The Regio- and Diastereoselectivity of the Intramolecular 2 + 2 Photocycloadditions of 4-(2'-Isopropyl-3'-butenyl)-2,5-cyclohexadien-1-ones

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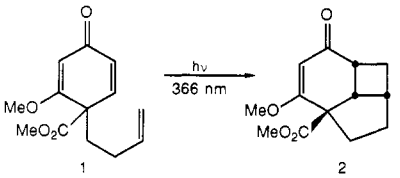
Irradiation (366 nm) of 4-carbomethoxy-4-(2'-isopropyl-3'-butenyl)-2,5-cyclohexadien-1-one (**3**) in pentane solution at −78 °C gave the tricyclodecenone **4** rather than the alternative diastereomer, **5**. The ability of the C(3) methoxy substituent to direct the regioselectivity of photocycloaddition to give the less stable diastereoisomeric series (cf. **5**) was examined. However, irradiation of **7b** (benzene, 25 °C), in mixture with **8b**, gave **9** rather than **11**, while **8b** gave the expected **10**. The diastereoselectivity of reductive alkylation of methyl 2-methoxybenzoate with *dl*-4-iodo-3-isopropyl-1-butene to give **7a** and **8a** was determined to be 1.6:1.

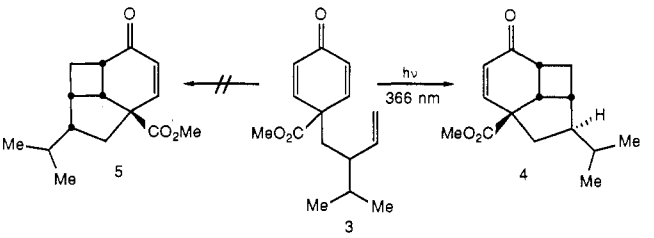
The first intramolecular 2 + 2 photocycloadditions of 4-(3'-alkenyl)-2,5-cyclohexadien-1-ones were reported in 1988.[1] With 4-(3'-butenyl)-4-carbomethoxy- and 4-(3'-butenyl)-4-cyano-2,5-cyclohexadien-1-ones, type A photorearrangements to bicyclo[3.1.0]hex-3-en-2-ones and intramolecular 2 + 2 photocycloadditions to tricyclo[5.2.1.$0^{5,10}$]dec-2-en-4-ones occur with comparable efficiencies at 25 °C in benzene solution. Type A photorearrangement is completely suppressed when the 3-methoxy substituent is present; irradiation of 4-(3'-butenyl)-4-carbomethoxy-3-methoxy-2,5-cyclohexadien-1-one (**1**) at 366 nm gives 1-carbomethoxy-2-methoxytricyclo[5.2.1.$0^{5,10}$]dec-2-en-4-one (**2**) in >95% yield with attendant formation of less than 5% of the regioisomeric tricyclodecenone. Thus, while the 3-methoxy substituent in **1** facilitates intramolecular 2 + 2 cycloaddition, cyclobutane formation occurs primarily at the unsubstituted double bond.



1 2

Regioselectivity of the type encountered with **1** should provide unique synthetic flexibility, particularly as a result of the reactivity of the vinylogous ester group in **2**.[2a] However, we were curious about the viability of a fundamentally different type of regioselectivity based on principles of remote stereocontrol. The concept is illustrated here with the "symmetrical" 2,5-cyclohexadienone **3**,[2b] in which the stereogenic center at C(2') of the 4-(3'-butenyl) group could, in principle, direct 2 + 2 photocycloaddition to preferentially one of the two dienone double bonds.[3]

Irradiation of **3** in benzene solution at 25 °C gave tricyclodecenone **4** in poor yield along with a substantial amount of phenolic products resulting from type A photoreactivity. After experimentation with the effect of changes in solvent and reaction temperature on product distribution, it was found that **4** could be obtained in 45% isolated yield after irradiation of **3** in pentane solution at −78 °C and flash chromatography on silica gel. The formation of the alternative tricyclodecenone **5** was not observed.



5 3 4

The origins of the solvent and temperature effects remain to be clearly established. Information concerning the electronic structure and, perhaps, conformation of the excited state(s) responsible for cyclobutane formation may be obtained from a more extensive study of solvent, temperature, and substituent effects. The modification of product distribution by simple changes in substrate and reaction variables has already been shown to have substantial synthetic value.[1]

The structure of **4** was easily determined by examination of IR, ^{1}H NMR, and chemical ionization mass spectra. Assignment of relative configuration required conversion of **4** (oil) to the crystalline 2,4-dinitrophenylhydrazone, which was subjected to X-ray crystallographic analysis. The molecular structure of the 2,4-DNP of **4** is shown in Figure 1.

Photocyclization of **3** results in formation of the most stable tricyclodecenone; **4** is more stable than **5** because the bulky isopropyl group in **4** is outside of the cup-shaped cavity defined by the tricyclodecenone ring system.[4] The selective formation of **4** and the earlier discovery[1] that 2 + 2 photocycloaddition probably involves reversible formation of 1,4-biradicals suggests that product development control may generally be operative in photocyclizations of 4-(3'-butenyl)-2,5-cyclohexadien-1-ones.[5]

It seemed worthwhile to test the possibility of changing the course of photocycloaddition to give the less stable diastereoisomeric series (cf. **5**) by incorporation of a methoxy substituent at C(3) of the cyclohexadienone ring. If, as determined for the conversion **1** → **2**, photocyclo-

(1) Schultz, A. G.; Plummer, M.; Taveras, A. G.; Kullnig, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 5547.

(2) (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. (b) Photocyclizations of **3**, in particular, were examined because of possible application to total syntheses of the isocyanopupukeananes. For isolation and structure determination studies, see: Burreson, B. J.; Scheuer, P. J.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 4763.

(3) For some other examples of internal "desymmetrization", see: (a) Schultz, A. G.; Napier, J. J.; Sundararaman, P. *J. Am. Chem. Soc.* **1984**, *106*, 3590. (b) Aube, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 151.

(4) Computer assisted molecular modeling (MacroModel, MM2) indicates that **4** is 0.89 kcal/mol more stable than **5**.

(5) For examples of the diastereoselectivity of the intramolecular 2 + 2 photocycloadditions of C(2) alkenyl substituted cyclopent- and cyclohex-2-en-1-ones, in which stereogenic centers are located at C(1') and C(3'), see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.

0022-3263/89/1954-3158$01.50/0

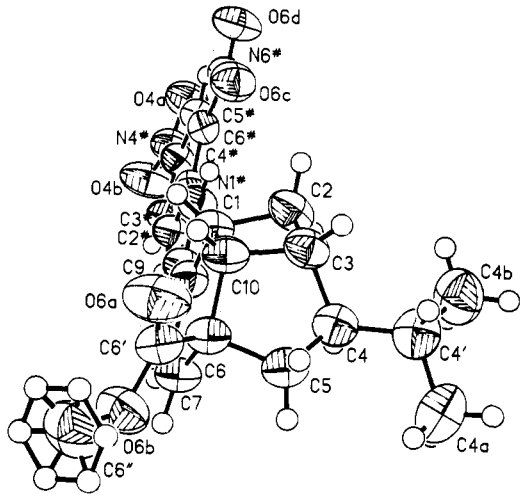


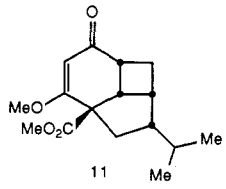
Figure 1. Molecular structure of the 2,4-dinitrophenylhydrazine derivative of **4**.

addition preferentially occurs at the least substituted double bond, then the effect of the C(2′) stereogenic center in **7b** might be offset. The net effect would be to increase the probability of formation of tricyclodecenone **11**. The results of this study are presented in Scheme I.

Birch reduction of methyl 2-methoxybenzoate in the usual manner,[1] followed by alkylation of the resulting ester enolate with *dl*-4-iodo-3-isopropyl-1-butene, gave an inseparable mixture (1.6:1) of **7a** and **8a** in 64% isolated yield. Bis-allylic oxidation of **7a** and **8a** with *tert*-butyl hydroperoxide and pyridinium dichromate[6] afforded 2,5-cyclohexadien-1-ones **7b** and **8b** in 82% yield, again as an inseparable 1.6:1 mixture. Irradiation of the mixture of **7b** and **8b** in benzene solution at 366 nm (25 °C, 2.5 h) provided two isomeric photoproducts that were separated by flash chromatography on silica gel. The major isomer **9** (mp 129–130 °C) was isolated in 46% yield, while the minor isomer **10** (mp 95–97 °C) was obtained in 30% yield.

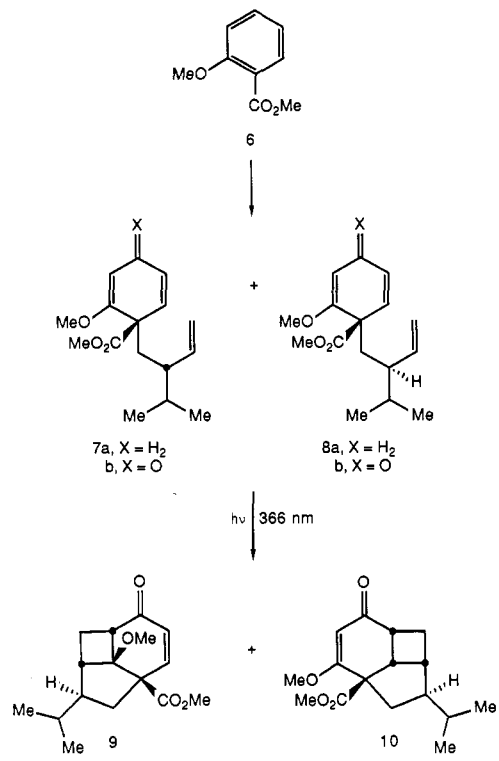
The distribution of photocycloaddition products **9** and **10** (1.5:1), together with their unambiguous structural assignments, allowed a definitive assignment of relative configuration to be made for reductive alkylation products **7a** and **8a**. Diastereoselectivity for alkylation of achiral anisic ester derived enolates with chiral alkyl halides appears not to have been previously reported.[7] Although stereoselectivity is modest at present, chiral anisic amide derived enolates[8] may offer greater stereocontrol via principles of double diastereoselection.

Cycloadduct **11** is absent from photoreactions of **7b**. Thus, the C(3) methoxy substituent is not capable of overriding the regioselectivity imparted by the C(2′) isopropyl group in **7b**. Overall, the remote control resulting from the C(2′) isopropyl group in **7b** and **8b** translates into regio- and stereospecificity for the photoconversions **7b** → **9** and **8b** → **10**.



(6) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.
(7) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35.
(8) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

Scheme I



Experimental Section

3-Carbomethoxy-3-(2′-isopropyl-3′-butenyl)-1,4-cyclohexadiene. Methyl benzoate (468 mg, 3.44 mmol) and *tert*-butyl alcohol (254 mg, 3.43 mmol) were placed into an oven-dried three-necked flask along with 20 mL of THF. Ammonia was condensed into the flask at −78 °C, and to the resulting solution was added lithium metal until a blue coloration persisted for 0.5 h. Anhydrous piperylene was added dropwise until the blue coloration was dissipated. The reaction mixture was allowed to warm to room temperature while a slow stream of nitrogen was passed through the flask to facilitate removal of ammonia. After recooling to −78 °C, 4-iodo-3-isopropylbut-1-ene (927 mg, 4.13 mmol) in 5 mL of THF (−78 °C) was added. The reaction mixture was allowed to slowly warm to room temperature and after 10 h was quenched with ammonium chloride. Addition of water, extraction with ethyl acetate, and chromatography on silica gel (ethyl acetate–hexane, 1:2) provided the title compound (713 mg, 88%) as an oil: ^{1}H NMR ($CDCl_3$) δ 5.78 (m, 4 H), 5.51 (m, 1 H), 4.87 (m, 2 H), 3.60 (s, 3 H), 2.59 (m, 2 H), 2.02–1.76 (m, 2 H), 1.63 (dd, 1 H, J = 12.8 Hz, J = 2.2 Hz), 1.52 (m, 1 H), 0.82 (d, 3 H, J = 4.5 Hz), 0.79 (d, 3 H, J = 4.5 Hz); IR (film) 3075, 3035, 2960, 2870, 2825, 1730, 1635, 1425, 1230, 915, 715 cm^{-1}; CIMS m/z (relative intensity) 235 (M^+ + 1, 100.0), 199 (29.5), 175 (29.5), 137 (12.0), 97 (46.0).

4-Carbomethoxy-4-(2′-isopropyl-3′-butenyl)-2,5-cyclohexadien-1-one (3). 3-Carbomethoxy-3-(2′-isopropyl-3′-butenyl)-1,4-cyclohexadiene (700 mg, 2.99 mmol) was treated with pyridinium dichromate (PDC) (3.38 g, 9.00 mmol) in refluxing chloroform for 12 h. Filtration of the reaction mixture through Florisil and subsequent chromatography on silica gel (ethyl acetate–hexane, 1:2) gave **3** (404 mg, 55%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.07 (m, 2 H), 6.32 (m, 2 H), 5.52 (m, 1 H), 5.03 (dd, 1 H, J = 10.2 Hz, J = 1.8 Hz), 4.90 (dd, 1 H, J = 17.0 Hz, J = 1.7 Hz), 3.71 (s, 3 H), 2.12 (dd, 1 H, J = 13.7 Hz, J = 9.8 Hz), 1.93 (dd, 1 H, J = 13.7 Hz, J = 2.3 Hz), 1.89 (m, 1 H), 1.56 (m, 1 H), 0.84 (d, 3 H, J = 3.5 Hz), 0.80 (d, 3 H, J = 3.5 Hz); IR (film) 3075, 3045, 2960, 2875, 1730, 1665, 1630, 1435, 1235, 1175, 920, 865 cm^{-1}; CIMS m/z (relative intensity) 249 (M^+ + 1, 100.0), 217 (25.0), 193 (24.0), 189 (14.0), 165 (81.0), 153 (35.0).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.63; H, 8.20.

(1*R,5*S**,7*S**,8*S**,10*R**)-1-Carbomethoxy-8-isopropyltricyclo[5.2.1.0^{5,10}]dec-2-en-4-one (4).** Dienone **3** (110 mg, 0.44

mmol) was irradiated at 366 nm in 20 mL of pentane at −78 °C for 4.5 h. The light source was a Hanovia 450-W medium-pressure mercury arc lamp. The lamp was placed in a water-cooled Pyrex immersion well, and a uranyl glass filter sleeve was employed to isolate the 366-nm line of the lamp. Reaction vessels containing solutions to be irradiated were attached to the immersion well and were saturated with nitrogen prior to irradiation. Chromatography on silica gel (ethyl acetate–methylene chloride, 1:10) gave **4** (49 mg, 45%) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1 H, J = 10.5 Hz), 6.16 (d, 1 H, J = 10.5 Hz), 3.74 (s, 3 H), 3.60 (m, 1 H), 3.07 (dt, 1 H, J = 4.7 Hz, J = 9.7 Hz), 2.75 (dt, 1 H, J = 8.2 Hz, J = 11.6 Hz), 2.48 (m, 1 H), 2.00 (m, 1.5 H), 1.73 (m, 2.5 H), 1.48 (m, 1 H), 0.88 (d, 3 H, J = 2.5 Hz), 0.84 (d, 3 H, J = 2.3 Hz); IR (film) 3030, 2955, 2875, 1725, 1665, 1430, 1225, 1030, 825 cm^{-1}; CIMS m/z (relative intensity) 249 (M^+ + 1, 100.0), 217 (5.4), 189 (29.6), 161 (3.9).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.08.

Preparation of the 2,4-Dinitrophenylhydrazone of Enone 4. Enone **4** in ethanol was added to a standard 2,4-dinitrophenylhydrazine reagent solution. After being heated at 55 °C for 2 min, the reaction mixture was cooled in an ice bath. The crystals that formed on cooling were collected by filtration and were recrystallized from ethyl acetate–hexane solution (mp 123–4 °C). The crystals so obtained were found suitable for X-ray diffraction studies.

(3*R,2′*R**)-3-Carbomethoxy-3-(2′-isopropyl-3′-butenyl)-2-methoxy-1,4-cyclohexadiene (7a) and (3*R**,2′*S**)-3-Carbomethoxy-3-(2′-isopropyl-3′-butenyl)-2-methoxy-1,4-cyclohexadiene (8a).** The Birch reduction–alkylation was performed as described above. Chromatography on silica gel (ethyl acetate–hexane, 1:2) provided **7a** and **8a** (554 mg, 64%) as an inseparable 1.6:1 mixture (^{1}H NMR integration): IR (film) 3075, 3030, 3000, 2960, 2940, 2880, 2855, 1730, 1685, 1640, 1435, 1365, 1220, 1165, 1035, 910, 785, 730 cm^{-1}; CIMS m/z (relative intensity) 265 (M^+ + 1, 36.5), 233 (100.0), 205 (3.8), 173 (3.0). **7a**: ^{1}H NMR ($CDCl_3$) δ 5.91 (ddt, 1 H, J = 8.8 Hz, J = 1 Hz, J = 3.4 Hz), 5.54 (m, 1 H), 5.39 (m, 1 H), 4.87–4.63 (m, 3 H), 3.67 (s, 3 H), 3.42 (s, 3 H), 284 (m, 2 H), 2.12 (m, 1 H), 1.70 (m, 2 H), 1.54 (m, 1 H), 0.81 (dd, 6 H, J = 6.8 Hz, J = 1.9 Hz). **8a**: δ 5.72 (ddt, 1 H, J = 8.9 Hz, J = 1 Hz, J = 3.4 Hz), 5.54 (m, 1 H), 5.35 (m, 1 H), 4.87–4.63 (m, 3 H), 3.66 (s, 3 H), 3.52 (s, 3 H), 2.84 (m, 2 H), 2.12 (m, 1 H), 1.79 (m, 2 H), 1.54 (m, 1 H), 0.79 (d, 6 H, J = 6.8 Hz).

(4*R,2′*R**)-4-Carbomethoxy-4-(2′-isopropyl-3′-butenyl)-3-methoxy-2,5-cyclohexadien-1-one (7b) and (4*R**,2′*S**)-4-Carbomethoxy-4-(2′-isopropyl-3′-butenyl)-3-methoxy-2,5-cyclohexadien-1-one (8b).** Dienes **7a** and **8a** (536 mg, 2.03 mmol) in 50 mL of benzene containing 3.05 g of Celite were treated with PDC (3.05 g, 8.10 mmol) and 90% *tert*-butyl hydroperoxide (0.90 mL, 8.09 mmol) at 10 °C for 0.5 h and then at room temperature for 3 h. Filtration through Celite and chromatography on silica gel (ethyl acetate–hexane, 1:1) provided **7b** and **8b** (461 mg, 82%) as an inseparable 1.6:1 mixture (^{1}H NMR integration): mp 94–97 °C; IR (KBr) 3075, 2960, 2945, 2905, 2880, 1735, 1630, 1595, 1430, 1370, 1215, 1175, 995, 865 cm^{-1}; CIMS m/z (relative intensity) 279 (M^+ + 1, 100.0), 250 (1.7), 247 (3.5), 195 (4.5), 183 (2.7). **7b**: ^{1}H NMR ($CDCl_3$) δ 6.45 (d, 1 H, J = 9.9 Hz), 6.34 (dd, 1 H, J = 9.8 Hz, 1.3 Hz), 5.56 (d, 1 H, J = 1.2 Hz), 5.43 (m, 1 H), 4.86 (dd, 1 H, J = 10.2 Hz, J = 1.9 Hz), 4.72 (dd, 1 H, J = 16.9 Hz, J = 1.9 Hz), 3.69 (s, 3 H), 3.62 (s, 3 H), 2.31 (m, 1 H), 2.12 (m, 1 H), 1.52 (m, 2 H), 0.80 (dd, 6 H, J = 6.6 Hz, J = 3.7 Hz). **8b**: δ 6.47 (d, 1 H, J = 9.8 Hz), 6.20 (dd, 1 H, J = 9.9 Hz, J = 1.4 Hz), 5.73 (d, 1 H, J = 1.3 Hz), 5.54 (m, 1 H), 4.93 (dd, 1 H, J = 10.2 Hz, J = 1.8 Hz), 4.76 (dd, 1 H, J = 17.1 Hz, J = 1.9 Hz), 3.76 (s, 3 H), 3.68 (s, 3 H), 2.38 (m, 1 H), 2.05 (m, 1 H), 1.52 (m, 1 H), 0.80 (d, 6 H, J = 6.7 Hz).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.88; H, 8.08.

(1*R,5*S**,7*S**,8*S**,10*S**)-1-Carbomethoxy-8-isopropyl-10-methoxytricyclo[5.2.1.0^{5,10}]dec-2-en-4-one (9) and (1*R**,5*R**,7*R**,8*R**,10*S**)-1-Carbomethoxy-8-isopropyl-2-methoxytricyclo[5.2.1.0^{5,10}]dec-2-en-4-one (10).** Dienones **7b** and **8b** (96.3 mg, 0.346 mmol) were irradiated at 366 nm in 20 mL of benzene at room temperature for 2.5 h. Chromatography on silica gel (ethyl acetate–hexane, 1:1) provided **9** (44.4 mg, 46%) and **10** (28.5 mg, 30%) as colorless crystalline materials. **9**: mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 6.62 (d, 1 H, J = 10.2 Hz), 6.19 (d, 1 H, J = 10.4 Hz), 3.69 (s, 3 H), 3.33 (s, 3 H), 3.27 (m, 1 H), 2.62 (d, 1 H, J = 7.1 Hz), 2.57 (d, 1 H, J = 8.6 Hz), 2.40 (d, 1 H, J = 12.6 Hz), 2.34 (d, 1 H, J = 11.8 Hz), 1.93 (d, 1 H, J = 5.4 Hz), 1.87 (d, 1 H, J = 5.1 Hz), 1.53 (m, 4 H), 0.91 (d, 3 H, J = 5.9 Hz), 0.88 (d, 3 H, J = 5.5 Hz); IR (KBr) 3030, 2960, 2940, 2865, 2840, 1730, 1650, 1435, 1280, 1245, 1220, 1090, 835 cm^{-1}; CIMS m/z (relative intensity) 279 (M^+ + 1, 100.0), 247 (8.0), 219 (0.2), 182 (0.1).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.08; H, 7.95.

10: mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 5.63 (s, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 3.12 (m, 2 H), 2.75 (m, 1 H), 2.44 (m, 1 H), 2.21 (d, 1 H, J = 1.8 Hz), 2.17 (dd, 1 H, J = 18.8 Hz, J = 13.2 Hz), 1.77 (dt, 1 H, J = 12.28 Hz, J = 4.0 Hz), 1.52 (m, 2 H), 0.89 (d, 3 H, J = 6.3 Hz), 0.84 (d, 3 H, J = 6.3 Hz); IR (film) 3060, 2960, 2940, 2875, 1730, 1640, 1610, 1450, 1435, 1355, 1220, 1170, 1085, 1035, 845 cm^{-1}; CIMS m/z (relative intensity) 279 (M^+ + 1, 100.0), 265 (0.1), 247 (0.1), 219 (0.1), 182 (0.5).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.89; H, 7.97.

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Registry No. (±)-**3**, 120790-05-8; (±)-**4**, 120790-06-9; (±)-**4** ((2,4-dinitrophenyl)hydrazone), 120790-07-0; (±)-**7a**, 120790-09-2; (±)-**7b**, 120790-08-1; (±)-**8a**, 120790-10-5; (±)-**8b**, 120790-11-6; (±)-**9**, 120828-88-8; (±)-**10**, 120790-12-7; methyl benzoate, 93-58-3; methyl 2-methoxybenzoate, 606-45-1; (±)-3-carbomethoxy-3-(2′-isopropyl-3′-butenyl)-1,4-cyclohexadiene, 120790-04-7; (±)-4-iodo-3-isopropylbut-1-ene, 120790-13-8.

Supplementary Material Available: Tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and H-atom coordinates for the 2,4-DNP of **4** (7 pages). Ordering information is given on any current masthead page.