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Taxane Diterpenes 3: Formation of the Eight-Membered B-Ring by Semi-Pinacol Rearrangement

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Abstract: The substituted furan carboxaldehyde **15** was converted into enone **20** *via* a stereoselective intramolecular pyrylium ylide-alkene cyclization. Subsequent elaboration of **20** into the triflate **23**, followed by solvolysis in acidic trifluoroethanol resulted in quantitative rearrangement to the taxane B/C core **24**. At a higher oxidation level **27** was ring expanded to give **28**. The ring expansion strategy could also be initiated by β-elimination of the 3α,10α-oxido bridge. Treatment of **50** with MeOH at reflux gave **52**. Similar transformations in the 7-oxy series resulted in ring B expansion of **67** to give **68**, and **75** to give **76**.

Introduction

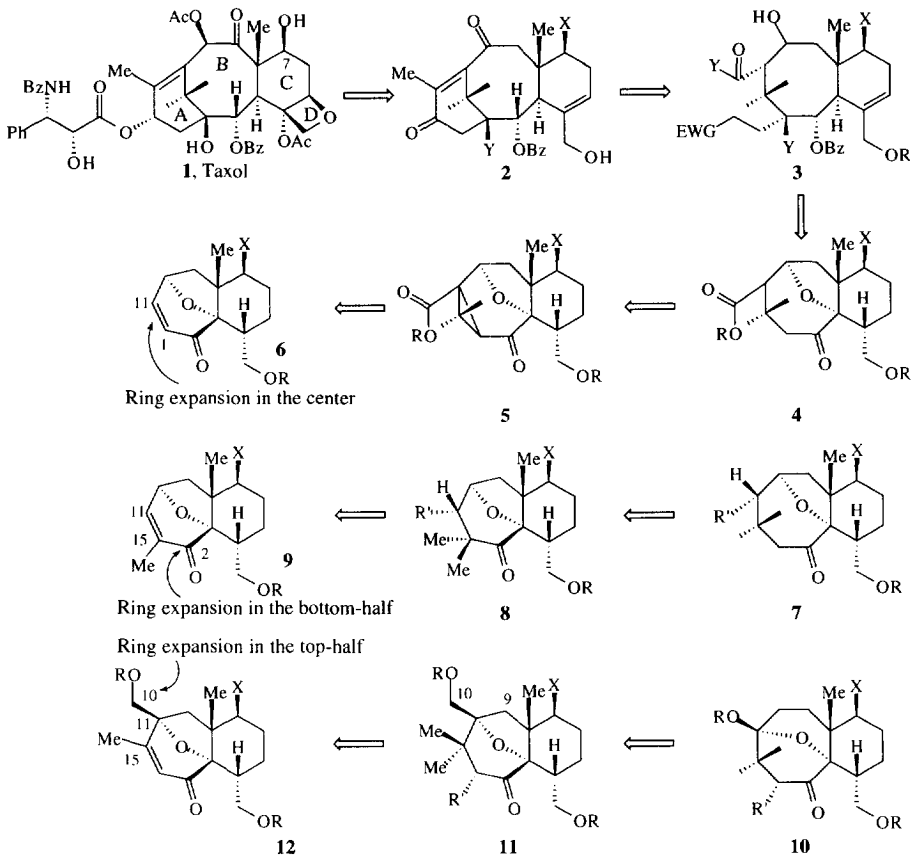
The previous papers describe the pyrylium ylide strategy for the enantiospecific synthesis of a number of bicyclo[5.4.0]undecenones as precursors to the taxane ABC core skeleton, and as potential precursors to the antitumor agent TAXOL®† **1**, and simpler taxane analogues.[1,2] We have divided the strategy into three distinct avenues that would eventually converge upon advanced intermediates such as **2** and **3** (or equivalents). All three options involve ring expansion of the B-ring from a seven-membered ring into an eight-membered ring, **Scheme 1**.

The first option, as described in the previous paper, involves ring expansion *via gem*-methycyclopropanation; thus **4** is available from **6** through the intermediacy of **5** (ring expansion in the center).

The second option involves ring expansion in the bottom-half, and requires the conversion of **9** into **8**, and subsequently into **7**. While the former reaction of **9** to give **8** was straightforward, we could not achieve any success in the ring expansion step because of the reluctance of **8** to undergo carbonyl addition reactions (steric hindrance).[3]

The third option incorporates the additional B-ring carbon atom into the bicyclo[5.4.0]undecenone core as **12**, which after forming the *gem*-methyl group **11**, is suitably arranged for a semi-pinacol-type ring expansion[4] resulting in **10** (or a regioisomer).[5] Ring expansion in the top-half does not need the formation of a hindered carbon-carbon bond since the C-10 carbon atom can be built into the furan component precursor to the pyrylium ylide cyclization. The first requirement is the synthesis of **12** (or an equivalent) using the pyrylium ylide-alkene cyclization strategy.

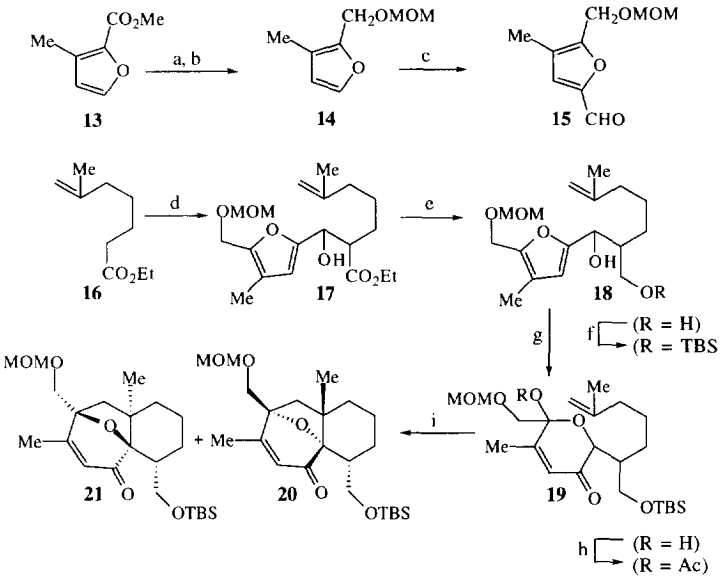
Scheme 1, Ring Expansion Strategy



Ring Expansion in the Top-Half: Reductive Elimination of the Oxido-Bridge

It was initially decided to examine the feasibility of this ring expansion strategy in the racemic 7-deoxy series (X = H, **Scheme 1**). The aldehyde **15** was obtained in three steps from the known methyl furoate **13, Scheme 2**.[6] Reduction of **13** with lithium aluminum hydride, followed by protection as its methoxymethyl (MOM) ether gave **14** (84% overall yield). Lithiation of **14** with *n*-butyl lithium, followed by quenching with DMF afforded the desired aldehyde **15** (74%). The lithium enolate of **16** was treated with **15** at -70°C to give **17**, which was reduced *in situ* with lithium aluminum hydride to give **18** (R = H, 82%). The primary hydroxyl group of **18** (R = H) was selectively protected as its TBS ether under standard conditions. Oxidative rearrangement[7] of **18** (R = TBS) with *tert*-BuOOH/catalytic $VO(acac)_2$ gave hydroxypyranenone **19** (R = H). Subsequent acetylation afforded the pyrylium ylide precursor **19** (R = Ac) in excellent overall yield. Heating a solution of **19** (R = Ac) in toluene, in the presence of DBU provided the desired enone **20/21** as an 8:1 mixture of diastereomers. The observed diastereoselectivity is in keeping with previous results.[1] It is also noteworthy that the cyclization of **19** to give **20** results in the creation of three quaternary centers.

Scheme 2



Conditions:- a) $LiAlH_4$/THF/-30°C, (93%). b) $CH_3OCH_2Cl/NEtPr_2^i/CH_2Cl_2$/-10° to 25°C, **14** (90%). c) *n*-BuLi/THF, followed by DMF, **15** (74%). d) LDA/THF/-70°C, followed by **15**. e) $LiAlH_4$/-70° to 25°C, **18** (R = H, 82%). f) TBSCl/imidazole/DMF, **18** (R = TBS, 97%). g) *t*-BuOOH/VO(acac)$_2$(cat)/CH_2Cl_2, **19** (R = H, 92%). h) Ac_2O/Et_3N/DMAP, **19** (R = Ac, 92%). i) DBU/PhMe/100°C, **20/21** (70%, 8:1).

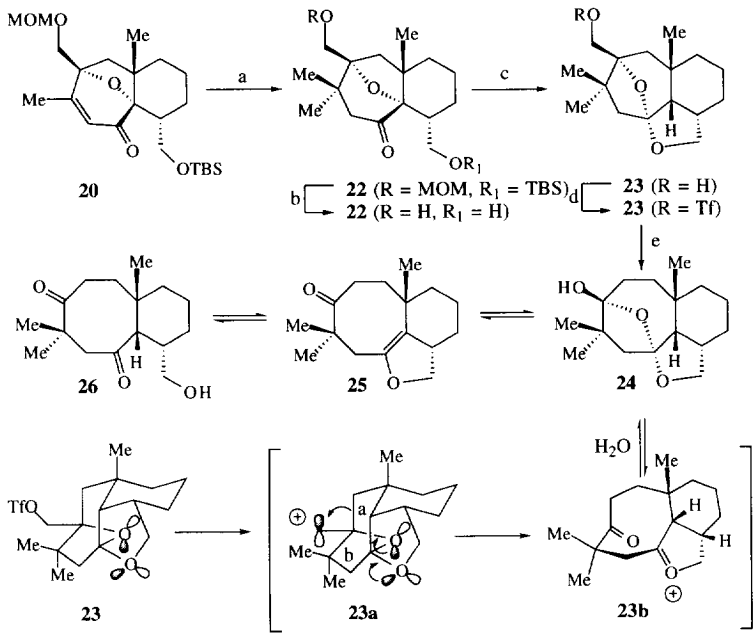
Treatment of **20** with MeMgBr/CuBr/Me_2S, followed by exposure to *p*-TsOH/MeOH gave the diol **22**, **Scheme 3**. Reductive cleavage (Hg/Zn amalgam) of the oxido-bridge under acidic conditions resulted in internal ketalization to give **23** (**Figure 1**, Chem 3D from X-ray coordinates). Treatment of the derived triflate **23** with CF_3CH_2OH/H_3O^+ (low nucleophilicity) resulted in a rapid and clean conversion into the spiro-hemiketal **24** (100%, **Figure 2**, Chem 3D from X-ray coordinates). When **24** was heated in toluene with catalytic *p*-toluenesulfonic acid, azeotropic removal of water resulted in the formation of **25**. When water was added to the reaction mixture, **24** was reformed.

In an acyclic systems the migratory aptitude of a *tert*-butyl group is 240 times greater than that of an ethyl group[8], and thus the more substituted C-11 atom might be expected to migrate preferentially. In a cyclic system such as **23**, these rearrangements are often controlled by powerful stereoelectronic effects[9] and the preferred migration is governed by the relative alignment of the molecular orbitals involved. In such cases, the donating electron pair should be anti-periplanar to the bond that is migrating, and this migrating C-C bond should be anti-periplanar to the leaving group. In the case of **23**, the migrating bonds **a** and **b** both have an anti-periplanar electron pair on the bridging oxygen. We only have observed the products resulting from migration of the C-9 bond (pathway **a**).

In order to conduct the ring expansion at a higher oxidation level, alcohol **23** was oxidized with TPAP /NMO[10] to the aldehyde **27** (64%), **Scheme 4**. Treatment of **27** with excess boron trifluoride etherate resulted in ring expansion and α-ketol shift (acyloin rearrangement) to give the ketone **28** (70%), (**Figure 3**, Chem 3D

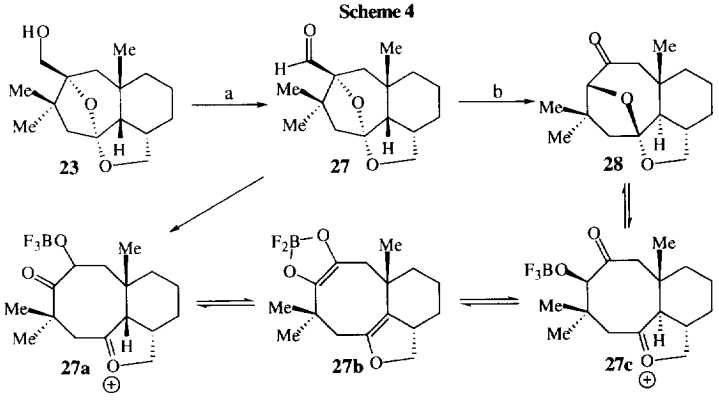
from X-ray coordinates). It is interesting to note that the B/C ring fusion in **24** is *cis*-fused, whereas **28** is *trans*-fused. A plausible mechanistic interpretation of this transformation involves conversion of **27** to the intermediate oxonium ion **27a**, and equilibration *via* **27b** and **27c** to eventually arrive at the thermodynamically most stable product, namely **28**.

Scheme 3



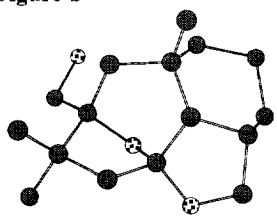
Conditions:- a) MeMgBr/CuBr.SMe$_2$ (80%). b) *p*-TsOH/MeOH **22** (R = R$_1$ = H, 76%). c) Zn/Hg/HCl/PhMe, **23** (R = H, 79%). d) Tf$_2$O/2,6-di-*tert*-butyl-4-methylpyridine/CH$_2$Cl$_2$/-10°C, **23** (R = Tf, 80%). e) CF$_3$CH$_2$OH/H$_2$O/H$_2$SO$_4$/80°C/1 h, **24** (100%).

Scheme 4



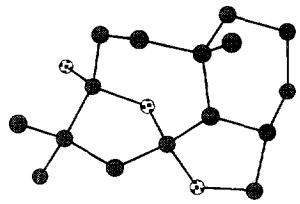
Conditions:- a) TPAP/NMO/MeCN, **27** (64%). b) BF$_3$.OEt$_2$/CH$_2$Cl$_2$, **28** (70%).

Figure 1



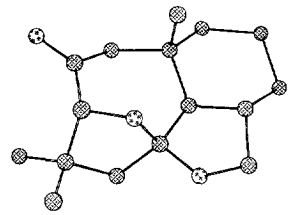
Chem 3D of **23** (R = H) from X-ray coordinates

Figure 2



Chem 3D of **24** from X-ray coordinates

Figure 3

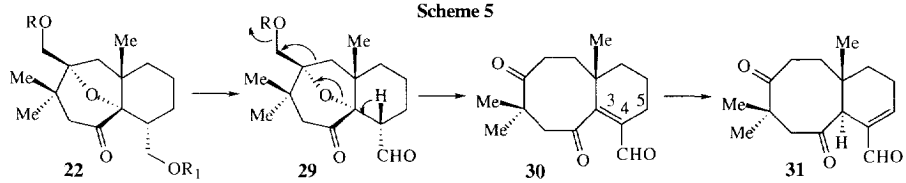


Chem 3D of **28** from X-ray coordinates

Ring Expansion in the Top-Half: β-Elimination of the Oxido-Bridge

While the above results establish the validity of the semi-pinacol ring expansion strategy, the reductive cleavage of the oxido-bridge does not allow, in a more direct fashion, the correct oxidation level at C-3/4 and eventually at C-4/5. Consequently, it was decided to examine the semi-pinacol rearrangement where the oxido-bridge is β-eliminated rather than reductively opened, **Scheme 5**. In order to implement this strategy it is necessary to oxidize the C-20 alcohol **22** (R_1 = OH) to the corresponding aldehyde **29**, which should undergo the depicted β-elimination to give **30**. We know from related studies on the 7-hydroxy series that the newly created C-3/4 double bond can be isomerized into the C-4/5 position (**31**), and also give the thermodynamically more stable trans-B/C ring fusion.[11]

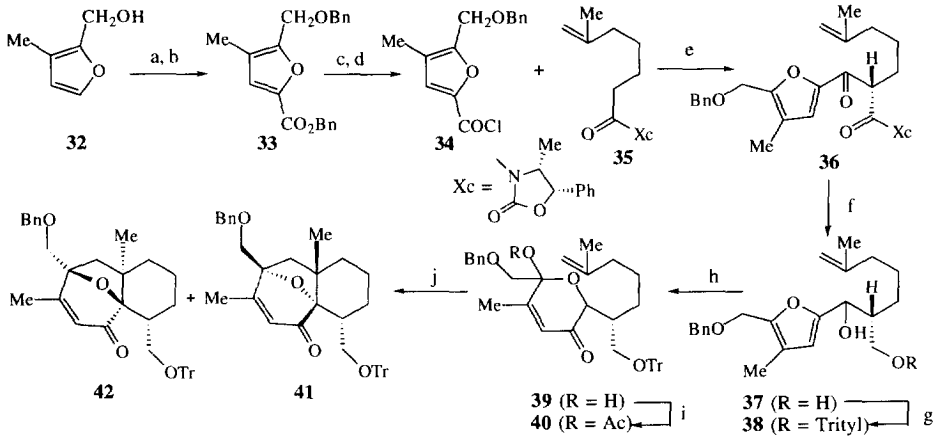
Scheme 5



To examine the above option we required that the protecting groups on the primary alcohols (**22**, R and R_1) be readily distinguishable, and we also carried out the reactions in the an enantiomerically enriched series, **Scheme 6**.

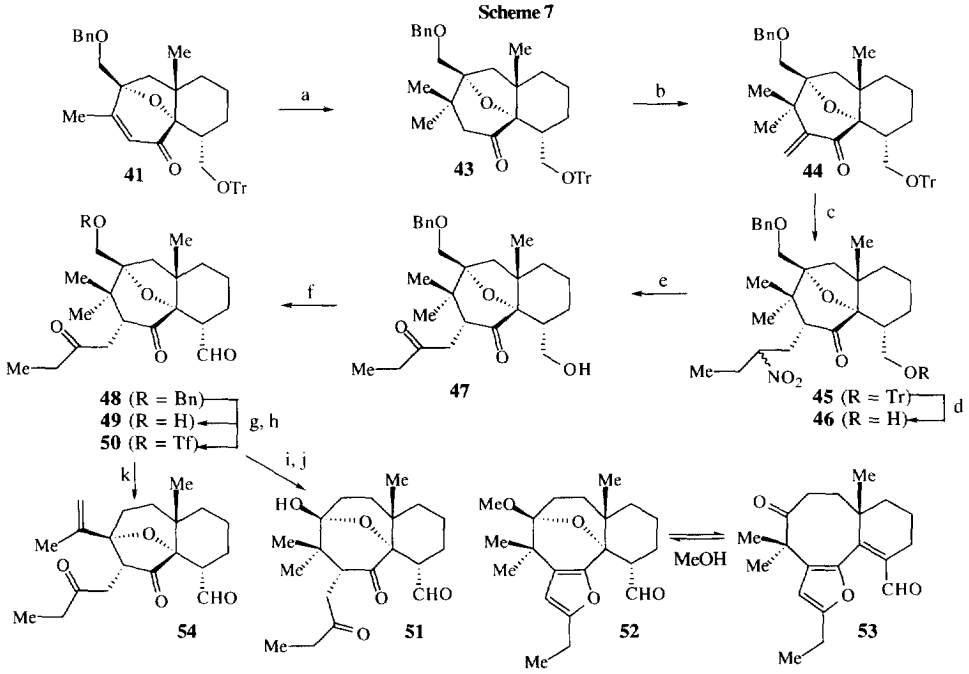
The furyl alcohol **32** was converted into the benzyl ester **33** by treatment with *n*-BuLi, followed by carbon dioxide gas, and the resulting hydroxyacid was benzylated to give **33**. Subsequently hydrolysis and treatment with oxalyl chloride gave the acid chloride **34**. Claisen condensation of **34** with **35** gave **36**, which was not isolated, but directly reduced with $LiBH_4$/MeOH to give the diol **37** as a mixture of diastereomers at the secondary alcohol. The diastereomeric excess for the formation of **36** is expected to be greater than 95% based upon the studies with less substituted furan aldehydes.[1] Tritylation and oxidative rearrangement served to convert **37** into **39** *via* **38**.[12] Acetylation of **39** gave **40**, which on heating in toluene in the presence of DBU resulted in the formation of the two diastereomers **41** and **42** (11:1). One crystallization provided the desired pure diastereomer **41**. At this stage we decided to introduce the necessary A-ring carbon atoms *via* the C-1 exomethylene adduct **44**, **Scheme 7**.

Scheme 6



Conditions:- a) *n*-BuLi/THF/-40 to 0°C, followed by cooling to -70°C/CO_2. b) BnBr/DMF/NaH/*n*-Bu_4NI/100°C/18h, **33** (86% overall). c) NaOH/THF/reflux (63%). d) Oxalyl chloride/CH_2Cl_2/DMF. e) **35**/LiN(TMS)$_2$/THF/-78°C followed by **34**. f) $LiBH_4$/THF/MeOH, **37** (81% overall). g) TrCl/CH_2Cl_2/Et_3N/DMAP/25°C, **38** (80%). h) O_2/rose bengal/CH_2Cl_2/MeOH/-55°C, followed by Me_2S. i) Ac_2O/CH_2Cl_2/Et_3N/DMAP/25°C, **40**. j) PhMe/DBU/reflux, **41/42** (45% from **38**, 11:1).

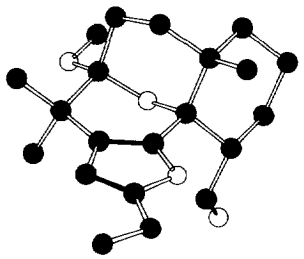
Scheme 7



Conditions:- a) MeMgBr/CuBr.SMe_2, **43** (95%). b) KN(TMS)$_2$/$(CH_2O)_n$/RT, **44** (95%). c) 2-Nitropropane/DMSO/K_2CO_3/1hr/RT, **45** (93%). d) CSA/CH_2Cl_2/MeOH, **46** (76%). e) $TiCl_3$/MeOH/12hr/RT, **47** (75%). f) Dess-Martin oxidation, **48** (86%). g) Pd(OH)$_2$/cyclohexene/*i*-PrOH, **49** (97%). h) Tf_2O/2,6-di-*tert*-butyl-4-methylpyridine/CH_2Cl_2/-40°C (used immediately). i) H_2O/2,6-lutidine/reflux, **51** (50% from **49**). j) MeOH/reflux/20hr, **52** (53%). k) *t*-BuOH/2,6-di-*tert*-butyl-4-methylpyridine/reflux, **54** (65%).

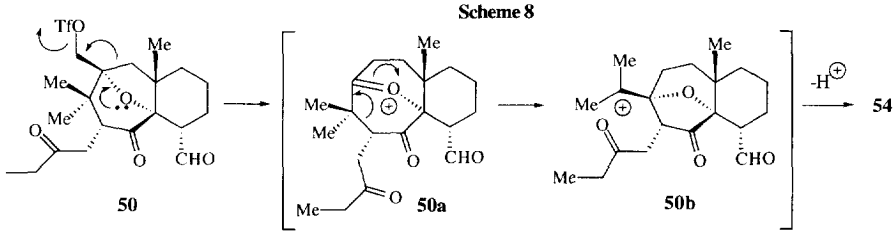
Treatment of **43** with KHMDS in tetrahydrofuran followed by paraformaldehyde resulted in the exomethylene enone **44** (95%). The exomethylene ketone **44** was exposed to 1-nitropropane/DMSO/K_2CO_3 to give the conjugate addition adduct **45** (>90%). The nitro group was transformed into a ketone by the titanium trichloride modification of the Nef reaction[13], and the C-20 -trityl group removed to give **47**. Dess-Martin oxidation of **47** gave **48**. Hydrogenolysis of the benzyl ether provided **49**, which was converted into the triflate derivative **50** (80% from **48**). Solvolysis of **50** in methanol in the presence of lutidine gave the ring-expanded methoxy ketal **52** (**Figure 4**, Chem 3D from X-ray coordinates). Treatment of **52** with lithium diisopropylamide caused β-elimination to give **53**, which readily reforms **52** when exposed to methanol. Under the reaction conditions the 1,4-diketone **51** is rapidly converted into the furan **52**. If the reaction is conducted under more basic conditions (DBU), that prevent furan formation, ring expansion does not take place and a C-10 spiro-epoxide was isolated.[14] Curiously, when **50** was treated with *t*-BuOH/2,6-di-*tert*-butyl-4-methylpyridine/reflux, the rearranged adduct **54** was isolated (65%). **Scheme 8**, suggests a possible mechanistic rationale for this transformation. In the presence of a nucleophile, such as water, the oxonium ion **50a** is trapped to give **51**, whereas, in a non-nucleophilic medium further rearrangement takes place to **50b**, which on proton loss gives **54**. It appears likely that these rearrangements do not proceed by β-elimination as envisioned in **Scheme 5**, since much stronger bases would be required, and spiro-epoxide formation would be a competitive, if not predominant pathway (see above).

Figure 4



Chem 3D of **52**
from X-ray coordinates

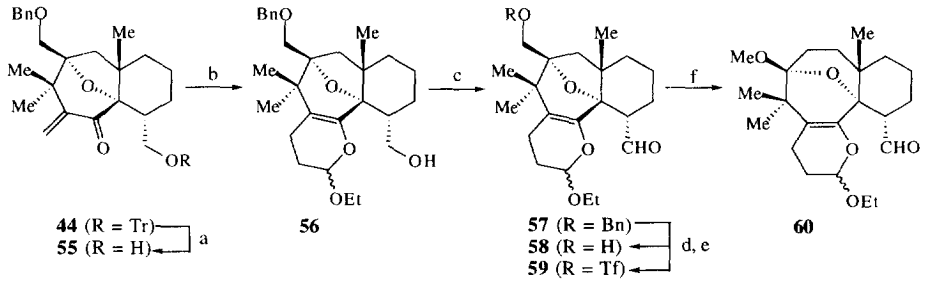
Scheme 8



Since we could not effectively prevent the 1,4-dicarbonyl system in the ring expansion reaction from forming a furan, we explored other ways of masking the C-1 side-chain. While the exomethylene ketone **44** did not react with ethylvinyl ether under the Danishefsky[15] conditions using [Eu(FOD)$_3$] as a catalyst, the C-20 deprotected compound **55** cleanly gave the dihydropyran **56** as a mixture of epimers at the anomeric position. Dess-Martin oxidation of **56**, gave **57**. Removal of the benzyl group by hydrogen transfer hydrogenolysis provided **58**, which on treatment with Tf_2O/2,6-lutidine gave the neopentyl triflate **59**. Heating **59** in methanol in the presence of 2,6-lutidine (trific acid scavenger) resulted in ring expansion to give **60** (82%).

Attempts to manipulate the functionality for elaboration of the A-ring in both the furan and pyran adducts **52** and **60** respectively, did not lead to any productive advances.

Scheme 9

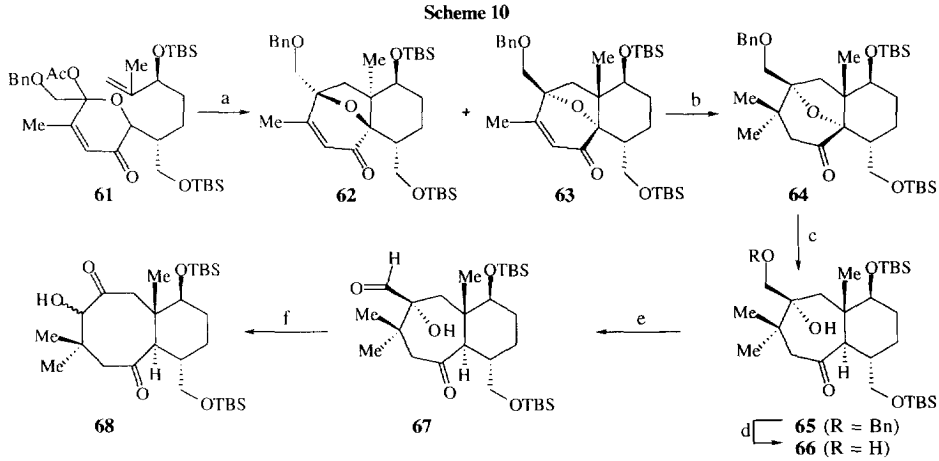


Conditions:- a) *p*-TSA/CH_2Cl_2/MeOH, **55** (89%). b) Ethylvinylether/Eu(FOD)3, **56** (84%). c) Dess-Martin oxidation, **57** (84%). d) $Pd(OH)_2$/cyclohexene/*i*-PrOH, **58** (95%). e) Tf_2O/2,6-lutidine/CH_2Cl_2/-40°C, **59** (used immediately). f) MeOH/2,6-lutidine, **60** (82% from **58**).

Ring Expansion in the Top-Half: Base Induced α-Ketol Shift, 7-Oxy Series

Using the same pyrylium ylide alkene cyclization methodology, the pyranenone **61** was heated in toluene in the presence of DBU to give **63** (73%). Only small amounts of the other diastereomer **62** (ca. 6-8%) were formed. The enone **63** was converted into **64**, and the oxido-bridge reductively cleaved by treatment with sodium in *n*-Bu_2O to give **65** (43%). The B/C-ring fusion is assigned as *trans* on the basis of the vicinal coupling of the C-3β proton, δ 3.23 (J = 8.8 Hz). The benzyl ether protecting group was removed by standard hydrogenolysis to give **66**, and Swern oxidation provided the aldehyde **67**. Treatment of **67** with $LiN(TMS)_2$ in THF resulted in clean conversion into the rearranged α-ketol **68** (75%). The C-11 proton appears as a singlet at δ 3.80, and two AB spin systems were evident. The stereochemistry at the C-11 position was not assigned. It is probable that the regiochemistry of the α-ketol shift is determined by protonation of the intermediate enediolate, and consequently no conclusions should be made about which bond migrates.

Scheme 10

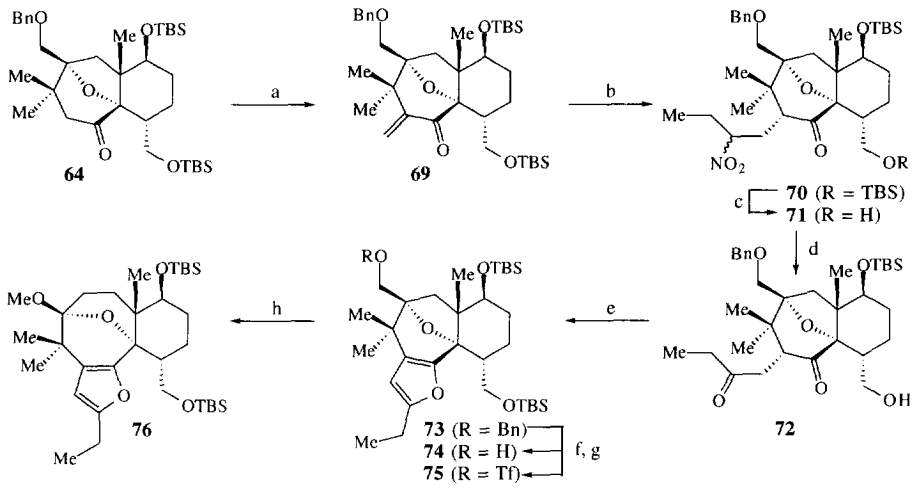


Conditions:- a) PhMe/DBU/reflux 16.5 h, **63** (73%). b) MeMgBr/CuBr.SMe_2, **64** (85%). c) Na/*n*-Bu_2O, **65** (43%). d) 10% $Pd/C/H_2$/EtOH, **66** (98%). e) DMSO/$(COCl)_2$/Et_3N/CH_2Cl_2, **67** (83%). f) $LiN(TMS)_2$/THF/-78°C to 25°C, **68** (75%).

Ring Expansion in the Top-Half: Solvolysis of C-10 Triflate, 7-Oxy Series

Finally, we applied the solvolytic ring expansion conditions, where the 1,4-diketone (see **72**) has been converted into a furan, **Scheme 11**. The ketone **64** was converted into the 1,4-diketone **72** by methylenation to give **69**, conjugate addition of nitropropane, followed by deprotection of the labile C-20 -TBS and a Nef reaction to provide **72**. Exposure of **72** to acid catalyzed dehydration conditions gave the furan **73** (after reprotection at C-20). This sequence of deprotection and reprotection was mandated by the lability of the -TBS group to the dehydration conditions. The benzyl ether in **73** was hydrogenolyzed to **74**, and converted into the triflate **75**. Merely heating **75** in methanol, resulted in very clean conversion into the ring expanded product **76**, thus supporting that the β-elimination in **Scheme 5**, need not take place for ring expansion to occur.

Scheme 11



Conditions:- a) $KN(TMS)_2/(CH_2O)_n$/RT, **69** (85%). b) 2-Nitropropane/DMSO/THF/K_2CO_3/1hr/25°C, **70** (86%). c) HF.py/MeCN, **71** (80%). d) NaOMe/MeOH followed by conc. H_2SO_4, **72** (72%). e) i. CSA/PhMe/reflux. ii. TBSCl/imidazole/DMF, **73** (60%). f) 10% Pd/C/H_2/EtOH, **74** (68%). g) Tf_2O/2,6-di-*tert*-butyl-4-methylpyridine/CH_2Cl_2/-5° to 25°C **75** (used immediately). h) MeOH/reflux, **76** (81%).

Summary

The solvolytic semi-pinacol type rearrangement of the neopentyl triflates **23** (R = Tf), **50** (R = Tf), **59** R = Tf) and **75** (R = Tf) all provide a very high yielding and regiospecific method for construction of the eight-membered B-ring of the taxanes. The rearrangements require the extremely potent leaving group ability of a triflate, since the corresponding tosylates did not undergo rearrangement under forcing conditions.

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 under usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140°C, 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; dichloromethane and benzene were distilled from calcium hydride under argon.

5-Methoxymethoxymethyl-4-methyl-2-furancarboxaldehyde 15. To a solution of methyl 3-methylfuroate (63.5 g, 0.454 mol) in tetrahydrofuran (600 mL) at -30°C was added lithium aluminum hydride (18.1 g, 0.454 mol) portion wise over 1 h, keeping the temperature below 0°C. After stirring the mixture for a further 1 h at 0°C, the mixture was quenched by slow addition of EtOAc (50 mL), followed by water (50 mL). Further quantities of water (200 mL), EtOAc (200 mL), aqueous sodium hydroxide (2 N, 50 mL) and celite (100 g) were added, and after stirring the mixture vigorously for 30 min it was filtered, the layers were partitioned, and the aqueous layer extracted with EtOAc (2x150 mL). The combined extracts were dried ($MgSO_4$), and evaporated to yield **32** (47.1 g, 93%), which was used without further purification. IR (neat) 3340, 2928, 2870, 1507, 1446, 1414, 1248, 1209, 1154, 1108, 1003, 925, 891, 764, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (3H, s), 2.71 (1H, bs), 4.47 (2H, s), 6.16 (1H, s), 7.24 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.5, 54.8, 112.9, 117.4, 141.3, 149.2. HRMS calcd for $C_6H_8O_2$ (M^+) 112.0524. Found 112.0526.

To a solution of **32** (47.0 g, 0.420 mol) in dichloromethane (500 mL) was added diisopropylethylamine (85.5 mL, 0.50 mol), and the solution cooled to -10°C. Chloromethyl methyl ether (63.7 ml, 0.84 mol) was added drop wise over 1 h, and the reaction mixture stirred at 25°C for 3 h. Saturated aqueous $NaHCO_3$ (300 mL) was added slowly with stirring, and after gas evolution had ceased (30 min) the layers were partitioned, and the aqueous layer extracted with dichloromethane (2x150 mL). The combined extracts were dried ($MgSO_4$), and evaporated *in vacuo* to give **14** (61.1 g, 90%). IR (neat) 2932, 1639, 1211, 1147, 1095, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.0 (3H, s), 3.4 (3H, s), 4.5 (2H, s), 4.6 (2H, s), 6.2 (1H, d, J = 1.6 Hz), 7.3 (1H, d, J = 1.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.1, 56.1, 58.4, 94.9, 112.7, 119.1, 141.8, 146.62. HRMS (CI) calcd for $C_8H_{12}O_3$ (M^+) 156.0786. Found 156.0776.

A solution of **14** (61.0 g, 0.39 mol) in dry tetrahydrofuran (500 mL) at -70°C was treated with *n*-BuLi (10 M in hexanes) added over 30 min, and the mixture warmed to 0°C over 1 h, before recooling to -70°C. Dry dimethylformamide (25 mL) was added drop wise, the mixture stirred for 30 min, and quenched with saturated aqueous NH_4Cl (200 mL). The layers were separated, and the aqueous layer was extracted with

dichloromethane (2x200 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Kugelrohr distillation afforded **15** as a pale yellow oil (53.5 g, 74 %). IR (neat) 2933, 2887, 2825, 1682, 1528, 1449, 1359, 1318, 1211, 1150, 1100, 1039, 1001, 943, 921, 828, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (3H, s), 3.37 (3H, s), 4.55 (2H, s), 4.64 (2H, s), 7.04 (2H, s), 9.55 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.5, 55.4, 58.9, 95.6, 121.9, 123.5, 151.5, 153.4, 177.9. HRMS (CI) calcd for $C_9H_{13}O_4$ (M^+) 184.0736. Found 184.0745.

(±)-2-[2-(5-Methoxymethoxymethyl-4-methylfuryl)-2-hydroxymethyl]-6-methyl-6-hepten-1-ol 18 (R = H). A solution of **16** (26.6 g, 0.156 mol) in tetrahydrofuran (50 mL) was slowly added to a cold (-75°C) solution of lithium diisopropylamide (0.163 mol) in tetrahydrofuran (400 mL) such that the internal temperature stayed below -60°C. After stirring the solution for 30 min a solution of **15** (27.2 g 0.148 mol) in tetrahydrofuran (50 mL) was added, and the mixture stirred for 1 h. Lithium aluminum hydride (14.0 g, 0.35 mol) was added portion wise, and the mixture allowed to warm to 25°C overnight. The mixture was quenched with EtOAc (50 mL) followed by 10% aqueous sodium tartrate solution (50 mL). Further quantities of EtOAc (200 mL), 10% sodium tartrate solution (200 mL) and celite (100 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 layer extracted with EtOAc (2x150 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Chromatography over silica gel (20%-40%-60% EtOAc/hexanes) gave **18** (R = H) as a colorless oil (36.9 g, 82%) (mixture of two diastereomers). IR (neat) 3396, 3073, 2934, 1650, 1568, 1454, 1285, 1211, 1151, 1092, 1038, 921, 883, 812, 741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.1-1.3 (4H, m), 1.3-1.5 (6H, m), 1.63 (6H, s), 1.85-1.95 (4H, m), 1.99 (6H, s), 3.34 (6H, s), 3.6-3.8 (4H, m), 4.43 (4H, s), 4.55-4.65 (9H, m), 4.82 (1H, d, J = 3.6 Hz), 6.07 (2H, d, J = 3.0 Hz). HRMS (CI) calcd for $C_{17}H_{28}O_5$ (M^+) 312.1937. Found 312.1938.

(±)-2-[2-(5-Methoxymethoxymethyl-4-methylfuryl)-2-hydroxymethyl]-6-methyl-6-hepten-1-(*tert*-butyldimethylsilyl)oxy ether 18 (R = TBS). A solution of **18** (R = H) (36.0 g, 0.115 mol) in dimethylformamide (200 mL) was treated with imidazole (9.40 g, 0.138 mol) and cooled to -10°C. The mixture was treated with *tert*-butyldimethylsilyl chloride (19.1g, 0.127 mol) and stirred at 25°C for 3 h. Et_2O (300 mL) was added, and the precipitate filtered, washing with Et_2O. Saturated aqueous $NaHCO_3$ (200 mL) was added to the filtrate, and the layers separated. The aqueous layer was extracted with Et_2O (2x200 mL). The combined extracts were washed with water (4x150 mL), brine (150 mL), dried ($MgSO_4$) and evaporated to yield **18** (R = TBS) as a pale yellow oil (47.6 g, 97%) (mixture of diastereomers). IR (neat) 3471, 2930, 1672, 1649, 1471, 1386, 1255, 1211, 1149, 1097, 1039, 939, 886, 837, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.21 (6H, s), 0.52 (6H, s), 0.85 (6H, s), 0.87 (6H, s), 1.2-1.5 (10H, m), 1.66 (6H, s), 1.9-2.0 (4H, m), 2.01 (6H, s), 3.36 (6H, s), 3.6-3.8 (4H, m), 4.45 (4H, s), 4.60 (4H, s), 4.6-4.7 (5H, m), 4.87 (1H, br s), 6.08 (2H, d, J = 9.6 Hz). HRMS (CI) calcd for $C_{23}H_{42}O_5Si$ (M^+) 426.2808. Found 426.2801.

(±)-2-[2-(6-Hydroxy-6-methoxymethoxymethyl-5-methylpyran-4-en-3-one)]-6-methyl-6-hepten-1-(*tert*-butyldimethylsilyl)oxy ether 19 (R = H). A solution of **18** (R = TBS) (47.0 g, 0.110 mol) in dichloromethane (200 mL) was stirred at room temperature and *tert*-butyl hydroperoxide (110 mL, 3 M in isooctane 0.33 mol) added. The mixture was cooled to -30°C and solid vanadyl acetoacetate (0.9 g, 3.39

mmol) added. The solution became burgundy in color and was stirred at -10°C for 14 h. Water (200 mL) was added and the layers separated. The aqueous phase was extracted with dichloromethane (2x150 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to give **19** (R = H) as a brown oil (44.4 g, 92%) (mixture of two diastereomers). IR (neat) 378, 2933, 2856, 1339, 1683, 1463 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.04 (6H, s), 0.03 (6H, s), 0.82 (9H, s), 0.85 (9H, s), 1.1-1.2 (10H, m), 1.62 (3H, s), 1.68 (3H, s), 1.8-2.0 (4H, m), 1.90 (3H, s), 2.00 (3H, s), 2.20 (2H, m), 3.39 (6H, s), 3.5-3.6 (4H, m), 3.75 (4H, m), 4.43 (1H, s), 4.5-4.7 (8H, m), 4.85 (1H, s), 5.90 (1H, s), 5.95 (1H, s). MS (CI) 293 (31), 385 (52), 386 (12), 389 (12), 425 (100), 426 (28), 427 (32), 441 (11), 443 (96).

(±)-2-[2-(6-Acetoxy-6-methoxymethoxymethyl-5-methylpyran-4-en-3-one)]-6-methyl-6-hepten-1-(*tert*-butyldimethylsilyl)oxy ether 19 (R = Ac). To a solution of the **19** (R = H) (44.3 g, 0.10 mol) in Et_3N (100 mL) was added 4-dimethylaminopyridine (DMAP) (100 mg) and the solution cooled to -10°C. Acetic anhydride (100 mL) was added, and the mixture stirred at 25°C for 3 h. Saturated aqueous $NaHCO_3$ (200 mL) was added at -10°C, and the mixture extracted with dichloromethane (3x150 mL). The dichloromethane layers were washed with saturated aqueous $NaHCO_3$ (2x200 mL), water (200 mL), brine (200 mL), dried ($MgSO_4$), and evaporated to yield **19** (R = Ac) as a brown oil (44.4 g, 92%) (mixture of two diastereomers). IR (neat) 2929, 2857, 1750, 1683, 1436, 1367, 1226, 1045, 947, 837, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.24 (6H, s), 0.02 (6H, s), 0.78 (9H, s), 0.84 (9H, s), 1.1-1.4 (10H, m), 1.62 (3H, s), 1.65 (3H, s), 1.8-1.95 (4H, m), 1.95 (4H, m), 1.95 (6H, s), 2.38 (2H, m), 3.30 (3H, s), 3.33 (3H, s), 3.4-3.6 (4H, m), 4.00 (4H, m), 4.45 (1H, s), 4.5-4.65 (8H, m), 4.74 (1H, s), 6.02 (1H, s), 6.08 (1H, s). Used directly in the next stage.

(±)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-8β,11-dimethyl-10β-methoxymethoxymethyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-1-en-2-one 20. To a solution of **19** (R = Ac) (44.4 g, 0.10 mol) in dry toluene (4.0 L) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (45.6 mL, 0.30 mol) and the solution heated at 100°C for 14 h. The reaction mixture was cooled and the toluene removed *in vacuo*. The residue was dissolved in Et_2O (500 mL) and washed with 2N HCl (4x100 mL), water (150 mL), and brine (150 mL). The Et_2O layer was dried ($MgSO_4$) and evaporated to give a brown oil. Chromatography over silica gel eluting with 10% EtOAc/hexanes gave **20** and **21** as a pale yellow oil (27.1 g, 70%) (mixture of diastereomers 8:1). IR (neat) 2929, 2823, 2770, 1683, 1627, 1463, 1386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.04 (3H, s), -0.03 (3H, s), 0.85 (9H, s), 0.92 (3H, s), 1.0-1.05 (2H, m), 1.1-1.2 (2H, m), 1.25-1.35 (4H, m), 2.00 (3H, s), 2.5 (1H, m), 3.30-3.55 (2H, m), 3.34 (3H, s), 3.65 (1H, d, J = 14.1 Hz), 3.82 (1H, d, J = 14.2 Hz), 4.84 (2H, m), 5.76 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.6, -5.5, 18.0, 18.4, 21.1, 21.5, 24.6, 25.8, 38.0, 40.1, 40.3, 49.8, 55.2, 64.9, 68.7, 81.6, 91.8, 96.5, 125.23, 168.1, 197.3. HRMS (CI) calcd for $C_{23}H_{40}O_5Si$ (M^+ + 1) 425.2723. Found 425.2720.

(±)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-8β,11,11-trimethyl-10β–methoxymethoxymethyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undecan-2-one 22 (R = MOM, R_1 = TBS). To a solution of **20** (4.01 g, 9.11 mmol) in tetrahydrofuran (100 mL) containing $CuBr.SMe_2$ (200 mg) was added MeMgBr (13.7 mL, 1.4 M in tetrahydrofuran, 18.2 mmol) over 3 h *via* syringe pump. The mixture was quenched with saturated aqueous NH_4Cl (100 mL), and extracted with chloroform (3x75 mL). The combined extracts were dried ($MgSO_4$) and

the evaporated to yield **22** (R = MOM, R_1 = TBS) as a yellow oil (3.30 g, 80 %). IR (neat) 2931, 2858, 1715, 1471, 1385, 1253, 1226, 1150, 1105, 1095, 1009, 887, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.07 (3H, s), 0.05 (3H, s), 0.84 (9H, s), 0.86 (3H, s), 0.90 (3H, s), 1.09 (3H, s), 1.0-1.6 (6H, m), 1.75 (2H, dd, J = 4.7, 13.0 Hz), 2.12 (2H, s), 2.25 (1H, m), 3.3-3.54 (2H, m), 3.37 (3H, s), 3.65 (2H, dd, J = 2.8, 11.0 Hz), 4.68 (2H, dd, J = 1.6, 6.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.5, -5.3, 17.9, 19.7, 21.3, 24.6, 24.8, 24.9, 25.9, 37.4, 37.5, 39.8, 42.8, 42.9, 51.8, 55.2, 65.1, 67.4, 84.7, 91.7, 96.8, 209.4. HRMS (CI) calcd for $C_{24}H_{44}O_5Si$ (M^+ + 1) 441.3036. Found 441.3048.

(±)-10β-Hydroxymethyl-4α-hydroxymethyl-3α,10α-oxido-8β,11,11-trimethylbicyclo[5.4.0^{3,8}] undeca-2-one 22 (R = H, R_1 = H). To a stirred solution of **22** (R = MOM, R_1 = TBS) (1.10 g, 2.50 mmol) in methanol (60 mL) was added *p*-toluenesulfonic acid monohydrate (20 mg). The mixture was heated at 65°C for 24 h, and on cooling, the solvent was evaporated. The residue was dissolved in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), and evaporated *in vacuo* to give **22** (R = H, R_1 = H) (535 mg, 76%). IR (neat) 3420, 2945, 2864, 1706, 1641, 1463, 1385, 1138 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s), 0.90 (3H, s), 1.11 (3H, s), 1.20-1.80 (4H, m), 1.86, (1H, d, J = 13.1 Hz), 2.00 (1H, d, J = 13.1 Hz), 2.20, (2H, s), 2.29 (2H, m), 2.40 (1H, br m), 3.50 (2H, m), 3.62 (1H, dd, J = 11.8, 3.7 Hz), 3.86 (1H, br d, J = 11.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 21.3, 24.1, 24.4, 24.5, 36.2, 37.3, 39.7, 42.5, 43.1, 51.7, 62.0, 65.5, 86.4, 94.1, 209.2. HRMS (CI) calcd for $C_{16}H_{26}O4$ (M^+ + 1) 283.1909. Found 283.1906.

(±)-10β-Hydroxymethyl-4α-methylene-2α,10α-oxido-2β,13-oxido-8β,11,11-trimethylbicyclo [5.4.0^{3,8}]undecane 23. To zinc powder (12.0 g, 0.18 mol) and mercury (II) chloride (1.2 g, 4.4 mmol) was added 10% aqueous HCl, and the mixture stirred for 5 min. The acid was decanted and 2N HCl/water (2:1) (25 mL) added, followed by a solution of **22** (R = MOM) (1.0 g, 3.5 mmol) in toluene (10 mL). The mixture was heated at 95°C for 1 h, cooled, water (100 mL) was added, and the mixture extracted with EtOAc (3x75 mL). The combined extracts were washed with water (100 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography over silica gel eluting with 20% EtOAc/hexanes gave **23** (R = H) as a white solid (745 mg, 79%). M.pt. 118-120°C. IR (neat) 3445, 2936, 1456, 1361, 1306, 1209, 1151, 1115, 1051, 1017, 955, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, s), 1.05 (3H, s), 1.09 (3H, s), 1.2-1.4 (2H, m), 1.5-1.7 (6H, m), 1.67 (1H, d, J = 7.6 Hz), 1.85 (2H, dd, J = 4.2, 13 Hz), 2.23 (1H, m), 3.55-3.65 (1H, m), 3.7-3.9 (3H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 23.6, 26.5, 27.6, 30.3, 31.8, 36.7, 37.0, 37.3, 41.7, 53.4, 55.1, 65.2, 74.0, 83.4, 111.5. HRMS (CI) calcd for $C_{16}H_{26}O_3$ (M^+) 266.1882. Found 266.1890. Crystals suitable for X-ray crystallography were grown from EtOAc.

(±)-10β-(Trifluoromethanesulfonyl)oxymethyl-4α-methylene-2α,10α-oxido-2β,13-oxido-8β,11,11-trimethylbicyclo[5.4.0^{3,8}]undecane 23 (R = Tf). To a solution of **23** (R = H) (210 mg, 0.75 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (309 mg, 1.50 mmol) in dichloromethane (10 mL) at -10°C was added drop wise trifluoromethanesulfonic anhydride (150 µl, 0.825 mmol). After 5 min a white solid precipitated and the reaction was quenched with water (20 mL), and extracted with chloroform (3x30 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Chromatography over silica gel gave **23** (R = Tf) as a white solid (252

mg, 80%). IR (neat) 2956, 2867, 1457, 1418, 1245, 1208, 1147, 1031, 958, 840 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, s), 1.08 (3H, s), 1.11 (3H, s), 1.2-1.4 (4H, m), 1.5-1.65 (4H, m), 1.69 (1H, d, J = 7.0 Hz), 1.81 (1H, d, J = 13.3 Hz), 1.97 (1H, d, J = 13.3 Hz), 2.25 (1H, m), 3.75 (1H, d, J = 8.3 Hz), 3.84 (1H, dd, J = 8.4, 5.0 Hz), 4.45 (1H, d, J = 10.0 Hz), 4.52 (1H, d, J = 10.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 23.1, 25.9, 27.6, 30.2, 32.1, 36.7, 36.8, 37.0, 42.6, 52.8, 55.0, 74.4, 78.0, 80.7, 112.2, 118.52, 300 (q). HRMS (CI) calcd for $C_{17}H_{25}F_3O_5S$ (M^+ + 1) 399.1453. Found 399.1437.

(±)-11β-Hydroxy-4α-methylene-2α,11α-oxido-2β,13-oxido-8β,11,11-trimethylbicyclo[6.4.0^{3,8}] dodecane 24. A solution of **23** (R = Tf) (200 mg, 0.50 mmol) in 2,2,2-trifluoroethanol (7 mL) containing water (1 mL) and sulfuric acid (1-2 drops) was heated at 80°C for 1 h. The solvent was evaporated *in vacuo*, water (25 mL) was added to the residue, and the mixture extracted with chloroform (3x25 mL). After drying ($MgSO_4$) the chloroform was evaporated *in vacuo* to give **24** as a white solid (136 mg, 100%) M.pt. 97-98°C (from hexanes). IR (neat) 3459, 2932, 2863, 1463, 1445, 1362, 1315, 1260, 1090, 1067, 1001, 919, 887, 846, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.04 (3H, s), 1.08 (3H, s), 1.3-1.6 (6H, m), 1.72 (1H, d, J = 7.3 Hz), 1.85-1.95 (2H, m), 2.05-2.25 (4H, m), 2.35 (1H, m), 2.57 (1H, s), 3.7-3.8 (2H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0, 22.6, 25.3, 27.6, 31.9, 32.5, 32.5, 32.9, 36.6, 37.1, 41.3, 54.4, 58.1, 73.8, 107.8, 109.2. HRMS (CI) calcd for $C_{16}H_{20}O_3$ (M^+) 266.1882. Found 266.1865. Crystals suitable for X-ray crystallography were grown from hexanes.

(±)-4α-Methylene-2,13-Oxido-8β,11,11-trimethylbicyclo[6.4.0^{3,8}]dodeca-2-en-11-one 25. A solution of **23** (R = Tf) (38 mg, 0.095 mmol) in methanol was heated at reflux for 30 min, and the solvent was evaporated *in vacuo*. Chromatography over silica gel gave **25** as a colorless oil (20 mg, 84 %). IR (neat) 2929, 2866, 1730, 1695, 1464, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.10 (3H, s), 1.12 (3H, s), 1.4-1.6 (4H, m), 1.7-1.9 (2H, m), 2.0-2.2 (1H, m), 2.6-2.7 (2H, m), 2.85-2.95 (1H, m), 3.58 (1H, t, J = 8.6 Hz), 4.20 (1H, t, J = 9.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 25.3, 25.7, 25.7, 33.7, 35.6, 35.7, 37.4, 37.5, 37.6, 42.4, 48.8, 73.4, 114.7, 145.4, 215.3. HRMS calcd for $C_{16}H_{25}O_2$ (M^+ + 1) 249.1855. Found 249.1851.

(±)-10β-Formyl-4α-methylene-2α,10α-oxido-2β,13-oxido-8β,11,11-trimethylbicyclo[5.4.0^{3,8}] undecane 27. To a solution of **23** (R = H) (500 mg, 1.90 mmol) in acetonitrile (10 mL) was added powdered 3 Å molecular sieves (oven dried) and the mixture stirred for 10 min. *N*-Methylmorpholine *N*-oxide (450 mg, 3.8 mmol) was added followed by tetrapropylammonium perruthenate (5 mg). The mixture was stirred at 25°C for 14 h, and filtered through a silica plug (20% EtOAc/hexanes) to give **27** (320 mg, 64 %). IR (neat) 2939, 2853, 2811, 1731, 1463, 1366, 1297, 1208, 1153, 1116, 1068, 1005, 978, 958, 846, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, s), 1.07 (3H, s), 1.17 (3H, s), 1.1-1.7 (6H, m), 1.65 (2H, dd, J = 3.1, 6 Hz), 1.7 (1H, d, J = 7.5Hz), 1.9 (2H, dd, J = 4.0, 13 Hz), 2.23 (1H, m), 3.85 (2H, m), 9.81 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1, 22.5, 26.2, 27.4, 29.7, 31.8, 36.7, 37.4, 37.7, 45.1, 52.1, 55.3, 74.6, 86.8, 112.5, 204.6. HRMS (CI) calcd for $C_{16}H_{24}O_3$ (M^+ + 1) 265.1804. Found 265.1792.

(±)-4α-Methylene-2β,11β-oxido-2α,13-oxido-8β,11,11-trimethylbicyclo[6.4.0^{3,8}] dodeca-2-one 28. To a solution of **27** (300 mg, 1.14 mmol) in dichloromethane (30 mL) was added $BF_3.OEt_2$ (0.5 mL), and the mixture was stirred at 25°C for 72 h. Water (20 mL) was added, and the mixture was extracted with chloroform (3x20 mL), dried ($MgSO_4$) and evaporated. Filtration through a short silica gel plug eluting with 20% EtOAc/hexanes gave **28** as a white solid (210 mg, 70%) which was recrystallised from pentane. M.pt.113-115°C. IR (neat) 2962, 2866, 1740, 1462, 1259, 1063, 1033, 770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.16 (3H, s), 1.24 (3H, s), 1.0-1.4 (4H, m), 1.51 (1H, d, J = 12.3 Hz), 1.6-1.7 (2H, m), 2.1 (2H, dd, J = 3.7, 14 Hz), 2.2 (1H, m), 2.45 (2H, dd, J = 3.1, 13 Hz), 3.3 (1H, m), 3.96 (1H, s), 4.17 (1H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.9, 21.5, 23.0, 28.7, 30.4, 34.8, 37.8, 39.5, 41.3, 53.4, 58.2, 66.5, 73.4, 94.4, 115.2, 210.8. HRMS (CI) calcd for $C_{16}H_{24}O_3$ (M^+ + 1) 265.1804. Found 265.1803. Crystals suitable for X-ray crystallography were grown from pentane.

Benzyl 2-benzyloxymethyl-3-methyl-4-furoate 33. To a solution of **32** (100 g, 0.89 mol) in tetrahydrofuran (2.5 L) at -70°C was added *n*-BuLi (2.5M in tetrahydrofuran, 450 mL and 1.6M in tetrahydrofuran , 450 mL, 1.83 mol, 2.06 equiv) *via* cannula at such a rate as to maintain an internal temperature of -50 to -40°C. The mixture was allowed to warm to 0°C, and stirred for 2.5 h. The mixture was cooled to -70°C and dry CO_2 was bubbled into the solution. The reaction warmed to -40°C and sparging with CO_2 was continued for 1.25 h. The reaction was quenched with saturated aqueous NH_4Cl (1 L) and stirred 18 h. The phases were separated, and the aqueous phase chilled by the addition of ice and was then acidified with cold, concentrated HCl until the pH reached 1. The solution was extracted with EtOAc (6x1 L), and combined extracts dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the acid as a light brown solid (120 g, 86%). The compound was used without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 2.14 (3H, s), 4.58 (2H, s), 4.98 (2H, br s), 7.05 (1H, s).

A solution of the hydroxy acid (25 g, 0.16 mol) in DMF (175 mL) was cooled to 0°C and treated with NaH (14.1 g, 60% dispersion in mineral oil, 0.35 mol, 2.25 equiv). The mixture was allowed to warm to 25°C, and stirred for 1 h before being treated with *n*-Bu_4NI (5.8 g, 0.016 mol, 0.1 equiv) and benzyl bromide (47 mL, 0.39 mol, 2.5 equiv). The mixture was heated to 100°C for 18 h, quenched with water (500 mL), and extracted with EtOAc (3x250 mL). The combined extracts were washed with water (2x150 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography over silica gel eluting with 75% hexanes/Et_2O gave **33** as a yellow oil (53 g, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (3H, s), 4.48 (2H, s), 4.56 (2H, s), 5.35 (2H, s), 7.50-7.23 (11H, m).

2-benzyloxymethyl-3-methyl-4-furoyl chloride 34. To a solution of **33** (55 g, 0.16 mol) in tetrahydrofuran (250 mL) was added an aqueous solution of NaOH (32.5 g, 0.81 mol), and the mixture was stirred vigorously at reflux for 18 h. After cooling the mixture to 25°C, the volatiles were removed *in vacuo*, and the aqueous residue was cooled to 0°C and acidified with cold concentrated HCl to pH 1. The mixture was extracted with EtOAc (4x200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Recrystallization of the residue from EtOAc/hexanes gave the acid as tan crystals (25 g, 63% yield). IR (thin film) 3000-2500 , 1710, 1682, 1455 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s), 4.50 (2H, s), 4.55 (2H, s), 7.40-7.24 (6H, m).

^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 9.6, 62.1, 72.8, 122.5, 127.5, 127.9, 128.0, 128.5, 137.2, 144.3, 155.4, 156.1, 164.9, 167.8. HRMS (CI) calcd for $C_{14}H_{15}O$ ($M^+ + 1$) 247.0970. Found 247.0974.

To a solution of the acid (48 g, 0.19 mol) in dichloromethane (500 mL) and DMF (0.5 mL) at 0°C was added dropwise, *via* syringe, oxalyl chloride (21 mL, 0.24 mol, 1.2 equiv). The mixture was stirred at 0°C for 1 h, and warmed to 25°C for 18 h. The crude acid chloride **34** was concentrated *in vacuo* and used without further purification. IR (thin film) 3031, 2929, 2861, 1753, 1513 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s), 4.50 (2H, s), 4.55 (2H, s), 7.45-7.20 (6H, m).

2-[2-(5-Benzyloxymethyl-4-methylfuryl)-2-hydroxymethyl]-6-methyl-6-hepten-1-ol 37 (R = H). A solution of **35** (20g, 66 mmol) in tetrahydrofuran (75 mL) at -78°C was treated with lithium bis(trimethylsilyl)amide (1M solution in tetrahydrofuran, 66 mL). After 1.5 h at -78°C, the solution was transferred, *via* cannula, into a solution of **34** (19 g, 73 mmol) in tetrahydrofuran (80 mL) at -78°C. After 1.5 h, the mixture was treated with methanol (16 mL), followed by lithium borohydride (2M solution in tetrahydrofuran, 100 mL) and warmed to 0°C. The mixture was maintained at 0°C for 0.5 h, quenched with saturated aqueous NH_4Cl (200 mL), diluted with water (100 mL), and extracted with Et_2O (3x200 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→2:1) gave **37** as a colorless oil (3:1 mixture of diastereoisomers (19.3 g, 81%). IR (film) 3400, 1675, 1480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.3-1.5 (m), 1.5 (s), 1.9-2.2 (m), 1.9 (s), 2.9 (d, J = 5.2 Hz), 3.7-3.9 (m), 4.4 (s), 4.5 (s), 4.6 (d, J = 0.9 Hz), 4.66 (s), 4.8-4.9 (m), 6.1 (s), 6.12 (s), 7.2-7.3 (m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 11, 22, 25, 26, 37, 44, 62, 64, 72, 73, 111, 112, 120, 127, 127.5 (2), 128 (2), 137, 146, 147, 153. HRMS (CI) calcd for $C_{22}H_{30}O_4$ (M^+) 358.214. Found 358.213. Further elution of the column with petrol/Et_2O (1:2) gave the recovered oxazolidinone (**Xc**, **Scheme 6**) (8.4g, 71%).

2-[2-(5-Benzyloxymethyl-4-methylfuryl)-2-hydroxymethyl]-6-methyl-6-hepten-1-(triphenyl methyl)oxy ether 38 (R = Tr). A solution of **37** (19.2 g, 53.6 mmol) in dichloromethane (100 mL) at 0°C was treated with DMAP (500 mg), Et_3N (16 mL), and trityl chloride (16.5g, 59.1 mmol). The mixture was warmed to 25°C and stirred for 12 h, diluted with water (100 mL), and extracted with dichloromethane (3x200 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→5:1) gave **38** as a yellow oil (25.7 g, 80%). IR (film) 3460, 1500, 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.53 (m), 1.53 (s), 1.86-2.20 (m), 1.93 (s), 3.22 (d, J = 5.4 Hz), 3.29 (d, J = 5.7 Hz), 4.36 (s), 4.41 (s), 4.42-4.88 (m), 5.93 (s), 7.18-7.32 (m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.9, 14.1, 22.4, 25.3, 25.4, 25.9, 31.6, 37.8, 43.3, 61.8, 63.8, 64.5, 71.0, 71.3, 71.4, 87.3, 109.8, 109.8, 110.0, 119.8, 127.1, 127.6, 127.8, 127.8, 128.3, 128.6, 138.1, 143.5, 143.7, 145.7, 146.0, 154.9, 167.8. HRMS (CI) calcd for $C_{41}H_{44}O_4$ (M+) 600.324. Found 600.324.

2-[2-(6-Hydroxy-6-benzyloxymethyl-5-methylpyran-4-en-3-one)]-6-methyl-6-hepten-1-(triphenyl methyl)oxy ether 39 (R = H). A solution of **38** (40 g, 67 mmol) in dichloromethane (400 ml) and methanol (200 mL) was cooled to -55°C and treated with rose bengal (50 mg). Oxygen gas was passed through the mixture, which was irradiated with a fluorescent lamp for 12 h. Dimethyl sulfide (8.2 g) was added, and the mixture allowed to warm to 25°C. The solvent was evaporated in *vacuo*, and the residue purified by

chromatography over silica gel eluting with petrol/Et_2O (10:1→2:1) to give **39** (R = H) as a colorless oil (35g, mixture of diastereoisomers). IR (film) 3403, 1670, 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.45 (m), 1.58 (s), 1.64-1.95 (m), 1.92 (s), 2.40-2.75 (m), 3.06-3.71 (m), 4.39-4.64 (m), 4.90 (d, J = 1.8 Hz), 5.88-6.00 (m), 5.93 (d, J = 1.1 Hz), 7.10-7.45 (m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.9, 19.2, 22.3, 25.1, 25.7, 25.8, 26.5, 28.4, 37.6, 37.8, 38.9, 40.6, 62.3, 62.7, 62.8, 70.5, 72.5, 73.8, 73.9, 74.3, 74.6, 77.8, 86.2, 94.9, 95.2, 96.5, 109.7, 109.9, 126.6, 126.8, 126.9, 127.1, 127.3, 127.6, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 137.6, 143.9, 144.1, 144.2, 145.5, 156.6, 167.7, 196.9. HRMS (CI) calcd for $C_{41}H_{44}O_5$ (M^+) 616.319. Found 616.317. Used immediately in the next step.

2-[2-(6-Acetoxy-6-benzyloxymethyl-5-methylpyran-4-en-3-one)]-6-methyl-6-hepten-1-(triphenyl methyl)oxy ether 40 (R = Ac). A solution of **39** (R = H) (35 g, 56.8 mmol) in dichloromethane (250 mL) was cooled to 0°C and treated with DMAP (200 mg), NEt_3 (50 mL), and Ac_2O (38 mL). The mixture was allowed to warm to 25°C, and stirred for 10 h. The mixture was diluted with water (100 mL), and extracted with dichloromethane (3x200 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel, eluting with petrol/ether (10:1→5:1) gave **40** (R = Ac) (37 g, as a mixture of diastereoisomers). IR (film) 1741, 1447 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12-1.99 (m), 1.84 (s), 1.96 (s), 2.33-2.60 (m), 3.01-3.14 (m), 3.94 (s), 4.41-4.59 (m), 5.08 (d, J = 1.8 Hz), 6.11 (d, J = 0.9 Hz), 7.14-7.44 (m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2, 21.4, 22.3, 25.7, 26.2, 37.7, 39.4, 62.5, 72.5, 73.8, 76.8, 86.6, 100.6, 109.7, 126.7, 126.8, 127.5, 127.6, 127.7, 128.3, 128.5, 128.6, 128.8, 137.7, 144.2, 144.3, 145.6, 154.5, 167.7, 167.8. HRMS (CI) calcd for $C_{43}H_{46}O_6$ (M^+) 658.329. Found 658.329. Used immediately in the next step

(-)-4α-(Triphenylmethyl)oxymethyl-8β,11-dimethyl-10β-benzyloxymethyl-3α,10α-oxido-bicyclo [5.4.0^{3,8}]undec-1-en-2-one 41/42. To a solution of **40** (R = Ac) (37g, 56.2 mmol) in toluene (5 L) (dried by azeotropic distillation) was added DBU (37 mL), and the mixture heated at reflux for 10 h. The solvent was evaporated by distillation, and the residue purified by chromatography over silica gel eluting with petrol/Et_2O (10:1→5:1) to give **41** and **42** as a yellow oil (11:1 mixture of diastereoisomers), (18 g, 45% from **38**). Crystallization from hexane/Et_2O (5:1) gave **41** as a pale yellow solid. M.pt. 154-155°C. $[\alpha]_D^{25}$ = -122.9 (c = 0.42, chloroform). IR (film) 2913, 1665, 1455 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-1.65 (7H, m), 0.94 (3H, s), 1.96 (3H, s), 2.81-2.83 (2H, m), 3.14-3.22 (1H, m) 3.58 (2H, AB, J = 11.2 Hz), 4.44-4.52 (2H, m), 5.72 (1H, s), 7.10-7.44 (20H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.5, 21.2, 21.7, 25.6, 35.9, 40.0, 40.3, 50.1, 65.5, 71.3, 73.4, 82.2, 86.4, 92.0, 125.2, 126.5, 127.4, 127.7, 127.8, 127.9, 128.2, 128.6, 128.7, 137.8, 144.3, 168.3, 197.3. HRMS (CI) calcd for $C_{41}H_{42}O_4$ (M^+) 598.308. Found 598.307. Anal. calcd. C, 82.45; H, 7.07. Found C, 82.38; H, 7.41%.

(-)-4α-(Triphenylmethyl)oxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undecan-2-one 43. A solution of **41** (5.0 g, 8.4 mmol) in Et_2O (500 mL) was treated with CuBr.SMe_2 (4.0 g). Argon gas was passed through the mixture for 10 min, followed by the dropwise addition of MeMgBr (3M solution in Et_2O, 30 mL). After 4 h at 25°C, the mixture was quenched with saturated aqueous NH_4Cl (100 mL), diluted with water (100 mL), and extracted with Et_2O (3x100 mL). The combined

extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→5:1) gave **43** (4.9 g, 95%). IR (film) 1702, 1485, 1444 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s), 0.97 (3H, s), 1.00 (3H, s), 1.00-2.05 (10H, m), 2.65-2.80 (1H, m), 2.99-3.18 (2H, m), 4.62 (2H, AB, J = 12.3 Hz), 7.19-7.57 (20H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.7, 21.3, 24.7, 25.7, 35.4, 37.3, 39.5, 42.7, 43.2, 51.7, 66.1, 70.6, 73.3, 84.7, 86.5, 91.8, 125.2, 126.6, 127.0, 127.2, 127.5, 127.7, 127.8, 127.9, 128.1, 128.4, 128.7, 138.4, 144.4, 209.2. HRMS (CI) calcd for $C_{42}H_{46}O_4$ (M^+ + 1) 615.347. Found 615.347.

(-)-4α-(Triphenylmethyl)oxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-methylene-bicyclo[5.4.0^{3,8}]undecan-2-one 44. A solution of **43** (4.86 g, 7.9 mmol), in tetrahydrofuran (200 mL) was treated with potassium bis(trimethylsilyl)amide (5.8 g) and stirred at 25°C for 15 min. Paraformaldehyde (4 g) was added, and the mixture was stirred at 25°C for 30 min. The mixture was quenched with saturated aqueous NH_4Cl (500 mL), diluted with water (100 mL), and extracted with Et_2O (3x100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel, eluting with petrol/Et_2O (10:1→5:1) gave **44** as a colorless foam (4.9 g, 95%). IR (film) 1757, 1696, 1449, 669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, s), 0.96 (3H, s), 1.03 (3H, s), 0.82-1.60 (5H, m), 1.78-1.94 (3H, m), 2.62-2.96 (3H, m), 3.50 (2H, AB, J = 12.4 Hz), 4.50 (2H, AB, J = 12.3 Hz), 5.30 (1H, s), 6.13 (1H, s), 7.12-7.43 (20H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.3, 21.4, 22.5, 22.5, 26.0, 26.2, 36.7, 43.4, 44.7, 45.7, 66.0, 71.1, 73.5, 84.1, 86.6, 91.6, 122.2, 126.6, 127.2, 127.4, 127.6, 128.3, 128.8, 128.9, 138.5, 144.5, 152.6, 167.8, 198.38. HRMS (CI) calcd for $C_{43}H_{47}O_4$ (M^+ + 1) 627.347. Found 627.344.

(-)-4α-(Triphenylmethyl)oxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-nitrobutyl)-bicyclo[5.4.0^{3,8}]undecan-2-one 45. A solution of **44** (200 mg, 0.32 mmol) in DMSO (12 mL) was treated with 2-nitropropane (0.3 mL) and K_2CO_3 (400 mg). After 1 h at 25°C, the mixture was quenched with saturated aqueous NH_4Cl (10 mL), diluted with water (20 mL), and extracted with Et_2O (3x50 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→2:1) gave **45** as a colorless foam (Mixture of two diastereoisomers, 212 mg, 93%). Higher R_f isomer IR (film) 2935, 1715, 1546, 1458 1367, 1099 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (3H, s), 0.83 (3H, s), 0.88 (3H, s), 0.98 (3H, t, J = 7.0 Hz), 1.10-2.00 (13H, m), 2.07-2.20 (1H, m), 2.40-2.52 (1H, m), 2.73-2.86 (2H, m), 3.47 (2H, AB, J = 10 Hz), 4.48 (2H, AB, J = 12 Hz), 4.71-4.83 (1H, m), 7.10-7.50 (20H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.3, 18.0, 19.0, 21.1, 21.3, 26.5, 27.9, 29.5, 35.6, 38.0, 42.8, 43.0, 44.1, 51.5, 66.6, 70.4, 73.5, 85.7, 86.2, 91.1, 91.5, 126.6, 126.7, 127.3, 127.5, 127.6, 128.3, 128.7, 128.8, 138.4, 144.4, 209.7. HRMS (CI) calcd for $C_{46}H_{52}O_6$ (M^+) 714.379. Found 714.379. Lower R_f isomer IR (film) 1704, 1547, 1490, 1461 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (3H, s), 0.79 (3H, s), 0.83 (3H, s), 0.89 (3H, t, J = 7.3 Hz), 1.13-1.59 (7H, m), 1.70-2.15 (7H, m), 2.40-2.52 (1H, m), 2.68-2.88 (2H, m), 3.47 (2H, AB, J = 10 Hz), 4.51 (2H, AB, J = 12 Hz), 4.72-4.78 (1H, m), 7.10-7.47 (20H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.1, 18.1, 19.4, 21.3, 21.7, 25.3, 26.4, 28.8, 35.6, 37.8, 42.8, 43.1, 44.1, 51.4, 66.6, 70.7, 73.6, 85.5, 86.3, 89.1, 91.8, 126.7, 127.4, 127.4, 127.5, 128.3, 128.8, 138.3, 144.4, 209.2. HRMS (CI) calcd for $C_{46}H_{52}O_6$ (M^+) 714.379. Found 714.379.

(-)-4α-Hydroxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-nitrobutyl)-bicyclo[5.4.0^{3,8}]undecan-2-one 46. A solution of **45** (500 mg, 0.69 mmol) in dichloromethane (10 mL) and methanol (10 mL) was treated with CSA (10 mg), and stirred at 25°C for 2h. The mixture was diluted with water (20 mL), extracted with Et_2O (3x50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel, eluting with petrol/Et_2O (10:1→2:1) gave **46** as a colorless oil (a mixture of diastereoisomers, 250 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H,s), 0.90 (3H, s), 0.91 (3H, s), 0.98 (3H, t, J = 7.0 Hz), 1.20-2.25 (18H, m), 3.41-3.69 (3H, m), 4.59 (2H, AB, J = 12 Hz), 7.20-7.38 (5H, m). Used directly in the next stage.

(-)-4α-Hydroxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-oxobutyl)-bicyclo[5.4.0^{3,8}]undecan-2-one 47. To a solution of titanium (III) chloride (2 g) in water (10 mL) was added ammonium acetate (6 g) in water (20 mL), and the solution stirred at 25°C for 15 min. A solution of **46** (803 mg, 1.7 mmol) in methanol (70 mL) was treated with NaOMe (155 mg), and stirred for 15 min before addition of titanium (III) chloride. After 12 h at 25°C, Rochelle's salt (2 g) was added and the mixture evaporated *in vacuo* to remove methanol. The aqueous residue was extracted with EtOAc (6x100 mL), dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→2:1) gave **47** (560 mg, 75%). IR (film) 3532, 1705, 1454, 1113 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, s), 0.89 (3H, s), 0.94 (3H, s), 0.82-1.59 (5H, m), 1.09 (3H, t, J = 7.2 Hz), 1.86-2.40 (6H, m), 2.56-2.74 (3H, m), 3.14 (1H, d, J = 9.7 Hz), 3.45-3.63 (4H, m), 4.59 (2H, AB, J = 12.2 Hz), 7.24-7.33 (5H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.8, 18.7, 19.4, 21.3, 22.1, 24.6, 36.4, 36.4, 36.6, 38.0, 42.9, 43.5, 44.1, 52.4, 65.7, 70.7, 73.7, 86.9, 92.9, 127.3, 127.5, 128.4, 138.3, 209.2, 209.8. HRMS (CI) calcd for $C_{27}H_{38}O_5$ (M^+) 442.272. Found 442.271.

(-)-4α-Formyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-oxobutyl)-bicyclo [5.4.0^{3,8}]undecan-2-one 48. To a solution of the Dess- Martin reagent (920 mg, 2.2 mmol) in dichloromethane (30 mL) at 0°C was added **47** (790 mg, 1.8 mmol) in dichloromethane (30 mL). The mixture was warmed 25°C, and after 3 h the mixture was evaporated, diluted with water (100 mL) and extracted with Et_2O (3x100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel, eluting with petrol/Et_2O (10:1→5:1) gave **48** (678 mg, 86%). IR (thin film) 1724, 1707 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, s), 0.94 (3H, s), 1.00 (3H, s), 1.08 (3H, t, J = 7.2 Hz), 1.16-1.54 (3H, m), 1.70-2.06 (1H, m), 2.15 (2H, AB, J = 13.3 Hz), 2.57-2.85 (5H, m), 3.24 (1H, dd, J = 1.2, 9.8 Hz), 3.60-3.65 (2H, m), 4.66 (2H, AB, J = 12.2 Hz), 7.24-7.33 (5H, m) 9.47 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.7, 18.1, 19.1, 21.0, 22.0, 36.3, 36.4, 37.5, 42.7, 43.4, 45.2, 47.6, 51.8, 70.4, 73.7, 87.3, 89.0, 127.3, 127.5, 128.3, 138.3, 202.5, 208.6, 209.8. HRMS (CI) calcd for $C_{27}H_{36}O_5$ (M^+) 440.256. Found 440.256.

(-)-4α-Formyl-8β,11,11-trimethyl-10β–hydroxymethyl-3α,10α-oxido-1-(2-oxobutyl)-bicyclo [5.4.0^{3,8}]undecan-2-one 49. A solution of **48** (670 mg, 1.5 mmol) in isopropanol (6 mL), cyclohexene (4 mL) was treated with $Pd(OH)_2$ (230 mg), and heated at reflux under an atmosphere of argon for 6 h. The mixture was filtered through a plug of silica (washing with isopropanol), and the filtrate evaporated. Purification by

chromatography over silica gel eluting with petrol/Et_2O (10:1→2:1) gave **49** (515 mg, 97%). IR (film) 3433, 1725, 1566, 1459 1379 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s), 0.94 (3H, s), 1.03 (3H, s), 1.08 (3H, t, J = 7.4 Hz), 1.16-1.86 (7H, m), 2.01-2.28 (3H, m), 2.51-2.82 (3H, m), 2.96 (1H, dd, J = 4.6, 12.3 Hz), 3.29 (1H, dd, J = 1.6, 9.9 Hz), 3.53 (1H, d, J = 11.8 Hz), 3.92 (1H, d, J = 11.8 Hz), 9.47 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.8, 18.3, 19.2, 20.9, 21.4, 21.9, 36.2, 36.4, 37.6, 42.5, 43.4, 44.6, 47.6, 51.8, 62.0, 87.4, 89.5, 202.1, 208.13, 209.7. HRMS (CI) calcd for $C_{20}H_{31}O_5$ (M^+ + 1) 351.217. Found 351.217.

(-)-4α-Formyl-8β,11,11-trimethyl-10β-hydroxy-3α,10α-oxido-1-(2-oxobutyl)-bicyclo[6.4.0^{3,8}] dodecan-2-one 51. A solution of **49** (259 mg, 0.74 mmol) in dichloromethane (10 mL) was treated with 2,6-di-*tert*-butyl-4-methyl pyridine (770 mg) and cooled to -40°C. Trifluoromethane sulfonic anhydride (0.25 ml) was added dropwise and the mixture stirred at -40°C for 3h. The mixture was quenched with saturated aqueous NH_4Cl solution, and extracted with dichloromethane (2x50 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel, eluting with petrol/Et_2O (10:1→2:1) gave the triflate **50** as a colorless oil which was used immediately. ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, s), 1.02 (3H, s), 1.05 (3H, s), 1,08 (3H, t, J = 7.4 Hz), 1.18-1.90 (7H, m), 2.01-2.40 (3H, m), 2.51-2.96 (4H, m), 3.29 (1H, d, J = 10 Hz), 4.62 (1H, AB, J = 12 Hz), 9.47 (1H, s).

A solution of **50** in water (35 mL) was treated with 2,6-lutidine (0.5 mL) and heated at reflux for 14 h. After cooling, the mixture was extracted with Et_2O (3x25 mL), the combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→2:1) gave **51** as a colorless solid (130 mg, 50% for two steps). A sample was recrystallized from petrol/Et_2O (1:1). M.pt. 182-184°C. $[\alpha]_D^{25}$ = -48.7 (c = 0.19, chloroform). IR (film) 3447, 1717, 1704, 1691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H,s), 0.88 (3H, s), 1.02 (3H, s), 1.03 (3H, t, J = 7.8 Hz), 1.02-1.95 (7H, m), 2.03-2.75 (7H, m), 2.81 (1H, dd, J = 9.5, 16.6 Hz), 2.95 (1H, dd, J = 3.8, 11.7 Hz), 3.50 (1H, d, J = 8.9 Hz), 9.42 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.2, 18.7, 20.7, 21.2, 22.0, 23.5, 29.1, 31.7, 32.9, 36.3 (2), 37.5, 45.7, 50.3, 54.1, 86.3, 98.4, 202.8, 208.8, 209.7. HRMS (CI) calcd for $C_{20}H_{31}O_5$ (M^+ + 1) 351.217. Found 351.216.

(-)-4α-Formyl-8β,11,11-trimethyl-10β-methoxy-3α,10α-oxido-1,2-(2-ethylfuryl)-bicyclo[6.4.0^{3,8}] dodecan-2-one 52. A solution of **49** (236 mg, 0.67 mmol) in dichloromethane (15 mL) was treated with DBMP (674 mg) and cooled to -30°C. Trifluoromethane sulfonic anhydride (0.19 mL) was added dropwise and the mixture was stirred at -30°C for 2 h. The mixture was quenched with methanol (2 drops) and the solvent evaporated *in vacuo*. Methanol (10 mL) was added, and the mixture heated at reflux for 20 h. After cooling, the mixture was poured into saturated aqueous K_2CO_3 solution (50 mL), and extracted with dichloromethane (3x50 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in tetrahydrofuran (3 mL), water (3 mL) and treated with *p*-toluene sulfonic acid (20 mg). The reaction mixture was stirred for 2h, and poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with Et_2O (3x50 mL). The combined extracts were dried ($MgSO_4$), filtered, evaporated and purified by chromatography over silica gel, eluting with petrol/Et_2O (10:1) to give **52** colorless solid (124 mg, 53%). Crystals for X-ray analysis were grown from petrol/Et_2O (5:1). IR (film) 1740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, s), 1.01 (3H, s), 1.13 (3H, s), 1.28 (3H, t, J = 7.6 Hz), 1.34-1.45 (2H, m), 1.54-1.83 (6H,

m), 2.15-2.25 (2H, m), 2.57 (2H, q, J = 7.5 Hz), 2.90 (1H, dd, J = 4.9, 11.2 Hz), 3.37 (3H, s), 5.83 (1H, s), 9.40 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.2, 20.0, 21.0, 21.5, 21.9, 22.6, 22.7, 27.0, 31.0, 33.5, 34.7, 40.0, 48.8, 49.8, 79.0, 101.7, 101.8, 128.9, 144.1, 157.6, 204.9. HRMS (CI) calcd for $C_{21}H_{30}O_4$ ($M^+ + 1$) 346.214. Found 346.214.

(-)-4α-Formyl-8β-methyl-11-isopropenyl-3α,11α-oxido-1-(2-oxobutyl)-bicyclo [5.4.0^{3,8}]undecan-2-one 54. A solution of the triflate **50** (10 mg, 0.021 mmol) in *t*-BuOH (5 mL) was treated with DBMP (40 mg) and the mixture heated at reflux for 48 h. After cooling, the mixture was extracted with Et_2O (3x25 mL), the combined extracts were dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1) gave **54** as a colorless oil (4.5 mg, 65%). $[\alpha]_D^{25}$ = -82.1 (c = 0.067, $CHCl_3$). IR (film) 1748, 1718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.02 (3H, s), 1.20-1.67 (6H, m), 1.58 (3H, s), 1.77-2.25 (4H, m), 2.37-2.81 (5H, m), 3.06 (1H, dd, J = 3.1, 7.8 Hz), 4.92 (1H, s), 4.99 (1H, s), 9.35 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.8, 19.6, 19.9, 21.0, 21.7, 30.4, 30.9, 32.9, 34.5, 36.6, 41.3, 47.9, 48.6, 83.7, 84.8, 112.6, 144.6, 201.1, 209.1, 217.7. HRMS (CI) calcd for $C_{20}H_{29}O_4$ ($M^+ + 1$) 333.207. Found 333.206.

(-)-4α-Hydroxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-methylene-bicyclo[5.4.0^{3,8}]undecan-2-one 55. A solution of **44** (285 mg, 0.45 mmol) in dichloromethane (5 mL), methanol (5 mL) was treated with *p*-toluene sulfonic acid (50 mg) and the mixture stirred at room temperature for 5 h. The mixture was diluted with water (20 mL), extracted with Et_2O (3x50 mL), dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel, eluting with petrol/Et_2O (10:1→2:1) gave **55** (155 mg, 89%). IR (film) 3479, 1694, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.21 (3H, s), 1.28 (3H, s), 1.29-1.45 (2H, m), 1.53-1.67 (4H, m), 1.92-2.0 (2H, m), 2.24 (1H, dd, J = 2.5, 9.4 Hz), 3.45-3.70 (2H, m), 3.66 (2H, AB, J = 10.6 Hz), 4.60 (2H, AB, J_{AB} = 12.2 Hz), 5.44 (1H, s), 6.23 (1H, s), 7.24-7.34 (5H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 16, 19, 22, 23, 24, 32, 37, 38, 44, 45, 46, 66, 72, 74, 86, 94, 123, 126 (2), 127, 128 (2), 138, 152. HRMS (CI) calcd for $C_{24}H_{32}O_4$ ($M^+ + 1$) 385.238. Found 385.239.

(-)-4α-Hydroxymethyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1,2-(2-ethoxy pyranenyl)-bicyclo[5.4.0^{3,8}]undecane 56. A solution of **55** (500 mg, 1.3 mmol) in ethyl vinyl ether (20 mL) was treated with $Eu(FOD)_3$ (300 mg, 25 mol%) and the mixture heated at reflux for 48 h. The solvent was evaporated *in vacuo* and the residue purified by chromatography over silica gel, eluting with petrol/Et_2O (10:1→5:1) to give **56** (10:1 mixture of diastereoisomers, 500 mg, 84%). IR (film) 3468, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, s), 1.02 (3H, s), 1.03 (3H, s), 1.16 (3H, t, J = 7.1 Hz), 1.18-1.89 (10H, m) 2.05-2.15 (3H, m), 3.47-3.86 (6H, m), 4.58 (2H, AB, J = 12.3 Hz), 4.94 (1H, bs), 7.20-7.40 (5H, m). HRMS (CI) calcd $C_{28}H_{40}O_5$ (M^+) 456.288. Found 456.288.

(-)-4α-Formyl-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1,2-(2-ethoxy pyranenyl)-bicyclo[5.4.0^{3,8}]undecane 57. A solution of the Dess-Martin reagent (2.3 g) in dichloromethane (50 mL) was cooled to 0°C and treated with a solution of **56** (2.05 g, 4.5 mmol) in dichloromethane (50 mL). The mixture was warmed to 25°C, and the Dess-Martin reagent (50 mg) was added to complete the reaction. After 3 h, the

mixture was evaporated *in vacuo*, diluted with water (100 mL) and extracted with Et_2O (3x100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→5:1) gave **57** (10:1 mixture of diastereoisomers, 1.7 g, 84%). IR (film) 1724, 1669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, s), 0.96 (3H, s), 1.02 (3H, s), 1.11 (3H, t, J = 7.2 Hz), 1.15-1.45 (2H, m), 1.40-2.10 (10H, m), 2.71 (1H, dd, J = 4, 12 Hz), 3.41-3.65 (3H, m), 3.70-3.88 (1H, m), 4.51 (2H, AB, J = 12 Hz), 4.93 (1H, bs), 7.20-7.45 (5H, m), 9.64 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 14.8, 19.2, 19.9, 20.9, 21.1, 22.6, 26.8, 35.3, 41.8, 43.0, 46.6, 47.4, 63.8, 71.6, 73.5, 82.2, 85.4, 96.2, 111.6, 127.1 (2), 128.1 (3), 138.5, 143.4, 204.8. HRMS (CI) calcd for $C_{28}H_{38}O_5$ (M^+) 454.272. Found 454.270.

(-)-4α-Formyl-8β,11,11-trimethyl-10β-hydroxymethyl-3α,10α-oxido-1,2-(2-ethoxy pyranenyl)-bicyclo[5.4.0^{3,8}]undecane 58. A solution of **57** (710 mg, 1.6 mmol) in isopropanol (3 mL), cyclohexene (9 mL) was treated with $Pd(OH)_2$ (400 mg) and the resulting mixture heated at reflux, under an atmosphere of argon, for 4 h. The mixture was filtered through a plug of silica gel (washing with isopropanol), and the filtrate evaporated. Purification by chromatography over silica gel, eluting with petrol/Et_2O (10:1→2:1) gave **58** (10:1 mixture of diastereoisomers, 541mg, 95%). IR (film) 3436, 1712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.03 (3H, s), 1.08 (3H, s), 1,17 (3H, t, J = 7.1 Hz), 1.18-1.57 (5H, m), 1.73-1.91 (6H, m), 2.02-2.16 (1H, m), 2.93 (1H, dd, J = 4.9, 12.3 Hz), 3.45-3.57 (3H, m), 3.81-3.87 (2H, m), 4.98 (1H, t, J = 2.4 Hz), 9.68 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 14.8, 16.3, 19.0, 20.3, 20.8, 21.0, 23.1, 26.8, 35.5, 41.4, 42.9, 46.7, 47.5, 62.5, 63.9, 82.8, 86.1, 96.4, 111.6, 143.3, 204.6. HRMS (CI) calcd for $C_{21}H_{32}O_5$ (M^+) 364.225. Found 364.224.

(-)-4α-Formyl-8β,11,11-trimethyl-10β-methoxy-3α,10α-oxido-1,2-(2-ethoxypyranenyl)-bicyclo [6.4.0^{3,8}]dodecan-2-one 60. A solution of **58** (1.1 g, 3.0 mmol) in dichloromethane (25 mL) was treated with 2,6-lutidine (2 mL) and cooled to -30°C. Trifluoromethane sulfonic anhydride (0.8 mL) was added drop wise and the mixture stirred at -30°C for 1 h. The mixture was quenched with methanol (0.5 mL), and diluted with water (50 mL). The mixture was extracted with Et_2O (3x100 mL), and the combined extracts were dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1→5:1) gave **59** as a colorless oil which was used directly. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.06 (3H, s), 1.07 (3H, s), 1,16 (3H, t, J = 7 Hz), 1.18-2.18 (12H, m), 2.89 (1H, dd, J = 5, 12 Hz), 3.40-3.80 (2H, m), 4.57 (2H, AB, J = 12 Hz), 4.98 (1H, bs), 9.65 (1H, s). The triflate **59** was dissolved in methanol (30 mL) and 2,6-lutidine (2 mL) was added. The mixture was heated at reflux for 4 h. After cooling, the reaction mixture was poured into saturated aqueous $KHCO_3$ (50 mL) and extracted with Et_2O (3x100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica gel eluting with petrol/Et_2O (10:1) gave **60** as a colorless oil (10:1 mixture of diastereoisomers, 936 mg, 82% for two steps). IR (film) 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (6H, s), 0.99 (3H, s), 1.20 (3H, t, J = 7 Hz), 1.15-1.30 (2H, m), 1.51-2.26 (12H, m), 2.82 (1H, dd, J = 7, 9 Hz), 3.39 (3H, s), 3.40-3.90 (2H, m), 4.78-4.88 (1H, m), 9.67 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.1, 16.4, 20.1, 20.7, 21.1, 21.7, 23.5, 23.8, 27.4, 31.8, 33.3, 33.9, 41.6, 48.2, 48.5, 64.4, 79.2, 97.4, 100.1, 114.5, 140.4, 205.9. HRMS (CI) calcd for $C_{22}H_{34}O_5$ (M^+) 378.241. Found 378.240.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11-dimethyl-10β-benzyloxymethyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-1-en-2-one 63. DBU (27 mL, 180 mmol) was added over 5 min to a stirred solution of **61** (38.46 g, 59.6 mmol) in dry toluene (4 L). The mixture was heated at reflux for 16.5 h after which the toluene was evaporated *in vacuo*. The residue was partitioned between ether (500 mL) and 1M HCl (500 mL). The separated aqueous layer was washed with ether (2x100 mL), the combined extracts washed with water (400 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography over silica gel eluting with hexane/EtOAc (95:5) to give **63** (26.3 g, 73%). $[\alpha]_D^{25}$ = -93.3 (c = 0.40, $CHCl_3$). IR (Thin film) 2952, 2857, 1674, 1626, 1463, 1381, 1252, 1094 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.03 (3H, s), -0.01 (3H, s), 0.00 (3H, s), 0.02 (3H, s), 0.83 (9H, s), 0.84 (12H, s), 1.40 (1H, d, J = 12.7 Hz), 1.63-1.20 (4H, m), 1.97 (3H, d, J = 1.3 Hz), 2.05 (1H, d, J = 12.7 Hz), 2.59-2.53 (1H, m), 3.37 (1H, t, J = 9.6 Hz), 3.58-3.50 (3H, m), 3.72 (1H, d, J = 11.0 Hz), 4.58 (1H, d, J = 13.3 Hz), 4.67 (1H, d, J = 13.3 Hz), 5.78 (1H, br s), 7.37-7.24 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.3, -5.0, -3.7, 14.6, 18.0, 18.2, 18.5, 23.5, 25.8, 25.9, 29.7, 37.9, 46.4, 46.8, 64.8, 71.4, 73.7, 77.3, 84.5, 93.9, 125.1, 127.7, 127.8, 128.3, 137.8, 169.0, 196.6. HRMS (CI) calcd for $C_{34}H_{57}O_5Si_2$ (M^+ + 1) 601.374. Found 601.374.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undecan-2-one 64. A solution of **63** (25.55 g, 42.51 mmol) in ether (600 mL) was treated with $CuBr.SMe_2$ (1.32 g, 6.4 mmol). Argon was passed through the mixture for 10 min, followed by the dropwise addition of MeMgBr (3M solution in Et_2O, 21.3 mL, 63.8 mmol) over 2 h. After 4 h at 25°C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (500 mL). The mixture was diluted with water (300 mL) and extracted with Et_2O (3x100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with Et_2O/hexane (49:1 to 95:5) gave **64** as a pale yellow oil (22.25 g, 85%). IR (thin film) 2955, 2856, 1716, 1472, 1387, 1256, 1094 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.07 (3H, s), -0.03 (3H, s), -0.02 (3H, s), -0.01 (3H, s), 0.79 (3H, s), 0.84 (9H, s), 0.86 (9H, s), 0.90 (3H, s), 1.04 (3H, s), 1.60-1.15 (3H, m), 1.64 (1H, d, J = 13.6 Hz), 2.02-1.95 (1H, m), 2.12 (2H, s), 2.30-2.26 (1H, m), 2.38 (1H, d, J = 13.6 Hz), 3.34 (1H, t, J = 9.4 Hz), 3.54-3.49 (2H, m), 3.61 (1H, d, J = 10.5 Hz), 3.88-3.83 (1H, m), 4.64-4.55 (2H, m), 7.34-7.24 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, -4.89, -4.0, 12.8, 18.0, 18.3, 23.5, 24.5, 24.9, 25.8, 26.0, 29.9, 37.2, 39.7, 40.0, 48.6, 51.8, 64.8, 70.8, 73.5, 75.0, 85.4, 93.5, 127.5, 128.3, 138.5, 208.1. HRMS (CI) calcd for $C_{35}H_{61}O_5Si_2$ (M^+ + 1) 617.406. Found 617.404.

(-)-3αH-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-10α-hydroxy-bicyclo[5.4.0^{3,8}]undecan-2-one 65. Sodium metal (1.0 g) in *n*-Bu_2O (15 mL) was heated to 110°C with stirring until the sodium was finely divided. A solution of **64** (2.1 g, 3.4 mmol) in *n*-Bu_2O (5 mL) was added dropwise to the molten sodium at 110°C. The mixture was stirred for 0.5 h at 110°C then cooled to room temperature. The *n*-Bu_2O was decanted and the sodium washed with Et_2O (3x10 mL). The combined extracts were washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography over silica gel eluting with using hexane/Et_2O (95:5) to give **65** as a white solid (903 mg, 43%). M.pt. 100-101°C. IR (thin film) 3564, 2953, 2856, 1703, 1471, 1386, 1256, 1092, 835 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (3H, s), -0.03 (3H,

s), 0.01 (6H, s), 0.80 (3H, s), 0.84 (9H, s), 0.85 (9H, s), 0.89 (3H, s), 1.09 (3H, s), 1.42 (1H, d, J = 16.0 Hz), 1.68-1.20 (4H, m), 2.00-1.87 (1H, m), 1.97 (1H, d, J = 12.4 Hz), 2.31 (1H, d, J = 16.0 Hz), 2.69 (1H, bs), 2.80 (1H, d, J = 12.4 Hz), 3.23 (1H, d, J = 8.8 Hz), 3.39-3.32 (3H, m), 3.51-3.46 (2H, m), 4.55-4.47 (2H, m), 7.32-7.22 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, -5.5, -4.9, -3.4, 15.6, 18.1, 18.2, 25.4, 25.9, 26.4, 27.1, 30.7, 35.3, 38.7, 38.9, 42.0, 53.9, 58.1, 65.3, 73.4, 74.1, 78.0, 78.6, 127.7, 128.4, 137.6, 213.0. HRMS (CI) calcd for $C_{35}H_{63}O_5Si_2$ (M^+ + 1) 619.421. Found 619.420.

(-)-3αH-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-hydroxymethyl-10α-hydroxy-bicyclo[5.4.0^{3,8}]undecan-2-one 66. A mixture of **65** (425 mg, 0.69 mmol) and 10% palladium on carbon (100 mg) in ethanol (8 mL) was evacuated, and placed under an atmosphere of H_2. The mixture was stirred for 4 h, evacuated, and the mixture passed through a plug of celite using Et_2O as eluent. The solvent was evaporated *in vacuo* to give **66** as a white solid (354 mg, 98%). M.pt. 136-138°C. IR (thin film) 3467, 2953, 2857, 1687, 1256, 1078, 835 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (3H, s), -0.03 (3H, s), 0.04 (3H, s), 0.08 (3H, s), 0.81 (3H, s), 0.85 (9H, s), 0.86 (9H, s), 0.90 (3H, s), 1.10 (3H, s), 1.32 (1H, d, J = 16.0 Hz), 1.73-1.25 (4H, m), 2.01-1.89 (1H, m), 1.96 (1H, d, J = 12.1 Hz), 2.26 (1H, d, J = 16.0 Hz), 2.49 (1H, s), 2.83 (1H, d, J = 12.1 Hz), 3.40-3.33 (4H, m), 3.52 (1H, dd, J = 4.5, 10.7 Hz), 3.66 (1H, dd, J = 5.1, 10.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, -5.6, -4.8, -3.3, 15.7, 18.1, 18.2, 25.2, 25.9, 26.2, 27.1, 30.6, 35.3, 38.9, 40.5, 53.9, 58.2, 65.2, 66.0, 78.2, 78.3, 213.1. HRMS (CI) calcd for $C_{28}H_{57}O_5Si_2$ (M^+ + 1) 529.374. Found 529.373.

(-)-3αH-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-formyl-10α-hydroxy-bicyclo[5.4.0^{3,8}]undecan-2-one 67. Dimethyl sulfoxide (169 μl, 2.38 mmol) was added dropwise to a solution of oxalyl chloride (104 μl, 1.19 mmol) in dichloromethane (5 mL) at -78°C. The mixture was stirred for 0.5 h at -78°C, and a solution of **66** (210 mg, 0.4 mmol) in dichloromethane (1.5 mL) was added. The solution was stirred at -78°C for 2 h, and Et_3N (700 μl, 5 mmol) was added, and the cooling bath removed. After stirring at 25°C for 1 h the reaction mixture was poured into water and extracted with dichloromethane (3x15 mL). The extracts were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oily residue. Purification over silica gel eluting with hexane/EtOAc (9:1) gave **67** as a white solid (174 mg, 83%). M.pt. 88-90°C. IR (thin film) 3478, 2929, 2857, 1704, 1472, 1381, 1257, 1077, 835 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.08 (3H, s), -0.05 (3H, s), -0.02 (3H, s), 0.00 (3H, s), 0.81 (9H, s), 0.84 (3H, s), 0.86 (9H, s), 0.88 (3H, s), 1.14 (3H, s), 1.38 (1H, d, J = 15.8 Hz), 1.67-1.30 (4H, m), 1.84 (1H, d, J = 10.6 Hz), 1.96 (1H, d, J = 15.8 Hz), 2.02-1.90 (1H, m), 3.00 (1H, d, J = 10.6 Hz), 3.40-3.31 (2H, m), 3.52 (1H, d, J = 11.5 Hz), 3.59 (1H, dd, J = 4.4, 10.4 Hz), 3.64 (1H, d, J = 1.5 Hz), 9.56 (1H, d, J = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, -5.6, -5.0, -3.7, 16.5, 18.0, 18.2, 24.5, 25.6, 25.8, 25.9, 27.2, 30.4, 35.6, 35.7, 39.0, 39.9, 54.2, 58.1, 65.1, 76.4, 82.6, 202.4, 212.4 . HRMS (CI) calcd for $C_{28}H_{55}O_5Si_2$ (M^+ + 1) 527.359. Found 527.358.

(-)-3αH-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,12,12-trimethyl-11-hydroxybicyclo[6.4.0^{3,8}]dodecan-2,10-dione 68. A solution of lithium bis(trimethylsilyl)amide (1.0 M) in tetrahydrofuran (410 μl, 0.41 mmol) was added dropwise to a stirred solution of **67** (195 mg, 0.37 mmol) in tetrahydrofuran at -78°C. The mixture allowed to warm to room temperature, and after 0.5 h saturated aqueous

NH_4Cl (1 mL) was added, and the mixture partitioned between Et_2O(10 mL) and brine (10 mL). The aqueous layer was washed with Et_2O (2x10 mL), the extracts combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography over silica gel eluting with hexane/EtOAc (95:5) to give **68** (146 mg, 75%). IR (thin film) 3444, 2955, 2856, 1699, 1471, 1257, 1080 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.06 (3H, s), -0.04 (3H, s), 0.08 (6H, s), 0.83 (9H, s), 0.85 (12H, s), 1.01 (3H, s), 1.19 (3H, s), 1.68-1.23 (4H, m), 1.95-1.86 (1H, m), 2.31 (1H, d, J = 15.7 Hz), 2.46 (1H, d, J = 13.6 Hz), 2.61 (1H, d, J = 11.1 Hz), 2.78 (1H, d, J = 15.7 Hz), 2.92 (1H, d, J = 13.6 Hz), 3.29 (2H, d, J = 3.7 Hz), 3.72 (1H, dd, J = 4.4, 10.8 Hz), 3.80 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -4.8, -4.0, -3.9, 14.1, 18.0, 18.4, 24.6, 25.8, 25.9, 26.6, 29.3, 29.6, 36.6, 38.4, 43.2, 46.2, 54.5, 57.0, 65.2, 74.6, 84.4, 211.9, 213.0. HRMS (CI) calcd for $C_{28}H_{55}O_5Si_2$ (M^+ + 1) 527.359. Found 527.359.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-methylenebicyclo[5.4.0^{3,8}]undecan-2-one 69. A solution of **64** (3.0 g, 4.9 mmol) in tetrahydrofuran (40 mL) was treated with potassium bis(trimethylsilyl)amide (2.91 g, 14.6 mmol) and stirred at 25°C for 15 min. Paraformaldehyde (2.0 g) was added in one portion and the mixture stirred at 25°C for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL), diluted with water (100 mL) and extracted with Et_2O (3x100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with hexane/EtOAc (95:5) gave **69** as an oil (2.6 g, 85%). IR (thin film) 2930, 1701, 1604, 1472, 1388, 1362, 1255 1089 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.07 (3H, s), -0.03 (3H, s), 0.01 (3H, s), 0.02 (3H, s), 0.76 (3H, s), 0.83 (9H, s), 0.86 (9H,s), 1.12 (3H, s), 1.14 (3H, s), 1.45 (1H, d, J = 13.5 Hz), 1.6-1.2 (3H, m), 1.97-1.94 (1H, m), 2.32 (1H, d, J = 13.5 Hz), 2.43-2.30 (1H, m), 3.38 (1H, t, J = 9.4 Hz), 3.56-3.52 (2H, m), 3.66 (1H, d, J = 10.4 Hz), 3.89-3.84 (1H, m), 4.66-4.56 (2H, m), 5.38 (1H, s), 6.17 (1H, s), 7.34-7.24 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, -4.9, -4.0, 13.2, 18.0, 18.3, 22.3, 23.3, 25.8, 25.9, 26.2, 29.9, 37.9, 40.9, 46.1, 49.1, 64.7, 71.1, 73.5, 74.3, 84.7, 93.2, 122.2, 127.5, 128.3, 138.4, 152.6, 197.5. HRMS (CI) calcd for $C_{36}H_{61}O_5Si_2$ (M^+ + 1) 629.406. Found 629.404.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-nitrobutyl)-bicyclo[5.4.0^{3,8}]undecan-2-one 70. A solution of **69** (2.0 g, 1.59 mmol) in DMSO-tetrahydrofuran (5:2, 14 mL) was treated with 2-nitropropane (710 μl, 8.0 mmol) and K_2CO_3 (500 mg, 3.62 mmol). After 1 h at 25°C, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), diluted with water (50 mL) and extracted with Et_2O (3x50 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with hexane/Et_2O (9:1) gave **70** as an oil (mixture of two diastereoisomers, 984 mg, 86%). IR (thin film) 2929, 2856, 1713, 1548, 1463, 1256, 1096 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (12H, m), 1.00-0.75 (30H, m), 2.47-1.15 (12H, m), 3.32-3.24 (1H, m), 3.65-3.43 (3H, m), 3.85-3.75 (1H, m), 4.63-4.50 (2H, m), 4.87-4.75 (1H, m), 7.38-7.24 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.2, -5.0, -4.0, 10.0, 10.3, 12.0, 12.5, 18.0, 18.2, 18.3, 21.08, 21.6, 23.6, 23.8, 25.4, 25.8, 25.9, 27.9, 28.5, 29.5, 29.7, 37.2, 39.6, 39.8, 44.6, 44.8, 48.5, 51.5, 64.8, 65.0, 70.3, 70.6, 73.5, 73.5, 75.4, 86.2, 86.4, 89.0, 91.0, 92.8, 92.9, 127.4, 127.4, 127.5, 128.3, 138.3, 138.4, 207.6, 208.4. HRMS (CI) calcd for $C_{39}H_{68}NO_7Si_2$ (M^+ + 1) 718.453. Found 718.455.

(-)-4α-Hydroxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-nitrobutyl)-bicyclo[5.4.0^{3,8}]undecan-2-one 71. Hydrogen fluoride-pyridine solution was added dropwise to a stirred solution of **70** (3.8 g, 5.29 mmol) in acetonitrile at 0°C. The mixture was warmed to 25°C and stirred for 1.5 h. The solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was separated, washed with water, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography over silica gel eluting with hexane/EtOAc (4:1) give **71** as a white foam (2.42 g, 80%). IR (thin film) 3399, 2936, 2856, 1709, 1548, 1102 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.07 (3H, s), -0.06 (3H, s), -0.04 (3H, s), -0.02 (3H, s), 1.00-0.77 (21H, m), 2.51-1.30 (12H, m), 3.66-3.40 (4H, m), 3.84-3.79 (1H, m), 4.60-4.54 (2H, m), 4.88-4.65 (1H, m), 7.45-7.22 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -4.1, 10.1, 10.3, 12.0, 12.5, 16.4, 17.9, 18.3, 21.1, 21.6, 23.0, 25.7, 27.9, 28.6, 29.4, 29.7, 36.1, 36.1, 39.3, 39.5, 44.7, 44.9, 48.7, 51.6, 51.9, 65.0, 65.1, 70.0, 70.3, 73.4, 73.5, 74.8, 86.9, 87.2, 89.2, 90.9, 94.6, 127.4, 127.4, 127.6, 127.6, 128.4, 137.9, 138.0, 207.8, 208.8. HRMS (CI) calcd for $C_{33}H_{54}NO_7Si$ (M^+ + 1) 604.367. Found 604.366.

(-)-4α-Hydroxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1-(2-oxobutyl)-bicyclo[5.4.0^{3,8}]undecan-2-one 72. Sodium methoxide (2.2 g, 40.7 mmol) was added to a stirred solution of **71** (2.25 g, 3.73 mmol) in methanol (35 mL) at 25°C. The mixture was stirred for 15 min, cooled to -10°C, and 12M sulfuric acid (1.5 mL) added dropwise over 2 min. After stirring for 20 min at -10°C, water (5 mL) was added and stirring was continued for 15 min. The reaction mixture was warmed to 25°C, diluted with water (200 mL) and extracted with Et_2O (3x50 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with hexane/EtOAc (9:1) gave **72** (1.54 g, 72%), which was recrystallised from EtOAc/hexane. M.pt. 102-103°C. IR (thin film) 3545, 2936, 2856, 1706, 1472, 1457, 1256, 1105, 1055 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (3H, s), -0.02 (3H, s), 0.85 (9H, s), 0.87 (3H, s), 0.89 (6H, s), 1.08 (3H, t, J = 7.3 Hz), 2.17-1.36 (7H, m), 2.73-2.43 (4H, m), 3.16 (1H, br d, J = 8.3 Hz), 3.65-3.43 (4H, m), 3.82 (1H, dd, J = 3.7, 11.8 Hz), 4.58 (2H, s), 7.36-7.24 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, -4.0, 7.8, 11.9, 18.0, 19.4, 22.1, 23.0, 25.8, 29.7, 36.1, 36.4, 36.6, 39.3, 44.1, 49.1, 52.2, 65.1, 70.3, 73.5, 74.9, 87.3, 94.5, 127.4, 127.6, 128.4, 138.1, 207.8, 209.6. HRMS (CI) calcd for $C_{33}H_{52}O_6Si$ (M^+) 572.353. Found 572.351.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-benzyloxymethyl-3α,10α-oxido-1,2-(2-ethylfuryl)-bicyclo[5.4.0^{3,8}]undecan-2-one 73. Camphorsulfonic acid (100 mg, 0.43 mmol) was added to a stirred solution of **72** (420 mg, 0.73 mmol) in toluene (10 mL). The solution was heated at reflux for 10 h, cooled and partitioned between Et_2O (10 mL) and aqueous $NaHCO_3$ (10 mL). The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was dissolved in DMF (5 mL), then imidazole (200 mg, 2.9 mmol) followed by *tert*-butyldimethylsilyl chloride (221 mg, 1.47 mmol) was added. After stirring for 4 h at 25°C the reaction mixture was partitioned between Et_2O (20 mL) and water (30 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography over silica gel eluting with using hexane/EtOAc (95:5) to give **73** (297 mg, 60%) as a colorless oil. IR (thin film) 2932, 1557, 1463, 1361, 1255, 1090 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (3H, s), -0.01 (6H, s), 0.00 (3H, s), 0.67 (3H, s), 0.83

(9H, s), 0.85 (9H, s), 1.07 (3H, s), 1.12 (3H, s), 1.17 (3H, t, J = 7.6 Hz), 1.48-1.35 (2H, m), 1.47 (1H, d, J = 13.0 Hz), 1.69-1.60 (1H, m), 2.05-1.95 (1H, m), 2.18 (1H, d, J = 13.0 Hz), 2.28-2.14 (1H, m), 2.56 (2H, q, J = 7.6 Hz), 3.52-3.35 (3H, m), 3.66 (1H, d, J = 10.0 Hz), 3.92-3.87 (1H, m), 4.64-4.53 (2H, m), 5.79 (1H, s), 7.34-7.24 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2, -4.8, -3.9, 12.3, 13.7, 18.0, 18.3, 21.6, 22.0, 23.2, 25.9, 26.0, 26.1, 30.5, 38.3, 40.0, 40.2, 54.9, 65.2, 71.9, 73.5, 74.2, 85.6, 86.3, 101.9, 125.6, 127.4, 127.5, 128.3, 138.7, 149.1, 156.1. HRMS (CI) calcd for $C_{39}H_{65}O_5Si_2$ (M^+ +1) 669.437. Found 669.436.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-hydroxymethyl-3α,10α-oxido-1,2-(2-ethylfuryl)-bicyclo[5.4.0^{3,8}]undecan-2-one 74. A flask containing a stirred mixture of **73** (90 mg, 0.13 mmol), 10% palladium on carbon (60 mg) in ethanol (3 mL) was evacuated, and placed under an atmosphere of H_2. The mixture was stirred under an atmosphere of H_2 for 0.5 h, the flask was evacuated, and opened to the air. The mixture was passed through a plug of celite using ether as solvent. The solvent was evaporated *in vacuo* to give an oily residue which was purified by chromatography over silica gel eluting with hexane/EtOAc (9:1) to give **74** (53 mg, 68%). IR (thin film) 3479, 2956, 2856, 1463, 1360, 1253, 1091 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.02 (3H, s), -0.01 (3H, s), 0.04 (3H, s), 0.07 (3H, s), 0.66 (3H, s), 0.84 (18H, s), 1.09 (3H,s), 1.13 (3H, s), 1.17 (3H, t, J = 7.4 Hz), 1.49 (1H, d, J = 13.0 Hz), 1.72-1.25 (3H, m), 2.05-1.96 (1H, m), 2.06 (1H, d, J = 13.0 Hz), 2.29-2.16 (1H, m), 2.57 (2H, q, J = 7.4 Hz), 3.37 (1H, t, J = 10.0 Hz), 3.59-3.48 (2H, m), 3.89-3.78 (2H, m), 5.80 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.3, -4.8, -3.9, 12.3, 13.9, 18.0, 18.3, 21.6, 21.6, 23.2, 25.9, 25.9, 26.7, 30.4, 38.3, 39.6, 40.2, 54.9, 62.8, 64.9, 74.1, 86.4, 87.2, 101.8, 125.4, 148.8, 156.2. HRMS (CI) calcd for $C_{32}H_{58}O_5Si_2$ (M^+) 578.382. Found 578.378.

(-)-4α-(*tert*-Butyldimethylsilyl)oxymethyl-7β-(*tert*-butyldimethylsilyl)oxy-8β,11,11-trimethyl-10β-methoxy-3α,10α-oxido-1,2-(2-ethylfuryl)-bicyclo[6.4.0^{3,8}]dodecan-2-one 76. Triflic anhydride (50 μl, 0.3 mmol) was added to a stirred solution of **74** (70 mg) and DBMP (160 mg, 0.78 mmol) in dichloromethane (5 mL) at -5°C. The reaction was warmed to 25°C and stirred for 1 h, after which a further of triflic anhydride (30 μl) was added. After stirring the mixture for a further 1 h, the dichloromethane was evaporated *in vacuo* and methanol (5 mL) added. After heating the solution under reflux for 6 h the mixture was allowed to cool and the solvent evaporated *in vacuo*. The residue was partitioned between Et_2O (10 mL) and water (10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with hexane/EtOAc (95:5→9:1) gave **76** (60 mg, 81%). IR (thin film) 3447, 2954, 2857, 1459, 1256, 1063, 835 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.07 (3H, s), 0.75 (3H, s), 0.86 (9H, s), 1.06 (3H, s), 1.14 (3H, s), 1.16 (3H, t, J = 7.6 Hz), 1.84-1.50 (5H, m), 2.26-1.97 (3H, m), 2.56 (2H, q, J = 7.6 Hz), 2.72 (1H, bd, J = 8.5 Hz), 3.37 (3H, s), 3.56-3.35 (2H, m), 4.26 (1H, dd, J = 5.0, 10.6 Hz), 5.82 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.9, -3.7, 12.3, 16.2, 18.0, 21.4, 21.5, 21.6, 22.8, 25.8, 27.5, 28.1, 30.0, 38.4, 39.8, 40.6, 48.8, 65.0, 68.9, 85.1, 101.6, 101.9, 128.5, 144.6, 157.1. HRMS (CI) calcd for $C_{27}H_{47}O_5Si$ (M^+ + 1) 479.319. Found 479.318.

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References and Footnotes

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

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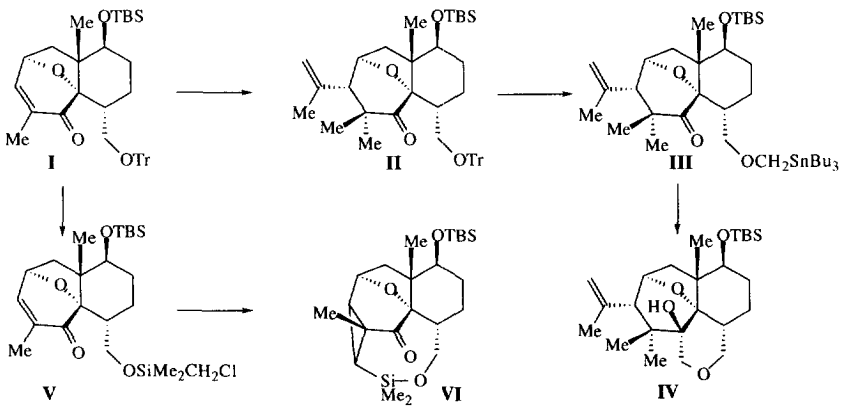
3. To conduct a ring expansion reaction in the bottom-half (**see Scheme 1**), the C-2 carbonyl group (taxol numbering) requires a one carbon addition followed by ring expansion. The requred bicyclo[5.4.0]undecenone **I** was made in the usual manner using 3-methylfurfural. It was found that the α,β-unsaturated ketone **I** was particularly susceptible to conjugate addition reactions even without the normal necessity for cuprate chemistry. For example, treatment of **I** with 2-propenyl lithium in tetrahydrofuran at -70 °C followed by methyl iodide gave **II** in >95% yield. All attempts to add carbon nucleophiles to the carbonyl group of **II** failed. Removal of the bulky C-20 trityl group did not change the situation. Conversion of the C-20 alcohol into its -CH_2SnBu_3 ether **III**, followed by butyl lithium gave **IV**. So at least an intramolecular addition is feasible. Deprotection of **I** and conversion of the C-20 alcohol into the ether **V**, followed by treatment with *t*-butyl lithium gave the carbenoid cyclopropanation adduct **VI** (structure by X-ray). The reluctance of the compound **I** to undergo addition directed our efforts towards examining a semi-pinacol-type rearrangement in the top-half of the bicyclo[5.4.0]undecenone structure.



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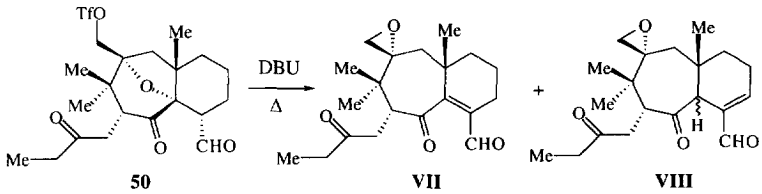
14. Treatment of **50** with DBU gave a mixture which contains two unsaturated aldehydes, tentatively assigned the structures **VII** and **VIII**. The presence of **VIII** was indicated by a proton at δ 6.9 (dd); The formation of **VIII** indicates that the isomerization of the C-3/4 double bond into the C-4/5 position, as suggested in **Scheme 5** is feasible, but under basic conditions no ring expansion was observed.



50 **VII** **VIII**

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