Photochemistry of Substituted Benzoylformate Esters. A Convenient Method for the Photochemical Oxidation of Alcohols

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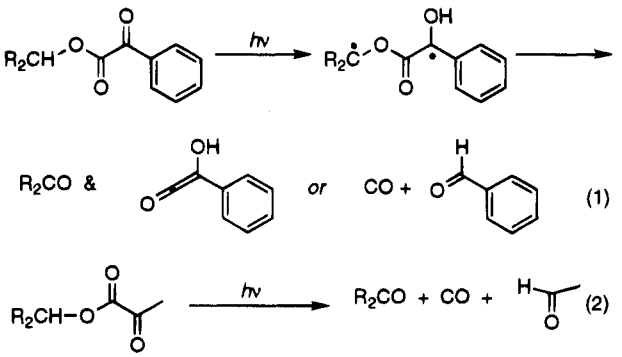
The production of aldehydes and ketones via photochemical hydrogen atom transfer in substituted benzoylformate esters of primary and secondary alcohols has been investigated. Substituent effect studies have shown that (2,4-dimethoxybenzoyl)formate (DMBF) esters give superior performance. A divergence in the byproducts derived from the ester group (the benzaldehyde (and presumably CO) or the benzoic acid (and presumably CO_2)) is observed depending on the presence of oxygen. A mechanistic rationale for the formation of the benzoic acid has been advanced based on the known trapping of intermediate 1,4-biradicals by oxygen followed by fragmentation.

Introduction

Photochemically-removable groups have several applications in bioorganic chemistry. Besides providing deprotection that can be accomplished under conditions that leave most other protecting groups untouched,[1] they can be used in the technique of caging,[2] wherein a biological molecule is rendered both inactive and membrane-permeable by the protecting group. Once located inside a cell or an enzyme active site,[3] the protecting group can be released on a time scale much faster than that of the biological or enzymatic process, permitting the study of the time evolution of the phenomena.



In this work, we have aimed to protect the intermediate oxidation state of carbon, aldehyde or ketone, with a photochemically-removable group as a complement to our recently-developed approaches for the photochemically-labile protection of functional groups such as alcohols and carboxylic/phosphoric acids.[4] Known nitrobenzyl photochemistry might be used for the deprotection of acetals derived from a nitrobenzyl alcohol, but it has significant disadvantages, including reactive, toxic, and highly-absorbing byproducts such as nitrosocarbonyl and azo compounds. We have therefore investigated the photochemical oxidation of an alcohol to the carbonyl oxidation state.

Carbonyl production is one photochemical reaction pathway available to α-ketoacids and esters thereof. For example, early work by Huyser and Neckers[5] showed that Pyrex-filtered photolysis of cyclohexyl benzoylformate in ethanol produces cyclohexanone (86%) and ethyl mandelate (82%) in a reaction that was explained as shown in eq 1. Norrish Type 2 reaction would produce the ketone and a hydroxyketene intermediate that could be trapped by the alcohol. On the other hand, Leermakers reported that broadband irradiation of ethyl benzoylformate in benzene produces benzaldehyde, carbon monoxide, and acetaldehyde in only ~30% yield each.[6] Davidson has reported that the direct and sensitized irradiation of ethyl benzoylformate in the presence of oxygen produces carbon dioxide in 14–18% yield, but did not study the other products.[7] Binkley showed[8] that pyruvate esters of sugar alcohols are transformed into ketoses, acetaldehyde, and (presumably) CO by Pyrex-filtered irradiation (eq 2), but this is likely too short a wavelength for most biological applications. Benzoylformates would have more attractive wavelength, extinction coefficient, and intersystem crossing rates, and these key parameters could be modified *via* substituents. Scaiano has shown that alkyl benzoylformates undergo photolysis at 366 nm by an n,π^* triplet mechanism to produce the carbonyl compound.[9] The quantum yields for formation of carbonyl are uniformly high (0.4–0.73), and distilled yields are in the 80% range. The lifetimes of the intermediate triplets are 0.5–1 μs. Byproducts identified in this study are the hydroxyketene, or the benzaldehyde plus carbon monoxide. The ketene accumulates during the reaction as a yellow species that can be dissipated by inclusion of water. Kresge has used the addition of water to the ketene to generate phenylethenetriol (the enol of man-

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(2) Adams, S. R.; Kao, J. P. Y.; Tsien, R. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7957–7968. *Chemical Triggering* Sabongi, G. J., Plenum, New York, 1987. *Photochemical Probes in Biochemistry*; Nielsen, P. E., Ed., Kluwer: Boston, 1989. *Bioorganic Photochemistry*, Morrison, H., Ed.; Wiley: New York, 1990.

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(5) Huyser, E. S.; Neckers, D. C. *J. Org. Chem.* **1964**, *29*, 276.

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(7) Davidson, R. S.; Goodwin, D.; Pratt, J. E. *Tetrahedron* **1983**, *39*, 1069–1074. *Tetrahedron* **1983**, *39*, 2373.

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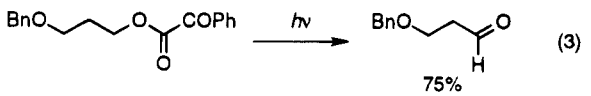
Table 1. Oxidation of Acetophenones to Substituted Benzoylformic Acids

methyl ketone	equiv of SeO_2	reflux (h)	yield
p-methoxyacetophenone	1.0	3.0	59
3,4-dimethoxyacetophenone	1.2	4.5	82
2,4-dimethoxyacetophenone	2.6	5.0	94

delic acid).[10] One further investigation of the photochemistry of benzoylformates has been reported by Kraus,[11] who showed examples of direct oxidation by 1,5-hydrogen atom abstraction (eq 3) but also observed a 1,9-hydrogen migration process in some cases. On the basis of these precedents, irradiation of substituted benzoylformate esters was expected to be an efficient route to carbonyl compounds.



(3)

Results

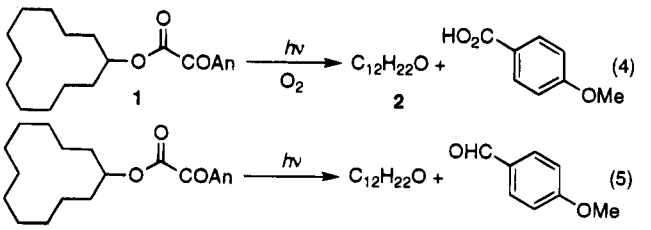
A variety of benzoylformic esters was required to examine the substituent effects in their irradiation. These compounds were prepared by a conventional route involving selenium dioxide oxidation of the corresponding acetophenones to the benzoylformic acids (Table 1), which were then converted into their cyclododecyl esters by activation with carbonyldiimidazole followed by treatment with cyclododecanol. NMR experiments in d_6-benzene with an internal standard of ethylene carbonate and a 5 s delay time to ensure complete proton relaxation were used to examine the efficiencies of the production of cyclododecanone relative to the parent system from the following substituted cyclododecyl benzoylformates: 3,4-dimethoxy, 2,4-dimethoxy, 4-methoxy, 3,4,5-trimethoxy, and 4-dimethylamino. These irradiations were conducted in a Rayonet reactor with 350 nm lamps. These experiments showed that the 4-methoxy, 2,4-dimethoxy, and the unsubstituted parent give the cleanest reactions and highest yields. The dimethylamino-substituted benzoylformate was examined in several other solvents because the n, π^* and π,π^* photochemistry of *p*-aminoacetophenones is divergent and solvent-dependent.[12] It is converted within 30 min of irradiation in hexane or cyclohexane, as shown by gas chromatographic analysis with eicosane as internal standard, to cyclododecanone in 75% yield, but gives little or no ketone in methanol, acetonitrile, benzene, chloroform, carbon tetrachloride, or dichloromethane. This behavior affords a useful opportunity to turn off or turn on the photochemistry with the choice of solvent.

The preparative photochemistry of cyclododecyl (*p*-methoxybenzoyl)formate (**1**) was first examined. In argon-purged acetonitrile (1 mg/mL), it is converted within 15 min of irradiation at 350 nm to cyclododecanone (**2**) and *p*-anisic acid (eq 4). This latter product was unexpected based on previous reports on analogous reactions; control experiments demonstrate that the expected product, *p*-anisaldehyde, is stable under the irradiation conditions. When this reaction is conducted in freeze-thaw degassed acetonitrile, the aldehyde is produced along with other unknown aromatic compounds and the ketone (eq 5).

Table 2. Conversion of Alcohols to the (2,4-Dimethoxybenzoyl)formate (DMBF) Esters

alcohol	percent yield
cyclododecanol	87[a]
cyclododecanemethanol	87
cis-Methyl 2,2-dimethyl-3-hydroxycyclobutan-1-yl acetate	90
(*1R*,2*S*,5*R*)-menthol	73

[a] UV: 275 nm (ϵ 1.42 × 10^4 (max)), 300 nm (ϵ 2.82 × 10^3), 309 nm (ϵ 1.00 × 10^4 (max)), 340 nm (ϵ 517), 350 nm (ϵ 272).

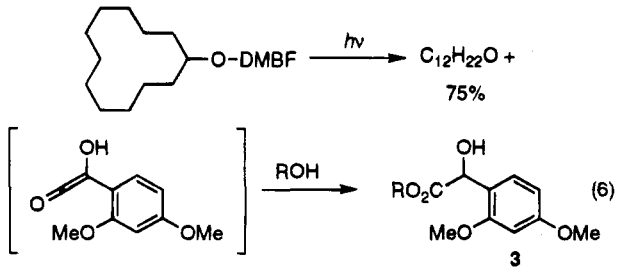


Because of its high reaction rate (much faster in benzene than in acetonitrile) and high (>90%) yield in the production of cyclododecanone, the (2,4-dimethoxybenzoyl)formate (DMBF) group was chosen for further development. Four esters were prepared from 2,4-dimethoxybenzoylformic acid (Table 2) using carbonyl diimidazole activation. The absorption properties of cyclododecyl 2,4-dimethoxybenzoylformate in diethyl ether are also given in Table 2. The photochemical behavior of these compounds is dependent on the presence of oxygen and substitution at the carbinol center. Primary and secondary alcohols give similar yields of the desired carbonyl irrespective of the presence or absence of O_2, but the DMBF-derived fragment is different. When O_2 is present, 2,4-dimethoxybenzoic acid is obtained, but in degassed solutions 2,4-dimethoxybenzaldehyde is produced. The DMBF ester of cyclododecanemethanol produces cyclododecanecarboxaldehyde on irradiation in degassed benzene, but it was rapidly air-oxidized upon isolation. In order to eliminate the variable of the oxygen concentration, the majority of these studies were done in solutions degassed by freeze-pump-thaw cycling; purging with oxygen-free gases does not seem effective in reducing the oxygen concentrations sufficiently to prevent carboxylic acid formation. However, this is likely not crucial for reactions where the alcohol-derived fragment is the only desired material, and in some biological applications the acid may be more innocuous than the aldehyde.

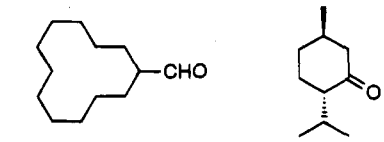
The cyclododecyl DMBF ester provides cyclododecanone on irradiation in acetonitrile or benzene in very high yield by GLC; the small scale isolated, chromatographed yields are in the 75–90% range. When the benzene includes 2% 2-propanol, the isopropyl ester of mandelic acid (**3**) is obtained among other products, indicating the intermediacy of the hydroxyketene (eq 6). When it contains neither oxygen nor alcohol, the other product is 2,4-dimethoxybenzaldehyde, as was the case with **1**. However, when oxygenated benzene is used, the other product is 2,4-dimethoxybenzoic acid.

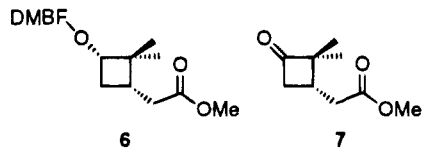
With the cyclododecanemethyl ester, anoxic irradiation in benzene produces the benzaldehyde and the cyclododecanecarboxaldehyde **4** in comparable yield (65%), as occurs with the conversion of the menthyl ester to menthone **5**.

(10) Chiang, Y.; Kresge, A. J.; Pruszynski, P.; Schepp, N. P.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 792–793.
(11) Kraus, G. A.; Wu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8705–8707.
(12) Porter, G.; Suppan, P. *Proc. Chem. Soc.* **1964**, 191–192.



Because the oxidation of cyclobutanols to cyclobutanones through the agency of chromium reagents can be problematic,[13] we examined the irradiation of **6** (the DMBF ester of a pinene-derived cyclobutanol we have previously studied)[14] to produce **7**. When this reaction is conducted in the presence of trace methanol, a mixture of the mandelate ester (**3**, R = Me) derived from trapping of the intermediate hydroxyketene and the benzaldehyde are obtained in addition to **7**.

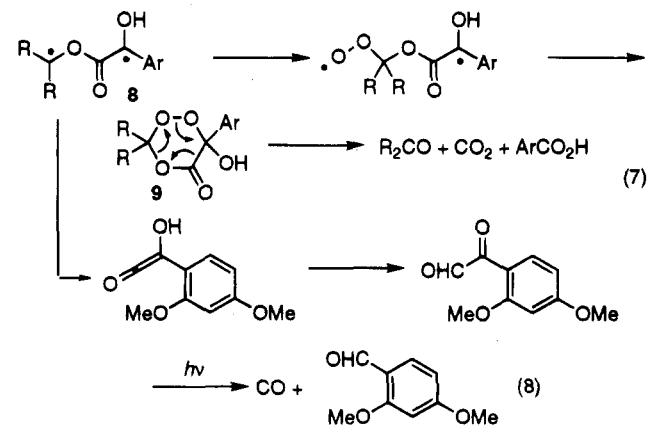




In order to address the utility of this chemistry for preparative purposes, cyclododecyl dimethoxybenzoylformate was also irradiated in benzene at a concentration of 10 mg/mL. The isolated yield of cyclododecanone was 82% and the reaction time was 3 h.

Discussion

While the photochemical reaction pathways available to benzoylformate esters, at least in skeletal form, were available before this study, their preparative photochemistry was not well-established. The effect of oxygen discovered here is novel and can be readily explained. It has been shown by Scaiano that the 1,4-biradical produced during other Norrish Type 2 processes can be trapped by oxygen to produce a peroxy radical.[15] This precedent can be applied to the fairly long-lived biradical that has been earlier detected in these reactions (eq 7).[16] If it reacts with molecular oxygen, formation of a 1,3,4-trioxane intermediate **9** can be proposed. A cyclic reorganization of electrons would generate the carbonyl, benzoic acid, and carbon dioxide. Though the latter was not studied here, it has been detected in the earlier studies of benzoylformate photochemistry.[7] Tautomerization of the hydroxyketene to the arylglyoxal followed by photochemical decarbonylation[17] would explain the formation of the aldehyde when oxygen is absent (eq 8).



In addition to use of this method in photodeprotection, it may prove to be a practical and convenient method for oxidation in organic synthesis, particularly because of the long wavelength radiation that can be used.

Experimental Section

(2,4-Dimethoxybenzoyl)formic Acid. A round bottom flask which had been flushed with argon was charged with 10.00 g (0.055 mol) of 2,4-dimethoxyacetophenone, 15.94 g (0.144 mol) of SeO_2, and 50 mL of freshly distilled pyridine. The solution was heated at 110 °C. The temperature gradually dropped to 90 °C over 1 h and was heated for an additional 4 h. The solution was concentrated by rotary evaporator until a small amount of liquid was present. The black selenium was rinsed several times with ethyl acetate. The combined organic layers were transferred to a separatory funnel containing 100 mL of 0.1 M HCl. The aqueous layer was extracted three times with ethyl acetate. The aqueous layer was discarded, and the organic layers were combined and extracted several times with saturated aqueous $NaHCO_3$. The aqueous layers were combined, brought to pH 1 with concd HCl, and extracted three times with ethyl acetate. The final organic layers were dried over Na_2SO_4 and concentrated, producing 10.985 g (94%) of (2,4-dimethoxybenzoyl)formic acid as a yellowish solid, mp 103–104 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 1H), 6.62 (dd, J = 8.8, 2.2 Hz, 1H), 6.47 (d, J = 2.2 Hz, 1H), 3.90 (s, 6H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 208.42, 186.53, 167.71, 163.34, 132.69, 116.01, 108.18, 98.70, 56.37, 56.11; IR (KBr) 3454, 2987, 1714, 1652 cm^{-1}; HRMS (FAB, neg ion, $(M-H)^-$) m/e calcd for $C_{10}H_9O_5$ 209.0450, found 209.0441.

(4-Methoxybenzoyl)formic Acid. By a procedure similar to that described above was produced the title compound in 59% yield: mp 84 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 3.92 (s, 3H); IR (KBr) 3155, 2850, 1741, 1662, 1651, 1602, 1511, 1426, 1262, 1200, 1162, 1014, 974, 853 cm^{-1}; LRMS (FAB, neg ion) 179 $(M-H)^-$; HRMS m/e calcd for $C_9H_8O_4$ 180.0423, found 180.0420.

Esterification of (2,4-Dimethoxybenzoyl)formic Acid. A round bottom flask that had been flushed with argon was charged with 500 mg (2.379 mmol, 1.5 equiv) of 2,4-dimethoxybenzoylformic acid, 386 mg (2.379 mmol, 1.5 equiv) of carbonyldiimidazole, and 25 mL of freshly distilled THF. After

(13) Wiberg, K.; Mukherjee, S. K. *J. Am. Chem. Soc.* **1974**, *96*, 6647. Rocek, J.; Hasan, F. *J. Am. Chem. Soc.* **1974**, *96*, 534. Rocek, J.; Aylward, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 5452.

(14) Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824–5831.

(15) Small, R. D., Jr.; Scaiano, J. C. *J. Am. Chem. Soc.*, **1978**, *100*, 4512.

(16) Kraus's study of the photochemistry of the phenylglyoxalate ester of a cyclopropyl carbinol, which gave a quantitative yield of the corresponding ketone, raises questions concerning such a mechanism. It might be expected that a radical adjacent to a cyclopropane ring would undergo ring opening at a rate competitive with even a diffusion-controlled bimolecular reaction, at least if the simple cyclopropylcarbinyl radical is used as a model. However, biradical **8** is expected to be much more stable than a cyclopropylcarbinyl radical, as is evidenced by the long lifetime measured by Scaiano. Both radical sites are tertiary, oxygen-substituted, and conjugated, which likely increases the kinetic stability.

(17) Maruyama, K.; Ono, K.; Osugi, J. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 847–851.

30 min were added a solution of alcohol (1.59 mmol) and 5 mg of sodium ethoxide in 25 mL of THF. The reaction mixture was transferred to a separatory funnel containing 50 mL of saturated aqueous $NaHCO_3$ and 100 mL of ethyl acetate. The aqueous layer was extracted three times with 100 mL of ethyl acetate. The organic layers were then combined, dried over Na_2SO_4, and concentrated with a rotary evaporator.

Cyclododecyl (2,4-Dimethoxybenzoyl)formate. After a reaction time of 25 h on a 3.4 mmol scale, the product was purified by silica gel chromatography with 30% dichloromethane, 5% ethyl acetate, and 65% hexanes: mp 134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 1H), 6.59 (dd, =8.8, 2.1 Hz, 1H), 6.43 (m, 1H), 5.23 (d, J = 2.1 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 1.80 (m, 2H), 1.67 (m, 2H), 1.20–1.54 (m, 18H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 185.30, 166.54, 165.74, 162.14, 132.92, 115.88, 106.51, 98.03, 74.01, 55.72, 55.68, 28.92, 24.01, 23.67, 23.32, 23.16, 20.85; IR (neat) 2935, 2859, 1733, 1650, 1593, 1470, 1424, 1288, 1248, 1197, 1111, 991, 844 cm^{-1}; UV-vis (c = 1.374 × 10^{-4}, diethyl ether) λ_{max} 275 (14200), 309 (10000) nm; HRMS (M + H$^+$) m/e calcd for $C_{22}H_{33}O_5$ 377.2328, found 377.2337; LRMS (CI) 377 (M + H$^+$), 394 (M + NH_4^+).

Cyclododecanemethyl (2,4-Dimethoxybenzoyl)formate. After a reaction time of 25 h, column chromatography with 25% ethyl acetate/75 % hexanes produced 568 mg of the title ester (1.454 mmol, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 1H), 6.61 (dd, J = 8.8, 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 4.16 (d, J = 5.4 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 1.92 (m, 1H), 1.50 –1.20 (m, 22H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 184.88, 166.62, 166.17, 162.19, 132.65, 115.64, 106.67, 97.91, 69.18, 55.93, 55.60, 33.23, 26.09, 24.16, 23.57, 23.28, 21.71; IR (neat) 2933, 2856, 1738, 1658, 1601, 1470, 1286, 1217, 1128, 1026, 998, 841 cm^{-1}; HRMS m/e calcd for $C_{23}H_{35}O_5$: 391.2484, found 391.2500; LRMS (CI) 391 (M + H$^+$), 408 (M + NH_4^+).

(2,4-Dimethoxybenzoyl)formic Acid, *cis*-Methyl 2,2-Dimethyl-3-hydroxycyclobutaneacetate Ester. After a reaction time of 25 h on a 3.6 mmol scale, purification by column chromatography produced the (2,4-dimethoxybenzoyl)-formic acid ester of *cis*-methyl 2,2-dimethyl-3-hydroxycyclobutaneacetate in a 90% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 1H), 6.60 (dd, J = 8.8, 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 4.87 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H), 2.28 - 2.63 (m, 3H), 2.12 (m, 1H), 1.82 (m, 1H), 1.23 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 184.46, 172.58, 166.47, 165.22, 162.00, 132.30, 115.23, 106.66, 97.70, 74.09, 55.63, 55.38, 51.15, 43.56, 34.36, 33.52, 30.90, 27.45, 15.60; IR (neat) 2954, 1737, 1656, 1600, 1466, 1288, 1218, 1127, 1023, 993, 840 cm^{-1}. HRMS m/e calcd for $C_{19}H_{24}O_7$ 365.1600, found 365.1604; LRMS (CI) 365 (M + H$^+$)

***(1R, 2S, 5R)*-Menthyl (2,4-Dimethoxybenzoyl)formate.** After a reaction time of 18 h on a 1.92 mmol scale, column chromatography with 40% dichloromethane, 1% ethyl acetate, and 59% hexanes produced 356 mg of the title ester (1.022 mmol, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 6.43 (dd, J = 8.8, 2.0 Hz, 1H), 4.88 (m, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.20 (m, 1H), 2.02 (m, 1H), 1.71 (m, 2H), 1.42 –1.64 (m, 3H), 1.10 (m, 2H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 7.1 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 185.08, 166.49, 165.49, 162.02, 132.66, 115.48, 106.54, 97.74, 75.55, 55.62, 55.37, 46.57, 40.28, 33.86, 31.17, 25.65, 23.17, 21.88, 20.54, 16.16; IR (neat) 2951, 2866, 1731, 1660, 1601, 1501, 1465, 1297, 1220, 1131, 1032, 997, 836 cm^{-1}; HRMS m/e calcd for $C_{20}H_{29}O_5$ 349.2014, found 349.2015.

Cyclododecyl (*p*-Methoxybenzoyl)formate. To a round bottom flask which had been flushed with argon were added 500 mg (2.78 mmol) of (*p*-methoxybenzoyl)formic acid, 687 mg (3.33 mmol) of dicyclohexylcarbodiimide, 614 mg of cyclododecanol (3.33 mmol), 24 mg of DMAP, and 50 mL of freshly distilled dichloromethane. The solution was stirred for 12 h, at which time a white precipitate was removed by gravity filtration. The filtrate was transferred to a separatory funnel containing 100 mL of dichloromethane. The organic layer was extracted three times with water, twice with 5% acetic acid, and twice with brine. The organic layer was then dried over $MgSO_4$ and concentrated with a rotary evaporator. The product was purified by column chromatography with 5% ethyl acetate/95% hexanes. This produced 691 mg of the desired ester (72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 5.30 (m, 1H), 3.88 (s, 3H), 1.83 (m, 2H), 1.66 (m, 2H), 1.50 - 1.25 (m, 18H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 185.37, 164.87, 164.25, 132.43, 125.60, 114.20, 75.01, 55.62, 29.03, 23.99, 23.79, 23.32, 23.16, 20.92; IR (neat) 2937, 2864, 1729, 1677 cm^{-1}; HRMS m/e calcd for $C_{21}H_{31}O_4$ 347.2222, found 347.2226.

Photolysis of (2,4-Dimethoxybenzoyl)formate Esters. Cyclododecyl. On a 0.523 mmol scale in 100 mL of twice freeze-thaw degassed acetonitrile, the ester was irradiated in an air-cooled Rayonet reactor equipped with 350 nm lamps for 8 h, and no starting material was detectable by ^{1}H NMR. The product mixture was purified by column chromatography to yield cyclododecanone (84 mg, 88%). 2,4-Dimethoxybenzaldehyde was obtained in a 25% yield. On a 0.543 mmol scale in 100 mL of a twice freeze-thaw degassed 2% isopropyl alcohol/benzene solution, the ester was irradiated at 350 nm for 1 h. The ^{1}H NMR showed no starting material. Purification by column chromatography produced cyclododecanone (72 mg, 73%). In addition, a mixture of 2,4-dimethoxybenzaldehyde and an unknown aromatic compound was obtained. A third compound was shown to be isopropyl 2,4-dimethoxymandelate (**3**) by synthesis of an authentic sample (*vide infra*). On a 0.544 mmol scale in 100 mL of a twice freeze-thaw degassed benzene solution, the ester was irradiated at 350 nm for 2.25 h. Column chromatography using a gradient of ethyl acetate from 10 to 20% in hexanes provided cyclododecanone (86 mg, 87%) and 2,4-dimethoxybenzaldehyde (64 mg, 71%). Under conditions identical to those above except for omission of the degassing step, a product mixture was obtained that was extracted with aqueous sodium bicarbonate. The organic layer was dried over Na_2SO_4 and the solvent was removed. The products were purified by column chromatography with 10% ethyl acetate in hexane, giving cyclododecanone (82 mg, 82%). The aqueous layer was acidified with HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent removed to give 2,4-dimethoxybenzoic acid (77 mg, 77%).

Cyclododecylmethyl. Under the degassed benzene (100 mL) conditions described above on a 0.561 mmol scale, irradiation was conducted at 350 nm for 2 h. Column chromatography gave 2,4-dimethoxybenzaldehyde (65%) and cyclododecanecarboxaldehyde (65%), identical by ^{1}H NMR to that reported,[18] which rapidly oxidized to cyclododecanecarboxylic acid in air.

***(1R,2S,5R)*-Menthyl.** Under the degassed benzene conditions described above on a 0.958 mmol scale, irradiation was conducted at 350 nm for 2 h. Column chromatography gave menthone (71%) and 2,4-dimethoxybenzaldehyde (73%).

2,2-Dimethyl-3-[(methoxycarbonyl)methyl]cyclobutan-1-yl. On a 0.601 mmol scale in 100 mL of a twice freeze-thaw degassed 0.5% methyl alcohol/benzene solution, the ester was irradiated at 350 nm for 2 h. Column chromatography using 15% ethyl acetate/hexane gave methyl 2,2-dimethyl-3-oxocyclobutaneacetate (68 mg, 66%), 2,4-dimethoxybenzaldehyde (27 mg, 27%), and methyl 2,4-dimethoxymandelate (34 mg, 25%), identical to an authentic sample (*vide infra*).

Photolysis of Cyclododecyl (*p*-Methoxybenzoyl)formate. Compound **1** (310 mg, 0.895 mmol) was dissolved in 80 mL of benzene. The solution was irradiated for 4.25 h, and the solvent was removed by rotary evaporator. ^{1}H NMR showed *p*-anisic acid among other products. The reaction mixture was dissolved in ether and extracted with aqueous $NaHCO_3$. The aqueous layer was acidified with HCl and extracted with ether. The solution was dried over Na_2SO_4 and solvent was removed with a rotary evaporator to produce 84 mg (62%) of *p*-anisic acid. The organic layer was dried over Na_2SO_4, solvent was removed with a rotary evaporator, and the residue was purified by column chromatography to give

(18) Hayakawa, Y.; Yokoyama, K.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1799.

137 mg (84%) of cyclododecanone. A small amount (11 mg) of *p*-anisaldehyde was also obtained.

Cyclododecyl [*p*-(Dimethylamino)benzoyl]formate: mp 126–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 9.1 Hz, 2H), 6.66 (d, J = 9.1 Hz, 2H), 5.30 (m, 1H), 3.09 (s, 6H), 1.83 (m, 2H), 1.66 (m, 2H), 1.50 - 1.25 (m, 18H). IR (KBr) 2929, 2855, 1720, 1650, 1591, 1543, 1468, 1379, 1344, 1235, 1161, 1007, 942, 831 cm^{-1}; HRMS calcd for $C_{22}H_{33}NO_3$ 359.2454, found 359.2457.

Isopropyl (2,4-Dimethoxybenzoyl)formate. After a reaction time of 72 h, column chromatography with a gradient from 15–20% ethyl acetate/hexane produced 341 mg of the title ester (1.356 mmol, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 8.8, 1.8 Hz, 1H), 6.43 (d, J = 1.8 Hz, 1H), 5.22 (septet, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 1.37 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 185.17, 166.62, 165.50, 162.14, 132.75, 115.65, 106.61, 97.87, 69.46, 55.64, 55.60, 21.60; IR (neat) 2982, 2940, 2840, 1734, 1656, 1600, 1468, 1286, 1220, 1106, 1027, 994, 842 cm^{-1}; LRMS (CI) 253 ($C_{13}H_{16}O_5$ + H^+).

Isopropyl 2,4-Dimethoxymandelate (3). To a round bottom flask was added 198 mg of the isopropyl ester of (2,4-dimethoxybenzoyl)formic acid (0.785 mmol), 30 mg of $NaBH_4$ (0.785 mmol), and 10 mL of methanol. The solution was stirred for 1 h and solvent was removed with a rotary evaporator. The solid was transferred to a separatory funnel containing 100 mL of ethyl acetate and 100 mL of water. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated with a rotary evaporator giving the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1H), 6.45 (m, 2H), 5.15 (s, 1H), 5.09 (m, 1H), 3.79 (m, 6H), 1.23 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.52, 161.08, 158.17, 130.24, 119.96, 104.14, 98.83, 70.01, 69.33, 55.31, 21.64, 21.42; IR (neat) 3487, 2934, 1730, 1613, 1507, 1210 cm^{-1}; HRMS calcd for $C_{13}H_{18}O_5$ 254.1163; found 254.1171.

Methyl 2,4-Dimethoxymandelate (3, R = Me). This compound was obtained by a similar procedure to that described above: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 9.0 Hz, 1H), 6.48 (m, 2H), 5.23 (s, 1H), 3.81 (m, 6H), 3.74 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.45, 161.25, 158.19, 130.15, 119.59, 104.40, 99.02, 69.73, 55.55, 55.38, 52.70; IR (neat) 3492, 3000, 2951, 2839, 1740, 1613, 1590, 1463, 1297, 1212, 1160, 1077, 1036, 838 cm^{-1}; LRMS (CI): 209 ($C_{11}H_{14}O_5$ + H^+ − H_2O); 244 ($C_{11}H_{14}O_5$ + NH_4^+); HRMS calcd for $C_{11}H_{14}O_5$ 226.0842; found 226.0840.

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Supplementary Material Available: ^{1}H NMR spectra of compounds characterized by high-resolution mass spectrometry (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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