Methodology for the Synthesis of 3-Oxygenated Ingenanes. The First Ingenol Analogs with High Affinity for Protein Kinase C†,‡

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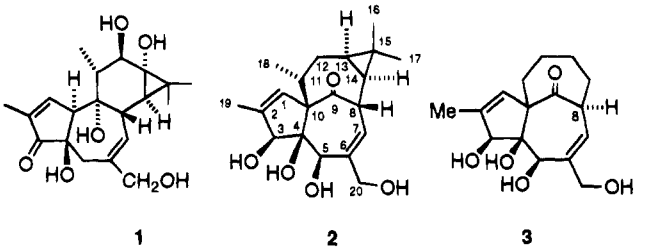
Previous work from our laboratories has demonstrated that the intramolecular dioxenone photocycloaddition reaction leads to a stereoselective synthesis of the carbocyclic ring system of the ingenane diterpenes with the "inside-outside" stereochemical relationship that is required for biological activity. Two different approaches for the synthesis of C-3 oxygenated analogs of ingenol and the preparation of the first ingenane analog with high affinity for protein kinase C are described.

Introduction

Protein kinase C (PKC) is the phosphorylating enzyme mediating cellular signal transduction for a large class of hormones and cellular effectors that activate phosphatidylinositol 4,5-bis(phosphate) turnover.[3] Several structurally diverse naturally occurring compounds, including the bryostatins, teleocidin, asplysiatoxin, and esters of phorbol, **1**, and ingenol, **2** (Scheme 1), mimic the function of diacyl glycerol (DAG), the endogenous activator of protein kinase C.[4] As a result, the study of the structural requirements for the activation of protein kinase C has focused on the synthesis and study of specifically modified derivatives of these natural product leads.

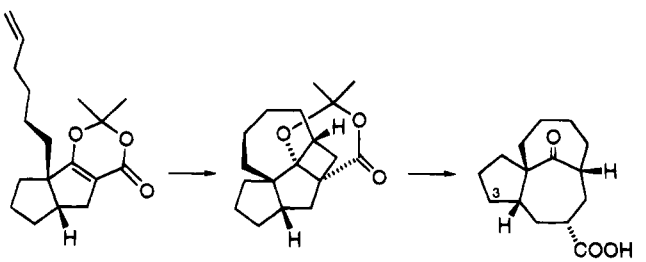
Unlike phorbol, the structurally related diterpene ingenol has not yet yielded to total synthesis.[5,6] One of the more imposing challenges in the synthesis of the highly oxygenated diterpene ingenol is the stereochemically controlled synthesis of the carbocyclic ring system of the ingenanes that embodies an "inside-outside" or trans intrabridgehead stereochemical relationship. This unique stereochemical feature appears to play a very important role in the biological properties of the ingenanes as Paquette has reported that the highly functionalized ingenane analog **3**, which has cis rather than trans intrabridgehead stereochemistry (the C-8 epimer of ingenol), is completely devoid of biological activity.[7]

Scheme 1



1 **2** **3**

Scheme 2



4 **5** **6**

We have previously reported the application of the intramolecular dioxenone photocycloaddition to the first synthesis of the ingenane ring system, **6** (Scheme 2), with the trans intrabridgehead stereochemical relationship.[8–10] That model system, however, was devoid of most of the functionality that appears in the natural product. Of particular importance was the lack of oxygenation at C-3, which is the point of attachment of the ester substituents that are required for biological activity.[11]

† Dedicated to our friend and colleague Professor Amos B. Smith, III, on the occasion of his 50th birthday.

‡ Inside-Outside Stereoisomerism VII. For the preceding paper in this series, see Winkler, J. D.; Henegar, K. E.; Hong, B.-C. and Williard, P. G., *J. Am. Chem. Soc.* **1994**, *116*, 4183–4188.

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(1) Recipient of the American Cyanamid Young Faculty Award (1989–1992) and a National Institutes of Health Research Career Development Award (1988–1993).

(2) Address correspondence to this author regarding the biological testing of the ingenane analogs.

(3) Schmidt, R.; Aitken, A. In *Naturally Occurring Phorbol Esters*; Evans, F., Ed., CRC Press, Inc.: Boca Raton, 1986; pp 245–289.

(4) Since it is likely that the various tumor promotors bind to the same site on the regulatory domain of PKC, there should be structural commonalities in these agents, which possess much greater potency than DAG. Several models for the PKC pharmacophore have been proposed: (a) Jeffrey, A.; Liskamp, R. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 241. (b) Wender, P.; Cribb, C.; Koehler, K.; Sharkey, M.; Herald, C.; Kamano, Y.; Pettit, G.; Blumberg, P. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7197. (c) Itai, A.; Kato, Y.; Tomioka, N.; Iitaka, Y.; Endo, Y.; Hasegawa, M.; Shudo, K.; Fujiki, H.; Sakai, S. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3688. (d) Nakamura, H.; Kishi, Y.; Pajares, M.; Rando, R. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 9672.

(5) Wender, P. and McDonald, F. *J. Am. Chem. Soc.* **1990**, *112*, 4956.

(6) For studies directed towards the synthesis of ingenanes, see (a) Paquette, L.; Nitz, T.; Ross, R.; Springer, J. *J. Am. Chem. Soc.* **1984**, *106*, 1446. (b) Sato, T.; Okuda, T.; Kaneko, Y.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 1401. (c) Rigby, J.; Moore, T. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (d) Funk, R.; Bolton, G. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (e) Mehta, G.; Pathak, V. *J. Chem. Soc., Chem. Commun.* **1987**, 876. (f) Ross, R.; Paquette, L. *J. Org. Chem.* **1987**, *52*, 5497. (g) Rigby, J.; Kierkus, P. *J. Am. Chem. Soc.* **1989**, *111*, 4125. (h) Rigby, J.; Moore, T. *J. Org. Chem.* **1990**, *55*, 2959.

(7) Paquette, L.; Ross, R.; Springer, J. *J. Am. Chem. Soc.* **1988**, *110*, 6192.

(8) Winkler, J.; Henegar, K.; Williard, P. *J. Am. Chem. Soc.* **1987**, *109*, 2850.

(9) Winkler, J.; Henegar, K.; Hong, B.; Williard, P. *J. Am. Chem. Soc.* **1994**, *116*, 4183–4188.

(10) For an alternative approach to the synthesis of trans-bridged bicyclo[4.4.1]undecanones, see Funk, R.; Olmstead, T.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298.

(11) For the biological activity of the parent tetraol, see Hasler, C., Acs., G., Blumberg, P. *Cancer Res.* **1992**, *52*, 202.

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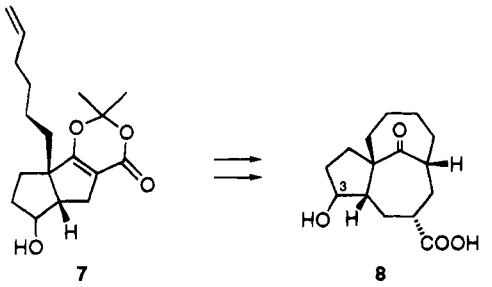
Scheme 3



We have now extended our preliminary findings to the synthesis of C-3 oxygenated analogs of ingenol. These compounds are the first reported biologically active analogs of the natural product. We describe herein two different approaches to the synthesis of saturated and unsaturated analogs of ingenol that have substantial affinity for protein kinase C.[12] These new compounds could be the prototypes of a new class of therapeutic agents that acts by controlling protein phosphorylation.[13]

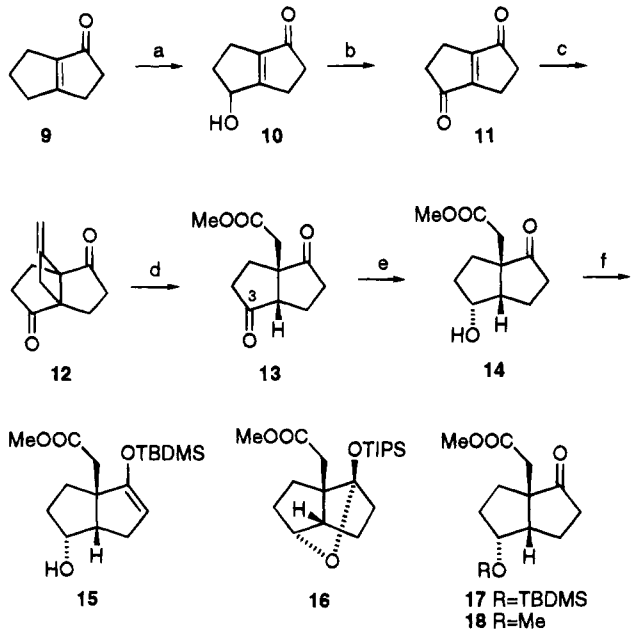
Results and Discussion

We reasoned, in direct analogy to the sequence **4** → **6** outlined in Scheme II, that photoaddition and fragmentation of a C-3 (ingenol numbering) oxygenated photosubstrate would lead to the formation of the requisite A-ring functionality in the ingenane ring system, i.e., **7** → **8** (Scheme 3).

The most efficient method for the angular functionalization of the hydroxylated enone **10** was reductive alkylation (vide infra), in analogy to our previously reported synthesis of **4** (Scheme II). However, several alternative approaches to the angular functionalization of the C-3 (ingenol numbering) oxygenated enone **10**[14] (Scheme 4) were also examined. It was found that neither cuprate addition[15] nor Diels–Alder cycloaddition[16] to either **10** or **11** could be achieved. We were therefore gratified to learn that enedione **11** did undergo [2 + 2] a highly efficient photocycloaddition with allene (quantitative yield), as outlined in Scheme IV. Ozonolysis of photoadduct **12** in methanol gave the keto ester **13** in 82% yield. Selective reduction of the dione at C-3 with L-selectride cleanly differentiated the carbonyls to give keto alcohol **14** in 93% yield, albeit with the incorrect stereochemistry of the C-3 hydroxyl for the synthesis of ingenol, **2**.

Protection of the C-3α hydroxyl of **14** could be achieved by either silylation or methylation, although the silylated product was obtained only after considerable experimentation. Attempted silylation of **14** with TBDMSCl in dichloromethane led to only recovered starting material. Reaction of **14** with TBDMSCl (KHMDS, THF) led to exclusive formation of silyl enol ether **15**. The use of the more reactive silyl triflates led to different products as a function of the substitution on silicon as well as of the conditions of the reaction. Reaction of **14** with TIPS-OTf

Scheme 4[a]



[a] (a) (1) 30% H_2O_2, NaOH, MeOH, 85%; (2) aqueous $HClO_4$, 42%; (b) PCC, CH_2Cl_2, 79%; (c) $CH_2{=}C{=}CH_2$, $h\nu$, 100%; (d) O_3, MeOH, Me_2S, 82%; (e) L-Selectride, THF, 93%; (f) R_3SiX or CH_3I (see text for details).

led to the formation of the internal ketal, **16**, in 77% yield, while treatment of **14** with the less sterically demanding TBDMSOTf gave the C-3α [(*tert*-butyldimethylsilyloxy]-bicyclooctanone **17** in 67% yield.

Alternatively, methylation of the sterically hindered C-3α hydroxyl of **14** could be achieved by reaction with 2,6-di-*tert*-butyl-4-methylpyridine and methyl triflate to give methyl ether **18** in 64% yield. The angular functionalization of a C-3 oxygenated bicyclo[3.3.0]octane had been achieved, and it remained now to convert **18** to the requisite photosubstrate, **30**, by elaborating the carboxymethyl group to a 5-hexenyl chain, as outlined in Scheme 5.

Protection of the ketone proceeded uneventfully (ethylene glycol, *p*-TsOH, benzene, 90%) to give ketal **19**, which on reduction (LAH, Et_2O, 91%) gave alcohol **20**. However, exposure of the alcohol to tosyl chloride (TsCl, Et_3N, CH_2Cl_2, cat. DMAP) resulted in none of the desired tosylate **21** and instead gave cyclic ether **22** in 70% yield. While substitution of mesyl chloride for tosyl chloride did lead to the formation of the desired mesylate **23**, the product was labile and was rapidly transformed to the corresponding keto mesylate at ambient temperature.

An alternative approach (**24** → **27**) for the introduction of the requisite 5-hexenyl substituent was therefore examined. Reduction of keto ester **18** to diol **24**[17] (LAH, diethyl ether, 89%) followed by selective tosylation (TsCl, DMAP, Et_3N, CH_2Cl_2, 76%) of the primary hydroxyl of **24** gave **25**, which on reaction with 4-(bromomagnesio)-1-butene and Li_2CuCl_4 gave the desired hexenylated product **26** in 92% yield. Oxidation of alcohol **26** (PCC, CH_2Cl_2, 83%) provided ketone **27**, which was then converted to the requisite dioxenone photosubstrate **30** by a three-step protocol [(1) carboxylation: LDA, MeOOC-CN, 99%; (2) ester exchange: *p*-$MeOC_6H_4CH_2OH$, tolu-

(12) For a preliminary account of this work, see Winkler, J.; Hong, B.; Bahador, A.; Kazanietz, M.; Blumberg, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 577.

(13) Bradsaw, D.; Hill, C.; Nixon, J.; Wilkinson, S. *Agents Actions* **1993**, *38*, 135.

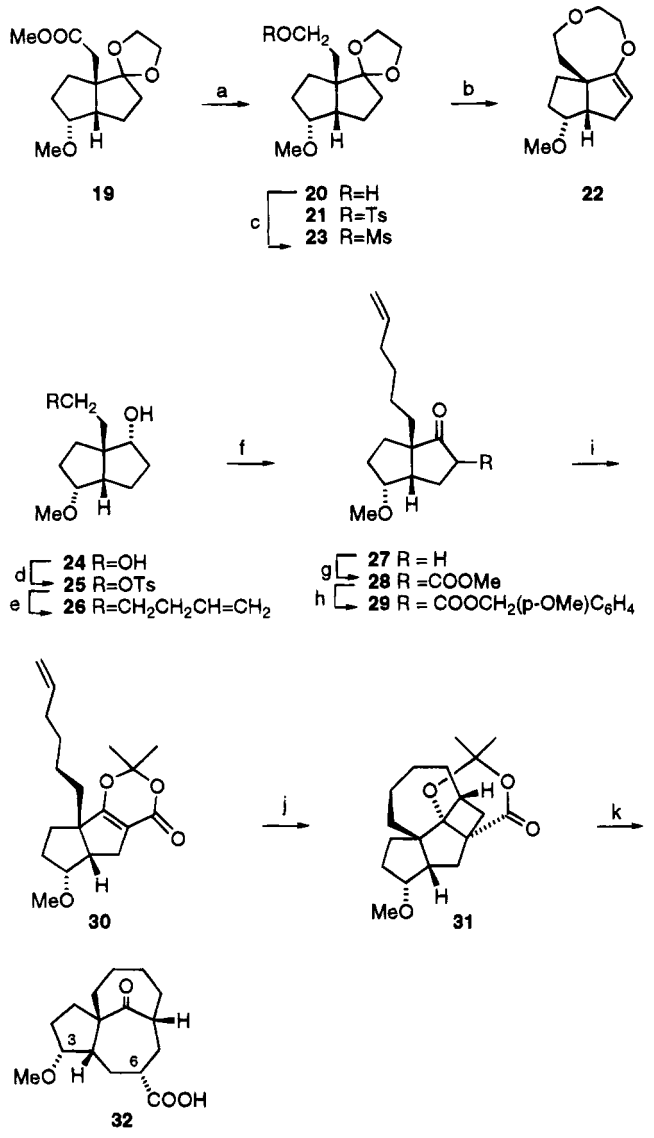
(14) We thank Professor Philip E. Eaton for providing an unpublished procedure for the conversion of **9** to **10**.

(15) The addition of cuprates to **10** using BF_3–Et_2O has recently been achieved in our laboratory: B. Hulshizer, unpublished results.

(16) For an example of the Diels–Alder reaction of enediones, see Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. *J. Am. Chem. Soc.* **1981**, *103*, 3460.

(17) Reduction proceeded to give a 7:1 mixture of C-9 α/β alcohol epimers (ingenol numbering).

Scheme 5[a]



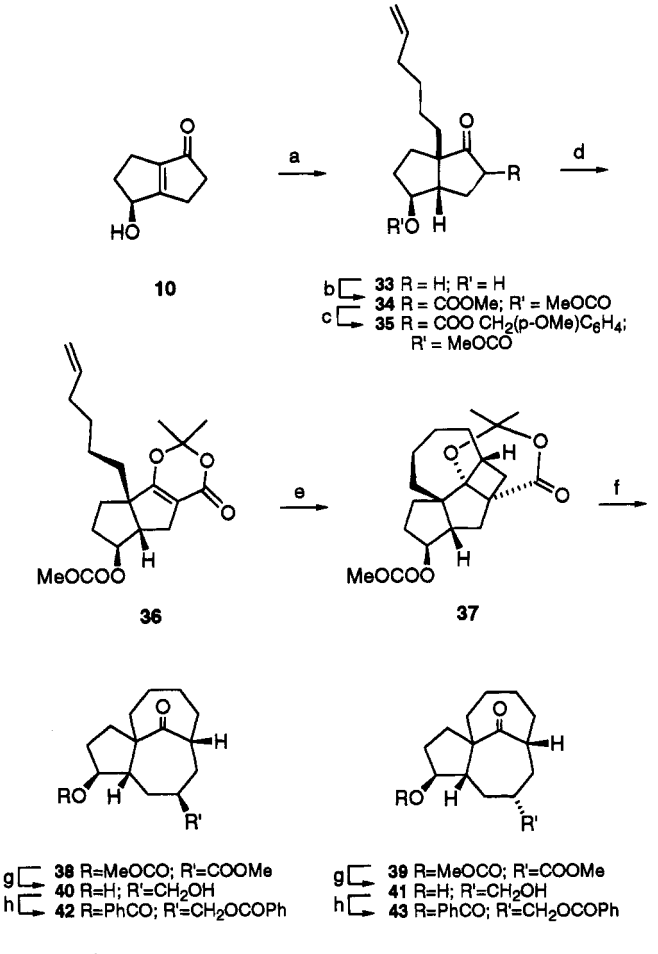
[a] (a) LAH, Et_2O, 91%; (b) TsCl, Et_3N, CH_2Cl_2, 70%; (c) MsCl, n-BuLi, THF, 67%; (d) TsCl, Et_3N, CH_2Cl_2, 76%; (e) CH_2=CH-$(CH_2)_2$MgBr, Li_2CuCl_4, 92%; (f) PCC, CH_2Cl_2, 83%; (g) LDA, MeOCOCN, THF, HMPA, 99%; (h) *p*-OMe-C_6H_4-CH_2OH, $PhCH_3$, 82%; (i) TFA, TFAA, Me_2CO, 65%; (j) *hν*, MeCN/Me_2CO (9:1), 82%; (k) 2 N KOH/MeOH, 80%.

ene, 82%); and (3) dioxenone formation: TFA, TFAA, acetone, 65%].

Irradiation of a 2 mM solution of **30** (3:1 acetonitrile: acetone; 450 W medium pressure Hg arc lamp; Pyrex immersion well) led to the formation of a unique photoadduct, **31**, in 80% yield, which on treatment with 2 N aqueous KOH in methanol led to the formation of the desired tricyclic ingenane **32**, thereby completing the first synthesis of a C-3 oxygenated ingenane congener. That the C-3 oxygenated photosubstrate **30** led to the requisite trans intrabridgehead stereochemical relationship in the formation of **32** could be demonstrated unequivocally by single crystal X-ray crystallographic analysis of the photoadduct **31**. However, the length of this sequence (16 steps from bicyclooctenone **9**) and low overall yield (1.2%) prompted us to develop a more efficient sequence before undertaking the synthesis and biological evaluation of structural analogs of ingenol.

An Improved Preparation of the C-3 Oxygenated Ingenane Tricyclic Skeleton. The direct incorporation

Scheme 6[a]

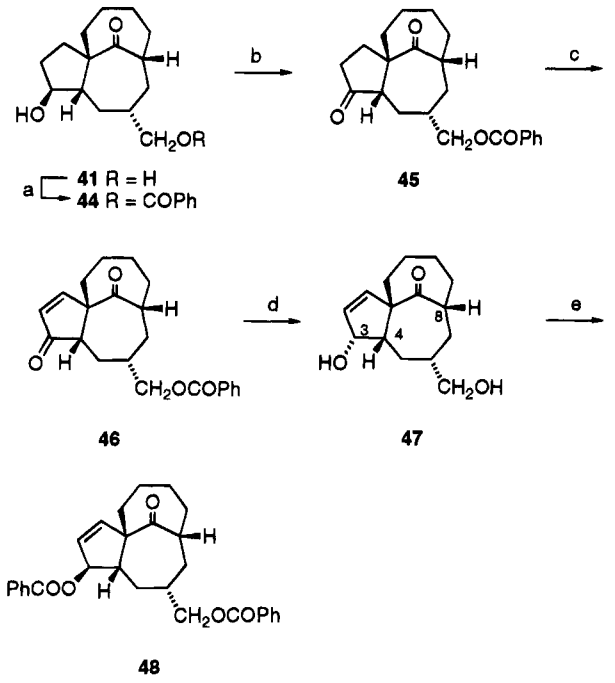


[a] (a) Li^0, NH_3, CH_2=$CH(CH_2)_4I$, 45–52%; (b) LDA, MeOCOCN, THF, HMPA, 89%; (c) (*p*-OMe)$C_6H_4CH_2OH$, $PhCH_3$, 81%; (d) TFA, TFAA, Me_2CO, 77%; (e) *hν*, MeCN/Me_2CO (4:1), 61%; (f) *p*-TsOH/MeOH, 84%; (g) DIBAL-H, THF, 85%; (h) PhCOCl, DMAP, $PhCH_3$, 90%.

of the angular 5-hexenyl group *via* reductive alkylation of **10** was also examined. We were delighted to find that the reductive alkylation could be achieved to give the angularly alkylated product **33** in 45–52% yield. While the yield was modest, this result was significant for two reasons: first, it reduced the length of the sequence required for the preparation of the C-3 oxygenated ingenane tricycle by six steps; and second, it delivered the angularly alkylated bicyclo[3.3.0]octane **33** with the C-3β oxygen stereochemistry found in the natural product.

The elaboration of **33** to ingenane tricycle **38/39** (C-6 epimers) is outlined in Scheme 6. Carboxylation of the enolate derived from **33** (LDA, MeOCOCN, 89%) followed by ester exchange with anisyl alcohol (toluene, reflux, 81%) led to the formation of **35**. Condensation with acetone (TFA, TFAA, acetone, 77%) led to the formation of dioxenone **36**. Irradiation of a 5 mM solution of **36** in 4:1 acetonitrile:acetone through a Pyrex filter gave the desired photoadduct **37** in 61% yield. Heating the photoadduct with a catalytic amount of *p*-toluenesulfonic acid in refluxing methanol gave the ingenane tricycle with the correct C-3β oxygen functionality as a 4:3 mixture of C-6 β:α ester epimers **38** and **39**, respectively (84% yield), that could be readily separated by flash column chromatography. With a considerably improved method for the preparation of the C-3 oxygenated in-

Scheme 7[a]



[a] (a) PhCOCl, Et_3N, $PhCH_3$, 87%; (b) PCC, CH_2Cl_2, 94%; (c) (1) LDA, PhSeCl, 82%; (2) H_2O_2, 86%; (d) DIBAL-H, 88%; (e) DEAD, Ph_3P, PhCOOH, 82%.

genane tricycle in hand, it remained to prepare ingenol analogs that could be used for structure–activity relationship studies.

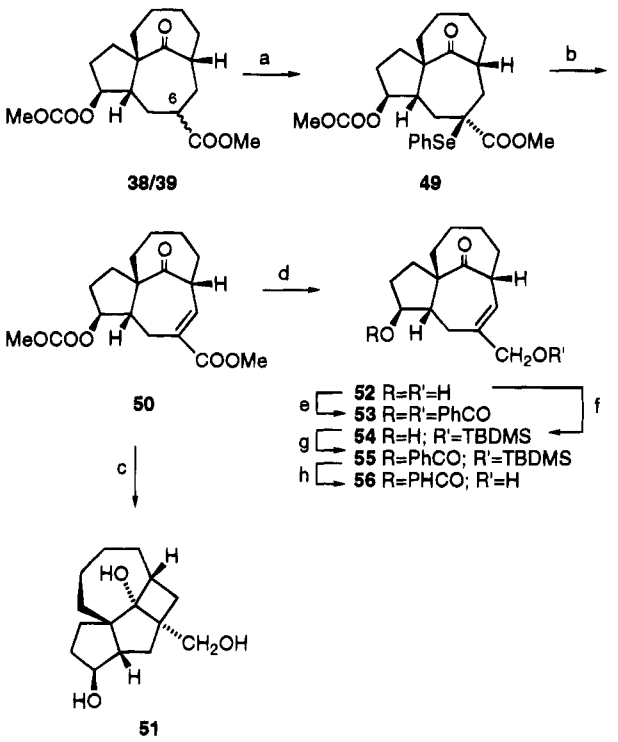
Preparation of Ingenane Analogs. The first analogs prepared were the fully saturated dibenzoates **42** and **43**, which were synthesized from keto esters **38** and **39**, as outlined in Scheme VI. DIBAL-H reduction of **38** and **39** gave the corresponding diols **40** and **41** without recourse to protection of the C-9 ketone. The diols could then be dibenzoylated (PhCOCl, DMAP, toluene, 90%) to give the saturated dibenzoates **42** and **43**.

The preparation of the $\Delta^{1,2}$ A ring alkene was achieved as outlined in Scheme 7. Treatment of diol **41** with 1 equiv of benzoyl chloride gave monobenzoate **44**, which on PCC oxidation gave ketone **45**. Selenation (LDA, PhSeCl) and oxidation (H_2O_2, CH_2Cl_2) gave enone **46**, which on reaction with DIBAL-H gave the C-3α alcohol **47**, by reduction of the C-3 ketone from the less hindered β-face of **46**.

The C-3α hydroxyl stereochemistry of **47** was established unambiguously by NMR spectroscopy. Irradiation of the C-4 bridgehead methine caused a 10.5% enhancement of the C-3 proton and an 8.6% enhancement of the C-8 proton, the "inside-outside" methine, confirming the cis stereochemistry of the C-3, C-4, and C-8 protons as shown in **47**. Mitsunobu inversion of the C-3α alcohol proceeded with concomitant C-20 benzoylation to give the C-3β,C-20-dibenzoate **48**.

Introduction of the ingenane B ring alkene into the framework of **38/39** was achieved as outlined in Scheme 8. Selenation (KHMDS, PhSeCl, THF, 71%) of a mixture of **38** and **39** gave **49** as a single selenide, which on exposure to H_2O_2 in CH_2Cl_2 gave the unsaturated ester **50** in 83% yield. Initial attempts to form diol **52** by treatment of **50** with $LiAlH_4$ at low temperature led not to the formation of the desired allylic alcohol, but instead to the formation of triol **51**, the product of conjugate reduction of the ester followed by transannular addition

Scheme 8[a]



[a] (a) KHMDS, PhSeCl, 71%; (b) 30% aqueous H_2O_2, CH_2Cl_2, 85%; (c) LAH, Et_2O, 86%; (d) DIBAL-H, 70%; (e) PhCOCl, DMAP, $PhCH_3$, 82%; (f) TBDMSOTf, Et_3N, DMAP, CH_2Cl_2, 74%; (g) PhCOCl, DMAP, CH_2Cl_2, 88%; (h) $HClO_4$, MeOH, THF, 83%.

of the ester enolate to the C-9 carbonyl group of **50**. Proof of the structure of **51** was obtained by LAH reduction of photoadduct **37**, which gave a triol product that was identical with **51**. Reaction of **50** with DIBAL-H in THF gave the desired unsaturated diol **52** in 74% yield, which on reaction with benzoyl chloride (cat. DMAP, Et_3N, CH_2Cl_2, 90%) gave the $\Delta^{6,7}$ unsaturated dibenzoate **53**.

Biological Evaluation of Ingenol Analogs. Compounds were evaluated for their ability to interact with the regulatory site on protein kinase C, as quantitated by inhibition of [^{3}H]PDBU binding to enzyme reconstituted in the presence of phosphatidylserine and assayed for 5 min at 37 °C.[18] In initial studies, the 3,20-dibenzoates **42**, **43**, **48**, and **53** were examined, together with the 3,20-dibenzoate of ingenol, **2**. Ingenol 3,20-dibenzoate yielded a K_i of 240 ± 9 nM (mean ± range, n = 2) for protein kinase C-α compared to 0.54 nM for phorbol 12,13-dibutyrate. The dibenzoates **42**, **43**, **48**, and **53** were all inactive.

These biochemical measurements stood in marked contrast to the *in vivo* reports that ingenol 3,20-dibenzoate yielded an inflammatory potency in the mouse ear of 0.054 nmol/ear,[19] compared to 0.067 nmol/ear for phorbol 12,13-dibutyrate.[20] We hypothesized that the *in vivo* measurements might be misleading, since loss of the C-20 ester of the ingenol diester might occur *in vivo*, affording the more active monoester. If so, we would wish to evaluate *in vitro* the potencies of the monoesters

(18) Teng., K.; Marquez, V. E.; Milne, G. W. A.; Barchi, J. J., Jr.; Kazanietz, M. G.; Lewin, N. E.; Blumberg, P. M.; Abushanab, E. *J. Am. Chem. Soc.* **1992**, *114*, 1059.

(19) Sorg, B.; Hecker, E. *Z. Naturforsch.* **1982**, *37b*, 748.

(20) Thielmann, H. W.; Hecker, E. In Schmidt, C. G.; Wetter, O., Eds. *Fortschritte der Krebsforschung*; Schattauer: Stuttgart-New York 1969; Vol. VII, pp 171–179.

themselves. Consistent with our hypothesis, ingenol 3-monobenzoate yielded an apparent K_i of 0.14 ± 0.04 nM (mean ± SEM, n = 3) for protein kinase C-α, a 3-order of magnitude increase relative to the corresponding dibenzoate. As an initial step, we therefore prepared the monobenzoates of the diesters that had been previously examined and found that the only active compound was **56**, the 3-monobenzoate of **52**, with a K_i of 165 ± 21 nM (mean ± SEM, n = 3).

Preparation of the 3-monoesters is continuing, as is a detailed evaluation of binding affinities, kinetics, and metabolic transformation of the compounds. We can already conclude unambiguously, however, that our strategy is successful and we can prepare potent analogs of ingenol in 10-15 step synthetic sequences. Further testing of these and related compounds, as well as the synthesis and biological evaluation of more highly functionalized ingenol congeners, is currently underway in our laboratory and our results will be reported in due course.

Experimental Section

All solvents were reagent grade. Anhydrous tetrahydrofuran (THF) was distilled from sodium. Organolithium reagents were obtained from Aldrich and standardized by titration with diphenylacetic acid. Merck precoated silica gel plates (250 μm) with fluorescent indicator were used for analytical TLC. Merck silica gel 60 (partical size 0.04–0.063 mm) was employed for flash chromatography. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet SX-20, an FT instrument equipped with TGS detector, or a Perkin-Elmer Model 281B spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-500 or GE OMEGA-300, 500 (or 300) MHz and 12.5 (or 75.5) MHz NMR in $CDCl_3$, respectively. Most of the ^{13}C spectra have been studied by APT (attached proton test) to determine the number of protons attached to each carbon. High resolution mass spectra were obtained with a VG Micromass 7070H high resolution chemical ionization spectrometer connected to a Kratos DS-50-S data system.

Diketone 12. A solution of 6 g of enedione **11** (44.1 mmol) in 150 mL of acetonitrile was degassed with N_2 for 45 min. The solution was cooled to −40 °C with a dry ice−acetonitrile bath and then irradiated through a Pyrex filter while a slow stream of N_2 and allene was bubbled through the solution for 2 h. The solution was then concentrated *in vacuo* to yield 7.75 g of **12** that was used in the next step without further purification (100% yield base on enedione **11**). IR (neat): 2494, 1733, 1653, 1558, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.87–1.98 (m, 4H), 2.01–2.47 (m, 2 H), 2.68–3.01 (m, 4 H), 4.85–4.95 (m, 1 H), 5.09–5.12 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 25.68, 25.93, 38.84, 39.81, 39.89, 50.18, 64.14, 111.60, 143.09, 214.80, 218.05. MS (*m/z*, relative intensity) 176 (M^+, 72), 147 (21), 133 (19), 120 (13), 106 (53), 105 (54). Exact mass calculated for $C_{11}H_{12}O_2$: 176.0837, found 176.0862.

Diketo Ester 13. A stream of ozone was bubbled through a solution of 3 g of ketone **12** (56.8 mmol) in 500 mL of methanol at −78 °C until the solution turned a pale blue color. Excess dimethyl sulfide was added slowly and the resulting solution was allowed to warm to 25 °C over 4 h. The solution was diluted with 500 mL ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, concentrated, and purified by flash column chromatography with 30% ethyl acetate/hexane (R_f = 0.19) to give 3.82 g of keto ester **13** (82% yield). Mp 60–61 °C. IR (neat): 2950, 1734, 1452, 1435, 1400, 1347 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.86–2.16 (m, 3 H), 2.25–2.45 (m, 4 H), 2.50–2.60 (m, 1 H), 2.63 (d, J = 16.9 Hz, 1 H), 2.85–2.92 (m, 1 H), 2.97 (d, J = 16.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 22.17 (CH_2), 29.19 (CH_2), 36.81 (CH_2), 36.96 (CH_2), 39.47 (CH_2), 51.65 (CH), 54.17 (C), 54.58 (OCH_3), 171.06, 218.47, 219.21. MS (*m/z*, relative intensity) 210 (M^+, 18), 179 (15), 155 (20), 137 (100), 123 (31), 109 (53). Exact mass calculated for $C_{11}H_{14}O_4$: 210.0892, found 210.0880.

Keto Alcohol 14. To a solution of 1.05 g of **13** (5.0 mmol) in 150 mL of dry THF at −78 °C was added dropwise 6 mL of L-Selectride (6 mmol, 1.2eq) over 5 min. After completion of the addition, 0.5 mL of MeOH was added into the solution, which was then allowed to warm to 0 °C. The reaction mixture was then treated with 0.75 mL of 15% aqueous NaOH in 3 mL of 30% H_2O_2, and the resulting solution was allowed to stir for 3 min. The solution was diluted with Et_2O, washed with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and purified by flash column chromatography with 50% EtOAc/hexane (R_f = 0.28) to give 1357 mg of hydroxy ester **14** (93% yield). IR (neat): 3449, 2955, 1734, 1439, 1356, 1208, 1181, 1159 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.46–1.65 (m, 2 H), 1.74–2.06 (m, 5 H), 2.34–2.46 (m, 2 H), 2.40 (d, J = 16.4 Hz, 1 H), 2.54–2.65 (m, 1 H), 2.81 (d, J = 16.4 Hz, 1 H), 3.59 (s, 3 H), 4.32–4.42 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 18.72 (CH_2), 33.17 (CH_2), 33.70 (CH_2), 38.19 (CH_2), 41.39 (CH_2), 50.12 (CH_3), 51.64 (CH), 55.74 (C), 75.41 (CH), 171.76, 223.26. MS (*m/z*, relative intensity) 212 (M^+, 21), 194 (29), 181 (22), 166 (24), 152 (100), 121 (29). Exact mass calculated for $C_{11}H_{16}O_4$: 212.1049, found 212.1045.

Methyl Ether 18. A solution of 960 mg of hydroxy ester **14** (4.5 mmol), 4.62 g of 2,6-di-*tert*-butyl-4-methyl pyridine (22.5 mmol), and 2.6 mL of methyl triflate (22.5 mmol) in 10 mL of $CHCl_3$ was heated to reflux for 1 h. The solution was cooled, diluted with diethyl ether, and washed with saturated $NaHCO_3$ solution. The residue was purified by flash column chromatography with 20% EtOAc/hexane (R_f = 0.28) to yield 650 mg of ester **18** (64% yield). IR (neat): 2951, 1734, 1457, 1202, 1160, 1121 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.39–1.61 (m, 2 H), 1.71–1.95 (m, 4 H), 2.23–2.45 (m, 2 H), 2.38 (d, J = 16.6 Hz, 1 H), 2.64–2.74 (m, 1 H), 2.81 (d, J = 16.6 Hz, 1 H), 3.25 (s, 3 H), 3.57 (s, 3 H), 3.78–3.88 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 18.30 (CH_2), 29.55 (CH_2), 32.70 (CH_2), 38.07 (CH_2), 41.37 (CH_2), 47.77 (CH_3), 51.54 (CH), 55.44 (C), 57.12 (CH_3), 83.95 (CH), 171.71, 222.91. MS (*m/z*, relative intensity) 226 (M^+, 47), 194 (92), 166 (100), 152 (91), 134 (50), 121 (46), 107 (53). Exact mass calculated for $C_{12}H_{18}O_4$: calcd 226.1205, found 226.1223.

Ketal 19. A solution of 1 g of keto ester **18** (4.4 mmol), 15 mL of ethylene glycol, and a catalytic amount of *p*-TsOH in 100 mL of benzene was heated to reflux for 22 h under a Dean–Stark trap. The reaction was followed by GC-MS and the ratio of **19** to **18** was larger than 46 to 1 after 22 h. The solution was washed with brine, concentrated, and purified by flash column chromatography with 20% EtOAc/hexane (R_f = 0.30) to give 1.070 g of ester **19** (90% yield). IR (neat): 2953, 2880, 1734, 1437, 1360, 1305, 1272, 1121, 1164 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40–1.70 (m, 6 H), 1.73–1.98 (m, 2 H), 2.30 (d, J = 16 Hz, 1 H), 2.39 (d, J = 16 Hz, 1 H), 2.55–2.65 (m, 1 H) 3.23 (s, 3 H), 3.58 (s, 3 H), 3.66–3.76 (m, 1 H), 3.78–3.91 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 19.75 (CH_2), 29.33 (CH_2), 30.18 (CH_2), 34.55 (CH_2), 39.77 (CH_2), 47.35 (CH_3), 51.08 (CH), 54.25 (C), 57.10 (CH_3), 64.51 (CH_2), 65.00 (CH_2), 83.16 (CH_3), 119.29 (C), 173.09. MS (*m/z*, relative intensity) 270 (M^+, 11), 238 (30), 165 (10), 99 (100). Exact mass calculated for $C_{14}H_{22}O_5$: 270.1467, found 270.1458.

Alcohol 20. A solution of 200 mg of ester **18** (0.74 mmol) in 10 mL of diethyl ether was added dropwise into a solution of $LiAlH_4$ (19 mg, 0.50 mmol) in diethyl ether (40 mL). The resulting mixture was allowed to stir for 2.5 h and was then quenched with H_2O and diluted with CH_2Cl_2. The organic solution was washed with brine, saturated aqueous $NHCl_4$, concentrated and purified by flash column chromatography with 60% EtOAc/hexane (R_f = 0.24) to give 163 mg of alcohol **20** (91% yield).

IR (neat): 3419, 2956, 2881, 2824, 1457, 1215, 1184, 1147 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.35–2.75 (m, 7 H), 1.80–1.95 (m, 3 H) 2.25–2.36 (m, 1 H), 2.45 (br s, 1 H), 3.23 (s, 3 H), 3.35–3.76 (m, 3 H), 3.80–4.00 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 19.38 (CH_2), 29.37 (CH_2), 30.12 (CH_2), 34.05 (CH_2), 38.96 (CH_2), 48.80 (CH), 53.67 (C), 57.11 (CH_3), 59.74 (CH_2), 64.01 (CH_2), 64.24 (CH_2), 83.29 (CH), 119.55 (C). MS (*m/z*, relative intensity) 242

(M^+, 27), 181 (100), 143 (43), 120 (13). Exact mass calculated for $C_{13}H_{22}O_4$: 242.1518, found 242.1539.

Cyclic Ether 22. A solution of 70 mg of alcohol **20** (0.29 mmol), 57.2 mg of *p*-toluenesulfonyl chloride, 20 μL of Et_3N, and a catalytic quantity of DMAP was allowed to stir at ambient temperature for 11 h. The resulting solution was washed with brine, concentrated, and purified by flash column chromatography with 25% EtOAc/hexane (R_f = 0.32) to give 45 mg of ether **22** (70% yield). IR (neat): 2930, 2863, 1602, 1343, 1133, 1105 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.00–1.26 (m, 1 H), 1.40–1.57 (m, 2 H), 1.70–1.88 (m, 2 H) 1.96–2.22 (m, 2 H), 2.32–2.52 (m, 2 H), 3.23 (s, 3 H), 3.54–3.80 (m, 5 H), 3.82–3.94 (m, 1 H), 3.97–4.07 (m, 1 H), 4.86–4.92 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 25.34 (CH_2), 28,91 (CH_2), 33.49 (CH_2), 40.33 (CH_2), 45.36 (CH), 54.82 (C), 57.11 (CH_3), 69.46 (CH_2), 69.86 (CH_2), 74.66 (CH_2), 83.44 (CH), 107.37 (CH), 162.17 (C). MS (*m/z*, relative intensity) 224 (M^+, 100), 193 (10), 164 (14), 149 (46), 134 (29), 120 (49).

Diol 24. To a solution of 757 mg of keto ester **19** (3.35 mmol) in 40 mL of dry ether was added 70 mg of $LiAlH_4$ (1.85 mmol). The solution was allowed to stir at ambient temperature for 2.5 h, quenched with H_2O, washed with saturated aqueous NaCl, extracted with ethyl acetate, and dried over $MgSO_4$. Purification by flash column chromatography with 50% EtOAc/hexane (R_f = 0.12) gave 599 mg of diol **24** (89% yield), as a 7:1 ratio of C-9 α/β (ingenane numbering) epimers. IR (neat): 3345, 2948, 2875, 1119, 1066 cm^{-1}. ^1H NMR ($CDCl_3$) for the major product: δ 1.11–1.27 (m, 1 H), 1.36–2.05 (m, 10 H), 2.10–2.21 (m, 1 H), 3.24 (s, 3 H), 2.64–2.78 (m, 3 H), 2.86–4.00 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 18.71 (CH_2), 24.02 (CH_2), 30.90 (CH_2), 33.15 (CH_2), 43.84 (CH_2), 50.30 (CH), 53.14 (C), 56.55 (CH_3), 58.83 (CH_2), 79.44 (CH), 82.83 (CH). ^1H NMR ($CDCl_3$) for the minor product: δ 1.11–1.27 (m, 1H), 1.36–2.05 (m, 10 H), 2.10–2.21 (m, 1 H), 3.27 (s, 3 H), 2.64–2.78 (m, 3 H), 2.86–4.00 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 21.18 (CH_2), 29.43 (CH_2), 31.94 (CH_2), 33.66 (CH_2), 39.12 (CH_2), 49.87 (CH), 56.64 (C), 58.56 (CH_3), 60.10 (CH_2), 80.54 (CH), 83.05 (CH). MS (*m/z*, relative intensity) 200 (M^+, 23), 168 (50), 155 (26), 150 (29), 137 (23), 124 (100). Exact mass calculated for $C_{11}H_{20}O_3$: 200.1412, found 200.1434.

Tosylate 25. A solution of 1.72 g of diol **24** (8.6 mmol), 1.68 g of *p*-TsCl (8.8 mmol), 40 mL of Et_3N, and 100 mg of DMAP in 80 mL of CH_2Cl_2 was allowed to stir at ambient temperature for 24 h. The solvent and Et_3N were removed by evaporation under reduced pressure. The resulting residue was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and purified by flash column chromatography with 30% EtOAc/hexane (R_f = 0.30) to give 1.41 g of tosylate **25** (76% yield based on recovered starting material) and 670 mg of recovered diol **24**. IR (neat): 3446, 2963, 2874, 2824, 1598, 1456, 1360, 1176 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07–1.32 (m, 2 H), 1.37–2.03 (m, 8 H), 2.09–2.20 (m, 1 H), 2.38 (d, J = 7.5 Hz, 1 H), 2.42 (s, 3 H), 3.25 (s, 3 H), 3.53–3.64 (m, 1 H), 3.67–3.77 (m, 1 H), 4.04–4.20 (m, 2 H), 7.30 (d, J = 8.3 Hz, 2 H), 7.75 (d, J = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 19.58 (CH_2), 21.64 (CH_3), 26.12 (CH_2), 31.69 (CH_2), 35.56 (CH_2), 39.65 (CH_2), 52.08 (CH_2), 54.50 (C), 56.77 (CH_3), 68.38 (CH_2), 78.43 (CH), 83.06 (CH), 127.86 (2C of CH), 129.87 (2C of CH), 133.17 (C), 145.02 (C).

Alkene 26. A three-necked round bottom flask, which was fitted with a reflux condenser, glass stopper, and rubber septum, was charged with 1.5 g (62.5 mmol) of Mg and 110 mL of dry THF under N_2 atmosphere. To this suspension was added 6.07 mL of 4-bromobutene by syringe. After dissolution of the Mg (5 min), the resulting mixture was allowed to stir for 15 min. To the ice-cooled mixture was added 3.67 mL of Li_2CuCl_4/THF (0.1 M). The brown Li_2CuCl_4 solution became colorless immediately on addition to the Grignard solution. The resulting reaction mixture was then treated with 1.41 g (3.98 mmol) of tosylate **25** in 6 mL of dry THF. The reaction mixture was stirred and allowed to warm to 25 °C over 14 h. TLC analysis revealed destruction of starting material, so the reaction was quenched by addition of 1 mL of H_2O, and the resulting mixture was washed with brine, dried over $MgSO_4$, and purified by flash column chromatography with 20% EtOAc/hexane (R_f = 0.25) to give 868 mg of alkene **26** (92% yield). IR (neat): 3434, 2930, 2876, 1464, 1457, 1117 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12–2.20 (m, 17 H), 2.62 (d, J = 8 Hz, 1 H), 3.25 (s, 3 H), 3.52–2.62 (m, 1 H), 3.66–3.77 (m, 1 H), 4.83–5.00 (m, 2 H), 5.67–5.85 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 19.81 (CH_2), 24.78 (CH_2), 26.21 (CH_2), 29.66 (CH_2), 31.90 (CH_2), 33.67 (CH_2), 35.84 (CH_2), 40.76 (CH_2), 51.83 (CH), 56.55 (CH_3), 56.66 (C), 78.31 (CH), 83.49 (CH), 114.31 (CH_2), 138.88 (CH). MS (*m/z*, relative intensity) 238 (M^+, 7), 220 (4), 206 (65), 188 (17), 179 (18), 162 (67), 155 (46), 149 (61), 137 (63), 123 (100). Exact mass calculated for $C_{15}H_{26}O_2$: 238.1933, found 238.1922.

Ketone 27. A solution of 1 g of pyridinium chlorochromate (4.64 mmol) and 868 mg of alcohol **26** (3.65 mmol) in 100 mL of dry dichloromethane was allowed to stir for 7 h at 25 °C. The resulting mixture was then filtered through a small florisil pad, which was washed with several portions of CH_2Cl_2, and the solvent was removed *in vacuo*. Silica gel chromatography of the crude product with 10% EtOAc/hexane (R_f = 0.27) gave 715 mg of ketone **27** (83% yield) as a colorless oil. IR (neat): 2940, 1735, 1374, 1299, 1270, 1261 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.03–2.08 (m, 14 H), 2.14–2.40 (m, 2 H), 2.49–2.60 (m, 1 H), 3.28 (s, 3 H), 3.74–3.84 (m, 1 H), 4.86–5.03 (m, 2 H), 5.65–5.85 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 18.74 (CH_2), 24.60 (CH_2), 29.28 (CH_2), 29.80 (CH_2), 32.11 (CH_2), 33.48 (CH_2), 37.19 (CH_2), 38.67 (CH_2), 48.19 (CH), 56.98 (CH_3), 58.60 (C), 84.39 (CH), 114.43 (CH_2), 138.65 (CH), 224.59. MS (*m/z*, relative intensity) 236 (M^+, 7), 218 (2), 204 (7), 179 (10), 162 (16), 154 (100), 153 (39), 149 (35), 139 (33), 121 (65). Exact mass calculated for $C_{15}H_{24}O_2$: 236.1776, found 236.1759.

Keto Ester 28. To a solution of 0.14 mL of diisopropylamine (1 mmol) in 60 mL of dry THF at −78 °C were added 11.1 mL of 2.5 M n-BuLi/hexane (27.8 mmol) and 2.5 mL (14.7 mmol) of HMPA. The resulting solution was stirred for 0.5 h and then treated with a solution of 2.44 g of ketone **27** (10.3 mmol) in 10 mL of dry THF. After stirring for an additional 20 min, the resulting solution was treated with 1 g of methyl cyanoformate (11.8 mmol). The resulting solution was warmed to 25 °C with stirring over 3 h. The reaction mixture was then quenched with 1 mL of H_2O, washed with aqueous saturated NaCl solution, dried over $MgSO_4$, and purified by flash column chromatography with 10% EtOAc/Hexane (R_f = 0.27, the same as ketone **27**) to give 3.35 g of ketone **28** (99% yield) as a ca. 1:1 mixture of enol and keto isomers. IR (neat) 2934, 1751, 1724, 1652, 1620, 1457 cm^{-1}. ^1H NMR for the enol component (major isomer; $CDCl_3$): δ 1.00–2.06 (m, 12 H), 2.10–2.33 (m, 2 H), 2.35–2.64 (m, 1 H), 3.19 (s, 3 H), 3.68 (s, 3 H), 3.73–3.88 (m, 1 H), 4.83–5.00 (m, 2 H), 5.64–5.84 (m, 1 H), 10.16 (br s, 1 H); for the epimeric keto esters ^1H NMR ($CDCl_3$): δ 3.24 (s, 3 H), 3.38–3.50 (m, 1 H), 3.71 (s, 3 H). MS (*m/z*, relative intensity) 294 (M^+, 5), 276 (7), 266 (8), 244 (11), 230 (13), 212 (29), 180 (100). Exact mass calculated for $C_{17}H_{26}O_4$: 294.1831, found 294.1844.

Anisyl Ester 29. A solution of 3.35 g of keto ester **28** (11.4 mmol) and 9 mL of anisyl alcohol in 150 mL toluene was heated to reflux under a Dean–Stark trap for 12 h. The resulting solution was concentrated under reduced pressure and the residue purified by flash column chromatography with 15% EtOAc/hexane (R_f = 0.32) to give 3.74 g of keto ester **29** (82% yield) as a ca. 1:1 mixture of enol and keto tautomers. IR (neat): 2934, 1726, 1617, 1457, 1245, 1159 cm^{-1}. ^1H NMR for the enol component ($CDCl_3$): δ 1.01–2.65 (m, 6 H), 3.20 (s, 3 H), 2.75 (s, 3 H), 4.85–5.01 (m, 2 H), 5.09 (s, 2 H), 5.64–5.85 (m, 1 H), 6.81–6.91 (m, 2 H), 7.24–7.36 (m, 2 H), 10.23 (s, 1 H). ^1H NMR for the epimeric ketoesters ($CDCl_3$): δ 3.25 (s, 3 H), 2.64–2.90 (m, 1 H), 3.76 (s, 3 H), 5.11 (s, 2 H). MS (*m/z*, relative intensity): 400 (M^+, 10), 236 (5), 204 (5), 180 (10), 154 (26), 137 (14), 121 (100). Exact mass calculated for $C_{24}H_{32}O_5$: 400.2250, found 400.2274.

Dioxenone 30. A solution of 5 g of keto ester **29** (0.04 mmol) in 53 mL of acetone was cooled to −78 °C and treated, dropwise, with a mixture of 53 mL of TFAA and 53 mL TFA. The resulting solution was allowed to warm to 25 °C with stirring over 10 h. The resulting solution was added dropwise into cold aqueous saturated $NaHCO_3$ solution. The aqueous solution was extracted with ethyl acetate, and the organic residue thus obtained was purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.13) to yield 2.6 g of dioxenone **30** (65% yield). λ_{max} (CH_3CN) = 259.7 nm (ϵ =

6178). IR (neat): 2933, 1738, 1656, 1413, 1276, 1256, 1201 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12–1.52 (m, 8 H), 1.63 (s, 3 H), 1.68 (s, 3 H), 1.75–1.90 (m, 2 H), 1.97–2.10 (m, 2 H), 2.40 (dd, J = 15, 9.8 Hz, 1 H), 2.48–2.58 (m, 1 H), 2.71 (dd, J = 15, 3.8 Hz, 1 H), 3.27 (s, 3 H), 3.11–3.81 (m, 1 H), 4.88–5.03 (m 2 H), 5.67–5.85 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.44 (CH_2), 24.33 (CH_2), 24.61 (CH_3), 26.00 (CH_3), 29.14 (CH_2), 29.76 (CH_2), 31.81 (CH_2), 33.46 (CH_2), 37.24 (CH_2), 44.28 (CH), 57.14 (CH_3), 58.19 (C), 82.88 (CH), 103.74 (C), 108.06 (C), 114.57 (CH_2), 138.57 (CH), 160.50 (C), 172.30. MS (*m/z*, relative intensity) 320 (M^+, 1), 262 (12), 230 (9), 180 (100), 165 (18). Exact mass calculated for $C_{19}H_{28}O_4$: 320.1987, found 320.1998.

Photoadduct 31. A solution of 560 mg of dioxenone **30** (1.75 mmol) in 300 mL of 9:1 acetonitrile: acetone was degassed for 0.5 h, and the resulting solution was irradiated through a Pyrex filter at 0 °C for 2 h. The resulting solution was concentrated and the residue purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.30 in 15% EtOAc/hexane) to give 459 mg of photoadduct **31** (82% yield). IR (neat): 2930, 1740, 1457, 1282, 1240 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.13–1.92 (m, 10 H), 1.63 (s, 3 H), 1.75 (s, 3 H), 1.96–2.18 (m, 4 H), 2.26–2.38 (m, 1 H), 2.39–2.50 (m, 1 H), 2.58–2.75 (m, 2 H), 3.20 (s, 3 H), 3.70–3.80 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.74 (CH_2), 25.12 (CH_2), 29.55 (CH_2), 30.27 (CH_2), 30.80 (CH_3), 31.28 (CH_3), 31.63 (CH_2), 33.28 (CH_2), 35.45 (CH_2), 39.78 (CH), 41.88 (CH_2), 43.64 (C), 55.83 (CH_3), 56.61 (CH), 59.71 (C), 83.07 (CH), 93.71 (C), 107.90 (C), 171.54. Exact mass calculated for $C_{19}H_{28}O_4$: 320.1987, found 320.1983.

Keto Acid 32. A solution of 80 mg of compound **31** (0.25 mmol) in 10 ml of 2 N KOH/MeOH was allowed to stir at 25 °C for 12 h. The resulting solution was diluted with water and extracted with 40 ml of ethyl acetate. The organic solution was washed with 2 N aqueous HCl solution, dried over $MgSO_4$, and purified by flash column chromatography with ethyl acetate (R_f = 0.13) to give 56 mg of **32** (80% yield). IR (neat): 3000–3600, 2932, 1725, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00–2.04 (m, 14 H), 2.28–2.31 (m, 1 H), 2.36–2.40 (m, 1 H), 2.64–2.69 (m, 1 H), 2.90–2.92 (m, 1 H), 3.02–3.07 (m, 1 H), 3.32 (s, 3 H), 3.77–3.86 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 25.51 (CH_2), 26.10 (CH_2), 26.61 (CH_2), 29.47 (CH_2), 29.55 (CH_2), 30.23 (CH_2), 31.46 (CH_2), 41.89 (CH), 42.67 (CH_2), 47.44 (CH), 50.66 (CH), 57.05 (CH_3), 61.20 (C), 82.95 (CH), 180.68, 214.52. MS (*m/z*, relative intensity) 280 (M^+, 39), 262 (10), 248 (100), 234 (47), 230 (44), 175 (68). Exact mass calculated for $C_{16}H_{24}O_4$: 280.1675, found 280.1670.

Ketone 33. To 1.5 L of liquid NH_3 at −78 °C was added 460 mg of Li metal (65.7 mmol, 2.3 equiv) and the resulting solution stirred at −78 °C for 20 min. To the blue solution was added dropwise 4 g of hydroxyenone **10** (28.99 mmol) in 30 mL of dry THF, and the resulting solution was stirred for 50 min with an overhead mechanical stirrer. To the solution was then added 4.8 mL of 6-iodohexene (1 equiv) and the resulting solution stirred for 6 h as bath temperature was allowed to increase to 0 °C. The reaction was quenched with aqueous NH_4Cl solution, diluted with diethyl ether, washed with brine, dried over $MgSO_4$ and purified by flash column chromatography with 30% EtOAc/hexane (R_f = 0.58, in 70% EtOAc/hexane) to give 3.09 g of hydroxyketone **33** (48% yield). IR (neat): 3435, 2934, 2857, 1728, 1640, 1460, 1409, 1140, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00–2.20 (m, 18H), 3.97–4.02 (m, 1H), 4.82–5.00 (m, 2H), 5.62–5.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 22.78 (CH_2), 24.85 (CH_2), 29.22 (CH_2), 33.44 (CH_2), 33.66 (CH_2), 34.22 (CH_2), 37.68 (CH_2), 37.85 (CH_2), 54.00 (CH), 59.02 (C), 79.69 (CH), 114.39 (CH_2), 138.62 (CH), 224.60. MS (*m/z*, relative intensity): 222 (M^+, 5), 204 (5), 163 (3), 149 (4), 140 (100), 122 (17). Exact mass calculated for $C_{14}H_{22}O_2$: 222.1620, found. 222.1582.

Dioxenone 36. To a solution of 4.1 mL (29.1 mmol) of diisopropylamine in 45 mL of dry THF at −78 °C were added 11.8 mL of 2.5 M n-BuLi in hexane (29.4 mmol) and 2.5 mL (14.7 mmol) of HMPA. To the resulting solution, after stirring for 0.5 h at −78 °C, was added a solution of 2.5 g of hydroxyenone **33** (11.3 mmol) in 30 mL of dry THF. The resulting solution was stirred for 30 min at −78 °C and then treated with a solution of 2.2 mL of methyl cyanoformate (27 mmol, 2.4 equiv). The resulting solution was stirred for 3 h at −78 °C and the reaction temperature was then allowed to increase to 25 °C. The reaction mixture was quenched with 1 mL of H_2O, washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and purified by flash chromatography with 20% EtOAc/hexane (R_f = 0.57 in 50% EtOAc/hexane) to give 3.4 g of the intermediate methyl ester **34** (89% yield, three isomers with similar R_f value). IR (neat): 2935, 1725, 1650, 1620, 1460 cm^{-1}. ^1H NMR (major component, $CDCl_3$): δ 0.75–2.00 (m, 13H), 2.02–2.75 (m, 3H), 3.70 (s, 3H), 3.74 (s, 3H), 4.65–4.98 (m, 3H), 5.60–5.80 (m, 1H). MS (*m/z*, relative intensity): 338 (M^+, 1), 280 (2), 204 (13), 186 (3), 163 (3), 147 (3), 122 (100).

A solution of 3.0 g (8.9 mmol) of methyl ester **34** and 3.3 mL of anisyl alcohol (26.3 mmol) in 100 mL toluene was heated at reflux under a Dean–Stark condenser for 17 h. The resulting solution was evaporated under reduced pressure and the residue purified by flash chromatography with 10% EtOAc/hexane (R_f = 0.69 in 30% EtOAc/hexane) to give 3.2 g of anisyl ester **35** (81% yield, three isomers with same R_f value). IR (neat): 2935, 1725, 1615, 1460, 1250, 1200 cm^{-1}. ^1H NMR (major component, $CDCl_3$): δ 1.20–2.80 (m, 16H), 3.75 (s, 3H), 3.79 (s, 3H), 4.72 (br s, 1H), 4.88–4.99 (m, 2H), 5.11 (s, 2H), 5.62–5.85 (m, 1H), 6.82–6.90 (m, 2H), 7.24–7.32 (m, 2H).

A solution of 2.0 g of anisyl ester **35** (4.50 mmol) in 25 mL acetone was cooled to −78 °C under N_2 atmosphere and then a mixture of 5 mL of TFAA, 4 mL of acetic anhydride, and 25 mL of TFA were added dropwise. The reaction mixture was warmed to 25 °C over 10 h, and the resulting solution was then added dropwise to a 0 °C solution of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ethyl acetate. The resulting organic extracts were evaporated and the residue purified by flash chromatography with 15% EtOAc/hexane (R_f = 0.5 in 30% EtOAc/hexane) to yield 1.2 g of **36** (73% yield). IR (neat): 2956, 2880, 1750, 1655, 1450, 1420, 1275, 1201, 1155, 1000 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20–1.80 (m, 6H), 1.64 (s, 3H), 1.68 (s, 3H), 1.82–2.20 (m, 6H), 2.23 (dd, J = 3.0, 15.5 Hz, 1H), 2.42–2.52 (m, 1H), 2.85 (dd, J = 10, 15.5 Hz, 1 H), 3.76 (s, 3H), 4.78 (br s, 1H), 4.88–5.00 (m, 1H), 5.62–5.84 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 24.82 (two C of CH_3), 25.65 (CH_2), 29.01 (CH_2), 29.69 (CH_2), 30.86 (CH_2), 33.15 (CH_2), 33.43 (CH_2), 36.87 (CH_2), 49.11 (CH_3), 54.70 (CH), 59.14 (C), 86.76 (CH), 101.73 (C), 108.37 (C), 114.63 (CH_2), 138.52 (CH), 155.12 (C), 159.91 (C), 172.36 (C). MS (*m/z*, relative intensity) 364 (M^+, 6), 305 (9), 229 (38), 201 (21), 147 (100). Exact mass calculated for $C_{20}H_{28}O_6$: 364.1886, found 364.1894.

Photoadduct 37. A solution of 523 mg of dioxenone **36** (1.44 mmol) in 300 mL of 20% acetone in acetonitrile was degassed for 0.5 h, and the resulting solution was cooled to 0 °C and irradiated through a Pyrex filter for 2.5 h. The solution was evaporated and the residue purified by flash chromatography with 15% EtOAc/hexane (R_f = 0.52 in 50% EtOAc/hexane) to give 321 mg of photoadduct **37** (61% yield). IR (neat): 2927, 2853, 1745, 1457, 1267, 1240, 1203 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20–1.40 (m, 2H), 1.50–1.95 (m, 9H), 1.65 (s, 3H), 1.80 (s, 3H), 2.10–2.30 (m, 3H), 2.35–2.65 (m, 4H), 3.77 (s, 3H), 4.70–4.74 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 23.51 (CH_2), 25.21 (CH_2), 30.48 (CH_2), 30.58 (CH_3), 31.38 (CH_3), 31.91 (CH_2), 32.74 (CH_2), 35.40 (CH_2), 38.94 (CH_2), 39.89 (CH), 41.11 (CH_2), 42.60 (C), 54.63 (CH_3), 58.94 (CH), 60.36 (C), 86.11 (CH), 93.65 (C), 108.22 (C), 155.29 (C), 171.85. MS (*m/z*, relative intensity): 364 (M^+, 5), 229 (38), 201 (21), 147 (100). Exact mass calculated for $C_{20}H_{28}O_6$: 364.1886, found 364.1874.

Fragmentation Products 38 and 39 (mixture of C-6 α and β ester epimers): A solution of 321 mg of **37** (0.88 mmol) and 20 mg of *p*-TsOH in 100 mL of methanol was heated to reflux for 18 h. Evaporation of volatiles and purification of the residue by flash chromatography (15% EtOAc/hexane, **38**: R_f = 0.41; **39**: R_f = 0.46) to give 108 mg of **38** (36% yield) and 142 mg of **39** (48% yield). IR (for both epimers, neat): 2960, 2885, 1752, 1740, 1450, 1275, 1205, 1175 cm^{-1}.

Keto Ester 38. ^1H NMR ($CDCl_3$): δ 1.00–2.15 (m, 15H), 2.30–2.55 (m, 3H), 2.68–2.75 (m, 1H), 3.56 (s, 3H), 3.71 (s, 3H), 4.52–4.62 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 25.71 (CH_2), 27.78 (CH_2), 29.72 (CH_2), 30.29 (CH_2), 30.74 (CH_2), 31.13 (CH_2), 33.18 (CH_2), 41.34 (CH_2), 41.66 (CH_3), 50.31 (CH), 51.71 (CH), 52.09 (CH), 54.50 (CH_3), 62.14 (C), 86.19 (CH), 155.13 (C),

174.95, 214.73. MS (*m/z*, relative intensity): 338 (M^+, 18), 261 (100), 244 (91), 201 (58), 184 (83). Exact mass calculated for $C_{18}H_{26}O_6$: 338.1729, found 338.1705.

Keto Ester 39. ^1H NMR ($CDCl_3$): δ 1.15–1.60 (m, 6H), 1.65–2.00 (m, 8H), 2.05–2.20 (m, 2H), 2.25–2.45 (m, 1H), 2.60–2.68 (m, 1H), 2.95–3.05 (m, 1H), 3.64 (s, 3H), 3.70 (s, 3H), 4.48–4.55 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 25.78 (CH_2), 27.73 (CH_2), 30.08 (CH_2), 30.38 (CH_2), 30.79 (CH_2), 33.55 (CH_2), 34.87 (CH_2), 41.90 (CH_2), 47.46 (CH), 51.68 (CH), 52.39 (CH_3), 54.52 (CH), 55.72 (CH_3), 62.55 (C), 87.08 (CH), 155.14 (C), 174.38, 213.81.

Diol 41. To a solution of 235 mg of **39** (0.70 mmol) in 50 mL of dry THF at −78 °C was added 2 mL of DIBAL (1M in THF) and the resulting solution warmed with stirring to 25 °C over 1 h. The reaction was quenched with water, and the ethereal layer was washed with 1 N aqueous HCl solution and dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography with 80% ethyl acetate/hexane (R_f = 0.13) gave 151 mg of **41** (86% yield). IR (neat): 3350, 2900, 2850, 1720, 1650, 1560, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.70–2.30 (m, 20H), 2.82–2.95 (m, 1H), 3.29 (dd, J = 7, 10.5 Hz, 1H), 3.46 (dd, J = 5.5, 10.5 Hz, 1H), 3.73–3.79 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 26.08 (CH_2), 27.80 (CH_2), 30.51 (CH_2), 30.57 (CH_2), 33.71 (CH_2), 33.91 (CH_2), 36.26 (CH_2), 42.61 (CH_2), 45.55 (CH), 52.72 (CH), 58.69 (CH), 62.90 (C), 67.38 (CH_2), 81.91 (CH), 215.85.

The same procedure was applied to 290 mg of **38** to give 184 mg of **40**, the C-6 epimer of **41** (85% yield). ^1H NMR: ($CDCl_3$): δ 0.90–2.00 (m, 17H), 2.25–2.40 (m, 1H), 3.00–3.10 (m, 1H), 3.30–3.50 (m, 3H), 3.95 (br s, 1H), 4.40 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 25.47 (CH_2), 26.94 (CH_2), 29.35 (CH_2), 29.41 (CH_2), 30.05 (CH_2), 30.52 (CH_2), 32.50 (CH_2), 36.39 (CH), 41.15 (CH_2), 47.66 (CH), 53.12 (CH), 60.47 (C), 65.68 (CH_2), 75.84 (CH), 216.59. MS (*m/z*, relative intensity): 270 (M^+ + NH_4, 22), 253 (15), 235 (100), 217 (48), 199 (15), 131 (32), 105 (100). Exact mass calculated for $C_{15}H_{24}O_3$: 252.1725, found 252.1713.

Saturated Dibenzoate 43. A solution of 30 mg of **41** (0.12 mmol), 0.03 mL of benzoyl chloride (0.3 mmol, 2.5 equiv), and 57 mg of DMAP (0.47 mmol, 4 equiv) in 20 mL of toluene was stirred for 1 h at 25 °C. Evaporation of volatiles and purification of the residue by flash chromatography with 15% ethyl acetate/hexane (R_f = 0.45 in 30% EtOAc/hexane) gave 51 mg of **43** (93% yield), mp (ethyl acetate) 129–130 °C. IR (neat): 2931, 2852, 1720, 1452, 1315, 1274, 1112, 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00–2.28 (m, 16H), 2.30–2.40 (m, 1H), 2.52–2.66 (m, 1H), 2.85–3.00 (m, 1H), 4.05 (dd, J = 6, 11 Hz, 1H), 4.14 (dd, J = 6, 11 Hz, 1H), 4.99–5.02 (m, 1H), 7.39–7.62 (m, 6H), 8.00–8.10 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 26.04 (CH_2), 28.28 (CH_2), 30.36 (CH_2), 30.61 (CH_2), 31.13 (CH_2), 33.91 (CH_2), 35.70 (CH_2), 42.18 (CH), 42.70 (CH_2), 52.83 (CH), 56.47 (CH), 63.04 (C), 68.71 (CH_2), 84.40 (CH), 128.36 (two C of CH), 128.39 (two C of CH), 129.50 (two C of CH), 129.56 (two C of CH), 130.08 (C), 130.34 (C), 132.92 (CH), 132.97 (CH), 166.01, 166.40, 214.77. MS (*m/z* relative intensity): 460 (M^+, 5), 338 (22), 320 (7), 310 (6), 233 (24), 216 (92), 198 (100), 188 (70), 173 (22), 159 (24), 145 (34), 131 (64). Exact mass calculated for $C_{29}H_{32}O_5$: 460.2250, found 460.2289.

Hydroxybenzoate 44. A solution of 120 mg of diol **41** (0.48 mmol), 0.053 mL of benzoyl chloride (0.53 mmol, 1.1 equiv), and 156 mg of DMAP (1.28 mmol, 2.7 equiv) in 10 mL of toluene was stirred at 25 °C for 1 h. Evaporation of volatiles and purification of the residue by flash chromatography with 30% EtOAc/hexane (R_f = 0.16 in 30% EtOAc/hexane) gave 55 mg of monobenzoate **44** (87% yield). IR (neat): 2990, 2880, 1740, 1720, 1450, 1315, 1275, 1110, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85–2.15 (m, 18H), 2.25–2.35 (m, 1H), 2.86–2.92 (m, 1H), 3.75–3.79 (m, 1H), 4.02–4.22 (m, 2H), 7.39–7.43 (m, 2H), 7.51–7.54 (m, 1H), 7.97–7.99 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 26.03 (CH_2), 27.80 (CH_2), 30.44 (CH_2), 30.51 (CH_2), 33.91 (CH_2), 33.95 (CH_2), 36.50 (CH_2), 42.18 (CH), 42.62 (CH_2), 52.62 (CH), 58.59 (CH), 62.91 (CH_2), 68.96 (C), 81.80 (CH), 128.36 (two C of CH), 129.52 (2C of CH), 130.12, 132.94 (CH), 166.46, 215.43. MS (*m/z*, relative intensity) 374 (M^+ + NH_4, 5), 339 (25), 313 (13), 234 (60), 217 (55), 189 (33), 105 (100). Exact mass calculated for $C_{22}H_{28}O_4$: 356.1988, found 356.1973.

Ketobenzoate 45. A solution of 40 mg of pyridinium chlorochromate (0.14 mmol) and 29 mg of hydroxy ester **44** (0.08 mmol) in 30 mL of dry dichloromethane was stirred for 12 h and then filtered through a pad of florisil. Evaporation of volatiles and purification of the residue by flash chromatography with 15% EtOAc/hexane (R_f = 0.39 in 30% EtOAc/hexane) gave 27 mg of keto ester **45** (94% yield). IR (neat): 2955, 2880, 1750, 1735, 1465, 1285, 1120 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.00–1.90 (m, 11H), 2.00–2.15 (m, 3H), 2.20–2.55 (m, 4H), 2.79–2.85 (m, 1H), 4.07 (dd, J = 6, 11 Hz, 1H), 4.14 (dd, J = 6, 11 Hz, 1H), 7.39–7.43 (m, 2H), 7.51–7.54 (m, 1H), 7.97–8.00 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.18 (CH_2), 25.47 (CH_2), 29.91 (CH_2), 30.58 (CH_2), 33.26 (CH_2), 33.70 (CH_2), 37.97 (CH_2), 38.78 (CH_2), 42.33 (CH), 52.87 (CH), 57.67 (CH), 60.45 (C), 68.48 (CH_2), 128.38 (two C of CH), 129.56 (two C of CH), 130.03 (C), 132.97 (CH), 166.36, 214.65, 217.86. MS (*m/z*, relative intensity) 354 (M^+, 51), 231 (100), 203 (26), 146 (36), 121 (80). Exact mass calculated for $C_{22}H_{26}O_4$: 354.1830, found 354.1822.

Enone Benzoate 46. To 4 mL of a 0.0475 M solution of LDA in THF at −78 °C [prepared by addition of 0.56 mL of 1.7 M of n-butyllithium to 0.13 mL of diisopropylamine (0.95 mmol) in 20 mL of dry THF] was added a solution of 42 mg of keto ester **45** (0.12 mmol) in 10 mL of dry THF. After 30 min at −78 °C, 24 mg of PhSeCl in 3 mL of dry THF was added and the resulting solution was stirred for 1 h at −78 °C. The solution was quenched with aqueous NH_4Cl, diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography with 15% ethyl acetate/hexane (R_f = 0.55 in 30% ethyl acetate/hexane) gave 20 mg of the α-seleno ketone (82% yield base on recovered **45**) and 25 mg of recovered starting material **45**. To a solution of 20 mg of the α-seleno ketone in 15 mL of CH_2Cl_2 was added 0.8 mL of 30% H_2O_2(aq). The resulting solution was stirred for 1 h, diluted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography with 20% EtOAc/hexane (R_f = 0.30 in 30% EtOAc/hexane) gave 12 mg of **46** (86% yield). IR (neat) 2950, 2880, 1730, 1720, 1455, 1280, 1115, 715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.70–1.10 (m, 1H), 1.20–2.05 (m, 10H), 2.10–2.20 (m, 2H), 2.37 (dd, J = 2.0, 12.0 Hz, 1H), 2.85–2.92 (m, 1H), 4.09 (dd, J = 6.0, 10.8 Hz, 1H), 4.15 (dd, J = 6.0, 11.0 Hz, 1H), 6.08 (d, J = 5.8 Hz, 1H), 7.40–7.45 (m, 2H), 7.51–7.56 (m, 1H), 7.73 (d, J = 5.8 Hz, 1H), 7.96–8.02 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.59 (CH_2), 30.08 (CH_2), 30.20 (CH_2), 33.40 (CH_2), 35.84 (CH_2), 37.04 (CH_2), 41.71 (CH), 53.29 (CH), 54.87 (CH), 66.13 (C), 68.45 (CH_2), 128.41 (two C of CH), 129.60 (two C of CH), 129.99 (C), 131.54 (CH), 133.03 (CH), 164.81 (CH), 166.39 (C), 208.86 (C), 212.58 (C). MS (*m/z*, relative intensity) 370 (M^+ + NH_4, 9), 353 (M^+ + H, 9), 233 (8), 202 (8), 105 (100). Exact mass calculated for $C_{22}H_{24}O_4$: 352.1675, found 352.1631.

Allylic Alcohol 47. To a solution of 8 mg of enone **46** in 10 mL of dry THF at −78 °C was added 1 mL of DIBAL (1 M in THF), and the reaction temperature was then allowed to warm to 25 °C over 1 h. The reaction mixture was quenched with water and washed with 1 N aqueous HCl, and the ethereal layer was dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography with 80% ethyl acetate/hexane (R_f = 0.16) gave 5 mg of allylic alcohol **47** (88% yield). IR (neat): 3160–3580, 2950, 2880, 1730, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.60–0.72 (m, 1H), 1.15–1.30 (m, 2H), 1.36–1.95 (m, 12H), 2.10–2.20 (m, 1H), 2.40–2.46 (m, 1H), 2.84–2.92 (m, 1H), 3.38 (dd, J = 6.7, 10.4 Hz, 1H), 3.48 (dd, J = 5.8, 10.4 Hz, 1H), 5.05–5.12 (m, 1H), 5.65 (dd, J = 5.9, 1.4 Hz, 1H), 6.01 (dd, J = 2.3, 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.85 (CH_2), 28.03 (CH_2), 29.61 (CH_2), 30.35 (CH_2), 33.85 (CH_2), 37.90 (CH_2), 45.24 (CH), 52.35 (CH), 52.52 (CH), 67.71 (CH_2), 69.02 (C), 76.96 (CH), 133.13 (CH), 133.60 (CH), 215.04 (C). MS (*m/z*, relative intensity) 249 (M^+ − H, 30), 233 (100), 215 (43), 187 (28), 162 (21), 133 (14), 113 (30). Exact mass calculated for $C_{15}H_{22}O_3$: 250.1569, found 250.1560.

A-Ring Unsaturated Dibenzoate 48. A solution of 12 mg of triphenylphosphine (0.045 mmol, 2.25 eq) in 2 mL of dry THF was added dropwise into a solution of 0.008 mL of diethyl

azodicarboxylate (0.045 mmol, 2.25 equiv), 15 mg of benzoic acid (0.32 mmol, 6 equiv), and 4 mg of allylic alcohol **47** (0.02 mmol) in 2 mL of dry THF. The resulting solution was stirred in the absence of light at 25 °C for 18 h. Evaporation of volatiles and purification of the residue by flash chromatography with 10% EtOAc/hexane (R_f = 0.60 in 30% EtOAc/hexane) gave 5 mg of dibenzoate **47** (82% yield). IR (neat): 2960, 2880, 1730, 1720, 1450, 1275, 1100, 715 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.14–2.24 (m, 13H), 2.37 (d, J = 11.6 Hz, 1H), 2.88–2.96 (m, 1H), 4.10 (dd, J = 6.2, 10.9 Hz, 1H), 4.17 (dd, J = 6.0, 10.9 Hz, 1H), 5.39 (d, J = 2.5 Hz, 1H), 5.93 (dd, J = 2.5, 5.7, 1H), 6.32 (d, J = 5.7 Hz, 1H), 7.38–7.46 (m, 4H), 7.50–7.60 (m, 2H), 7.90–8.08 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 25.87 (CH_2), 29.78 (CH_2), 30.26 (CH_2), 33.62 (CH_2), 35.88 (CH_2), 38.79 (CH_2), 42.01 (CH), 52.67 (CH), 54.24 (CH), 68.84 (C), 69.31 (CH_2), 86.92 (CH), 127.85 (CH), 128.42 (four C of CH), 129.57 (two C of CH), 129.65 (two C of CH), 130.16 (C), 130.36 (C), 132.96 (CH), 133.01 (CH), 141.05 (CH), 166.26 (C), 166.47 (C), 215.11. MS (m/z, relative intensity): 476 ($M^+ + NH_4$, 8), 337 (7), 214 (8), 181 (12), 131 (37), 105 (100). Exact mass calculated for $C_{29}H_{30}O_5$: 458.2093, found 458.2118.

Unsaturated Ester 50. To a solution of 110 mg of a mixture of esters **38** and **39** (C-6 ester epimers; 0.33 mmol) in 10 mL of THF at −78 °C was added 1 mL of KHMDS (0.5 M in toluene, 0.5 mmol). The resulting solution was stirred for 5 min at −78 °C and then treated with a solution of 96 mg (0.50 mmol) of PhSeCl in 2 mL of dry THF. The bath temperature was allowed to warm to 0 °C over 1 h. The resulting solution was quenched with 1 mL of water, diluted with ethyl acetate, washed with brine, and the organic layers were dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography with 15% EtOAc/hexane (seleno ester **49**: R_f = 0.52; unsaturated ester **50**: R_f = 0.45 in 30% EtOAc/hexane) to give 280 mg of α-seleno ester **49** (71%) and 50 mg of a mixture of unsaturated ester **50** and the starting esters **38** and **39**.

To a solution of 255 mg of selenide **49** in 15 mL of CH_2Cl_2 was added 0.8 mL of 30% aqueous H_2O_2 solution. The resulting solution was stirred for 1 h at 25 °C and then diluted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. Evaporation of volatiles gave a crude product which was determined by ^{13}C NMR to be a 5:1 mixture of double bond isomers. Purification of the crude product by flash chromatography with 13% EtOAc/hexane (R_f = 0.44 in 30% EtOAc/hexane) gave 148 mg of the $\Delta^{6,7}$ alkene product **50** (85% yield). Mp (ethyl acetate): 104–105 °C.

α-Seleno Ester. ^{1}H NMR ($CDCl_3$): δ 1.00–2.15 (m, 15H), 2.28–2.48 (m, 1H), 2.82–2.88 (m, 1H), 3.25–3.32 (m, 1H), 3.54 (s, 3H), 3.78 (s, 3H), 4.46–4.52 (m, 1H), 7.20–7.26 (m, 2H), 7.32–7.38 (m, 1H), 7.48–7.54 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.87 (CH_2), 27.78 (CH_2), 29.65 (CH_2), 30.20 (CH_2), 31.25 (CH_2), 37.61 (CH_2), 38.05 (CH_2), 41.87 (CH_2), 48.72 (CH), 52.09 (CH_3), 52.23 (CH_3), 54.65 (CH), 56.12 (C), 62.89 (C), 86.96 (CH), 126.33 (C), 128.78 (two C of CH), 128.87 (CH), 129.61 (CH), 137.92 (two C of CH), 155.01, 173.27, 214.22.

Unsaturated Ester 50. IR (neat): 2950, 2880, 1730, 1720, 1455, 1280, 1115 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.00–1.45 (m, 4H), 1.70–1.95 (m, 6H), 2.02–2.20 (m, 3H), 2.38–2.50 (m, 2H), 2.90–2.97 (m, 1H), 3.65 (s, 3H), 3.75 (s, 3H), 3.98–4.04 (m, 1H), 4.67–4.71 (m, 1H), 7.04 (dd, J = 2.0, 4.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.94 (CH_2), 26.71 (CH_2), 27.23 (CH_2), 30.39 (CH_2), 31.05 (CH_2), 31.73 (CH_2), 40.61 (CH_2), 51.39 (CH_3), 51.87 (CH_3), 54.56 (CH), 54.69 (CH), 64.59 (C), 85.05 (CH), 131.01 (C), 142.04 (CH), 155.15, 166.97, 208.26. MS (m/z, relative intensity): 354 ($M^+ + NH_4$, 33), 337 ($M^+ + H$, 58), 260 (65), 232 (70), 201 (42), 173 (100), 131 (43). Exact mass calculated for $C_{18}H_{24}O_6$: 336.1573, found 336.1585.

Diol 52. To solution of 180 mg of **50** (0.54 mmol) in 50 mL of dry THF at −78 °C was added 2 mL of DIBAL (1 M in THF), and the resulting solution was warmed with stirring to 25 °C over 1 h. The reaction mixture was quenched with water and washed with 1 N aqueous HCl solution, and the organic layers were dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography with 80% ethyl acetate/hexane (R_f = 0.14) gave 99 mg of **52** (74% yield). IR (neat): 3500, 2980, 2880, 1730, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.00–1.10 (m, 1H), 1.26–1.46 (m, 2H), 1.58–1.70 (m, 3H), 1.75–1.84 (m, 3H), 1.90–2.20 (m, 5H), 2.44–2.50 (m, 1H), 2.64 (d, J = 15.5 Hz, 1H), 3.72 (dd, J = 6.5, 12.8 Hz, 1H), 3.93 (s, 3H), 4.00–4.08 (m, 1H), 5.85 (d, J = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.87 (CH_2), 26.81 (CH_2), 27.51 (CH_2), 30.79 (CH_2), 31.32 (CH_2), 31.85 (CH_2), 39.44 (CH_2), 50.64 (CH), 56.07 (CH), 62.81 (C), 67.29 (CH_2), 76.46 (CH), 127.18 (CH), 140.19 (C), 211.27. MS (m/z, relative intensity): 268 ($M^+ + NH_4$, 10), 250 (M^+, 10), 233 (82), 215 (100), 205 (76), 187 (48), 173 (25), 145 (28), 131 (40), 105 (41). Exact mass calculated for $C_{15}H_{22}O_3$: 250.1569, found 250.1565.

B-Ring Unsaturated Dibenzoate 53. A solution of 12 mg of diol **52** (0.048 mmol), 0.04 mL of benzoyl chloride (0.4 mmol, 9.3 equiv), and 156 mg of DMAP (1.28 mmol, 26 equiv) in 10 mL toluene was stirred for 1 h at 25 °C. Evaporation of volatiles and purification of the residue by flash chromatography with 20% ethyl acetate/hexane (R_f = 0.59 in 30% ethyl acetate/hexane) gave 18 mg of **53** (82% yield). IR (neat): 2990, 2880, 1730, 1720, 1455, 1275, 1100, 715 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.10–1.60 (m, 5H), 1.68–2.30 (m, 7H), 2.50–2.56 (m, 3H), 3.98–4.40 (m, 1H), 4.58 (d, J = 12.8 Hz, 1H), 4.66 (d, J = 12.8 Hz, 1H), 5.00–5.06 (m, 1H), 5.98 (br s, 1H), 7.38–7.46 (m, 4H), 7.50–7.56 (m, 2H), 8.00–8.04 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 26.15 (CH_2), 27.04 (CH_2), 27.53 (CH_2), 30.56 (CH_2), 31.46 (CH_2), 34.46 (CH_2), 41.40 (CH_2), 50.85 (CH), 55.22 (CH), 64.70 (C), 68.55 (CH_2), 82.45 (CH), 128.36 (CH), 128.42 (two C of CH), 129.35 (CH), 129.53 (two C of CH), 129.65 (CH), 129.70 (two C of CH), 130.07 (C), 130.28 (C), 132.97 (CH), 133.03 (CH), 134.46 (C), 166.07 (C), 166.25 (C), 209.87. MS (m/z, relative intensity): 476 ($M^+ + NH_4$, 30), 337 (18), 267 (7), 215 (36), 187 (20), 162 (13), 131 (100), 105 (40). Exact mass calculated for $C_{29}H_{30}O_5$ 458.2093, found 458.2115.

Silyl Ether 54. A solution of 8.5 mg diol **52** (0.034 mmol), 8 mL of TBDMSOTf, 0.5 mL of Et_3N, and 13 mg of DMAP in 10 mL of methylene chloride was stirred for 1 h at 25 °C. Addition of 1 mL of methanol to destroy excess triflate, followed by evaporation of volatiles and purification of the residue by flash chromatography using 20% EtOAc/hexane (R_f = 0.39 in 30% EtOAc/hexane), gave 9.2 mg of compound **54** (74% yield). IR (neat): 3450, 2980, 2880, 1730, 1720, 1450, 1250, 1070, 835, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 0.95–1.10 (m, 1H), 1.20–2.10 (m, 13H), 2.44–2.52 (m, 1H), 2.54–2.62 (m, 1H), 3.68–3.72 (m, 1H), 3.93 (dd, J = 12.5, 18.2 Hz, 2H), 3.98–4.04 (m, 1H), 5.81 (d, J = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −5.31 (two carbon), 18.55, 25.88, 26.00 (three carbon), 26.83, 27.62, 30.84, 30.87, 31.87, 39.54, 50.55, 56.17, 62.70, 67.59, 76.54, 125.98, 139.81, 210.75. Exact mass calculated for $C_{21}H_{36}O_3Si$: 364.2434, found 364.2449.

Benzoate 55. A solution of 8 mg of **54** (0.0322 mmol), 10 mL of benzoyl chloride, and 13 mg of DMAP in 10 mL of methylene chloride was stirred for 1 h at 25 °C. Evaporation of volatiles and purification of the residue by flash chromatography using 8% EtOAc/hexane (R_f = 0.20 in 10% EtOAc/hexane) gave 9 mg of benzoate **54** (88% yield). IR (neat): 2990, 2880, 1730, 1720, 1450, 1275, 1110, 840, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.01 (s, 6H), 0.86 (s, 9H), 1.10–1.50 (m, 6H), 1.62–1.70 (m, 1H), 1.75–2.02 (m, 13H), 2.10–2.18 (m, 1H), 2.20–2.30 (m, 1H), 2.42–2.64 (m, 3H), 3.87 (d, J = 13.3 Hz, 1H), 3.91 (d, J = 13.3 Hz, 1H), 3.95 (d, J = 12.1 Hz, 1H), 5.00–5.04 (m, 1H), 5.81 (br.s., 1H), 7.38–7.46 (m, 2H), 7.50–7.60 (m, 1H), 8.01 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −5.41, −5.30, 18.34, 25.93 (three carbon), 26.18, 27.11, 27.66, 30.66, 31.39, 33.45, 41.44, 50.65, 55.14, 64.37, 66.91, 82.47, 124.61, 128.41, 128.47, 129.53, 130.18, 132.98, 133.69, 138.99, 166.04, 210.29.

C-3 Monobenzoate 56. A solution of 8 mg of **55** (0.017 mmol) in MeOH/THF (5 mL/2 mL) was treated with 10 mL of $HClO_4$ at 25 °C. After stirring for 15 min at 25 °C, the solution was diluted with 3 M pH 7 phosphate buffer and extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. Evaporation of volatiles and purification of the residue by flash chromatography using 35% EtOAc/hexane (R_f = 0.12 in 30% EtOAc/hexane) gave 5 mg of **56** (83% yield). IR (neat): 3480, 2990, 2880, 1730, 1720, 1450, 1275, 1115, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.10–1.25 (m, 2H), 1.32–1.42 (m, 1H), 1.48–1.54 (m, 1H), 1.62–1.72 (m, 1H), 1.78–1.90 (m, 3H),

1.92–2.05 (m, 3H), 2.10–2.20 (m, 1H), 2.22–2.30 (m, 1H), 2.50–2.62 (m, 3H), 3.91 (t, J = 14.9 Hz, 2H), 3.97 (d, J = 11.8 Hz, 1H), 5.00–5.04 (m, 1H), 5.85 (br s, 1H), 7.38–7.46 (m, 2H), 7.52–7.60 (m, 1H), 7.96–8.02 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 26.15 (CH_2), 27.04 (CH_2), 27.71 (CH_2), 30.62 (CH_2), 31.30 (CH_2), 33.79 (CH_2), 41.19 (CH_2), 50.72, (CH) 55.22, (CH) 64.50 (C), 67.26 (CH_2), 82.28 (CH), 126.12 (CH), 128.43 (two C of CH), 129.55 (two C of CH), 130.14 (C), 133.05 (CH), 139.59(C), 166.16 (C), 210.47. MS (m/z, relative intensity): 372 ($M^+ + NH_4$, 40), 337 (8), 232 (37), 215 (28), 204 (15), 105 (100). Exact mass calculated for $C_{22}H_{26}O_4$: 354.1831, found 354.1849.

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Supplementary Material Available: Copies of ^{13}C NMR spectra of **12–14**, **18–20**, **22**, **24–33**, **36–41**, **43–48**, **50**, and **52–56** (35 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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