The stereochemistry of the methyl group was assigned as endo based on the observed 3.4 Hz coupling constant between the *exo* C*H*Me and the bridgehead proton. The facile formation of **3** was probably due to the stability of the final radical by the adjacent carbonyl group. Even though the phenyl group is known to stabilize the adjacent radical better than the carbonyl group, in the present situation, the intermediate radical, PhC(•)R-cyclopropyl, is likely more strained than the following radical, RCOC(•)MeR, because of the presence of the strained cyclopropane ring in the former. In order to suppress the cyclopropane opening, the carbonyl group in **2** was modified. First the carbonyl group in **2** was converted into the corresponding ketal **4**. Supporting our



hypothesis, radical cyclization reaction of the bromoketal **4** under the standard conditions furnished the 3-*exo*-trig cyclized product **5** and the homoallyl−homoallyl rearrangement product **6** (1:5 ratio) in 72% yield. Acid-catalyzed hydrolysis of the ketal **6** furnished the ketone **3**, establishing their relationship.

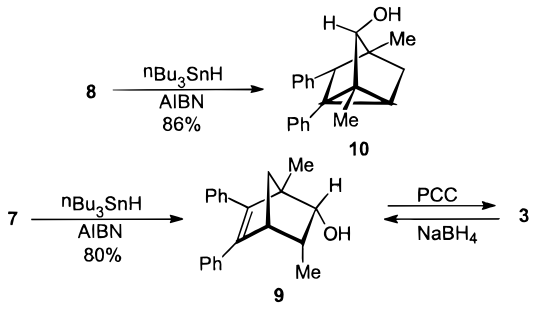


Subsequently radical reactions of the corresponding hydroxy derivatives were contemplated. Thus, sodium borohydride reduction of the adduct **2** generated an ≈3:2 mixture of *syn* and *anti* alcohols **7** and **8** which was separated by silica gel column chromatography. The stereostructures of the alcohols **7** and **8** were deduced from the established NMR pattern of the downfield shift of the C-5 and 6 *exo* protons in *anti* alcohol compared to

(1) Newcomb, M.; Glenn, A. G.; Williams, W. G. *J. Org. Chem.* **1989**, *54*, 2675; Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1996**, *61*, 8547.
(2) Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.* **1994**, *116*, 2710.
(3) Venkatesan, H.; Greenberg, M. M. *J. Org. Chem.* **1995**, *60*, 1053.
(4) Weng, W.-W.; Luh, T.-Y. *J. Org. Chem.* **1993**, *58*, 5574 and references cited therein; Halgren, T. A.; Firkins, J. L.; Fujimoto, T. A.; Suzukawa, H. H.; Roberts, J. D. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 3216 and references cited therein.

S0022-3263(97)00246-6 CCC: $14.00

the *syn* alcohol,[5] which was further confirmed by the observed W-type coupling between the C*H*OAc and C-6 *endo* proton in the acetate derived from the *anti* alcohol. The radical cyclization reactions of both the *syn* and *anti* alcohols **7** and **8** were carried out using standard conditions. The radical cyclization reaction of the *syn* and *anti* alcohols took different course. Completely in agreement with our expectation, the radical cyclization of the *anti* alcohol **8** furnished predominantly the cyclopropane compound **10** (≈6:1 mixture of epimers).[6] The observed NOESY correlation between the C*H*OH and the C*H*Ph protons established the orientation of the phenyl group



as *endo* in the major epimer. In contrast, the *syn* alcohol **7** failed to generate the cyclopropane compound and resulted in exclusively the rearranged product **9**.[6] Jones oxidation of the compound **9** furnished the ketone **3**, whereas the sodium borohydride reduction of rearranged ketone **3** furnished the alcohol **9**, establishing unambiguously the stereostructure of the rearranged alcohol **9**. It is not clear why the *syn* and *anti* compounds are resulting in different products. The formation of the same kind of products from alcohol as well as from the corresponding acetate and ethers[6] ruled out the influence of the hydrogen bonding, between the hydroxy group with olefin or the phenyl rings, on the reaction course. Probably the stereoelectronic effects are responsible for the observed behavior of the *syn* and *anti* alcohols.[7]

Experimental Section

***endo*-5-Bromo-1,4-dimethyl-2,3-diphenylbicyclo[2.2.1]hept-2-en-7-one (2).** A solution of hemicyclone [**1** (dimer), 1 g, 3.85 mmol] and vinyl bromide (3 mL, 42.1 mmol) in benzene (5 mL) was placed in a sealed tube and heated to 100 °C for 14 h. The reaction mixture was cooled, and the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent gave a 9:1 mixture (by ^{1}H NMR) of the *endo* and *exo* adducts (1.34 g, 95%), which on recrystallization from chloroform−hexane furnished the pure *endo* adduct **2**. Mp 102−103 °C. IR (Nujol): 1775 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4−7.0 (10 H, m), 4.39 (1 H, dd, J = 8.9 and 4.5 Hz), 2.60 (1 H, dd, J = 13.8 and 8.9 Hz), 2.22 (1 H, dd, J = 13.8 and 4.5 Hz), 1.35 (3 H, s), 1.25 (3 H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 201.0 (s, C=O), 144.8 (s), 142.0 (s), 134.2 (s), 130.5 (d), 129.4 (d), 129.0 (d), 128.8 (d), 128.1 (d), 127.7 (d), 127.5 (d) and 127.1 (d), 59.7 (s), 53.7 (s), 52.2 (d), 43.2 (t), 11.9 (q), 10.9 (q). Anal. Calcd for $C_{21}H_{19}BrO$: C, 68.67; H, 5.21. Found: C, 68.85; H, 5.21%.

***endo*-1,3-Dimethyl-5,6-diphenylbicyclo[2.2.1]hept-5-en-2-one (3).** A solution of bromo ketone **2** (183 mg, 0.5 mmol), tri-*n*-butyltin hydride (0.15 mL, 0.53 mmol), and AIBN (10 mg) in benzene (28 mL) was refluxed for 3.5 h. The reaction mixture was cooled, washed with 1% aqueous ammonia followed by brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (0:1 to 1:10) as eluent furnished the rearranged ketone **3** (142 mg, 98.6%), which was recrystallized from hexane. Mp 110 °C. IR (neat): 1730 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3 (3 H, m), 7.15 (5 H, m), 6.98 (2 H, m), 3.51 (1 H, bs, bridgehead CH), 2.53 (1 H, dd, J = 9.15 and 2.5 Hz), 2.02 (1 H, dd, J = 9.14 and 1.03 Hz), 2.41 (1 H, d of q, J = 7.05 and 3.4 Hz, C*H*Me), 1.14 (3 H, d, J = 7.1, *sec*-Me), 1.12 (3 H, s, *tert*-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 216.5 (s, C=O), 146.9 (s), 139.7 (s), 135.7 (s), 135.5 (s), 128.6 (d), 128.1 (d), 127.5 (d), 127.3 (d), 64.0 (s), 53.8 (t), 45.7 (d), 44.3 (d), 15.3 (q), 12.3 (q). Mass: *m*/*z* 288 (M$^+$, 36%). HRMS calcd for $C_{21}H_{20}O$: 288.1514. Found: 288.1524. Anal. Calcd for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.1; H, 6.93%.

***endo*-5-Bromo-1,4-dimethyl-2,3-diphenylbicyclo-[2.2.1]hept-2-en-7-one Ethylene Ketal (4).** A magnetically stirred solution of the ketone **2** (305 mg, 0.83 mmol), ethylene glycol (0.23 mL, 4.15 mmol), trimethyl orthoformate (0.36 mL, 3.32 mmol), and *p*-toluenesulfonic acid (catalytic) in dry benzene (5 mL) was refluxed for 8 h. The reaction mixture was cooled, washed with saturated aqueous $NaHCO_3$ followed by brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and rapid purification on a silica gel column using ethyl acetate−hexane as eluent first furnished the ketal **4** (110 mg, 65% based on starting material consumed). Further elution of the column furnished the unreacted starting material. For the ketal **4**: IR (neat): 1095, 755, 695 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 6.96−7.36 (10 H, m, Ar*H*), 4.48 (1 H, dd, J = 9 and 4.5 Hz, C*H*Br), 4.0 (4 H, s), 2.56 (1 H, d of $^1/_2$ ABq, J = 14 and 9 Hz), 1.9 (1 H, d of $^1/_2$ ABq, J = 14 and 4.5 Hz), 1.18 (3 H, s), 1.06 (3 H, s). Mass: *m*/*z* 410 (M$^+$, 1%). HRMS: *m*/*z* calcd for $C_{23}H_{23}BrO_2$: 410.0881. Found: 410.0859. Anal. Calcd for $C_{23}H_{23}BrO_2$: C, 67.16; H, 5.63. Found: C, 66.5; H, 5.52%.

Radical Cyclization Reaction of the Ketal 4. Radical cyclization reaction of the bromo ketal **4** (140 mg, 0.341 mmol) with tri-*n*-butyltin hydride (0.1 mL, 0.33 mmol) and AIBN (10 mg) in benzene (20 mL) for 4 h as described for the ketone **2**, followed by purification on a silica gel column using ethyl acetate−hexane (0:1 to 1:20) as eluent, furnished the rearranged ketal **6** (70 mg, 60%) and the 3-*exo*-trig cyclized product **5** (14 mg, 12.3%). For the rearranged ketal **6**: Mp 107−110 °C. IR (Nujol): 1455, 1160, 700 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.25 (5 H, s), 7.09 (5 H, s), 3.96 (4 H, m), 3.1 (1 H, m), 2.38 (1 H, d of quartet J = 7.56 and 3.96 Hz), 1.9 (2 H, d, J = 3.45 Hz), 1.0 (3 H, s), 0.84 (3 H, d, J = 7.2 Hz). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 145.09, 143.27, 137.81, 137.29, 129.48, 127.92, 126.36, 118.17, 66.15, 64.71, 60.68, 53.14, 47.94, 47.16, 14.51, 12.95. Mass: *m*/*z* 332 (M$^+$, 18%). HRMS: *m*/*z* calcd for $C_{23}H_{24}O_2$: 332.1776. Found: 332.1791. Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 83.09; H, 7.35%. For the cyclized ketal **5**: Mp 183−185 °C. ^{1}H NMR (90 MHz, $CDCl_3$, for the major isomer): δ 7.1−7.2 (10 H, m), 4.08 (4 H, m), 3.6 (1 H, s), 1.96 (1 H, br s), 1.62 (2 H, m), 0.92 (3 H, s), 0.8 (3 H, s). Mass: *m*/*z*: 332 (M$^+$, 100%). HRMS: *m*/*z* Calcd for $C_{23}H_{24}O_2$: 332.1776. Found: 332.1769. Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 83.12; H, 7.24%.

Hydrolysis of the Rearranged ketal 6. To a magnetically stirred solution of the rearranged ketal **6** (10 mg, 0.03 mmol) in THF (0.3 mL) was added 3 N aqueous HCl (0.3 mL) and the mixture stirred at room temperature for 4 h. The reaction mixture was then extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ followed by brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the ketone **3** (6 mg, 69.4%), which was identified by spectral (IR and ^{1}H NMR) comparison with the sample obtained *via* radical cyclization reaction.

***endo*-5-Bromo-1,4-dimethyl-2,3-diphenylbicyclo[2.2.1]-hept-2-en-7-ols (7 and 8).** To a cold (−78 °C) magnetically stirred solution of the bromo ketone **2** (1 g, 2.73 mmol) in 10 mL of 1:1 methanol−THF was added sodium borohydride (196 mg, 5.44 mmol). The reaction mixture was allowed to warm up

(5) Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065.

(6) In an analogous manner, radical cyclization reaction of the corresponding acetate and ethoxyethyl ethers derived from the *anti* alcohol **8** produced exclusively the respective cyclopropane compounds *via* 3-exo-trig cyclization, and the acetate and ethoxyethyl ethers derived from the *syn* alcohol **7** furnished only the corresponding rearranged products.

(7) Molecular mechanics (MMX) calculations on the two pairs of the cyclized and ring opened radicals failed to provide any reasonable explanation for the observed behavior of the *syn* and *anti* alcohols **7** and **8**.

to room temperature over a period of 15 min. Then the solvent was removed under reduced pressure, and the residue was partitioned between ether and dilute aqueous HCl. The ether extract was washed with water, aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and careful purification of the residue on a silica gel column using ethyl acetate−hexane (1:20 to 1:5) furnished the *anti* alcohol **8** (392 mg, 39%) and the *syn* alcohol **7** (590 mg, 58.7%) sequentially. For the *anti* alcohol **8**: IR (neat): 3570, 3450 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35−7.0 (10 H, m), 4.5 (1 H, dd, J = 8.4 and 3.6 Hz), 3.42 (1 H, s), 2.57 (1 H, d of $^1/_2$AB q, J = 13.0 and 8.4 Hz), 1.95 (1 H, m of $^1/_2$AB q, J = 13.0 Hz), 1.6 (1 H, brs), 1.30 (3 H, s), 1.14 (3 H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 148.7 (s), 142.9 (s), 135.7 (s, 2 C), 130.4 (d), 129.3 (d), 127.8 (d), 127.4 (d), 126.6 (d), 126.3 (d), 87.9 (d), 60.2 (s), 57.5 (d), 53.3 (s), 43.3 (t), 14.9 (q), 13.4 (q). Mass: *m*/*z* 370 and 368 (M + 2 and M^+, 24%). HRMS: calcd for $C_{21}H_{21}BrO$: 368.0776. Found: 368.0779. For the *syn* alcohol **7**: IR (neat): 3540, 3440 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35−7.0 (10 H, m), 4.33 (1H, dd, J = 8.6 and 4.0 Hz), 3.34 (1H, d, J = 11.9 Hz), 2.46 (1 H, d of $^1/_2$AB q, J = 13.7 and 8.6 Hz), 2.05 (1 H, d of $^1/_2$AB q, J = 13.7 and 4.0 Hz), 2.01 (1 H, d, J = 11.9, exchanged with D_2O), 1.36 (3 H, s), 1.21 (3 H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 144.0 (s), 141.1 (s), 135.5 (s), 130.3 (d), 129.1 (d), 127.8 (d), 127.4 (d), 126.7 (d), 126.4 (d), 90.2 (d), 61.5 (s), 55.2 (s), 54.6 (d), 43.7 (t), 15.2 (q), 14.6 (q). Mass: *m*/*z* 370 and 368 (M + 2 and M^+, 8%). HRMS: calcd for $C_{21}H_{21}BrO$: 368.0776. Found: 368.0770. For a mixture of the alcohols **7** and **8**. Anal. Calcd for $C_{21}H_{21}BrO$: C, 68.29; H, 5.73. Found C, 68.58; H, 6.01%.

2,3-bis-*endo*-1,3-Dimethyl-5,6-diphenylbicyclo[2.2.1]hept-5-en-2-ol (9). Radical cyclization reaction of the *syn* alcohol **7** (37 mg, 0.1 mmol) with tri-n-butyltin hydride (0.03 mL, 0.11 mmol) and AIBN (10 mg) in benzene (5.6 mL) for 4 h as described for the ketone **2**, followed by purification on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the homoallyl−homoallyl radical rearrangement product **9** (25 mg, 86.2%). IR (neat): 3590 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (5 H, m), 7.12 (5 H, m), 4.15 (1 H, d, J = 8.6 Hz), 3.18 (1 H, m), 2.6 (1 H, d of quintet, J = 7.33 and 3.5 Hz), 1.8 (1 H, d of $^1/_2$AB q, J = 8.7 and 2.1 Hz), 1.46 (1 H, d of $^1/_2$AB q, J = 8.7 and 1.12 Hz), 1.4 (1 H, br s), 1.25 (3 H, s), 0.84 (3 H, d, J = 7.3 Hz). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 144.3, 143.5, 137.9, 137.2, 129.3, 128.2, 128.0, 126.5, 79.0, 59.2, 52.7, 49.9, 40.8, 17.4, 13.3. Mass: *m*/*z* 290 (M^+, 30%).

Oxidation of the Rearranged Alcohol 9. To a magnetically stirred solution of the rearranged alcohol **9** (11 mg, 0.038 mmol) in methylene chloride was added a mixture of PCC (11 mg, 0.5 mmol) and silica gel (11 mg). The reaction mixture was stirred at room temperature for 1 h and filtered through a small plug of silica gel. Evaporation of the solvent and purification of the residue on a silica gel column furnished the ketone **3** (9 mg, 82.6%) which was identified by spectral (IR and ^1H NMR) comparison with the sample obtained *via* radical cyclization reaction.

Reduction of the Rearranged Ketone 3. Reduction of the rearranged ketone **3** (13 mg, 0.045 mmol) with sodium borohydride (5 mg, 0.138 mmol) in methanol (0.5 mL) as described for the alcohols **7** and **8**, followed by purification on a silica gel column furnished the alcohol **9** (11 mg, 85%) which exhibited spectral data (IR and ^1H NMR) identical to that obtained in the radical cyclization reaction of **7**.

(3α,5α)-2,4-Dimethyl-5,6-diphenyltricyclo[2.2.1.0^{2,6}]heptan-3-ol (10). Radical cyclization reaction of the *anti* alcohol **8** (110 mg, 0.3 mmol) with tri-*n*-butyltin hydride (0.1 mL, 0.33 mmol) and AIBN (20 mg) in benzene (17 mL) for 4 h as described for the ketone **2**, followed by purification on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the 3-*exo*-trig radical cyclized product **10** (70 mg, 80.5%). IR (neat): 3380 cm^{-1}. For the major isomer ^1H NMR (200 MHz, $CDCl_3$): δ 7.4−7.0 (10 H, m), 3.54 (1 H, s), 3.084 (1 H, s), 1.84 (1 H, s), 1.63 and 1.49 (2 H, AB q, J = 11.2 Hz), 1.04 (3 H, s), 0.944 (3 H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 138.5 (s), 138.0 (s), 129.5 (d), 128.7 (d), 128.0 (d), 127.6 (d), 126.2 (d), 125.5 (d), 85.0 (d), 53.7 (d), 47.9 (s), 38.7 (s), 33.2 (s), 33.0 (t), 26.0 (d), 12.5 (q), 10.0 (q). Mass: *m*/*z* 290 (M^+, 85%). HRMS: calcd for $C_{21}H_{22}O$: 290.1671. Found: 290.1657.

Acknowledgment. We thank Dr. P. Hemamalini for carrying out preliminary experiments. V.J. and T.J.R. thank U.G.C. and D.V. and P.P.K. thank C.S.I.R. for the award of research fellowships.

JO970246V