166 (30), 165 (100, Ph_2C^+-H), 77 (48). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.89; H, 5.73; N, 11.37. Found: C, 82.55; H, 5.67; N, 10.84.

Expt 6: Electroreduction of Benzophenone Anil (8) in MeCN in the Presence of 4-Chlorobutyryl Chloride (1b, Method B). The substrate (0.6 g, 2.33 mmol) is reduced at -1.78 ± 0.08 V in the presence of **1b** (0.27 mL, 2.4 mmol): n = 2.21; crude product, 0.685 g. The first time, the chromatographic column is eluted with benzene; **13b** (23%) and **14d** (9%) are thus isolated. Then the column is eluted with diethyl ether, and 0.415 g of a mixture of four compounds is collected. In a second experiment, the column is eluted with 70:30 diethyl ether–hexane, and **15d** (20%), **10c** (6%), and **15c** (8%) are isolated. At least, **19** (5%) is collected from the column with diethyl ether as the eluant.

α,α-Diphenyl-α-anilinoacetylcyclopropane (14d): mp 157 °C (hexane); IR (KBr) 3400 (NH), 1692 (C=O), 1592, 1497, 1445, 1424, 1368, 1315, 1156, 1055, 746, 727, 706, 689 cm^{-1}; NMR ($CDCl_3$) δ 0.6–1.6 (m, 4 H, cyclopropyl H), 1.8–2.4 (m, 1 H, cyclopropyl H), 5.7 (br, 1 H, exchangeable with D_2O, NH), 6.2–7.8 (m, 15 H, aromatic H); mass spectrum, m/e (relative intensity) 327 (1, M^+), 259 (16), 258 (100, Ph_2CNHPh^+), 257 (6), 180 (11), 155 (6), 77 (16). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28; O, 4.89. Found: C, 84.25; H, 6.45; N, 4.25; O, 4.93.

***N*-Benzhydryl-*N*-phenylcyclopropanecarboxamide (15d)**, mp 75 °C (benzene) [lit.[16] mp 74–77 °C (petroleum ether)].

4,4-Diphenyl-4-anilinobutyronitrile (10c): colorless crystals; mp 188 °C ($CHCl_3$); IR (KBr) 3425 (NH), 2245 (C≡N), 1592, 1488, 1439, 765, 750, 742, 704, 695, 689, 635 cm^{-1}; NMR ($CDCl_3$) δ 1.95–2.45 (m, 2 H, CCH_2), 2.75–3.25 (m, 2 H, CH_2CN), 4.45 (br, 1 H, NH), 6.25–7.15 (m, 15 H, aromatic H); mass spectrum, m/e (relative intensity) 313 (13, M + 1), 312 (59, M^+), 311 (32), 259 (16), 258 (91), 221 (21), 220 (100, $Ph_2C(CH_2)_2CN^+$), 219 (9), 181 (9), 180 (66), 179 (67), 178 (35), 165 (38), 115 (39), 93 (71), 77 (58).

***N*-Benzyhydryl-4-chlorobutananilide (15c)**: viscous liquid; IR (film) 1655 (NC=O), 1592, 1492, 1389, 1254, 698 cm^{-1}; NMR ($CDCl_3$) 1.8–2.6 (m, 4 H, $COCH_2CH_2$), 3.52 (t, J = 6 Hz, 2 H, CH_2Cl), 6.65–7.50 (m, 16 H, aromatic H); mass spectrum, m/e (relative intensity) 365 (11, M^+, ^{37}Cl), 363 (32, M^+, ^{35}Cl), 327 (2), 258 (4), 168 (15), 167 (100, Ph_2CH^+), 166 (9), 165 (23), 152 (17), 77 (15). An authentic sample of **15c** was prepared from *N*-benzhydrylaniline and 4-chlorobutyryl chloride (**1b**). Spectral data were identical with those observed for **15c**.

1,6,6-Triphenyl-2-piperidinone (19): colorless crystals; mp 172 °C (diethyl ether–hexane) [lit.[16] mp 172.5–173.5 °C (methanol)]; IR (KBr) 1639 (NC=O), 1587, 1488, 1432, 1353, 1329, 762, 746, 712, 702, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.4–1.8 (m, 2 H, CH_2), 2.5–2.9 (m, 4 H, $COCH_2CH_2CH_2$), 6.9 and 7.25 (double s, 15 H, aromatic H); mass spectrum, m/e (relative intensity) 328 (10, M + 1), 327 (37, M^+), 250 (2), 207 (6), 206 (24), 193 (40), 192 (52), 180 (30), 179 (21), 178 (37), 165 (33), 129 (15), 128 (15), 115 (50), 103 (8), 93 (100, $PhNH_2^+$), 91 (38), 77 (10). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.36; H, 6.46; N, 4.27; O, 4.88. Found: C, 83.67; H, 6.48; N, 4.33.

Expts 7 and 8. The chemical reductions by alkali metals of **7** in diethyl ether or HMPT and that of **8** in HMPT are performed according to an experimental procedure described in ref 1.

Registry No. 1a, 927-58-2; **1b**, 4635-59-0; **6**, 486-25-9; **7**, 10183-82-1; **8**, 574-45-8; **10a**, 79817-28-0; **10b**, 79817-29-1; **10c**, 79817-30-4; **11a**, 79817-31-5; **11c**, 79817-32-6; **12b**, 79817-33-7; **12c**, 79817-34-8; **13a**, 31859-87-7; **13b**, 1865-12-9; **14a**, 79817-35-9; **14b**, 79817-36-0; **14d**, 79817-37-1; **15a**, 79817-38-2; **15b**, 79817-39-3; **15c**, 79817-40-6; **15d**, 59434-94-5; **16a**, 7578-45-2; **16b**, 2759-52-6; **17**, 4641-57-0; **18a**, 2286-54-6; **18b**, 3531-25-7; **19**, 59434-96-7; fluorenol, 1689-64-1.

Intramolecular Photochemical Cycloaddition Reactions of 3-(1,5-Dimethylhex-4-enyl)cyclohex-2-enone: Regio- and Stereochemical Aspects

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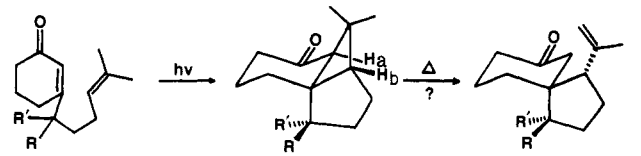
Received May 6, 1981

The intramolecular photocycloaddition reaction of the title enone (1) and its 1-demethyl analogue (2) gives head-to-head, [2 + 2] adducts containing cyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one skeletons and none of the head-to-tail isomers of the tricyclo[5.3.1.$0^{2,7}$]undecan-3-one variety. In addition, formal photoene adducts of a spiro[5,4]decan-3-one nature which are related to the acorane sesquiterpene carbon skeleton are also observed. The stereochemical consequences of the acyclic methyl-bearing chiral center in 1 are probed, and the ratio of epimeric products is found to be temperature dependent. Attempts to thermally convert the *gem*-dimethylcyclobutane moiety in the [2 + 2] adducts to spirocyclic precursors of the acoranes results instead in reversion to starting enone.

Intramolecular [2 + 2] photocycloaddition reactions of olefinic enones[2] and the retro-ene reaction of *cis*-1-acyl-2-alkylcyclopropanes and -butanes[3] are well-established synthetic transformations. We have attempted to apply these reactions sequentially to natural product synthesis. Specifically, we have studied the irradiation of enones 1 and 2 with the intention of first forming and then pyrolyzing the cyclobutanes 3 and 4 to provide the spirocyclic isopropenyl compounds 5 and 6.[4] Methyl epimers **5a** and



1 R,R′ = CH_3, H
2 R,R′ = H, H

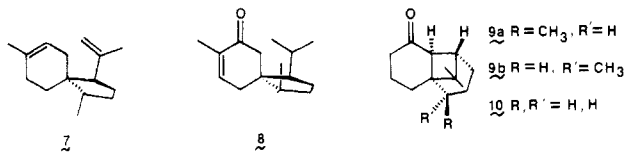
3a R = CH_3, R′ = H
3b R = H, R′ = CH_3
4 R,R′ = H, H

5a R = CH_3, R′ = H
5b R = H, R′ = CH_3
6 R,R′ = H, H

(1) (a) NSF-URP, summer 1979. (b) University of Minnesota Graduate School Dissertation Fellow, 1980–1981.
(2) For a recent review see: Baldwin, S. W. In "Organic Photochemistry"; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, Chapter 2.
(3) Conia, J. M.; Perchec, P. L. *Synthesis* **1975**, 1.

0022-3263/82/1947-0331$01.25/0

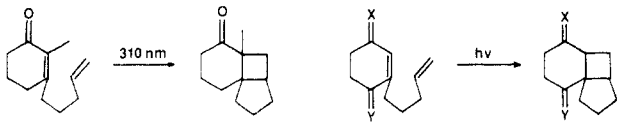
5b were envisioned as convenient precursors to several members of the acorane family of spirocyclic sesquiterpenes. The choice of these particular synthetic targets furnished an additional bonus. Successful synthesis, total or formal, would provide a means by which to assay the degree of stereoselectivity exerted by the allylic methyl substituent in the cycloaddition of **1**. For example, correlation of **5a** and **5b** with acoradiene (**7**)[5] and acorenone (**8**)[6] would define the stereochemistry in the former pair.



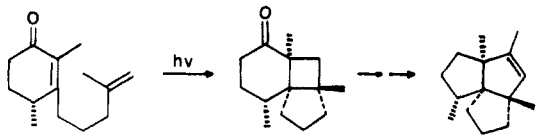
7 8

Background

At the outset of this work there was good reason to believe that the photocycloaddition reaction of enones **1** and **2** would occur in the desired head-to-head (hth) sense rather than to give crossed, head-to-tail (htt) adducts of type **9** or **10**. In the first place, the cycloaddition of **2** in pentane with a medium-pressure Hanovia lamp to give cyclobutane **4** as the sole volatile product in 38% yield is recorded as an unpublished observation by Corey and Sestanj in a review by Dilling.[7] Furthermore, the reaction of substrate **11** gives an 8:1 mixture of cyclobutanes **12**

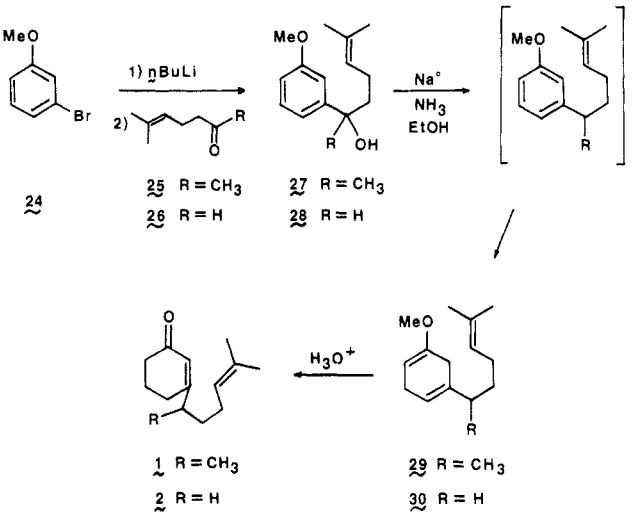


when irradiated at 310 nm although convincing evidence for the regiochemical assignment was not presented.[8] A similar observation was reported by Cargill and co-workers shortly after we began this study. They found that the cycloaddition of cyclohexenones **13** and **14** gave single adducts **15** and **16** whose regionatures were established by chemical correlation.[9] Finally, the photoaddition in enone **17** led exclusively to cyclobutane **18**, an intermediate in

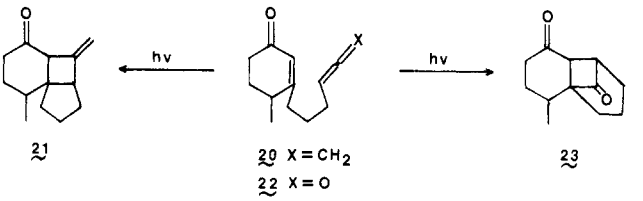


which ring strain was ultimately utilized to drive rearrangement to an isocomene (**19**) carbon skeleton in the Pirrung synthesis of that hydrocarbon.[10]

Scheme I



The previous results mentioned above as well as others[11] strongly suggest that the number of atoms connecting the cyclohexenone β-carbon to the olefinic cycloaddend is a more critical factor in determining the regiochemical outcome of the cycloaddition than is the degree of alkyl substitution on the olefin or enone. However, regiochemistry can be altered in this system if the electronic nature of the olefinic 2π partner is severely perturbed, as seen by the outcome of the intramolecular photoaddition of allene **20** which gave hth adduct **21** vs. ketene **22** which provided the htt adduct **23**.[12]



Results and Discussion

Enones **1** and **2** were prepared as shown in Scheme I by starting with *m*-bromoanisole (**24**).[13] Lithiation of **24** at −78 °C, addition of ketone or aldehyde **25** or **26**,[14] one-pot alcohol hydrogenolysis and Birch reduction of **27** or **28** to the dihydrobenzene **29** or **30** with excess sodium in liquid ammonia,[15] and hydrolysis with concomitant conjugation gave enone **1** or **2** in good overall yield.

(4) For a recent synthesis of a very similar vinyl-substituted spirocycle via coupling of [2 + 2] photocycloaddition and reductive fragmentation of the resultant cyclobutane, see: Oppolzer, W.; Gorrichon, L.; Bird, T. G. C. *Helv. Chim. Acta* **1981**, *64*, 186.

(5) Tomita, B.; Hirose, Y. *Tetrahedron Lett.* **1970**, 143.

(6) Vrkoc, J.; Herout, V.; Sorm, F. *Coll. Czech. Chem. Commun.* **1961**, *26*, 3183.

(7) Dilling, W. L. *Chem. Rev.* **1966**, *66*, 373.

(8) Ramage, R.; Sattar, A. *Tetrahedron Lett.* **1971**, 649.

(9) Cargill, R. L.; Dalton, J. R.; O'Connor, S.; Michels, D. G *Tetrahedron Lett.* **1978**, 4465.

(10) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82.

(11) A general rule appears to be that, in the absence of strong electronic perturbations of the two olefins about to participate in the [2 + 2] cycloaddition (cf. ref 12), if the two internal vinylic carbon atoms are separated by two connecting atoms, then bridged bicyclo[2.1.1] subunits are favored over fused bicyclo[2.2.0] systems (see, e.g.: Hodgson, G. L.; MacSweeney, D. F.; Money, T. *J. Chem. Soc., Chem. Commun.* **1973**, 236. Meinwald, J.; Schneider, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 5218. Bond, F. T.; Ho, C.-Y.; McConnell, O. *J. Org. Chem.* **1976**, *41*, 1416. Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *Ibid.* **1975**, *40*, 2702. Wolff, S.; Ayral-Kaloustian, S.; Agosta, W. C. *Ibid.* **1976**, *41*, 2947. Tamura, Y.; Kita, Y.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1971**, 1167; **1973**, 101; *Tetrahedron Lett.* **1972**, 1977), whereas if the olefins are linked by three intervening atoms, the resulting cyclobutanes tend to be of the fused bicyclo[3.2.0] type rather than of the bridged (crossed) bicyclo[3.1.1] variety. See, e.g.: ref 7–10, 22a. Oppolzer, W.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 1199. *J. Chem. Soc., Chem. Commun.* **1979**, 235. Mellor, M.; Otieno, D. A.; Pattenden, G. *Ibid.*, **1978**, 138.

(12) Becker, D.; Harel, Z.; Birnbaum, D. *J. Chem. Soc., Chem. Commun.* **1975**, 377.

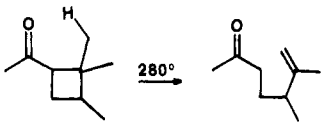
(13) This route was chosen after repeated difficulty in the addition of the appropriate Grignard reagents to 3-ethoxycyclohexenone was encountered.

(14) Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 2095.

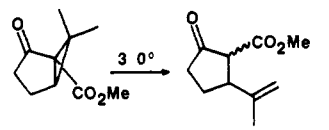
(15) Birch, A. J. *J. Proc. R. Soc. N. S. W.* **1949**, *83*, 245.

Photochemical studies were initiated with enone **2** which lacks any stereocenters. Irradiation was first performed in carbon tetrachloride with 350-nm light in a Rayonet reactor. Clean conversion to a single volatile product (3 H singlets at δ 1.03 and 1.06 and absorption at 1694 cm^{-1}) was observed. Distinction between hth and htt isomers **4** and **10** was made via the classical method of Corey[16] which involved Baeyer–Villiger conversion to a lactone, saponification to a hydroxy acid, Fischer esterification, and Jones oxidation to a cyclobutanone which possessed no absorptions below δ 2.5 in its ^1H NMR spectrum. This indicated that there were no protons on the α-carbons of the cyclobutanone,[17] allowed formulation of structure **34** for this ketone, and proved that the cycloadduct was regioisomer **4** and not **10** since the cyclobutanone **35** derived from **10** has an α-proton (see Scheme II). Compounds **31–33** are therefore the intermediates in this sequence. The cis ring fusion between the six- and four-membered rings in **4** was assigned since only a single isomer was formed in the reaction, and it showed no tendency to isomerize upon silica gel or gas chromatographic purification. Molecular models suggest that the trans-fused isomer of **4** is considerably more strained.

With **4** in hand we examined its thermal chemistry in an attempt to effect retro-ene cleavage. The molecule fragmented at 300 °C (neat liquid) over a period of several hours to a host of volatile products, none of which corresponded (vide infra) to the desired spirocyclic product **6**. This was surprising, as well as disappointing, in light of our analysis of models of **6** which suggested that the carbonyl and *cis*-methyl groups have available to them very similar conformations and proximity as do the same groups in the acyclic ketone **36**, which ring opens at 280 °C to enone **37**.[18] That is to say, the methyl hydrogen in **4** can



36 **37**

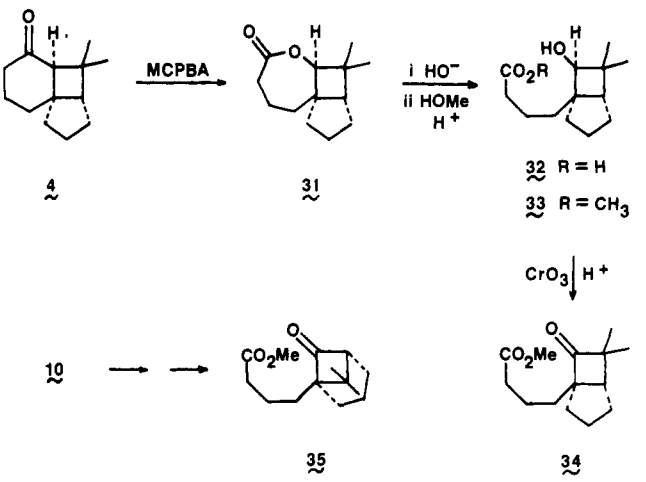


38 **39**

approach the ketone carbonyl either from a perpendicular direction for direct interaction with the carbonyl 2π electrons or through an in-plane mode for initial interaction with the carbonyl nonbonding electrons. This latter possibility was recently suggested as a retro-ene pathway available to the ester but not the ketone carbonyl in the cleavage of cyclopropane **38** at 350 °C to the isopropenyl keto ester **39**.[19]

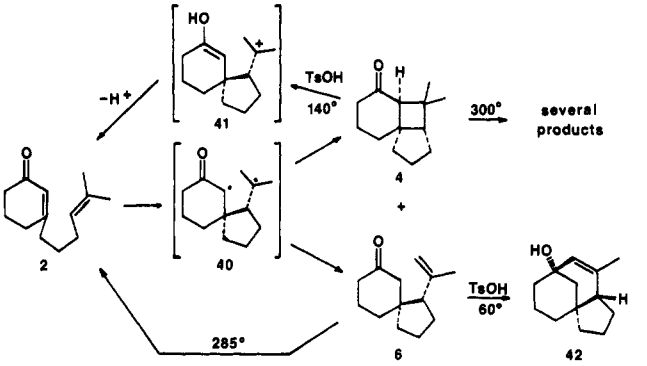
In view of our inability to prepare spirocycle **6** by the sequential [2 + 2]–retro-ene sequence, it was fortunate to discover that on irradiation of **4** in a variety of solvents other than carbon tetrachloride (cyclohexane, CH_2Cl_2, THF, HOAc, $CH_3C{\equiv}N$, CH_3COCH_3) a second volatile product was formed along with cyclobutane **4**. Isolation

Scheme II



4 **31** **10** **35** **34**

Scheme III



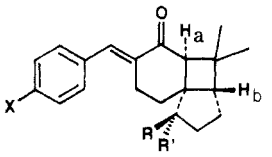
by preparative gas chromatography gave a material identified as spirocycle **6** [^1H NMR δ 4.90 (1 H br s), 4.68 (1 H, br s), 1.73 (3 H, br s); IR 3080, 1700, 1640, 895 cm^{-1}]. The **4** to **6** ratio varied between 4:1 and 2.5:1 in these solvents. Irradiations in cyclohexane at 300 or 254 nm or with a Hanovia medium-pressure mercury lamp, at 100 °C instead of ambient temperature,[20] and of the enone **2** absorbed on a silica gel TLC plate all resulted in **4** to **6** ratios in this same range. We rationalized the formation of these two products from the common diradical precursor **40** (see Scheme III) but were unable to greatly influence the relative ease of competitive reactions of **40** by the solvent, temperature, and wavelength changes cited above. In no case was the formal photo-ene adduct, **6**, observed as the major photoproduct.

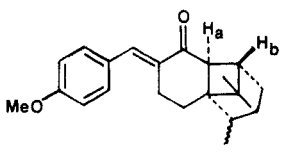
Pyrolysis of **6** at 285 °C (neat liquid) effected its conversion back to the thermodynamically favored starting enone **2** by an alternative retro-ene process involving the ketone α-hydrogen. This result ruled out the possibility for transforming **4** into **6** by a purely thermal retro-ene process since **4** was stable to the conditions required to convert **6** to **2**. Therefore, an acid-catalyzed fragmentation of **4** was attempted. At 140 °C in toluene solution containing a trace of *p*-toluenesulfonic acid, **4** slowly but cleanly reverted to enone **2** presumably through the enolic cation **41**. This intermediate must collapse directly to **2** with proton loss rather than first tautomerize and then lose a proton since no trace of **6** was observed, which is reactive via other pathways under much milder conditions. Spe-

(16) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.
(17) Protons on α-carbons of cyclobutanone itself resonate at δ 3.13 in $CDCl_3$.
(18) Conia, J. M.; Leyendecker, F. *Bull. Soc. Chim. Fr.* **1967**, 830.
(19) Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148.
(20) For a study of temperature effects on the fate of photochemically generated triplet diradical species capable of closure to cyclobutanes or hydrogen atom transfer to give olefins, see: Wolff, S.; Barany, F.; Agosta, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2378.

cifically, treatment of **6** under the same acidic conditions but at 60 °C led to several new products, the major of which was isolated and shown to be the tertiary alcohol **42**. This result lends support to the stereochemistry assigned to the spirocycle **6**.

With these preliminary results in hand, we turned our attention to the photochemistry of the methyl-substituted enone **1**. Irradiation of **1** in cyclohexane as with enone **2** gave a product mixture of, in this case, four major volatile products, I–IV (2:1:1:1 ratio estimated from GC). Products I and II were isolated by MPLC on silica gel and gave NMR spectra which were consistent with the methyl epimers **3a** and **3b** although the regioisomeric epimers **9a** and **9b** could not be excluded. Products III and IV coeluted on SiO_2, but preparative GC separation gave pure III and a mixture enriched in IV. Each of these materials contained an isopropenyl unit and they were assigned structures **5b** and **5a**. It was at this juncture that we learned of the results of Fetizon,[21] who investigated the irradiation of **1** in methylene chloride at −77 °C. In that study no primary photoproducts were isolated, the crude product ketones were derivatized as *p*-anisylidene derivatives, and the major two were isolated. The structure of the major crystalline adduct (70% from **1**) was determined by single-crystal X-ray diffraction analysis and shown to be **43a**.





43a X=OCH_3, R=CH_3, R'=H

43b X=OCH_3, R=H, R'=CH_3

43c X=Br, R=H, R'=CH_3

44

The oily minor product (15% from **1**) was assigned the regioisomeric structure **44** primarily on the basis of a 1-Hz coupling constant between H_a and H_b. Indeed, product II from our irradiation also exhibited a 1-Hz coupling for the methine proton α to the ketone. However, the same proton is a broadened singlet in the ^1H NMR spectra of product I and compound **43a**, which suggests that long-range coupling is feasible in the hth adducts. We derivatized I to give **43a** and II to give the oily compound whose spectral properties matched those from the material assigned structure **44** by Fetizon. The implications of the Fetizon result—that the allylic methyl group led to formation of a single epimer of the hth adduct (i.e., **3a**) and a single epimer of the htt adduct (i.e., **9a** or **9b**)—were significant. However, that result was suspect in view of our prior knowledge that the unmethylated enone **2** gave only the single regiomeric cyclobutane **4**. To clarify this matter, we converted II to its crystalline *p*-bromobenzylidene derivative and performed a singel-crystal X-ray structure determination which showed it to be compound **43c**. Therefore, product II has structure **3b**, and the minor Fetizon derivative has structure **43b** and not **44**. The observed 1-Hz coupling in compounds **3b**, **43b**,[21] and **43c** is thus attributed to long-range interactions between the trans protons H_a and H_b on the cyclobutane ring of each.[22]

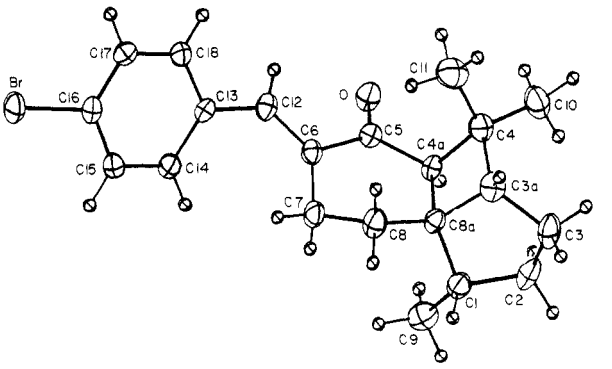
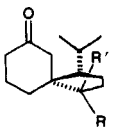


Figure 1. ORTEP drawing of **43c**.

An ORTEP drawing of **43c** is shown in Figure 1. Table I lists selected bond distances and angles. It is worth noting the distortion of bond angles C_{8a}–C_1–C_9 = 117° and C_2–C_1–C_9 = 114° in the endo adduct **43c** relative to those values (114° and 110°, respectively) in the exo adduct **43a**.[21] This reflects a minimization of through-space steric interactions of the *endo*-methyl group. It is also of interest to note a characteristic spectroscopic difference that was observed for compounds **3b**, and **43b**, and **43c** (endo series) vs. **3a** and **43a** (exo series): namely, the C_1-methyl group gave rise to a very broad doublet in the former series in contrast to a more typical sharp doublet in the latter pair of compounds. It is likely that this is due to virtual coupling of the *endo*-C_1-methyl to one of the C_2 protons via H_1.

In contrast to the lack of temperature effect in the partitioning of diradical intermediates between pathways leading to cyclobutane vs. isopropenyl-containing products, the ratio of epimers **3a** to **3b** (i.e., I to II) changed from 2:1 in cyclohexane at room temperature to 5:1 in frozen cyclohexane at −70 °C (cf. ultimate 5:1 ratio of **43a**/**43b** in CH_2Cl_2 at −77 °C in the Fetizon[21] work).[23] However, the ratios of (**3a** + **3b**) to (**5a** + **5b**) again remained constant at ~2:1 over this temperature range. Moreover, in a series of control experiments designed to demonstrate that the spirocyclic compounds were primary photoadducts rather than secondary products resulting from Norrish type II cleavage of the cyclobutanes, purified **3a** or **3b** was irradiated (350 nm or 450-W Hanovia/Pyrex) in cyclohexane (ambient temperature or methylene chloride (−10 to 0 °C and ambient temperature). Little (<5%, GC/internal standard) fragmentation to **5a** or **5b** was observed under the conditions of the original irradiation of enone **1**. Extending the time of irradiation led to substantial decomposition to nonvolatile products, slightly more (<10%, isolated) **5a** or **5b**, and traces of other unidentified volatile byproducts.[24]

Finally, the isopropenyl compound **5b** was hydrogenated over Rh/Al_2O_3 to give a dihydro compound, assigned structure **45** since it was not identical with the epimer **46**,



45 R=CH_3 R'=H

46 R=H R'=CH_3

(21) Fetizon, M.; Lazare, S.; Pascard, C.; Prange, T. *J. Chem. Soc., Perkin Trans 1*, **1979**, 1407.

(22) For examples of long range coupling in cyclobutane systems, see: (a) Haywood, D. J.; Reid, S. T. *Tetrahedron Lett.* **1979**, 2637. (b) Georgian, V.; Georgian, L.; Robertson, A. V. *Tetrahedron* **1963**, *19*, 1219. (c) Wiberg, K. B.; Barth, D. E. *J. Am. Chem. Soc.* **1969**, *91*, 5124.

(23) For recent examples of diastereospecificity induced by allylic and benzylic methyl substituents in the photochemical construction of the isocomene, precapnellene, and cedrene skeletons see: Reference 10. Birch, A. M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1980**, 1195. Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688.

(24) Professor Fetizon has informed us of his observation that extended irradiation of enone **1** (36 h, 0–5 °C) gave a reaction mixture from which **5a** was isolated in 55% yield.

Table I. Bond Distances and Selected Angles from the X-ray Structure of 43c Relative to Those of 43a[21]

	distances, Å			angles, deg	
atoms	43c	43a[21]	atoms	43c	43a[21]
C1-C2	1.528 (7)	1.551	C2-C1-C8a	103.8 (4)	102.4
C1-C8a	1.521 (6)	1.520	C2-C1-C9	114.1 (4)	109.6
C1-C9	1.519 (7)	1.510	C8a-C1-C9	117.4 (4)	113.9
C2-C3	1.500 (7)	1.524	C1-C2-C3	103.6 (4)	104.3
C3-C3a	1.528 (7)	1.531	C2-C3-C3a	105.7 (4)	105.7
C3a-C4	1.549 (7)	1.549	C3-C3a-C4	118.9 (4)	119.3
C3a-C8a	1.549 (6)	1.570	C3-C3a-C8a	105.2 (4)	105.1
C4-C10	1.525 (6)	1.516	C8a-C3a-C4	90.8 (4)	90.1
C4-C11	1.503 (7)	1.541	C3a-C4-C4a	88.4 (4)	88.9
C4-C4a	1.569 (6)	1.568	C3a-C4-C10	117.8 (4)	112.8
C4a-C5	1.500 (6)	1.505	C3a-C4-C11	111.8 (4)	
C4a-C8a	1.554 (6)	1.557	C4a-C4-C10	115.4 (4)	
C5-O	1.222 (5)	1.217	C4a-C4-C11	113.6 (4)	113.9
C5-C6	1.516 (6)	1.509	C10-C4-C11	108.8 (5)	108.2
C6-C7	1.497 (6)	1.508	C4-C4a-C5	117.1 (4)	119.6
C6-C12	1.338 (6)	1.346	C4-C4a-C8a	89.9 (3)	89.9
C7-C8	1.510 (6)	1.529	C5-C4a-C8a	121.6 (4)	120.5
C8-C8a	1.537 (6)	1.532	C4a-C5-C6	118.5 (4)	117.9
C12-C13	1.492 (5)	1.465	C4a-C5-O	121.0 (4)	120.1
C13-C14	1.394 (6)	1.387	C6-C5-O	120.5 (4)	121.9
C13-C18	1.381 (6)	1.396	C5-C6-C7	115.5 (4)	117.7
C14-C15	1.376 (6)	1.389	C5-C6-C12	115.4 (4)	125.2
C16-Br	1.900 (4)		C7-C6-C12	129.1 (4)	117.1
C16-C17	1.394 (6)		C6-C7-C8	112.8 (4)	111.1
C17-C18	1.381 (6)	1.378	C7-C8-C8a	114.0 (4)	109.6
			C1-C8a-C3a	106.1 (4)	107.4
			C1-C8a-C4a	114.7 (4)	
			C1-C8a-C8	115.3 (4)	116.6
			C3a-C8a-C4a	88.9 (4)	88.6
			C3a-C8a-C8	116.3 (4)	
			C4a-C8a-C8	112.6 (4)	109.6

an intermediate in the Oppolzer synthesis of acorenone (8).[25] Similar reduction of the inseparable mixture of **5b** and **5a** gave a mixture (again homogeneous to HPLC and GC) of **45** and **46** in which the presence of the latter was detected by the chemical shifts of methyl doublets at δ 0.90, 0.94, and 1.00.

Experimental Section

General Methods. Melting points were determined on a Kofler hot-stage and are uncorrected. Elemental analyses were performed by M-H-W Laboratories. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer, proton magnetic resonance spectra were obtained on Varian HFT-80 or Bruker 270 MHz instruments in the Fourier transform mode, and mass spectra were determined on AEI MS-30 (electron impact, EI) and Finnigan 4000 (chemical ionization, CI) instruments. Medium-pressure chromatography was performed on EM Lobar columns packed with LiChroprep Si60 (40–63 μm).

Preparation of Enones 1 and 2. *n*-Butyllithium (43 mL, 2.5 M solution in hexane, 0.1 mol) was added over a period of 20 min to a solution of *m*-bromoanisole (18.7 g, 0.1 mol) in 250 mL of dry THF at −70 °C under nitrogen. A white precipitate was formed, the slurry was stirred for 45 min, and neat 6-methylhept-5-en-2-one (15.8 mL, 13.5 g, 0.107 mol) was added over 10 min, during which time the precipitate disappeared. The solution was allowed to warm to room temperature, quenched with water, and extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$), concentrated, and distilled [bp 118 °C, (0.5 mmHg)] to give (±)-2-(3-methoxyphenyl)-6-methylhept-5-en-2-ol (**27**): 16.6 g (0.071 mol, 71%): ^1H NMR ($CDCl_3$) δ 1.50 (6 H, br s), 1.65 (3 H, br s), 3.75 (3 H, s), 5.02 (1 H, br t), 6.5–7.3 (5 H, m). Attempted purification by preparative gas chromatography (SE-30, 170 °C) resulted in partial dehydration. This alcohol (16.6 g) was dissolved in 450 mL of liquid NH_3 and 120 mL of absolute EtOH. Over the course of 3 h sodium (16.9 g, 0.73 mol) was added to the refluxing solution which was then allowed to warm to room temperature. Water was added, and the mixture was extracted with Et_2O. The organic layers were washed with brine, dried, and concentrated to leave the crude triene **29**: 11.3 g; ^1H NMR ($CDCl_3$) δ 1.01 (3 H, d, J = 7 Hz), 1.55 (3 H, br s), 1.63 (3 H, br s), 2.62 (4 H, m), 3.50 (3 H, s), 4.55 (1 H, br s), 5.02 (1 H, br t), 5.35 (1 H, br s). This enol ether (4.2 g) was dissolved in 50 mL of THF containing 5 mL of 5% aqueous H_2SO_4 and refluxed for 2 h. Dilution with water, extraction with Et_2O, washing of the organic layer with water (twice), and brine, drying ($NaSO_4$), concentration, and distillation gave a forerun of nonconjugated enone (0.33 g) and (±)-3-(1,5-dimethylhex-4-enyl)cyclohex-2-enone (**1**): bp 100 °C (0.3 mmHg); 2.4 g (11.6 mmol, 44% from **27**); ^1H NMR ($CDCl_3$) δ 1.04 (3 H, d, J = 7 Hz), 1.54 (3 H, br s), 1.64 (3 H, br s), 5.01 (1 H, br t), 5.87 (1 H, br s); IR (neat) 3020, 1670, 1620, 885 cm^{-1}; mass spectrum (EI), m/e 206, 191, 178, 163, 150, 148, 138, 137, 124, 95, 82, 67, 55, 41; UV (cyclohexane) λ_{max} 370 nm (ε 15), 352 (27), 338 (38), 325 (37), 228 (1.25×10^4). Anal. Calcd: C, 81.50; H, 10.75. Found: C, 81.44; H, 10.93.

By the same procedure just described, *m*-methoxyphenyllithium was reacted with 5-methylhex-4-enal[14] to give (±)-1-(3-methoxyphenyl)hex-4-en-1-ol (**28**, 63%) and 3-(5-methylhex-4-enyl)-cyclohex-2-enone (**2**; chromatographed on SiO_2, 9:1 hexanes–EtOAc): 71% (from **28**); ^1H NMR ($CDCl_3$) δ 1.53 (3 H, br s), 1.64 (3 H, br s), 5.02 (1 H, br t), 5.89 (1 H, br s); IR (neat) 3040, 1675, 1630, 895 cm^{-1}; mass spectrum (EI), m/e 192, 177, 164, 149, 136, 113, 110, 82, 62, 55, 41; UV (cyclohexane) λ_{max} 368 (ε 9), 351 (25), 338 (36), 325 (39), 313 (38), 228 (2.75×10^4). Anal. Calcd: C, 81.20; H, 10.48. Found: C, 81.14; H, 10.68.

Irradiation of 2. Enone **2** (1.22 g) was dissolved in 150 mL of cyclohexane in a cylindrical Pyrex vessel (2 × 20 cm), and nitrogen was bubbled through the solution for 10 min. Ths mixture was irradiated in a Rayonet reactor with eight 350-nm lamps for 6.5 h. GC analysis showed complete consumption of **2**. Concentration and chromatography (SiO_2, 9:1 hexanes–EtOAc) gave a 3:1 mixture of (±)-(3aα,4aβ,8aS*)-octahydro-4,4-dimethylcyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (**4**) and (±)-(1*R**,7*R**)-7-(1-methylethenyl)spiro[5.4]decan-3-one (**6**), 942 mg (77%). Separation by preparative GC (10% FFAP, 200 °C) or careful SiO_2 chromatography (97:3 hexanes–EtOAc) gave pure **4**: ^1H NMR ($CDCl_3$) δ 1.03 (3 H, s), 1.05 (3 H, s), 1.4–2.0 (11 H,

(25) Oppolzer, W. L.; Mahalanabis, K. K.; Bättig, K. *Helv. Chim. Acta* **1977**, *60*, 2388.

m), 2.17 (1 H, br s), 2.23 (2 H, br t); ^{13}C NMR ($CDCl_3$) δ 21.1 (t), 24.8 (q), 26.6 (t), 27.3 (q), 27.9 (t), 34.3 (t), 36.6 (s), 40.1 (t), 40.8 (t), 44.8 (s), 51.8 (d), 57.2 (d), 178.1 (s); IR (CCl_4) 1695, 1470, 1475, 1405, 1380, 1365, 1160; mass spectrum (EI), *m/e* 192, 177, 164, 149, 136, 123, 110, 82, 57, 41; UV (cyclohexane) λ_{max} 335 nm (ε 9), 323 (19), 312 (27), 302 (28), 293 (25), 284 (21). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.14; H, 10.15. Compound and **6** was also obtained: ^1H NMR ($CDCl_3$) δ 1.78 (3 H, br s), 1.3–2.0 (10 H, m), 2.0–2.4 (5 H, m), 4.71 (1 H, br s), 4.92 (1 H, br s); IR ($CHCl_3$) 3080, 1700, 1640, 895 cm^{-1}; UV (cyclohexane) λ_{max} 305 (ε 17), 296 (22), 288 (22); mass spectrum (EI), *m/e* 192, 177, 174, 149, 136, 123, 110, 67, 55, 41. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.96; H, 10.20.

(±)-(1α,3β,9*S)-2,2-Dimethyl-4-oxatricyclo[7.3.0.0^{3,9}]dodecan-5-one (31).** Ketone **4** (275 mg, 1.4 mmol) was treated with *m*-chloroperbenzoic acid (85%, 329 mg, 1.6 mmol) in CH_2Cl_2 at room temperature for 2 days. The organic layer was washed with 1 N NaOH solution (twice), water, and brine, dried ($MgSO_4$), filtered, and concentrated to leave 289 mg of light yellow oil which was used in further reactions. A sample was purified by preparative gas chromatography (SE-30, 170 °C): ^1H NMR ($CDCl_3$) δ 0.95 (3 H, s), 1.19 (3 H, s), 1.3–2.1 (11 H, m), 2.2–2.45 (2 H, m), 3.90 (1 H, br s); IR (CCl_4) 1740, 1450, 1385, 1340, 1220, 1210, 1135, 1070 cm^{-1}; mass spectrum (CI, NH_3), *m/e* 226 (positive ion, M + NH_4^+), 209 (M + H^+), 207 (negative ion, M − H^+). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.21; H, 9.88.

(±)-[1α(*R),5α]-Methyl 6,6-Dimethyl-7-oxobicyclo[3.2.0]heptane-1-butanoate (34).** The oily lactone **31** described above (76 mg, 0.363 mmol) was dissolved in 1 mL of absolute MeOH, and 5% NaOH solution (150 μL) was added under nitrogen. After 15 h the mixture was acidified with 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to leave the acid **32** as a crude oil [101 mg; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, s), 1.08 (3 H, s), 2.38 (2 H, br t, *J* = 6 Hz), 3.49 (1 H, s), 4.5 (2 H, br s)] which was immediately dissolved in 1.5 mL of absolute MeOH and treated with camphorsulfonic acid (10 mg). After 18 h this mixture was partitioned between saturated $NaHCO_3$ and CH_2Cl_2, and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the crude ester **33**: 66 mg; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, s), 1.09 (3 H, s), 2.34 (2 H, br t, *J* = 7 Hz), 3.47 (1 H, s), 3.65 (3 H, s). This material (29 mg) was dissolved in 0.5 mL of acetone and treated with Jones reagent (80 μL of a solution of 7.0 g of CrO_3 in 30 mL of H_2O and 6.1 mL of concentrated H_2SO_4) at 0 °C and then room temperature for 3 h. Sodium bisulfite was added to consume excess brown color, water was added, and the mixture was extracted with low-boiling petroleum ether. The organic layer was washed with brine, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated to give crude cyclobutanone **34** (57% crude yield from ketone **4**). A portion of this was purified by preparative gas chromatography (SE-30, 165 °C): ^1H NMR ($CDCl_3$) δ 0.96 (3 H, s), 1.29 (3 H, s), 1.5–2.1 (12 H, m), 2.35 (2 H, br t, *J* = 6 Hz), 3.66 (3 H, s); IR (CCl_4) 1775, 1740, 1380, 1355, 1165 cm^{-1}; mass spectrum (CI, NH_3), *m/e* 256 (positive ion, M + NH_4^+), 239 (M + H^+), 237 (negative ion, M − H^+). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.54; H, 9.48.

(±)-(1*R,4*S**,8*R**)-3-Methyltricyclo[6.3.1.0^{4,8}]undec-2-en-1-ol (42).** Spirocyclic ketone **6** (9 mg) was dissolved in 1 mL of dry toluene. *p*-Toluenesulfonic acid (2 mg) was added, and the mixture was heated at 60 °C for 20 min. Saturated $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The usual workup left 7.5 mg of a pale yellow oil which was purified by preparative GC (SE-30, 150 °C) to give alcohol **42**: ^1H NMR ($CDCl_3$) δ 1.2–1.8 (14 H, m), 1.70 (3 H, d, *J* = 1.5 Hz), 2.10 (1 H, m), 5.15 (1 H, q, *J* = 1.5 Hz): IR (CCl_4) 3600, 1655, 1445, 1370, 1030 cm^{-1}; mass spectrum (CI, NH_3), *m/e* 192 (positive ion, M + NH_4^+ − H_2O), 191 (negative ion, M − H^+).

Irradiation of Enone 1. Under the same conditions described above for the irradiation of **2**, enone **1** was converted in 4 h to a mixture of **3a,b** and **5a,b** (~2:1:1:1 ratio by GC). Chromatography (SiO_2, 9:1 hexane–EtOAc) gave a 52% yield of this mixture. Careful chromatography (SiO_2, 2% EtOAc in hexanes) gave fractions from which, with the aid of further preparative gas chromatography (5% SE-30, 136 °C), compounds **3b**, **5b**, and **3a** (order of MPLC elution) were isolated. A sample of a mixture of **5a** and **5b** was also obtained. (±)-(1α,3aβ,4aα,8a*S**)-Octahydro-1,4,4-trimethylcyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (**3b**): ^1H NMR ($CDCl_3$) δ 0.88 (3 H, br d, *J* = 6 Hz), 1.02 (3 H, s), 1.06 (3 H, s), 1.3–2.3 (12 H, m), 2.30 (1 H, d, *J* = 1 Hz); IR (CCl_4) 1690, 1455, 1150 cm^{-1}; mass spectrum (CI, NH_3), *m/e* 224 (positive ion, M + NH_4^+), 207 (M + H^+), 205 (negative ion, M − H^+). Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.68; H, 10.81. (±)-(1*R**,7*R**,10*R**)-10-Methyl-7-(1-methylethenyl)spiro[5.4]decan-3-one (**5b**): ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, *J* = 7 Hz), 1.75 (3 H, br s), 1.3–2.5 (14 H, m), 4.66 (1 H, br s), 4.91 (1 H, br s); IR (CCl_4) 3080, 1710, 1640, 1450, 1255, 895 cm^{-1}; mass spectrum, (EI), *m/e* (relative intensity) 206 (16), 191 (20), 169 (100); exact mass calcd for $C_{14}H_{22}O$ 206.1669, found 206.1671. (±)-(1α,3aα,4aβ,8a*S**)-Octahydro-1,4,4-trimethylcyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (**3a**): ^1H NMR ($CDCl_3$) δ 0.84 (3 H, d, *J* = 7 Hz), 1.04 (3 H, s), 1.08 (3 H, s), 1.5–2.1 (m, 10 H), 2.18 (1 H, br s), 2.1–2.3 (m, 2 H); IR (CCl_4) 1690, 1455, 1160 cm^{-1}; mass spectrum, (CI, NH_3), *m/e* 224 (positive ion, M + NH_4^+), 207 (M + H^+), 205 (negative ion, M − H^+). Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.30; H, 10.73. Since only a 1:1 mixture of **5a** and **5b** was obtained, the ^1H NMR ($CDCl_3$) data for **5a** is obtained from subtraction of the peaks of **5b** from the spectrum of this mixture: δ 0.90 (3 H, d, *J* = 7 Hz), 1.75 (3 H, br s), 4.75 (1 H, br s), 4.85 (1 H, br s).

(±)-(1*R,7*R**,10*R**)-10-Methyl-7-(2-propyl)spiro[5.4]decan-3-one (45).** Olefin **5b** (from preparative GC, ~4 mg) was dissolved in EtOAc (1 mL) and exposed to 1 atm of H_2 in the presence of 5% Rh/Al_2O_3 (3 mg). After 16 h the catalyst was removed by filtration through Celite, and the solvent was evaporated to leave the reduced compound **45** (~4 mg) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d, *J* = 7 Hz), 0.86 (3 H, d, *J* = 7 Hz), 0.98 (3 H, d, *J* = 7 Hz), 1.2–2.0 (11 H, m), 2.1–2.4 (4 H, m); IR (CCl_4) 2960, 2880, 1715, 1460, 1425, 1380, 1375, 1315, 1275, 1225 cm^{-1}.

(±)-(1α,3aβ,4aα,6*E*,8a*S)-Octahydro-6-[(4-bromophenyl)methylene]-1,4,4-trimethylcyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (43c).** *p*-Bromobenzaldehyde (40.1 mg, 0.216 mmol) and ketone **3b** (28.0 mg, 0.131 mmol) were dissolved in 800 μL of absolute methanol and treated with 80 μL of 20% aqueous sodium hydroxide solution under N_2 at room temperature. After 12 h the mixture was partitioned between water and CH_2Cl_2. The dried organic layer was concentrated to leave a crude yellow solid (55.6 mg, greater than quantitative recovery) which was recrystallized by allowing a methanol solution to partially evaporate at room temperature over several days. One of these pale yellow crystals (mp 113–115.5 °C) was subjected to single-crystal X-ray analysis: ^1H NMR ($CDCl_3$) δ 0.93 (3 H, v br d, *J* = 5 Hz), 1.09 (6 H, s), 1.4–1.9 (7 H, m), 2.15 (1 H, br d, *J* = 6 Hz), 2.50 (1 H, d, *J* = 1 Hz), 2.89 (2 H, m), 7.24 (2 H, d, *J* = 8 Hz), 7.49 (1 H, br, s), 7.50 (2 H, d, *J* = 8 Hz); IR (CCl_4) 1675, 1600, 1490, 1460, 1455, 1250, 1165, 1075, 1010, 830 cm^{-1}; mass spectrum (CI, NH_3), *m/e* 394/392, (positive ion, M + NH_4^+), 377/375 (M + H^+), 314 (M + NH_4^+ − HBr), 297 (M + H^+ − HBr), 375/373 (negative ion, M − H^+), 293 (M − H^+ − HBr).

X-ray Analysis of 43c. The crystal is monoclinic: *a* = 7.218 (3) Å, *b* = 16.904 (2) Å, *c* = 15.118 (3) Å, β = 100.89 (2)°. There are four molecules of $C_{21}H_{25}BrO$ (FW 373.34)/unit cell; *d*(calcd) = 1.369 g cm^{-3}. Systematic extinctions (0*k*0, *k* = 2*n* + 1; *h*0*l*, *h* + *l* = 2*n* + 1) require the space group to be $P2_1/n$ (No. 14). A total of 3832 independent reflections with θ < 26° were measured of which the 1584 reflections with $I > 2.5\sigma(I)$ were used in the calculations.[26] Mo Kα radiation (λ = 0.7107 Å) was used; no correction for absorption was made (μ = 24.3 cm^{-1}). Data were collected by using a ω–2θ scan with stationary background counts of one quarter of the scan time at each end of the scan. A trial structure was determined from Patterson and Fourier maps and refined by using least-squares methods with anisotropic thermal parameters for the nonhydrogen atoms. The hydrogen atoms were included at their idealized positions with isotropic thermal pa-

(26) All calculations were carried out on PDP 8 A and 11/34 computers using the Enraf-Nonius CAD 4-SDP programs. This crystallographic computing package is described by: Frenz, B. A. In "Computing in Crystallography"; Schenck, H., Olthof-Hazekamp, R., van Konigsveld, H., Bassie, G. S., Eds.; Delft University Press: Delft, Holland, 1978; pp 64–71. "CAD 4 and SDP Users Manual"; Enraf-Nonius: Delft, Holland, 1978.

rameters one unit larger than the isotropic equivalent of that atom to which they are bound. Refinement converged at a conventional R factor of 0.042. A final difference Fourier map showed no peaks higher than 0.25 e/Å^3.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for their support of this work. National Science Foundation Grants CHE 77-28505 and CHE 76-05167 aided in the purchase of the Enraf-Nonius X-ray diffractometer and Varian NMR spectrometer, respectively. We thank Professors L. Pignolet and D. Britton and Mr. M. McGuiggan for assistance in the X-ray study and Professor W. Oppolzer for providing copies of spectral data for compound **46**.

Registry No. (±)-**1**, 72055-87-9; **2**, 79449-50-6; (±)-**3a**, 79449-51-7; (±)-**3b**, 79516-65-7; (±)-**4**, 79449-52-8; (±)-**5a**, 79449-53-9; (±)-**5b**, 79516-66-8; (±)-**6**, 79449-54-0; (±)-**27**, 79449-55-1; (±)-**28**, 79449-56-2; (±)-**29**, 79449-57-3; (±)-**31**, 79449-58-4; (±)-**32**, 79449-59-5; (±)-**33**, 79449-60-8; (±)-**34**, 79449-61-9; (±)-**42**, 79449-62-0; (±)-**43c**, 79449-63-1; (±)-**45**, 56326-39-7; 6-methylhept-5-en-2-one, 110-93-0; *m*-bromoanisole, 2398-37-0; *m*-methoxyphenyllithium, 31600-88-1; 5-methylhex-4-enal, 764-32-9; *p*-bromobenzaldehyde, 1122-91-4.

Supplementary Material Available: Numbering scheme and lists of final atomic positional parameters, atomic thermal parameters, and bond distances and angles (17 pages). Ordering information is given on any current masthead page.

New Approaches to the Synthesis of Vitamin D Metabolites. 1. Stereocontrol in the Intramolecular Diels–Alder Reaction

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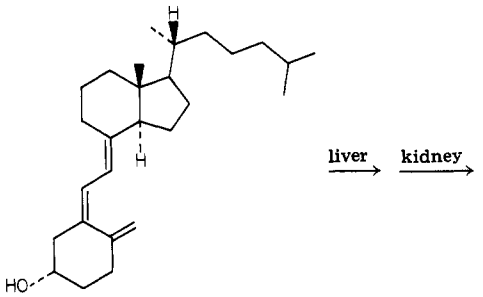
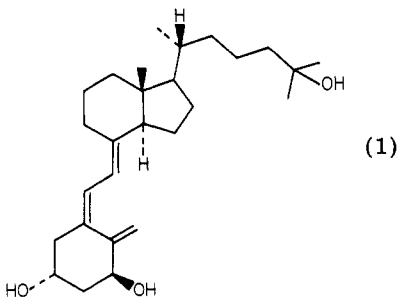
Received July 24, 1981

A short sequence which couples the Ireland–Claisen rearrangement with the intramolecular Diels–Alder reaction gives a 1:1 mixture of hydrindenes **3** and **13**. Hydrindenes **3** are known intermediates in the total synthesis of vitamin D derivatives.

Although cholecalciferol (vitamin D_3, **1**) was regarded as the active antirachitic hormone for many years, modern biochemical techniques have made it possible to trace the metabolism of D_3 through 25-hydroxycholecalciferol to 1α,25-dihydroxycholecalciferol (**2**, 1α,25-$(OH)_2D_3$), now believed to be the active compound[1] (eq 1). The role of



1 (D_3)



(1)

2 (1α, 25-$(OH)_2D_3$)

1α,25-$(OH)_2D_3$ as a hormone is complex and not totally understood; its main involvement appears to be in the regulation of bone formation and calcium availability. An inability to metabolize D_3 (**1**) to 1α,25-$(OH)_2D_3$ (**2**) results in the vitamin D deficiency diseases.

Because of the obvious importance of the vitamins D and their metabolites, particularly 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$), in the treatment and prophylaxis of bone disease, a number of groups have turned their attention to the chemical synthesis of these compounds.[2] In 1959, Inhoffen isolated vitamin D_3 from the photolysis of 5,7-cholestadienol;[3] since that time numerous syntheses of related compounds have been based on this key photochemical ring opening.[4,5]

Approaches to the total synthesis of the vitamins D from nonsteroidal precursors are rare. The extensive work of

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(1) Recent reviews on the vitamin D metabolites and their functions: (a) H. F. DeLuca, H. E. Paaren, and H. K. Schnoes, *Top. Curr. Chem.*, **83**, 3–65 (1979); (b) H. F. DeLuca, *Monogr. Endocrinol.*, **13**, (1979); (c) H. F. DeLuca, in "Trace Metals in Health and Disease", N. Kharasch, Ed., Raven Press, New York, 1979, pp 189–215.

(2) (a) P. A. Bell, in "Vitamin D", D. E. M. Lawson, Ed., Academic Press: New York, 1978; (b) P. E. Georghiou, *Chem. Soc. Rev.*, **6**, 83 (1977).

(3) H. H. Inhoffen, *Angew. Chem.*, **72**, 875 (1959).

(4) For example, the vitamin D_3 metabolite 25(*S*),26-dihydroxycholecalciferol was recently prepared from dehydroepiandrosterone; see J. J. Partridge, S.-J. Shiuey, N. K. Chadha, E. G. Baggiolini, J. F. Blount, and M. Uskokovic, *J. Am. Chem. Soc.*, **103**, 1253 (1981). For the synthesis of 24(*R*),25- and 24(*S*),25-dihydroxycholecalciferol, see J. J. Partridge, V. Toome, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **98**, 3739 (1976). See also: E. Baggiolini, J. J. Partridge, M. R. Uskokovic, U.S. Patent 4 021 423 (1977); *Chem. Abstr.*, **87**, 102541 (1977); E. Baggiolini, J. J. Partridge, and M. R. Uskokovic, U. S. Patent 4 026 882; *Chem. Abstr.*, **87**, 118020 (1977).

(5) Methods for functionalizing the steroid or hydrindane side chain[5a,b] and for attaching a side-chain synthon to the steroid nucleus with correct stereochemistry at C-20[5c-j] have appeared recently: (a) N. C. Deno and M. D. Meyer, *J. Org. Chem.*, **44**, 3383 (1979); (b) Z. Cohen, E. Berman, and Y. Mazur, *ibid.*, **44**, 3077 (1979); (c) J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, **102**, 7382 (1980); (d) B. M. Trost and R. Verhoeven, *ibid.*, **100**, 3435 (1978); (e) A. D. Batcho, D. E. Berger, M. R. Uskokovic, and B. Snider, *ibid.*, **103**, 1293 (1981); (f) W. G. Dauben and T. Brookhart, *ibid.*, **103**, 237 (1981); (g) J. Wicha and K. Bal, *J. Chem. Soc., Perkin Trans. 1*, 1282 (1978); 1405 (1980); (h) M. Koreeda, Y. Tanaka, and A. Schwartz, *J. Org. Chem.*, **45**, 1172, (1980). (i) N. Tanabe and K. Hayashi, *J. Am. Chem. Soc.*, **102**, 862 (1980). (j) J. P. Marino and H. Abe, *ibid.*, **103**, 2907 (1981).

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