1-(1′,1′,2′-Trimethyl-2′-propenyl)-2-phenyl-3-methylisoindoline (20d): ^{1}H NMR δ 0.80 (3 H, s), 1.16 (3 H, s), 1.76 (3 H, d, J = 6.6 Hz), 2.11 (3 H, s), 4.78 (1 H, q, J = 6.6 Hz), 4.82 (1 H, s), 4.99 (1 H, s), 5.38 (1 H, br s), 6.75–6.80 (1 H, m), 7.00–7.05 (2 H, m), 7.10–7.20 (3 H, m), 7.20–7.30 (3 H, m); ^{13}C NMR δ 20.8 (q), 22.9 (q), 23.4 (q), 27.1 (q), 45.9 (s), 65.5 (d), 68.4 (d), 112.8 (t), 151.6 (s), and aromatic carbon peaks; MS m/z 291 (M^+), 276 ($M^+ - CH_3$), 208 ($M^+ - C_6H_{11}$); HRMS calcd for $C_{21}H_{25}N$ 291.199 30, found 291.144 01.

1-Methyl-2-phenylisoindoline (21d): bp 140 °C (3 mmHg); mp 74–75 °C; ^{1}H NMR δ 1.48 (3 H, d, J = 6.7 Hz), 4.48 (1 H, A of AB q), 4.77 (1 H, B of AB q), 4.95–5.20 (1 H, m), 6.45–6.80 (3 H, m), 7.15–7.60 (6 H, m); ^{13}C NMR δ 20.5 (q), 54.0 (t), 59.1 (d), and aromatic carbon peaks.

Sensitizing and Quenching Experiments. A benzene solution of **1a** (112.5 mg) and **2a** (0.5 mL) in the presence of thioxanthone (in such a ratio that the sensitizer absorbs >95% of the incident light) was degassed with argon and then irradiated at 366 nm for 3 h. Workup gave **3** in 22% yield. In the absence of thioxanthone, **3** was produced 25% yield. A Pyrex filter and methanol solution of naphthalene (5 g/L) were used to isolate the 366-nm light, and a 300-W high-pressure mercury lamp was used as an irradiation source. A benzene solution of **1a** (112.5 mg) and **2a** (0.5 mL) containing 10 molar equiv of a quencher was irradiated under the same conditions. Yield of **3**: 5% (*trans*-stilbene); 3% (2,5-dimethyl-2,4-hexadiene).

Photochemical Reactions of 1,3-Dihydroisobenzofuran-1-thione (22) and 1,3-Dihydroisobenzothiophene-1-thione (23) in the Presence of Tetramethylethylene (2a). A solution of the thione **22** or **23** (200 mg) and tetramethylethylene (~1 mL) in benzene (70 mL) was irradiated. Usual workup gave the thietane derivatives **24** and **25**. Satisfactory microanalyses for **24** and **25** were obtained.

1:1-Adduct 24: mp 104–105 °C; ^{1}H NMR δ 1.05 (3 H, s), 1.35 (3 H, s), 1.40 (3 H, s), 1.82 (3 H, s), 5.08 (2 H, AB q), 7.10–7.40 (3 H, m), 7.50–7.65 (1 H, m); ^{13}C NMR δ 20.2 (q), 24.4 (q), 26.3 (q), 30.4 (q), 49.5 (s), 58.0 (s), 72.1 (t), 100.7 (s), and aromatic carbon peaks; MS m/z 234 (M^+), 160 ($M^+ - C_3H_6S$), 145 ($M^+ - C_3H_5OS$).

1:1-Adduct 25: bp 165 °C (2 mmHg); ^{1}H NMR δ 1.08 (3 H, s), 1.36 (3 H, s), 1.49 (3 H, s), 1.81 (3 H, s), 3.80 (1 H, A of AB q), 4.17 (1 H, B of AB q), 7.15–7.35 (3 H, m), 7.55–7.70 (1 H, m); ^{13}C NMR δ 23.8 (q), 25.0 (q), 26.3 (q), 30.2 (q), 37.3 (t), 49.7 (s), 56.7 (s), 72.3 (s), and aromatic carbon peaks.

Remote Oxidation of Perhydrophenanthrenes by Template-Directed Hydrogen Atom Abstraction[1]

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Received October 25, 1991

The use of Breslow's remote functionalization paradigm for installation of an axial C-7 hydroxy group into a perhydrophenanthrene nucleus, with a view toward synthesis of bruceantin (1), has been investigated. The substrates that were evaluated were **9a–c**, **11**, **17**, **18**, and **20**. Substrates **9a–c** all undergo preferential functionalization at C-12. After oxidative cleavage of the initial photoproduct, ketones **18a–c** were obtained in yields of 18–26% (36–41%, based on unrecovered starting material). Unsaturated substrate **11** undergoes remote functionalization exclusively at the secondary allylic position (C-12); enone **20** is obtained in 83% overall yield after oxidative cleavage of the initial photoadduct, **19a,b**. Thus, in this system, C-12 appears to be the preferred site of intramolecular functionalization. Attempts to block reaction at this position by the use of saturated ketone **18**, the derived ketal **17**, or enone **20**, were all unsuccessful. In the case of **18** the only photoproduct was the intramolecular pinacol. Enone **20** gave an exceedingly complex mixture, consisting of many products. Ketal **17** afforded the unusual macrocyclic lactone **21** in 33% yield. The main conclusion of this study is that it is difficult to extrapolate from the excellent regioselectivity observed by Breslow in the steroid system to the trans-anti-trans perhydrophenanthrene system, which is only slightly less rigid. A second factor which we believe is important in the system we have studied is the apparently minor perturbation of having an equatorial substituent at C-4. We postulate that this substituent, which was not present in the model steroidal systems investigated previously by Breslow, disfavors functionalization at C-7.

Biological syntheses of highly functionalized natural products typically involve enzymes that oxidize unactivated carbon positions with exquisite regio- and stereocontrol. Synthetic chemists strive for the level of selectivity exemplified by these biological systems. More than 20 years ago, Breslow reported his group's attempts to mimic the selectivity of enzymatic transformations by employing covalently-attached, benzophenone-containing templates to direct the remote oxidation of steroid substrates.[2] We have evaluated the Breslow remote functionalization strategy for a key step in the synthesis of the quassinoid group of terpenoid natural products.[3] We sought to explore the possibility of employing these template-directed remote functionalization reactions on substrates lacking the steroid D-ring, namely perhydrophenanthrenes. We focused on the benzophenone-mediated reactions because of our interest in functionalization of unactivated methylene positions.[4] In particular, we sought to use the technology of Breslow to introduce the oxygen functionality at position 7 of bruceantin (1).

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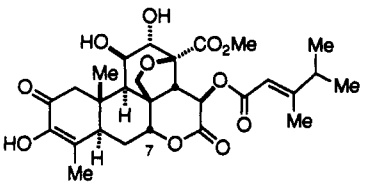
(1) Taken in part from the Ph.D. Thesis of Sean M. Kerwin, University of California, Berkeley, 1989.

(2) For a recent review see: Breslow, R. *ChemTracts* **1988** *1*, 333. Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

(3) For a review of quassinoid synthesis work see: Kawada, K.; Kim, Moonsun; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521. For our previous work in the quassinoid area see: Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686.

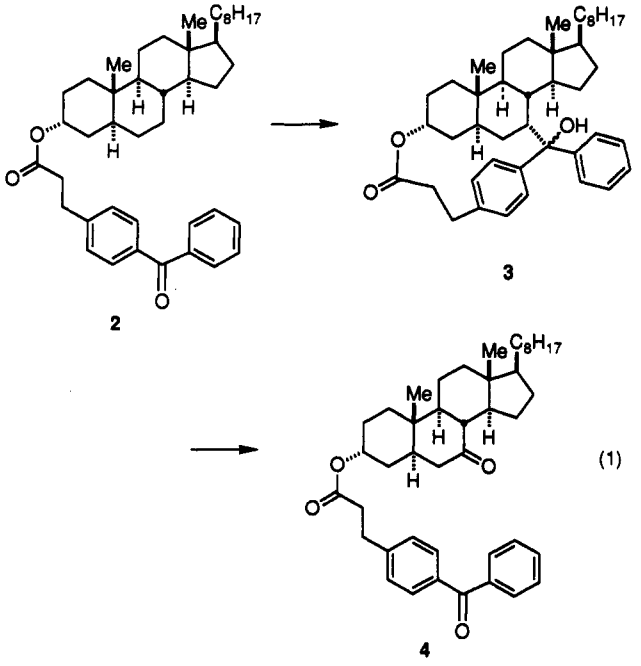
(4) Although the radical-relay remote functionalization reactions are in general more efficient than the benzophenone-mediated remote functionalization reactions, the former are quite specific for methine hydrogen atom abstraction, while the later are much less so. Breslow, R.; Corcoran, R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905. A recently developed alternative to the benzophenone-mediated functionalization of remote methylene positions utilizes a oxometaloporphyrin-containing template: Grieco, P. A.; Stuk, T. L. *J. Am. Chem. Soc.* **1990**, *112*, 7799.

0022-3263/92/1957-4005$03.00/0



1

Two obstacles restrict the use of Breslow's benzophenone remote functionalization reaction. First there is the obvious concern of regioselectivity. For certain length tethers, Breslow and co-workers realized exclusive regioselectivity in the functionalization of cholestanol. For example, irradiation of the 3-α-cholestanol ester of 4-benzoylphenylacetic acid afforded the Δ^{14}-cholesten-3α-ol ester of 4-(hydroxybenzyl)phenylacetic acid as the sole product of remote functionalization.[5] Although less selective, the functionalization of the 7 position of the cholestanol skeleton was also accomplished by the Breslow group. In this case the major product of remote functionalization was the macrocyclic lactone **3** (see eq 1).[6] This remote functionalization strategy was expected to evidence similar levels of regioselectivity with perhydrophenanthrene substrates.



2 3 4 (1)

The second obstacle to the use of the benzophenone-mediated remote functionalization is the conversion of photoproducts into synthetically useful intermediates. In the case of lactones such as **3**, this presented a significant stumbling block. Breslow and co-workers used two different routes to convert lactones such as **3** into the corresponding cholestenol or hydroxycholestanone derivatives (**4**, eq 1).[5] Neither of these multistep sequences was synthetically attractive due to unsatisfactory low yields. We therefore required a general and high-yielding route to convert photoproduct lactones into synthetically useful products. Specifically, we sought a method for direct oxidative cleavage of lactones such as **3** into carbonyl products such as **4**. The work presented here describes our observations of the photochemistry of hydroxyperhydrophenanthrene esters of 3-(4-benzoylphenyl)propanoic acid and the conversion of the resulting photoproducts into synthetically useful carbonyl compounds.

Preparation of the Remote Functionalization Substrates. Three perhydrophenanthrene-containing substrates were prepared as shown in Scheme I. The three variously substituted dodecahydrophenanthrenes **5a–c** that had been previously prepared in our lab[7] served as starting materials. Sequential reduction of the A-ring enone moiety of the dodecahydrophenanthrenones **5a–c** afforded the axial dodecahydrophenanthrenols **6a–c** as the major isomers in each case. Catalytic hydrogenation of the C-ring double bond afforded the perhydrophenanthrenols **7a–c**. Esterification of these alcohols with 3-(4-benzoylphenyl)propanoic acid proceeded to give the desired photosubstrates **9a–c** in an unoptimized overall average yield of 40%. The dodecahydrophenanthrene photosubstrate **11** was prepared by esterification of the alcohol **6a**.

As shown in Scheme II, alcohol **6a** also served as the starting material for the synthesis of two more photosubstrates. The alcohol moiety of **6a** was protected as the trimethylsilyl ether prior to oxidation with the dimethylpyrazole-chromium trioxide complex.[8] The resulting enone **13**, produced in 55% yield, was reduced with lithium–bronze[9] to the saturated ketone **14**. Detailed analysis of the COSEY NMR of **14** confirmed the relative stereochemical assignments shown for the carbomethoxy-substituted series of compounds and allowed assignment of the relative stereochemistry of the other compounds based on analogy.[10] Concomitant ketalization and desilylation of **14** afforded the alcohol **16**, which was esterified to give **17**. Compound **14** was also desilylated with potassium fluoride to afford the alcohol **15**. Esterification of **15** produced the photosubstrate **18**.

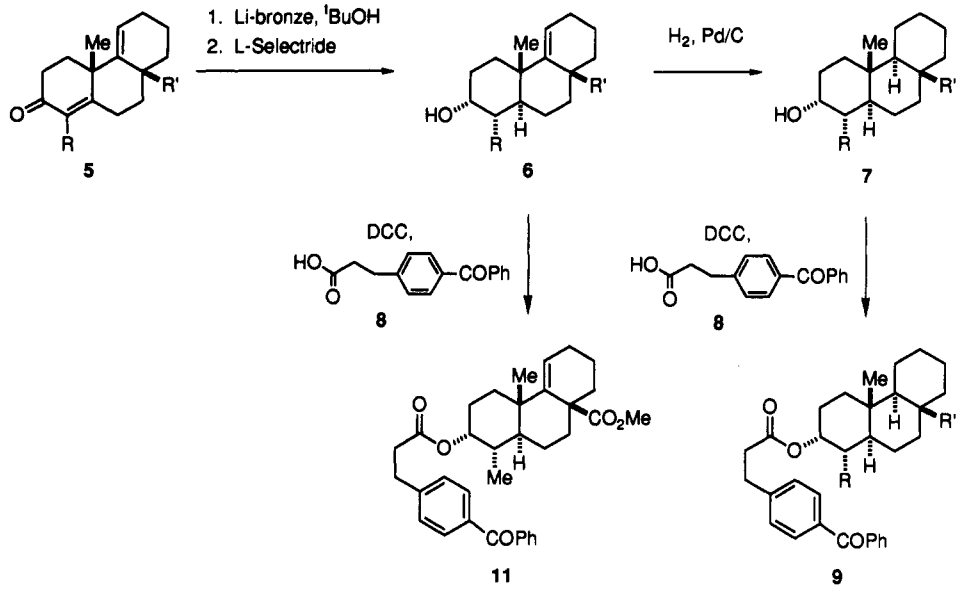
Results and Discussion

A dilute solution of **11** in benzene was irradiated through a uranium glass filter until the resonance due to the benzophenone carbonyl in the IR spectrum of the reaction mixture was absent. The resulting photoproduct consisted of two diastereomeric cyclic lactones, **19a** and **19b** (Scheme III), which were separated by flash chromatography in high combined yield and in a ratio of 1:1.15. No attempt was made to assign the relative stereochemistry of the carbinol centers of these isomers. Instead, the mixture of the two photoproducts was oxidized with chromium trioxide and acetic acid in methylene chloride. When this oxidation was performed at room temperature, a complex mixture of products was obtained; however, oxidation at −30 °C gave the enone **20** in high yield after column chromatography.

The conversion of **11** to **20** via **19a** and **19b** is noteworthy for a number of reasons. First, the regioselectivity in this remote functionalization is markedly different from that observed in the steroid series investigated by Breslow. In the case of the irradiation of a benzene solution of 3-α-cholestanol ester of 3-(4-benzoylphenyl)propanoic acid (**2**), a mixture of three photoproducts was obtained. The major product, formed in 45% yield, was the lactone **3**, the product of hydrogen atom abstraction at the 7 position. The product of hydrogen atom abstraction at the 14

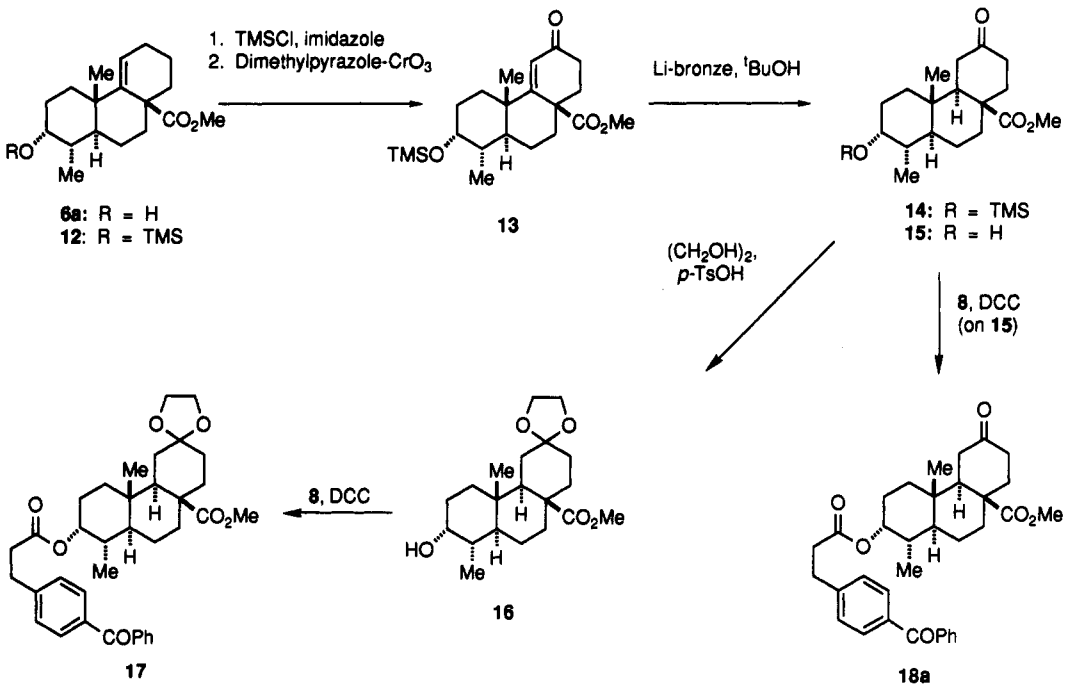
(5) Breslo, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3252.
(6) Wife, R. L.; Prezant, D.; Breslow, R. *Tetrahedron Lett.* **1976**, 517.
(7) Kerwin, S. M. Ph.D. *Diss. Abstr. Int. B.* **1990**, *50*, 4540. Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264.
(8) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(9) Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647.
(10) The assignment of the resonances of the hydrogens attached to the C ring was aided by the observation of a long-range 1-Hz coupling between the equatorial C-11 proton and the equatorial C-13 proton. The coupling constants for the C-ring protons are best explained by a trans-BC ring juncture. This corresponds to catalytic hydrogenation from the least hindered α-face of alkene **6a**.

Scheme I[a]



[a] Key: (a) R = Me, R′ = CO_2Me; (b) R = R′ = Me; (c) R = H, R′ = Me.

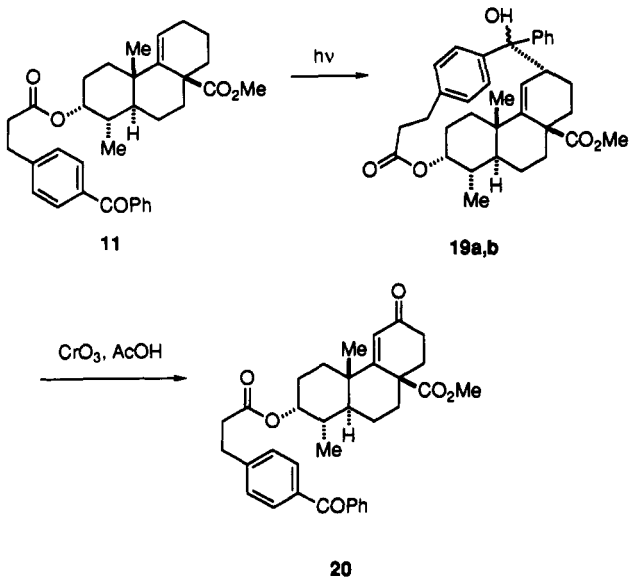
Scheme II



position, Δ^{14}-cholesten-3α-ol ester of 3-(4-(hydroxybenzyl)phenyl)propanoic acid, was isolated in 35% yield, and the product of hydrogen atom abstraction at the 12 position was formed in only 19% yield. In the case of the irradiation of a benzene solution of dodecahydrophenanthrene **11**, the only products of hydrogen atom abstraction that could be isolated were those resulting from abstraction of the hydrogens at the 12 position. Thus, in benzene as solvent, the same benzophenone-containing template functionalizes the cholesterol skeleton predominantly at the 7 and 14 positions but the dodecahydrophenanthrene skeleton exclusively at position 12.[11] The regioselectivity for the functionalization of compound **11** at position 12 is due no doubt to the relative ease of H atom abstraction at the allylic 12 position but also has contributions from an inherent preference for the functionalization of this type of photosubstrate at position 12 (vide infra). Second, the conversion of **19a** and **19b** to **20** is significant. Unlike the multistep sequences used by Breslow's group to convert photoproduct lactones into steroid ketones, the oxidative cleavage of lactones **19** to ketone **20** is direct and high yielding. Thus, for the first time, lactone products of benzophenone-mediated remote functionalization can be converted into synthetically useful intermediates. While the mechanism of this transformation remains to be elucidated, we propose it involves initial formation of a chromate ester of the tertiary alcohol followed by homolysis of the C-12-benzyl carbon–carbon bond. This would lead to the formation of a C-ring allyl radical that is oxidized by the chromium reagent to the

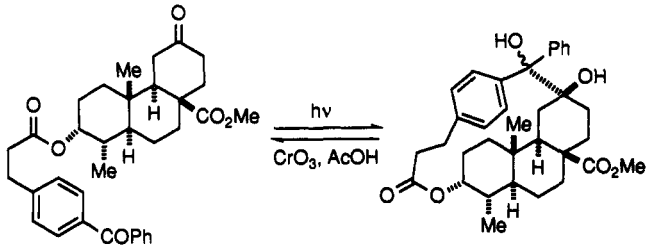
(11) The irradiation of a carbon tetrachloride solution of ester **2** produces a mixture of photoproducts that includes products resulting from hydrogen atom abstraction at C-12, although the selectivity for functionalization at C-12 cannot be deduced from these results: Breslow, R.; Baldwin, S. W. *J. Am. Chem. Soc.* **1970**, *92*, 732.

Scheme III



11 19a,b 20

Scheme IV



18a

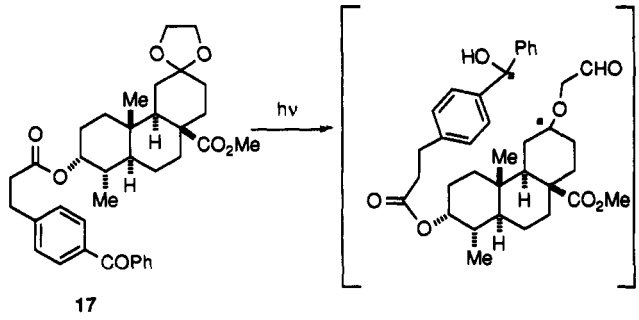
enone. An alternative mechanism involving heterolysis of the carbon–carbon bond resulting in an allyl cation is also possible. In this case the mechanism resembles that proposed for the oxidative rearrangement of tertiary allylic alcohols to enones.[12] The facility of the oxidative cleavage of the lactones is also noteworthy.[13] The two-step photolysis–oxidation route from **11** to **20** shown in Scheme III proceeds in 83% overall yield.

Attempted irradiation of enone **20** under conditions identical to those employed for the production of the lactones **19a** and **19b** produced a very complex mixture of photoproducts that was not analyzed further. We believe that the facile energy transfer from the benzophenone excited state to the enone moiety of **20** is responsible for the complexity of the product mixture in this case.

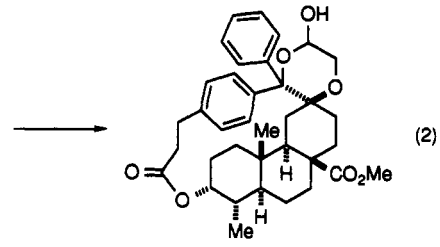
The irradiation of ketone **18** resulted in rapid and complete loss of the IR resonance due to the carbonyls. Evaporation of the solvent afforded the crude reaction product, a nearly 1:1 ratio of cyclic pinacols (Scheme IV), which was not further purified. Oxidation of the crude product mixture afforded the starting ketone in moderate yield.

The photochemical behavior of enone **20** and ketone **18** demonstrates a limitation of the benzophenone-mediated remote functionalization reaction: sequential application of the remote functionalization is precluded by the reactivity of the initially produced carbonyl group under the reaction conditions. The facile formation of macrocyclic products from the irradiation of **18** again illustrated the preference of the arylpropionate template for interaction with the 12 position of perhydrophenanthrenes.

The ketal **17** serves as a substrate that has the reactive keto group at position 12 blocked as a dioxolane moiety. The irradiation of the ketal **17** afforded a rather complex mixture of products. Flash chromatography of this product mixture resulted in the isolation of one major product, the lactone **21** (eq 2), in modest yield. Compound



17



(2)

21

21 appeared to be homogeneous by ^{1}H NMR, but in the NMR spectrum of the crude product mixture there appeared to be other diastereomers of the lactone **21**. It is estimated that **21** and its distereomers represent between 60 and 70% of the crude photolysis product. The formation of lactone **21** involves initial hydrogen atom abstraction from the ketal ring followed by cleavage of the ketal ring, as shown. Inspection of molecular models of the ketal **17** demonstrates that the template is sufficiently flexible to interact with the methylene hydrogens of the ketal ring.

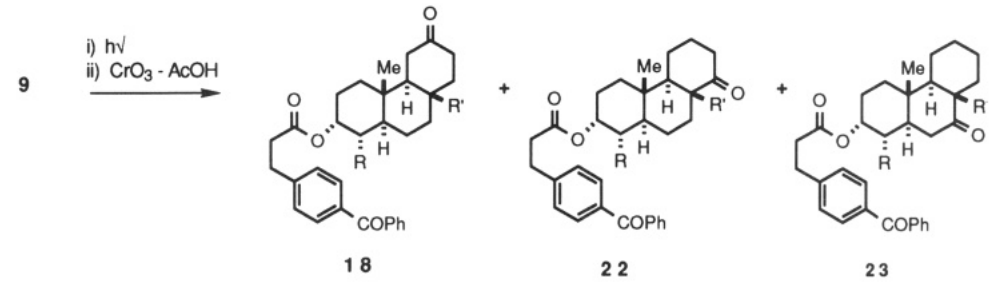
As shown in Table I, the products of irradiation of the perhydrophenanthrene substrates **9a**, **9b**, and **9c** were not isolated, but rather the entire crude photoproduct was subjected to oxidation with chromium trioxide and acetic acid. The products from this two-step functionalization procedure were isolated and characterized. The functionalization of perhydrophenanthrene **9a** afforded the ketone **18a**, which was isolated in 26% yield. In addition, the starting material **9a** was recovered from the functionalization mixture in 27% yield. Because care was exercised during the irradiation step of the functionalization to ensure that all of the starting material was consumed, it is clear that the reisolation of perhydrophenanthrene **9a** was due to its production during the oxidation step of the functionalization procedure. Most probably, the reisolated **9a** arises from oxidation of the corresponding benzhydrol, which is produced during irradiation as a result of solvent hydrogen atom abstraction by the benzophenone triplet.[14] In a similar fashion, functionalization of perhydrophenanthrene **9b** afforded the ketone **18b** in 18% yield and recovered **9b** in 56% yield. In the case of the functionalization of perhydro-

(12) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(13) In our hands, the allylic oxidation of C-ring alkenes like **11** occurs only at room temperature or above using chromium trioxide in acetic acid solvent. Heathcock, C. H.; Paul, A. G.; Kerwin, S. M. Unpublished results.

(14) Beckett, A.; Porter, G. *Trans. Faraday Soc.* **1961**, *57*, 1686.

Table I. Photolysis–Oxidation of Perhydrophenanthrenes with Attached Benzophenone Templates



starting perhydrophenanthrene	yield of 18 (%)	yield of 22 (%)	yield of 23 (%)	amount of recovered starting material 9[a] (%)
a: R = Me, R′ = CO_2Me	26 (36)[b]	–[c]	–[c]	27
b: R = Me; R′ = Me	18 (41)[b]	–[c]	–[c]	56
c: R = H; R′ = Me	19 (41)[b]	4[d] (9[d])[b]	4[d] (9[d])[b]	54

[a] Recovered **9** arises from the oxidation of the photoreduced starting material. [b] Yield corrected for the amount of recovered starting material. [c] Not observed. [d] Isolated as an inseparable mixture of the 7-oxo and 14-oxo compounds.

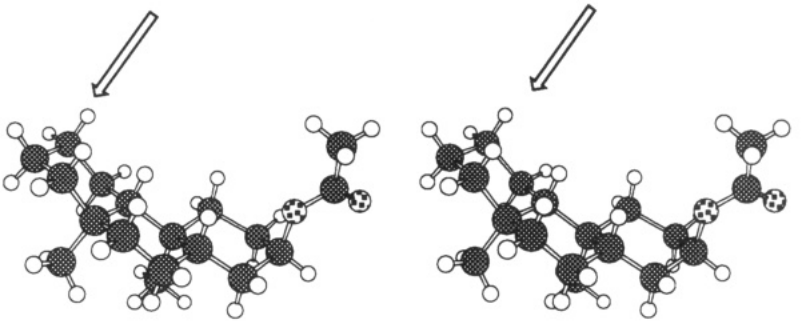


Figure 1. Stereopair model of the MM2-minimized conformation of compound **24**. The arrows point to the functionalized 12 position.

phenanthrene **9c**, a more complex product mixture was obtained. In addition to the expected C-12 ketone **18c**, isolated in 19% yield and reisolated starting material **9c** (54%), there was obtained a further product. This material is an unseparated 1:1 mixture of the C-7 and C-14 keto compounds **22c** and **23c**, each accounting for 4% of the reaction product.

The yields of these remote functionalization reactions are rather low. This is due to the low overall conversion. The large amount of recovered starting material from the remote functionalization reactions is due to the extensive photoreduction of the benzophenone moiety that occurs during the photolysis step. This is to be contrasted with the small amount of photoreduction observed by Breslow and co-workers in their photolysis of cholestanol derivative **3**. We believe that these differences in the relative amounts of hydrogen atom abstraction from the substrate versus the solvent indicates that the benzophenone template interacts less favorably with the perhydrophenanthrene skeleton than it does with the cholestanol skeleton. In the latter case there is evidence that the benzophenone template adopts a preferred conformation in which many favorable contacts are made with atoms on the α-face of the cholesterol nucleus.[15] In the former case, there are fewer atoms in the perhydrophenanthrene skeleton, and so there is less opportunity for favorable van der Waals interactions between the template atoms and the atoms of the perhydrophenanthrene skeleton. Moreover, we believe that the shape of the perhydrophenanthrene ring system in compounds such as **9a** does not allow for a conformation in which the template can pack onto the perhydrophenanthrene skeleton.

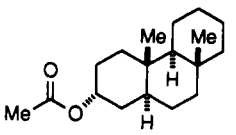
Taken together, the results of the remote functionalizations of the dodecahydro- and perhydrophenanthrenes demonstrate a remarkable level of selectivity for functionalization at position 12.[16] In the case of perhydrophenanthrenes **9a** and **9b**, the only products of remote functionalization that were isolated were those involving position 12. The functionalization of perhydrophenanthrene **9c** occurs predominantly at position 12, with less than half of the functionalization occurring at positions 7 and 14 combined. The behavior of dodecahydrophenanthrene **11** and ketone **18** are also commensurate with selective attack of the arylpropionate template at position 12.

We believe that there are two factors responsible for the selectivity observed in these remote functionalization reactions. First, unlike the cholestanol derivatives, in which the steroid ring system is relatively flat, we propose that the perhydrophenanthrene derivatives studied here have A, B, and C rings that are slightly cupped. Molecular mechanics calculations of the model system **24** demonstrates that the perhydrophenanthrene skeleton adopts a cupped shape where the α face is slightly concave and the β face is convex (Figure 1).[17]

(15) In ref 5, the authors quantitiate the degree of interaction between the various benzophenone templates and the cholestanol sketeton by measuring the induced circular dichroism in the benzophenone UV spectrum for each ester. A positive correlation exists between the magnitude of the circular dichroism of the benzophenone moiety and the degree of photochemical remote functionalization.

(16) For a case of high selectivity in the remote functionalization of C-12 in a cholestanol system see: Orito, K.; Ohto, M.; Sugawara, N.; Suginome, H. *Tetrahedron Lett.* **1990**, *41*, 5921.

(17) Calculations were performed using Still's MACROMODEL program (Dept of Chemistry, Columbia University) and the MM2 force field.[19] All possible combinations of chair, boat, and twist conformations for each six-membered ring were employed as starting conformations; the conformation described refers to the lowest energy conformation.



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This deviation from planarity is due to steric repulsion of the axial C-8 and C-10 substituents which is relieved by slight distortions in the B ring torsional angles. The result of this buttressing of the C-8 and C-10 substituents is that hydrogen atoms on the α-face that are near the center of the molecule are sterically less accessible than those on the exterior of the molecule. Thus, hydrogens attached to positions 7 and 14, which are readily abstracted in the cholesterol series, are shielded from attack in the perhydrophenanthrenes due to their location on the interior of the concave face, while hydrogen at position 12 is more readily attacked in the perhydrophenanthrene system due to its position on the rim of the concave face. Another effect of the cupped shape of the perhydrophenanthrenes is that the planar benzophenone moiety of the template, which interacts favorably with the relatively planar ring system of the cholesterol derivatives, does not interact as favorably with the phenanthrene ring system. In the case of dodecahydrophenanthrene 11, the C-ring double bond makes the cupped shape less pronounced, and the chemoselectivity of the benzophenone triplet for allylic hydrogen atom abstraction make the remote functionalization both selective and high yielding.

A second factor affecting the selectivity of the remote functionalization reaction of perhydrophenanthrenes studied here is the steering effect of an equatorial substituent at position 4. We propose that in order to effectively access the hydrogens at positions 7 and 14, the benzophenone ester template must adopt a conformation in which the ester carbonyl oxygen adopts a position close to C-4. The presence of an equatorial methyl group at the 4 position as in compounds **9a** and **9b** prevents the template from assuming this conformation. Thus, no functionalization at positions 7 and 14 is observed in these cases. In the case of compound **9c**, which lacks an alkyl substituent at position 4, the ester template side chain is able to adopt the conformation required for abstraction of the hydrogens at positions 7 and 14, and a small amount of functionalization at these positions is observed.

Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Ether and THF were distilled from sodium/benzophenone immediately prior to use. Benzene and CH_2Cl_2 were distilled from CaH_2. 2-Methyl-2-propanol was distilled from sodium and stored over 4-Å molecular sieves. Absolute ethanol and methanol were distilled from magnesium. Chlorotrimethylsilane was distilled from calcium hydride/diethylaniline immediately prior to use. Chromium trioxide was dried overnight at reduced pressure and stored over P_2O_5. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere unless otherwise noted. Glassware used in the handling of moisture-sensitive reagents was oven dried and stored in a desiccator prior to use. Melting points (open capillary) are uncorrected. IR spectra were determined neat or as a $CHCl_3$ solution. All NMR spectra were determined with $CDCl_3$ as the solvent; J values are given in Hz. Unless otherwise stated, organic solutions were dried over $MgSO_4$ and concentrated for product isolation with a rotary evaporator. Photochemical reactions were carried out using a 450-W medium-pressure Hanovia lamp and a uranium glass filter in a jacketed, water-cooled immersion well. Flash chromatography refers to the method of Still, Kahn, and Mitra.[18]

Compound 6a. To a 100-mL round-bottomed three-necked flask fitted with an inlet for ammonia, a dry-ice condenser, and a pressure-equalizing addition funnel equipped with an outlet to a nitrogen atmosphere was added 103 mg (14.7 mmol) of lithium wire and 30 mL of dry THF. The flask was cooled to −78 °C, and ammonia was slowly condensed into the flask with vigorous stirring until no solid lithium remained. The resulting suspension of metallic lithium–bronze was stirred for an additional 10 min at −78 °C. A solution of 1.035 g (3.6 mmol) of compound **5a** and 0.34 mL (3.6 mmol) of 2-methyl-2-propanol in 15 mL of THF was added slowly with stirring over 30 min. After the addition was complete, the reaction mixture was stirred an additional 1.5 h, and the reaction was quenched by the addition first of some methanol and then some aqueous saturated NH_4Cl. After being warmed to room temperature, the reaction mixture was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were dried, filtered, and evaporated. Flash chromatography (10 g of SiO_2, 0–20% EtOAc in hexanes) of the residue gave 878 mg (84%) of the saturated ketone as a white solid. A solution of 98 mg (0.338 mmol) of the saturated ketone in 6 mL of THF was cooled to −78 °C. To this rapidly stirring solution was slowly added 0.4 mL (0.4 mmol) of a 1 M solution of lithium tri-*sec*-butylaluminum hydride in THF. After the addition was complete, the reaction mixture was stirred an additional 1 h at −78 °C. The reaction mixture was slowly allowed to warm to 0 °C over 10–15 min, and the reaction was quenched by the addition of saturated NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were dried. The residue upon evaporation of solvent was purified by flash chromatography (1 g of SiO_2, 0–20% EtOAc in hexane) to give 73 mg (74%) of compound **6a** as a white solid. An analytical sample was obtained by recrystallization from hexanes to give white crystals, mp 122–123 °C: IR 3500, 1718 cm^{-1}; ^1H NMR (250 MHz) δ 0.78 (s, 3), 0.91 (d, 3 J = 7), 1.15–1.60 (m, 9), 1.66–1.89 (m, 5), 2.09 (m, 2), 2.50 (dm, 1, J = 13), 3.65 (s, 3), 3.74 (s (br), 1), 5.67 (t (br), 1, J = 4). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.79; H, 9.57.

Compound 6b. Compound **6b** was prepared in the same manner as compound **6a**. Flash chromatography (15 g of SiO_2, 0–30% EtOAc in hexanes) gave 643 mg (75%) of compound **6b** as a white solid, mp 96–97 °C: IR 3500, 3015 cm^{-1}; ^1H NMR (250 MHz) δ 0.91 (d, 3, J = 7), 0.98 (s, 3), 1.16 (s, 3), 1.19–1.88 (m, 15), 2.02 (dd, 1, J = 8.5, 4), 2.03 (m, 1), 3.72 (d (br), J = 2.5), 5.38 (t, 1, J = 4). Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.13; H, 11.42.

Compound 6c. Compound **6c** was prepared in the same manner as compound **6a**. Flash chromatography (10 g of SiO_2, 0–15% EtOAc in hexanes) gave 160 mg (63%) of compound **6c** as a clear oil: IR 3500, 3005 cm^{-1}; ^1H NMR (250 MHz) δ 0.97 (s, 3), 1.19 (s, 3), 1.20–1.88 (m, 16), 2.06 (m, 2), 4.04 (m, 1), 5.36 (m, 1); ^{13}C NMR (125 MHz) δ 18.21, 18.41, 25.74, 26.22, 28.95, 29.18, 31.73, 34.37, 36.20, 38.59, 38.67, 42.26, 43.35, 66.44, 117.53, 151.14. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.08; H, 11.10.

Compound 7a. A mixture of 51 mg (0.175 mmol) of compound **6a**, 7 mg of 10% palladium on carbon, and 3.5 mL of absolute ethanol were placed under 50 psi of hydrogen with vigorous stirring for 12 days. The reaction mixture was filtered through a plug of diatomaceous earth, and the solvent was evaported. Purification by flash chromatography (2 g of SiO_2, 0–20% EtOAc in hexanes) gave 51 mg (98%) of compound **7a** as a clear oil: IR 3500, 1735 cm^{-1}; ^1H NMR (250 MHz) δ 0.62 (s, 3), 0.89 (d, 3, J = 7), 0.90–1.97 (m, 19), 2.32 (dm, 1, J = 13), 3.64 (s, 3), 3.74 (m, 1); mass spectrum (60 eV) m/z 294 (M^+), 276, 261, 217, 202, 189; HRMS calcd for $C_{18}H_{30}O_3$ 294.2196, found 294.2196.

Compound 7b. Compound **7b** was prepared in the same manner as compound **7a**. Purification by flash chromatography (8 g of SiO_2, 0–2% EtOAc in hexanes) gave 136 mg (57%) of compound **7b** as a white solid, mp 112 °C: IR 3500 cm^{-1}; ^1H NMR (250 MHz) δ 0.71 (s, 3), 0.91 (d, 3, J = 7), 0.91 (s, 3), 1.05–1.85 (m, 20), 3.74 (d (br), 1, J = 2.5); ^{13}C NMR (50 MHz) δ 12.66, 16.34, 20.40, 20.90, 21.82, 27.78, 28.87, 32.87, 34.32, 34.76, 36.80, 42.81,

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45.54, 46.21, 56.13, 71.93. Anal. Calcd for $C_{17}H_{30}O$: C, 81.53; H, 12.08. Found: C, 81.54; 12.06.

Compound 7c. Compound **7c** was prepared in the same manner as compound **7a**. Evaporation of the solvent gave 108 mg (98%) of compound **7c** as a white solid, mp 110 °C: IR 3500, 1660, 1590 cm^{-1}; ^1H NMR (250 MHz) δ 0.70 (s, 3), 0.94 (s, 3), 1.07–1.64 (m, 18), 1.66–1.83 (m, 2), 4.04 (m, 1); ^{13}C NMR (125 MHz) δ 11.50, 20.44, 20.70, 21.88, 25.58, 27.73, 28.69, 32.89, 34.88, 35.73, 36.49, 40.29, 42.60, 46.22, 56.02, 66.59. Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.40; H, 11.94.

Compound 9a. Compound **9a** was prepared in the same manner as compound **11**. Flash chromatography (6 g of SiO_2, 0–30% EtOAc in hexane) gave 85 mg (74%) of compound **9a** as a clear oil: IR 1720, 1660 cm^{-1}; ^1H NMR (250 MHz) δ 0.56 (s, 3), 0.66 (d, 3, J = 7), 0.90–1.00 (m, 2), 1.10–1.26 (m, 5), 1.38–1.52 (m, 5), 1.62–1.64 (m, 3), 1.72 (d (br), 1, J = 13), 1.87 (ddd, 1, J = 25, 12.8, 3.9), 2.26 (t, 2, J = 7), 3.58 (s, 3), 4.85 (s (br), 1), 7.34 (d, 2, J = 8), 7.47 (dt, 2, J = 7, 1.5), 7.57 (dt, 1, J = 7.4, 1.3), 7.77 (m, 4); ^{13}C NMR (125 MHz) δ 12.27, 15.75, 20.51, 21.62, 22.28, 26.20, 26.81, 31.02, 32.46, 33.54, 35.47, 37.06, 39.16, 40.46, 45.25, 46.89, 50.96, 57.11, 74.84, 128.19, 128.21, 129.91 (2 C), 130.42 (2 C), 145.63, 172.25, 176.69, 196.26; mass spectrum (60 eV) m/z 530 (M^+), 470, 277, 275, 255, 217. Anal. Calcd for $C_{34}H_{42}O_5 \cdot H_2O$: C, 74.42; H, 8.08. Found: C, 74.10; H, 7.80.

Compound 9b was prepared in the same manner as compound **11**. Flash chromatography gave 29 mg (75%) of compound **9b** as a clear oil: IR 1728, 1662, 1612 cm^{-1}; ^1H NMR (250 MHz) δ 0.72 (s, 3), 0.76 (d, 3, J = 7), 0.91 (s, 3), 0.93–1.82 (m, 19), 2.72 (t, 2, J = 8), 3.06 (t, 2, J = 8), 4.94 (d (br), 1, J = 3), 7.34 (d, 2, J = 8), 7.48 (m, 2), 7.58 (m, 1), 7.77 (t, 4, J = 8); mass spectrum (FAB, glycerol/thioglycerol) m/z 487 (MH), 469, 255; HRFABMS calcd for $C_{33}H_{43}O_3$ 487.3212, found 487.3212.

Compound 9c. Compound **9c** was prepared in the same manner as compound **11**. Flash chromatography (2.5 g of SiO_2, 0–20% EtOAc in hexane) afforded 72 mg (86%) of compound **9c** as a clear oil: IR 1737, 1662, 1610 cm^{-1}; ^{1} H NMR (250 MHz) δ 0.71 (s, 3), 0.92 (s, 3), 0.92–1.81 (m, 20), 2.72 (t, 2, J = 7), 3.06 (t, 2, J = 7), 5.03 (m, 1), 7.34 (d, 2, J = 8), 7.48 (t, 2, J = 7.5), 7.59 (m, 1), 7.78 (m, 4); ^{13}C NMR (50 MHz) δ 11.67, 20.46, 20.73, 21.86, 25.40, 25.82, 27.71, 30.99, 32.75, 33.56, 34.88, 35.66, 36.17, 41.31, 42.55, 46.19, 55.96, 70.50, 128.18 (4 C), 129.89 (2 C), 130.41 (2 C), 132.20, 135.53, 137.71, 145.67, 171.98, 196.24. Anal. Calcd for $C_{32}H_{40}O_3$: C, 81.31; H, 8.53. Found: C, 81.04; H, 8.45.

Compound 11. In a 10-mL round-bottomed flask under N_2 was placed 46 mg (0.158 mmol) of compound **6a**, 59 mg (0.23 mmol) of 3-(4-benzoylphenyl)propanoic acid,[20] 1 mL of ether, and enough CH_2Cl_2 to make the solution homogeneous (ca. 0.1 mL). To this solution was added 21 mg (0.17 mmol) of DMAP and 36 mg (0.17 mmol) of DCC. The reaction mixture was stirred for 8 h and then filtered, and the precipitate was washed with cold ether. The combined filtrate was washed with 2 N NaOH, water, and brine. Drying and concentration gave 72 mg (86%) of compound **11** as a white foam: IR 3005, 1720, 1660, 1611 cm^{-1}; ^1H NMR (250 MHz) δ 0.74 (d, 3, J = 7), 0.75 (s, 3), 0.96–2.17 (m, 18), 2.50 (d (br), 1, J = 12), 2.69 (t, 2, J = 9), 3.03 (t, 2, J = 9), 4.92 (d, 1, J = 2), 5.66 (m, 1), 7.33 (d, 2, J = 8), 7.47 (m, 2), 7.56 (m, 1), 7.76 (t (br), 4, J = 8); ^{13}C NMR (50 MHz) δ 15.84, 17.40, 17.89, 22.15, 25.41, 26.34, 30.96, 31.29, 34.05, 35.42, 38.16, 38.28, 39.39, 44.95, 45.50, 51.52, 74.58, 121.34, 128.13 (4 C), 129.82 (2 C), 130.33 (2 C), 132.18, 135.48, 137.61, 144.50, 145.51, 172.17, 177.31, 196.17; mass spectrum (FAB, glycerol/thioglycerol) m/z 529 (MH), 511, 461, 336.

Compound 12. To a solution of 128 mg (0.438 mmol) of compound **6a** and 107 mg (1.59 mmol) of imidazole in 17 mL of CH_2Cl_2 cooled to 0 °C was slowly added 0.10 mL (0.8 mmol) of chlorotrimethylsilane. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. After being stirred for an additional 30 min, the reaction mixture was diluted with CH_2Cl_2 and washed with ice-cold 2 N HCl (2 × 10 mL), saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and evaporated to give 143 mg of crude product, which was purified by flash chromatography (2.5 g of SiO_2, 0–10% EtOAc in hexane) to give 110 mg (69%) of compound **12** as a clear oil, which slowly solidified to a white solid, mp 93–94 °C: IR 1715 cm^{-1}; ^1H NMR (250 MHz) δ 0.02 (s, 9), 0.74 (s, 3), 0.77 (d, 3, J = 7), 1.05–1.85 (m, 16), 2.10 (m, 2), 2.47 (d (br), 1, J = 13), 3.66 (s, 3), 3.67 (s (br), 1). Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45. Found: C, 69.05; H, 10.18.

Compound 13. A mixture of 0.265 g (2.65 mmol) of CrO_3 and 5 mL of CH_2Cl_2 was cooled to −40 °C in a dry ice/acetone bath, and 0.250 g (2.56 mmol) of 3,5-dimethylpyrazole was added in one portion with vigorous stirring. The resulting deep-red solution was stirred for an additional 30 min, and a solution of 95 mg (0.261 mmol) of compound **12** in 5 mL of CH_2Cl_2 was added. The reaction mixture was stirred for an additional 2 h at −30 °C, and 5 mL of hexane was added. The resulting heterogeneous mixture was filtered through a plug of silica gel which was then eluted with ether. The combined eluate was washed with ice-cold 2 N HCl (2 × 20 mL), 2 N NaOH (1 × 20 mL), saturated $NaHCO_3$ (1 × 20 mL), and brine (1 × 25 mL) and dried over Na_2SO_4. Evaporation of the solvent gave 77 mg of a yellow oil which was purified by flash chromatography (1.2 g SiO_2, 0–10% EtOAc in hexane) to give 54 mg (55%) of compound **13** as a white solid, mp 82–84 °C. An analytical sample was prepared by recrystallization from hexanes to give white prisms, mp 110–112 °C: IR 1730, 1685 cm^{-1}; ^1H NMR (250 MHz) δ 0.05 (s, 9), 0.82 (d, 3, J = 7), 0.84 (s, 3), 1.20–1.85 (m, 10), 1.97 (dd, 1, J = 15, 5), 2.07 (ddd, 1, J = 13, 6, 2), 2.29 (ddd, 1, J = 18, 5, 2), 2.57 (dd, 1, J = 15, 6), 2.63 (m, 1), 3.67 (s, 3), 6.09 (s, 1); ^{13}C NMR (50 MHz) δ 0.27 (3 C), 16.73, 17.53, 21.58, 29.68, 30.17, 33.62, 35.77, 36.69, 38.06, 41.02, 42.99, 45.96, 52.05, 71.40, 125.04, 169.65, 173.94, 200.33. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 66.62; H, 9.05. Found: C, 66.68; H, 9.26.

Compound 14. Into a 25-mL round-bottomed three-necked flask fitted with an inlet for ammonia, a dry-ice condenser, and a pressure-equalizing addition funnel equipped with an outlet to a N_2 atmosphere were placed 3.5 mg (0.5 mmol) of lithium wire and 5 mL of dry THF. The flask was cooled to −78 °C, and NH_3 was slowly condensed into the flask with vigorous stirring until no solid lithium remained. The resulting suspension of lithium–bronze was stirred for an additional 10 min at −78 °C. A solution of 20 mg (0.053 mmol) of compound **13** in 2 mL of THF was added slowly with stirring over 15 min. After the addition was complete, the reaction mixture was stirred an additional 1.5 h, and the reaction was quenched by the addition first of some methanol and then some aqueous saturated NH_4Cl. After being warmed to room temperature, the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried, filtered, and evaporated. Flash chromatography (0.5 g of SiO_2, 0–20% EtOAc in hexanes) of the residue gave 8 mg (40%) of compound **14** as the first fraction and 6 mg (33%) of starting material **13** as the second fraction: IR 1705 cm^{-1}; ^1H NMR (250 MHz) δ 0.05 (s, 9), 0.64 (s, 3), 0.77 (d, 3, J = 7), 1.06 (ddd, 1, J = 13, 12.5, 4), 1.20–1.69 (m, 10), 1.89 (ddd, 1, J = 14, 7, 2), 2.20 (dd, 1, J = 16, 6), 2.29–2.44 (m, 2), 2.51 (dq, 1, J = 16, 7), 2.91 (dd, 1, J = 15, 14.5), 3.66 (m, 1), 3.68 (s, 3). Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 66.26; H, 9.64.

Compound 15. To a solution of 62 mg (0.163 mmol) of compound **14** in 5 mL of MeOH was added 5 mL of a saturated solution of KF in MeOH. The mixture was stirred for 1 h and concentrated. The residue was dissolved in water and extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were dried, filtered, and evaporated. Flash chromatography (1.5 g of SiO_2, 0–20% EtOAc in hexanes) of the residue gave 50 mg (100%) of compound **15** as a white foam: IR 3500, 1732 (sh), 1705 cm^{-1}; ^1H NMR (250 MHz) δ 0.64 (s, 3), 0.92 (d, 3, J = 6.5), 1.07 (m, 1), 1.21–1.77 (m, 11), 1.98 (ddd, 1, J = 15, 7, 2), 2.28 (ddd, 1, J = 16, 5, 1), 2.40 (ddd, 1, J = 15, 3, 1), 2.49 (dd, 1, J = 17, 3), 2.60 (ddd, 1, J = 16, 14, 7), 2.99 (dd, 1, J = 17, 3), 3.71 (s, 3), 3.73 (m, 1); MS (60 eV) m/z 308 (M^+), 290, 280, 276, 248, 231, 215; HRMS calcd for $C_{18}H_{28}O_4$ 308.1988, found 308.1991.

Compound 16. Into a 10-mL flask fitted with a Dean-Stark trap were placed 20 mg (0.0526 mmol) of compound **14**, 0.1 mL of ethylene glycol, 3 mg of *p*-toluenesulfonic acid, and 4 mL of benzene. The mixture was heated at reflux for 4.5 h, cooled to room temperature, diluted with CH_2Cl_2, and washed with 2 N NaOH (1 × 10 mL) and brine (1 × 10 mL) and dried. The residue upon evaporation of solvent was purified by flash chromatography

(20) Borsche, W.; Sinn, F. *Liebigs Ann. Chem.* **1942**, *533*, 260.

(1 g of SiO_2, 0–20% EtOAc in hexane) to give 16 mg (86%) of compound **16**: IR 3500, 1717 cm^{-1}; ^1H NMR (500 MHz) δ 0.61 (s, 3), 0.88 (d, 3, J = 6.8), 1.03 (dt, 1, J = 13.1, 3.9), 1.21 (dt, 1, J = 12.9, 3.2), 1.22–1.58 (m, 8), 1.65 (m, 4), 1.74 (m, 1), 1.88 (ddd, 15.1, 13.8, 4.4), 2.25 (dd, 1, J = 13.2, 13.1), 2.36 (dt, 1, J = 13.2, 3.3), 3.64 (s, 3), 3.70 (d, 1, J = 2.5), 3.95 (m, 4); ^{13}C NMR (125 MHz) δ 11.90, 16.21, 22.30, 28.88, 30.67, 31.01, 31.71, 34.71, 36.99, 44.28, 45.11, 51.12, 52.94, 63.97, 64.24, 71.63, 110.04, 176.41; mass spectrum (60 eV) m/z 352 (M^+), 205, 200, 99; HRMS calcd for $C_{20}H_{32}O_5$ 352.2251, found 352.2252.

Compound 17. To a solution of 21 mg (0.0833 mmol) of compound **16**, 19 mg (0.0748 mmol) of 3-(4-benzoylphenyl)-propanoic acid,[20] 0.5 mL of ether, and enough CH_2Cl_2 to make the solution homogeneous (ca. 0.1 mL) was added 9.5 mg (0.0864 mmol) of DMAP and 16 mg (0.0784 mmol) of DCC. The reaction mixture was stirred for 4 h and filtered and the precipitate washed with cold ether. The combined filtrate was washed with 2 N NaOH, water, and brine. Drying and concentration gave 37 mg of crude product, which was purified by flash chromatography (1 g of SiO_2, 0–30% EtOAc in hexanes) to give 26 mg (74%) of compound **17** as a clear oil: IR 1717, 1655, 1610 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3), 0.72 (d, 3, J = 6.7), 0.80–1.80 (m, 14), 1.89 (ddd, 1, J = 17, 13, 4), 2.28 (d, 1, J = 13), 2.40 (d (br), 1, J = 16), 2.71 (t, 2, J = 7.5), 3.06 (t, 2, J = 7.5), 3.66 (s, 3), 3.94 (m, 4), 4.93 (d, 1, J = 2.4), 7.34 (d, 2, J = 8.1), 7.48 (m, 2), 7.58 (m, 1), 7.77 (m, 4); mass spectrum (60 eV) m/z 588 (M^+), 529, 335, 225, 195, 167, 119; HRMS calcd for $C_{36}H_{44}O_7$ 588.3088, found 588.3079.

Compound 18a. From Compound **15**: To a solution of 14 mg (0.045 mmol) of compound **15**, 12 mg (0.047 mmol) of 3-(4-benzoylphenyl)propanoic acid,[18] 0.5 mL of ether, and enough CH_2Cl_2 to make the solution homogeneous (ca. 0.1 mL) was added 6 mg (0.0497 mmol) of DMAP and 12 mg (0.058 mmol) of DCC. The mixture was stirred for 4 h and filtered and the precipitate washed with cold ether. The combined filtrate was washed with 2 N NaOH, water, and brine. Drying and concentration gave 23 mg of crude product, which was purified by flash chromatography (1 g of SiO_2, 0–30% EtOAc in hexanes) to give 18 mg (73%) of compound **18a** as a white foam.

From Compound 9a. A solution of 48 mg (0.09 mmol) of compound **9a** in 300 mL of degassed benzene was irradiated for 45 min. The solvent was evaporated to give 35.5 mg of a yellow oil. To a solution of 18 mg of this oil in 2 mL of CH_2Cl_2 was added 58 mg (0.58 mmol) of CrO_3. The rapidly stirred mixture was cooled to −30 °C, and 1 mL of glacial acetic acid was added. The brown reaction mixture was stirred at −20 to −30 °C for 1.8 h, and the reaction was stopped by the addition of water. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with brine and dried over Na_2SO_4. The residue upon evaporation of solvent was purified by flash chromatography (3 g of SiO_2, 0–5% EtOAc in hexane) to afford 6 mg (27%) of starting material **9a** as the first fraction and 6 mg (26%) of compound **18a** as the second fraction: IR 1720, 1660 cm^{-1}; ^1H NMR (500 MHz) δ 0.67 (s, 3), 0.74 (d, 3, J = 6.7), 0.99–1.15 (m, 2), 1.20–1.39 (m, 3), 1.53–1.70 (m, 6), 1.98 (ddd, 1, J = 14, 7, 1.7), 2.29 (dd, 1, J = 16, 5), 2.34 (dd, 1, J = 13, 5), 2.60 (ddd, 1, J = 16, 14, 7), 2.69 (t, 2, J = 8), 3.01 (dd, 1, J = 15, 14), 3.02 (t, 2, J = 8), 3.71 (s, 3), 4.93 (d, 1, J = 2.5), 7.32 (d, 2, J = 8), 7.45 (dt, 2, J = 8, 1.5), 7.58 (m, 1), 7.76 (m, 4); ^{13}C NMR (125 MHz) δ 11.30, 15.76, 22.04, 25.97, 30.97, 31.88, 33.56, 35.42, 37.31, 37.44, 37.59, 38.13, 38.30, 43.54, 46.17, 51.64, 54.76, 74.26, 128.16, 128.23, 129.93 (2 C), 130.43 (2 C), 132.29 (2 C), 135.67, 137.70, 145.50, 172.14, 175.56, 196.30, 212.33. Anal. Calcd for $C_{34}H_{40}O_6$: C, 74.97; H, 7.40. Found: C, 74.88; H, 7.46.

Compound 18b. A solution of 27 mg (0.055 mmole) of compound **9b** in 55 mL of degassed benzene was irradiated for 40 min. Evaporation of the solvent gave 35 mg of a yellow oil. Oxidation of 28 mg of this oil in the same manner as for compound **18a** gave 20 mg of crude product, which was purified by flash chromatography (0.5 g of SiO_2, 0–20% EtOAc in hexanes) to give 12 mg (56%) of starting material **9b** as the first fraction and 4 mg (18%) of compound **18b** as the second fraction: IR 1740 (sh), 1772, 1710, 1660, 1605 cm^{-1}; ^1H NMR (500 MHz) δ 0.76 (d, 3, J = 6.8), 0.77 (s, 3), 1.12 (s, 3), 1.13–1.25 (m, 3), 1.31 (dd, 1, J = 14.0, 13.4), 1.33–1.41 (m, 2), 1.45 (dd, 1, J = 13.7, 4.9), 1.48–1.70 (m, 6), 2.25 (dd, 1, J = 15.0, 14.0), 2.31 (m, 1), 2.35 (dm, 1, J = 13.5), 2.42 (ddd, 1, J = 14.7, 14.0, 6.5), 2.68 (t, 2, J = 7.6), 3.03 (t, 2, J = 7.6), 4.94 (d, 1, J = 2.6), 7.32 (d, 2, J = 8.1), 7.47 (t, 2, J = 7.3), 7.57 (t (br), 1, J = 7.4), 7.73 (d, 2, J = 8.1), 7.77 (d, 2, J = 7.3); mass spectrum (FAB, glycerol/thioglycerol) m/z 501 (MH), 399, 307; HRFABMS calcd for $C_{33}H_{41}O_4$ 501.3006, found 501.3001.

Compounds 19a and 19b. A solution of 62 mg (0.117 mmol) of compound **11** in 350 mL of degassed benzene was irradiated for 1 h. The solvent was evaporated to give 84 mg of a slightly yellow foam. Purification by flash chromatography (2.5 g of SiO_2, 0–20% EtOAc in hexane) gave 30 mg of compound **19a** as the first fraction and 26 mg of compound **19b** as the second fraction (95% total yield). Compound **19a**: mp 145–150 °C; IR 3500, 1715 cm^{-1}; ^1H NMR (500 MHz) δ 0.49 (d (br), 1, J = 12), 0.61 (dd, 1, J = 12.5, 4), 0.68 (s, 3), 0.74 (d, 3, J = 7), 0.90 (m, 2), 1.20–1.97 (m, 8), 2.08–2.25 (m, 2), 2.41 (s, 1), 2.60–3.09 (m, 4), 3.36 (dd, 1, J = 11, 4), 3.63 (s, 3), 4.49 (d, 1, J = 2), 5.22 (s, 1), 6.55 (dd, 1, J = 8, 2), 6.86 (dd, 1, J = 8, 1.5), 7.26 (m, 1), 7.30–7.46 (m, 3), 7.59 (d, 2, J = 7), 7.68 (dd, 1, J = 8, 2); ^{13}C NMR (50 MHz) δ 15.82, 20.54, 21.77, 25.28, 30.51, 30.78, 33.95, 34.91, 35.27, 36.15, 40.13, 45.27, 45.57, 46.56, 51.61, 76.67, 80.44, 95.65, 125.77, 126.01, 126.31, 127.34, 127.50, 127.58, 128.30, 129.70, 130.77, 138.77, 142.93, 148.93, 172.69, 178.23. Anal. Calcd for $C_{34}H_{40}O_5$: C, 77.24; H, 7.63. Found: C, 76.93; H, 7.91.

Compound 19b: mp 262 °C; IR 3500, 1712 cm^{-1}; ^1H NMR (500 MHz) δ 0.46 (ddd, 1, J = 14, 13, 3.5), 0.58 (ddd, 1, J = 12, 11, 2.1), 0.68 (s, 3), 0.76 (d, 3, J = 6.7), 0.98 (d (br), 1, J = 12.9), 1.08 (ddd, 1, J = 12.7, 12.4, 4.4), 1.19–1.64 (m, 7), 1.76 (dd, 10.7, 2.2), 1.94 (m, 1), 2.14 (d (br), 1, J = 12.5), 2.29 (s, 1), 2.71 (m, 1), 2.78 (m, 1), 2.92 (m, 1), 3.00 (m, 1), 3.24 (dd, 1, J = 12.9, 4.1), 3.59 (s, 3), 4.54 (d, 1, J = 2), 5.36 (s, 1), 7.16–7.40 (m, 6), 7.51 (dd, 2, J = 6.5, 1), 7.81 (d (br), 1, J = 7.5). ^{13}C NMR (125 MHz) δ 15.67, 16.39, 21.81, 22.86, 25.34, 30.55, 30.77, 33.92, 34.62, 34.97, 36.49, 40.13, 45.38, 46.65, 48.84, 51.48, 76.74, 81.43, 125.71, 126.81, 127.27, 127.71, 127.76, 127.86, 128.36, 138.64, 139.98, 144.12, 144.62, 172.72, 178.35. Anal. Calcd for $C_{34}H_{40}O_5$: C, 77.24; H, 7.63. Found: C, 76.88; H, 7.77.

Compound 20. To a solution of 24 mg (0.045 mmol) of a mixture a compounds **19a** and **19b** in 2 mL of CH_2Cl_2 was added 60 mg (0.6 mmol) of chromium trioxide. The mixture was cooled to −30 °C, and 1 mL of glacial acetic acid was added via syringe. The resulting dark brown mixture was stirred at −20 °C for 1 h. The reaction was quenched by the addition of water and the reaction mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the brown residue was purified of chromium byproducts by filtration through a short plug of silica gel, which was then eluted with ether. Evaporation of the combined eluate gave 21.5 mg (87%) of compound **20** as a white foam: IR 1727, 1663, 1610 cm^{-1}; ^1H NMR (500 MHz) δ 0.78 (d, 3, J = 6.8), 0.88 (s, 3), 1.21 (m, 2), 1.38 (m, 2), 1.61–1.75 (m, 4), 1.82 (m, 2), 1.94 (ddd, 1, J = 14.8, 14.5, 4.8), 2.10 (dd, 1, J = 14.1, 3.6), 2.32 (dd, 1, J = 17.4, 2.5), 2.56 (dd, 1, J = 15.3, 5.6), 2.60 (m, 1), 2.67 (t, 2, J = 8.0), 3.03 (t, 2, J = 8.0), 3.69 (s, 3), 4.96 (d, 1, J = 2.4), 6.06 (s, 1), 7.31 (d, 2, J = 8.1), 7.45 (d, 2, J = 8.1), 7.49 (m, 1), 7.75 (t, 4, J = 7.7); mass spectrum (FAB, glycerol/thioglycerol) m/z 543 (MH), 459, 401, 289; HRFABMS calcd for $C_{34}H_{38}O_6$ 543.2746, found 543.2752.

Compound 21. A solution of 12 mg (0.02 mmol) of compound **17** in 50 mL of degassed benzene was irradiated for 40 min. Evaporation of the solvent gave 13 mg of a yellow oil which was purified by flash chromatography (0.5 g of SiO_2, 0–30% EtOAc in hexane) to give 4 mg (33%) of compound **21** as a white solid: IR 3500, 3010, 1719 cm^{-1}; ^1H NMR (250 MHz) δ −0.49 (dt, 1, J = 13, 5), 0.49 (s, 3), 0.79 (d, 3, J = 6.7), 0.80 (m, 4), 1.00–1.83 (m, 10), 2.38 (m, 2), 2.64 (m, 2), 2.87 (dd, 1, J = 14, 7), 2.95 (m, 1), 3.59 (s, 1), 3.64 (s, 3), 3.95 (dd, 1, J = 9, 6), 4.34 (d, 1, J = 9), 4.52 (d (br), 1, J = 2), 5.01 (d, 1, J = 6), 7.18 (d (br), 2, J = 7), 7.27 (m, 3), 7.54 (m, 4); mass spectrum (60 eV) m/z 588 (M^+), 570, 556, 545; HRMS calcd for $C_{36}H_{44}O_7$ 588.3088, found 588.3084.

Compounds 18c, 22c, and 23c. A solution of 54 mg (0.114 mmol) of compound **9c** in 350 mL of degassed benzene was irradiated for 35 min. Evaporation of the solvent gave 62 mg of a yellow oil. Oxidation of 53 mg of this oil under the conditions employed for compound **18a** gave 47 mg of crude product. Purification by flash chromatography gave 29 mg (54%) of starting material **9c** as the first band, 2.5 mg (5%) of a 1:1 mixture of compounds **22c** and **23c** as the second fraction, and 7 mg (14%)

of compound **18c** as the third fraction. Compound **18c**: IR 1727, 1665, 1615 cm^{-1}; ^1H NMR (500 MHz) δ 0.76 (s, 3), 0.83–0.99 (m, 4), 1.12 (s, 3), 1.24 (s (br), 1), 1.25–1.30 (m, 2), 1.32–1.47 (m, 4), 1.56–1.65 (m, 3), 2.23 (dd, 1, J = 14.5, 14.3), 2.26 (m, 1), 2.29 (d (br), 1, J = 19.7), 2.41 (dt, 1, J = 14.4, 6.7), 2.68 (t, 2, J = 7.7), 3.03 (t, 2, J = 7.7), 5.04 (m, 1), 7.31 (m, 1), 7.47 (t, 2, J = 8.1), 7.77 (d, 2, J = 7.0); mass spectrum (FAB, glycerol/thioglycerol) m/z 509 (M + Na), 487 (MH), 471, 255; HRFABMS calcd for $C_{32}H_{39}O_4$ 487.2848, found 487.2854.

Compounds 22c and 23c: IR 1720, 1660, 1605 cm^{-1}; ^1H NMR (an approximate 1:1 mixture of **22c** and **23c**) (250 MHz) δ 0.71 (s, 3/2), 0.81 (s, 3/2), 0.81–0.95 (m, 3), 0.96 (s, 3/2), 1.24 (s, 3/2), 1.24–1.78 (m, 12), 2.04 (m, 1/2), 2.06 (d, 1/2, J = 12), 2.22 (m, 1/2), 2.26 (d (br), 1/2, J = 13), 2.54 (dd, 1/2, J = 12, 6), 2.56 (m, 1/2), 2.69 (t, 2, J = 7.5), 3.04 (t, 2, J = 7.5), 5.01 (m, 1/2), 5.14 (m, 1/2), 7.32 (d, 2, J = 8), 7.48 (t, 2, J = 7.5), 7.59 (m, 1), 7.76 (m, 4); mass spectrum (FAB, glycerol/thioglycerol) m/z 509 (M + Na), 487 (MH), 471, 255; HRFABMS calcd for $C_{32}H_{39}O_4$ 487.2848, found 487.2860.

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Registry No. 1, 41451-75-6; **5a**, 141396-78-3; **5b**, 91237-33-1; **5c**, 91191-70-7; **6a**, 141396-79-4; **6a** ketone, 141396-80-7; **6b**, 141396-81-8; **6b** ketone, 141396-82-9; **6c**, 141396-83-0; **6c** ketone, 141396-84-1; **7a**, 141396-85-2; **7b**, 141396-86-3; **7c**, 141396-87-4; **8**, 71388-83-5; **9a**, 141396-88-5; **9a** (phosphoproduct, isomer 1), 141396-89-6; **9a** (photoproduct, isomer 2), 141435-17-8; **9b**, 141396-90-9; **9b** (photoproduct, isomer 1), 141396-91-0; **9b** (photoproduct, isomer 2), 141435-18-9; **9c**, 141396-92-1; **9c** (CH12 photoproduct, isomer 1), 141396-93-2; **9c** (C-12 photoproduct, isomer 2), 141435-19-0; **9c** (C-7 photoproduct, isomer 1), 141396-94-3; **9c** (C-7 photoproduct, isomer 2), 141435-20-3; **9c** (C-14 photoproduct, isomer 1), 141396-95-4; **9c** (C-14 photoproduct, isomer 2), 141435-21-4; **11**, 141396-96-5; **12**, 141396-97-6; **13**, 141396-98-7; **14**, 141396-99-8; **15**, 141397-00-4; **16**, 141397-01-5; **17**, 141397-02-6; **18a**, 141397-03-7; **18a** (photo-pinacol, isomer 1), 141397-04-8; **18a** (photo-pinacol, isomer 2), 141435-22-5; **18b**, 141397-05-9; **18c**, 141397-06-0; **19** (isomer 1), 141411-05-4; **19** (isomer 2), 141505-43-3; **20**, 141397-07-1; **21**, 141397-08-2; **22c**, 141397-09-3; **23c**, 141397-10-6; **24**, 141397-11-7.

Supplementary Material Available: ^1H NMR spectra for compounds **9b**, **11**, **15**, **16**, **17**, **20**, **18c**, **22c**, and **23c** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Notes

Electrochemically Supported Reformatsky Reaction: A Convenient Preparation of 2-Substituted 1-Ethyl 3-Oxoalkanedioates

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The Reformatsky reaction of ethyl 2-bromoalkanoates with zinc and aldehydes or ketones is an important method for the preparation of various ethyl 3-hydroxyalkanoates.[1] The success of the reaction strongly depends on the reactivity of the zinc. Therefore, much effort has been applied to the activation of the metal.[2] Washing of zinc with diluted hydrochloric acid,[3] reduction of zinc halides with potassium[4] or lithium naphthalenide,[5] preparation of zinc–copper[6] or zinc–silver couples,[7] and ultrasonic irradiation[8] are among the methods that have been employed to achieve a proper activation of the zinc. Even with the use of these methods, the problem remains that Reformatsky reactions are often difficult to control. Usually, the reactions take a highly exothermic course once a critical temperature has been reached.

Electrosynthesis has proven to be an efficient method for the preparation of organometallic compounds.[9] Especially organometallics, generated by sacrificial anodes such as magnesium,[10] aluminum,[11] and zinc,[12] present a useful alternative to purely chemical synthesis in the preparation of nucleophilic intermediates suited for further reactions with electrophiles in order to form new carbon–carbon bonds.[13]

With the application of an electrochemical procedure, we are now able to circumvent both the problems of zinc activation and the difficulties connected with the uncontrolled exothermic course of the Reformatsky reaction of ethyl 2-bromoalkanoates with cyclic carboxylic anhydrides.[14]

Ethyl 2-bromo-2-methylpropanoate (**3a**) was electrolyzed in the presence of succinic anhydride (**1**) in DMF containing tetrabutylammonium bromide as supporting electrolyte. We used a closed undivided cell with a zinc rod as anode and a nickel net as cathode, with an initial external voltage of 50 V. The temperature of the system was maintained at 50 °C by reducing the voltage to about 30 V during the course of the electrolysis. At the end of

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