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Taxane Diterpenes 1. Control of Relative and Absolute Stereochemistry in Intramolecular Pyrylium Ylide-Alkene Cyclizations for the Synthesis of Taxol Precursors.

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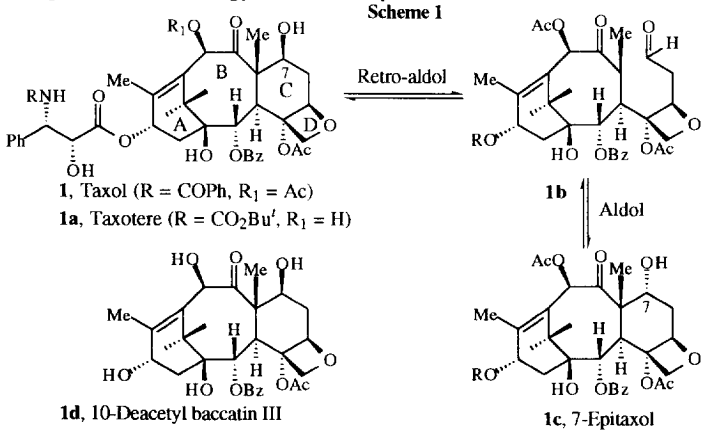
Abstract: Intramolecular pyrylium ylide-alkene cyclizations provide control of the absolute stereochemistry at the crucial C-19 angular methyl group, and leads to bicyclo[5.4.0^{3,8}]undecenones that contain the structural elements of the B/C rings of the taxanes.Copyright © 1996 Elsevier Science Ltd

Introduction

While the taxus diterpenes have been a popular target for total synthesis for the past fifteen years, it is only within the last few years that the need for a practical total synthesis of TAXOL®† **1**, **Scheme 1**, has become genuinely important.[1] During the past two years three total syntheses of taxol have been reported, and a very large number of diverse strategies have been developed.[2] Extensive reviews provide the current background to the biology and chemistry of the taxanes.[3]

Scheme 1



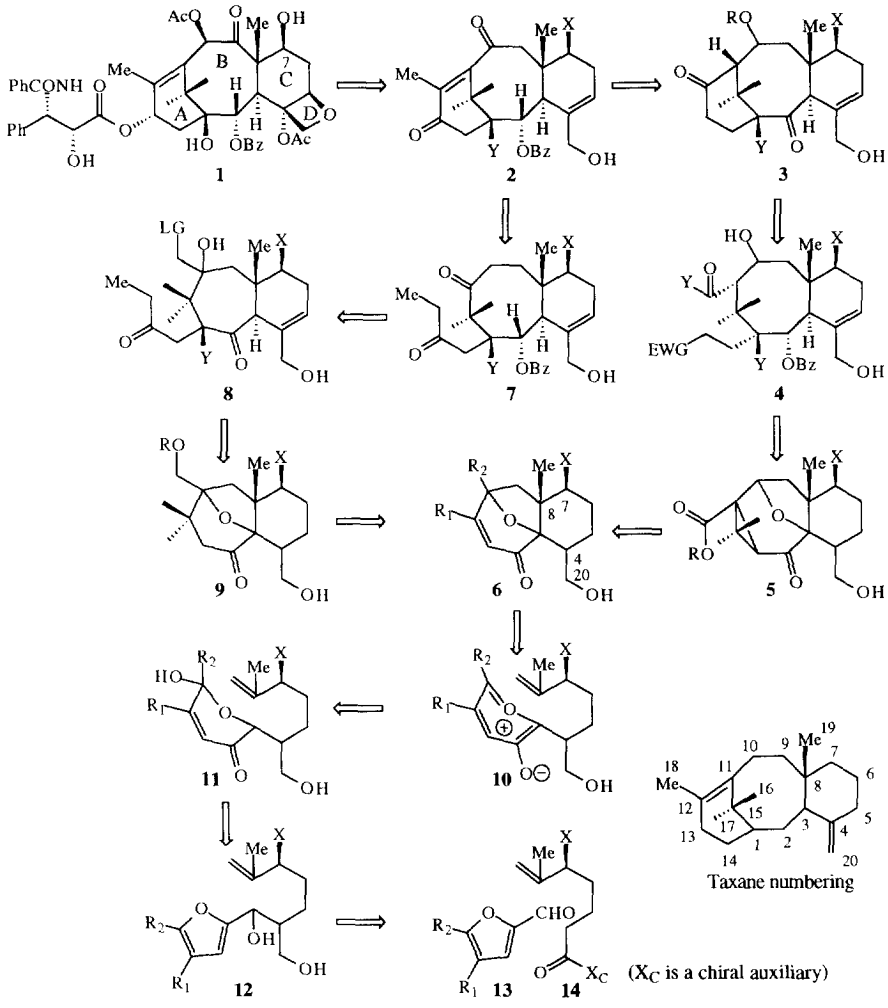
1, Taxol (R = COPh, R_1 = Ac)
1a, Taxotere (R = CO_2Bu^t, R_1 = H)
1b
1c, 7-Epitaxol
1d, 10-Deacetyl baccatin III

The structure activity relationship (SAR) studies, designed to explore the full range of tumor response to taxol chemotherapy, is limited by the scarcity of taxol itself. Taxol is isolated from the North American Yew tree, but only in very small amounts, and a very time consuming purification is required.[4] The yew tree is an environmentally protected species and cannot be considered a permanent source of taxol. It has been reported that 10-deacetyl baccatin III **1d**, isolated from pine needles (a readily renewable source), can be converted into taxol.[5] Taxol is not particularly potent and requires dose levels of 250 mg per patient, although the N-Boc derivative TAXOTERE® **1a** is more potent.[6]

Overall Strategy

At first sight the synthesis of taxol **1** appears to present some formidable stereochemical problems. Traditionally, quaternary carbon atoms are the most difficult stereogenic centers to install in terpenoid synthesis. Consequently, we considered that the absolute stereochemistry of the C-19 methyl group should be established at an early stage. The *trans*-B/C-ring fusion in taxol is the thermodynamically more stable stereochemistry as evidenced by the base catalyzed retro-aldol reaction of taxol to give 7-epitaxol **1c** *via* **1b**.[7]

Scheme 2, Retrosynthetic Analysis of Taxol (X = OH or H; Y = OH or H)



Scheme 2 outlines our retrosynthetic analysis. We have considered two main strategies for the formation of the A-ring, leading to **2** or **3**. Claisen-type condensation of **4** leads to **3**, and aldol condensation of **7** leads to **2**. We reasoned that **4** can be derived from ring expansion of **5** by reductive cleavage of the internal

cyclopropane carbon-carbon bond, and in turn **5** can arise from *gem*-methylcyclopropanation of the pyranenone **6**. Alternatively, the eight-membered B-ring could be formed by a semi-pinacol rearrangement of **8** to give **7**, and **8** itself can be made from **9**, which likewise can arise from **6**. The cyclopropanation route from **6** requires $R_1 = CO_2R$ or CN and $R_2 = H$, and for the semi-pinacol rearrangement strategy $R_1 = Me$ and $R_2 = CH_2OR$. Pyranenones such as **6** are available from the intramolecular pyrylium ylide-alkene cyclization of **10** which is derived from **11**, and in turn **11** is made from **12** by the well known oxidative rearrangement process of a 2-furan carbinol.[8] Finally, compound **12** has a very simple origin; it is the aldol or Claisen product of a furfuraldehyde **13** and a 6-heptenoic acid derivative **14** (X_c = chiral auxiliary). It was also anticipated that the 3,10-oxido bridge could at some later point be manipulated by β-elimination and double bond shift *via* β,γ-isomerization, thus establishing the 4,5-double bond for construction of the oxetane D-ring.

The first phase of this strategy was to examine the relative stereochemical outcome of the pyrylium ylide-alkene cyclization in a racemic series, and use this information to devise a solution to control the absolute stereochemistry of **6**. It also poses a question whose answer was not specifically known. What are the stereochemical factors that control the pyrylium ylide-alkene cyclization of **10** to give **6**? While there has been some effective use of pyrylium ylide methodology, and the conversion of **10** into **6** would be expected to proceed in good yield, the stereochemical outcome was not evident from the published literature.[9] We have examined two series of substrates, those that include the 7-hydroxyl group (X = OR), and the 7-deoxy series (X = H).[10]

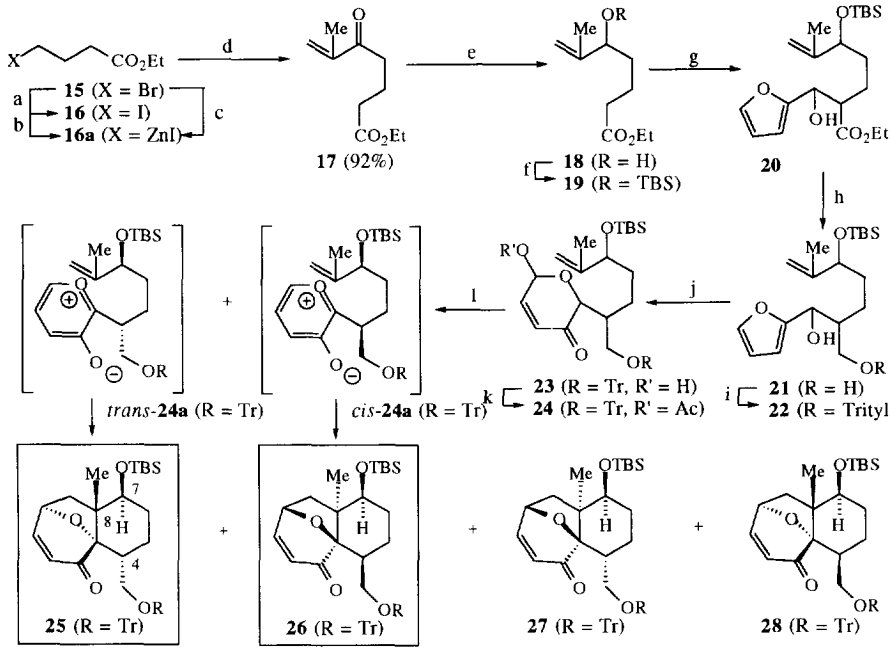
Relative Stereochemistry of the Pyrylium Ylide-Alkene Cyclization: 7-Hydroxy-Racemic Series (Scheme 3).

The starting material is ethyl 6-methyl-5-oxo-6-heptenoate **17**, and it comprises carbon atoms C-9, 8, 19, 7, 6, 5, 4 and 20 of the taxane core. The ester **17** is a known compound and is readily prepared on a large scale.[11] Commercially available ethyl 4-bromobutyrate **15** was converted into the iodide **16** (84%), and treated with a zinc-copper couple in toluene/dimethylacetamide (DMA) to generate **16a**. The intermediate organozinc reagent was treated with $Pd(PPh_3)_2Cl_2$ (0.45 mole %) and methacryloyl chloride to give **17** (92%). A more convenient procedure, that avoids the separate preparation of the iodide **16**, involves direct treatment of **15** with tetra-*n*-butyl ammonium iodide (0.25 mol)/toluene/DMA/zinc dust/Me_3SiCl/$Pd(PPh_3)_2Cl_2$ (0.085 mole%) to give **17** (97%) in a single step.[12]

The C-5 carbonyl group can be selectively reduced with sodium borohydride/cerium (III) chloride heptahydrate in ethanol to give **18** (80%).[13] Protection of **18** by treatment with DMF/imidazole/*tert*-butyldimethylsilyl chloride (TBSCl) gave **19** (82%). Use of TBSOTf/CH_2Cl_2/$EtNPr_2^i$/0-25 °C gave **19** (98%).

A solution of **19** in tetrahydrofuran at -78 °C was added to a solution of lithium diisopropylamide in tetrahydrofuran followed by addition of 2-furfural. After 20 min, lithium aluminum hydride was added and the mixture warmed to 25 °C to give the diol **21** (75%). The aldol adduct **20** can be isolated, and as expected it was a mixture of diastereoisomers. In this initial study we needed both C-4 and C-7 diastereoisomers to assess the stereochemical consequences of the pyrylium ylide-alkene cyclization. The stereochemistry at the secondary benzylic hydroxyl group in **20/21** is not important because it is destroyed in the generation of the pyrylium ylide. Tritylation of **21** with Ph_3CCl/Et_3N/DMAP/CH_2Cl_2 gave **22** (97%). Oxidative rearrangement of **22** by treatment with *tert*-butyl hydroperoxide/vanadyl acetoacetate/CH_2Cl_2 at -12 °C for 17 hours gave **23** (98%).

Scheme 3 (Racemic Series)



Conditions:-a) NaI/acetone/reflux (84%). b) Zn/Cu couple/DMA/PhMe. c) n-$Bu_4N^+I^-$/Zn dust/TMSCl/1,2-dibromoethane/PhMe/DMA/85°C/12h. d) $Pd(PPh_3)_2Cl_2$/methacryloyl chloride (92% *via* b or 97% *via* c). e) $NaBH_4/CeCl_3.7H_2O$/EtOH (80%). f) TBSCl/Imidazole/DMF/25°C/3h (82%) or TBSOTf/$NEtPr_2^i/CH_2Cl_2$ (98%). g) $LiNPr_2^i$/THF/-78°C, followed by 2-furfural (98%). h) $LiAlH_4$/THF/-78° to 25°C/3h (99%). i) Ph_3CCl/Et_3N/DMAP/CH_2Cl_2 (97%). j) *t*-BuOOH/VO(acac)2/CH_2Cl_2/-12°C/17h (98%). k) Ac_2O/PhMe/Et_3N/DMAP. l) DBU/PhMe/110°C/2h (88%, **25** and **26**, 1:1).

The hydroxypyranenone **23** in toluene was dried by azeotropic removal of water, and DMAP/Et_3N/Ac_2O was added. After stirring for 15 hours at room temperature 5-diazabicyclo[5.4.0]undecene-5 (DBU) was added and the mixture was heated for two hours at reflux to give **25** and **26** (88%, 1:1). The isomers were readily separated by fractional crystallization from methanol. The relative stereochemistry of **26** was determined by X-ray crystallography, and surprisingly, revealed that the cyclohexane ring adopted a boat conformation with both the C-4 and C-7 substituents equatorial.

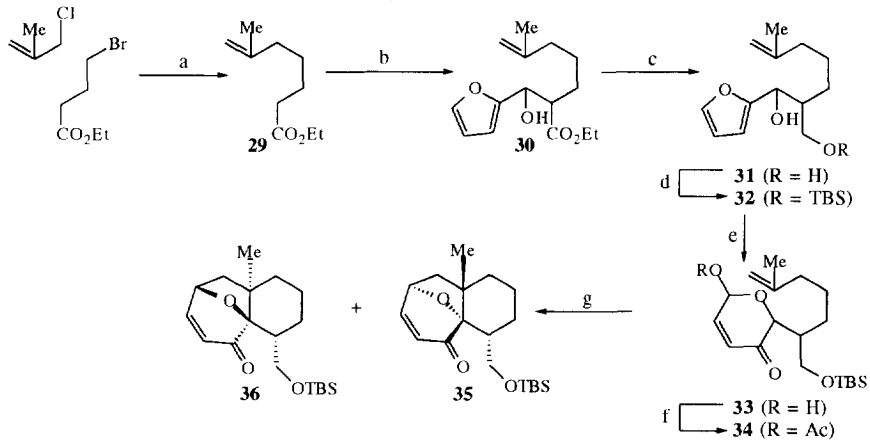
The relative stereochemistry of the other isomer **25** was also determined by X-ray crystallography of a derivative **(iii)** that was made in a series utilizing 3-methyl-2-furfural.[14] The C-ring (taxol ring) is in a chair conformation and the C-4 and C-7 substituents are equatorial. While there were minor components (<5%) that were clearly diastereomers of the major products, they were not produced in sufficient quantities to be isolated and characterized. If the diastereomers **27** and **28** are present they are at very most, minor products. The stereochemical outcome can be summarized by the following statements: a) The newly formed tetrahydrofuran ring prefers to be *cis*-fused to the cyclohexane ring; b) The angular methyl group (C-19) is *trans* to the C-4 hydroxymethyl substituent in order to minimize 1,3-diaxial interactions that would occur in the transition state and in the product.[15]

The important conclusion of this study is that the pyrylium ylide cyclization of *cis*-**24a** and *trans*-**24a**-leads to the two products that are antipodal at the crucial C-8 quaternary carbon, and as a consequence only the diastereoisomer *trans*-**24a** can result in the correct absolute stereochemistry of the taxane precursor **25** at *both C-7 and C-8*. While, of course, this conclusion was deduced from the above results in the racemic series it must hold, and does, in the optically active series.

Relative Stereochemistry of the Pyrylium Ylide-Alkene Cyclization: 7-Deoxy-Racemic Series (Scheme 4).

The absence of the 7-hydroxy group considerably simplifies the synthesis, **Scheme 4**. While **30** can be isolated, it is possible to reduce **30** *in situ* with lithium aluminum hydride to give the diol **31** in 97% overall yield. We have used three protecting groups for the primary hydroxyl group, the *tert*-butyldimethylsilyl (TBS) ether, triphenylmethyl (Tr) ether and the triisopropylsilyl ether (TIPS).

Scheme 4 (Racemic Series)



Conditions:-a) *n*-$Bu_4N^+I^-$/Zn dust/TMSCl/1,2-dibromoethane/THF/DMA/ethyl 4-bromobutanoate/24h, then add CuCN/methallyl chloride/12h/25°C, (87%). b) KN(TMS)$_2$/THF/-75°C, followed by 2-furfural/45min. c) $LiAlH_4$/25°C/12h, (97%). d) TBSCl/Imidazole/DMF/25°C/14h (81%). e) *t*-BuOOH/VO(acac)$_2$/CH_2Cl_2/-12°C/14h (94%). f) Ac_2O/CH_2Cl_2/Et_3N/DMAP (84%). g) DBU/PhMe/110°C/1h (78%, **35** and **36**, 4:1).

The hydroxypyranenone **33** was converted into the acetate **34** (84%), and subsequently heated in toluene containing DBU at 110°C for 14 h. The enones **35** and **36** were isolated as a pale yellow solid (78%), (mixture of diastereomers 4:1). This sequence provides **35** in seven discrete reactions. The conversion of **30** into the diol **32** can be carried out in a single reaction vessel, as can the transformation of **33** into **35**.

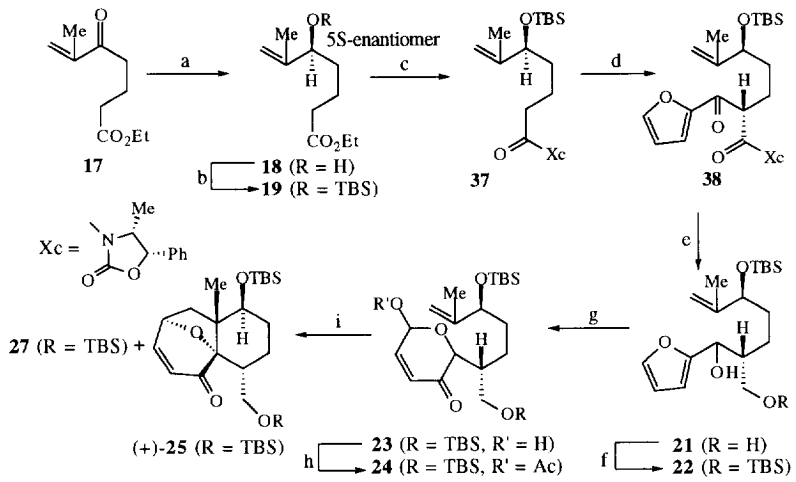
Absolute Stereochemistry of the Pyrylium Ylide-Alkene Cyclization: 7-Hydroxy- Enantio-Enriched Series (Scheme 5).

To control the absolute stereochemistry in the pyrylium ylide-alkene cyclization the stereogenic centers at C-4 and C-7 must be fixed. The secondary alcohol (C-7) should be available by asymmetric catalytic reduction

of the α,β-unsaturated ketone **17**. The more difficult stereogenic center at C-4 can be established by using a chiral auxiliary, with the important proviso that it can be conveniently recycled.

Reduction of the enone carbonyl group in **17** with borane-dimethylsulfide in tetrahydrofuran in the presence of a catalytic amount of the chiral reagent (S)-(-)-diphenyl-2-pyrrolidino methanol oxazaborole gave (**5R**)-**18** (89%) (**Scheme 5**).[16] The enantiomeric excess is >93% as judged from the ^{1}H NMR spectrum of the derived Mosher ester. The (R)-(-)-diphenyl-2-pyrrolidino methanol oxazaborole catalyst gave the (**5S**)-**18** enantiomer, which corresponds to the natural absolute configuration at the C-7 secondary hydroxyl group in taxol.[17] The enantioselective reduction has been scaled-up to >100 g without any discernible loss of yield or enantiomeric excess, and the chiral catalyst was recovered and recycled.

Scheme 5 (Chiral Series)



Conditions:-a) $BH_3.SMe_2$/(*R*)-(-)-diphenyl-2-pyrrolidino methanol oxazaborole (cat)/THF/-20°C/18h, (89%). b) TBSCl/Imidazole/DMF/25°C/4h (86%). c) i. NaOH/Me_2CHOH/82°C ii. $(COCl)_2$/PhMe/CH_2Cl_2/DMF (cat)/-10°C to 25°C/12h. iii. LiXc/THF/PhMe/-78°C/4h (99% from **18**). d) $LiN(TMS)_2$/THF/-78°C/2h, followed by 2-furoyl chloride/4h, (100%) e) $LiBH_4$/MeOH/-20 to 0°C/12h (85%, from **37**). f). TBSCl/Imidazole/DMF/-18°C/1h (87%). g) $^1O_2$/rose bengal/MeOH/CH_2Cl_2/hv/12h, Me_2S work-up (80%). h) Ac_2O/Et_3N/DMAP/CH_2Cl_2/0°C to 25°C/0.75h (91%). i) DBU/PhMe/110°C/1.5h (77%), **25/26** (10:1).

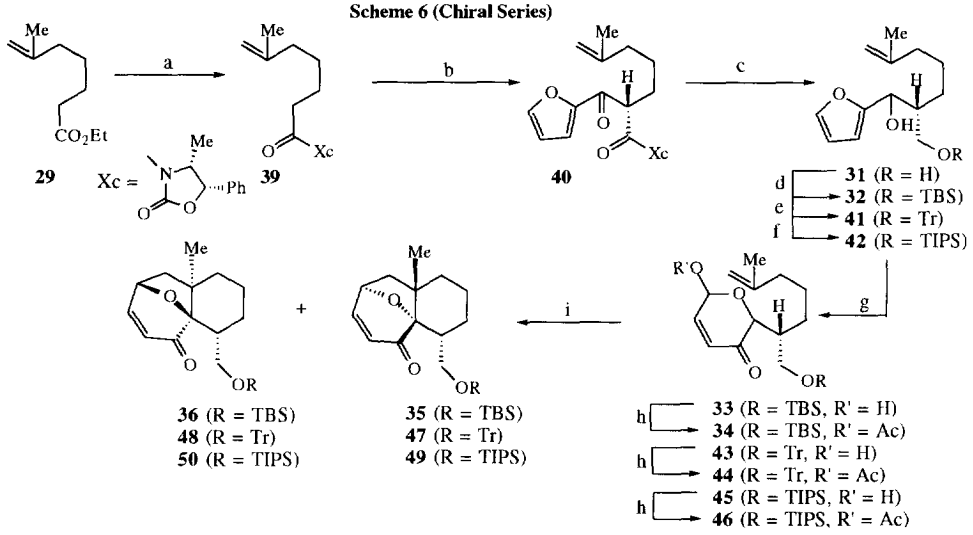
While there are a large number of chiral auxiliaries that could be used, we required an inexpensive one that is readily available in large amounts and can be recycled. The most suitable choice was the oxazolidinone prepared from (1S,2R)-(+)-norephedrine.

The alcohol **18** was converted into the protected derivative **19** (86%). Hydrolysis of the ester **19** gave the acid (sodium salt), which was directly treated with oxalyl chloride followed by *N*-lithio-oxazolidinone (Xc) resulting in **37** (99%). Treatment of **37** with lithium bis(trimethylsilyl)amide in tetrahydrofuran at -78 °C and quenching the resulting amide enolate with 2-furoyl chloride gave **38**.[18] It is not necessary to isolate **38**. It can be reduced *in situ* by the addition of lithium borohydride and methanol to give the diol **21** (85%) in a single operation. The chiral auxiliary was recovered and recycled (80-90%).

The diol **21** was converted into (+)-**25** *via* **22**, **23** and **24** exactly as in the racemic series. The absolute configuration of (+)-**25** was confirmed by comparison of the CD curve with an analogue, whose absolute stereochemistry was determined by X-ray crystallography (see ref. 17).

Absolute Stereochemistry of the Pyrylium Ylide-Alkene Cyclization: 7-Deoxy- Enantio-Enriched Series (Scheme 6).

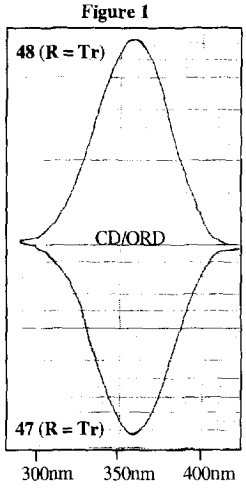
Scheme 6 (Chiral Series)



Conditions:-a) i. NaOH/Me_2CHOH/82°C ii. $(COCl)_2$/PhMe/Et_2O/DMF (cat)/-10°C to 25°C/12h. iii. LiXc/THF/-78°C/4h (92% from **29**). b) LiN$(TMS)_2$/THF/-78°C/2h, followed by 2-furoyl chloride/2h. c) $LiBH_4$/MeOH/-20 to 0°C/12h (81%, from **39**). d) TBSCl/Imidazole/DMF/-18°C/1h (92%). e) TrCl/DMAP/Et_3N/CH_2Cl_2/25°C/3days, (90%). f) TIPSCl/DMF/imidazole/-10°C/10h, (91%). g) $^1O_2$/rose bengal/CH_2Cl_2/hν/12h/-50°C, Me_2S work-up **33** (78%), **43** (75%) and **45** (80%). h) Ac_2O/Et_3N/DMAP/CH_2Cl_2, **34** (96%), **44** (96%) and **46** (97%). i) DBU/PhMe/110°C/1.5h (77%, **35** and **36**, 4:1), (75%, **47** and **48**, 8:1) and (83%, **49** and **50**, 5:1).

Hydrolysis of the ester **29** gave the acid (sodium salt), which was directly treated with oxalyl chloride followed by *N*-lithio-oxazolidinone resulting in **39** (90%), **Scheme 6**. Treatment of **39** with lithium bis(trimethylsilyl)amide in tetrahydrofuran at -78 °C and quenching the resulting amide enolate with 2-furoyl chloride gave **40**. It is not necessary to isolate **40**, it can be reduced *in situ* by the addition of lithium borohydride and methanol to give the diol **31** (81%) in a single operation. The chiral auxiliary was recovered and recycled. The diol **31** was converted into its TBS-ether **32**, trityl ether **41** and TIPS-ether **42** respectively. The ethers **32**, **41** and **42** were subsequently transformed into the pyrylium ylide cyclization precursors **34**, **44** and **46**, *via* **33**, **43** and **45**. Treatment of each under the usual cyclization conditions (DBU/PhMe/110°C) gave the respective adducts **35/36** (4:1, identical to the racemic series), **47/48** (8:1) and **49/50** (5:1). In the trityl ether series it was possible to separate **47** and **48** by fractional crystallization. **Figure 1** shows the CD curves, and convincingly demonstrates that the helicity of the enone chromophore in **47** and **48** have a mirror image relationship. This is in agreement with the conclusion drawn from the racemic series, **Scheme 3**.

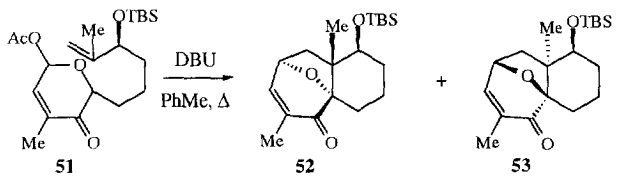
Figure 1



While the trityl series gave the best ratio of enones and they were readily separable, in subsequent reactions (see accompanying paper) it proved incompatible with the reductive cleavage of a cyclopropane. Consequently, we were left with two options: Remove the trityl group at a later stage and replace it with, for example, a -TBS group; or forgo the better diastereomer ratio and use the -TBS and -TIPS ethers **35/36** and **49/50** directly. As the accompanying paper will indicate, we have exercised both options.

The above results clearly show that the absence of the 7-hydroxyl substituent has a detrimental influence on the diastereomer ratio in the pyrylium ylide-alkene cyclization. In order to ascertain the contribution made by the 7-substituent we synthesized the substrate **51** (derived from 3-methylfurfural) and subjected it to the usual pyrylium ylide-alkene cyclization conditions. The two adducts **52** and **53** were isolated in a combined 77% yield and 2.5 to 1 ratio.[19]

Scheme 7



51 **52** **53**

In summary, the diastereoselectivity of the pyrylium ylide-alkene cyclization increases from 2.5:1 (7-OTBS, no C-4) to 4:1 (4-CH_2OTBS, no C-7) to 10:1 (7-OTBS and 4-CH_2OTBS). The larger the protecting group on the C-20 hydroxyl group the greater the diastereoselectivity. With these taxane B/C ring precursors available through the routes outlined above, the next step was to investigate ring expansion of the seven-membered ring to an eight-membered ring and the construction of the A-ring. This is described in the following paper.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer either neat or in $CHCl_3$ as indicated. Proton NMR spectra were recorded on a GE-300 MHz spectrometer in the indicated solvent, and are reported in ppm downfield from TMS. Low resolution chemical ionization (CI) mass spectra were obtained on a TSQ 70 instrument, and the exact mass determinations were obtained on a VG analytical ZAB2-E instrument. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Preparative layer chromatography was performed using Merck 60H F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel.

Air and moisture sensitive reactions were performed using usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in flame-dried glassware or in an oven at 140°C, then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified

before use. Et_2O and THF were distilled from sodium benzophenone ketyl under argon; dichloromethane and benzene were distilled from calcium hydride under nitrogen.

Ethyl 6-methyl-5-oxo-6-heptenoate 17. To a stirred solution of **16**[20] (507 g, 2.1 mol) in toluene (2.0 L) and *N,N*-dimethylacetamide (250 mL) was added zinc-copper couple (295 g, 4.5 mol). After heating at reflux for 16 h the mixture was cooled to 25°C allowed to settle and the supernatant transferred under nitrogen through a wide bore cannula to a sintered glass filter layered with a short pad of Celite. A positive nitrogen pressure was maintained during intermittent application of vacuum as the solution was filtered and the residue was washed with toluene (200 mL). The resulting yellow solution was treated with bis-(triphenylphosphine)palladium(II) dichloride (6.6 g, 0.45 mole %) and stirred at 25°C for 5 min. During this time the solution became black in color and a black precipitate formed. A solution of methacryloyl chloride (250 mL, 2.23 mol) in toluene (450 mL) was slowly added to the black solution *via* a dropping funnel such that the temperature of the reaction mixture never rose above 55°C. After addition of methacryloyl chloride, the mixture was cooled to 25°C and filtered through Celite. The deep red solution was diluted with Et_2O (1.0 L) and the resulting two layers (Et_2O/toluene and dimethylacetamide) separated. The dimethylacetamide layer was diluted with water (1.0 L) and washed with Et_2O (3x200 mL). The Et_2O/toluene layers were washed with 1M NH_4Cl (500 mL), saturated $NaHCO_3$ (500 mL), 1M $Na_2S_2O_3.5H_2O$ (500 mL) and brine (500 mL). The organic layer was dried ($MgSO_4$) and evaporated to give **17** (354 g, 92% crude, used directly in the next stage). ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 1.84 (3H, s), 1.91 (2H, t, J = 7.2 Hz), 2.33 (2H, t, J = 7.2 Hz), 2.73 (2H, t, J = 7.2 Hz), 4.10 (2H, q, J = 7.1 Hz), 5.74 (1H, s), 5.94 (1H, s).

(±)-Ethyl 5-hydroxy-6-methyl-6-heptenoate 18. To a solution of cerium (III) chloride heptahydrate (716 g, 1.92 mol) in ethanol (4.0 L) at 25°C was added **17** (330 g, 1.8 mol) and the mixture was stirred at 25°C for 10 min. Sodium borohydride (83.0 g, 2.2 mol) was added portion wise such that the temperature of the solution never rose above 35°C. The resulting slurry was stirred at 25°C for 2 h. The slurry was slowly added to water (3.5 L) containing ice (500 g). After stirring for 15 min the aqueous mixture was diluted with Et_2O (4.0 L) and acidified by the addition of glacial acetic acid (200 mL). The Et_2O layer was separated and the aqueous layer washed with additional Et_2O (2.0 L). The combined Et_2O layers were washed with saturated $NaHCO_3$ until the aqueous layers remained basic. The Et_2O layer was washed with brine (2.0 L), dried (Na_2SO_4), and evaporated to give **18** as an oil (265 g, 80%). IR (film) 3454, 2981, 2940, 1736, 1652 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 1.52-1.68 (4H, m), 1.69 (3H, s), 2.31 (2H, t, J = 7.0 Hz), 4.02-4.13 (3H, m), 4.82 (1H, s), 4.92 (1H, s).

(±)-Ethyl 5-(*tert*-butyldimethylsilyl)oxy-6-methyl-6-heptenoate 19. A solution of **18** (265 g, 1.4 mol) in *N,N*-dimethylformamide (1.4 L) was treated with imidazole (242 g, 3.55 mol), and the mixture was stirred at 25 °C until the imidazole was dissolved. The resulting solution was treated with *tert*-butyldimethylsilyl chloride (272 g, 1.8 mol) and stirred at 25°C for 3 h. The reaction mixture was quenched by addition of water (1.0 L) and Et_2O (1.0 L). The phases were separated and the aqueous layer washed with additional Et_2O (2x500 mL). The combined Et_2O layers were washed with 1M NH_4Cl (4x500 mL), brine (500 mL), dried ($MgSO_4$), and evaporated to give a bright yellow oil. Distillation (bp. 108-112 °C at 1mm).gave **19**

as a colorless oil (347 g, 82%). IR (thin film) 2957, 2858, 1738, 1250, 1082 cm^{-1}. ^1H NMR ($CDCl_3$) δ -0.04 (3H, s), 0.00 (3H, s), 0.84 (9H, s), 1.20 (3H, t, J = 7.2 Hz), 1.43-1.61 (4H, m), 1.62 (3H, s), 2.25 (2H, t, J = 7.1 Hz), 3.99 (1H, t, J = 6.0 Hz), 4.07 (2H, q, J = 7.1 Hz), 4.72 (1H, s), 4.82 (1H, s). ^{13}C NMR ($CDCl_3$) δ -5.2, -4.8, 14.2, 17.0, 18.2, 21.0, 25.8, 34.2, 35.4, 60.1, 76.3, 110.8, 147.3, 173.5. HRMS(CI) calcd for $C_{16}H_{33}O_3Si$ ($M^+ + 1$) 301.2199. Found 301.2186.

Alternative Method. To a solution of the crude allylic alcohol **18** (20.7 g, 111 mmol) in dichloromethane (125 mL) at 0°C was added diisopropylethyl amine (21.3 mL) followed by *tert*-butyldimethylsilyl triflate (27.1 mL, 118 mmol) over 1 min. The light brown solution was removed from the ice bath and maintained at room temperature for 1.75 h. The reaction mixture was poured into water and the aqueous layer was back-extracted with dichloromethane (3x100 mL). The dried ($MgSO_4$) extract was evaporated *in vacuo* to give a yellow oil. Chromatography over silica gel eluting with 2.5% EtOAc/pentane gave **19** (32.9 g, 98%) as a colorless oil.

(±)-Ethyl 2-[2-(furyl)-2-hydroxymethyl]-5-(*tert*-butyldimethylsilyl)oxy-6-methyl-6-heptenoate 20. A solution of **19** (12.4 g, 41.3 mmol) in tetrahydrofuran (55 mL) was slowly added to a cold (-78°C) stirred solution of lithium diisopropylamide (46.4 mmol) in tetrahydrofuran (160 mL) such that the internal temperature never rose above -60°C. After 20 min at -78°C, 2-furfural (6.00 g, 62.4 mmol, freshly distilled) was added, and the mixture stirred for an additional 20 min. The reaction mixture was quenched with water, warmed to 25°C, and diluted with Et_2O. The Et_2O layer was washed with water, brine, dried ($MgSO_4$), and evaporated. The resulting yellow oil was heated to 40-50°C at 1 mm Hg to remove excess furfural to give **20** (16.0 g, 98%). The aldol reaction gave two separable bands (by flash chromatography) each containing two diastereomers. Each set of two diastereomers were brought independently through the synthetic sequence to the pyrylium ylide-alkene cyclization stage. Both sets of diastereomers gave the same products from the pyrylium ylide cyclization (1:1 mixture). Less polar. ^1H NMR (mixture of two diastereomers, C_6D_6) δ 0.05 (6H, s), 0.07 (3H, s), 0.08 (3H, s), 0.85 (3H, t, J = 7.1 Hz), 0.85 (3H, t, J = 7.1 Hz), 0.98 (9H, s), 0.99 (9H, s), 1.48 - 2.05 (8H, m), 1.63 (3H, s), 1.65 (3H, s), 2.39 (2H, t, J = 4.6 Hz), 2.95 -3.00 (2H, m), 3.85 (4H, q, J = 7.1 Hz), 4.00-4.05 (2H, m), 4.76 (2H, bs), 4.89 (1H, bs), 4.94 (3H, bm), 6.03 (2H, m), 6.22 (2H, m), 7.02 (2H,m). More polar. ^1H NMR (mixture of two diastereomers, C_6D_6) δ 0.02, 0.03 (12H s), 0.92 (3H, t, J = 7.1 Hz), 0.93 (3H, t, J = 8.1 Hz), 0.95 (9H, s), 0.96 (9H, s), 1.50 - 1.92 (14H, m), 2.65 (1H, d, J = 7.0 Hz), 2.83 (1H, d, J = 7.4 Hz), 3.03-3.10 (2H, m), 3.91-4.00 (6H, m), 4.72 (2H, m), 4.8-4.89 (4H, m), 5.99-6.02 (2H, m), 6.06 (1H, d, J = 3.2 Hz), 6.09 (1H, d, J = 3.2 Hz), 7.02 (2H, m). IR (neat, mixture of four diastereomers) 3468, 2931, 1732, 1464, 1374, 1259s, 1174, 1082, 837, 776 cm^{-1}. MS (CI) (% rel intensity) 397 ($M^+ + 1$) (5), 380 (42), 265 (28), 247 (100).

(±)-2-[2-(Furyl)-2-hydroxymethyl]-5-(*tert*-butyldimethylsilyl)oxy-6-methyl-6-hepten-1-ol 21. A solution of ester **20** (16.3 g, 41.1 mmol) in tetrahydrofuran (150 mL) was slowly added to a suspension of lithium aluminum hydride (2.45 g, 64.6 mmol) in tetrahydrofuran (150 mL) at -78°C. After the addition was complete the mixture was stirred at 25°C for 3 h. The mixture was cooled to -78°C and water was slowly added. The mixture was warmed to 25°C and diluted with Et_2O. The organic layer was washed with

water, brine, dried ($MgSO_4$), and evaporated to give **21** (14.5 g, 99%) as a yellow oil. Less polar. ^1H NMR (mixture of two diastereomers, C_6D_6) δ 0.05 (6H, s), 0.06 (3H, s), 0.07 (3H, s), 0.98 (9H, s), 0.99 (9H, s), 1.2 -1.61 (12H, m), 1.63 (3H, s), 1.64 (3H, s), 1.90 - 1.98 (2H, m), 2.69 (1H, bs), 2.76 (1H, bs), 3.43 (2H, m), 3.52-3.59 (2H, m), 3.96 (2H, m), 4.75 (2H, s), 4.86-4.89 (4H, m), 6.10 (2H. m), 6.20 (2H, t, J = 3.2 Hz), 7.07 (2H, m). More polar. ^1H NMR (mixture of two diastereomers, C_6D_6) δ 0.52 (12H, m), 0.96 (18H, m), 1.2-1.6 (8H, m), 1.61 (3H, s), 1.62 (3H, s), 1.95 (2H, m), 3.22 (2H, m), 3.46 - 3.52 (2H, m), 3.70-3.77 (2H, m), 3.94 (2H, t, J = 5.8 Hz), 4.58 (2H, t, J = 7.2 Hz), 4.72-4.77 (2H, m), 4.88 (2H, bs), 6.06-6.14 (4H, m), 7.10 (2H, m). IR (neat, mixture of all diastereomers) 3242, 2932, 2858, 1472, 1462, 1257, 1149, 1074, 836, 775 cm^{-1}. MS (CI) (% rel intensity) 355 (M^+ + 1) (2), 337 (-H_2O, 100), 205 (62), 187 (39). HRMS (CI) calcd for $C_{19}H_{34}O_4Si$ (M^+) 354.2226. Found 354.2226.

(±)-2-[2-(Furyl)-2-hydroxymethyl]-5-(*tert*-butyldimethylsilyl)oxy-6-methyl-6-hepten-1-triphenylmethyl ether 22. To a stirred solution of diol **21** (30.6 g, 85.2 mmol) in dichloromethane (250 mL) at 25°C was added triethylamine (17.8 mL, 128 mmol) and 4-dimethylaminopyridine (DMAP) (1.04 g, 8.52 mmol), followed by triphenylmethyl chloride (26.1 g, 93.8 mmol). After 40 h, the mixture was poured into water (1.0 L) and the organic layer separated. After washing with saturated NH_4Cl (1.0 L), water (1.0 L), the solution was dried ($MgSO_4$) and filtered. Evaporation of the solvent *in vacuo* gave **22** as a viscous brown oil (49.1 g, 97% crude yield). IR (neat) 3486, 2955, 2930, 1449, 1251, 1069, 704 cm^{-1}. Due to the complexity of the ^1H NMR spectrum further characterization was not attempted until the pyrylium ylide-alkene cyclization to give **25** and **26**.

(±)-2-[2-(6-Hydroxy-4-pyranen-3-one)]-5-(*tert*-butyldimethylsilyl)oxy-6-methyl-6-hepten-1-triphenylmethyl ether 23. A solution of **22** (42.2 g, 69 mmol) in dichloromethane (225 ml) was stirred at 25°C and *tert*-butylhydroperoxide (26 ml of a 3M solution in 2,2,4-trimethylpentane, 78 mmol) was added in one portion. The reaction mixture was cooled to -30°C and solid vanadyl acetoacetate (0.566 g, 2.13 mmol) was added. The solution became burgundy in color and was maintained at -12°C for 17 hours. After this time, water (400 ml) was introduced and the layers were separated. The aqueous phase was extracted with dichloromethane (100 ml) and the combined organic phase was dried (Na_2SO_4). The supernatant liquid was filtered through a short pad of silica gel, eluting with EtOAc to give, after concentration, **23** as a pale yellow foam (42.41 g, 98%). IR (neat) 3417, 2932, 1693, 1449, 1251, 1069, 1036 cm^{-1}. Used directly in the next step.

(±)-4α-(Triphenylmethyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-1-en-2-one 25 and 26. The hydroxypyranenone **23** (405 mg, 0.646 mmol) in toluene (70 mL) was dried by azeotropic distillation to a volume of 50 mL. 4-DMAP (4.0 mg, 0.032 mmol) was added, followed by triethylamine (108 mL, 0.735 mmol), and finally acetic anhydride (64 mL, 0.678 mmol). After stirring for 15 h at 25°C, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (290 mL, 1.948 mmol) was added, and the mixture was heated for 2 h at reflux. The cooled solution was filtered through a silica gel pad eluting with EtOAc. Concentration under reduced pressure gave an orange oil which was purified by chromatography over silica gel eluting with 10% EtOAc/hexanes to give a white foam (346 mg, 88%) which

was a 1:1 mixture of diastereomers **25** and **26**. Crystallization from methanol gave pure **26**. For Isomer **25**. IR (neat) 2955, 1685, 1449, 1257, 1112, 1073, 836, 775, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.01 (3H, s), 0.23 (3H, s), 0.85 (9H, s), 0.90 (3H, s), 1.43-1.64 (4H, m), 1.95-2.01 (1H, m), 2.29 (1H, dd, J = 8.0, 12.6 Hz), 2.82 (1H, t, J = 7.8 Hz), 2.88-2.92 (1H, m), 3.00 (1H, dd, J = 4.6, 7.9 Hz), 3.46 (1H, dd, J = 4.0, 11.3 Hz), 4.49-4.52 (1H, m), 5.85 (1H, d, J = 9.6 Hz), 7.12-7.42 (16H, m). ^{13}C NMR ($CDCl_3$) δ -5.0, -3.7, 15.0, 18.0, 24.3, 25.8, 29.7, 35.7, 44.5, 45.2, 65.1, 70.8, 78.1, 86.6, 93.9, 126.4, 126.7, 127.6, 128.8, 144.2, 155.4, 196.3 ppm. HRMS calcd for $C_{38}H_{46}O_4Si$ (M^+) 594.3165. Found 594.3170. For Isomer **26**. M.pt. 203-206°C (methanol). IR ($CHCl_3$) 3018, 2957, 1684, 1449, 1258, 1101, 1072, 838, 724 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.16 (3H, s), 0.26 (3H, s), 0.83 (9H, s), 0.92 (3H, s), 1.18-1.27 (1H, m), 1.44-1.64 (3H, m), 1.97-2.04 (1H, m), 2.52-2.64 (2H, m), 2.84 (1H, t, J = 8.5 Hz), 3.24-3.28 (1H, m), 3.47-3.53 (1H, m), 4.50-4.54 (1H, m), 4.75-4.79 (1H, m), 5.80 (1H, d, J = 9.7 Hz), 7.16-7.28 (9H, m), 7.40 (6H, d, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ -5.0, -3.9, 18.0, 21.2, 23.8, 25.8, 26.6, 32.6, 36.4, 45.9, 65.6, 71.9, 75.3, 86.4, 93.0, 126.7, 127.6, 128.8, 144.4, 153.6, 196.5. Anal. calcd for $C_{38}H_{46}O_4Si$, C, 76.73; H, 7.80. Found C, 76.85; H, 7.84%. Crystals for X-ray structure determination were grown from methanol.

Ethyl 6-methyl-6-heptenoate 29. To a 500 mL 3-necked flask fitted with a reflux condenser was added zinc dust (243.0 g, 0.371 mol) and tetra *n*-butyl ammonium iodide (55.0 g), followed by tetrahydrofuran (1.0 L) and *N,N*-dimethylacetamide (750 mL). The zinc dust was activated by treatment with trimethylsilyl chloride (12.5 mL), followed by slow addition of 1,2-dibromoethane (15.0 mL). When the exotherm had subsided, 4-bromobutanoate (178.5 g, 1.20 mol) was added over 15 minutes. After heating at reflux for 24 h, cooling to 25°C allowed the zinc dust to settle. The supernatant liquid was transferred by cannula into a flask containing copper (I) cyanide (33.0 g). 3-Methallyl chloride (110.0 mL, 1.73 mol) was added slowly, and the mixture was stirred at room temperature for 12 h. Et_2O (1.0 L) and water (500 mL) were added to the mixture and the layers separated. The aqueous layer was further extracted with Et_2O and the organic phases were combined. After washing with water (4x200 mL) and drying ($MgSO_4$), the solvent was removed to afford **29** as a pale yellow oil (176.5 g, 87 %). IR (thin film) 3074, 2980, 2937, 2865, 1736, 1650, 1447, 1374, 1350, 1182, 1145, 1096, 1080, 1034, 887, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 1.46 (2H, m), 1.59 (2H, m), 1.68 (3H, s), 2.0 (2H, t, J = 7.4 Hz), 2.28 (2H, t, J = 7.4 Hz), 4.09 (2H, q, J = 7.2 Hz), 4.66 (2H, d, J = 9.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.3, 24.5, 27.0, 34.2, 37.4, 60.2, 110.0, 145.5, 173.7. HRMS (CI) calcd for $C_{10}H_{18}O_2$ (M^+) 170.1367. Found 170.1360.

2-[2-(Furyl)-2-hydroxymethyl]-6-methyl-6-hepten-1-ol 31. A solution of **29** (34.5 g, 0.203 mol) in tetrahydrofuran (50 mL) was slowly added to a cold (-75°C) solution of potassium bis(trimethylsilyl)amide (44.6 g, 0.22 mol) in tetrahydrofuran (500 mL) such that the internal temperature stayed below -60°C. After stirring the solution for 45 min a solution of 2-furfural (16.8 mL, 0.202 mol) was added over 10 min, and the resulting mixture stirred for 3 h. Lithium aluminum hydride (15.0 g, 0.38 mol) was added portion wise and the reaction allowed to warm to 25°C overnight. The reaction was quenched with EtOAc (20 mL) and 10% sodium tartrate solution (20 mL) added. Further quantities of EtOAc (100 mL), 10% sodium tartrate solution (100 mL) and Celite (50 g) were added, and after stirring vigorously for 30 min the mixture was filtered washing the Celite with EtOAc. The layers were separated and the aqueous phase extracted with EtOAc

(2x100 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated to yield **31** as a yellow oil (46.3 g, 95%) (mixture of 2 diastereomers). IR (neat) 3354, 3074, 2935, 1650, 1504, 1462, 1373, 1221, 1149, 1008, 914, 885, 811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.5 (10H, m), 1.23 (3H, s), 1.26 (3H, s), 1.8-2.1 (4H, m), 2.3 (1H, br s, 2.6 (1H, br s), 3.15 (2H, br m), 3.65-3.90 (4H, m), 4.7 (1H, m), 4.60 (4H, br d, J = 15.9 Hz), 4.95 (1H, m), 6.26 (2H, d, J = 3.1 Hz), 6.32 (2H, d, J = 3.1 Hz), 7.36 (1H, s), 7.38 (1H, d, J = 1.4 Hz). HRMS (CI) calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412. Found 224.1404.

(±)-2-[2-(Furyl)-2-hydroxymethyl]-6-methyl-6-hepten-1-(*tert*-butyldimethylsilyl)oxy ether 32. Using the same conditions as described for **19**. **32** (48.6 g, 81 %) (mixture of diastereomers). IR (thin film) 3472, 3074, 2930, 2857, 1649, 1471, 1388, 1255, 1146, 1082, 1005, 938 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.03 (6H, s), 0.86 (9H, s), 0.87 (9H, s), 1.2-1.5 (10H, m,), 1.64 (6H, s), 1.9-2.0 (4H, m), 3.61 (1H, dd, J = 11.1, 5.2 Hz), 3.68 (2H, d, J = 5.4 Hz), 3.75 (1H, dd, J = 11.0, 2.9 Hz), 3.94 (1H, d, J = 5.7 Hz), 4.19 (1H, d, J = 5.7 Hz), 4.61 (4H, d, J = 12.6 Hz), 4.69 (1H, t, J = 5.9 Hz), 4.90 (1H, m,), 6.20 (1H, d, J = 3.1 Hz), 6.22 (1H, d, J = 3.3 Hz), 6.29 (2H, d, J = 2.2 Hz), 7.31 (2H, s). HRMS (CI) calcd for $C_{19}H_{35}O_3Si$ (M^+ + 1) 339.2356. Found 339.2353.

(±)-2-[2-(6-Hydroxy-4-pyranen-3-one)]-6-methyl-6-hepten-1-(*tert*-butyldimethylsilyl) oxy ether 33. Using the same conditions as described for **23**. **33** (29.9 g, 94%). IR (neat) 3390, 3074, 2931, 2858, 1693, 1681, 1651, 1470, 1365, 1255, 1092, 1035, 887 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.05 (3H, s), -0.04 (3H, s), 0.04 (6H, s), 0.81 (9H, s), 0.86 (9H, s), 1.1-1.5 (8H, m), 1.65 (3H, s), 1.68 (3H, s), 1.9-2.25 (4H, m), 2.4-2.5 (2H, m), 3.56 (4H, m), 4.52 (1H, d, J = 1.5 Hz), 4.62 (2H, d, J = 12.7 Hz), 4.66 (2H, d, J = 9.9 Hz), 4.86 (1H, d, J = 1.85 Hz), 5.62 (2H, s), 6.08 (1H, d, J = 3.4 Hz), 6.12 (1H, d, J = 3.4 Hz), 6.80 (1H, dd, J = 3.6, 3.7 Hz), 6.87 (1H, dd, J = 3.7, 3.5 Hz). HRMS (CI) calcd for $C_{19}H_{35}O_4Si$ (M^+ + 1) 355.2305. Found 355.2297.

(±)-2-[2-(6-Acetoxy-4-pyranen-3-one)]-6-methyl-6-hepten-1-(*tert*-butyldimethylsilyl) oxy ether 34. Using the same conditions as described for **24**. **34** (28.2 g, 84%). ^1H NMR (300 MHz, $CDCl_3$) δ -0.05 (3H, s), -0.04 (3H, s), -0.02 (3H, s), -0.01 (3H, s), 0.02 (3H, s), 0.022 (3H, s), 0.03 (3H, s), 0.04 (3H, s), 0.81 (9H, s), 0.83 (9H, s), 0.84 (9H, s), 0.86 (9H, s), 1.2-1.5 (16H, m), 1.68 (12H, s), 1.9-2.0 (8H, m), 2.07 (3H, s), 2.08 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.37 (2H, m), 2.52 (2H, m), 3.57 (8H, m), 4.17 (1H, d, J = 4.0 Hz), 4.44 (2H, s), 6.60 (8H, m), 4.80 (1H, d, J = 1.8 Hz), 6.2 (4H, m), 6.49 (4H, br s), 6.75 (4H, m). HRMS (CI) calcd for $C_{21}H_{37}O_5Si$ (M^+ + 1) 397.2410. Found 397.2393.

(±)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}] undec-1-en-2-one 35. A solution of DBU (60.0 g, 0.40 mol) in toluene (3.5 L) was dried by azeotropic distillation using a Dean-Stark apparatus. After 4 h a solution of **34** (55.7 g, 0.141 mol) in toluene (100 mL) was added over 20 min. Heating was continued at 110°C for 1 h, before allowing the solution to cool overnight. The toluene was evaporated until only 300 mL remained. After dilution with Et_2O (800 mL) the organic phase was washed with 2M H_2SO_4 (4x200 mL), water (200 mL) and brine (200 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a brown oil. Chromatography over silica gel eluting with 10% EtOAc/hexanes

afforded a mixture of **35** and **36** as a pale yellow solid (37.0 g, 78%) (**35**:**36** is 4:1). **35** M.pt. 81-83°C (MeOH). IR (neat) 2932, 2857, 1697, 1462, 1384, 1253 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 0.95 (3H, s), 1.20-1.40 (2H, m), 1.50-1.70 (4H, m), 1.40 (1H, m), 2.04 (1H, dd, J = 12.1, 7.9 Hz), 2.64 (1H, m), 3.38 (1H, t, J = 9.6 Hz), 3.51 (1H, dd, J = 9.6, 5.0 Hz), 4.62 (1H, m), 5.94 (1H, d, J = 9.6 Hz), 7.39 (1H, dd, J = 9.6, 5.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.4, 18.2, 21.1, 22.1, 24.8, 25.9 (3C), 37.9, 39.1, 40.7, 47.3, 65.1, 71.6, 91.8, 126.6, 155.4, 197.5. HRMS (CI) calcd for $C_{19}H_{33}O_3Si$ (M^+ + 1) 337.2200. Found 337.2201. Selected data for **36**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (2H, m), 5.88 (1H, d, J = 9.8 Hz), 7.14 (1H, dd, J = 9.8, 5.0 Hz). For further characterization see chiral series.

(+)-(5S)-Ethyl 5-hydroxy-6-methyl-6-heptenoate 18. The enone **17** (10 g, 54.3 mmol) was dissolved in tetrahydrofuran (150 mL) over 4Å molecular sieves (20 g) and occasionally swirled (ca 1.5 h). The solution was transferred using a cannula to a 500 mL three-neck round bottom-flask. To the solution was added the (S)-oxazaborole catalyst (4.5 mL of a 1.1 M solution in toluene, 4.87 mmol, 0.09 equiv). The resulting solution was cooled to -15°C. In a separate vessel borane-methyl sulfide (4.0 mL of a 10 M solution) was dissolved in dry tetrahydrofuran (70 mL) and added to the enone/catalyst solution at such a rate as to maintain the internal temperature at -15°C (ca 50 min). After the borane was added, the reaction mixture was stirred for 1.75 h. The reaction mixture was quenched by the cautious addition of methanol (100 mL) [there was a significant induction period (1-2 min) before hydrogen was evolved], maintaining the temperature at approximately -15°C (50 min). After complete addition of methanol, the reaction mixture was stirred at -10°C for 1 h, and allowed to warm to 25 °C, and stirred for 3h. The resulting solution was evaporated *in vacuo*. Additional methanol (100 mL) was added and evaporated to remove any residual volatile boron species. Chromatography over silica gel eluting with hexanes, followed by 30% EtOAc/hexanes, afforded **18** (9.0 g, 89%). $[\alpha]_D^{23}$ +3.5° (c = 1.73, $CHCl_3$). Eluting the column with 95% MeOH/Et_3N gave 0.89 g of (S)-(-)-diphenyl-2-pyrrolidinemethanol.

Preparation of Mosher Ester. To a stirred solution of the allylic alcohol **18** (46 mg, 0.25 mmol), DMAP (30 mg, 0.25 mmol), and Et_3N (0.18 mL, 1.25 mmol) in dichloromethane (5 mL) was added dropwise a solution of freshly prepared (+)-Mosher acid chloride (0.35 mmol) in dichloromethane (1 mL). The mixture was stirred at 25 °C for 2.5h, evaporated in *vacuo*, and the residue filtered through silica gel eluting with 20% EtOAc/hexanes. The ^1H NMR spectrum of the crude Mosher ester showed only traces of the second diastereomer, ee > 93%.

(+)-*N*-[1-Oxo-5-(*tert*-butyldimethylsilyl)oxy-6-methylhept-6-ene]-2-methyl-3-phenyl-4-oxazolidin-5-one 37. A solution of **19** (derived from chiral **18** as described for the racemic series) (25.0g, 0.083 mol) and sodium hydroxide (25.0g, 0.083g) in isopropanol (166 ml) was heated under reflux for 5 hours. The mixture was diluted with dry toluene (100 mL) then concentrated to a volume of 100 mL by atmospheric distillation. This dilution/distillation process was repeated twice. The crude sodium salt was used without purification in the subsequent reaction. To a stirred solution of the sodium salt in toluene/dichloromethane at -10°C was added DMF (4-5 drops) followed by oxalyl chloride (10.9 mL, 0.125

mol). After 15 minutes at -10°C, the resulting solution was warmed to 25°C and stirred overnight. The solution was concentrated to a volume of 75 mL *in vacuo*, diluted with dry toluene (300 mL) and concentrated to a volume of 75 mL *in vacuo*. The crude acid chloride was used without purification in the subsequent reaction. To a stirred solution of oxazolidinone in tetrahydrofuran (380 mL) at -78°C was added *n*–BuLi (2.5M) in hexanes dropwise over 10 min. After 20 min the solution was added *via* cannula to a stirring suspension of acid chloride in tetrahydrofuran/toluene (250 mL) at -78°C. The resulting mixture was stirred at -78°C for 4 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (40 mL) and Et_2O (100 mL). The layers were separated and the aqueous layer washed with additional Et_2O (2x200 mL). The combined Et_2O layers were washed with 1M NH_4Cl (4x150 mL), brine (150 mL), dried ($MgSO_4$), and evaporated. Chromatography over silica gel eluting with 15 to 25% EtOAc/Hexanes gave **37** as a colorless oil (35.66 g, 100% from **19**). $[\alpha]_D^{25}$ +24 (c = 1, $CHCl_3$). IR (film) 2931, 2860, 1784, 1702, 1455, 1367, 1249, 1196, 1072, 832 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.10 (3H, s), 0.03 (3H, s), 0.87 (9H, s), 0.88 (3H, d, J = 6.3 Hz), 1.65 (3H, s), 1.70-1.50 (4H, m), 3.03-2.82 (2H, m), 4.04 (1H, t, J = 6.0 Hz), 4.78-4.69 (2H, m), 4.86 (1H, s), 5.63 (1H, d, J = 7.3 Hz), 7.43-7.27 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.0, 1.4, 20.7, 23.3, 23.8, 24.4, 26.4, 26.4, 31.8, 31.4, 40.3, 41.5, 41.6, 60.0, 81.5, 82.4, 85.1, 85.1, 117.1, 117.3, 132.1, 134.6, 139.8, 153.0, 159.2, 179.1. HRMS (CI) Calcd for $C_{24}H_{38}NO_4Si$ (M^+ + 1) 432.2571. Found 432.2581.

(+)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-1-en-2-one 25 (R = TBS). To a solution of DBU (4.15 mL, 27.7 mmol, 3 equiv) in toluene (500 ml) at 110°C was added a solution of **24** (prepared in an identical fashion as described for **34**) (4.87 g,9.24 mmol) in dry toluene (100 mL), dropwise over a period of 1 h from an addition funnel. After cooling to room temperature over 18 h, the toluene was removed *in vacuo* and the residue taken up in Et_2O (300 mL). This solution was washed successively with cold 10% aqueous H_2SO_4 (2x200 mL), water (2x200 mL), and brine (200 mL). The solution was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product (10:1, **25**:**27** by NMR) was purified by column chromatography over silica gel using 80% hexanes/Et_2O as eluant to give **25** (R = TBS) as a crystalline solid (3.29 g, 77%). M.pt. 49-50°C (pentane). $[\alpha]_D^{25}$ -56° (c = 3, $CHCl_3$). IR (thin film) 2931, 2860, 1684, 1467, 1249, 1091, 832 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.10 (6H, s), 0.01 (6H, s), 0.87 (18H, s), 0.89 (3H, s), 1.19 (1H, m), 1.48-1.70 (4H, m), 1.95 (1H, m), 2.35 (1H, dd, J = 9.9, 14.4 Hz), 3.36 (1H, t, J = 5.4 Hz), 3.45-3.60 (2H, m), 4.64 (1H, m), 5.94 (1H, d, J = 9.6 Hz), 7.42 (1H, dd, J = 6.9, 9.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.7, 0.8, 1.2, 2.5, 21.1, 24.4, 23.7, 23.8, 31.3, 32.1, 32.8, 35.9, 42.8, 43.9, 50.6, 51.4, 70.3, 77.2, 78.1, 81.4, 84.5, 100.0, 132.6, 161.3, 202.7. HRMS (FAB) calcd for $C_{25}H_{46}O_4Si_2$ (M^+ + 1) 467.301. Found 467.302.

(+)-*N*-(1-Oxo-6-methylhept-6-ene)-2-methyl-3-phenyl-4-oxazolidin-5-one 39. To a solution of **29** (31.65 g, 185.90 mmol) in isopropyl alcohol (200 mL) was added sodium hydroxide (7.44 g, 186.00 mmol) in the minimal amount of water required to make the mixture homogeneous. The resulting mixture was heated at 82°C for 1.0 h. The isopropyl alcohol was removed *in vacuo*, and toluene (500 mL) added. The reaction mixture was heated to 111°C, and the water removed azeotropically using a Dean Stark apparatus. The reaction vessel was filled with argon, and cooled to 0°C. Et_2O (300 mL) and DMF (3 mL) were added to the reaction followed by slow addition of oxalyl chloride (24.50 mL, 279.87 mmol). The reaction

mixture warmed to 24°C over 3.0 h. After an additional 12 h, the Et_2O and excess oxalyl chloride were removed *in vacuo*. The reaction vessel was filled with argon, dry tetrahydrofuran (200 mL) was added, and the temperature was lowered to -78°C. In a separate argon filled flask oxazolidinone (39.00 g, 220.1 mmol) was dissolved in dry tetrahydrofuran (300 mL). The oxazolidinone/tetrahydrofuran solution was cooled to -78°C, and 2.5M *n*-BuLi in hexanes (87.57 mL, 220.00 mmol) slowly added. After 1.0 h, the *N*-lithio-oxazolidinone in tetrahydrofuran was added *via* cannula to the acyl chloride/toluene/tetrahydrofuran solution at -78°C. The reaction temperature warmed to 24°C over 13 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL), and the resulting mixture diluted with water (500 mL), and separated. The aqueous phase was extracted with Et_2O (3x200 mL), and the organic fractions combined, and dried (Na_2SO_4). The solvent was removed *in vacuo* leaving a pale yellow viscous oil. The oil was diluted with petroleum ether (3x50 mL), chilled in a carbon dioxide/acetone bath, and scratched against the glass reaction vessel. A colorless crystalline solid **39** (39.74 g, 71%) was collected *via* vacuum filtration. The remaining crude product was purified over silica gel eluting with EtOAc/petroleum ether (3:7) to afford further **39** (6.16 g, 11%). Total yield for three steps was 82%. M.pt. 64-66°C (EtOAc/hexanes). $[\alpha]_D^{25}$ +16 (c = 0.5, CH_2Cl_2). IR (Nujol) 3069, 2935, 1783, 1701, 1648, 1455 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.5 Hz), 1.47-1.70 (7H, m), 2.04 (2H, t, J = 7.4 Hz), 2.80-3.00 (2H, m), 4.66-4.76 (3H, m), 5.65 (1H, d, J = 7.3 Hz), 7.24-7.43 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 22.3, 23.8, 26.9, 35.4, 37.4, 54.7, 78.9, 110.0, 125.4, 128.6, 133.3, 145.4, 153.0, 172.9, (quaternary missing). HRMS (CI) calcd for $C_{18}H_{24}NO_3$ ($M^+ + 1$) 302.1760. Found 302.1750. Anal. calcd. for $C_{18}H_{23}NO_3$, requires: C, 71.73; H, 7.69; N, 4.65%. Found C, 71.41; H, 8.06; N, 4.53%.

2-[2-(Furyl)-2-hydroxymethyl]-6-methyl-6-hepten-1-ol 31 ***via*** **40**. To a solution of **39** (35.14 g, 116.74 mmol) in dry tetrahydrofuran (500 mL) under an argon atmosphere at -78°C was slowly added 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran (117.29 mL, 116.74 mmol) over 0.5 h. After a further 2.0 h, 2-furoyl chloride (13.79 mL, 139.92 mmol) was added to the reaction mixture. The temperature of the reaction mixture was warmed to 0°C over 3.0 h. The diketone **40** has been isolated, and characterized (see spectral data at the end of this experiment). At 0°C, dry methanol (18.91 mL, 467 mmol) was added to the reaction mixture, followed by slow addition of 2M lithium borohydride in tetrahydrofuran (212.8 mL, 420.26 mmol) over 0.5 h. After a further 3.0 h, the reaction was quenched with water (50 mL) at 0°C. Most of the solvent was removed *in vacuo,* and the remaining mixture rinsed with saturated aqueous Rochelles salt (100 mL) and distilled water (200 mL). The resulting mixture was extracted with Et_2O (3x200 mL). The combined extracts were dried (Na_2SO_4), and the solvent removed *in vacuo* to give a colorless oil. The oil was diluted with EtOAc/petroleum ether (1:9, 150 mL). The resulting mixture was allowed to stand for 2.0 h at 24°C, and greater than 60% of the oxazolidinone was collected *via* vacuum filtration as colorless cubic crystals. The solvent from the mother liquors was removed *in vacuo*, and the remaining residue purified over a short plug of silica gel. The chromatography was run under pressure eluting with Et_2O/petroleum ether (3:17), followed by Et_2O/petroleum ether (1:1). The product **31** was isolated as a colorless oil (21.47 g, 81%). A further quantity of oxazolidinone (30-40%) was recovered. See (±)-**31** for spectral data. For **40**. M.pt. 97-98°C (EtOAc/hexanes). $[\alpha]_D^{25}$ +12.8 (c = 10, CH_2Cl_2). IR (Nujol) 2935, 1778, 1709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.89 (3H, d, J = 6.5 Hz), 1.48-1.60 (2H, m), 1.67 (3H, s), 1.75-1.9 (1H, m), 1.97-2.1 (4H, m), 4.64 (1H, bs), 4.66 (1H, s), 4.78 (1H, m), 5.16 (1H, dd, J = 4.2, 8.8 Hz), 5.64 (1H, d, J = 7.3 Hz), 6.51 (1H, m), 7.31-7.39 (5H, m), 7.54 (1H, s).

^{13}C NMR ($CDCl_3$) δ 13.9, 16.3, 22.2, 25.7, 27.8, 37.4, 54.1, 54.9, 79.1, 110.2, 112.5, 117.6, 125.6(2), 128.6, 128.7, 133.0, 145.0, 146.5, 151.7, 153.0, 168.7, 184.9. HRMS (CI) calcd for $C_{23}H_{25}NO_5$ (M^+) 395.1810. Found 395.1810. Anal. Calcd. for $C_{23}H_{25}NO_5$, requires: C, 69.9; H, 6.4; N, 3.5%. Found C, 70.0; H, 6.7; N, 3.5%.

2-[2-(Furyl)-2-hydroxymethyl]-6-methyl-6-hepten-1-triphenylmethyl ether 41. Using standard conditions, see **22**. **41** (200 g, 90% as a 3:1 mixture of diastereomers). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.14 (23H, m), 6.21 (1H, m), 6.06 (1H, m), 4.90 (1H, d, J = 3.8 Hz), 4.86 (1H, d, J = 3.8 Hz), 4.58 (2H, m), 4.52 (1H, s), 3.18 (2H, m), 2.08-1.82 (4H, m), 1.63 (1H, s), 1.57 (3H, s), 1.57-1.10 (6H, m). HRMS (CI) calcd for $C_{32}H_{34}O_3$ (M^+) 466.2508. Found 466.2501.

2-[2-(6-Hydroxy-4-pyranen-3-one)]-6-methyl-6-hepten-1-triphenylmethyl ether 43. A solution of **41** (55 g, 118 mmol) in dichloromethane (220 mL) and methanol (140 mL) was transferred to a photochemical reactor equipped with a cold finger and a glass sinter. Rose bengal (0.11 g, 0.001 mg/mmol of substrate) was added, oxygen was bubbled through the reactor, and the reaction was cooled to below -50°C using a cryostat. The reactor was irradiated with a bank of fluorescent lights for 48 h. The reaction mixture was quenched by addition of dimethyl sulfide (40 mL, 588 mmol, 5 equiv) and allowed to warm to room temperature. The solvents were evaporated *in vacuo* and the residue was purified by chromatography over silica gel, eluting with 80% hexanes/Et_2O to 50% hexanes/Et_2O to give **43** as a colorless oil (42.6 g, 75%, mixture of diastereoisomers). IR (thin film) 3400, 3057, 2934, 1688, 1448 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-1.00 (7H, m), 1.60 (4H, s), 1.65 (1H, s), 2.05-1.80 (4H, m), 2.38 (1H, d, J = 5.8 Hz), 2.70-2.50 (3H, m), 3.20-3.05 (2H, m), 3.35-3.20 (2H, m), 4.55 (1H, s), 4.61 (2H, m), 4.96 (1H, d, J = 1.8 Hz), 5.29 (1H, s), 5.48 (1H, t, J = 5.5 Hz), 6.15-6.05 (2H, m), 6.90-6.80 (2H, m), 7.50-7.15 (26H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 14.1, 22.2, 22.3, 25.1, 25.7, 25.8, 26.1, 26.3, 37.6, 37.7, 37.7, 39.2, 39.9, 62.1, 62.4, 73.9, 74.6, 78.5, 86.4, 86.5, 87.4, 91.4, 109.7, 110.0, 126.7, 126.8, 126.9, 127.5, 127.7, 127.8, 127.9, 128.7 (2C), 128.8, 129.6, 143.9, 144.0, 144.1, 145.6, 148.3, 196.8, 197.1. HRMS (CI) calcd for $C_{32}H_{34}O_4$ (M^+) 482.2457. Found 482.2440.

2-[2-(6-Acetoxy-4-pyranen-3-one)]-6-methyl-6-hepten-1-triphenylmethyl ether 44. Using standard conditions, see **24**. **44** (44.4 g, 96% yield, mixture of diastereomers). IR (thin film) 3058, 2935, 1756, 1695, 1448 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.00 (10H, m), 1.65-1.50 (7H, m), 1.80-1.70 (3H, m), 1.87 (5H, s), 2.00 (1H, d, J = 2.2 Hz), 2.08 (3H, s), 3.14-2.97 (5H, m), 4.61-4.40 (6H, m), 5.07 (1H, d, J = 2.1 Hz), 6.21-6.11 (2H, m), 6.47 (2H, m), 6.84-6.60 (2H, m), 7.44-7.13 (15H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 20.7, 20.8, 20.9, 22.2, 25.0, 25.5, 25.6, 25.9, 26.2, 27.9, 37.4, 37.5, 37.6, 39.1, 40.2, 40.6, 61.8, 62.0, 62.4, 76.6, 79.4, 79.4, 86.5, 86.6, 86.7, 87.0, 87.2, 88.2, 88.9, 109.7, 109.8, 109.9 (2C), 126.7, 126.8 126.9, 127.5, 127.7, 127.8, 128.5, 128.6, 128.7, 129.2, 129.6, 130.0, 139.5, 141.2, 143.9, 144.0, 144.1, 144.2, 144.5, 145.3, 145.4, 145.5, 168.7, 169.4, 195.0, 195.5, 196.3. HRMS (CI) calcd for $C_{34}H_{36}O_5$ (M^+) 524.2563. Found 524.2547.

(-)-4α-(Triphenylmethyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-1-en-2-one 47 and 48. To a solution of **44** (46 g, 88 mmol) in dry toluene (4 L) was added DBU (40 mL, 268 mmol, 3 equiv) and the mixture was heated at reflux for 3 h. After cooling to room temperature, the toluene was removed *in vacuo* and the residue was taken up in dichloromethane (500 mL). This solution was washed with cold 10% aqueous H_2SO_4 (200 mL), and water (200 mL). The solution was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was recrystallized from dichloromethane/hexanes to give **47** (20.9 g) as an off-white solid. The residue from the liquor was recrystallized from isopropyl alcohol/hexanes to afford an additional 9.3 g. Total yield of **47/48** 30.2 g (75%). For **47**. $[\alpha]_D^{25}$ -15.5° (c = 1.0, $CHCl_3$). M.pt. 225–228°C. IR (thin film) 3052, 2924, 2873, 1678, 1486, 1446, 1212, 1067, 1013, 764, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, s), 1.70-0.80 (7H, bm), 2.05-1.80 (2H, m), 2.80-2.95 (2H, m), 3.05-2.95 (1H, dd, J = 4.0, J = 7.5 Hz), 4.53-4.48 (1H, m), 5.85 (1H, d, J = 9.6 Hz), 7.41-7.14 (16H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 21.2, 22.2, 25.5, 35.9, 39.3, 40.5, 47.4, 65.5, 70.4, 86.6, 92.0, 126.6, 127.5, 127.8, 128.8, 144.3, 155.2, 197.4. HRMS (CI) calcd for $C_{32}H_{32}O_3$ (M^+) 464.2351. Found 464.2344. For **48**. M.pt. 122-124°C. IR (thin film) 2940, 1686, cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.4-1.8 (7H, m), 1.93 (1H, dd, J = 12, 7.5 Hz), 2.09 (1H, m), 3.2 (2H, m), 4.65 (1H, dd, J = 7.3, 4.6 Hz), 5.78 (1H, d, J = 9.7 Hz), 7.11 (1H, dd, J = 9.7, 4.6 Hz), 7.13-7.27 (9H, m), 7.42-7.5 (6H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 17.7, 19.3, 24.6, 33.3, 41.4, 41.7, 43.9, 64.0, 71.7, 86.4, 90.4, 126.7 (3C), 127.5 (3C), 128.3, 128.9 (3C), 144.4 (3C), 151.3, 197.3. HRMS (CI) calcd for $C_{32}H_{32}O_3$ (M^+) 464.2351. Found 464.2344.

2-[2-(Furyl)-2-hydroxymethyl]-6-methyl-6-hepten-1-triisopropylsilyl ether 42. To a solution of **31** (21.40 g, 95.53 mmol) in dry dimethylformamide (140 mL) under an argon atmosphere was added imidazole (14.30 g, 210.2 mmol). After 0.5 h, the reaction mixture was cooled to -10°C (NaCl/ice), and triisopropylsilyl chloride (21.24 mL, 100.3 mmol) was added over 0.55 h *via* syringe pump. Water (300 mL) was added to the reaction after 10 h, and the resulting mixture extracted with Et_2O (3x200 mL). The extracts were combined, dried (Na_2SO_4), and the solvent evaporated *in vacuo* . The remaining residue was purified over silica gel eluting with Et_2O/petroleum ether (1:9) to afford **42** (33.84 g, 91%) as a colorless oil. IR (thin film) 3473, 2942, 2868, 1651, 1461, 1087, 1011, and 883 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (18H, m), 1.25-1.30 (8H, m), 1.66 (3H, s), 1.92-2.15 (3H, m), 3.81-3.83 (2H, m), 4.62 (2H, d, J = 13.4 Hz), 4.90 (1H, m), 6.25-6.32 (2H, m), 7.32 (1H, s). HRMS (CI) calcd for $C_{22}H_{41}O_3Si$ (M^+ + 1) 381.2815. Found 381.2824.

2-[2-(6-Hydroxy-4-pyranen-3-one)]-6-methyl-6-hepten-1-triisopropylsilyl ether 45. To a solution of **42** (32.19 g, 84.51 mmol) in dry dichloromethane (280 mL) and dry methanol (140 mL) under an argon atmosphere was added a catalytic amount of rose bengal. The reaction mixture was cooled to -78°C, and argon was replaced by dry oxygen bubbled beneath the surface of the reaction mixture. A mercury lamp was placed with the bulb 2.0 cm from the glass reaction vessel, and irradiation commenced. The lamp was turned off after 16 h. Dimethylsulfide (31.25 mL, 422.56 mmol) was added to the reaction, and the temperature raised to 24°C over a 1.0 h period. After an additional 1.0 h, the solvent was evaporated *in vacuo*, and the remaining residue purified over silica gel eluting with EtOAc/petroleum ether (1:9) employing gravity followed by pressure. The product was a viscous yellow oil **45** (26.77 g, 80%). IR (thin film) 3411, 3075, 2942, 1687,

1649, 1462, 1099, 883 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96-1.04 (18H, m), 1.07-1.38 (6H, m), 1.64 (3H, s), 1.9-2.02 (2H, m), 2.43-2.50 (2H, m), 2.68 (1H, d, J = 4.7 Hz), 3.57-3.72 (2H, m), 4.46-4.67 (2H, m), 4.95 (1H, d, J = 2.1 Hz), 5.57-565 (1H, m), 6.08-6.17 (1H, m), 6.77-6.92 (1H, m). HRMS (CI) calcd for $C_{22}H_{39}O_4Si$ (M^+ + 1) 395.2617. Found 395.2625.

2-[2-(6-Acetoxy-4-pyranen-3-one)]-6-methyl-6-hepten-1-triisopropylsilyl ether 46. Using standard conditions, see **34**. **46** (28.60 g, 97%). IR (thin film) 2943, 2867, 1759, 1699, 1648, 1219, 1107, 883 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.03 (18H, m), 1.07-1.46 (3H, m), 1.65 (3H, t, J = 5.6 Hz), 1.89-2.03 (2H, m), 2.05 (1H, s), 2.14 (1H, s), 2.44-2.51 (1H, m), 3.53-3.70 (3H, m), 4.59-4.67 (4H, m), 4.89 (1H, d, J = 1.9 Hz), 6.17-6.23 (1H, m), 6.47-6.50 (2H, m), 6.77-6.88 (2H, m). HRMS (CI) calcd for $C_{24}H_{43}O_5Si$ (M^+ + 1) 439.2879. Found 439.2867.

4α-(Triisopropylsilyloxy)methyl-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-1-ene-2-one 49 and 50. Toluene (1.8 L) and DBU (39.20 mL, 257.7 mmol) were combined under an argon atmosphere, and heated to 111°C to remove any moisture. The solution was cooled to 24°C, and **46** (28.30 g, 64.42 mmol) was added *via* cannula (3x50 mL toluene to aid transfer). The reaction was heated to 111°C for 1.0 h, and the solvent subsequently evaporated *in vacuo*. The remaining residue was purified over silica gel eluting with EtOAc/petroleum ether (2:8), to afford the product as a yellow oil (20.20 g, 83%). IR (thin film) 2940, 2867, 1684, 1463, 1008, and 882 cm^{-1}. Major diastereomer **49**. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.01-1.03 (18H, m), 1.07-1.09 (3H, m), 1.60-1.64 (4H, m), 1.95-2.07 (4H, m), 2.62-2.69 (1H, m), 3.45 (1H, t, J = 9.2 Hz), 3.59 (1H, dd, J = 4.8, 9.4 Hz), 4.59-4.63 (1H, m), 5.94 (1H, d, J = 9.7 Hz), 7.38 (1H, dd, J = 4.5, 9.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.4, 18.2, 21.1, 22.1, 24.8, 25.9, 37.9, 39.1, 40.7, 47.2, 65.1, 71.6, 91.8, 126.6, 155.4, 197.5. HRMS (CI) calcd for $C_{22}H_{39}O_3Si$ (M^+ + 1) 379.2668. Found 379.2652.

7β-(*tert*-Butyldimethylsilyl)oxy-8β-methyl-3α,10α-oxido-1-methylbicyclo[5.4.0^{3,8}] undec-1-ene-2-one 52 and 53. DBU (1.17 mL, 7.8 mmol) was added over 5 min to a stirred solution of **51** (1.04 g, 2.62 mmol) in dry toluene (200 mL) at reflux. The mixture was heated at reflux for 2h, stirred at room temperature for 2h, then the toluene evaporated *in vacuo*. The residue was partitioned between Et_2O (50 mL) and 1M H_2SO_4 (50 mL). The separated aqueous layer was washed with ether (2x20 mL), the organics combined, washed with water (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography over silica gel using hexane/EtOAc (97:3) as eluant to yield **52** and **53** (630 mg, 77%) as a 2.5:1 mixture of diastereomers. IR (film) 2954, 2856, 1682, 1462, 1380, 1253, 1109, 1079 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.02-0.01 (12H, m), 0.89-0.79 (24H, m), 1.73-1.27 (18H, m), 2.60-2.24 (4H, m), 3.58-3.44 (2H, m), 4.61-4.55 (2H, m), 6.91-6.89 (1H, m), 7.12-7.10 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -3.9, -3.7, 14.1, 14.5, 15.2, 15.4, 16.4, 17.9, 18.0, 19.2, 20.2, 23.3, 25.0, 25.7, 30.2, 35.5, 44.4, 44.5, 45.5, 71.2, 72.5, 75.4, 77.7, 90.6, 92.0, 132.3, 132.6, 147.7, 150.4, 197.8, 198.2. HRMS (CI) calcd for $C_{19}H_{33}O_3Si$ (M^+ + 1) 337.212. Found 337.212.

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References and Footnotes

†. Paclitaxel is the generic name for Taxol, which is now a registered trademark.

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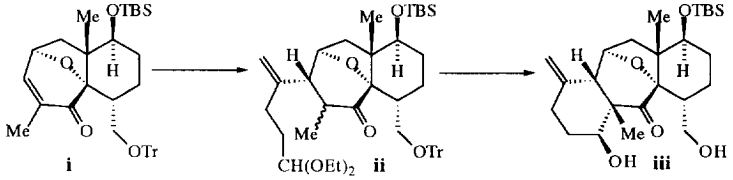
14. The compound **i** was converted into **ii** by conjugate addition of the appropriate vinyl lithium species, and acid hydrolysis followed by treatment with KCN resulted in the aldol product **iii** rather than cyanohydrin formation.



15. MM2 calculations support the notion that the major diastereomer formed in these cyclizations is the least sterically strained.

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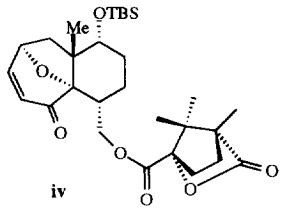
17. We initially used the (S) catalyst and converted the resulting alcohol into **iv**, whose structure and absolute stereochemistry was established by X-ray crystallography.



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19. The absolute stereochemistry of **52** was determined by an X-ray structure of a camphanate ester derivative.

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