Oxygenated Chimpanzee Metabolites of [(2-Cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyl)oxy]acetic Acid (MK-473): Their Structural Elucidation and Synthesis

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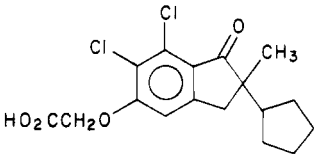
Four nonconjugated chimpanzee metabolites of the uricosuric diuretic [(2-cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyl)oxy]acetic acid (1) were isolated from urine and found to bear hydroxy groups at C-1′ (metabolite A), cis C-4′ (metabolite B), or trans C-3′ (metabolite C) or a ketone function at C-4′ (metabolite D). The metabolites were isolated and characterized as their methyl esters. Their structural assignments were confirmed by synthesis. Thus, the cyclopentane structures **9** and **10** were prepared, separated, and converted in two steps to *trans*-3′-ol (**12c**), starting with ene **10**, and *trans*-4′-ol (**15c**), starting with ene **9**. The benzyloxy group of each compound was converted in three steps to the corresponding oxyacetic acid, thereby affording racemic metabolite C (**13c**) and the *trans*-4′-ol counterpart (**16c**). Metabolite B methyl ester and **16d** were oxidized to a common ketone (**18**) which, in the latter instance, corresponds to racemic metabolite D methyl ester. Calculations support the ^{1}H NMR data indicating a preferred rotamer population of the cyclopentane ring relative to the indanone ring.

Studies[1a,b,d] in these laboratories led to the development of indanone **1** (MK-473), a potent salidiuretic agent with desirable adjunctive uricosuric and antihypertensive properties.[1c] During an investigation of the physiological distribution of **1** in the chimpanzee, four nonconjugated, oxygenated urinary metabolites were found.[2] These metabolites, designated A, B, C, and D based upon the relative GC retention times displayed by their respective methyl ester derivatives, were shown to represent the major metabolic fate of **1** in the chimpanzee. Subsequently, man and the rat were observed to produce the same metabolites, whereas metabolite production as well as salidiuretic response proved to be erratic in the dog. Perhaps of greater interest was the observation that the urinary appearance of metabolite C closely paralleled saluresis in the rat and man with respect to both time and rate.[2,3] The latter observation suggested that the saluretic parameter of the biological properties of **1** might arise from



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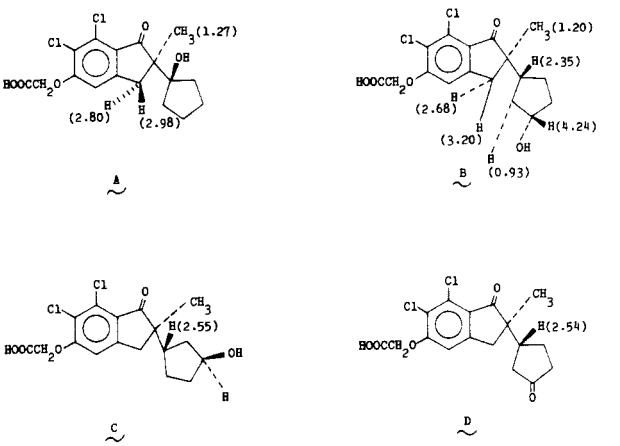
metabolite C. Therefore, it was deemed essential to undertake the isolation and structural elucidation of each of the metabolites and, by synthesis, to confirm these assignments. In addition, sufficient quantities of racemic metabolite C were needed to facilitate extensive biological evaluation. The structures of the metabolites have been published and a preliminary account of their structural elucidation given.[2] We report herein a full account of the structure determination and proof of structure of the metabolites, a convenient synthesis of metabolite C, and the results of molecular modeling supporting the rotamer population preference of the cyclopentyl–indanone bond, inferred from ^{1}H NMR spectral data.

Chart I



Structural Elucidation. A cold methanolic solution of the crude unconjugated metabolites obtained from chimpanzee urine[2] was treated with excess ethereal diazomethane to prepare the methyl esters.[4] By repetitive two-dimensional thin layer chromatography (TLC) small samples of metabolites A, B, and C were separated as their methyl esters. The metabolite structures[5] are shown in Chart I.

GC/mass spectral data showed that metabolites A, B, and C were hydroxylated on the cyclopentane ring;[2] each of these metabolites underwent the McLafferty rearrangement.[6] The ^{1}H NMR spectrum of metabolite A methyl ester was devoid of both the distinctive carbinol CH and an apical proton at the 1′ position. Based upon

(1) (a) Cragoe, E. J., Jr.; Schultz, E. M.; Schneeberg, J. D.; Stokker, G. E.; Woltersdorf, O. W., Jr.; Fanelli, G. M., Jr.; Watson, L. S. *J. Med. Chem.* **1975**, *18*, 225. (b) Woltersdorf, O. W., Jr.; deSolms, S. J.; Schultz, E. M.; Cragoe, E. J., Jr. *J. Med. Chem.* **1977**, *20*, 1400. (c) A compound which causes excretion of uric acid, salt, and water and, in addition, lowers the blood pressure of hypertensives. (d) The + enantiomer of **1** has slightly more activity as a salidiuretic in chimpanzee than the − enantiomer while the uricosuric activity is reversed. See ref 1b.

(2) Zacchei, A. G.; Wishousky, T. I.; Arison, B. H.; Hitzenberger, G. *Drug Metab. Dispos.* **1978**, *6*, 303.

(3) Zacchei, A. G.; Wishousky, T. I.; Watson, L. S. *Drug Metab. Dispos.* **1978**, *6*, 313.

(4) Arndt, F. "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. I, p 165.

(5) In order to facilitate discussion of the relative configuration of the asymmetric centers in the metabolites, the cyclopentane ring is numbered clockwise beginning with the tertiary carbon as 1′. The term cis is used to describe atoms or groups oriented in the same direction as the methyl group at the 2-position, trans in the opposite direction. To impart clarity to the structural arguments, critical chemical shifts are shown on the structures.

(6) McLafferty, F. W. "Interpretation of Mass Spectra", 2nd ed.; W. A. Benjamin; Reading, MA, 1973; p 57.

0022-3263/85/1950-3490$01.50/0

these data, the tertiary carbinol structure was assigned to metabolite A.

In order to determine the position of hydroxylation, the methyl esters of metabolites B and C were oxidized with Jones reagent (chromic acid in acetone) at 0 °C and the products isolated by two-dimensional TLC. The IR spectrum of each product diketone showed the requisite three carbonyl bands. Although the signal-to-noise ratio was low, the ^{1}H NMR spectrum of each diketone showed a relatively small chemical shift of the apical proton and a net downfield shift (ca. 0.5 ppm) of four protons in the aliphatic envelope. Of the possible cyclopentanones, only those bearing oxygen at the 3′ or 4′ positions are compatible with the ^{1}H NMR spectra observed for the diketone oxidation products of metabolites B and C methyl esters. Further, the diketone spectra are clearly different, indicating that the oxygen of each is on a different carbon (i.e., the 3′ or 4′ position). Therefore, it follows that metabolites B and C are hydroxylated at either the 3′ or 4′ position and that each metabolite is hydroxylated at a different position. The evidence necessary to distinguish between hydroxylation at the 3′ or 4′ position with respect to metabolites B and C and, more importantly, to establish the stereochemistry of their hydroxylation sites is presented below.

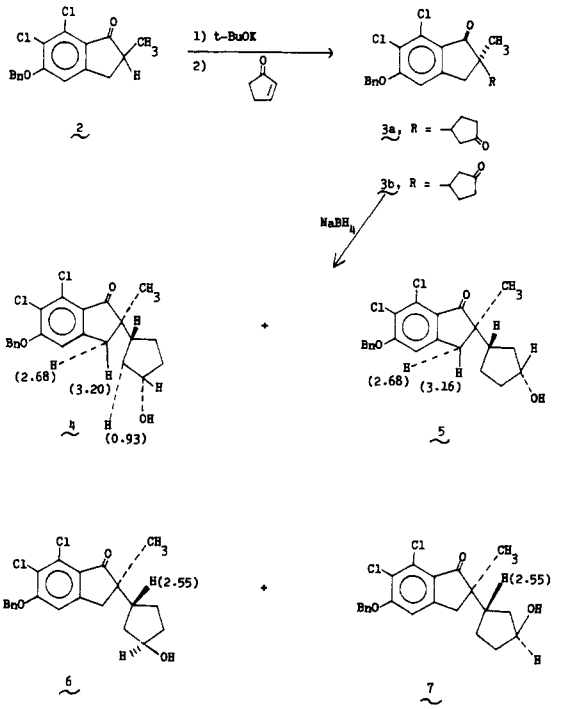
The ^{1}H NMR spectrum of metabolite B methyl ester revealed a distinctive downfield shift (0.26 ppm) of one of the indanone methylene (C-3) protons compared to parent structure **1**, which suggested that cis hydroxylation had occurred at either the 3′ or 4′ position. Either assignment would place the hydroxyl group in close proximity to the affected C-3 proton. The apical proton (C-1′) was shifted only slightly from its position in parent compound **1**.

The ^{1}H NMR spectrum of metabolite C methyl ester showed a distinctive downfield shift (0.33 ppm) of the apical proton. The downfield shift of an axial proton three carbons removed from an axial hydroxyl group (i.e., resulting from 1,3-diaxial interaction) in cyclohexanols is 0.47 ± 0.1 ppm.[7] This observation suggested that trans hydroxylation had occurred at either the 3′ or 4′ position. In either of these positions, the apical proton and the hydroxyl group are positioned in a quasi 1,3-diaxial relationship and, thereby, would account for the observed downfield shift of the apical proton.

The final piece of evidence needed to complete the structural assignments for metabolites B and C was obtained by unambiguous synthesis of the four possible racemic 3′ and 4′ alcohols as outlined in Scheme I.

Generation of the anion of **2**[1b] and subsequent treatment with cyclopentenone gave Michael adducts **3a** and **3b**. The ^{1}H NMR spectrum of the resulting mixture of diketones was quite similar (i.e., above δ 5) to that derived by summing the ^{1}H NMR spectra of the diketone oxidation products of metabolites B and C. The diastereoisomers **3a** and **3b** proved inseparable by either chromatography or crystallization. The ketone mixture was reduced with sodium borohydride,[8] and the resulting mixture of alcohols was chromatographed. A small sample of each of the cis alcohols, **4** and **5**, was obtained. Each sample proved to be substantially free of the other isomer. Samples of the two trans alcohols, **6** and **7**, were mixtures containing only these isomers. The ^{1}H NMR spectrum of the first compound to emerge from the column was identical with that of metabolite B methyl ester from δ 5 upfield.[9] This

Scheme I



sample, due to its availability in reasonable quantity, permitted fine structure to be seen clearly. Of particular interest was a shielded proton positioned upfield of the methyl group at δ 0.93. When this signal was irradiated, perturbation of two additional signals (i.e., the apical proton at C-1 and the carbinol CH) was induced. When the apical proton was irradiated, the highly shielded proton at δ 0.93 was perturbed. Hence, this highly shielded proton must be flanked by both the apical proton and the carbinol methine. In addition, this isomer exhibited the distinctive deshielding of one of the methylene protons of the indanone ring (C-3) and to exactly the same extent as that observed in metabolite B. By rotating the cyclopentanol ring of **4** 60° clockwise, it can be seen that the cis-5′ proton now is positioned over the indanone π system where it would be expected to experience a strong shielding effect. This orientation also places the hydroxyl function close to the nearest proton of the indanone ring 3 position where it would be expected to cause a deshielding of that proton. Hence, these data clearly indicate that structure **4** must be assigned to this compound. Since **4** is identical with metabolite B methyl ester except for replacement of the acetyl group by the benzyl moiety, it can be concluded that metabolite B possesses the same cis-4′ hydroxyl functionality.

The ^{1}H NMR spectrum of the second alcohol to emerge from the column also showed deshielding of the nearest indanone methylene proton (albeit to a lesser extent) and the absence of a highly shielded proton. This compound was clearly dissimilar to metabolite B and, accordingly, was assigned structure **5**.

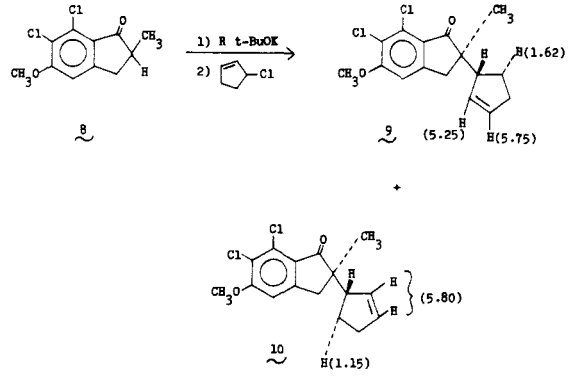
The ^{1}H NMR spectra of the two remaining 3′ and 4′ alcohols displayed a highly deshielded apical proton identical with that in metabolite C. Since the deshielding of the apical proton is caused by a 1,3-quasi-diaxial interaction, these compounds are trans 3′ and 4′ alcohols and, accordingly, are assigned structures **6** and **7**. These structural assignments also confirm that metabolite C is

(7) Danneels, D.; Anteunis, M. *Tetrahedron Lett.* **1975**, 690.

(8) Because of electronic and steric effects, the indanone carbonyl does not reduce under any of the conditions used. Unpublished results, O. W. Woltersdorf.

(9) The benzyl group causes no perturbation of the signals of the rest of the molecule upfield.

Scheme II



either a trans-3′ or -4′ alcohol. Isomers **6** and **7** could not be separated sufficiently to afford ^{1}H NMR spectra which would serve to differentiate between them. However this differentiation was not needed.

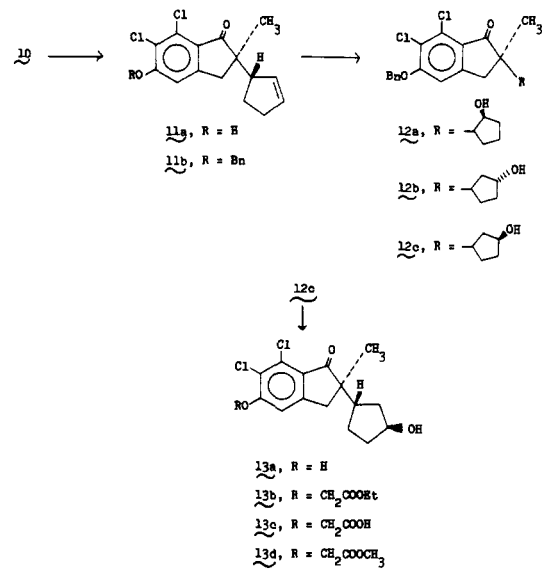
Having established previously that metabolites B and C are hydroxylated on different carbons and that these must be the 3′ and 4′ positions and, furthermore, having shown that metabolite B is a cis-4′ alcohol and that metabolite C is a trans-3′ or -4′ alcohol, metabolite C therefore must be a trans-3′ alcohol.

Synthesis. H. C. Brown et al.[10,11] have studied the steric requirements for the hydration of double bonds by the oxymercuration–demercuration method and found that mercury is attached to the most hindered carbon. The hydroxyl group then prefers to substitute the least hindered carbon. Reductive removal of the mercury leaves the least hindered alcohol as the final product. These workers have shown that this method also gives the alcohol resulting from preferred attack of water not only at the least hindered carbon but also from the least hindered side of a double bond in cyclic system.[11] Therefore, this method seemed appropriate for the preparation of the trans-3′ and -4′ alcohols in the present system.

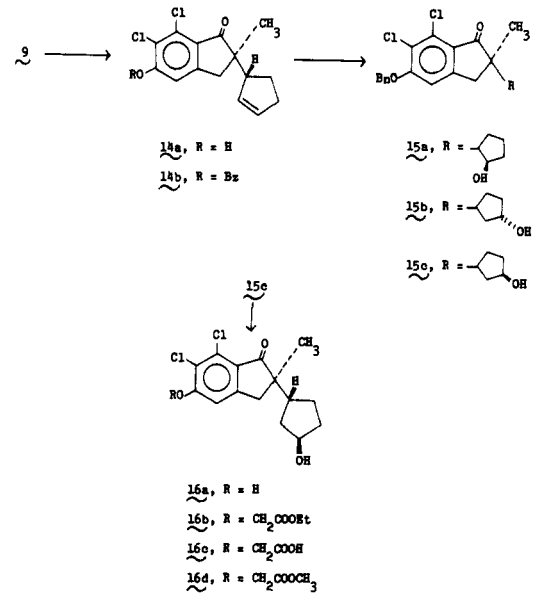
The approach was to establish the relative configuration of the contiguous asymmetric centers by preparing and separating the two cyclopentene compounds **9** and **10** (Scheme II) and, subsequently, hydrating the double bond of each by oxymercuration–dermercuration.

The anion of **8** was preformed[1b] and alkylated with freshly distilled 3-chlorocyclopentene[12] to give diastereomers **9** and **10**. Unfortunately, the analogous mixture of the more synthetically desirable benzyl ethers could not be separated. However, the methyl ethers were separated by crystallization to give **9** and **10** in 92% and 94% isomer purity, respectively. Further isomer separation resulted in an unacceptable diminution of product yield. The structural assignments of the two compounds were made on the basis of their respective ^{1}H NMR spectra. When the cyclopentene ring in **9** and **10** is rotated 60° clockwise from its illustrated location, it is in the same preferred orientation as that established for the cis-4′ alcohol (**4**), which accounted for its distinctive observed chemical shifts. When in this preferred rotamer form, the 5′ vinyl proton of **9** is situated over the indanone π cloud and would be expected to be shielded.[13] Thus, the compound with the vinyl proton shifted upfield by δ 0.5 was assigned to structure **9**. In a similar way, the compound with the shielded cis-5′ proton was assigned structure **10**.

Scheme III



Scheme IV



Scheme III outlines the remainder of the synthesis of metabolite C beginning with **10**, which has the correct relative configuration. When **10** was heated briefly with pyridine hydrochloride, methyl ether cleavage gave **11a** in good yield. The benzyl group was introduced by using potassium carbonate and benzyl bromide in DMF to give **11b**. Oxymercuration–demercuration of **11b** gave a mixture of alcohols **12a–c** which was separated by chromatography. The desired isomer **12c** was isolated in 49% yield (97% ± 3% isomer purity as determined by integration of the methyl signals in the ^{1}H NMR spectrum). The next most abundant isomer was **12b**, whose ^{1}H NMR spectrum was identical with that of compound **5** (Scheme I), in agreement with the use of the cyclopentene **10** as the olefin required to give metabolite C. The least abundant alcohol, **12a**, was characterized by a 6-Hz downfield shift of the methyl protons which is attributable to the proximity of the hydroxyl group to the methyl group in **12a**. The desired isomer **12c** was debenzylated by hydrogenolysis to give the phenol **13a**. Alkylation of the corresponding phenoxide with ethyl bromoacetate gave the ester **13b**, which, without isolation, was hydrolyzed with aqueous

(10) Brown, H. C.; Geoghegan, P. J. *J. Org. Chem.* **1970**, *35*, 1844.
(11) Brown, H. C.; Lynch, G. J.; Hammar, W. J.; Lin, L. C. *J. Org. Chem.* **1979**, *44*, 1910.
(12) Moffett, R. B. "Organic Syntheses", Wiley: New York, 1969; Collect. Vol. IV, p 238.
(13) For comparison, 2-cyclopentene-1-acetic acid δ 5.7 (m, 2, vinyl-H) and 10.

Table I. Molecular Modeling and ab Initio Calculations of the Preferred Cyclopentyl Ring Orientation

no.	angle, deg	MM2, kcal	Δ, kcal	25 °C % conf	G82 STO-3G HF	Δ, kcal	25 °C % conf
21a	54.1	22.99	1.41	7.7	−568.445 024	1.97	3.2
	173.9	22.87	1.29	9.4	−568.445 851	1.45	7.7
	−59.9	21.58	0.0	82.9	−568.448 163	0	89.1
21b	57.1	18.74	1.10	12.5	−493.399 138	1.35	8.7
	172.0	19.05	1.41	7.4	−493.398 837	1.54	6.3
	−64.5	17.64	0.0	80.1	−493.401 285	0	85.0
21c	67.7	18.43	0.23	34.6	−493.399 996	0.157	38.1
	170.6	18.95	0.75	14.4	−493.398 903	0.843	12.1
	−50.2	18.20	0.0	51.0	−493.400 246	0	49.9

potassium hydroxide in ethanol to give acid **13c**. After purification, this crystalline, final product was free of any detectable isomeric alcohols. A small amount of **13c** was converted to racemic methyl ester **13d** with diazomethane and shown to be identical with metabolite C methyl ester by all physical measurements (except specific rotation) used to characterize the latter.

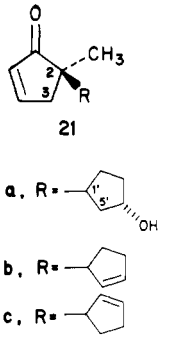
Scheme IV depicts a similar synthetic sequence beginning with diastereomer **9**. O-Demethylation of **9** by fusion with pyridine hydrochloride led to extensive isomerization of the double bond. Compound **14a** was obtained in only 76% isomer purity; the principle byproduct was the 3′-ene[14] as indicated by ^{1}H NMR spectral analysis. The material which was isomerized to the 5′ isomer was removed by crystallization. The partially purified phenol **14a** was benzylated and oxymercurated–demercurated to give a mixture of alcohols which was separated by column chromatography. The first two alcohols to emerge from the column were **15a** and **15b**. The alcohol **15a** was identified by the ca. 0.47 ppm upfield shift of the carbinol CH. The preferred orientation of the cyclopentanol ring places this carbinol CH(cis-5′-H) over the indanone π system. The ^{1}H NMR spectrum of the other alcohol, **15b**, was identical with that of compound **4** (Scheme I). The distinctive ^{1}H NMR spectral characteristics of these alcohols served to verify the structural assignment of the cyclopentene compound **9**. The desired alcohol **15c**, isolated in 97% ± 3% isomer purity, was expected to afford the trans-4′ counterpart of metabolite C. The benzyl group was removed by hydrogenolysis and the resulting phenol alkylated with ethyl bromoacetate. The ester **16b** was hydrolyzed to give acid **16c**. A small sample of the latter was converted to the methyl ester **16d** with diazomethane. The spectral characteristics of **16d** were clearly different from those of metabolite C methyl ester although their ^{1}H NMR spectra displayed the same distinctive downfield shift of the apical proton.

In order to further match the synthetic metabolite **C** (i.e., compound **13c**) with authentic metabolite C, a small sample of **13c** was esterified with diazomethane and the resulting ester **13d** oxidized with Jones reagent to give the diketone **17**. The spectral properties of this diketone were identical with those of the oxidation product of metabolite C methyl ester. The isomeric alcohol **16d** was oxidized with Jones reagent to give the diketone **18**, which was identical in all its spectral properties with the diketone oxidation product of metabolite B methyl ester. Therefore, compound **16d** and metabolite B methyl ester must differ only in their relative configurations at the 4′ position. A comparison of the spectral properties of compound **18** with those of metabolite D methyl ester, which was known to be a cyclopentanone,[3] showed these compounds to be identical, thus establishing which of the two possible cyclopentanones was the correct structure.

In order to confirm that the diketone **18** was related to metabolite B methyl ester and to the alcohol **16d**, the acid **16c** was oxidized with Jones reagent, reduced with alkaline sodium borohydride, and esterified with diazomethane to give a mixture consisting of compound **16d** and racemic metabolite B (compound **20**) in a ratio of 2:3, respectively. Therefore, except for optical rotation, compound **16d** and metabolite B methyl ester must differ only in the configuration of their respective carbinol groups at the 4′ position, and, furthermore, metabolite D (i.e., compound **19**) is the common ketone resulting from oxidation of both **16d** and metabolite B methyl ester.

For a final check, compounds **13d** and **16d** were each compared by admixture with authentic metabolite C methyl ester in a two-dimensional TLC system known to cleanly separate **13d** and **16d**. In this system, compound **13d** was shown to be identical with metabolite C methyl ester, whereas compound **16d** was clearly not.

Molecular Modeling. A preferred orientation of the cyclopentane ring relative to the indanone ring has been invoked in order to explain the ^{1}H NMR spectral data. Support for the existence of this preferred orientation emerged from molecular modeling. For simplicity, the molecule to be modeled was reduced to the essentials depicted in **21**. By inspection, three conformational



minima were generated by rotating the cyclopentyl ring around the central bond (3,2,1′,5′), giving dihedral angles at 60°, 180°, and −60°. For each of these three orientations, all ten pseudorotations of the respective cyclopentyl ring were generated and strain minimized to ensure that the lowest energy conformation was found. The minimizations were performed by using the MOLECULAR MODELING 2 (MM2) program.[15] Each of the three minimum strain energy conformations was further subjected to STO-3G/HF fixed point calculations (Gaussian 82)[16] to provide a second estimate of their relative energies. The

(14) Although the vinyl protons in the ^{1}H NMR spectra of the 3′- and 2′-enes have about the same chemical shift, the 3′-ene is assigned to this byproduct based on the fact that there were no demonstrable hydroxylation products resulting from hydroxymercuration–demercuration of a 2′-ene vida infra. It, therefore, follows that the impurity is the 3′-ene, and fortunately it was hydroxylated in the desired 3′ direction.

(15) Allinger, N. L.; Yah, Y. H. *QCPE* **1981**, *13*, 395.

(16) Binkley, J. S.; Frisch, M.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A. "Gaussian 82" (IBM Version); Carnegie-Mellon University: Pittsburgh, PA, 1983.

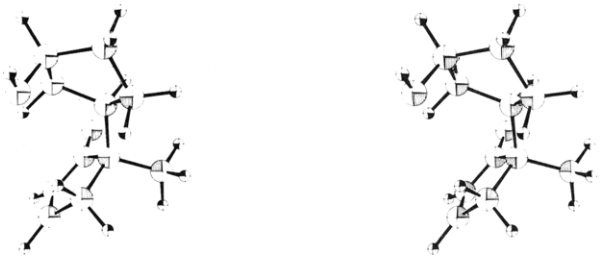


Figure 1. Stereoview of the strain energy minimized preferred rotamer of **21a**.

results are summarized in Table I.

These calculations clearly indicate that the cyclopentanol ring of **21a** and the cyclopentene ring of **21b** prefer the −59.9° and −64.5° rotamers by 1.4 to 2.0 kcal over the other possible rotamers and spend 89 and 85% of the time in their respective preferred rotamers. This accounts for the observed ^{1}H NMR spectral effects. The cyclopentene ring in **21c**, on the other hand, prefers a −50.2° rotamer by only 0.16 kcal but still resides in that state 50% of the time. This is apparently enough to account for the observed shielding of the 5′ proton. The diminished preference for the ca. −60° rotamer in **21c** as compared to **21b** probably reflects the importance of the interaction of the cis C-2′ hydrogen of the cyclopentene ring with the methyl and methylene hydrogens of the indanone ring of **21b** and the absence of this interaction in **21c**. An ORTEP stereoview of strain-minimized **21a** in the preferred rotamer is provided in Figure 1 where the proximity of the hydroxyl group to the deshielded indanone trans C-3 proton is evident and the shielded cyclopentanol cis C-5′ hydrogen is seen to reside over the π system.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian HA-100 spectrometer. A few spectra were recorded on a Nicolet 360 or a Varian A-60 spectrometer and are so indicated. Chemical shifts are expressed as δ values relative to Me_4Si as internal standard; C-3 J_{gem} is always 17.5 Hz. IR spectra were taken on a Perkin-Elmer 421 grating spectrophotometer and are reported in reciprocal centimeters. When used to prepare the thin film in these spectra, the solvent is indicated in parentheses. GC analyses were performed with a F&M Model 810 gas liquid chromatograph equipped with a 4 mm × 2 m glass column packed with 1% QF-1 on CSBG (100/120 mesh) and using an injection temperature of 230 °C with helium as the carrier gas. Melting points (capillary) are uncorrected.

Thin-layer chromatography (TLC) was carried out on Analtech silica gel GF plates (2000 μm thickness for two-dimensional elution and establishment of product purity). Bands and/or spots were visualized via mineral-light exposure. AR grade solvents were employed exclusively. Solvents were removed in vacuo (water aspirator) on a rotary evaporator except for the extracts resulting from the two-dimensional TLC purifications. The latter extracts were filtered through prerinsed glass wool plugs and evaporated at 20 °C under a gentle stream of highest purity N_2 delivered from a 30 ft × $^1/_8$ in. copper tube connected to a clean glass pipet. All glassware used in the isolation experiments was cleaned by successive exposure to aqua regia, distilled water, acetone, and $CHCl_3$ and was dried at 60 °C for 30 min prior to use. Product weights were determined in tared glass vials (9 mL) after drying in a vacuum pistol (0.1–0.05 mmHg) at 70 °C for 1 h and subsequent thermal equilibration on an analytical balance.

Isolation of Metabolites A, B, and C. The oily residue remaining after evaporation of the solvent from the methanol elution[2] was partitioned between $CHCl_3$ (400 mL) and 2.5% $NaHCO_3$ (400 mL). The phases were separated, and the organic phase was extracted with water (100 mL). The combined aqueous extracts were acidified to pH 1 with 12 N HCl and extracted with $CHCl_3$ (4 × 125 mL). The organic extract was dried over Na_2SO_4 and evaporated in vacuo, leaving a tacky foam (673 mg). A sample (583 mg) of the latter was subjected to preparative TLC on silica gel GF (four plates) by using $CHCl_3$–CH_3OH–HOAc (8:1:1 v/v/v) (system A) as eluent. Component visualization revealed two major bands: band I (R_f 0.60–0.70) and band II (R_f 0.35–0.54).

Band I was removed and extracted with refluxing $CHCl_3$-CH_3OH (9:1 v/v; 4 × 50 mL). Evaporation of the extract gave an oil which was dissolved in CH_3OH (2 mL). The resulting clear solution was cooled in an ice bath and treated cautiously with freshly prepared ethereal diazomethane (6 mL). After standing in the cold for 10 min, the pale yellow solution was warmed to 20 °C and evaporated in vacuo, leaving a tan residue. The residue was extracted with $CHCl_3$ (5 × 1 mL) at 20 °C and the combined extract filtered. Concentration of the filtrate in vacuo gave an impure sample (6.4 mg) of metabolite A methyl ester as a straw-colored oil; R_f 0.37 (major) with trace impurities at 0.76, 0.60, 0.42, and 0.26 using benzene–EtOAc–CH_3OH (5:50:1 v/v/v) (system B). Further purification was effected as follows. The impure oil (6.4 mg), uniformly applied as a single spot, was chromatographed two dimensionally on silica gel GF (5-75 × 90 cm microplates) using system B as eluent. The spots with R_f 0.43 were removed, combined, and extracted with $CHCl_3$ (5 × 1 mL) at 20 °C. Concentration of the filtered extract gave an oily product which was rechromatographed two dimensionally on silica gel GF (2-75 × 90 mm microplates), system B was used as eluent. Workup as described above afforded 149 μg of metabolite A methyl ester as a pale yellow oil; R_f 0.37 (homogeneous, system B); GC indicates 90% single component; IR ($CDCl_3$) 1740, 1710 cm^{-1}; NMR ($CDCl_3$), see Table I.

Band II was removed and extracted with refluxing $CHCl_3$–CH_3OH (9:1 v/v; 4 × 50 mL). Evaporation of the filtered extract gave a residual gum (54.3 mg) which was rechromatographed on a preparative silica gel GF plate with system A. The band with R_f 0.35–0.51 was removed and extracted with refluxing $CHCl_3$–CH_3OH (9:1 v/v; 3 × 50 mL) to give, after solvent removal, a tan, amorphous residue (13.4 mg). The residue was treated with ethereal diazomethane as described above. After the usual workup, a crude mixture (7.6 mg) of the methyl esters of metabolites B and C was obtained; R_f 0.37 (major) and 0.34 (major) with trace impurities at 0.54 and 0.46 (system B). Separation of the ester mixture was achieved as follows. A sample (3 mg) of the crude mixture was uniformly applied as a single spot and chromatographed two dimensionally on silica gel GF (9-75 × 90 mm microplates) with system B as eluent. The upper portion (ca. $^1/_2$) of the partially resolved spot doublet was removed and extracted with $CHCl_3$ (5 × 1 mL) at 20 °C. Evaporation of the filtered extract afforded an oily residue enriched in metabolite B methyl ester. Likewise, the lower portion (ca. $^1/_2$) was similarly treated to obtain enriched metabolite C methyl ester. The two enriched samples were rechromatographed (3-75 × 90 mm silica gel GF microplates each) and worked up in the same manner to give TLC homogeneous (system B) samples of metabolite B methyl ester [319 μg; R_f 0.37; GC indicates 96% single component; IR ($CHCl_3$) 3400 (v br), 1748 and 1695 cm^{-1}; NMR ($CDCl_3$), see Table I, supplementary material] and metabolite C methyl ester [170 μg; R_f 0.34; GC indicates 95% single component; IR (KBr) 3420 (v br) and 1716 cm^{-1}; NMR ($CDCl_3$), see Table I]. The isolated metabolite C methyl ester was shown to be identical with racemic ester **13d** by mixed TLC comparison (System B).

Oxidation of Metabolite B Methyl Ester. A magnetically stirred solution of metabolite B methyl ester (ca. 200 μg) in acetone (0.3 mL) was cooled in an ice bath and treated with Jones reagent (0.05 mL, excess). The resulting clear, deep yellow solution was stored at 0–5 °C for 1 h, and then excess oxidant was destroyed by dropwise addition of 2-propanol (0.3 mL), providing a heterogeneous mixture which was partitioned between water (5 mL) and ether (3 × 10 mL). The organic extract was dried over Na_2SO_4 and filtered. In vacuo evaporation of the clear, colorless filtrate left a waxy residue which was chromatographed two dimensionally on silica gel GF (2-75 × 90 mm microplates) with system B as eluent. Isolation of the new product was effected in the usual manner to give metabolite B methyl ester ketone as a colorless film (183 μg): R_f 0.48 (homogeneous, system B); IR (KBr) 1740 (s at 1760) and 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 2.54 (m, 1 H), 2.77 (d, 1 H), 3.00 (d, 1 H), 3.84 (s, 3 H), 4.82 (s, 2 H), 6.71 (s, 1 H).

Oxidation of Metabolite C Methyl Ester. Metabolite C methyl ester (ca. 100 μg) was oxidized with Jones reagent[17] by using essentially the same procedure and purification technique described above. Metabolite C methyl ester ketone was obtained as a colorless film (79 μg): R_f 0.48 (homogeneous, system B); IR (KBr) 1740 (s at 1760) and 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 2.53 (m, 1 H), 2.74 (d, 1 H), 3.03 (d, 1 H), 3.84 (s, 3 H), 4.80 (s, 2 H), 6.72 (s, 1 H).

5-(Benzyloxy)-6,7-dichloro-2-methyl-2-(4′-oxocyclopentyl)-1-indanone (3a) and 5-(Benzyloxy)-6,7-dichloro-2-methyl-2-(3′-oxocyclopentyl)-1-indanone (3b). 5-(Benzyloxy)-6,7-dichloro-2-methyl-1-indanone (**2**) (3.21 g, 10 mmol) was suspended and partially dissolved in *tert*-butyl alcohol (150 mg) and benzene (100 mL). To this was added potassium *tert*-butoxide (1.35 g, 12 mmol) under N_2 and the reaction refluxed for 3 h and then cooled to room temperature. 2-Cyclopentenone (0.90 g, 11 mmol) dissolved in 50 mL of dry benzene was added at a rapid drip. After the addition was complete, the reaction was stirred for 1 h. Acetic acid (10 mL) was added and the solvents were removed in vacuo to afford a residue which was partitioned between ether and water (100 mL each). The ether layer was separated, washed with water, dried ($MgSO_4$), and filtered and the ether evaporated to leave a gum which was chromatographed on 120 g of silica gel, eluting with chloroform. The fractions containing the desired mixture of ketones were collected, the solvent was evaporated, and the resulting material was crystallized from ethanol–water to give 0.33 g, mp 114–124 °C.

In a similar preparation, **2** (3.21 g, 10 mmol) was alkylated with 2-cyclopentenone (3.28 g, 40 mmol) in methanol–benzene (1:1 v/v; 100 mL) using sodium methoxide (2.70 g, 50 mmol) as the base under N_2 at room temperature for 20 h. The reaction was worked up in the same way followed by chromatography and crystallization from ethanol–water to give 0.28 g, mp 128–141 °C. The difference in the melting point of the two samples is ascribed to different ratios of the diasterioisomeric diketones. IR (mull) 1720, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.28 (s, 3 H), 1.4–2.4 (m, 12 H), 2.54 (m, 1 H), 2.76 (d, 2 H), 2.99 (d, 2 H), 5.24 (s, 4 H), 6.86 (s, 2 H), 7.35–7.55 (m, 10 H). Anal. Calcd for $C_{22}H_{20}Cl_2O_3$: C, 65.52; H, 5.00; Cl, 17.58. Found: C, 65.86; H, 4.82; Cl, 17.58.

Reduction of a Mixture of 5-(Benzyloxy)-6,7-dichloro-2-methyl-2-(4′-oxocyclopentyl)-1-indanone (3a) and 5-(Benzyloxy)-6,7-dichloro-2-methyl-2-(3′-oxocyclopentyl)-1-indanone (3b). A mixture of compounds **3a** and **3b** (0.40 g, 1 mmol) was dissolved in 25 mL of ethanol with warming. The solution was cooled to room temperature, and a solution of $NaBH_4$ (20 mg, 0.53 mmol) in 1 mL of 3 M NaOH was added. After 1 h at room temperature, 8 mL of 3 M NaOH solution was added, stirred for 30 min, and then partitioned between ether and water. The water layer was extracted further with ether, the combined either extracts were washed with water, dried ($MgSO_4$), and filtered, and the solvent was evaporated at reduced pressure to leave 0.38 g of a mixture of 3′ and 4′ alcohols. This mixture was chromatographed on 60 g of silica gel, eluting with chloroform. The first alcohol to emerge from the column was 5-(benzyloxy)-6,7-dichloro-2-(*cis*-4′-hydroxycyclopentyl)-2-methyl-1-indanone (**4**) a clear colorless gum: ^1H NMR ($CDCl_3$) δ 0.93 (septet, 1 H), 1.22 (s, 3 H), 1.4–2.08 (m, 6 H), 2.35 (m, 1 H), 2.68 (d, 1 H), 3.20 (d, 1 H), 4.26 (m, 1 H), 5.20 (s, 2 H), 6.90 (s, 1 H), 7.30–7.55 (m, 5 H). The second alcohol to emerge from the column was 5-(benzyloxy)-6,7-dichloro-2-(*cis*-3′-hydroxycyclopentyl)-2-methyl-1-indanone (**5**) contaminated with ca. 30% of **4**: ^1H NMR (**5**) ($CDCl_3$) δ 1.22 (s, 3 H), 1.3–2.1 (m, 6 H), 2.30 (m, 1 H), 2.68 (d, 1 H), 3.16 (d, 1 H), 4.32 (m, 1 H), 5.20 (s, 2 H), 6.90 (s, 1 H), 7.3–7.55 (m, 5 H). The two remaining compounds to emerge from the column were the two alcohols **6** and **7** obtained as a mixture (a clear colorless gum). ^1H NMR (**6** and **7**) ($CDCl_3$) δ 1.22 (s, 3 H), 1.24 (s, 3 H), 1.0–2.1 (m, 12 H), 2.55 (m, 2 H), 2.72 (d, 2 H), 2.96 (d, 2 H), 4.30 (m, 2 H), 5.22 (s, 4 H), 6.90 (s, 2 H), 7.3–7.55 (m, 10 H).

2-Cyclopent-4′-enyl-6,7-dichloro-5-methoxy-2-methyl-1-indanone (9) and 2-Cyclopent-2′-enyl-6,7-dichloro-5-methoxy-2-methyl-1-indanone (10). 6,7-Dichloro-5-methoxy-2-methyl-1-indanone (**8**) (29.8 g, 12.2 mmol) was dissolved in dry benzene (875 mL) and dry *tert*-butyl alcohol (875 mL). To this solution was added potassium *tert*-butoxide (16.8 g, 15 mmol). The mixture was refluxed with stirring under N_2 for 3 h and cooled to room temperature, and 3-chlorocyclopentene dissolved in dry benzene (50 mL) was added at a rapid drip. After the addition was completed the reaction mixture was heated at reflux for 30 min and cooled to room temperature. The reaction was worked up by adding distilled water (250 mL) followed by a saturated solution of sodium carbonate (50 mL). The solvents from the separated organic layer were evaporated on a rotary evaporator, and the remainder was partitioned between ether (500 mL) and water (200 mL). The ether layer containing the product was separated and washed with distilled water, dried ($MgSO_4$), and filtered, and most of the ether removed in vacuo, diluted with a small amount of hexane, and allowed to stand. The deposited crystals were collected and washed with hexane to give 12.88 g, mp 115–135 °C. The mother liquor was saved. The solid was combined with that from two smaller runs and recrystallized from hexane to give 15.0 g of solid, mp 132–140 °C, which consisted of 80% **10** and 20% **9**. The mother liquor was saved. One more crystallization from hexane gave 12.9 g, mp 140–143 °C, which by integration of the vinyl signals in the ^1H NMR spectrum was 94% **10** and 6% **9**. Further crystallization changed the ratio very little. The mother liquors were chromatographed on 1 kg of silica gel, eluting with chloroform. The fractions containing only **9** and **10** were combined to give 37.87 g. Repetitive fractional crystallization from hexane gave 10.5 g, mp 101–103 °C, which by integration of the vinyl signals in the ^1H NMR spectrum was 92% **9** and 8% **10**: ^1H NMR (**9**) ($CDCl_3$) δ 1.21 (s, 3 H), 1.62 (m, 1 H), 2.10 (m, 1 H), 2.33 (m, 2 H), 2.61 (d, 1 H), 2.96 (d, 1 H), 3.17 (m, 1 H), 3.96 (s, 3 H), 5.25 (m, 1 H), 5.75 (m, 1 H), 6.81 (s, 1 H); ^1H NMR (**10**) ($CDCl_3$) δ 1.15 (m, 1 H), 1.25 (s, 3 H), 1.92 (m, 1 H), 2.29 (m, 2 H), 2.65 (d, 1 H), 2.95 (d, 1 H), 3.13 (m, 1 H), 3.96 (s, 3 H), 5.80 (m, 2 H), 6.81 (s, 1 H). Anal. Calcd for $C_{16}H_{16}Cl_2O_2$: C, 61.75; H, 5.18; Cl, 22.78. Found for **10**: C, 61.60; H, 5.31; Cl, 22.88. Found for **9**: C, 61.63; H, 5.08; Cl, 22.55.

2-Cyclopent-2′-enyl-6,7-dichloro-5-hydroxy-2-methyl-1-indanone (11a). Pyridine hydrochloride (125 g) was heated to 180 °C for 20 min. To the resulting melt was added **10** (12.5 g, 40.2 mmol) with vigorous stirring. The compound required 2 min to dissolve, and the reaction was heated at 180 °C for 15 min after achieving solution. The reaction was poured immediately into 500 mL of crushed ice with swirling. The precipitated product was allowed to stand for 45 min with some swirling, and the product was collected, washed with distilled water, dried with aspiration, and then dried in a vacuum oven at 60 °C for 4 h. Two recrystallizations from butyl chloride gave 4.52 g, mp 201–205 °C. The mother liquors were collected and the solvent was evaporated to leave 6.5 g of solid. This was dissolved in 65 g of pyridine hydrochloride at 180 °C for 15 min and worked up as above to give, after three crystallizations, 2.73 g, mp 201–204 °C. This solid was combined with the first product and recrystallized from butylchloride to give 5.75 g, mp 202–206 °C, 92% isomer purity by integration of the vinyl signals in the ^1H NMR spectrum: ^1H NMR ($CDCl_3$) (A60) δ 1.13 (s, 3 H), 1.25 (m, 1 H), 1.78 (m, 1 H), 2.20 (m, 2 H), 2.72 (d, 1 H), 2.85 (d, 1 H), 3.00 (m, 1 H), 5.62 (m, 0.08 H), 5.76 (m, 1.84 H), 5.89 (m, 0.08 H), 7.04 (s, 1 H). Anal. Calcd for $C_{15}H_{14}Cl_2O_2$: C, 60.62; H, 4.74; Cl, 23.86. Found: C, 60.41; H, 4.78; Cl, 24.05.

5-(Benzyloxy)-2-cyclopent-2′-enyl-6,7-dichloro-2-methyl-1-indanone (11b). To a solution of **11a** (5.75 g, 19.4 mmol) in 20 mL of DMF was added benzyl bromide (5.14 g, 3 mmol) and anhydrous potassium carbonate (8.3 g, 60 mmol). The mixture was stirred and heated in a bath at 75–80 °C for 3.5 h under nitrogen. The reaction was then poured onto 300 mL of crushed ice, filtered, and triturated with a small amount of methanol to give, after drying, 7.23 g. Recrystallization from methanol gave 6.36 g, mp 138–141 °C, which by integration of the vinyl signals in the ^1H NMR spectrum was 94% isomerically pure: ^1H NMR (**11b**) ($CDCl_3$) (A60) δ 1.15 (m, 1 H), 1.21 (s, 3 H), 1.80 (m, 1 H), 2.23 (m, 2 H), 2.62 (d, 1 H), 2.88 (d, 1 H), 3.10 (m, 1 H), 5.19 (s, 2 H), 5.60 (m, 0.12 H), 5.77 (m, 1.88 H), 6.88 (s, 1 H), 7.20–7.50 (m, 5 H). Anal. Calcd for $C_{22}H_{20}Cl_2O_2$: C, 68.23; H, 5.20; Cl, 18.31. Found: C, 68.15; H, 5.21; Cl, 18.50.

(17) This oxidation proved much more facile than that of metabolite **B** methyl ester as judged by time lapse TLC analysis of the respective reaction mixtures.

5-(Benzyloxy)-6,7-dichloro-2-(*trans*-3′-hydroxycyclopentyl)-2-methyl-1-indanone (12c). To a solution of mercuric acetate (5.62 g, 17.6 mmol) in 14 mL of distilled water was added 42 mL of THF with vigorous stirring followed by **11b** (6.17 g, 16.0 mmol). The reaction was stoppered and stirred under N_2 until the precipitate and yellow color were gone (6 days).[18] Then 18 mL of 3 NaOH was added dropwise and stirred for 5 min followed by sodium borohydride (0.302 g, 8.0 mmol) dissolved in 18 mL of 3 M NaOH added dropwise over a period of 2 min. The mixture was allowed to stir for 5 min and then partitioned between ether and distilled water, 200 mL each. The ether was separated, and the water layer (containing mercury precipitate) was extracted with ether (5 × 75 mL). The combined ether extracts were washed twice with water, dried ($MgSO_4$), and filtered, and the solvent was removed to leave 7.13 g of a mixture of alcohols and starting material. This mixture was chromatographed on 1 kg of silica gel eluting with chloroform. Those fractions which contained only pure trans-3′-hydroxy compound, as indicated by the methyl signals in the ^1H NMR spectrum, were combined and the solvent was removed to give 2.73 g of **12c**. This sample (free of other isomers) was used in the next step without further purification. A small sample was recrystallized from benzene–hexane for analysis, mp 92–96 °C: ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.0–2.0 (m, 6 H), 2.55 (m, 1 H), 2.66 (d, 1 H), 2.91 (d, 1 H), 4.30 (m, 1 H), 5.22 (s, 2 H), 6.85 (s, 1 H), 7.25–7.47 (m, 5 H). Anal. Calcd for $C_{22}H_{22}Cl_2O_3$: C, 65.19; H, 5.47; Cl, 17.46. Found, C, 65.38; H, 5.21; Cl, 17.29.

The first compound to emerge from the chromatography column was starting ene **12b**, 0.86 g. The first fraction containing product was composed of a mixture of two alcohols. The major isomer was 5-(benzyloxy)-6,7-dichloro-(*trans*-2′-hydroxycyclopentyl)-2-methyl-1-indanone (**12a**), and the minor isomer was 5-(benzyloxy)-6,7-dichloro-(*cis*-3′-hydroxycyclopentyl)-2-methyl-1-indanone (**12b**): ^1H NMR (**12a** and **12b**) ($CDCl_3$) δ 1.10–2.07 (m, 12 H), 1.21 (s, 3 H), 1.28 (s, 3 H), 2.26 (m, 1 H), 2.71 (d, 1 H), 2.78 (d, 1 H), 3.81 (d, 1 H), 3.14 (d, 1 H), 4.04–4.40 (m, 2 H), 5.24 (s, 4 H), 6.86 (s, 1 H), 6.89 (s, 1 H), 7.28–7.56 (m, 10 H). The next compound to emerge from the column was **12b**: ^1H NMR ($CDCl_3$) δ 1.10–1.90 (m, 6 H), 1.20 (s, 3 H), 2.24 (m, 1 H), 2.66 (d, 1 H), 3.11 (d, 1 H), 4.29 (m, 1 H), 5.21 (s, 2 H), 6.87 (s, 1 H), 7.27–7.50 (m, 5 H). This compound was followed by a mixture of **12c** and *trans*-4′-ol which in turn was followed by pure **12c**.

6,7-Dichloro-5-hydroxy-2-(*trans*-3′-hydroxycyclopentyl)-2-methyl-1-indanone (13a). A suspension of **12c** (2.73 g, 6.74 mmol) and 600 mg of 5% Pd/C in 200 mL of ethanol was hydrogenated at 1 atmosphere and room temperature until 1 equiv of hydrogen was taken up. The reaction was then filtered and the solvent evaporated to leave a solid which was triturated with a small amount of methanol, collected, and dried at 60 °C for 20 h to give 1.57 g of solid methanolate, mp 178–181 °C with partial melt and resolidification at approximately 100 °C. The sample (homogeneous on TLC) was used directly in the next step without further purification. A small sample was recrystallized from ethanol–water to give the crystalline ethanolate, mp 180–182 °C, partial melt and resolidification at 102–105 °C (loss of ethanol): ^1H NMR ($CDCl_3$) δ 1.00–2.10 (m, 6 H), 1.22 (s, 3 H), 1.26 (t, 3 H), 2.55 (m, 1 H), 2.71 (d, 1 H), 2.94 (d, 1 H), 3.72 (q, 2 H), 4.37 (m, 1 H), 6.96 (s, 1 H). Anal. Calcd for $C_{17}H_{22}Cl_2O_4$: C, 56.52; H, 6.14; Cl, 19.63. Found: C, 56.60; H, 6.00; Cl, 19.52.

[(6,7-Dichloro-2-(*trans*-3′-hydroxycyclopentyl)-2-methyl-1-oxo-5-indanyl)oxy]acetic Acid (13b). To a suspension of **13a** (1.40 g) in 5 mL of ethanol under N_2 was added 4.9 mL of 1 M NaOH in ethanol. The mixture was warmed gently to achieve solution and cooled to room temperature, and ethyl bromoacetate (0.82 g, 4.9 mmol) was added. The reaction mixture was stirred under N_2 in a bath at 70 °C for 1.5 h. After cooling to room temperature, 1 mL of 1 M NaOH was added followed by 0.11 mL of ethyl bromoacetate and the reaction mixture again stirred and heated in a bath at 75 °C for 1.5 h. The addition of 1 mL of 1 M NaOH in ethanol followed by 0.11 mL of ethyl bromoacetate followed by stirring and heating in a bath at 75 °C for 1.5 h was repeated, at which time TLC showed that the formation of **13b** was complete. Aqueous NaOH (10 mL of 20%) was added and the reaction mixture heated in a bath at 70 °C for 2 h, cooled, and poured into 200 mL of distilled water. The aqueous solution was washed with ether and then cooled to 0 °C by the addition of ice. Ether (150 mL) was added followed by the slow addition of 6 N HCl (~15 mL) with vigorous shaking until the aqueous layer was acidic (pH ~3). The aqueous layer was extracted five more times with ether, the combined ether extracts were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo at a bath temperature less than 40 °C. The resulting oil was dissolved in a small amount of ether (~10 mL) and allowed to crystallize. This gave, after drying, 0.74 g, mp 181–185 °C (D): ^1H NMR (360 MHz) (Me_2SO-d_6) δ 0.86 (m, 1 H), 1.10 (s, 3 H), 1.28–1.51 (m, 3 H), 1.59–1.74 (m, 2 H), 2.40 (m, 1 H), 2.74 (d, 1 H), 2.94 (d, 1 H), 4.10 (br s, 1 H), 4.42 (br s, 1 H), 5.00 (s, 2 H), 7.24 (s, 1 H). Anal. Calcd for $C_{17}H_{18}Cl_2O_5$: C, 54.71; H, 4.86; Cl, 19.00. Found: C, 54.67; H, 5.15; Cl, 18.79.

2-Cyclopent-4′-enyl-6,7-dichloro-5-hydroxy-2-methyl-1-indanone (14a). Pyridine hydrochloride (88 g) was preheated to 184 °C bath temperature after melting. To this melt was added **9** (8.8 g, 28.3 mmol) with stirring; the reaction mixture was then stirred for 18 min, at which time the internal temperature went from 184 to 179 °C. The reaction mixture was then poured onto crushed ice. The solid was filtered, washed with distilled water, and dried to give 8.78 g, mp 165–178 °C. Recrystallization from butyl chloride gave 5.8 g, mp 190–193 °C. The ^1H NMR spectrum shows 76% of **14a** with the remainder primarily 3-ene (δ 5.81): ^1H NMR (Me_2SO-d_6) (A60) δ 1.08 (s, 3 H), 1.60 (m, 1 H), 1.91 (m, 1 H), 2.24 (m, 2 H), 2.66 (d, 1 H), 2.90 (d, 1 H), 3.10 (m, 1 H), 5.20 (m, 0.76 H), 5.71 (m, 0.76 H), 5.81 (m, 0.48 H), 7.03 (s, 1 H).

5-(Benzyloxy)-2-cyclopent-4′-enyl-6,7-dichloro-2-methyl-1-indanone (14b). To a solution of **14a** (5.8 g, 19.5 mmol) in 30 mL of DMF was added potassium carbonate (8.3 g, 60 mmol). The mixture was stirred under N_2 in an oil bath at 75 °C for 45 h, cooled, and poured onto crushed ice. The tacky solid was collected, washed with distilled water, and then triturated with a small amount of methanol to give 7.0 g, mp 114–124 °C. The ^1H NMR spectrum is consistent with 73% **14b**, with the remainder being primarily 3-ene. TLC was homogeneous, and this product was used directly in the next step. A small amount was recrystallized for analysis from methanol, mp 124–128 °C: ^1H NMR ($CDCl_3$) (A60) δ 1.3–2.5 (m, 4 H), 2.64 (d, 1 H), 2.84 (d, 1 H), 3.10 (m, 1 H), 5.0–5.3 (m, 2.73 H), 5.62 (m, 0.73 H), 5.74 (m, 0.54 H), 6.89 (s, 1 H), 7.2–7.54 (m, 5 H). Anal. Calcd for $C_{22}H_{20}Cl_2O_2$: C, 68.22; H, 5.20; Cl, 18.31. Found: C, 68.22; H, 5.16; Cl, 18.28.

5-(Benzyloxy)-6,7-dichloro-2-(*trans*-4′-hydroxycyclopentyl)-2-methyl-1-indanone (15c). Mercuric acetate (6.20 g, 19.4 mmol) was dissolved in warm distilled water (10 mL), and THF (30 mL) was added with vigorous stirring followed by the addition of finely powdered **14b** (6.80 g, 17.6 mmol). The reaction mixture was stirred under nitrogen for 72 h.[18] At this time there was still a small amount of precipitate remaining. The reaction mixture was cooled in a cold water bath, and 18 mL of 3 M NaOH was added dropwise and stirred for 3 min. Sodium borohydride (0.332 g, 8.80 mmol), dissolved in 16 mL of 3 M NaOH, was added dropwise over a period of 2 min, and stirring was continued for 3 min. The dark mixture was poured into 250 mL of ether and the water and mercury precipitate separated. The remaining ether solution was washed with distilled water, dried ($MgSO_4$), and filtered, and the solvent was evaporated to leave 6.9 g of a mixture of alcohols and starting material. The components of the mixture were separated by chromatography on 1 kg of silica gel, eluting with chloroform. Each fraction containing product was monitored by ^1H NMR spectroscopy. Those fractions containing greater than 98% of the desired product **15c**, as indicated by integration of the methyl signals in the ^1H NMR spectrum, were combined, the solvent was evaporated, and the residue was triturated with hexane to give 1.74 g, mp 102–105 °C. This product was used without further purification in the next step. A small portion was recrystallized from benzene–hexane for analysis, mp 102–105 °C: ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.17–2.32 (m, 6 H), 2.55 (m, 1 H), 2.72 (d, 1 H), 2.96 (d, 1 H), 4.28 (m, 1 H), 5.22 (s, 2 H), 6.87 (s, 1 H), 7.27–7.56 (m, 5 H). Anal. Calcd for $C_{22}H_{22}Cl_2O_3$: C, 65.32; H, 5.38; Cl, 17.67. Found: C, 65.19; H, 5.47; Cl, 17.49.

(18) This long reaction time is due to the insolubility of the ene. In a probe run (not reported) of a diastereoisomeric mixture of **2** and **3**, the reaction was complete in 4 h.

From the chromatography column, a sample of the starting material (1.5 g) was isolated from the first fractions containing indanone followed by fractions containing mixtures of 5-(benzyloxy)-6,7-dichloro-2-(*trans*-5′-hydroxycyclopentyl)-2-methyl-1-indanone (**15a**) and 5-(benzyloxy)-6,7-dichloro-2-(*cis*-4′-hydroxycyclopentyl)-2-methyl-1-indanone (**15b**). The two structures of the partially separated compounds were assigned on the basis of their ^1H NMR spectra. Compound **15b** had the distinctive features of compound **4**. In **15a** the carbinol hydrogen is highly shielded. ^1H NMR ($CDCl_3$) (partial) δ 2.72 (d, 1 H), 2.97 (d, 1 H), 3.79 (m, 1 H). Several fractions later, the desired product **15c** emerged and, by integration of the methyl signals, was greater than 98% isomerically pure.

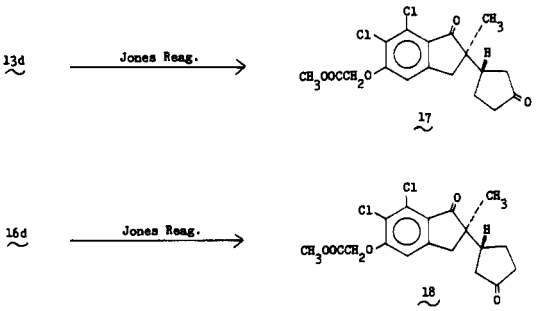
6,7-Dichloro-5-hydroxy-2-(*trans*-4′-hydroxycyclopentyl)-2-methyl-1-indanone (16a). To a solution of **15c** (1.74 g, 4.30 mmol) in 120 mL of ethanol was added 300 mg of 5% Pd/C. The mixture was hydrogenated at room temperature and 1 atm until 1 equiv of H_2 was consumed. The reaction was flushed with N_2 and filtered from the catalyst and the solvent evaporated to leave 1.1 g of product, mp 243–246 °C dec. This product was homogeneous on the TLC and used in the next step without further purification. A small amount was recrystallized from ethanol for analysis, mp 243–246 °C dec. ^1H NMR ($CDCl_3$/Me_2SO-d_6) (360 MHz) δ 1.02 (m, 1 H), 1.10 (s, 3 H), 1.22 (m, 2 H), 1.43 (m, 1 H), 1.76 (m, 2 H), 2.37 (p, 1 H), 2.68 (d, 1 H), 2.92 (m, 1 H), 3.34 (bm, 1 H), 4.03 (bm, 1 H), 4.34 (bm, 1 H), 7.02 (s, 1 H). Anal. Calcd for $C_{15}H_{16}Cl_2O_3$: C, 57.16; H, 5.12; Cl, 22.50. Found: C, 57.46; H, 5.28; Cl, 22.40.

[(6,7-Dichloro-2-(*trans*-4′-hydroxycyclopentyl)-2-methyl-1-oxo-5-indanyl)oxy]acetic Acid (16c). To a suspension of **16a** (0.95 g, 3.02 mmol) in 10 mL of dry ethanol under N_2 was added 1 M NaOH in ethanol (3.3 mL, 3.30 mmol) and the mixture warmed gently to effect solution. Ethyl bromoacetate (0.554 g, 3.3 mmol) was added, and the solution was heated at a bath temperature of 70 °C with stirring under N_2 for 1 h. TLC showed incomplete alkylation. The reaction mixture was cooled to room temperature, 0.5 mL of NaOH in EtOH was added followed by 0.11 mL of ethyl bromoacetate, and the resulting mixture heated at 75 °C bath temperature for 1 h. The process of adding NaOH followed by ethyl bromoacetate and heating at 75 °C for 1 h was repeated 3 times when TLC showed that the phenol had been alkylated to give **16b**. The esters were hydrolyzed by adding 7 mL of a 20% aqueous NaOH and heating with stirring at 75 °C bath temperature for 1.75 h. The solution was cooled to room temperature and poured into 200 mL of distilled water. The aqueous solution was extracted with ether and then cooled by the addition of ice. Ether (100 mL) was added followed by 6 N HCl (10 mL) added dropwise with shaking until the aqueous phase was strongly acidic; the temperature was still at 0 °C. After separating the layers, the aqueous layer was extracted with ether (5 × 75 mL). The combined ether extracts were washed with distilled water (25 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to leave 0.95 g of a gum. The gum was triturated with a small amount of ether, to give 0.70 g of **16c**, mp 180–183 °C dec: ^1H NMR ($CDCl_3$) δ 0.98 (m, 1 H), 1.18–1.87 (m, 5 H), 1.13 (s, 3 H), 2.38 (m, 1 H), 2.75 (d, 1 H), 2.95 (d, 1 H), 4.03 (br s, 1 H), 4.37 (br s, 1 H), 5.00 (s, 2 H), 7.24 (s, 1 H). Anal. Calcd for $C_{17}H_{18}Cl_2O_5$: C, 54.71; H, 4.86; Cl, 19.00. Found: C, 54.63; H, 5.08; Cl, 18.86.

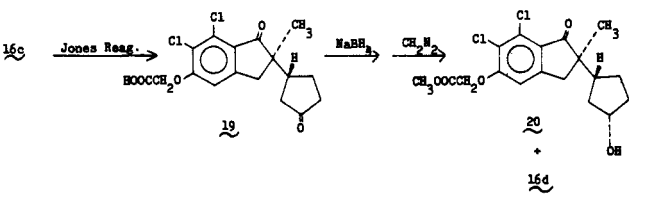
Methyl [(6,7-Dichloro-2-(*trans*-3′-hydroxycyclopentyl)-2-methyl-1-oxo-5-indanyl)oxy]acetate (13d). To a solution of **13c** (4.9 mg) in 1 mL of methanol was added an ether solution of diazomethane until the yellow color persisted. The reaction was allowed to stand for 20 min, and then nitrogen was bubbled into the solution until the yellow color was gone. The solution was then warmed in an air bath at 40 °C and a stream of purified nitrogen directed at the surface to remove the solvent. This sample was dried at ambient temperature under vacuum for 20 h with use of P_2O_5 as a desiccant. This sample, an oil, was identical with metabolite C methyl ester in all its spectral, GLC, and TLC properties.

Methyl [6,7-Dichloro-2-(3′-oxocyclopentyl)-2-methyl-1-oxo-5-indanyl)oxy]acetate (17). To a solution of **13d** (crude; derived from 11 mg of acid) in 1 mL of acetone at 0 °C was added 11 drops (excess) of Jones reagent. After stirring for 13 min, the reaction mixture was extracted with ether and washed with water, the ether layer dried, and the solvent removed to leave an oil. The oil was dissolved in approximately 1 mL of ether and allowed to crystallize to give 4.9 mg, mp 140–142 °C. The spectral properties of this compound were identical to the diketone oxidation product of metabolite C methyl ester.

Scheme V



Scheme VI



Methyl [(6,7-Dichloro-2-(*trans*-4′-hydroxycyclopentyl)-2-methyl-1-oxo-5-indanyl)oxy]acetate (16d). To a solution of **16c** (44 mg) in 2 mL of methanol was added diazomethane until the pale yellow color persisted. The excess diazomethane and methanol were removed in a stream of purified nitrogen with bath at 40 °C. The oily product, **16d**, was dried for 20 h at room temperature at 0.1 mm. TLC was homogeneous; the ^1H NMR and IR spectra of this sample differed from those of metabolite C methyl ester: IR (MeOH) 1705, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, 6 H), 1.24 (s, 3 H), 2.55 (m, 1 H), 2.73 (d, 1 H), 2.97 (d, 1 H); 3.83 (s, 3 H), 4.30 (m, 1 H), 4.80 (s, 2 H), 6.69 (s, 1 H).

Methyl [(6,7-Dichloro-2-methyl-(4′-oxocyclopentyl)-1-oxo-5-indanyl)oxy]acetate (18). To a solution of **16d** (crude, prepared from 11.2 mg of **16c**) in 1 mL of acetone at 0 °C was added 11 drops (an excess) of Jones reagent (Scheme V). This reaction solution was allowed to stand for 25 min and worked up by pouring onto ice. The product was extracted with ether, and the combined ether extracts were washed with saturated $NaHCO_3$ solution and then with water. The ether was dried over anhydrous $MgSO_4$ and filtered and the solvent evaporated. The remaining oil was dissolved in approximately 1 mL of ether. Upon standing, the product crystallized giving 3 mg, mp 173–175 °C. The spectral properties of this compound were identical with those of the oxidation product of metabolite B methyl ester and, except for optical rotation, were also identical with those of metabolite D methyl ester.

***trans*-4′-Ol (16c) to 4′-One (19) to *cis*- (20) and *trans*-4′-Ol (16d).** To a solution of **16c** (11.2 mg, 0.03 mmol) in acetone at 0 °C was added Jones reagent (6 drops, excess) (Scheme VI). TLC after 30 min showed the reaction to be complete. The reaction was allowed to stir an additional 20 min and worked up by adding 1 mL of 2-propanol with stirring. The reaction was then poured into 20 mL of water and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and filtered, and the solvent was removed to leave 10 mg of [(6,7-dichloro-2-methyl-1-oxo-2-(4-oxocyclopentyl)-5-indanyl)oxy]acetic acid (**19**). This crude acid was dissolved in 1 mL of ethanol and to this was added 0.3 mL of 3 M NaOH followed by 0.3 mL of distilled water. To the resulting mixture was added a solution of $NaBH_4$ (0.6 mg) in 0.5 mL of 3 M NaOH. After stirring for 1 h, the reaction mixture was washed into 25 mL of water. The aqueous solution was then washed with ether, and NaCl was added followed by ice to cool the aqueous layer to 0 °C. Ether (25 mL) was added and the aqueous phase made strongly acidic by the slow addition of 6 N HCl with frequent shaking. After five more extractions with ether, the combined ether extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated to leave an oily mixture of alcohols.

This mixture was dissolved in 3 mL of methanol. Diazomethane in ether was added until a persistent yellow color showed an excess. The reaction was allowed to stand for 10 min, and then N_2 was bubbled through to dispel excess diazomethane. A stream of N_2 was directed at the surface while warming in an air stream at 40 °C to remove the solvent. The esterified mixture of alcohols was separated from minor impurities by repetitive two-dimensional TLC (eluent, system B) as described earlier. The ^1H NMR spectrum of the mixture of alcohols clearly showed them to be compounds **16d** and **20** in a ratio of 2:3, respectively: **16d** ^1H NMR ($CDCl_3$) (partial) δ 2.72 (d, 1 H), 2.91 (d, 1 H); **20** ^1H NMR ($CDCl_3$) (partial) δ 0.93 (m, 1 H), 2.68 (d, 1 H), 3.20 (d, 1 H).

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Registry No. **2**, 57296-70-5; **3a**, 97522-88-8; **3b**, 97550-78-2; **8**, 53107-38-3; **9**, 97522-89-9; **10**, 97522-90-2; **11a**, 97522-91-3; **11b**, 97522-92-4; **12a**, 97522-93-5; **12b**, 97522-94-6; **12c**, 97589-60-1; **13a**, 97522-95-7; **13c**, 97589-61-2; **13d**, 97522-96-8; **14a**, 97522-97-9; **14b**, 97522-98-0; **15a**, 97590-49-3; **15b**, 97589-62-3; **15c**, 97589-63-4; **16a**, 97589-64-5; **16c**, 97589-65-6; **16d**, 97590-50-6; **17**, 97522-99-1; **18**, 97523-00-7; **19**, 97589-66-7; **20**, 97589-67-8; **A**, 97523-01-8; **B**, 97589-68-9; 2-cyclopentenone, 930-30-3; 3-chlorocyclopentene, 96-40-2.

Supplementary Material Available: Table of chemical shifts of 1 and metabolite methyl esters (1 page). Ordering information is given on any current masthead page.

Low Temperature Free-Radical Reactions Initiated with *tert*-Butyl *p*-Benzoylperbenzoate. Selective Acyl Radical Additions to Substituted Olefins

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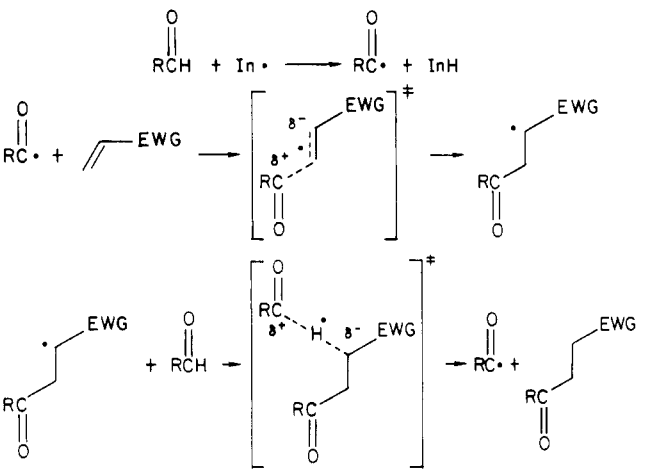
Competition experiments involving acyl radical additions to simple and electron-deficient olefins showed a definite preference for acylation of the latter olefin. This selectivity was significantly enhanced by using low temperature initiation with *tert*-butyl *p*-benzoylperbenzoate (1), which allows selective initiation of free-radical cyclization reactions that have synthetic importance.

In recent years free-radical cyclizations, originally elaborated by Julia,[1] Beckwith,[2] and others,[3] have been applied by Hart[4] and Stork[5] and their co-workers in a variety of total syntheses. Virtually all applications of radical cyclizations use a common strategy—a free-radical center is generated in proximity to a double bond such that addition of the radical to the double bond gives a five- or six-membered ring. These radical processes invariably employ thermal initiators as radical sources, such as AIBN or dibenzoyl peroxide. The reaction temperatures thus required are typically in excess of 50 °C simply because the initiators are stable at lower temperatures. Consequently, use of thermal initiators may impair the ability to prepare or employ thermally unstable reactants or intermediates, use volatile reactants, or enhance stereo- and regioselectivity.

tert-Butyl *p*-benzoylperbenzoate (1),[6] a photoinitiator, circumvents the potential disadvantages of a thermal initiation step. Radical centers, essentially identical with those produced from either benzoyl peroxide or *tert*-butyl perbenzoate, are formed via a singularly efficient photochemical dissociation process over a wide temperature range[7] and should prove useful in low temperature free-radical initiation. The quantum yield of homolysis of the peroxy linkage in (1) at 360 nm is 0.92 in benzene. In addition, this photochemical dissociation process utilizes long wavelength UV (360 nm) absorption, thus avoiding possible photochemical side reactions arising from excitation of chromophoric reactants such as α,β-unsaturated carbonyl compounds ($\lambda_{max} \leq 300$ nm). This photochemical

Scheme I



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(7) *tert*-Butyl *p*-benzoylperbenzoate is essentially a benzophenone combined with a *tert*-butyl perbenzoate moiety. When irradiated at 366 nm, one produces a benzophenone triplet which is quenchable, but marginally so, by typical triplet quenchers. An intersting mechanistic question is just how does the energy absorbed by the benzophenone component find its way to the weak -0-0- bond. We are studying this question at the present time.

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