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Studies Directed Towards the Synthesis of Taxol: Preparation of C-13 Oxygenated Taxane Congeners+

Jeffrey D. Winkler*[1] and Duvvuri Subrahmanyam

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104 USA

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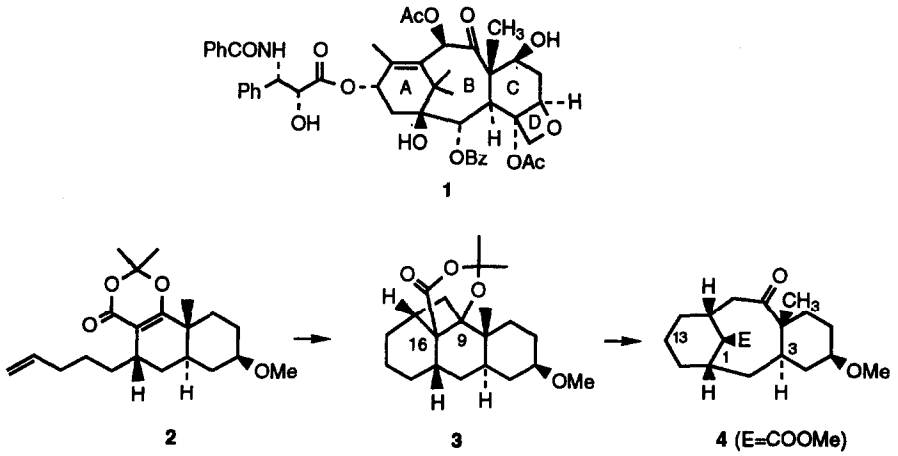
Abstract: The application of the intramolecular dioxenone photocycloaddition to the synthesis of C-13 oxygenated taxol analogs is described.

According to the National Cancer Institute, the naturally occurring diterpene ester taxol, **1**, is the most promising natural product lead in cancer chemotherapy in the last decade, with extremely promising activity against intractable ovarian cancer and other tumor systems.[2,3] Taxol is the only plant product known to promote the assembly of microtubules and inhibit the tubulin disassembly process,[4] and therefore appears to be the prototype of a new class of cancer chemotherapeutic agents as well as an important tool in cell research.

Because taxol is isolated in exceedingly low yield by extracting the bark of the Pacific yew tree,[5] a massive harvesting program has recently been undertaken to make available sufficient quantities to permit further clinical trials. However, the ecological ramifications of this harvesting program make it very undesirable. The unique mode of action of taxol, coupled with its extreme scarcity, have resulted in a prodigious effort directed towards both semi- and total synthesis of **1**.[6] While several research groups have been involved in these efforts, the synthesis of taxol remains to be achieved.

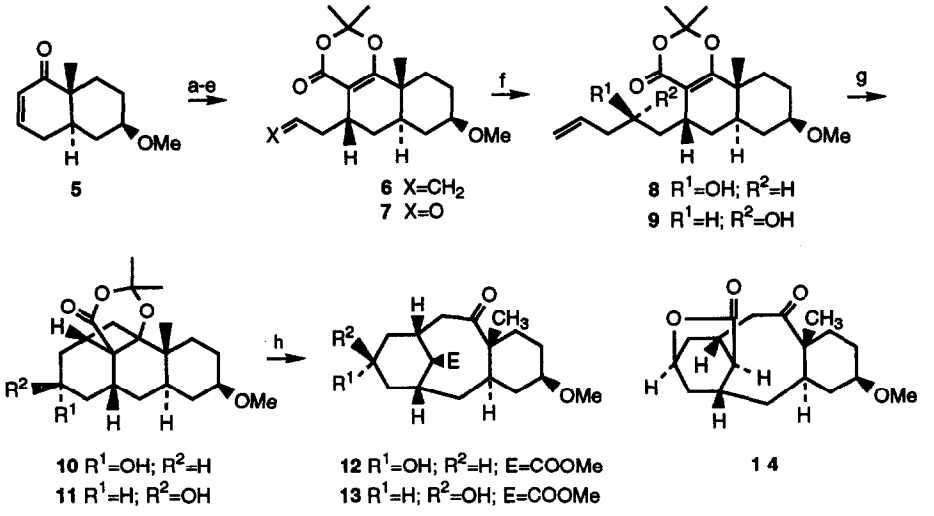


Scheme 1

+ Dedicated to Professor Ralph F. Hirschmann on the occassion of his seventieth birthday.

Previous work from our laboratories has established that the intramolecular dioxenone photocycloaddition can be applied to an efficient photoaddition-fragmentation construction of the tricyclic ring system of the taxane diterpenes (**2**→**4**), as outlined in Scheme 1.[7] Heterolysis of a bond connecting C-9 and C-16 in photoadduct **3** leads to the formation of the requisite taxane B ring in 75% overall yield from **2**. However, the product **4** lacks much of the functionality found in taxol, **1**. Of special note is the C-13 A-ring oxygen functionality, the point of attachment of the side chain ester that is critical for biological activity.

The recent report by Blechert describing the restriction of tubulin depolymerization by a fully saturated, non-oxetane containing taxane analog[8] promoted us to examine the incorporation of the C-13 hydroxyl and the attachment of the taxol side chain to **4**. Towards that end, the extension of our earlier work to the synthesis of the C-13 oxygenated analog of **4** was examined, as outlined in Scheme 2.



a) CH_2=CH-CH_2TMS, $TiCl_4$, CH_2Cl_2 (65%); b) LDA, MeOCOCN, THF (90%); c) p-$MeOC_6H_4CH_2OH$, DMAP, toluene (90%); d) Me_2CO, TFA, TFAA (50%, based on recovered ketone); e) O_3, Ph_3P, CH_2Cl_2 (70%); f) CH_2=CH-CH_2TMS, $TiCl_4$, CH_2Cl_2 (75%); g) hv (75%); h) 1. KOH, MeOH ; 2. CH_2N_2 (82% overall yield);

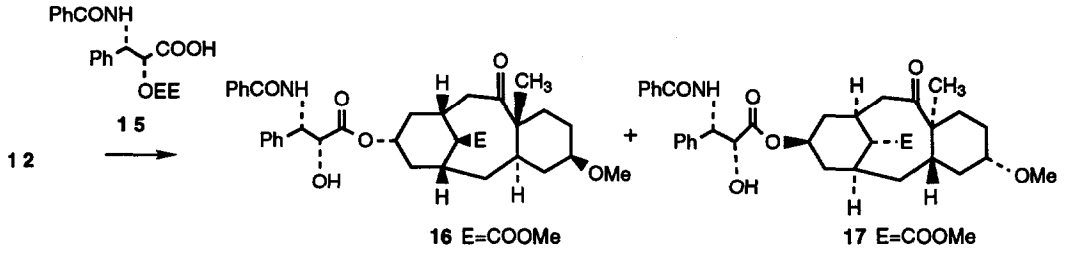
Scheme 2

Addition of allyltrimethylsilane to **5** ($TiCl_4$, dichloromethane, 65%), followed by carbomethoxylation (LDA, MeOCOCN, THF, 90%), transesterification with p-methoxybenzyl alcohol (DMAP, toluene, 90%), and condensation with acetone (TFA, TFAA, 50% based on recovered ketone) led to the formation of the requisite dioxenone, **6**. Selective ozonolysis of the terminal alkene of **6** (dichloromethane, Ph_3P workup) gave the aldehyde, **7** (X=O), in 70% yield. Treatment of **7** with allyltrimethylsilane ($TiCl_4$, dichloromethane, 75%) gave the photosubstrate **8/9** as a 3:1 mixture of C-13 (taxol numbering) epimers that could be separated by flash chromatography.

A significant difference in the efficiency of the photocycloaddition of the two epimers was observed. While irradiation of **8** [0.05M acetonitrile/acetone (9:1), 450W Hanovia lamp, pyrex filter, 30 min] led to the formation of **10** in 75% yield, reaction of **9** under identical conditions led to photoadduct **11** in 45% yield.

However, protection of the pro C-13 hydroxyl as the corresponding tert-butyldimethylsilyl ether led to photocycloaddition of both epimeric silyl ethers in excellent (70-80%) yield.

More striking was the difference observed on fragmentation of the epimeric photoadducts **10** and **11**. Treatment of **10** with 2N KOH in MeOH at 25°C led to the formation of **12** as a single diastereomer. However, treatment of **11** under the same conditions gave a 1:1 mixture of **13** and lactone **14**, establishing the cis relative stereochemical relationship of the C-13 hydroxyl and the C-16 ester in **13**, and therefore the trans relative stereochemistry of these functionalities in the epimeric photoaddition/fragmentation product **12**.[9]



16 E=COOMe **17** E=COOMe

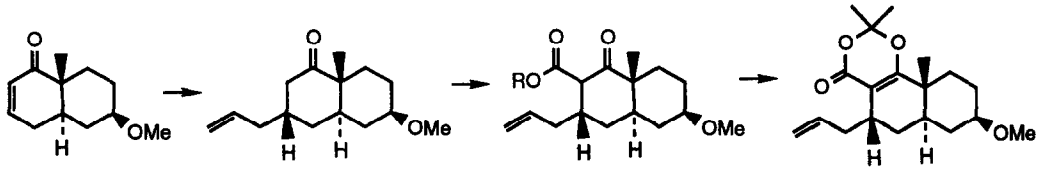
Scheme 3

It has been established by Kingston that the A-ring side chain is required for the biological activity of taxol, **1**.[2b] Attachment of the requisite side chain acid **15**[10] to **12** under conditions described by Swindell[11] [4.5 equiv **15**, 6 equiv dipyridiylcarbonate, cat. DMAP, toluene, 60°C, 12h, 65%] led, after removal of the ethoxyethyl protecting group (0.5% HCl, aq. EtOH, 70%), to the formation of diastereomeric esters **16** and **17**, that could be separated by HPLC (30% EtOAc/CH_2Cl_2). Subjection of the C-13 epimer **13** to the same conditions for side-chain attachment led to the exclusive formation of the lactone **14**, again a consequence of the cis stereochemistry of the hydroxyl and ester functionalities in **13**. In summary, the intramolecular dioxenone photocycloaddition leads to the efficient formation of C-13 hydroxylated tricyclic taxane analogs. Both cytotoxic and tubulin binding assays with **16** and **17** are currently underway and our results will be reported in due course.

Acknowledgments. Financial support from the National Institutes of Health, Glaxo and American Cyanamid is gratefully acknowledged.

EXPERIMENTAL PROCEDURES

Dioxenone **6**.



5 **i** **ii** R=Me **iii** R=p-anisyl **6**

Allyl ketone **i**: To a solution of enone **5** (3 g, 15.4 mmol) in dichloromethane (50 mL) under N_2 atmosphere at -78°C was added 4 equiv $TiCl_4$ (1M in dichloromethane). The resulting solution was stirred at -78°C for 20 min, and then treated with 2.5 equiv allyl trimethylsilane. The reaction mixture was then warmed to -50°C with continuous stirring over 2 h. The resulting solution was then slowly added to an aqueous solution of 10% $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure and purification of the residue by flash chromatography using a gradient of 5-10% ethyl acetate/petroleum ether furnished the allyl ketone **i** (2.25 g, 75%).

IR (neat): 2934, 1706, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 5.80-5.61 (m, 1H), 5.08-4.95 (m, 2H), 3.34 (s, 3H), 3.20-3.14 (m, 1H), 2.76 (dd, J = 6.1, 14.2 Hz, 1H), 2.28-1.19 (m, 13H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 215.16, 136.05, 116.52, 78.70, 55.49, 47.31, 41.42, 38.22, 37.29, 34.19, 32.92, 30.98, 30.41, 26.4, 15.27. Exact mass calculated for $C_{15}H_{24}O_2$ 236.1776, found 236.1777.

Ester **ii**: To a solution of diisopropylamine (2.3 mL, 1.8 equiv) in 10 mL of dry THF at -10°C under N_2 atmosphere was added n-BuLi (1.6M in hexanes, 1.2 equiv, 7 mL) and the resulting solution stirred for 20 min at -10°C. The reaction mixture was then cooled to -78°C and treated with ketone **i** (2.2 g, 9.3 mmol) in 20 mL of THF. The resulting solution was then warmed to -10°C over 30 min and stirring was then continued for 1h at -10°C. After cooling back to -78°C and stirring for an additional 15 min, the reaction mixture was treated with hexamethylphosphoramide (1 equiv, 1.6 mL). Methyl cyanoformate (1.1 equiv, 0.8 mL) was then added to the reaction mixture and stirring was continued at -78°C for 1h. The resulting solution was partitioned between diethyl ether and brine. Concentration of the ethereal layer afforded the methyl ester **ii** (2.5 g, 90%).

IR (neat): 2936, 1746, 1709, 1642, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz): δ 12.54 (s, enol, 1H), 5.80-5.60 (m, 1H), 5.11-4.98 (m, 2H), 3.75 (s, 3H), 3.32 (s, 3H), 3.11-3.20 (m, 2H), 2.55 (m, 1H), 2.30 (m, 1H), 1.20-2.12 (m, 10H), 1.15 (s, 3H).

p-Anisyl Ester **iii**: To a solution of ester **ii** (2.5 g, 8.5 mmol) in 40 mL of dry toluene was added p-anisyl alcohol (1.1 equiv, 1.29 g) and a catalytic amount of dimethylaminopyridine. The resulting solution was heated to reflux under a Dean-Stark apparatus for 16 h. Evaporation of volatiles and purification of the residue by flash chromatography (5% ethyl acetate/petroleum ether) provided the p-anisyl ester **iii** (2.4g, 90%).

IR (neat): 2936, 1741, 1708, 1604, 1229, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 8.50 (s, enol, 1H), 7.31 (d, J = 8.69Hz, 2H), 6.88 (d, J = 8.71 Hz, 2H), 5.8-5.61 (m, 1H), 5.14 (q, J = 9.5 Hz, 2H), 5.11-4.86 (m, 2H), 3.81 (s, 3H), 3.36 (s, 3H), 3.29-3.11 (m, 1H), 2.61-2.51 (m, 1H), 2.39-3.22 (m, 1H), 2.14-1.18 (m, 10H), 1.11(s, 3H).

Dioxenone **6**: To a solution of anisyl ester **iii** (15.5 g, 38 mmol) in acetone (90 equiv, 240 mL) at -70°C under N_2 atmosphere was added trifluoroacetic anhydride (10 equiv, 30 mL). The resulting solution was stirred for 30 min at -70°C and then freshly distilled trifluoroacetic acid (65 equiv, 208 mL) was introduced to the above solution over a period of 1h. The resulting mixture was then allowed to warm to 25°C over 2 h. After stirring

at 25°C for 65 h, the resulting solution was concentrated under reduced pressure with the final traces of trifluoroacetic acid removed under high vacuum. The residue was then purified by flash chromatography (0-5% ethyl acetate in dichloromethane gave dioxenone **6** (3 g, 25%) and the decarboxylated allyl ketone **i** (2.2 g, 25%).

IR (neat): 2937, 1723, 1630, 1388, 1270, 1108 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 5.91-5.74 (m, 1H), 5.10-4.96 (m, 2H), 3.37 (s, 3H), 3.29-3.16 (m, 1H), 2.79-2.64 (m, 1H), 2.60-2.45 (m, 1H), 2.20-1.14 (m, 10H), 1.638 (s, 3H), 1.634 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz) : δ 171.23, 162.08, 137.30, 116.34, 104.67, 103.86, 78.95, 55.79, 38.62, 37.61, 35.40, 32.80, 31.57, 31.04, 27.49, 27.01, 26.10,23.86, 16.81. Exact mass calculated for $C_{19}H_{28}O_4$ 320.1987, found 320.1929.

Aldehyde **7**:

A solution of dioxenone **6** (3 g, 6.2 mmol) in dichloromethane containing a few crystals of Sudan Red was cooled to -70°C. Ozone was bubbled through the resulting solution until the solution became colorless. The solution was then purged with O_2 for 5 min at -70°C. The reaction mixture was then treated with triphenyl phosphine (1.1 equiv, 1.9 g) and the resulting solution warmed to 25°C with stirring for 12 h. Evaporation of volatiles under reduced pressure and purification of the residue by flash chromatography (0-10% ethyl acetate/dichloromethane) gave the aldehyde **7** (2.1 g, 70%).

IR (neat): 3040, 2940, 2740, 1720, 1630, 1390, 1204, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 9.77 (br s, 1H), 3.35 (s, 3H), 3.30-3.11 (m, 1H), 2.95-2.85 (m, 1H), 2.49-2.36 (m, 1H), 2.05-1.19 (m, 10H), 1.64 (s, 6H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 201.63, 171.03, 161.84, 105.11, 102.01, 78.70, 55.78, 48.28, 37.57, 35.48, 32.47, 31.27, 29.36, 26.85, 26.26, 25.12, 24.70, 16.62. Exact mass calculated for $C_{18}H_{26}O_5$: 322.1780, found 322.1777.

Alcohols **8** and **9** (C-13 epimers):

To a solution of aldehyde **8** (2.1 g, 6.5 mmol) in 60 mL of dichloromethane at -70°C was added $TiCl_4$ (1M in dichloromethane, 5 equiv, 32 mL) dropwise. After stirring the resulting reddish brown reaction mixture at -70°C for 20 min, allyl trimethylsilane (4 equiv, 3.2 mL) was added. Stirring was continued at -70 to -50° C for 1 h and the reaction mixture was then quenched with a solution of 5% aqueous $NaHCO_3$. The reaction mixture was extracted with diethyl ether, and the ethereal extract washed with water, brine, and then dried over $MgSO_4$. Evaporation of volatiles followed by purification of the residue by flash chromatography (10-20% ethyl acetate/dichloromethane) afforded alcohols **8** and **9** (3:1 ratio) in 78% yield.

Alcohol **8**: IR (neat) : 3400, 3050, 2950, 1720, 1630, 1380, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 6.0-5.79 (m, 1H), 5.16-5.05 (m, 2H), 3.68-3.50 (m, 2H), 3.36 (s, 3H), 3.30-3.18 (m, 1H), 2.95-2.85 (m, 1H), 2.27 (t, J = 6.25 Hz, 2H), 2.05-1.25 (m, 11H), 1.66 (s, 3H), 1.64 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 171.74, 163.40, 134.99, 116.78, 104.35, 103.49, 78.53, 68.58, 55.47, 43.60, 41.28, 37.65, 35.53, 32.39, 31.39, 30.45, 27.81, 26.78, 26.25, 22.80, 16.73. Exact mass calculated for $C_{21}H_{32}O_5$: 365.2327, found 365.2328.

Alcohol **9:** IR (neat) : 3380, 3050, 2950, 1720, 1630, 1370, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 6.0-5.81 (m, 1H), 5.21-5.09 (m, 2H), 3.80-3.69 (m, 2H), 3.40 (s, 3H), 3.34-3.20 (m, 1H), 2.95-2.84 (m, 1H), 2.28 (t, J = 6.25Hz, 2H), 2.10-1.22 (m, 11H), 1.70 (s, 3H), 1.67 (s, 3H),1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 170.71, 162.46, 134.75, 116.80, 104.67, 103.99, 78.52, 68.89, 55.41, 42.38, 41.92, 37.30, 35.43, 32.54, 31.06, 29.03, 27.84, 26.59, 25.18, 24.15, 16.35. Exact mass calculated for $C_{21}H_{32}O_5$: 365.2327; found 365.2330.

Photoadduct **10**:

A solution of alcohol **8** (970 mg, 2.66 mmol) in 1 liter of 9:1 acetonitrile/acetone was placed in a Pyrex immersion well and degassed by bubbling a stream of N_2 gas through the solution for 15 min. The resulting solution was then irradiated using a 450W Hanovia medium pressure lamp for 25 min with continuous bubbling of N_2 gas. Removal of solvent under reduced pressure and purification of the residue by flash chromatography (50% ethyl acetate/dichloromethane) furnished the photoadduct **10** (725mg, 75%).

m.p. (CH_2Cl_2): 183°C. IR (CCl_4): 3460, 2960, 1730, 1460, 1380, 1270, 1100, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 4.0-3.80 (m, 1H), 3.35 (s, 3H), 3.18-3.04 (m, 1H), 2.92-2.73 (m, 2H), 2.40-2.09 (m, 3H), 1.96-1.04 (m, 13H), 1.80 (s, 3H), 1.57 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 173.04, 105.84, 84.85, 78.91, 65.86, 55.53, 42.12, 39.12, 38.44, 35.38, 35.31, 34.21, 33.65, 33.15, 31.48, 31.21, 30.46, 29.42, 28.54, 26.69, 14.95.

Photoadduct **11**:

A solution of alcohol **9** (345 mg, 0.95 mmol) in 250 mL of 9:1 acetonitrile/acetone was placed in a Pyrex immersion well and degassed by bubbling a stream of N_2 gas through the solution for 15 min. Then, the solution was irradiated using 450W Hanovia medium pressure lamp for 30 min with continuous bubbling of N_2 gas. Removal of solvent under reduced pressure and purification of the residue by flash chromatography (70% ethyl acetate/dichloromethane) furnished the photoadduct **11** (148 mg, 45%).

IR (CCl_4): 3450, 2960, 1730, 1460, 1370, 1270, 1120, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 4.05-3.91 (m, 1H), 3.35 (s, 3H), 3.20-2.85 (m, 4H), 2.61 (br s, 1H), 2.38-2.12 (m, 3H), 2.01-1.52 (m, 5H), 1.81 (s, 3H), 1.57 (s, 3H), 1.35-1.00 (m, 6H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 173.57, 105.90, 84.23, 78.76, 63.03, 55.47, 41.07, 40.56, 38.38, 35.30, 34.74 (2C), 34.35, 33.15, 32.48, 31.42, 30.36, 28.41, 28.11,26.70, 14.32.

Ketoester **12**:

A solution of photo-adduct **10** (400 mg, 0.9 mmol) in 6 mL 2 N methanolic potassium hydroxide was stirred under nitrogen atmosphere at 25°C for 12 h. The methanol was evaporated under reduced pressure and the resulting residue diluted with water and acidified with 10% aqueous HCl to pH 2. The resulting aqueous solution was then thoroughly extracted with chloroform. The organic layer was then washed with brine and dried ($MgSO_4$). The residue obtained after evaporation of volatiles was dissolved in diethyl ether and treated with diazomethane. Evaporation of volatiles followed by purification of the residue by flash chromatography

(80% ethyl acetate/dichloromethane) led to the tricyclic ketoester **12** (305mg, 82%).

m.p. (CH_2Cl_2): 152°C. IR (CCl_4): 3360, 2950, 1740, 1700, 1460, 1200, 1110, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 4.05-3.90 (m, 1H), 3.64 (s, 3H), 3.36 (s, 3H), 3.30-3.05 (m, 2H), 2.85-2.70 (m, 2H), 2.50-2.20 (m, 3H), 2.02-1.65 (m, 7H), 1.45-1.12 (m, 5H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 218.41, 175.51, 78.70, 64.97, 55.57, 52.00, 50.65, 44.09, 41.68, 38.12, 37.25, 35.50, 34.56, 33.98, 32.49, 32.01, 30.98, 26.15, 12.80. Exact mass calculated for $C_{19}H_{30}O_5$: 339.2171 (m+1), found 339.2153.

Ketoester **13** and Lactone **14**:

A solution of photoadduct **11** (140 mg, 0.38 mmol) in 4 mL 2 N methanolic potassium hydroxide was stirred under nitrogen atmosphere at 25°C for 12 h. Following the procedure outlined above for the preparation of **12**, there was obtained lactone **14** (42 mg, 36%) and ketoester **13** (43 mg, 30%).

Ketoester **13**: IR (CCl_4): 3360, 2950, 1740, 1700, 1460, 1200, 1120, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 4.35-4.15 (m, 1H), 3.65 (s, 3H), 3.38 (s, 3H), 3.32-3.15 (m, 1H), 2.99 (m, 1H), 2.75-2.65 (m, 1H), 2.48-1.15 (m, 16H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 217.56, 175.07, 78.79, 64.24, 55.70, 52.00, 51.56, 43.89, 40.18, 38.53, 37.59, 37.27, 37.21, 35.86, 34.04, 32.25, 31.48, 25.99, 12.69. Exact mass calculated for $C_{19}H_{30}O_5$: 339.2171 (m+1), found 339.2169.
Lactone **14**: IR (neat): 2950, 1750, 1700, 1450, 1370, 1220, 1010, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 250MHz): δ 4.82-4.75 (m, 1H), 3.37 (s, 3H), 3.35-3.20 (m, 1H), 2.90-2.81 (m, 1H), 2.71-2.53 (m, 2H), 2.39-1.21 (m, 15H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 250MHz): δ 215.65, 176.07, 78.79, 75.06, 55.76, 50.74, 43.14, 40.42, 37.02, 36.40, 36.35, 34.34, 33.57, 32.77, 28.48, 27.62, 25.98, 12.55. Exact mass calculated for $C_{18}H_{26}O_4$: 306.1831, found 306.1862.

Esters **16** and **17**:

A solution of tricyclic alcohol **12** (50 mg, 0.15 mmol), acid **15** (250 mg, 4.5 equiv), dipyridylcarbonate (150 mg, 6 equiv) and dimethylaminopyridine (30 mg, 2 equiv) in 6 mL dry toluene was heated to 70°C for 16h with continuous stirring under an atmosphere of N_2. The toluene was evaporated under reduced pressure, and the residue partitioned between chloroform and water. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of volatiles followed by purification of the residue by flash chromatography (0-10% ethyl acetate/dichloromethane) gave a mixture of diastereomeric esters (56 mg, 56%). This mixture of diastereomers was dissolved in 3 mL of absolute ethanol, treated with 0.5 mL of 0.1% aqueous HCl, and stirred at 25°C for 2 h. The reaction mixture was treated with 5% aqueous $NaHCO_3$ solution and the resulting mixture extracted with chloroform. The organic layer was washed with water, brine and then dried over $MgSO_4$. Evaporation of volatiles, followed by purification of the residue by flash chromatography (30% ethyl acetate/dichloromethane) afforded a mixture of diastereomeric esters **16** and **17** (30 mg, 67%). HPLC purification of this mixture (30% ethyl acetate/dichloromethane, flow rate: 4 mL/min) afforded the separated esters **16** and **17**.

Faster running isomer. IR (CCl_4): 3380, 3060, 2960, 1735, 1695, 1670, 1605, 1590, 1200, 1010, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz): δ 7.76 (d, J = 8.0 Hz, 2H), 7.58-7.28 (m, 8H), 7.01 (d, J = 9.5 Hz, 1H), 5.82

(dd, J = 2, 9.5 Hz, 1H), 5.14-5.04 (m, 1H), 4.63 (br s, 1H), 3.63 (s, 3H), 3.38 (br s, 1H), 3.35 (s, 3H), 3.25-3.16 (m, 1H), 3.05 (t, J = 11.5 Hz, 1H), 2.80-2.62 (m, 2H), 2.39-2.31 (m, 2H), 2.27 (t, J = 11.3 Hz, 1H), 2.01-1.10 (m, 12H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 500MHz): δ 217.92, 175.26, 172.22, 166.78, 138.59, 134.12, 131.90, 128.71, 128.69, 127.87, 126.96(2C), 126.93(2C), 126.86(2C), 78.58, 73.31, 71.62, 55.73, 54.52, 52.18, 50.74, 43.98, 41.85, 37.84, 37.30, 35.50, 34.74, 32.44, 30.57, 30.29, 27.72, 26.18, 12.94. Exact mass calculated for $C_{35}H_{43}O_8N$: 606.3067 (m+1); found 606.3097.

Slower running isomer. IR (CCl_4): 3370, 3060, 2960, 1735, 1695, 1675, 1605, 1590, 1220, 1010, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz): δ 7.74 (d, J = 8.0 Hz, 2H), 7.52-7.27 (m, 8H), 6.99 (d, J = 9.5 Hz, 1H), 5.82 (d, J = 9.5 Hz, 1H), 5.13-5.04 (m, 1H), 4.62 (br s, 1H), 3.63 (s, 3H), 3.38 (br s, 1H), 3.35 (s, 3H), 3.25-3.18 (m, 1H), 3.07 (t, J = 11.5 Hz, 1H), 2.82-2.67 (m, 2H), 2.39-2.29 (m, 3H), 2.02-1.21 (m, 11H), 1.07 (s, 3H), 1.01-0.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 500MHz): δ 217.89, 175.29, 172.10, 166.71, 138.73, 133.99, 131.86(2C), 128.71(2C), 127.91(2C), 126.97(2C), 126.92(2C), 78.74, 73.31, 71.55, 55.75, 54.43, 52.23, 50.77, 44.02, 41.55, 38.03, 37.41, 35.69, 34.68, 32.31, 30.42, 30.25, 28.37, 26.26, 12.96. Exact mass calculated for $C_{35}H_{43}O_8N$: 606.3067 (m+1), found 606.3101.

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