

# Inside–Outside Stereoisomerism. 6.<sup>+</sup> Synthesis of *trans*-Bicyclo[4.4.1]undecan-11-one and the First Stereoselective Construction of the Tricyclic Nucleus of the Ring System of the Ingenane Diterpenes<sup>†</sup>

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**Abstract:** The intramolecular dioxenone photocycloaddition reaction provides access to compounds which in many cases cannot be otherwise prepared. The application of this methodology to the construction of *trans*-bicyclo[4.4.1]undecan-11-one, **16**, which is ca. 10 kcal/mol more strained than the corresponding *cis*-bridged isomer, is described. The extension of this preliminary result to the first synthesis of the tricyclic ingenane nucleus with the requisite "inside–outside" or *trans* intrabridgehead stereochemical relationship is reported.

## Introduction

The mechanism of action of cocarcinogenic or tumor promoting substances is a subject of intense interest, particularly as it relates to the mechanism of carcinogenesis.<sup>3</sup> In the 1930s, Berenblum demonstrated that Croton oil could enhance the effect of certain carcinogens in inducing mouse skin neoplasia. The molecular structure of the primary tumor promoting substance in Croton oil was subsequently determined to be 12-*O*-tetradecanoylphorbol-13-acetate (TPA), **1** (Scheme 1), by Hecker.<sup>4</sup>

A molecular basis for the mechanism of action of these tumor promoting substances was established by Nishizuka, who found that tumor-promoting phorbol and ingenol esters are able to substitute for diacylglycerol, the endogenous activator of protein kinase C, but with much greater potency.<sup>5</sup> Protein kinase C 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. The importance of reversible phosphorylation as a major intracellular regulatory mechanism has been fully realized only within the last decade. Not only is this a mechanism for mediating neural and hormonal regulation of enzyme activity in a wide variety of metabolic processes but also the recent discovery of tyrosine-specific protein kinases from growth factor receptors and RNA tumor virus gene products has further emphasized the biological importance of this covalent modification of proteins.<sup>6</sup> Given the

biological responses induced by activators of protein kinase C,<sup>7</sup> the development of inhibitors of this enzyme based on these natural product leads may lead to therapeutic agents useful in the treatment of chronic inflammatory and proliferative diseases.<sup>8</sup>

Unlike phorbol, **1**, the structurally related diterpene ingenol, **2**, has not yet yielded to total synthesis.<sup>9,10</sup> Several formidable challenges are apparent in any effort directed toward the total synthesis of ingenol, **2**, with four carbocyclic rings and eight stereogenic centers. Of particular note is the "inside–outside" or *trans* intrabridgehead stereochemistry of the [4.4.1]-BC-ring system, the C-8/C-10 relative stereochemical relationship, a feature that has thwarted most synthetic efforts reported to date.<sup>11,12</sup> Paquette has recently reported the synthesis of a highly functionalized *iso*-ingenoid, **3**, with the *cis* intrabridgehead (C-8/C-10) stereochemical relationship (Scheme 1).<sup>13</sup> Biological testing of the C-3, C-20 palmitate dipalmitate of **3**, however, indicates that these compounds, which are epimeric with ingenol at C-8, are devoid of the biological activities associated with the naturally occurring ingenane esters. These results underscore

<sup>+</sup> For the preceding publication in this series, see: Winkler, J.; Hong, B. *J. Am. Chem. Soc.* **1991**, *113*, 8839. For a preliminary account of some of this work, see: Winkler, J.; Henegar, K.; Williard, P. *J. Am. Chem. Soc.* **1987**, *109*, 2850.

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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) Author to whom correspondence regarding X-ray structure of **23** should be addressed.

(3) For a comprehensive monograph, see: *Naturally Occurring Phorbol Esters*; Evans, F., Ed.; CRC Press, Inc., Boca Raton, FL, 1986.

(4) For excellent reviews of this work, see: (a) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423. (b) Adolf, W.; Hecker, E. *Isr. J. Chem.* **1977**, *6*, 75.

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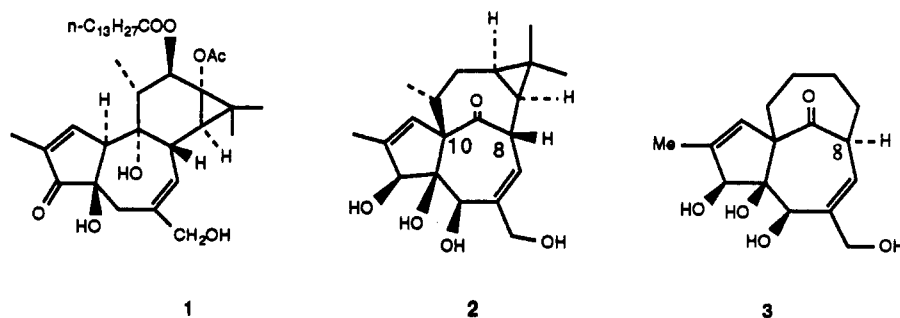
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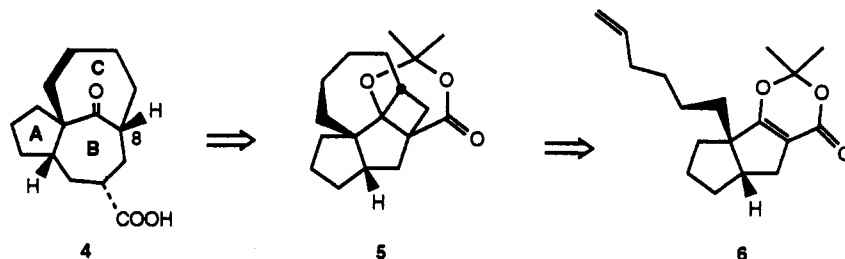
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Scheme 1



Scheme 2



the significance of the *trans* intrabridgehead stereochemistry for the biological activity of the ingenanes. In this paper we describe the efforts in our laboratory that culminated in the first synthesis of the tricyclic nucleus of the ingenane ring system with the requisite inside–outside stereochemical relationship.

## Results and Discussion

The intramolecular dioxenone photocycloaddition provides a general approach to the formation of cycloalkanone-2-propionates.<sup>14</sup> We have demonstrated that this methodology can be applied to the synthesis of bridged bicyclo[*x*.3.1]alkanones, where *x* = 4–8.<sup>15</sup> The photosubstrates in each of these cases consist of a four atom tether connecting the dioxenone chromophore and the alkene, and we have invoked a chair-like folding of the nascent ring to explain the *trans* selectivity of these photocycloadditions.<sup>16</sup> It remained to be seen whether this highly stereoselective photocycloaddition could be extended to the construction of other bridged bicycloalkanes, in particular the bicyclo[4.4.1]undecane moiety that constitutes the BC ring system of the ingenanes. That the parent *trans*-bridged bicyclo[4.4.1]undecane is calculated to be ca. 10 kcal/mol more strained than the *cis*-bridged isomer<sup>17</sup> underscores the challenge associated with the stereoselective construction of these highly strained “inside–outside” or *trans*-bridged bicyclic structures.

**A Model Study for the Synthesis of Ingenanes. Preparation of *trans*-Bicyclo[4.4.1]undecan-11-one.** The retrosynthetic analysis for the application of the intramolecular dioxenone photocycloaddition to the synthesis of the ingenane nucleus is shown for 4, which lacks most of the functionality of ingenol, 2, except for the C-9 carbonyl, the C-20 oxygen functionality (in the form of a carboxylic acid), and the critical C-8β hydrogen, as outlined in Scheme 2.

Since the bicyclo[4.4.1]undecane moiety that constitutes the BC ring system of the ingenanes embodies the critical *trans* intrabridgehead stereochemical feature, we first examined the

model system that is shown in Scheme 3 for the synthesis of 16. The construction of seven-membered rings using the intramolecular photocycloaddition reaction had already been established at the outset of this work.<sup>14</sup>

Alkylation of cyclopentanone with 6-iodohexene (LDA, THF, –78 °C → room temperature, 70%) gave ketone 7, which on carboxylation with methyl cyanofornate (LDA, MeOCOCN, THF, –78 °C → room temperature, 82%) gave ketoester 8. Ester exchange (anisyl alcohol, toluene, reflux, 94%) followed by photosubstrate formation (TFA, TFAA, acetone, 81%) provided photosubstrate 10. In contrast to our previous results in the formation of seven-membered rings and in the preparation of bridged bicyclic ring systems, both of which routinely proceeded to give single photoadducts in 70–80% yield, irradiation of 10 under the usual conditions (4.8 mM in 1:9 acetone/acetonitrile, Pyrex immersion well, 0 °C, 450 W medium pressure Hg lamp) led to the formation of two photoadducts in a 4.3:1 ratio in 30% yield. The formation of two photoadducts would be consistent with the formation of both *cis*- and *trans*-photoadducts, 11 and 12, as shown in Scheme 3, which could be a consequence of the considerable strain energy of the *trans*-bridged bicycloalkane.<sup>18</sup> However, fragmentation of the separated photoadducts (2 N KOH/MeOH, 25 °C, 85% yield) and Barton decarboxylation<sup>19</sup> led to the formation of a single bicyclicundecanone, 16, with the highly strained *trans* intrabridgehead stereochemical relationship. Since the ketoacids 14 and 15 obtained on fragmentation of the separated photoadducts were not the same, these results are consistent only with the formation of diastereomeric photoadducts, 11 and 13, both of which have *trans* intrabridgehead stereochemistry. The formation of 11 and 13 result from approach of the alkene to both the α- (leading to 13) and β-faces (leading to 11) of the dioxenone.

The observed selectivity for the formation of *trans*-bridged products is consistent with the conformations of 10 shown in Scheme 4. The seven-membered ring can be formed in either pseudochair or pseudoboat conformations. The pseudoboat conformation B suffers transannular eclipsing interactions which

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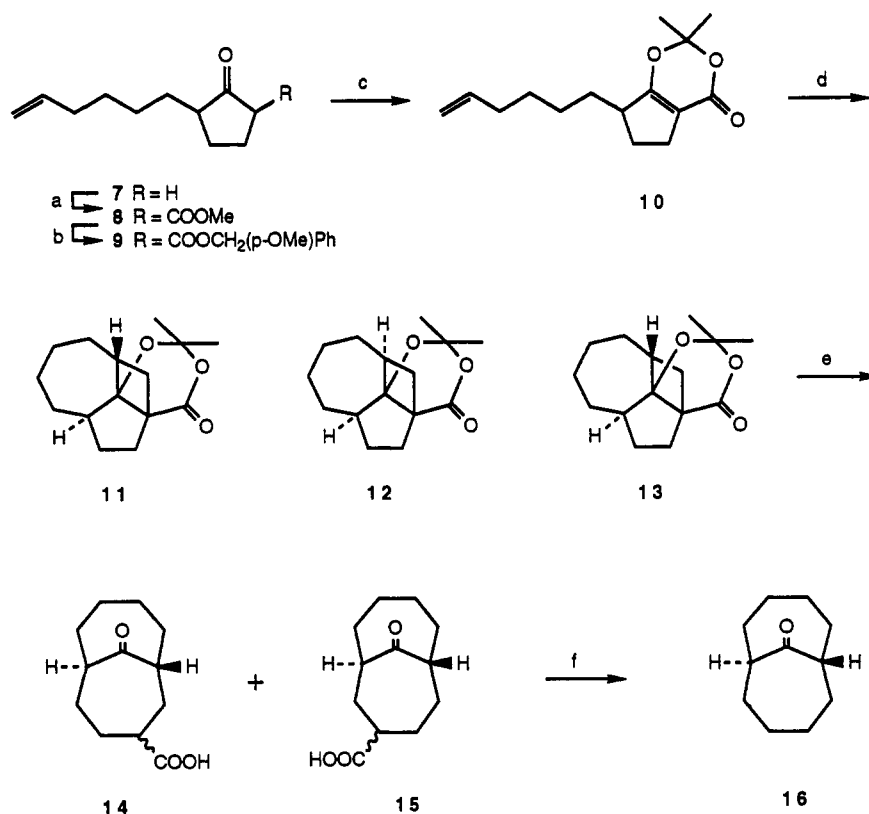
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(16) (a) Winkler, J.; Muller, C.; Hey, J.; Ogilvie, R.; Haddad, N.; Squattrito, P.; Williard, P. *Tetrahedron Lett.* **1989**, 5211. (b) Winkler, J.; Shao, B. *Tetrahedron Lett.* **1993**, 3344.

(17) These values were kindly provided to us by Professor Martin Saunders (Yale University) by the method that he has previously described: Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

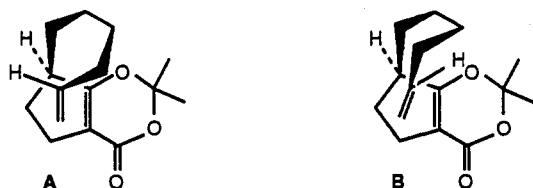
(18) For an example of an intramolecular dioxenone photocycloaddition that gives a preponderance of *cis*-bridged product, bicyclo[4.3.1]decan-10-one, presumably as a consequence of the large (ca. 20 kcal/mol) difference in strain energy between the *cis*- and *trans*-bridged products, see: Winkler, J.; Hey, J.; Williard, P. *Tetrahedron Lett.* **1988**, 4691.

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Scheme 3<sup>a</sup>

<sup>a</sup> (a) LDA, MeOCOCN, THF, 82%; (b) anisyl alcohol, toluene, 94%; (c) TFA, TFAA, acetone, 81%; (d)  $h\nu$ , 30%; (e) 2 N KOH/MeOH, 85%; (f) Reference 19.

Scheme 4



are not present in A, so that A, which leads to the desired "inside-outside" product, should best represent the conformation of dioxenone photosubstrate 10 that undergoes the photocycloaddition. Similar arguments can be made for the selectivity observed on the formation of 13.

The *trans* intrabridgehead stereochemistry of 16 was confirmed by examination of the  $^{13}\text{C}$  spectrum, which showed seven lines ( $\delta$  26.09, 29.24, 30.83, 31.89, 50.69, 51.19, 217.42), since the *trans*-bridged bicycloundecanone has a plane but not an axis of symmetry. In contrast, the  $^{13}\text{C}$  spectrum of the highly symmetrical *cis*-bicyclo[4.4.1]undecane-11-one reveals only four lines ( $\delta$  26.72, 28.55, 55.27, 219.62).<sup>20</sup> In addition, as we had previously reported for the *cis*- and *trans*-bicyclo[4.3.1]decanones, there is a marked difference in the infrared spectrum for the carbonyl stretches for the *cis*- (1692  $\text{cm}^{-1}$ ) and the more highly strained *trans*-bridged isomers (1719  $\text{cm}^{-1}$ ).

**Stereoselective Assembly of the *trans*-Bridged Tricyclic Nucleus of Ingenol.** We reasoned that annulation of the ingenol A ring onto photosubstrate 10 would reduce the degrees of freedom in the alkene-bearing chain and lead to a higher yield in the cyclization. The requisite photosubstrate was prepared as outlined in Scheme 5. Reductive alkylation of  $\Delta^{1,5}$ -bicyclo[3.3.0]octen-

2-one ( $\text{Li}^0$ , tetrahydrofuran, liquid ammonia)<sup>21</sup> with 5-hexenyl iodide provided the *cis*-fused angularly alkylated bicyclooctane 17 in 58% yield. The next step in the sequence was the carboxylation of 17 to provide 18. Attempted carboxylation of the enolate derived from 17 with carbon dioxide, dimethyl carbonate, di-*tert*-butyl dicarbonate, or *tert*-butyl cyanoformate was unsuccessful. However, treatment of the enolate derived from 17 (lithium diisopropylamide, tetrahydrofuran, 0  $^\circ\text{C}$ ) with *p*-methoxybenzyl cyanoformate (1.3 equiv cyanoformate, 1 equiv of HMPA,  $-78^\circ\text{C} \rightarrow$  room temperature) led to the formation of the desired  $\beta$ -ketoester 18 in 82% yield.<sup>22</sup> It was subsequently determined that the acid-labile anisyl ester could be more conveniently prepared by a two-step sequence involving carboxylation of the enolate derived from 17 with methyl cyanoformate,<sup>23</sup> followed by ester exchange (*p*-methoxybenzyl alcohol, toluene reflux). Conversion of the *p*-methoxybenzyl keto ester to photosubstrate 19 proceeded in 85% yield, using an excess of acetic anhydride (55 equiv) in 1:1 trifluoroacetic acid/acetone ( $-78^\circ\text{C} \rightarrow 25^\circ\text{C}$ , 12 h).

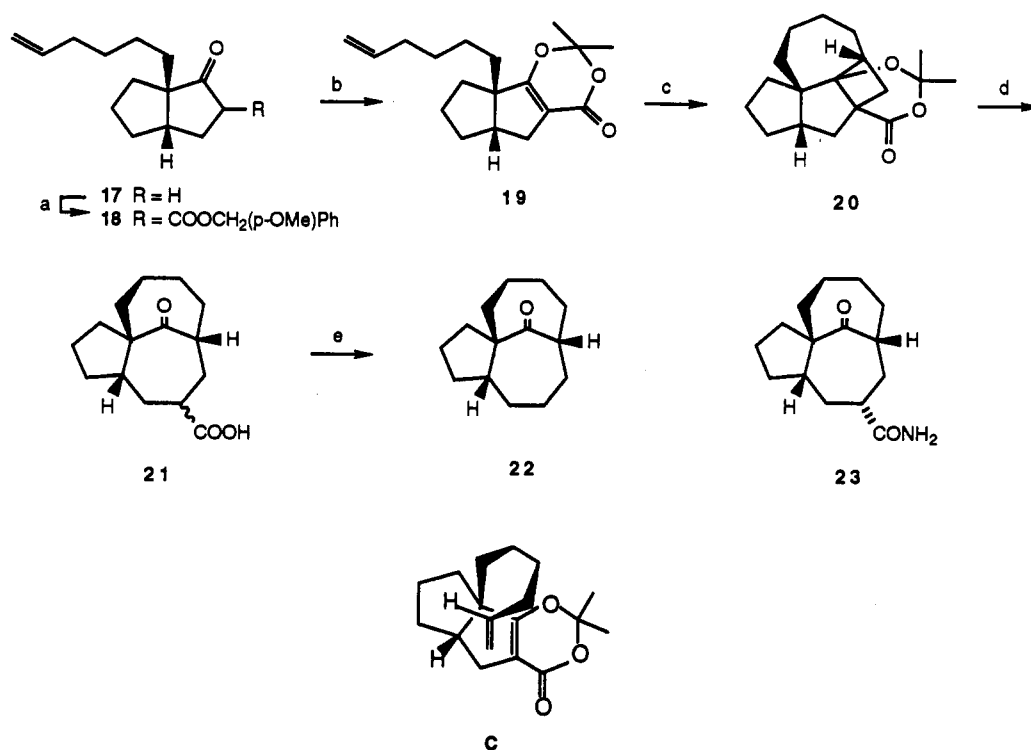
Irradiation of 19 (7.5 mM in 1:9 acetone/acetonitrile, Pyrex immersion well, 0  $^\circ\text{C}$ , 90 min) led to the formation of a single photoadduct 20 in 83% yield. Fragmentation of 20 (2 N KOH, methanol, 40  $^\circ\text{C}$ , 4 h, 88% yield) provided ketoacid 21 as a mixture of epimeric compounds, which could be interconverted as the corresponding methyl esters by using sodium methoxide in methanol. That the ketoacids were epimeric at C-6 could be demonstrated by Barton decarboxylation of the separated ketoacids to the same ketone 22. The chemical shift of the C-8 proton ( $\delta$  2.87, m, 1 H) and the infrared adsorption for the carbonyl in 22 were identical with the corresponding spectral data for *trans*-bicyclo[4.4.1]undecan-11-one, 16 (Scheme 3), but unambiguous proof of the inside-outside intrabridgehead stereochemical relationship in 22 follows from the single-crystal X-ray analysis

(20) The authentic sample of *cis*-bicyclo[4.4.1]undecane-11-one was prepared by cycloaddition of tropone with butadiene, followed by catalytic hydrogenation. Henegar, K., unpublished results.

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(22) Henegar, K.; Winkler, J. *Tetrahedron Lett.* **1987**, 1051.

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Scheme 5<sup>a</sup>

<sup>a</sup> (a) LDA, (*p*-OMe)*C*<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OCOCN, THF, 82%; (b) Ac<sub>2</sub>O, TFA, acetone, 85%; (c) *hν*, 83%; (d) 2 N KOH/MeOH, 88%; (e) Reference 19.

of ketoamide **23** [derived from the major epimer of **21** via treatment of the derived acid chloride (thionyl chloride, toluene) with aqueous ammonium hydroxide].

The exclusive formation of the inside–outside isomer can be explained by the same analysis that was presented for the stereoselective formation of *trans*-bicyclo[4.4.1]undecanone, **16**, i.e., photoaddition *via* the orientation shown in C (Scheme 5).

## Conclusion

The results described herein establish that the intramolecular dioxenone photocycloaddition can be used for the synthesis of *trans*-bicyclo[4.4.1]undecan-11-one as well as for the tricyclic nucleus of the ingenane ring system with the requisite *trans* intrabridgehead stereochemistry. The incorporation of C-3 oxygen functionality into the framework of **22** has recently been achieved, making the biological testing of ingenol ester analogs possible.<sup>24,25</sup> A full account of that work 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 μ) with fluorescent indicator were used for analytical TLC. Merck silica gel 60 (particle size 0.04–0.063 μm) 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 either an FT Nicolet SX-20 or a Perkin-Elmer Model 281B spectrophotometer. NMR spectra were measured with either Bruker AM-500 (500 MHz) or GE OMEGA-300 (300 MHz) spectrometers. <sup>13</sup>C chemical shifts are reported in δ values (parts per million) relative to chloroform (δ CDCl<sub>3</sub> = 77.0). Most of the <sup>13</sup>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.

**2-(5-Hexenyl)cyclopentanone, 7.** To a solution of 1.6 mL of diisopropylamine (10 mmol) in 40 mL of dry THF at –78 °C was added 3.6 mL of 2.5 M *n*-BuLi/hexane (10 mmol). The solution was stirred for 0.5 h at –78 °C and then treated with a solution of 806 mg of cyclopentanone (9.6 mmol) in 10 mL of dry THF. After 30 min at –78 °C, 1.6 mL of 5-iodohexene was added to the reaction mixture. The resulting solution was stirred for 6 h and warmed to 25 °C. The reaction mixture was quenched with 1 mL of H<sub>2</sub>O, washed with saturated aqueous NaCl, dried over MgSO<sub>4</sub>, and purified by flash chromatography with 4% EtOAc/hexane (*R*<sub>f</sub> 0.48 in 10% EtOAc/hexane) to give 810 mg of **7** (70% yield, based on recovered 220 mg of cyclopentanone): IR (neat) 2960, 2880, 1730, 1650, 1475, 1455 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.90–1.38 (m, 6 H), 1.40–1.64 (m, 2 H), 1.70–2.10 (m, 6 H), 3.78–3.90 (m, 1 H), 4.60–4.80 (m, 2 H), 5.44–5.64 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 20.25 (CH<sub>2</sub>), 26.51 (CH<sub>2</sub>), 28.36 (CH<sub>2</sub>), 29.01 (CH<sub>2</sub>), 29.11 (CH<sub>2</sub>), 33.10 (CH<sub>2</sub>), 37.54 (CH<sub>2</sub>), 48.51 (CH), 113.85 (CH<sub>2</sub>), 138.20 (CH), 220.21; MS (*m/z*, rel intensity) 166 (M<sup>+</sup>, 1), 148 (2), 137 (2), 123 (4), 97 (24), 84 (100).

**2-(5-Hexenyl)-5-Carbomethoxycyclopentanone, 8.** To a solution of 0.5 mL of diisopropylamine (3.5 mmol) in 40 mL of dry THF at –78 °C was added 1.4 mL of 2.5 M *n*-BuLi/hexane (3.5 mmol). The solution was stirred for 0.5 h at –78 °C and then treated with a solution of 390 mg of ketone **7** (2.35 mmol) in 10 mL of dry THF. After 30 min at –78 °C, 0.3 mL of methyl cyanofornate was added to the reaction mixture. The resulting solution was warmed to 25 °C with stirring over 3 h. The reaction mixture was quenched with 1 mL of H<sub>2</sub>O, washed with saturated aqueous NaCl, dried over MgSO<sub>4</sub>, and purified by flash chromatography with 10% EtOAc/hexane (*R*<sub>f</sub> 0.28) to give 432 mg of ketoester **8** (82% yield): IR (neat) 2960, 2880, 1760, 1735, 1440, 1270, 1205 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.20–1.50 (m, 6 H), 1.65–1.85 (m, 2 H), 2.00–2.40 (m, 5 H), 3.08–3.12 (m, 1 H), 3.73 (s, 3 H), 4.90–5.00 (m, 2 H), 5.70–5.82 (m, 1 H).

***p*-Methoxybenzyl 3-(5'-Hexenyl)-2-oxocyclopentanecarboxylate, 9.** A solution of 392 mg of ketoester **8** (1.75 mmol) and 0.75 mL of *p*-methoxybenzyl alcohol (6 mmol) in 100 mL of toluene was heated at reflux under a Dean-Stark trap for 18 h. The resulting solution was evaporated under reduced pressure and purified by flash column chromatography with 10% EtOAc/hexane (*R*<sub>f</sub> 0.18) to give 570 mg of

(24) The C-3 hydroxyl of ingenol is the point of attachment of the various ester functionalities that are necessary for biological activity in this system. For a notable exception, see: Hasler, C.; Acs, G.; Blumberg, P. *Cancer Res.* 1992, 52, 202.

(25) 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.

ketoester **9** (94% yield): IR (neat) 2960, 2880, 1760, 1730, 1620, 1520, 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.20–1.50 (m, 6 H), 1.60–1.80 (m, 2 H), 1.95–2.32 (m, 5 H), 3.08–3.15 (m, 1 H), 3.79 (s, 3 H), 4.85–5.00 (m, 2 H), 5.09 (s, 2 H), 5.70–5.82 (m, 1 H), 6.80–6.88 (m, 2 H), 7.25–7.30 (m, 2 H).

**Dioxenone 10.** A solution of 540 mg of ketoester **9** (1.64 mmol) in 7 mL of acetone was cooled to  $-78^\circ\text{C}$  under  $\text{N}_2$  pressure and treated with 3 mL of trifluoroacetic anhydride and 7 mL of trifluoroacetic acid, added dropwise. The reaction mixture was warmed to  $25^\circ\text{C}$  over 18 h. The resulting mixture was concentrated, diluted with ethyl acetate, and added dropwise to a cold solution of saturated aqueous  $\text{NaHCO}_3$ . The aqueous solution was extracted with ethyl acetate and purified by flash column chromatography with 13% EtOAc/hexane ( $R_f$  0.12 in 10% EtOAc/hexane) to yield 330 mg of dioxenone **10** (81% yield): IR (neat) 2960, 2880, 1740, 1645, 1420, 1260, 1600, 1150, 990  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10–1.30 (m, 6 H), 1.38–1.55 (m, 1 H), 1.51 (s, 3 H), 1.52 (s, 3 H), 1.80–1.90 (m, 2 H), 1.92–2.02 (m, 1 H), 2.24–2.40 (m, 2 H), 2.55–2.65 (m, 1 H), 4.70–4.86 (m, 2 H), 5.06–5.18 (m, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.00 ( $\text{CH}_2$ ), 24.40 ( $\text{CH}_3$ ), 25.11 ( $\text{CH}_3$ ), 25.87 ( $\text{CH}_2$ ), 26.04 ( $\text{CH}_2$ ), 28.34 ( $\text{CH}_2$ ), 31.36 ( $\text{CH}_2$ ), 33.09 ( $\text{CH}_2$ ), 43.20 ( $\text{CH}$ ), 102.12 ( $\text{C}$ ), 107.73 ( $\text{C}$ ), 114.07 ( $\text{CH}_2$ ), 138.13 ( $\text{CH}$ ), 159.88 ( $\text{C}$ ), 173.32; MS ( $m/z$ , rel intensity): 251 ( $\text{M}^+ + \text{H}$ , 68), 193 (95), 123 (18), 110 (100); exact mass calculated for  $\text{C}_{15}\text{H}_{22}\text{O}_3$  250.1569, found 250.1560.

**Irradiation of 10.** A solution of 300 mg of dioxenone **10** (1.20 mmol) in 250 mL of acetonitrile/acetone (7:3) was degassed for 0.5 h and then irradiated through a Pyrex filter at  $0^\circ\text{C}$  for 5 h, at which time all starting material was consumed (TLC). The solution was concentrated and purified by chromatography with 10% EtOAc/hexane ( $R_f$  0.51 and 0.45 in 20% EtOAc/hexane) to give 73 mg of photoadduct **11** and 17 mg of photoadduct **13** (30% total yield).

**Photoadduct 11:** IR (neat) 2980, 2859, 1749, 1485, 1875, 1284  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.15–1.40 (m, 3 H), 1.45–1.65 (m, 2 H), 1.55 (s, 3 H), 1.62 (s, 3 H), 1.70–1.80 (m, 2 H), 1.95–2.05 (m, 2 H), 2.08–2.16 (m, 3 H), 2.22–2.45 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.30 ( $\text{CH}_2$ ), 24.58 ( $\text{CH}_2$ ), 29.32 ( $\text{CH}_3$ ), 30.05 ( $\text{CH}_3$ ), 30.70 ( $\text{CH}_2$ ), 31.07 ( $\text{CH}_2$ ), 32.94 ( $\text{CH}_2$ ), 33.92 ( $\text{CH}_2$ ), 36.32 ( $\text{CH}_2$ ), 36.36 ( $\text{CH}$ ), 43.15 ( $\text{CH}$ ), 43.37 ( $\text{C}$ ), 90.50 ( $\text{C}$ ), 106.28 ( $\text{C}$ ), 174.42.

**Photoadduct 13:** IR (neat) 2980, 2859, 1749, 1485, 1875, 1284  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.20–1.50 (m, 3 H), 1.53 (s, 3 H), 1.63 (s, 3 H), 1.65–2.10 (m, 9 H), 2.35–2.60 (m, 2 H), 2.68–2.86 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.02 ( $\text{CH}_2$ ), 26.90 ( $\text{CH}_2$ ), 27.41 ( $\text{CH}_2$ ), 27.46 ( $\text{CH}_2$ ), 30.04 ( $\text{CH}_3$ ), 30.06 ( $\text{CH}_3$ ), 32.79 ( $\text{CH}_2$ ), 34.06 ( $\text{CH}_2$ ), 34.65 ( $\text{CH}_2$ ), 41.86 ( $\text{C}$ ), 43.48 ( $\text{CH}$ ), 48.69 ( $\text{CH}$ ), 87.78 ( $\text{C}$ ), 106.74 ( $\text{C}$ ), 182.08; MS ( $m/z$ , rel intensity) 251 ( $\text{M}^+ + \text{H}$ , 60), 231 (13), 181 (33), 147 (40), 131 (79), 110 (100); exact mass calculated for  $\text{C}_{15}\text{H}_{22}\text{O}_3$  250.1569, found 250.1554.

**Fragmentation of Photoadduct 11.** A solution of 50 mg of photoadduct **11** (0.20 mmol) in 10 mL of 2 N KOH/MeOH was stirred at  $25^\circ\text{C}$  for 18 h. The reaction was diluted with water and extracted with 40 mL of ethyl acetate. The organic layers were washed with 2 N aqueous HCl, dried over  $\text{MgSO}_4$ , and purified by flash column chromatography with 70% EtOAc/hexane ( $R_f$  0.07 in 30% EtOAc/hexane) to give 35 mg of keto acid **14** (83% yield; two epimers in a ratio of 5:1): IR (neat) 3100–3400, 2992, 2863, 1793, 1734, 1457  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.05–1.60 (m, 7 H), 1.65–1.90 (m, 4 H), 2.00–2.35 (m, 3 H), 2.40–2.50 (m, 2 H), 2.68–2.78 (m, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) for major isomer  $\delta$  25.93 ( $\text{CH}_2$ ), 28.79 ( $\text{CH}_2$ ), 29.00 ( $\text{CH}_2$ ), 30.48 ( $\text{CH}_2$ ), 31.08 ( $\text{CH}_2$ ), 31.70 ( $\text{CH}_2$ ), 32.25 ( $\text{CH}_2$ ), 48.05 ( $\text{CH}$ ), 49.23 ( $\text{CH}$ ), 50.40 ( $\text{CH}$ ), 180.57, 216.18; MS ( $m/z$ , rel intensity) 210 ( $\text{M}^+$ , 100), 192 (36), 182 (22), 164 (62), 136 (33), 122 (40), 109 (38); exact mass calculated for  $\text{C}_{12}\text{H}_{18}\text{O}_3$  210.1256, found 210.1240.

**trans-Bicyclo[4.4.1]undecan-11-one, 16.** To 17 mg of keto acid **14** (0.08 mmol) in 10 mL of benzene under  $\text{N}_2$  atmosphere was added 0.38 mL of oxalyl chloride. The reaction flask was then charged with  $\text{N}_2$ , and 50  $\mu\text{L}$  of dimethylformamide was added. The resulting solution was stirred for 1 h at  $25^\circ\text{C}$  and then evaporated under reduced pressure. The crude acid chloride was dissolved in 10 mL of toluene and added dropwise to a refluxing slurry of 66 mg of the sodium salt of 2-mercaptopyridine *N*-oxide, 5 mg of DMAP, and 0.8 mL of *tert*-butylmercaptan in 10 mL of THF. The reaction was cooled to  $25^\circ\text{C}$  and extracted with saturated sodium bicarbonate and water. The organic layers were evaporated under reduced pressure, and the resulting residue was purified by chromatography with 5% EtOAc/hexane ( $R_f$  0.41 in 10% EtOAc/hexane) to give 8 mg of bicyclic ketone **16** (60% yield): IR (neat) 2992, 2852, 1719, 1445, 1367, 1145  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.05–1.60 (m, 9 H), 1.68–1.82 (m, 5 H), 2.10–2.20 (m, 2 H), 2.35–2.42 (m, 1 H), 2.72–2.80 (m, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.09 ( $\text{CH}_2$ ), 29.24 ( $\text{CH}_2$ ), 30.83 ( $\text{CH}_2$ ),

31.89 ( $\text{CH}_2$ ), 50.69 ( $\text{CH}$ ), 51.19 ( $\text{CH}$ ), 217.42; MS ( $m/z$ , rel intensity) 166 ( $\text{M}^+$ , 30), 147 (10), 138 (20), 110 (36), 104 (35), 95 (60), 81 (85), 67 (100); exact mass calculated for  $\text{C}_{11}\text{H}_{18}\text{O}$  166.1358, found 166.1369.

**Fragmentation of Photoadduct 13.** A solution of 11 mg of photoadduct **13** (0.63 mmol) in 10 mL of 2 N KOH/MeOH was stirred at  $25^\circ\text{C}$  for 18 h. The reaction was diluted with water and extracted with 40 mL of ethyl acetate. The organic layers were washed with 2 N aqueous HCl, dried over  $\text{MgSO}_4$ , and purified by flash column chromatography with 70% EtOAc/hexane ( $R_f$  0.05 in 30% EtOAc/hexane) to give 8 mg of keto acid **15** (87% yield as two isomers in a 1:1 ratio): IR (neat) 3000–3500, 2960, 2880, 1730, 1715, 1450  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10–1.50 (m, 3 H), 1.55–2.30 (m, 12 H), 2.74–2.90 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.48 ( $\text{CH}_2$ ), 25.53 ( $\text{CH}_2$ ), 25.75 ( $\text{CH}_2$ ), 25.86 ( $\text{CH}_2$ ), 26.42 ( $\text{CH}_2$ ), 26.63 ( $\text{CH}_2$ ), 26.66 ( $\text{CH}_2$ ), 28.45 ( $\text{CH}_2$ ), 28.56 ( $\text{CH}_2$ ), 28.91 ( $\text{CH}_2$ ), 30.03 ( $\text{CH}_2$ ), 30.50 ( $\text{CH}_2$ ), 31.14 ( $\text{CH}_2$ ), 32.62 ( $\text{CH}_2$ ), 42.82 ( $\text{CH}$ ), 43.80 ( $\text{CH}$ ), 52.98 ( $\text{CH}$ ), 53.24 ( $\text{CH}$ ), 54.25 ( $\text{CH}$ ), 54.47 ( $\text{CH}$ ), 180.77, 181.16, 218.17, 218.42.

**Decarboxylation of 15.** To 8 mg of keto acid **15** (0.04 mmol) in 10 mL of benzene under  $\text{N}_2$  atmosphere was added 0.38 mL of oxalyl chloride. The reaction flask was then charged with nitrogen, and 50  $\mu\text{L}$  of dimethylformamide was added. The resulting solution was stirred for 1 h at  $25^\circ\text{C}$  and then evaporated under reduced pressure. The crude acid chloride was dissolved in 10 mL of toluene and added dropwise to a refluxing slurry of 66 mg of the sodium salt of 2-mercaptopyridine *N*-oxide, 5 mg of DMAP, and 0.8 mL of *tert*-butylmercaptan in 10 mL of THF. The reaction was cooled to  $25^\circ\text{C}$  and extracted with saturated sodium bicarbonate and water. The organic layers were evaporated under reduced pressure, and the resulting residue was purified by chromatography with 5% EtOAc/hexane ( $R_f$  0.41 in 10% EtOAc/hexane) to give 4 mg of bicyclic ketone **16** (60% yield), identical in all respects ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and MS spectrum and GC retention time) to the product of decarboxylation of **14**.

**cis-1-(5-Hexenyl)bicyclo[3.3.0]octan-2-one, 17.** Li wire (400 mg) was dissolved in THF (200 mL) and liquid  $\text{NH}_3$  (400 mL) at  $-78^\circ\text{C}$  for 20 min. A solution of  $\Delta^{1,5}$ -bicyclo[3.3.0]octen-2-one (3.66 g, 40 mmol) in THF (30 mL) was added dropwise to the solution and stirred at  $-78^\circ\text{C}$  for 50 min with mechanical stirring. The resulting blue solution was treated with 6-iodohexene (6 mL), and the resulting mixture was warmed to  $0^\circ\text{C}$  with stirring over 6 h. The reaction was quenched with aqueous  $\text{NH}_4\text{Cl}$  solution, washed with brine, dried over  $\text{MgSO}_4$ , and purified by flash column chromatography with 4% EtOAc/hexane ( $R_f$  0.50 in 10% EtOAc/hexane) to give ketone **17** (3.58 g, 58% yield): IR (neat) 2960, 2880, 1745, 1650, 1470, 1460  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.00–1.60 (m, 11 H), 1.75–1.90 (m, 2 H), 1.92–2.02 (m, 3 H), 2.15–2.30 (m, 2 H), 2.36–2.42 (m, 1 H), 4.82–4.94 (m, 2 H), 5.65–5.75 (m, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.66 ( $\text{CH}_2$ ), 25.10 ( $\text{CH}_2$ ), 25.35 ( $\text{CH}_2$ ), 29.33 ( $\text{CH}_2$ ), 33.46 ( $\text{CH}_2$ ), 33.65 ( $\text{CH}_2$ ), 36.45 ( $\text{CH}_2$ ), 36.61 ( $\text{CH}_2$ ), 37.81 ( $\text{CH}_2$ ), 45.67 ( $\text{CH}$ ), 60.12 ( $\text{C}$ ), 114.30 ( $\text{CH}_2$ ), 138.66 ( $\text{CH}$ ), 224.82; MS ( $m/z$ , rel intensity) 224 ( $\text{M}^+ + \text{NH}_4$ , 30), 207 ( $\text{M}^+ + \text{H}$ , 100), 189 (10), 165 (7), 136 (6); exact mass calculated for  $\text{C}_{14}\text{H}_{22}\text{O}$  206.1671, found 206.1749.

**Dioxenone 19.** To a solution of diisopropylamine (0.2 mL) and HMPA (2 mL) in THF (45 mL) was added *n*-BuLi (0.6 mL, 2.5 M in hexane, 1.5 mmol) at  $-78^\circ\text{C}$ . The solution was stirred for 10 min and then treated with a solution of ketone **17** (206 mg, 1 mmol) in THF (30 mL). After stirring for 30 min at  $-78^\circ\text{C}$ , anisyl cyanofornate (4 mL) was added into the reaction mixture. The resulting solution was warmed to  $25^\circ\text{C}$  with stirring over 3 h. The reaction was quenched with  $\text{H}_2\text{O}$  (1 mL), washed with brine, dried over  $\text{MgSO}_4$ , and purified by flash column chromatography with 10% EtOAc/hexane ( $R_f$  0.41 in 10% EtOAc/hexane) to give anisyl ketoester **18** (306 mg, 82% yield): IR (neat) 2950, 2860, 1745, 1722, 1614, 1516, 1247, 1175  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10–1.82 (m, 12 H), 1.60 (s, 3 H), 1.63 (s, 3 H), 1.92–2.08 (m, 3 H), 2.26–2.33 (m, 1 H), 2.68–2.72 (m, 1 H); MS ( $m/z$ , rel intensity) 370 ( $\text{M}^+$ , 7), 206 (3), 150 (7), 137 (15), 121 (100), 109 (4).

A solution of anisyl ketoester **18** (375 mg, 1.09 mmol) in acetone (5 mL) was cooled to  $-78^\circ\text{C}$  under  $\text{N}_2$  atmosphere. TFAA (5 mL) and TFA (5 mL) were added dropwise into the solution. The reaction mixture was warmed to  $25^\circ\text{C}$  over 18 h. The solution was added dropwise into a cold saturated aqueous  $\text{NaHCO}_3$  solution, extracted with EtOAc, and purified by flash column chromatography with 10% EtOAc/hexane ( $R_f$  0.21 in 10% EtOAc/hexane) to yield dioxenone **19** (249 mg, 85% yield): IR (neat) 2960, 2880, 1750, 1660, 1420, 1260, 1210, 1150, 1000  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10–1.82 (m, 12 H), 1.60 (s, 3 H), 1.63 (s, 3 H), 1.92–2.08 (m, 3 H), 2.26–2.33 (m, 1 H), 2.68–2.72 (m, 1 H), 4.82–4.92 (m, 2 H), 5.65–5.75 (m, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.47 ( $\text{CH}_2$ ), 24.52 ( $\text{CH}_3$ ), 25.47 ( $\text{CH}_2$ ), 25.58 ( $\text{CH}_3$ ), 29.05 ( $\text{CH}_2$ ), 32.25 ( $\text{CH}_2$ ), 33.30

(CH<sub>2</sub>), 35.66 (CH<sub>2</sub>), 36.08 (CH<sub>2</sub>), 37.02 (CH<sub>2</sub>), 43.14 (CH), 59.28 (C), 101.98 (C), 107.80 (C), 114.35 (CH<sub>2</sub>), 138.42 (CH), 160.26 (C), 173.55 (C); MS (*m/z*, rel intensity) 308 (M<sup>+</sup> + NH<sub>4</sub>, 12), 291 (M<sup>+</sup> + H, 100), 250 (23), 233 (50), 167 (12), 150 (62), 122 (10); exact mass calculated for C<sub>18</sub>H<sub>26</sub>O<sub>3</sub> 290.1882, found 290.1866.

**Photoadduct 20.** A solution of dioxenone **19** (155 mg, 0.53 mmol) in acetonitrile/acetone (63 mL of acetonitrile and 7 mL of acetone) was degassed for 0.5 h, and the resulting solution was irradiated through a Pyrex filter with cooling (external 0 °C ice-water bath) for 2 h. The solution was concentrated *in vacuo* and purified by flash column chromatography with 8% EtOAc/hexane as eluent (*R<sub>f</sub>* 0.31 in 10% EtOAc/hexane) to give photoadduct **20** (128 mg, 83% yield): IR (neat) 2948, 2861, 1723, 1449, 1385, 1339, 1311, 1283, 1243, 907, 750, 732 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.20–1.32 (m, 2 H), 1.40–1.95 (m, 12 H), 1.62 (s, 3 H), 1.76 (s, 3 H), 1.76 (s, 3 H), 2.03–2.12 (m, 2 H), 2.25–2.38 (m, 3 H), 2.58–2.65 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 23.61 (CH<sub>2</sub>), 25.25 (two C of CH<sub>2</sub>), 30.50 (CH<sub>2</sub>), 30.68 (CH<sub>3</sub>), 31.32 (CH<sub>3</sub>), 33.42 (CH<sub>2</sub>), 35.24 (CH<sub>2</sub>), 35.49 (CH<sub>2</sub>), 39.79 (CH), 40.73 (CH<sub>2</sub>), 41.96 (CH<sub>2</sub>), 43.12 (C), 52.72 (CH), 61.35 (C), 93.89 (C), 108.05 (C), 172.48 (C).

**Fragmentation of 20.** A solution of photoadduct **20** (131 mg, 0.45 mmol) in 2 N KOH/MeOH (10 mL) was stirred at 25 °C for 18 h. The solution was diluted with water and extracted with EtOAc (40 mL). The organic solution was washed with 2 N aqueous HCl solution, dried over MgSO<sub>4</sub>, and purified by flash column chromatography with 30% EtOAc/hexane (*R<sub>f</sub>* 0.20 in 30% EtOAc/hexane) to give acid **21** (99 mg, 88% yield): IR (neat) 2935, 2860, 1722, 1705, 1385, 1240 cm<sup>-1</sup>; for major component **21-α** (C<sub>6-α</sub>) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.00–2.10 (m, 20 H), 2.45–2.52 (m, 1 H), 2.80–2.88 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 25.17 (CH<sub>2</sub>), 25.93 (CH<sub>2</sub>), 30.27 (CH<sub>2</sub>), 30.48 (two C of CH<sub>2</sub>), 33.19 (CH<sub>2</sub>), 35.04 (CH<sub>2</sub>), 38.19 (CH<sub>2</sub>), 40.91 (CH<sub>2</sub>), 47.55 (CH), 49.84 (CH), 52.15 (CH), 63.86 (C), 180.51 (C), 215.74; for minor component **21-β** (C<sub>6-β</sub>) <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 25.10, 25.92, 29.97, 30.43, 30.75, 30.82, 34.63, 36.18, 40.67, 42.05, 46.17, 50.39, 63.37, 180.64, 216.50; MS (*m/z*, rel intensity) 268 (M<sup>+</sup> + NH<sub>4</sub>, 65), 251 (M<sup>+</sup> + H, 20), 233 (100), 207 (12), 189 (9), 124 (15); exact mass calculated for C<sub>15</sub>H<sub>22</sub>O<sub>3</sub> 250.1569, found 250.1603.

**Decarboxylation of 21.** To a solution of keto acid **21-α** (70 mg, 0.28 mmol) in benzene (10 mL) was added oxalyl chloride (0.38 mL) and dimethylformamide (50 μL). The resulting solution was stirred for 1 h at 25 °C and then evaporated under reduced pressure. The crude acid chloride was dissolved in toluene (10 mL) and added dropwise to a refluxing slurry of sodium salt of 2-mercaptopyridine *N*-oxide (110 mg), DMAP (10 mg), and *tert*-butylmercaptan (0.5 mL) in THF (10 mL) for 2 h. The solution was extracted with EtOAc and washed with brine. The organic layers were evaporated under reduced pressure, and the resulting residue

was purified by flash column chromatography with 2% EtOAc/hexane (*R<sub>f</sub>* 0.45 in 5% Et<sub>2</sub>O/hexane) to give tricyclic ketone **22** (35 mg, 61% yield): IR (neat) 2945, 2860, 2254, 1719, 1477, 1456, 1375, 1085 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.00–1.20 (m, 4 H), 1.35–2.10 (m, 17 H), 2.80–2.92 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 25.16 (CH<sub>2</sub>), 25.96 (CH<sub>2</sub>), 30.42 (CH<sub>2</sub>), 30.45 (CH<sub>2</sub>), 30.50 (CH<sub>2</sub>), 30.59 (CH<sub>2</sub>), 30.74 (CH<sub>2</sub>), 34.98 (CH<sub>2</sub>), 36.10 (CH<sub>2</sub>), 41.07 (CH<sub>2</sub>), 50.28 (CH), 54.22 (CH), 63.45 (C), 216.90; MS (*m/z*, rel intensity): 206 (M<sup>+</sup>, 31), 189 (100), 178 (2), 163 (15), 149 (10), 135 (18); exact mass calculated for C<sub>14</sub>H<sub>22</sub>O 206.1671, found 206.1658.

The same procedure was applied to keto acid **21-β** (0.14 mmol). Purification by flash column chromatography with 2% EtOAc/hexane (*R<sub>f</sub>* 0.45 in 5% Et<sub>2</sub>O/hexane) gave the same tricyclic ketone **22** (17 mg, 57% yield). The <sup>1</sup>H and <sup>13</sup>C NMR spectrum were identical to the product obtained from major keto acid **21-α**.

**Preparation of Amide 23.** To a solution of keto acid **21-α** (126 mg, 0.50 mmol) in benzene (10 mL) was added oxalyl chloride (0.28 mL) and dimethylformamide (50 μL). The resulting solution was stirred for 1 h at 25 °C, and then the volatiles evaporated under reduced pressure. The crude acid chloride was dissolved in a solution of ammonium hydroxide (5 mL) in toluene (10 mL). The resulting solution was warmed to 25 °C and concentrated under reduced pressure. The residue was purified by flash column chromatography with EtOAc (*R<sub>f</sub>* 0.14 in EtOAc) to give ketoamide **23** (86 mg, 68% yield): IR (neat) 3529, 3412, 2948, 1722, 1678, 1588, 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.05–1.50 (m, 5 H), 1.52–2.16 (m, 16 H), 2.35–2.42 (m, 1 H), 2.85–2.92 (m, 1 H), 5.26 (br s, 1 H), 5.38 (br s, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 25.22, 25.94, 30.31, 30.50, 34.10, 35.06, 39.39, 40.89, 50.07, 52.29, 53.42, 63.87, 177.06, 215.82.

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**Supplementary Material Available:** X-ray crystal structure data, stereoview, and tables of atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for the crystal structure of **23** (6 pages); table of crystal structure factor data of **23** (13 pages). This material is contained in many 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.