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(41) We are presently investigating the rate of substitution of $W(CO)_4$(NBD) with phosphines and phosphites and have observed that these reactions proceed via a chelate ring-opening mechanism with a limiting rate being observed at high phosphine concentrations. These rate data clearly indicate that the rate of ring opening is somewhat faster than intramolecular CO interchange. Therefore, ring opening and closing can take place without concomitant axial–equatorial CO exchange necessarily occurring, i.e., the barrier to ring closure for the intermediate is slightly less than the barrier to Berry rearrangement which involves olefin rotation; D. J. Darensbourg and B. Roop, unpublished results.
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An Easy Access to *exo*-Brevicomin[1]

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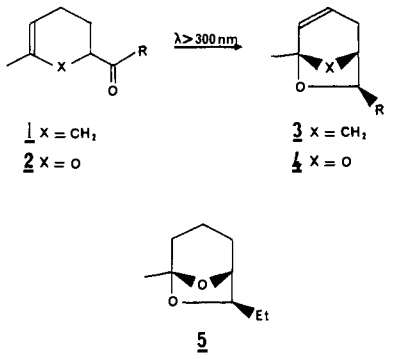
Abstract: Selective irradiation (or singlet sensitization and triplet quenching) of the carbonyl group of 2-propionyl-6-methyl-2,3-dihydro-4*H*-pyran gives stereoselectively the exo isomer of $\Delta^{2,3}$-dehydrobrevicomin. Catalytical hydrogenation of the latter leads to *exo*-brevicomin, the principal component of the sex attractant of *Dendroctonus brevicomis*.

2,3-Dihydro-4*H*-pyrans have been shown to undergo the *retro*-Diels-Alder reaction as well as ring contraction leading to cyclobutanes when irradiated in the absorption band of the double bond.[2,3]

On the other hand, selective irradiation[4] of the carbonyl group of 4-acylcyclohex-1-ene,[5] or of 2-acyl-2,3-dihydro-4*H*-pyrans,[3] induces the creation of a bond between the oxygen atom of the carbonyl group and the C(6) carbon atom of the

double bond, together with the migration of one hydrogen atom from C(4) to the carbon atom of the carbonyl group (Scheme I). Neither oxetane formation nor Norrish type II reaction are

Scheme I



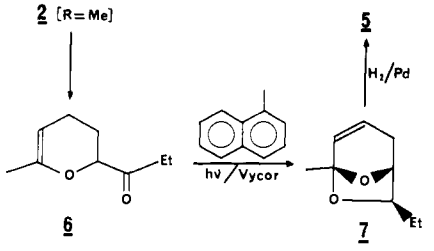
observed as long as a hydrogen atom, cis to the acyl group, is present for the transfer.[4] The stereoselectivity of the transfer has been demonstrated in the case of cis and trans 3,6-dimethyl-4-acylcyclohex-1-enes,[4] and the exo position of the R alkyl group in compound **3** is reached from lanthanide-induced NMR chemical shift measurements.[6]

The exclusive exo configuration of the R group in **4** prompted us to adopt this photochemical reaction to the stereoselective synthesis of *exo*-brevicomin (**5**). This compound, which is the principal component of the sex attractant produced in the frass of the female western pine beetle, *Dendroctonus brevicomis*, boring in ponderosa pine, has been characterized by Silverstein[7] and synthesized by several authors.[8] If one excepts the elegant procedure described by Mori,[8] who established the absolute configuration of both enantiomers of *exo*-brevicomin in 17 steps starting from D(−)-tartaric acid, all the already described methods need, at a certain stage, the separation of two (or three) isomers.

Selective excitation of the carbonyl group of compound **2** in pentane at 25 °C, using a Pyrex filter, yields ketal **4.** The same result is obtained by taking advantage of the intermolecular energy transfer technique, using 1-methylnaphthalene as singlet sensitizer and triplet quencher of the carbonyl group, with a Vycor filter.

The Diels-Alder dimer[9] of methyl vinyl ketone **2** (R = CH_3) affords ketone **6** with 65% yields when alkylated by the imine procedure[10] of Stork and Dowd. Irradiation of ketone **6,** using

Scheme II



the 1-methylnaphthalene sensitization procedure, forms the bicyclic ethylenic ketal **7** as the sole isomerization product (the yield, based on the ketal isolated by distillation, is 23%). The structure assigned to **7** is based on its constitution and its spectroscopic data which agree with the structure expected for 1-methyl-6-*exo*-ethyl-7,8-dioxabicyclo[3.2.1]oct-2-ene: IR (CCl_4) 3050, 1640, 1190, and 710 cm^{-1}; NMR (CCl_4) δ 5.66 (2 H, m, C_2 and C_3 vinyl), 4.08 (1 H, broad signal, C_5 methine), 3.65 (1 H, t of d, J = 6.2 and 1.6 Hz, C_6 methine), 2.8–1.3 (4 H, m, C_4 methylene and 6-*exo*-ethylmethylene), 1.4 (3 H, s, C_1 methyl), and 0.91 (3 H, t, J = 7 Hz, methyl of the 6-*exo*-ethyl group).

Catalytic hydrogenation (Pd over charcoal) of the double bond of **7** yields pure *exo*-brevicomin (**5**) with 95% (isolated) yields. The obtained compound is identical in spectroscopic properties (IR, ^1H NMR, and mass spectrum) with the authentic sample already described.[7]

This procedure provides easy access to pure *exo*-brevicomin in three steps and 14% overall yields starting from the Diels-Alder adduct of 1-buten-3-one.

Experimental Section

Infrared spectra were recorded in carbon tetrachloride or as films on a Perkin-Elmer 357 grating spectrophotometer and were calibrated with the 2850 and 1603 cm^{-1} bands of polystyrene. Ultraviolet spectra were recorded on a Varian-Techtron 635 ultraviolet-visible spectrophotometer. Proton magnetic resonance spectra were measured using a Varian Model EM-360 in carbon tetrachloride using hexamethyldisilane as internal standard. Band positions are reported in parts per million downfield from Me_4Si (δ scale). Microanalyses were performed at the Microanalyses Center of the University P. and M. Curie. The GLC analyses were conducted on a Varian Aerograph gas chromatograph Model 1400 with nitrogen as carrier gas on a 10 ft × ⅛ in. 15% SE30 column on Chromosorb W (80–100 mesh). Semipreparative GLC were performed on a Varian Aerograph 90-P instrument using a 10 ft × ⅜ in. 30% SE-30 on Chromosorb W (45–60 mesh).

2-Propionyl-6-methyl-2,3-dihydro-4*H*-pyran (6). The Diels-Alder dimer **2** (R = Me) of 1-buten-3-one is easily prepared according to Alder's procedure.[9] It also represents an important fraction of the monomer after standing for a while at room temperature.

2 (R = Me) (14 g, 0.1 mol) was heated with 1 equiv of cyclohexylamine in 150 ml of benzene and refluxed under a water separator until elimination of 1 equiv of water (5 h). After removal of the solvent under reduced pressure, the crude imine was used without further purification. Such a procedure eliminated the difficulties for distillating the imine which foams abundantly.

The crude imine was added to a 10% in excess of ethylmagnesium bromide (0.11 mol) in 120 ml of anhydrous THF. After refluxing for 3 h, the solution was cooled at 0 °C and 15.6 g (0.11 mol) of methyl iodide in 20 ml anhydrous THF was added. The mixture was stirred overnight at room temperature and then smoothly hydrolyzed at 0 °C by 1 equiv of a 5% aqueous solution of acetic acid, following the Buchi and Powell Jr. procedure.[11] After stirring for 0.5 h at 5–10 °C, the organic layer was separated and the aqueous fraction extracted by 4 × 40 ml of ether. The combined organic solutions were washed with brine (20 ml) and dried over Na_2SO_4, and the solvents were removed under reduced pressure. Vacuum distillation of the residue yielded 10.0 g (0.065 mol) of pure dihydropyran derivative **6:** colorless liquid, bp 83 °C (14 mm); IR (film) 1720 and 1685 cm^{-1}; UV (cyclohexane) 208 nm (ϵ 2100) and 281 nm (ϵ 38); ^1H NMR 4.45 (1 H, br, s), 4.18 (1 H, m), 2.58 (2 H, q, J = 7.2 Hz), 1.92 (4 H, br, s), 1.77 (3 H, s), and 1.02 (3 H, t, J = 7.2 Hz).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.14; H, 9.26.

Irradiation of Ketone 6. A pentane solution (600 ml) of ketone **6** (4 g) was irradiated under a nitrogen atmosphere with a medium-pressure mercury lamp (Hanovia 450 W) through a Vycor filter and in the presence of 8 g of methylnaphthalene for 22 h. The reaction mixture was carefully concentrated in vacuo; distillation of the residue afforded 0.92 g of ketal **7**; bp 65–66 °C (14 mm).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.86; H, 8.85.

Hydrogenation of Ketal 7 into *exo*-Brevicomin (5). The unsaturated ketal **7** (490 mg, 32 mmol) in 20 ml of ethyl acetate was stirred under hydrogen atmosphere in the presence of Pd over charcoal (absorption of 730 ml of H_2). Filtration followed by removal of the solvent under careful conditions gave over 95% pure *exo*-brevicomin (**5**). A pure sample was obtained by GLC (SE 30; 130 °C).

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Selective Halogenation of Steroids Using Attached Aryl Iodide Templates†

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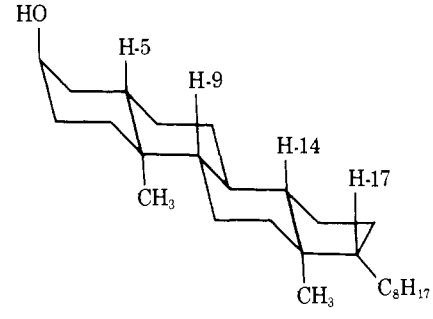
Abstract: The free radical chlorination of steroids by phenyliodine dichloride in aromatic solvents can be rather selective, leading to functionalization at unactivated tertiary positions. This process involves a solvent complex of the chlorine atom and can be directed by substituents in the substrate. More selectivity is achieved by a different mechanism when the aryliodine dichloride reagent is directly attached to the substrate. Thus 3α-cholestanyl *m*-iodobenzoate dichloride undergoes internal hydrogen abstraction in a free radical chain process to afford a 9α-chlorosteroid. The process is directed by the geometric relationship between substrate and reagent, and other geometries can be used to direct functionalization at C-14 or at C-17. A variant is the radical relay process, in which the intermediate chloroiodoaryl radical is generated by chlorine atom transfer to a template molecule attached to the substrate. Here too, geometric relationships can be adjusted to direct the reactions. The processes are illustrated by a cortisone synthesis, by the conversions of sitosterol and cholesterol to androsterone, and by synthesis of a cardenolide intermediate. In one case the template directed halogenation of an unactivated carbon took place even in the presence of an unprotected enone system.

Some years ago, we initiated a program to introduce certain enzymatic principles into the design of specific organic functionalization reactions. The essential idea[1] was that the selectivity of enzymatic reactions is determined in large part by the geometric demands of the reagent, rather than by the intrinsic reactivity pattern of the substrate. This is in marked contrast to the usual synthetic chemical style, in which functional group manipulation is used to adjust the substrate reactivity so as to produce a desired result.

Our first approach to this area involved the use of benzophenone photochemistry.[2] Various derivatives of benzophenone were attached to flexible substrates and to steroids and were then photolyzed. This led to attack on unactivated positions in the substrate dictated by the geometrical relationship between the substrate and the attached reagent. Good control was achieved using this technique, but such photochemistry with quantum yield less than unity is of limited practical synthetic interest. Therefore, a few years ago we set out to devise similar reactions by which free radical chain halogenation processes could be directed in this same general fashion. We hoped to attach a reagent to a substrate and then have the reagent carry out a free radical halogenation whose selectivity would be determined by the precise geometrical relationship between the reagent and substrate.

In our search for a suitable rigid free radical halogenating reagent, we were drawn to phenyliodine dichloride, which has great selectivity[3] for tertiary hydrogens compared with secondary or primary CH bonds. Such a reagent promised to let us combine chemical selectivity of this sort with geometrical control. While this is not ideal in terms of our ultimate goal, in which geometrical control alone is to determine reactivity, such a combination of factors has certain practical advantages in permitting selective functionalizations. We had found in our benzophenone photochemistry[2] that with only one point of connection between substrate and reagent, the ester link at which they were joined, we frequently saw attack at several positions in a steroid because the reagent could swing in an arc under the substrate hydrogens. With a reagent which has a large chemical preference for tertiary hydrogens, such motion is not a problem in steroid functionalization. The tertiary hydrogens on the α face of a steroid are distributed radially from the oxygen at carbon 3, so any arc whose center is that oxygen is likely to encounter only one of these tertiary hydrogens. We thus set out to attach aryl iodides to steroid substrates, in order to carry out intramolecular halogenations using the corresponding aryliodine dichlorides.

First we undertook a short study[4] of the selectivity of unattached phenyliodine dichloride in steroid functionalization.



3α-cholestanol

With convenient concentrations of various steroids and phenyliodine dichloride in nonaromatic solvents, such as methylene chloride, no appreciable amount of halogenation of the steroid was observed when a free radical process was

† Dedicated to R. B. Woodward on the occasion of his sixtieth birthday.