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Taxane Diterpenes 2: Synthesis of the 7-Deoxy ABC Taxane Skeleton, and Reactions of the A-Ring

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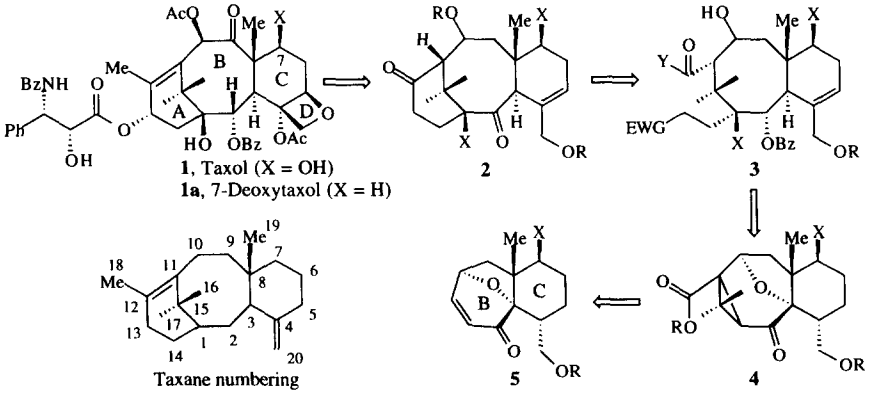
Abstract: The bicyclo[5.4.0]undecenones **5**, **6** and **7** are converted through a four step sequence involving activation, *gem*-methylcyclopropanation and reductive cleavage into the B/C rings of the taxanes, **18** and **19**. The A-ring has been attached to the B/C ring system by cyclization of the sulfone-ester **28** to give **29**, and also at a higher oxidation level; **33** gives **34**. The same type of anionic cyclization is successful in the presence of the C-1 hydroxyl group; **39** gives **40**. The A-ring can also be made using the classical aldol reaction; **43** to give **45**. A third A-ring closure method using the nitro-aldol reaction (Henry reaction) was also successful; **47** gives **48**. The A-ring has been elaborated by conversion into the tax-12,13-enes **53** and **58**. Hydroxyl directed epoxidation of **60** results in completely stereospecific oxidation to give **61**. Autoxidation of **41** gave the 12,13-dioxotaxane **67** which was further elaborated into the exomethylene ketone **70**. The α,β-unsaturated nitro alkene **74** has been converted into the 13-ketotaxane **76** using a reductive Nef reaction. Subsequent reduction of the C-13 carbonyl group with DIBAL-H gave the 13-α-alcohol **77** with the correct C-13 taxol stereochemistry. β-Elimination of the 3,10-oxido bridge *via* the dianion of the acid **81** results in transannular hydride shift to give the butenolide **83**.

Introduction

In the preceding paper we described the enantioselective syntheses of two bicyclo[5.4.0]undecenones **5** (X = OTBS and X = H) as potential precursors of the antitumor agent taxol **1**, 7-deoxytaxol **1a**, and simpler taxane analogs, **Scheme 1**.[1]

Scheme 1, Retrosynthetic Analysis of Taxol



The bicyclo[5.4.0]undecenone core **5** comprises thirteen carbon atoms of the diterpene skeleton. It has an intact C-ring, and the B-ring requires a one carbon ring-expansion reaction to give the eight-membered B-ring

of the taxanes. The shortest and most convenient route to the central eight-membered B-ring is to introduce the C-15, 16 and 17 carbon atoms in the form of a *gem*-methylcyclopropane to give **4**. Reductive cleavage of the internal cyclopropane bond of **4** would achieve the ring expansion and introduction of the C-16/17 *gem*-methyl group. It was also envisioned that in order to direct the reductive cleavage of the internal cyclopropane bond an additional electron withdrawing substituent at C-11 would be necessary.[2] If this substituent is an ester (or equivalent, such as -CN) it would constitute the C-12 carbon atom of the taxane A-ring. Compound **3** indicates a generalized formula where EWG (electron withdrawing group), and Y can be a wide range of carbanion stabilizing groups and carbanion accepting groups. Also X can be H or OH depending on whether the target is taxol, 7-deoxytaxol, 1-deoxytaxol or 1,7-dideoxytaxol. We have investigated cases where EWG = $-SO_2Ph$, $-SO_2Bu^t$, -CN, -CHO, $-CO_2Me$, $-CO_2Bu^t$, -S(O)Ph, -SPh and $-P(O)(OMe)_2$. Only in the cases where EWG = $-SO_2Ph$, $-NO_2$ and -CHO, and Y = -OMe and -H was the formation of the A-ring successful. In principle, the oxido-bridge (C-3 to C-10) can be β-eliminated, and through the process of β,γ-isomerization establish the thermodynamic *trans*-B/C ring fusion.[3] Furthermore, the new position of the double bond (C-4,5) is ideally placed for the eventual construction of the oxetane D-ring. Consequently, we considered that **2** would be a suitable substrate for conversion into taxol. We have also considered that the C-1 hydroxyl group (X = OH in **3**) can be introduced either prior to the formation of the A-ring, or after A-ring construction.[4] The latter choice requires the generation of a strained bridgehead enolate (C-1,2).[5]

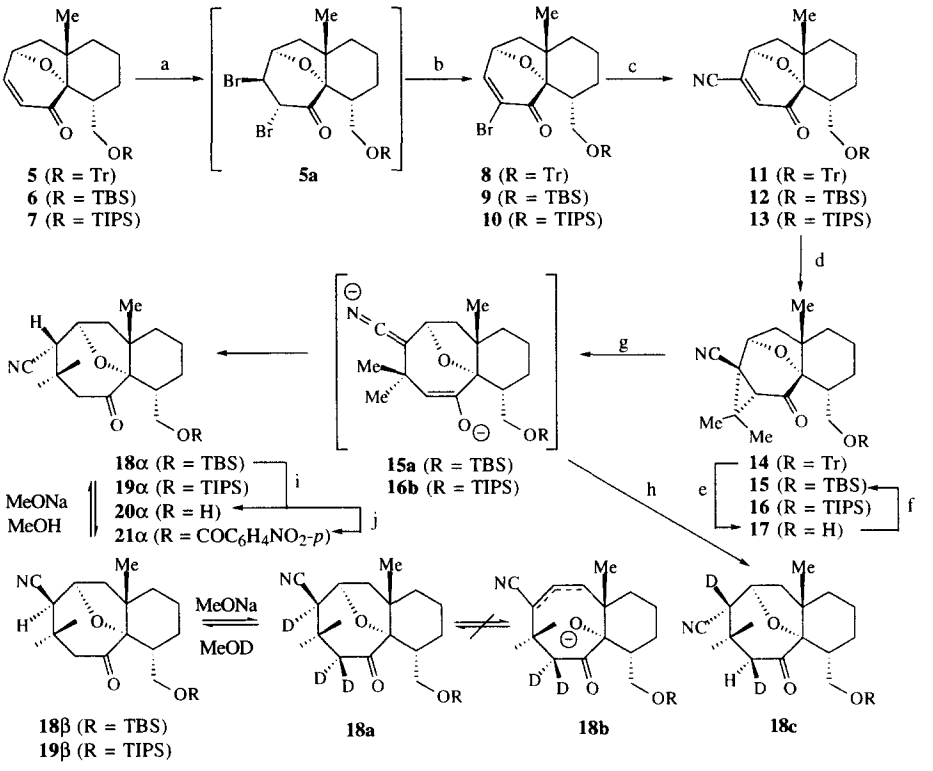
Gem-Methyl Cyclopropanation and Ring Expansion (Scheme 2)

The first stage in the development of this strategy requires activation of the enone **5** towards addition-elimination reactions, and introduction of a substituent at C-11 that allows the correct internal cyclopropane cleavage. Bromination of **5** gave the *trans*-dibromide **5a** (by ^1H NMR) which was not usually isolated, but treated directly with triethylamine to give the α-bromoenone **8** (99%). Exposure of **8** to an aqueous solution of sodium cyanide under phase transfer conditions gave the β-cyanoenone **11** (93%). Treatment of **11** with isopropylidenetriphenylphosphorane/THF/-70 to 25°C gave **14** (98%) as a single stereoisomer (X-ray).[6] The same sequence of reactions converts **6** through **9** (84%) and **12** (78%) into **15** (97%), and **7** through **10** (95%) and **13** (90%) into **16** (82%). The reason for using three different protecting group on the C-20 hydroxyl group stems from the ratio of diastereomers obtained from the pyrylium ylide cyclization (see previous paper). While the trityl protecting group gave the best ratio (8:1) of the correct diastereoisomer, it is not compatible with the reductive cleavage of the cyclopropane. The TBS (4:1) and TIPS (5:1) protecting groups give inferior ratios but do not require subsequent protecting group changes. Also from a purely practical standpoint, the trityl series was easier to purify. Consequently, it was convenient to hydrolyze **14** to the alcohol **17** (86%), and convert **17** into **15** (100%).

After experimenting with a number of reductive conditions it was found that treatment of **15** with sodium naphthalenide/THF/-78°C cleaved the internal cyclopropane bond to generate the dianion **15a**, which upon protonation gave a mixture of **18**α (65%) and **18**β (26%), (91%, 5:2).[7] Similarly, **16** gave **19**α (72%) and **19**β (28%), (100%, 5:3). Deprotection of **18**α gave **20**α (79%). The structure of the derived C-20 *p*-nitrobenzoate **21**α was established by X-ray crystallography. Treatment of the mixture of **18**α and **18**β with MeONa/MeOH resulted in equilibration to give **18**β as the major epimer (*ca.* 10:1). Furthermore, treatment of **18**α/**18**β with MeONa/MeOD incorporated three deuterium atoms to give **18a** (only β-cyano shown). This

thermodynamic equilibration experiment *appears* to preclude the involvement of a β-elimination process to give **18b**, since this would eventually introduce two deuterium atoms into the 9-position *via* an α,β-β,γ-equilibration process. A solution of the dianion **15a** was quenched with CF_3CO_2D to give the dideuterio compound **18c** (the β-cyano-compound is also formed). The deuterium atom at C-1 is assigned as β-axial on the basis of the chemical shift of the α-equatorial hydrogen atom (δ 3.2). The α- and β-nitrile epimers were readily distinguishable by ^{1}NMR; the C-11 proton appears as a singlet at δ 2.6 for the α-nitrile, and as a doublet at δ 3.1 (J = 4.5 Hz) for the β-nitrile.

Scheme 2

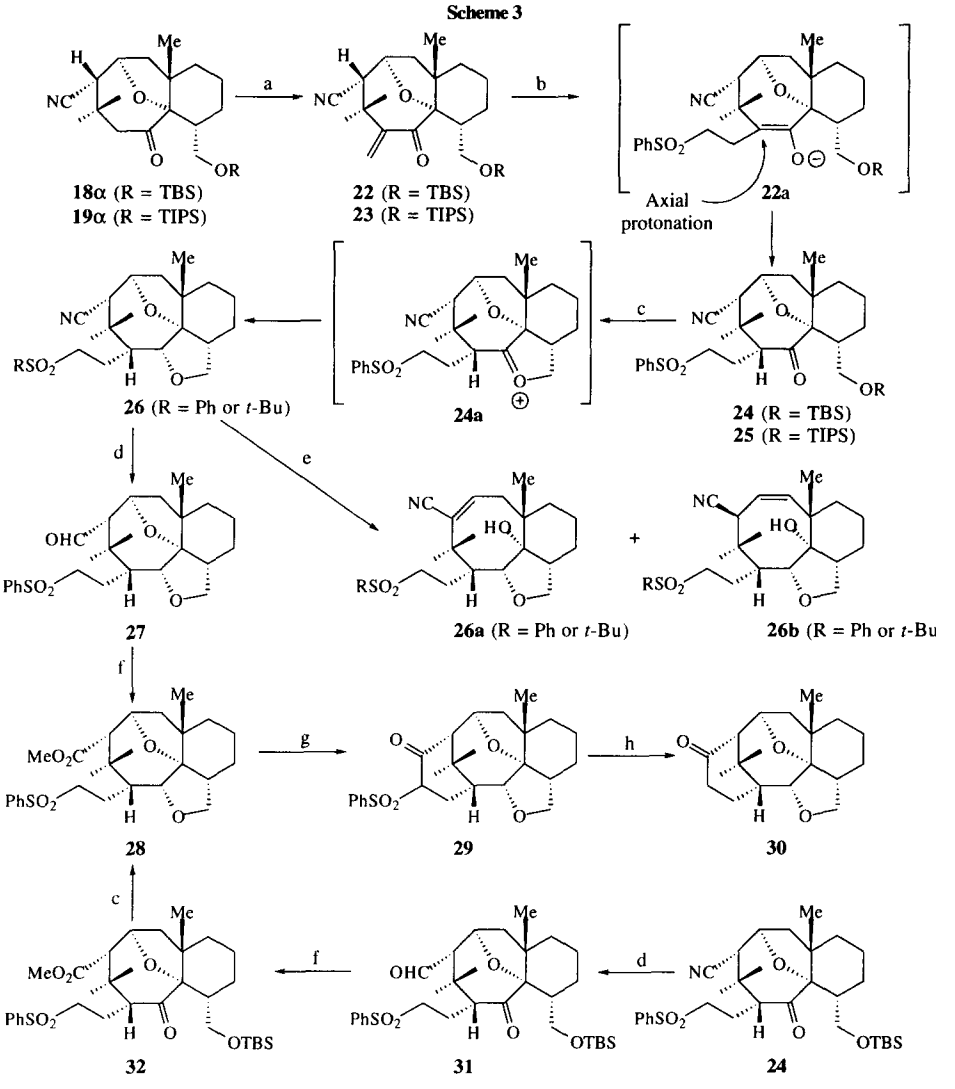


Conditions for **5** (R = Tr). The other series **6** and **7** are described in the experimental section:- a) $Br_2/CCl_4/CH_2Cl_2$/-10°C/1h. b) Et_3N/0°C/1h, **8** (99%). c) NaCN/*n*-$Bu_4NI/CH_2Cl_2/H_2O$/25°C/2h, followed by Et_3N/25°C/18h, **11** (86%). d) $Me_2C{=}PPh_3$/THF/-70 to 25°C/18h, **14** (98%). e) CSA/CH_2Cl_2/MeOH/3h, **17** (86%). f) TBSCl, imidazole/DMAP/DMF/25°C/18h, **15** (100%). g) Sodium naphthalenide/THF/-78°C, **18α** (65%), **18β** (26%). h) CF_3CO_2D. i) HF/py/THF/25°C, **20α** (79%). j) 4-Nitrobenzoylchloride/CH_2Cl_2/Et_3N/DMAP, **21α** (93%).

The overall sequence of bromination, cyanation, *gem*-methylcyclopropanation and reductive cleavage, provides an extremely quick and efficient (76% for these steps) route for the conversion of the pyrylium-ylide adducts **5**, **6** and **7** into the functionalized taxane B/C ring system.

Formation of the A-Ring (1-Deoxy series, EWG = -SO_2Ph, Scheme 3)

Scheme 3



Conditions- a) $KN(TMS)_2$/THF/$(CH_2O)_n$/25°C/2.5h, **22** (82%, 3:1, α:β). b) $PhSO_2CH_2Li$/THF/-70°C/1.5h, **24** (65%, α and 18% β). For **23** a and b) $KN(TMS)_2$/THF/$(CH_2O)_n$/26°C/0.75h, followed by $PhSO_2CH_2Li$/THF/-78°C/0.75h, **25** (87% from **23**, 5:3, α:β). c) $NaCNBH_3/CF_3CO_2H$/0°C, **26** (92%, from **25**, trace of β-epimer). d) DIBAL-H/CH_2Cl_2/-78°C. f) i. $NaClO_2$ ii. K_2CO_3/acetone/MeI, **28** (66% from **26**). **24** into **31**, d) DIBAL-H/CH_2Cl_2/-70°C, **31** (100%). e) LDA/THF/24°C/0.5h, **26b** (57% and a trace of **26a**). **31** into **32**, f) i. $NaClO_2$ ii. K_2CO_3/acetone/MeI, **32** (50% from **24**). **32** into **28**, c) $NaCNBH_3/CF_3CO_2H$/0°C, **28** (97%). g) LiN(TMS)$_2$/THF/70°C/1h, **29** (99%). h) Al/Hg/THF/H_2O/50°C/7d, **30** (65%).

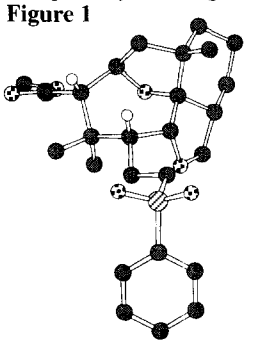
As expected, the C-1 enolate of **18/19** proved to be completely resistant to alkylation. However, treatment of **18α** with paraformaldehyde in the presence of excess $KN(TMS)_2$ resulted in the direct formation of

the C-1-exomethylene compound **22** (82%, 3:1 α:β, only α shown). Likewise, treatment of a mixture of **18α/18β** under the same conditions gave **22** (80%, 3:1 α:β). We did not expect the added bonus that the exomethylene would be directly formed. We attribute this fortuitous result to the adjacent *gem*-methyl group which supplies sufficient steric compression that the β-elimination of the intermediate hydroxymethyl adduct takes place *in situ*. [8]

Addition of $LiCH_2SO_2Ph$ to the α,β-unsaturated ketone **22/23** gave **24/25** as a single C-1 epimer that results from axial (β) protonation of the enolate **22a**. All attempts to cyclize **24/25** resulted in a retro-Michael reaction (-$PhSO_2CH{=}CH_2$) and the formation of **18/19**. Consequently, we required a method(s) to reduce the C-2 carbonyl group with the correct stereochemistry (α). It was found that treatment of **24/25** with $NaCNBH_3/CF_3CO_2H$ cleanly gave the tetrahydrofuran **26** (95%).[9] This reaction is speculated to proceed *via* the oxonium ion **24a**, since hydride addition to this intermediate from the top-face (β) leads to the less strained *cis*-2,4-tetrahydrofuran ring.

All attempts to effect A-ring closure by treatment of **26** with a variety of amide bases and *t*-BuOK/*t*-BuOH were unsuccessful. It was clear that β-elimination of the oxido-bridge was occurring but we were unable to characterize the compounds (**26a/26b**, R = Ph) in this series. Whereas, the case in which the $PhSO_2$- group is replaced by *t*-$BuSO_2$- (*t*-$BuSO_2CH_2Li$ addition to **23**, etc) we were able to characterize **26b** (R = *t*-Bu) (X-ray), which clearly indicate that β-elimination of the oxido-bridge takes place under kinetic conditions (LDA). This should be contrasted with the deuteration experiments described in **Scheme 2**, which anticipated the β-elimination of the oxido-bridge as a potential problem, but ruled it out under thermodynamic conditions (MeONa/MeOD). To hopefully avoid this pathway it was decided to convert the nitrile into an ester, which apart from possibly reducing the kinetic acidity of the C-11 proton would also make it more sterically inaccessible.

Figure 1



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

While the nitrile in **26** proved to be resistant to methanolysis under acidic conditions, it was readily reduced (DIBAL-H) to the aldehyde **27**, which was oxidized ($NaClO_2$) and esterified to give the methyl ester **28** (66%, overall). The structure of **28** was confirmed by X-ray (**Figure 1**) and shows the C-1 (-$CH_2CH_2SO_2Ph$) and C-11 (-CO_2Me) groups in a 1,3-diequatorial conformation. Clearly, these substituents will have to become 1,3-diaxial in the transition state needed to close the A-ring.

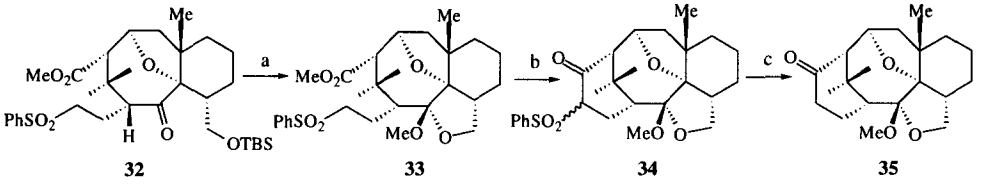
When a solution of **28** in THF at 70°C was treated with $LiN(TMS)_2$ (slow addition) it was cleanly converted into the β-ketosulfone **29** (99%, 6:1 C-13 -SO_2Ph epimers).[10] The -SO_2Ph group was removed by treatment of **29** with aluminum amalgam to give **30** (65%). The structure of **30** was confirmed by single crystal X-ray crystallography. Other amide bases such as LDA or LDCA did not convert **28** into **29**, nor did we observe any β-elimination of the 3,10-oxido-bridge as we had with the nitrile **26**.

The sequence of reactions leading to **28** can be reversed by converting **24** *via* **31** into **32**, and reduction of **32** with $NaCNBH_3$/TFA gave **28** (49% from **24**).

While the route shown in **Scheme 3** allows for introduction of the correct stereochemistry at C-2 prior to formation of the A-ring, we thought that it would be useful to maintain the C-2 carbonyl oxidation level until a later stage. We knew from parallel studies that the C-2 carbonyl function provides a potential method to isomerize the 3,4-double bond into the 4,5-position. The retro-Michael reaction precludes the direct use of a C-2

carbonyl compound during A-ring closure, but internal protection in the form of a ketal by utilizing the adjacent C-20 hydroxyl group should be feasible. Treatment **32** with $CH(OMe)_3$/MeOH/PPTS gave the ketal **33** (>99%). When a solution of **33** in THF at 70°C was treated with $LiN(TMS)_2$ (slow addition), it was cleanly converted into **34** (88%). Reductive removal (Na/NH_3) of the $-SO_2Ph$ group gave **35**, **Scheme 4**.

Scheme 4

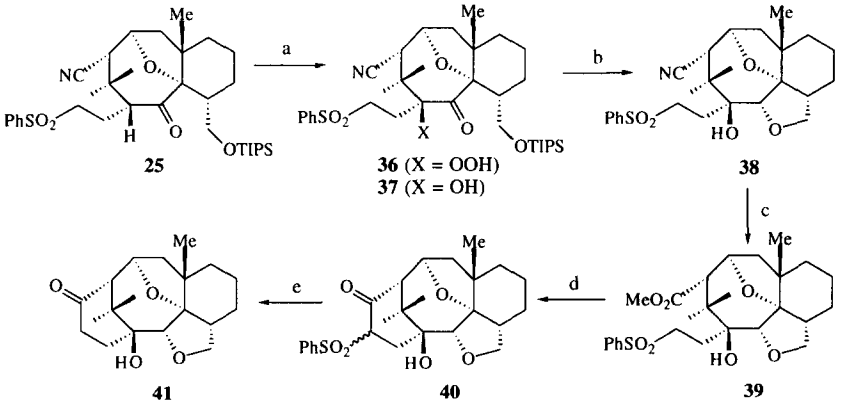


Conditions-: a) $(MeO)_3CH$/MeOH/PPTS, **33** (99.8%). b) $LiN(TMS)_2$/THF/70°C/1h, **34** (88%). c) Na/NH_3/THF/-40°C, **35** (64% from **32**).

Formation of the A-Ring (1-Oxy series, EWG = $-SO_2Ph$, Scheme 5)

The next major problem to be addressed in the construction of the fully functionalized taxol system is the introduction of the 1β-hydroxyl group. Presently, it is not known if the 1β-hydroxyl group is important for antitumor activity.[11] While several groups have introduced the 1β-hydroxyl group *via* oxygenation of the C-1/C-2 enolate, in all cases the A-ring has been present, and therefore only a single stereochemistry was possible. We have the opportunity to examine the introduction of the 1β-hydroxyl group prior to A-ring formation. Earlier studies in our laboratory have shown that the C-1/C-2 ketone enolate, both in seven and eight-membered ring series, is very sensitive to dioxygen.[12]

Scheme 5

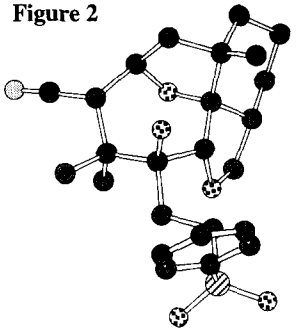


Conditions:- a) *t*-BuOK/THF/$P(OEt)_3/O_2$/-78°C, **37** (81%). b) $NaCNBH_3/CF_3CO_2H$/0°C, **38** (100%). c) i. DIBAL-H/CH_2Cl_2/-78°C. ii. $NaClO_2$. iii. K_2CO_3/acetone/MeI, **39** (66% from **38**). d) $LiN(TMS)_2$/THF/67°C, **40** (100%). e) Na/NH_3/THF/-78°C, **41** (100%).

Treatment of **25** with *t*-BuOK/*t*-BuOH/THF/O_2 at -78°C gave the hydroperoxide **36** (single stereoisomer). Conducting the oxygenation at -20°C gave directly the alcohol **37** but in only 65% yield. Using the Gardner modification of the original Barton autoxidation procedure, where the hydroperoxide is reduced *in*

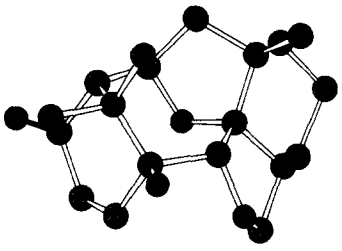
situ using $P(OEt)_3$, we obtained **37** (>85%).[13] Reduction of **37** with $NaCNBH_3/CF_3CO_2H$ gave **38** as a single stereoisomer. **Figure 2** shows a Chem 3D representation of **38** from the X-ray coordinates.

Figure 2



Chem 3D of **38** from X-ray coordinates

Figure 3



Chem 3D of **41** from X-ray coordinates

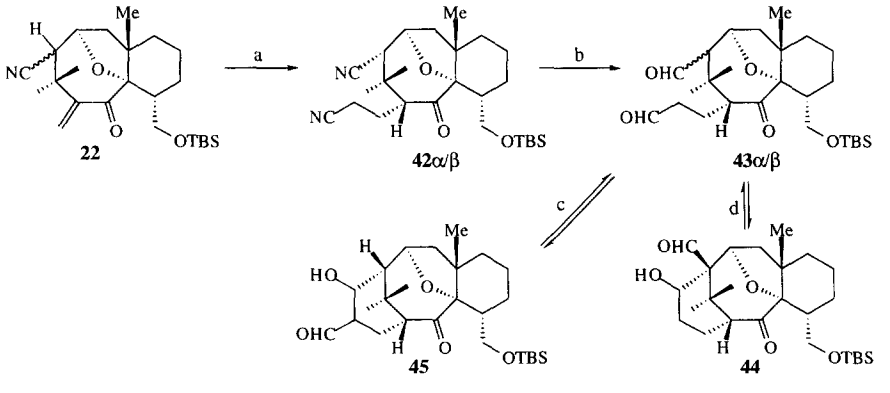
The exclusive formation of the required 1β-hydroxyl group results from axial addition of dioxygen to the C-1/C-2 enolate, and the C-1 side chain is forced into the more favorable equatorial conformation.[14] The cyano group in **38** was transformed into the methyl ester **39** (66%, overall from **38**) by the reduction-oxidation-esterification sequence. Treatment of a THF solution of **39** at 67°C with $LiN(TMS)_2$ (slow addition over 1h) gave **40** (>95%). Reductive removal of the $-SO_2Ph$ (Na/NH_3/THF/-78°C) gave **41** (100%). **Figure 3** shows a Chem 3D representation of **41** from the X-ray coordinates.

The above experiments demonstrate that the sulfone anion-ester ring-A closure is completely compatible with the presence of the 1β-hydroxyl group and allows for stereoselective introduction of this substituent prior to ring A formation.

Formation of the A-Ring (EWG = -CHO, Scheme 6)

The sulfone anion closure of the A-ring can be viewed as taking place under kinetic conditions (no equilibration). It was of interest to examine the classical aldol reaction to form the taxol A-ring under thermodynamic conditions (equilibration). Treatment of **22**α/β with $LiCH_2CN$ gave **42**α/β (2:1) which was reduced (DIBAL) to the dialdehyde **43**α/β. Purification of **43**α by chromatography over alumina resulted in cyclization to give **44**. Whereas, exposure of **43**α or **43**β to tetramethylguanidine/CH_2Cl_2/MeOH resulted in the alternative aldol product **45**.

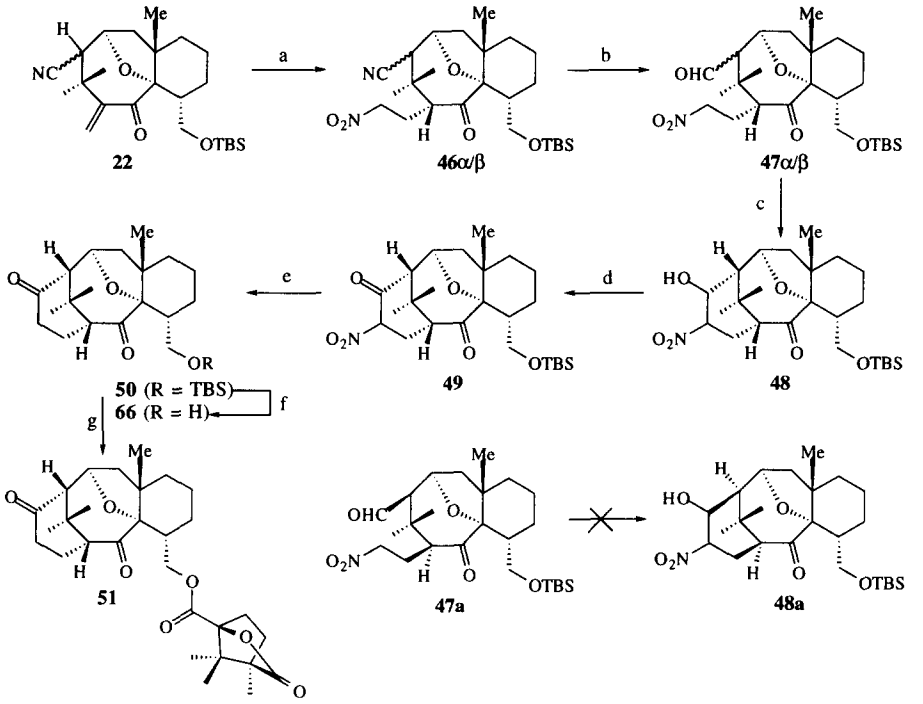
Scheme 6



Conditions:- a) $LiCH_2CN$/THF/-78°C, **42** (72%, α:β 2:1). b) DIBAL/CH_2Cl_2/-78°C, **43** (82%). c) Tetramethylguanidine/ CH_2Cl_2/MeOH/25°C/24h, **45** (64% from **42**). d) Neutral alumina column, **44** (30%).

Formation of the A-Ring (EWG = -NO_2, Scheme 7)

Scheme 7



Conditions:- a) $MeNO_2$ (10 eq)/DBU (5.0 eq)/CH_2Cl_2/-15°C **46** (85%, α:β 2:1). b) DIBAL/CH_2Cl_2/-78°C **47** (88%). c) Et_3N/CH_2Cl_2/25°C **48** (100%). d) Dess-Martin/CH_2Cl_2 **49** (79%). e) *n*-Bu_3SnH (5 eq)/AIBN/PhH reflux **50** (60%). f) HF.pyridine/THF (90%). g) (S)-(-)-Camphanic acid chloride/Et_3N/DMAP/CH_2Cl_2 **51** (96%).

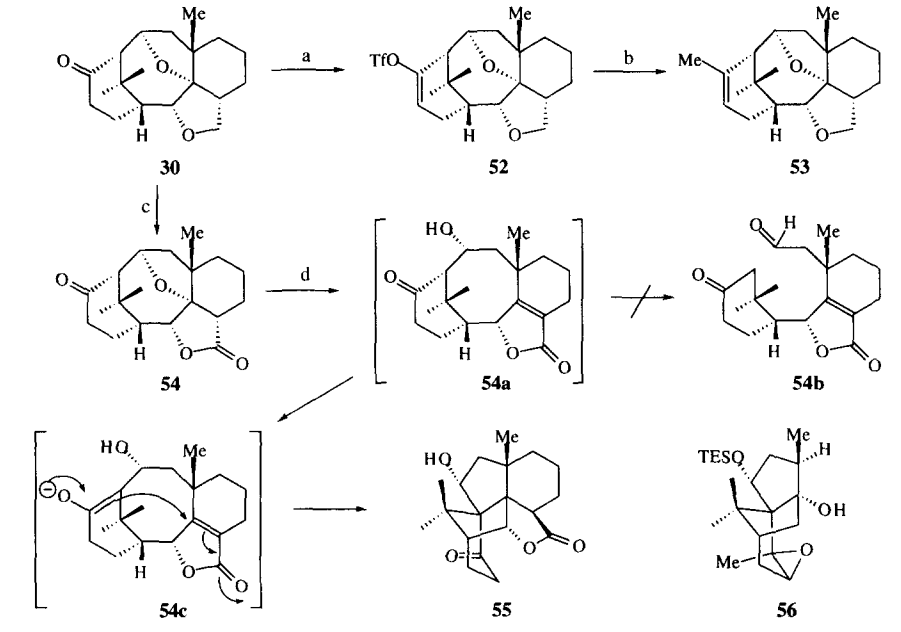
The nitro-aldol reaction (Henry reaction) takes place under particularly mild conditions, and the nitro functionality is very flexible with regard to subsequent transformations.[15] Therefore it was thought expedient to examine the closure of the A-ring using this methodology. The exomethylene ketones **22α/β** were treated with $MeNO_2$/DBU/CH_2Cl_2 to give the conjugate addition adducts **46α/β** (85%) as a 2:1 mixture at C-11 (-CN). The epimeric nitriles were readily separated, and each reduced with DIBAL/CH_2Cl_2/-78°C to give the nitroaldehydes **47α** and **47β** (90%). Merely stirring a solution of **47α** in CH_2Cl_2/25°C with triethylamine gave the nitro-alcohol **48** (100%) as a single stereoisomer. The **47β**-isomer did not cyclize under these conditions (no epimerization at C-11), whereas, treatment of **47α/β** with tetramethylguanidine (cat)/CH_2Cl_2/25°C resulted in C-11 epimerization and cyclization to give **48** (90%).[16] In this way we can use both C-11 epimers. Oxidation of the nitro-alcohol (Dess-Martin reagent) gave the nitro-ketone **49**, which when exposed to *n*-Bu_3SnH/AIBN (cat) gave the 12-keto-taxane **50**.[17] To unambiguously confirm the structure and absolute stereochemistry of **50**, the C-20 protecting group was removed to give **66** (**Scheme 7** and **9** for correlation with the sulfone series), and the camphanate ester derivative **51** prepared (X-ray). It should be noted that the C-1(β) and C-11(β) nitro-aldehyde diastereoisomer **47a**, does *not* undergo the nitro-aldol reaction, under the above conditions, to give **48a** with the A-ring on the β-face. Consequently, under thermodynamic equilibration reaction conditions, only

the correct (natural) A-ring stereochemistry is formed. The origin of this difference is the C-19 methyl group (MM2), and reinforces the notion that this quaternary center can be used to control the relative stereochemistry of crucial stereogenic carbon atoms.

In contrast to the sulfone series for cyclization of the A-ring, the nitro series is compatible with the presence of the C-2 carbonyl group (no retro-Michael reaction, $-CH_2CHNO_2$), but will not tolerate the autoxidation conditions necessary for introduction of the 1β-hydroxyl group.

Elaboration of the A-Ring (2α,20-tetrahydrofuran series, Scheme 8)

Scheme 8



Conditions:- a) NaHMDS/THF/-70°C/15 min, then *N*-(5-chloro-2-pyridyl)triflimide/0°C/1h, **52** (97%). b) CuI/MeLi/THF/-5 to -15°C/30 min, then add **52**, 0°C/48h, **53** (88%). c) $RuO_2.xH_2O$ (cat)/$NaIO_4$/CCl_4/H_2O/MeCN (98%)d) DBU/2.0 equiv/toluene/reflux, 2h, **55** (100%).

In order to functionalize the C-ring it is important to be able to open the 2α,20-THF ring in **30**. We found that oxidation of **30** using $RuO_2.xH_2O$ (cat)/$NaIO_4$ (ex)/CCl_4/H_2O/MeCN resulted in very clean conversion into the desired lactone **54** (100%).[18] Rather remarkably, when the lactone **54** was treated with DBU/PhMe/ 100°C it was converted, presumably *via* the 10α-hydroxy-12-ketotaxane **54a**, into the transannular cyclization product **55** (100%) (X-ray), **Scheme 8**. The relationship of **55** to Holtons bicyclic epoxy alcohol **56** [derived from (-)-β-patchoulene oxide (patchino)], the key intermediate in the "epoxy alcohol fragmentation" should be noted.[19] It is surprising that **54a** prefers to form a bridgehead-enolate **54c** and cyclize to **55**, rather than a retro-aldol reaction that would cleave the C-10/C-11 bond of the eight-membered ring leading to the keto-aldehyde **54b**. This result indicates that the 3,10-oxido bridge will have to be β-eliminated at a later point in the synthesis when the C-12 carbonyl group is no longer present.

The C-12 carbonyl group in **30** proved to be very resistant to the usual range of methylenating reagents (Ph_3PCH_2, Cp_2TiCH_2, Lombardo's reagent and the Takai modification)[20], presumably because of ready enolization. Consequently, we opted to take advantage of enolization and convert **30** into its derived enol triflate. Treatment of **30** with NaHMDS and quenching with *N*-(5-chloro-2-pyridyl)triflimide gave **52** (97%).[21] Coupling of **52** with $(CH_3)_2CuLi$ was slow, and required careful control of the temperature, but eventually resulted in **53** (88%).[22]

Elaboration of the A-Ring (2β-methoxy-2α,20-tetrahydrofuran series, Scheme 9)

Scheme 9

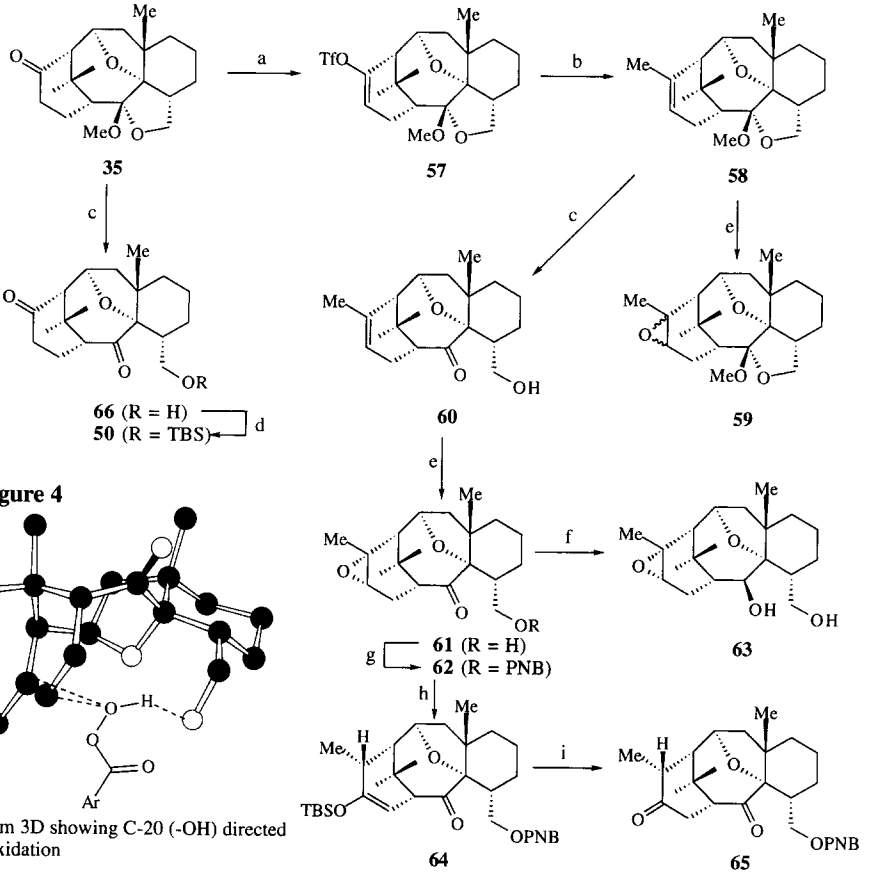


Figure 4

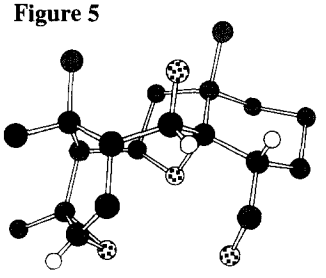
Chem 3D showing C-20 (-OH) directed epoxidation

Conditions:- a) NaHMDS/THF/-70°C/15 min, then *N*-(5-chloro-2-pyridyl)triflimide/0°C/1h, **57** (93%). b) CuI/MeLi/THF/-4°C/30 min, then add **57**, -30°C/48h, **58** (95%). c) AcOH/dioxane/75°C, **60** (93%), **66** (76%). d) TBSCl/DMF/Imidazole/DMAP/25°C/16h, **50** (80%). e) MCPBA/CH_2Cl_2/25°C, **61** (87%). f) SmI_2/THF/MeOH, **63**. g) *p*-$NO_2C_6H_4COCl/Et_3N$/DMAP/CH_2Cl_2. h) TBSOTf/CH_2Cl_2/0°C. i) HCl/dioxane.

The more advanced substrate **35** provided the opportunity to correlate the sulfone series with the nitro aldehyde series. Exposure of **35** to acid, hydrolyzed the internal ketal to give **66** which was identical to a sample made from **50**, and treatment of **66** with TBSCl/DMF/imidazole also gave **50**, **Schemes 7** and **9**.

Conversion of **35** into the alkene **58** proceeded *via* the enol triflate **57** as described for the series lacking the 2β-methoxy substituent (see **Scheme 8**). The C-12/13 alkene **58** exhibited very little stereoselectivity towards epoxidation; treatment of **58** with MCPBA/CH_2Cl_2 gave **59** as a 2:1 mixture of stereoisomers with the wrong (β) isomer being the major product. Both faces of the C12/13 alkene are hindered, and therefore we did not expect any marked stereoselectivity. To solve this problem of low selectivity we reasoned that the C-20 hydroxyl could promote a through-space directed epoxidation and provide access to the required α-epoxide.[23] **Figure 4** shows a Chem 3D representation of **60** with the peracid hydrogen bonded to the C-20 hydroxyl group which places the electrophilic oxygen atom close to the alkene on the desired α-face.

Figure 5

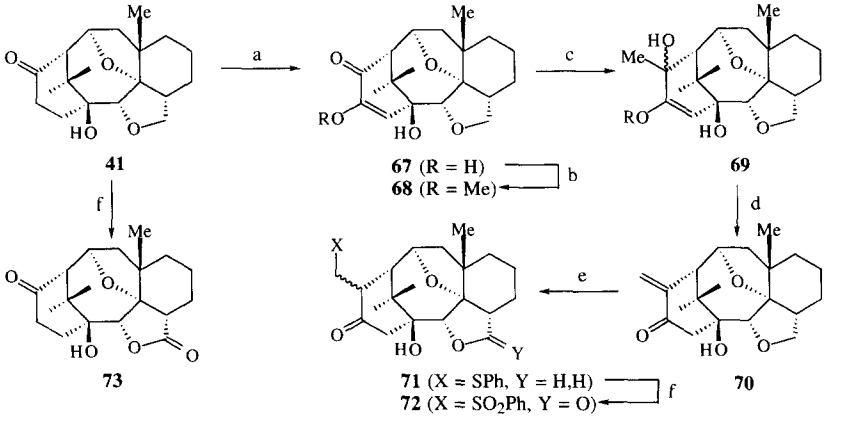


Chem 3D of **63** from X-ray coordinates

Acid hydrolysis of **58** gave **60**, which on treatment with MCPBA/CH_2Cl_2 gave a single epoxide **61**. The stereochemistry of **61** was determined by reduction (SmI_2) to the C-2(β) alcohol **63** (C-20 TBS group is also hydrolyzed), and **Figure 5** shows a Chem 3D representation from the X-ray coordinates. Clearly, the effect of C-20 deprotection has a dramatic and desirable stereochemical outcome on the introduction of C-13 oxygen functionality. It was also discovered that the C-12/13 epoxide could be readily rearranged to eventually provide the C-13 ketone **65** in a completely stereoselective manner. For example, treatment of the derived *p*-nitrobenzoate **62** with TBSOTf gave the enol ether **64** which on hydrolysis led to the ketone **65**, whose structure was determined by X-ray crystallography. The migration of the C-13(β) hydrogen atom to the C-12 position results in inversion at C-12 (suprafacial migration). Thus the C-12/13 epoxide functionality also allows access to the C-13 ketone derivative.

Elaboration of the A-Ring (1β-hydroxy-2α,20-tetrahydrofuran series, Scheme 10)

Scheme 10



Conditions:- a) *t*-BuOK/THF/O_2/-0°C, **67** (100%). b) MeI/K_2CO_3/acetone, **68** (100%). c) MeLi/THF/0°C, **69** (74%). d) 6N HCl/dioxane, **70** (100%). e) PhSH/Tetramethylguanidine/CH_2Cl_2, **71** (100%). f) $RuO_2.xH_2O$ (cat)/$NaIO_4$/CCl_4/H_2O, **72** (100%), **73** (100%).

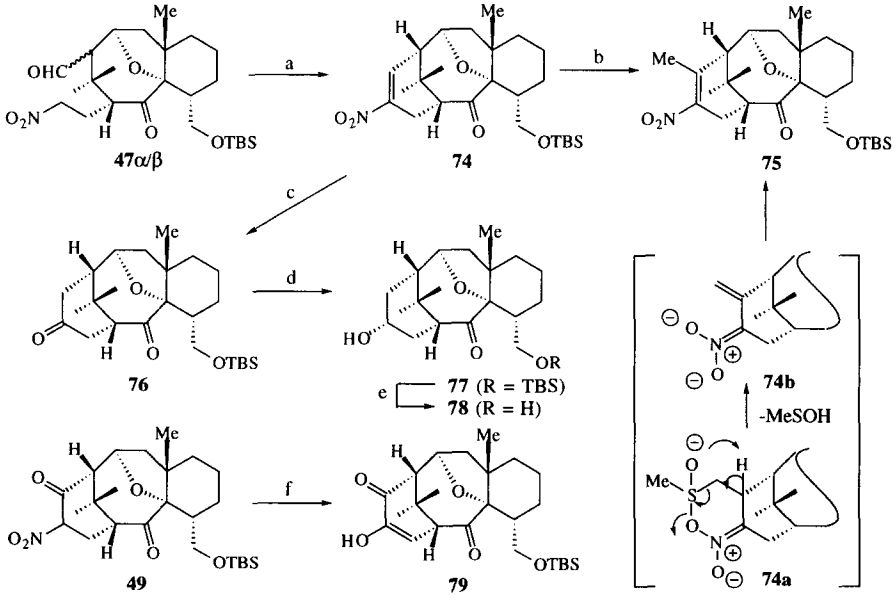
The C-13 oxygen atom can also be introduced *via* autoxidation of **41** to give **67** (95%).[24] The ^{1}H NMR spectrum of **67** showed that the C-12, C-13 1,2-dione existed predominantly (>90%) in the enolic form. Methylation of **67** under standard conditions gave **68** (95%), which on treatment with methyl lithium in Et_2O gave **69** (74%), accompanied by a small amount of conjugate addition at C-14 (ca. 10%). Mild acid hydrolysis of **69** resulted in the exocyclic enone **70**.

While we could oxidize **41** to give the lactone **73** in virtually quantitative yield, the exomethylene adduct **70** was destroyed. Consequently, we treated **70** with thiophenol, in the presence of 1,1,3,3-tetramethylguanidine (catalytic) to give **71** as an epimeric mixture at C-12 in greater than 95% yield. Oxidation of **71** gave the lactone **72** with concomitant oxidation of the sulfide to sulfone.

Elaboration of the A-Ring (Nitro Series, Scheme 11)

It was found that the nitro-aldol reaction product **48** could be dehydrated directly without isolation (MsCl/DBU) to give **74** (64%). At this stage we discovered a new and extremely useful transformation. Treatment of the α,β-unsaturated nitro compound **74** with dimsyl lithium ($MeS(O)CH_2Li$/THF) gave, after work-up (AcOH), the new α,β-unsaturated nitro compound **75**.[25] Presumably, this reaction proceeds through conjugate addition to give **74a** (or a non-cyclic equivalent), elimination of MeSOH to give the nitronate **74b**, and tautomerization to **75**.

Scheme 11

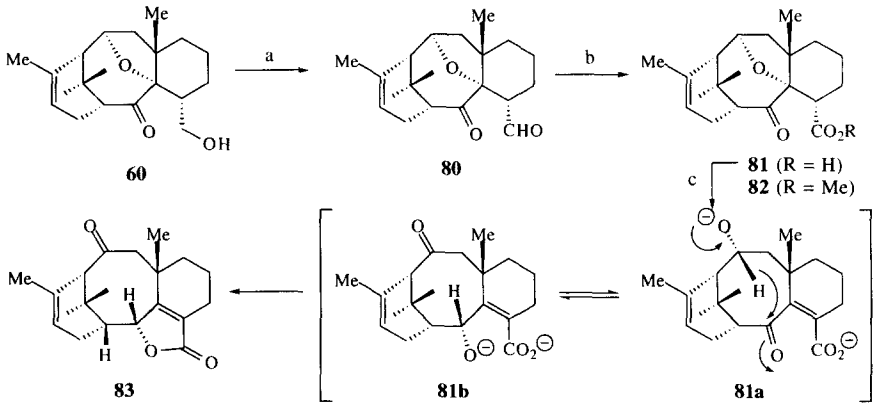


Conditions:- a) Tetramethylguanidine/CH_2Cl_2/24h, followed by $MeSO_2Cl$/DBU, **74** (64%). b) $LiCH_2S(O)Me$/THF/0°C, **75** (45%). c) $NaBH_4$/MeOH/0°C, followed by H_2O_2/K_2CO_3, **76** (60%). d) DIBAL-H/CH_2Cl_2/-78°C, **77** (84%). e) HF.py/THF, **78** (91%). f) MeONa/MeOH/O_3, followed by Me_2S, **79** (51%).

Reduction of nitroalkene **74** with sodium borohydride in methanol and subsequent treatment with hydrogen peroxide afforded the C-13 ketone **76** in 60% yield. Regioselective reduction with DIBAL at -78°C afforded a single diastereomeric product **77** in 84% yield. The stereochemistry at C-13 was initially assigned as the desired α-OH compound due to a sharp OH stretch in the IR spectrum at 3493 cm^{-1}. This was believed to be due to an intramolecular hydrogen bond between the newly formed hydroxyl group and the C3/10 bridging oxygen. This assignment was subsequently confirmed by X-ray crystallographic analysis of the desilylated derivative **78**. The nitro-ketone **49** undergoes an oxidative Nef-type reaction (MeONa/MeOH followed by ozone and reduction) to give the α-diketone **79** which exists predominantly in the depicted enolic tautomer (cf. **67**). These transformations complement the sulfone series, and demonstrate that 13-ketotaxanes and the derived 13-alcohol **77** are available from the nitro-aldol route.

β-Elimination of the 3,10-Oxido-Bridge (Scheme 12)

Scheme 12



Conditions:- a) Dess-Martin oxn, **80** (100%). b) $NaClO_2$/*t*-BuOH/2-methyl-2-butene/H_2O, **81** (35% from **60**). c) LDA/THF/25°C/2h, **83** (69%).

One of the key elements of the this overall strategy for synthesis of taxanes *via* the intermediacy of the bicyclo[5.4.$0^{3,8}$]undecenones derived from the oxidopyrylium ylide cyclization is the β-elimination of the 3,10-oxido-bridge. To examine this process the C-20 alcohol must be oxidized to provide the necessary C-4 acidic proton.

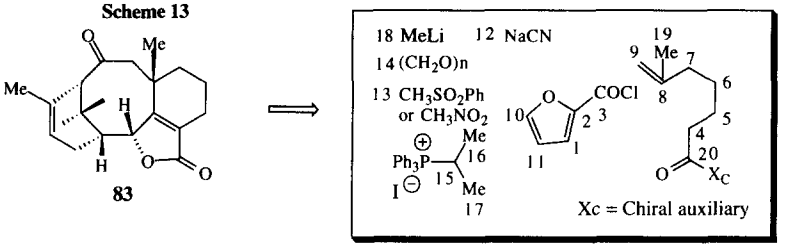
The ketoalcohol **60** underwent oxidation with Dess-Martin periodinane to give the aldehyde **80** as a 9:1 mixture of epimers at C-4. All attempts to β-eliminate the 3,10-oxido bridge in **80** failed. The only reaction pathway detected was epimerization at C-4. It is, of course, quite possible that β-elimination is taking place but the equilibrium favors **80**. This appears to be most likely since epimerization at C-4 shows that enolate formation has taken place. To render equilibration irreversible we considered that the dianion of the C-20 carboxylic acid would serve this purpose. It was also anticipated that β-elimination could be followed by a transannular hydride shift from the C-10 alkoxide to the C-2 carbonyl group resulting in the C-2(α) alcohol.[26] The aldehyde **80** was converted into the ketoacid **81**, which upon treatment with LDA (0°-25°C) underwent β-elimination (*via* the dianion), followed by transannular hydride migration, to give the ketolactone **83**. This

expected event serves to exchange oxidations levels between C-10 and C-2, and provide the correct C-2α-configuration! Presumably, after β-elimination the alkoxide **81a** undergoes reversible hydride migration to give **81b**, which on protonation leads to **83**.[27] It should be noted that the methyl ester **82** on treatment with LDA did not give **83**.[28]

Summary

The strategy described for the synthesis of taxanes represents a dramatic departure from previous approaches, and in particular allows a great deal of latitude for the construction of the A-ring and subsequent manipulations.[29] **Scheme 13**, shows an inventory of the origin of the various carbon atoms of the core structure. All of the components are commercially available except the heptenoic acid derivative.

Scheme 13



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.

(-)-1-Bromo-4α-(triphenylmethyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo [5.4.0^{3,8}]undec-1-ene-2-one 8. To a stirred solution of enone **5** (16.3 g, 0.035 mol) in dichloromethane (350 mL) cooled to -10°C in an acetone/ice bath was added bromine (2.0 mL, 0.038 mol, 1.1 equiv) in CCl_4 (20.0 mL) over 30 min. When the addition was complete, the mixture was stirred for a further 30 min at -10°C. Tlc analysis indicated complete consumption of **5**. Triethylamine (25 mL, 0.18 mol, 5 equiv) was added, and

the mixture was stirred an additional 1 h at -10°C. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous $Na_2S_2O_4$ (100 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2x25 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by trituration with 10% EtOAc/10% dichloromethane/80% hexanes to give **8** as an off-white microcrystalline solid (13.8 g, 72% yield). The mother liquors were purified by chromatography over silica gel eluting with 10% EtOAc/10% dichloromethane/80% hexanes to give **8** (5.8 g, 98.9% overall yield). $[\alpha]_D^{25} = -75°$ (c = 1.0, $CHCl_3$). M.pt. 210-213°C. IR (thin film) 2948, 2936, 1693, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.70-1.30 (6H, m), 1.95-1.80 (1H, m), 2.00 (1H, dd, J = 7.9, 4.4 Hz), 3.00-2.90 (3H, m), 4.53 (1H, t, J = 6.1 Hz), 7.50-7.10 (15H, m), 7.62 (1H, d, J = 5.3 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 16.4, 21.0, 22.3, 25.8, 36.5, 39.6, 40.5, 46.9, 65.4, 72.2, 86.7, 93.2, 122.0, 126.6, 127.2, 127.6, 127.9, 128.7, 128.8, 144.1, 155.1, 190.1. HRMS calcd for $C_{32}H_{32}BrO_3$ ($M^+ + 1$) 543.1436. Found 543.1436.

(-)-1-Bromo-4α-(*tert*-butyldimethylsilyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo [5.4.0^{3,8}]undec-1-ene-2 one 9. To a solution of **6** (9.7 g, 0.029 mol) in dichloromethane (200 mL) treated as above for **8**, gave **9** (10.0 g, 84%, 4:1 mixture of diastereomers). M.pt. 210-215°C. IR (thin film) 2931, 2856, 1694, 1602, 1471, 1386, 1306, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.01 (3H, s), 0.80-1.10 (2H, m), 0.85 (9H, s), 0.95 (3H, s), 1.20-1.30 (1H, m), 1.40-1.60 (2H, m), 1.68 (1H, d, J = 11.4 Hz), 1.80-1.90 (1H, m), 2.05 (1H, dd, J = 7.8, 12.3 Hz), 2.71 (1H, m), 3.43 (2H, m), 4.65 (1H, br dd, J = 7.8, 5.3 Hz), 7.70 (1H, d, J = 5.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, 18.4, 20.9, 22.2, 24.9, 26.0 (3C), 38.4, 39.5, 40.7, 46.8, 65.0, 72.3, 92.8, 122.0, 155.1, 190.1. HRMS (CI) calcd for $C_{19}H_{32}BrO_3Si$ ($M^+ + 1$) 415.1304. Found 415.1305.

1-Bromo-4α-(triisopropylsilyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}] undec-1-ene-2-one 10. To a solution of **7** (3.75 g, 9.89 mmol) in dichloromethane (50 mL) treated as above for **8**, gave **10** (4.28 g, 95%), which required no purification. IR (thin film) 2943, 2860, 1708, 1078, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.02-1.03 (18H, m), 1.26-1.47 (3H, m), 1.64-1.70 (3H, m), 1.89-1.96 (4H, m), 2.49 (1H, q, J = 7.9 Hz), 2.70-2.74 (1H, m), 3.45 (1H, q, J = 8.2 Hz), 3.54 (1H, dd, J = 5.4, 9.6 Hz), 4.62-4.67 (1H, m), 7.70 (1H, d, J = 5.1 Hz). HRMS (CI) calcd for $C_{22}H_{38}BrO_3Si$ ($M^+ + 1$) 457.1773. Found 457.1758.

(-)-11-Cyano-4α-(triphenylmethyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo [5.4.0^{3,8}]undec-1-ene-2-one 11. To a solution of **8** (28.95 g, 0.053 mol) in dichloromethane (890 mL) was added a solution of sodium cyanide (13 g, 0.265 mol) in water (186 mL), followed by tetra-*n*-butylammonium iodide (1.86 g). The reaction mixture was stirred vigorously at 25°C for 1.5 h. The organic phase was separated and transferred to another flask to which triethylamine (75 mL, 0.54 mol) was added and the mixture stirred for 12 h at 25°C. The solvent was removed *in vacuo* and the crude product purified by chromatography over silica gel eluting with 95%hexanes/EtOAc to give **11** as a bright yellow solid (24.0 g, 93%). $[\alpha]_D^{25} = -231°$ (c = 1.0, $CHCl_3$). M.pt. 157-158°C. IR (film) 2933, 2222, 1684, 1490, 1447, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, s), 1.85-1.20 (6H, m), 2.15 (1H, dd, J = 8.1, 4.7 Hz), 3.00-2.80

(3H, m), 4.55 (1H, d, J = 7.3 Hz), 6.33 (1H, s), 7.40-7.15 (15H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 16.6, 21.1, 22.0, 25.1, 36.0, 39.9, 40.3, 48.3, 65.1, 72.1, 87.3, 92.4, 127.0, 127.5, 127.8, 128.1, 128.9, 136.3, 137.5, 144.1, 168.0, 194.8. HRMS calcd for $C_{33}H_{31}NO_3$ (M^+) 489.2304. Found 489.2297.

(-)-11-Cyano-4α-(*tert*-butyldimethylsilyl)oxymethyl-8β-methyl-3α,10α-oxidobicyclo [5.4.0^{3,8}]undec-1-ene-2 one 12. To a solution of **9** (10.0 g, 0.024 mol, 4:1 mixture of diastereomers) in dichloromethane (50 mL) treated as for **11**, gave **12** as a yellow oil which crystallized upon standing (6.8 g, 78%, 5:1 mixture of diastereomers). M.pt. 110-111°C. IR (thin film) 2932, 2857, 2222, 1694, 1253, 1106, 1034, 838, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.03 (6H, s), 0.83 (9H, s), 0.95 (3H, s), 1.20-1.80 (6H, m), 1.73 (1H, dd, J = 12.2, 1.2 Hz), 2.20 (1H, dd, J = 12.2, 5.0 Hz), 2.64 (1H, m), 3.42 (2H, d, J = 7.2 Hz), 4.69 (1H, dd, J = 5.0, 1.2 Hz), 6.44 (1H, s). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ -5.6, -5.5, 20.8, 21.7, 24.3, 25.9 (3C), 37.9, 39.7, 40.4, 48.0, 64.6, 72.0, 92.0, 114.6, 136.1, 137.4, 167.8, 194.5. HRMS (CI) calcd for $C_{20}H_{32}NO_3Si$ (M^+ + 1) 362.2151. Found 362.2145.

11-Cyano-4α-(triisopropylsilyl)oxymethyl-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}] undec-1-ene-2-one 13. To a solution of **10** (4.25 g, 9.28 mmol) in dichloromethane (40 mL) treated as for **11**, gave **13** as a yellow oil (3.40 g, 90%). IR (thin film) 2944, 2866, 2223, 1695, 1463, 1107, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.00-1.04 (18H, m), 1.07-1.84 (10H, m), 2.20 (1H, dd, J = 8.1, 12.6 Hz), 2.62-2.69 (1H, m), 3.44-3.54 (2H, m), 4.68-4.70 (1H, m), 7.70 (1H, d, J = 5.1 Hz). HRMS (CI) calcd for $C_{23}H_{38}NO_3Si$ (M^+ + 1) 404.2617. Found 404.2617.

(-)-11β-Cyano-4α-(triphenylmethyl)oxymethyl-1α,11α-dimethylcyclopropano-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-2-one 14. A flask charged with isopropyltriphenylphosphonium iodide (26.3 g, 0.06 mol, 2.7 equiv) was heated under vacuum (10 mm) at 50°C in an oil bath for 12 h. After cooling to 25°C the phosphonium salt was dissolved in tetrahydrofuran (100 mL) and the stirred solution was treated with *n*-BuLi (2.5M in hexanes, 22.0 mL, 0.055 mol, 2.4 equiv), added *via* syringe over a period of 10 min. The deep red solution of phosphonium ylide was cooled to -70°C in an acetone/dry ice bath and a solution of **11** (11.0 g, 0.023 mol) in tetrahydrofuran (50 mL) added *via* cannula. The mixture was allowed to warm to 25°C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (100 mL) and extracted with dichloromethane (3x100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel eluting with hexanes followed by 10% EtOAc/10% dichloromethane/80% hexanes to give **14** as a white solid (11.5 g, 98%). $[\alpha]_D^{25}$ = -24.5° (c = 1.0, $CHCl_3$). IR (thin film) 3060, 2232, 1702, 1509, 1405, 1075, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.13 (3H, s), 1.27 (3H, s), 1.50-0.80 (6H, m), 1.90 (1H, s), 2.21-2.14 (2H, m), 2.86-2.58 (3H, m), 4.66 (1H, d, J = 6.8 Hz), 7.40-7.15 (15H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 16.8, 21.3, 25.4, 28.8, 29.7, 35.0, 37.0, 40.2, 41.5, 43.6, 48.3, 66.5, 71.4, 90.8, 91.0, 119.0, 127.0, 127.3, 127.8, 128.0, 128.7, 144.3, 202.6. HRMS (CI) calcd for $C_{36}H_{37}NO_3$ (M^+) 531.2773. Found 531.2773.

(-)-11β-Cyano-4α-hydroxymethyl-1α,11α-dimethylcyclopropano-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-2-one 17. A solution of **14** (9.13 g, 0.017 mol) in methanol (50 mL) and dichloromethane (20 mL), was treated with (±)-camphor sulfonic acid (0.40 g, 0.0017 mol, 10% mole) and stirred at 25°C for 60 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL), and the volatiles were removed *in vacuo*. The aqueous phase was extracted with dichloromethane (4x100 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with 90% hexanes/EtOAc to 50% hexanes/EtOAc to give **17** as a white solid (9.6 g, 86%). $[\alpha]_D^{25}$ = -84° (c = 0.98, $CHCl_3$). M.pt. 136-137°C. IR (thin film) 3499, 2935, 2235, 1697, 1029 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.40 (3H, s), 1.60 (3H, s), 1.80-1.15 (6H, m), 2.00 (2H, m), 2.23 (1H, dd, J = 7.4, 13.2 Hz), 2.40 (1H, m), 3.40 (2H, m), 4.81 (1H, d, J = 7.0 Hz) ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 16.8, 20.8, 21.5, 24.0, 28.9, 29.6, 35.0, 38.3, 40.0, 41.5, 43.7, 48.0, 64.9, 71.7, 91.5, 118.9, 203.4. HRMS (CI) calcd for $C_{17}H_{24}NO_3$ (M^+ + 1) 290.1756. Found 290.1753.

(-)-11β-Cyano-4α-(*tert*-butyldimethylsilyl)oxymethyl-1α,11α-dimethylcyclopropano-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-2-one 15. The alcohol **17** (9.6 g, 0.033 mol) in anhydrous dimethylformamide (100 mL) was treated with *tert*-butyldimethylsilyl chloride (6.3 g, 0.042 mol, 1.25 equiv), imidazole (5.7 g, 0.083 mol, 2.5 equiv), and 4-dimethylaminopyridine (DMAP) (0.40 g, 0.0033 moles, 10% mole). The mixture was stirred at 25°C for 12 h, and poured into water (500 mL), and extracted with dichloromethane (3x150 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash column chromatography over silica gel eluting with 50% hexanes/Et_2O gave **15** as a white solid (13.3 g, 100%). $[\alpha]_D^{25}$ -48.5° (c = 1.0, $CHCl_3$). M.pt. 103-106°C. IR (thin film) 2932, 2858, 2235, 1692, 1472, 1464, 1387, 1253 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.03 (3H, s), -0.20 (3H, s), 0.83 (9H, s), 0.99 (3H, s), 1.20-1.30 (2H, m), 1.39 (3H, s), 1.40-1.55 (3H, m), 1.59 (3H, s), 1.85 (1H, m), 1.95 (1H, dd, J = 13.2, 1.3 Hz), 2.00 (1H, s), 2.23 (1H, dd, J = 13.2, 7.3 Hz), 2.37 (1H, m), 3.26 (1H, t, J = 9.3 Hz), 3.37 (1H, dd, J = 9.5, 4.7 Hz), 4.77 (1H, dd, J = 7.3, 1.3 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ -5.5, -5.4, 16.4, 16.8, 18.3, 20.9, 21.2, 24.4, 26.0 (3C), 28.9, 29.9, 35.0, 39.1, 40.2, 41.8, 48.1, 65.3, 71.41, 90.8, 119.0, 202.9. HRMS (CI) calcd for $C_{23}H_{38}NO_3Si$ (M^+ + 1) 404.2621. Found 404.2626.

Synthesis of 15 from 12. Isopropyltriphenylphosphonium iodide (9.55 g, 22.1 mmol, 2.0 equiv) was dried overnight at 50°C and 10 mm Hg. The reagent was cooled to 25°C under an atmosphere of argon and dissolved in tetrahydrofuran (50 mL). The solution was cooled to -70°C and was treated with *n*-BuLi (2.5M in hexanes, 8.0 mL, 19.9 mmol, 1.8 equiv) dropwise using a syringe over a period of 15 min. To the deep red solution of the resultant phosphonium ylide was added *via* cannula a solution of **12** (4.0 g, 11.1 mmol) in tetrahydrofuran (20 mL). The mixture was allowed to warm to 25°C overnight. The mixture was quenched by addition of saturated aqueous NH_4Cl (100 mL), and extracted with EtOAc (4x150 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel eluting with 84:4:12 hexanes/Et_2O/dichloromethane gave **15** (4.32 g, 97% yield). For data see above.

11β-Cyano-4α-(triisopropylsilyl)oxymethyl-1α,11α-dimethylcyclopropano-8β-methyl-3α,10α-oxido-bicyclo[5.4.0^{3,8}]undec-2-one 16. Under an argon atmosphere at 24°C isopropyltriphenylphosphonium iodide (1.33 g, 3.10 mmol) was dissolved in dry tetrahydrofuran (15 mL), followed by slow addition of 2.5M *n*-BuLi in hexanes (1.14 mL, 2.85 mmol). After 0.75 h, the reaction mixture was cooled to -78°C, and **13** (0.50 g, 1.24 mmol) was added *via* cannula to the reaction at -78°C using dry tetrahydrofuran (2x5 mL) to aid the transfer. The reaction mixture was warmed to 24°C over 0.5 h, and after a further 0.5 h the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was poured into water (200mL), and separated. The aqueous phase was extracted with dichloromethane (3x100 mL). The extracts were combined, dried (Na_2SO_4), and the solvent evaporated *in vacuo* . The remaining residue was purified over silica gel eluting with EtOAc/petroleum ether (1:19). The product was isolated as a colorless crystalline solid (0.45 g, 82%). The proton NMR spectrum showed a 5:1 mixture of diastereomers. Fractional crystallization from methanol caused most (0.35 g) of the major diastereomer to form colorless octahedral rods. M.pt. 103-104°C (from methanol). IR (thin film) 2940, 2865, 2233, 1702, 1460, 1103, 833 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.07 (21H, m), 1.39 (3H, s), 1.57 (3H, s), 1.94-2.00 (11H, m), 2.22 (1H, dd, J = 7.4, 13.2 Hz), 2.39-2.43 (1H, m), 3.32 (1H, t, J = 9.2 Hz), 3.45 (1H, dd, J = 4.1, 9.0 Hz), 4.78 (1H, d, J = 6.7 Hz). HRMS (CI) calcd for $C_{26}H_{44}NO_3Si$ (M^+ + 1) 446.3090. Found 446.3086.

(-)-11α/β-Cyano-4α-(*tert*-butyldimethylsilyl)oxymethyl-3α,10α-oxido-8β,12,12-trimethyl-bicyclo[6.4.0^{3,8}]dodecan-2-one 18α and 18β. A solution of sodium naphthalenide (1.1M solution in tetrahydrofuran, 120 mL, 132 mmol) was titrated into a vigorously stirred solution of **15** (26.2g, 65 mmol), in tetrahydrofuran (1 L), at -70°C. The end-point was indicated by the persistence of a blue-green coloration and the reaction was quenched by the addition of saturated aqueous NH_4Cl (300 mL). The product was extracted into dichloromethane (3x200 mL), the combined extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. ^{1}H NMR indicated the presence of two diastereomeric products **18α** and **18β** in a 5:2 ratio. The diastereomers were separated by chromatography over silica gel (gradient 5%/40% EtOAc/hexanes) to afford **18α** as a low melting solid (17.1 g, 65%) and **18β** as a colorless oil (6.86 g, 26%). For the α-isomer. $[\alpha]_D^{25}$ -45.7° (c = 0.5, $CHCl_3$). IR (thin film) 2931, 2858, 2238, 1696, 1472, 1388, 1253, 1217 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.02 (6H, s), 0.83 (9H, s), 1.04 (3H, s), 1.05-1.20 (2H, m), 1.17 (3H, s), 1.31 (3H, s), 1.25-1.45 (2H, m), 1.50 (1H, m), 1.65 (1H, m), 1.85 (2H, m), 2.07 (1H, m), 2.13 (1H, d, J = 13.7 Hz), 2.65 (1H, s), 3.30 (1H, d, J = 13.7 Hz), 3.35 (1H, dd, J = 10.0, 7.0 Hz), 3.57 (1H, dd, J = 10.0, 6.7 Hz), 4.79 (1H, t, J = 8.0 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ -5.5 (2C), 18.3, 19.7, 20.9, 24.2, 25.9 (3C), 30.4, 32.0, 34.3, 38.1, 42.6, 44.0, 44.7, 46.7, 55.4, 64.6, 76.6, 93.0, 120.5, 214.4. HRMS (CI) calcd for $C_{23}H_{40}NO_3Si$ (M^+ + 1) 406.2777. Found 406.2772. For the β-isomer. $[\alpha]_D^{25}$ -42.0° (c = 1.0, $CHCl_3$). IR (thin film) 2931, 2858, 2237, 1695, 1684, 1472, 1394, 1259 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (3H, s), -0.03 (3H, s), 0.82 (9H, s), 1.00-1.25 (4H, m), 1.13 (3H, s), 1.40-1.60 (3H, m), 1.23 (3H, s), 1.67 (3H, s), 1.88 (1H, dd, J = 6.7, 3.2 Hz), 2.00 (1H, m), 2.07 (1H, d, J = 11.8 Hz), 3.10 (1H, d, J = 4.5 Hz), 3.28 (1H, d, J = 11.8 Hz), 3.35 (1H, dd, J = 10.0, 6.2 Hz), 3.53 (1H, dd, J = 10.0, 2.1 Hz), 4.68 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ -5.6 (2C), 16.4, 18.4, 19.6, 21.0, 24.2, 25.9 (3C), 34.6, 34.8, 38.2, 40.7, 43.5, 45.2, 45.5, 55.7, 64.4, 76.2, 92.2, 118.4, 215.5. HRMS (CI) calcd for $C_{23}H_{40}NO_3Si$ (M^+ + 1) 406.2777. Found 406.2763.

A solution of **18β** (251.8 mg, 0.62 mmol) in tetrahydrofuran (10 mL) was treated with solid potassium bis(trimethylsilyl)amide (372 mg, 0.1.86 mmol, 3 equiv). The mixture was stirred for 15 min and cooled to -70°C. After 30 min the reaction mixture was quenched by addition of (±)-camphorsulfonic acid (433 mg, 1.86 mmol, 3 equiv). After stirring at -70°C for 30 min the mixture was removed from the cooling bath and allowed to warm to 25°C. The solvent was removed *in vacuo* and the residue chromatographed over silica gel eluting with 75% hexanes/Et_2O to afford the **18β** (67.6 mg, 39%), and **18α** (134.3 mg, 53%).

11α/β-Cyano-4α-(triisopropylsilyl)oxymethyl-3α,10α-oxido-8β,12,12-trimethyl bicyclo[6.4.0^{3,8}]dodecan-2-one 19α and 19β. Under an argon atmosphere **16** (0.50 g, 1.12 mmol) was dissolved in dry tetrahydrofuran (50 mL), and the resulting solution cooled to -78°C. Sodium naphthalenide in dry tetrahydrofuran (stock solution: 1.80 g naphthalene, 40 mL dry tetrahydrofuran, 0.28 g sodium) was added dropwise to the reaction mixture. Addition of sodium naphthalenide turned the reaction mixture dark green for an instant, and a yellow to orange color emerged. When the dark green color persisted the reaction was left to stir for an additional 0.5 h. The reaction mixture was quenched at -78°C with saturated aqueous NH_4Cl (10 mL). The resulting mixture was poured into water (200 mL), and extracted with Et_2O (3x100 mL). The extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo*. The residue was purified over silica gel eluting with Et_2O/petroleum ether (1:19) to give **19α** (0.36 g) and **19β** (0.14 g, combined 100%), (5:3). For the β-isomer. IR (thin film) 2941, 2868, 2255, 1708, 1459, 1103 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (21H, m), 1.05 (3H, s), 1.38-1.51 (9H, m), 1.76-2.15 (6H, m), 2.65 (1H, s), 3.25 (1H, d, J = 13.7 Hz), 3.47 (1H, dd, J = 6.2, 10.0 Hz), 3.63-3.66 (2H, m), 4.08 (1H, m). HRMS (CI) calcd for $C_{26}H_{46}NO_3Si$ (M^+ + 1) 448.3246. Found 448.3231. For the α-isomer. IR (thin film) 2941, 2868, 2255, 1708, 1459, and 1103 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (21H, m), 1.4-1.6 (3H, s), 1.17 (3H, s), 1.23 (3H, s), 1.30-1.60 (7H, m), 1.87-1.89 (2H, m), 2.06 (1H, d, J = 11.5 Hz), 3.11 (1H, d, J = 4.4 Hz), 3.26 (1H, d, J = 11.6 Hz), 3.42 (1H, dd, J = 6.6, 9.9 Hz), 3.62 (1H, dd, J = 2.6, 9.8 Hz), 4.65-4.75 (1H, m). HRMS (CI) calcd for $C_{26}H_{46}NO_3Si$ (M^+ + 1) 448.3246. Found 448.3231.

11α-Cyano-4α-hydroxymethyl-3α,10α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}] dodecan-2-one 20α. Hydrogen fluoride-pyridine complex (150 μL) was added dropwise to a solution of **18α** (210 mg, 0.52 mmol) in tetrahydrofuran (10 mL). After 3 h water (20 mL) was added and the product extracted into dichloromethane (3x20 mL). The combined extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Chromatography over silica gel eluting with 40% EtOAc/hexanes afforded **20α** (120 mg, 79%). IR (thin film) 3498, 2933, 2882, 2239, 1695, 1468, 1386, 1274, 1217, 1141 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.17 (3H, s), 1.30-1.50 (4H, m), 1.33 (3H, s), 1.50-1.60 (2H, m), 1.80 (1H, dd, J = 13.7, 7.1 Hz), 1.95 (1H, d, J = 13.7 Hz), 2.10 (1H, m), 2.21 (1H, d, J = 14.0 Hz), 2.68 (1H, s), 3.21 (1H, d, J = 14.0 Hz), 3.52 (2H, d, J = 4.9 Hz), 4.85 (1H, t, J = 8.2 Hz). HRMS (CI) calcd for $C_{17}H_{26}NO_3$ (M^+ + 1) 292.1913. Found 292.1916.

11α-Cyano-4α-(4-nitrobenzoyl)oxymethyl-3α,10α-oxido-8β,12,12-trimethylbicyclo [6.4.0^{3,8}]dodecan-2-one 21α. 4-Nitrobenzoylchloride (92 mg, 0.5 mmol) was added to a solution of **20α** (110 mg, 0.38 mmol) in dry dichloromethane (5 mL). Triethylamine (0.2 mL) was added followed by DMAP (3

mg). After 2 h water (10 mL) was added and the product was extracted into dichloromethane (3x25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Chromatography over silica gel (30% EtOAc/hexanes) gave **21α** as a white solid (155 mg, 93%). Crystals suitable for X-ray analysis were obtained by recrystallization from ethanol/hexanes. M.pt. 158-160°C. IR ($CHCl_3$) 2935, 2237, 1715, 1693, 1607, 1528, 1463, 1348, 1275, 1103 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.10-1.50 (5H, m), 1.07 (3H, s), 1.18 (3H, s), 1.32 (3H, s), 1.68 (1H, m), 1.85 (1H, dd, J = 13.5, 7.2 Hz), 2.00 (1H, dd, J = 11.8, 9.3 Hz), 2.18 (1H, d, J = 14.0 Hz), 2.48 (1H, m), 2.70 (1H, s), 3.18 (1H, d, J = 14.0 Hz), 4.21 (1H, dd, J = 11.2, 5.9 Hz), 4.31 (1H, dd, J = 11.2, 6.6 Hz), 4.89 (1H, t, J = 8.4 Hz), 8.16 (2H, d, J = 8.8 Hz), 8.28 (2H, d, J = 8.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.9, 24.5, 30.7, 31.5, 34.7, 37.5, 38.7, 44.4, 44.8, 46.7, 53.4, 55.6, 66.9, 93.1, 120.3, 123.6 (2C), 130.8 (2C), 135.4, 150.5, 164.4, 214.3. HRMS (CI) calcd for $C_{24}H_{29}N_2O_6$ (M^+ + 1) 441.2026. Found 441.2017.

11-Cyano-4α-(*tert*-butyldimethylsilyl)oxymethyl-1-ylidene-3α,10α-oxido-8β,12,12-trimethyl-bicyclo-[6.4.0^{3,8}]dodecan-2-one 22. A solution of **18α** (2.6 g, 6.41 mmol) in tetrahydrofuran (100 mL) was degassed with argon for 20 min and treated with solid potassium bis(trimethylsilyl)amide (10.2 g, 51.3 mmol, 8 equiv), which was added portion wise to the stirred reaction mixture. After stirring for 15 minutes at room temperature, paraformaldehyde (10.2 g, 340 mmol, 50 equiv) was added portion wise. The mixture was stirred at 25°C for 2.5 h, and quenched with saturated aqueous NH_4Cl (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2x50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was filtered through a short column of neutral alumina, eluting with EtOAc to give **22** an oil (2.20 g, 82%, 3:1 mixture of α:β nitriles). For the α-epimer. IR (thin film) 2932, 2885, 2858, 2236, 1683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (3H, s), -0.01 (3H, s), 0.83 (12H, bs), 1.00-1.40 (5H, m), 1.32 (3H, s), 1.40 (3H, s), 1.51 (1H, m), 1.71 (1H, dd, J = 13.0, 7.6 Hz), 1.95 (1H, dd, J = 13.0, 8.9 Hz), 2.36 (1H, m), 2.56 (1H, s), 3.36 (1H, t, J = 9.4 Hz), 3.50 (1H, dd, J = 9.4, 3.7 Hz), 4.82 (1H, bt, J = 8.0 Hz), 5.36 (1H, s), 5.72 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.4, 18.3, 19.0, 20.8, 24.4, 25.9 (3C), 26.5, 29.4, 37.3, 38.7, 39.7, 43.6, 46.6, 47.4, 65.1, 76.6, 93.8, 120.4, 123.1, 157.4, 206.0. HRMS (CI) calcd for $C_{24}H_{40}NO_3Si$ (M^++ 1) 418.2777. Found 418.2781. For the β-epimer. IR (thin film) 2955, 2931, 2857, 2236, 1683, 1599, 1463, 1386, 1361, 1253, 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 0.89 (3H, s), 1.0-1.40 (5H, m), 1.34 (3H, s), 1.37 (3H, s), 1.55 (1H, m), 1.95 (1H, m), 2.08 (1H, dd, J = 13.5, 7.5 Hz), 2.37 (1H, m), 3.25 (1H, d, J = 6.9 Hz), 3.32 (1H, t, J = 9.4 Hz), 3.51 (1H, dd, J = 9.4, 3.5 Hz), 4.84 (1H, dd, J = 15.3, 7.9 Hz), 5.40 (1H, s), 5.73 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.4, 18.3, 18.9, 20.9, 24.5, 25.9 (3C), 28.6, 30.7, 37.5, 37.9, 40.1, 43.5, 43.9, 45.3, 65.1, 74.4, 94.1, 118.1, 123.3, 156.5, 206.9. HRMS (CI) calcd for $C_{24}H_{40}NO_3Si$ (M^+ + 1) 418.2777. Found 418.2774.

Direct synthesis of 22 from 15. A solution of sodium naphthalenide (0.37*M* solution in tetrahydrofuran; 3.4 mL, 1.26 mmol) was titrated into a stirred solution of **15** (250 mg; 0.62 mmol), in tetrahydrofuran (50 mL), at -70°C and the end-point was indicated by the persistence of a blue-green sodium naphthalenide coloration. Potassium bis(trimethylsilyl)amide (1.50 g, 7.50 mmol) was added and after a further 10 min paraformaldehyde (1.4 g) was added. After 10 min the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and the product was extracted into dichloromethane (3x20 mL). The

combined extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography over silica gel (tapered column; gradient: 5%→40% EtOAc/hexanes) afforded **22α** and **22β** (218 mg, 84%).

(-)-11α-Cyano-4a-(*tert*-butyldimethylsilyl)oxymethyl-3α,10α-oxido-1α-(2'-phenyl sulfonylethyl)-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecan-2-one 24. A solution of phenyl methyl sulfone (5.2 g, 32.8 mmol, 1.2 equiv) in tetrahydrofuran (150 mL) at 0°C was treated with *n*-BuLi (2.5M in hexanes, 12 mL, 30 mmol, 1.1 equiv) and stirred for 50 min. This solution was transferred *via* cannula to a solution of **22** (11.4 g, 27 mmol) in tetrahydrofuran (150 mL) at -70°C. The reaction mixture was stirred for 1.5 h at -70°C and quenched by the addition of a saturated aqueous NH_4Cl solution (100 mL) and allowed to warm to 25°C. The volatiles were removed *in vacuo* and the residue was partitioned between dichloromethane (100 mL) and water (100 mL). The aqueous phase was extracted with dichloromethane (3x150 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography over silica gel eluting with 80% hexanes/EtOAc gave **24α** (10.1 g, 65%) and **24β** (2.8 g, 18%). For the α-nitrile. $[\alpha]_D^{25}$ -3.9° (c = 0.9, $CHCl_3$). IR (thin film) 3460, 2934, 2857, 2239, 1690, 1302, 1153, 837 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (3H, s), -0.03 (3H, s), 0.83 (9H, s), 0.88 (3H, s), 1.14 (3H, s), 1.24 (3H, s), 1.60-1.10 (5H, m), 2.00-1.87 (2H, m), 2.39-2.08 (4H, m), 2.77 (1H, s), 3.08-2.94 (2H, m), 3.45-3.24 (3H, m), 4.93 (1H, dd, J = 6.4, 9.4 Hz), 7.55 (2H, m), 7.64 (1H, m), 7.86 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2, 18.4, 19.4, 21.0, 22.0, 25.0, 26.0, 31.1, 39.2, 40.0, 43.6, 48.2, 55.6, 58.6, 65.5, 76.8, 77.3, 77.4, 94.8, 105.0, 120.9, 127.9, 129.5, 133.9, 139.4, 210.4. HRMS (CI) calcd for $C_{31}H_{48}O_5NSiS$ (M^+ + 1) 574.3022. Found 574.3029. For the β-nitrile. $[\alpha]_D^{25}$ +55° (c = 1.0, $CHCl_3$). IR (thin film) 2933, 2859, 1691, 1148, 1307, 1091, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (3H, s), -0.03 (3H, s), 0.82 (12H, s), 1.08 (3H, s), 1.21 (3H, s), 1.50-0.80 (9H, m), 2.20-1.90 (5H, m), 3.14 (1H, d, J = 6.8 Hz), 3.24 (1H, m), 3.34 (1H, dd, J = 2.5, 7.8 Hz), 4.90-4.82 (1H, m), 7.70-7.55 (3H, m), 7.92 (2H, m). HRMS (CI) calcd for $C_{31}H_{48}O_5NSiS$ (M^+ + 1) 574.3022. Found 574.2995.

11α-Cyano-4α-(triisopropylsilyl)oxymethyl-1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}] dodecan-2-one 25 (via 23). Under an argon atmosphere, **19** (3.5 g, 7.81 mmol) was dissolved in dry tetrahydrofuran (300 mL) at 26°C. Potassium bis(trimethylsilyl)amide (14.13 g, 70.81 mmol) was added to the resulting solution, and the reaction mixture changed from colorless to orange. After 0.33 h, stirring became vigorous as paraformaldehyde (13.82 g, 460.35 mmol) was added to the reaction mixture, and the orange color turned red. After a further 0.75 h the reaction was quenched with saturated aqueous NH_4Cl (50 mL), and poured into water (500 mL). The resulting mixture was extracted with Et_2O (4x100 mL), dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue **23** was agitated under high vacuum for 1.0 h. A second argon filled flask was charged with phenylmethylsulfone (1.46 g, 9.37 mmol), and dry tetrahydrofuran (50 mL). The resulting solution was cooled to -78°C, and 2.5M *n*-BuLi in hexanes (3.72 mL, 9.37 mmol) was slowly added. The residue in the first flask was placed under argon, dissolved in tetrahydrofuran (100 mL), and cooled to -78°C. The sulfone was lithiated for 1.0 h before transfer *via* cannula (dry tetrahydrofuran 2x10 mL to aid transfer) to the first reaction vessel. After 0.75 h, the reaction mixture was quenched at -78°C with saturated aqueous NH_4Cl (20 mL), and poured into water (200 mL). The resulting mixture was extracted with dichloromethane (4x150 mL). The extracts were

combined, dried (Na_2SO_4), and the solvent removed *in vacuo*. The remaining residue was purified first over a short plug of silica gel eluting with EtOAc/petroleum ether (1:4) employing gravity to isolate the β-nitrile isomer of the product. The remaining crude residue was purified over a short plug of silica gel eluting under pressure with Et_2O/petroleum ether (3:7) to give **25** (4.16 g, 87%), isolated as a 5:3 mixture of stereoisomers. IR (thin film) 2940, 2866, 2239, 1691, 1447, 1105, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, s), 0.94 (21H, m), 1.08 (3H, s), 1.19 (3H, s), 1.36-1.49 (6H, m), 1.87 (1H, dd, J = 6.4, 13.7 Hz), 1.97-2.18 (4H, m), 2.72 (1H, s), 2.88-2.99 (2H, m), 3.25-3.38 (3H, m), 4.86 (1H, dd, J = 6.5, 9.0 Hz), 7.48-7.60 (3H, m), 7.80-7.82 (2H, d, J = 7.4 Hz). HRMS (CI) calcd for $C_{34}H_{54}NO_5SiS$ ($M^+ + 1$) 616.3492. Found 616.3488.

11α-Cyano-1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-2α,13α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecane 26 (R = Ph). To a solution of **25** (2.00 g, 3.25 mmol) in dry trifluoroacetic acid (100 mL) at 0°C was added sodium cyanoborohydride (0.646 g, 9.76 mmol) (rapid gas evolution). After 0.5 h, the mixture was poured slowly into saturated aqueous $NaHCO_3$ (500 mL), and extracted with dichloromethane (4x100 mL). The combined extracts were dried (Na_2SO_4), and the solvent removed *in vacuo*. The remaining residue was purified over silica gel eluting under pressure with EtOAc/hexanes (1:3), to give **26** (R = Ph) as a colorless foam (1.32 g, 92%). ^1H NMR showed predominantly the α-nitrile epimer, and only a trace of the β-epimer. For α-nitrile. M.pt 159-162°C. IR (thin film) 2940, 2231, 1304, 1148 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.08 (3H, s), 1.30 (3H, s), 1.34-1.53 (6H, m), 1.55-1.69 (1H, m), 1.91-2.10 (4H, m), 2.22 (1H, dd, J = 9.0, 12.2 Hz), 2.47 (1H, s), 3.11-3.28 (2H, m), 3.49 (1H, dd, J = 6.7, 12.1 Hz), 3.78 (1H, t, J = 7.4 Hz), 3.89 (1H, s), 4.65 (1H, t, J = 7.3 Hz), 7.54-7.68 (3H, m), 7.88 (2H, d, J = 7.3 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 18.4, 20.8, 22.1, 22.6, 31.0, 36.2, 39.7, 41.1, 42.1, 44.5, 49.7, 50.9, 54.6, 68.7, 75.6, 80.2, 90.4, 121.7, 127.9, 129.3, 133.8, 139.2. HRMS (CI) calcd for $C_{25}H_{34}NO_4S$ ($M^+ + 1$) 444.2202. Found 444.2203.

Methyl 1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-2α,13α-oxido-8β,12,12-trimethyl bicyclo[6.4.0^{3,8}]dodec-11α-oate 28. To a solution of **26** (R = Ph) (0.90 g, 2.04 mmol) in dry dichloromethane (25 mL) under an argon atmosphere at -78°C was added 1M DIBAL-H in toluene (5.104 mL, 5.10 mmol). After 4.5 h, the reaction was quenched at -78°C with 6M hydrochloric acid (5 mL), and saturated aqueous Rochelles salt added (20 mL). The resulting mixture was poured into water (50 mL), and extracted with dichloromethane (3x75 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue **27** was pumped under high vacuum for 1.0 h. The residue was dissolved in a solution of *t*-butanol (30 mL) and 2-methyl-2-butene (2.15 mL). The resulting mixture was warmed to 60°C, and a solution of aqueous NaH_2PO_4 (0.73 g, 5.27 mmol), and sodium chlorite (0.92 g, 10.13 mmol) in water (20 mL) was added to the reaction while stirring vigorously. After 2.5 h, *t*-butanol was evaporated *in vacuo,* and the remaining solution diluted with water (100 mL). The resulting mixture was extracted with dichloromethane (3x100 mL), dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was placed under high vacuum for 1.0 h to give a colorless foam. The foam was dissolved under an argon atmosphere at 22°C in dry acetone (15 mL). Potassium carbonate (0.84 g, 6.07 mmol) was added to the solution, and the colorless solution turned yellow. After 0.25 h, methyl iodide (1.26 mL, 20.23 mmol) was added to the reaction mixture, and vigorous stirring commenced for 2.0 h. The reaction mixture was poured into water (50 mL), and extracted

with dichloromethane (3x75 mL). The combined extracts were dried (Na_2SO_4), and the solvent removed *in vacuo*. The remaining residue was purified over silica gel eluting under pressure with Et_2O/petroleum ether (1:1) to afford the product **28** as a colorless foam (0.64 g, 66%). M.pt. 169-170°C (MeOH). IR (thin film) 2934, 2862, 1727, 1305, 1149 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, s), 1.04 (3H, s), 1.06 (3H, s), 1.16-1.67 (6H, m), 1.88-2.12 (6H, m), 2.31 (1H, s), 3.09-3.18 (1H, m), 3.23-3.33 (1H, m), 3.54 (1H, dd, J = 6.9, 11.9 Hz), 3.66 (3H, s), 3.75 (1H, t, J = 7.2 Hz), 3.83 (1H, d, J = 1.3 Hz), 4.54 (1H, dd, J = 6.9, 8.8 Hz), 7.52-7.66 (3H, m), 7.89 (2H, d, J = 7.6 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 18.7, 22.0, 22.7, 30.0, 36.3, 40.3, 41.0, 42.1, 46.2, 49.5, 51.5, 55.2, 63.5, 68.8, 74.8, 80.9, 89.6, 94.3, 102.2, 106.2, 128.0, 129.3, 133.6, 139.2, 175.2. HRMS(CI) calcd for $C_{26}H_{37}O_6S$ ($M^+ + 1$) 477.2309. Found 477.2310. Structure confirmed by single crystal X-ray analysis.

11β-Cyano-1α-(2'-*t*-butylsulfonylethyl)-2α,13α-oxido-8β,12,12-trimethylbicyclo [6.4.0^{3,8}]dodec-9-ene 26b (R = *t*-Bu). To a stirred solution of diisopropylamine (0.59 mL, 0.414 mmol) in dry tetrahydrofuran (15 mL) at 0°C, under an argon atmosphere, was added 2.5M *n*-BuLi in hexanes (1.64 mL, 20.62 mmol). After 0.75 h, **26** (R = *t*-Bu) (0.17 g, 0.414 mmol) was added to the reaction mixture. The reaction mixture was warmed to 24°C over 0.5 h, and quenched with saturated aqueous NH_4Cl solution (10 mL), diluted with water (10 mL), and the resulting solution extracted with dichloromethane (3x50 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo* . The remaining residue was purified over silica gel eluting under gravity with EtOAc/hexanes (4:6) to give a colorless solid (0.10 g, 57%). The product **26b** was crystallized from EtOAc/hexanes to give colorless rods. M.pt. 193-194°C. IR (thin film) 3421, 2925, 2237, 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) exhibited extreme broadening of the peaks due to conformational isomers. HRMS (CI) calcd for $C_{23}H_{38}NO_4S$ ($M^+ + 1$) 424.2540. Found 424.2521. Structure confirmed by single crystal X-ray analysis.

2,4Hβ-13-Phenylsulfonyl-11,12-dihydro-3α,10α-oxido-2α,20α-oxido-12-nortaxane-12-one 29. A 25 mL sealed tube was charged with the ester sulfone **28** (760 mg, 1.59 mmol) in tetrahydrofuran (8 mL), and degassed thoroughly with argon for 15 min. The mixture was stirred and heated to 70°C (external temperature) in an oil bath. Lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 4.0 mL, 4.0 mmol, 2.5 equiv) was added dropwise to the mixture over a period of 1 h *via* syringe pump. When the addition was complete, the mixture was stirred and heated for an additional 1 h. After cooling to 25°C, the reaction was quenched by addition of saturated aqueous NH_4Cl (4.0 mL). The volatiles were removed *in vacuo* , and the residue was partitioned between water and dichloromethane (3x30 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* . Purification by flash column chromatography over silica gel eluting with 75% Et_2O/hexanes gave **29** as a white foam (707 mg, 99% yield, 6:1 mixture of epimers at C-13). IR (thin film) 2924, 2865, 1714, 1306, 1147 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, s), 1.18 (3H, s), 1.22-1.24 (2H, m), 1.29-1.57 (6H, m), 1.63 (2H, dd, J = 7.9, 14.9 Hz), 1.70-2.00 (1H, m), 2.01 (1H, s), 2.09 (1H, s), 2.18 (2H, dd, J = 5.6, 14.3 Hz), 2.55-2.63 (1H, m), 3.33-3.39 (1H, dd, J = 7.5, 11.9 Hz), 3.83 (1H, t, J = 7.3 Hz), 4.21-4.26 (1H, m), 4.35 (1H, d, J = 5.4 Hz), 4.64-4.71 (1H, m), 7.49-7.63 (3H, m), 7.99 (2H, d, J = 7.9 Hz). HRMS (CI) calcd for $C_{25}H_{33}O_5S$ ($M^+ + 1$) 445.2056. Found 445.2048.

2,4Hβ-11,12-Dihydro-3α,10α-oxido-2α,20-oxido-12-nortaxane-12-one 30. To a solution of **29** (0.14 g, 0.31 mmol) in 10% aqueous tetrahydrofuran (35 mL) was slowly added aluminum/mercury amalgam (large excess). The reaction mixture was heated to 50°C, and stirred vigorously for 7 days. The mixture was filtered through a plug of Celite eluting with dichloromethane (250 mL). The organic phase was dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was purified by chromatography over silica gel eluting with EtOAc/petroleum ether (1:3) to give **30** (0.06 g, 65%). The solid product **30** was crystallized from pentane/EtOAc to give colorless needles. M.pt. 150-151°C. IR (thin film) 2918, 2862, 1702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.21 (3H, s), 1.27 (3H, s), 1.30-1.60 (4H, m), 1.62 (1H, s), 1.73 (2H, dd, J = 9.7, 13.3 Hz), 1.82-2.02 (3H, m), 2.07 (1H, t, J = 6.81 Hz), 2.20-2.31 (3H, m), 2.69-2.79 (1H, m), 3.51 (1H, dd, J = 7.4, 12.0 Hz), 3.85 (1H, t, J = 7.1 Hz), 4.26 (1H, ddd, J = 2.3, 4.1, 9.7 Hz), 4.39 (1H, d, J = 6.2 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 19.0, 19.1, 19.8, 22.2, 28.3, 32.3, 37.6, 41.4, 41.9, 44.6, 44.9, 46.9, 64.2, 70.5, 77.5, 82.7, 91.5, 215.9. HRMS (CI) calcd for $C_{19}H_{29}O_3$ ($M^+ + 1$) 305.2116. Found 305.2115. Structure confirmed by single crystal X-ray analysis.

11α-Formyl-4α-(*tert*-butyldimethylsilyl)oxymethyl-3α,10α-oxido-1-(2'-phenyl sulfonylethyl)-8β,12,12-trimethyl-bicyclo[6.4.0^{3,8}]dodecan-2-one 31. A solution of **24** (10.1 g, 17.6 mmol) in dichloromethane (100 mL) was cooled to -70°C and treated with DIBAL-H (1M in toluene, 20 mL, 19.4 mmol, 1.1 equiv) dropwise *via* syringe over a period of 15 min. The resulting yellow solution was stirred for 35 min at -70°C. The intermediate imine was hydrolyzed by the addition of a 10% (v/v) solution of HCl (40 mL). After stirring for 30 min, as the mixture warmed to 25°C, the phases were separated and the aqueous layer extracted with dichloromethane (3x50 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **31** which was used immediately without further purification (10 g, 100%). IR (thin film) 3406, 2934, 1688, 1647, 1304, 1145, 1087 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.05 (3H, s), -0.03 (3H, s), 0.82 (9H, s), 0.87 (3H, s), 1.01 (3H, s), 1.20-1.05 (3H, m), 1.23 (3H, s), 1.55-1.38 (2H, m), 1.98-1.92 (2H, m), 2.20-2.07 (3H, m), 2.22 (1H, d, J = 3.1 Hz), 2.39-2.27 (1H, m), 3.05-2.94 (2H, m), 3.24 (1H, t, J = 9.3 Hz), 3.50-3.32 (2H, m), 4.94 (1H, dd, J = 6.6, 9.4 Hz), 7.60-7.52 (2H, m), 7.70-7.60 (1H, m), 7.90-7.85 (2H, m), 9.90 (1H, d, J = 3.1 Hz). HRMS calcd for $C_{31}H_{49}O_6SiS$ ($M^+ + 1$) 577.2622. Found 577.2642.

11α-Carbomethoxy-4α-(*tert*-butyldimethylsilyl)oxymethyl-3α,10α-oxido-1-(2'-phenyl sulfonylethyl)-8β,12,12-trimethyl-bicyclo[6.4.0^{3,8}]dodecan-2-one 32. The crude aldehyde **31** (10.1 g, 17.6 mmol) was oxidized and esterified as for **27**, to give **32** (4.1 g, 50% for three steps). IR (thin film) 2933, 2856, 1736, 1684, 1370, 1148 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.06 (3H, s), -0.03 (3H, s), 0.80 (9H, s), 0.82 (3H, s), 0.93 (3H, s), 1.12 (3H, s), 1.50-1.00 (5H, m), 2.21-1.74 (5H, m), 2.25 (1H, m), 2.53 (1H, s), 2.80 (1H, m), 2.95 (1H, m), 3.50-3.25 (3H, m), 3.68 (3H, s), 4.77 (1H, dd, J = 6.5, 9.3 Hz), 7.65-7.50 (3H, m), 7.84 (2H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ -5.4, -5.3, 19.5, 20.1, 20.9, 21.4, 24.9, 25.9, 30.2, 39.1, 39.4, 40.0, 43.1, 48.4, 51.6, 55.7, 60.1, 61.5, 65.6, 75.8, 93.8, 127.8, 129.3, 133.6, 139.1, 174.1, 211.4. HRMS calcd for $C_{32}H_{51}O_7SiS$ ($M^+ + 1$) 607.3125. Found 607.3117.

Methyl 1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-2α,13α-oxido-8β,12,12-trimethyl bicyclo[6.4.0^{3,8}]dodec-11α-oate 28. To a solution of **32** (1.00 g, 1.65 mmol) in trifluoroacetic acid (20 mL) cooled to below 0°C in an acetone/ice bath and was added sodium cyanoborohydride (0.13 g, 2.00 mmol, 1.2 equiv). The mixture was stirred for 2 h. The solvent was evaporated *in vacuo* , and the residue was taken up in Et_2O (50 mL). The ether was washed with saturated aqueous $NaHCO_3$ (30 mL). The aqueous phase was extracted with Et_2O (3x50 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with 75% Et_2O/hexanes to give **28** as a white solid (764 mg, 97%). See above for data.

(-)-Methyl 1α-(2'-phenylsulfonylethyl)-2β-methoxy-3α,10α-oxido-2α,19α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodec-11α-oate 33. To a solution of **32** (1.02 g, 1.69 mmol) in anhydrous methanol (8.0 mL) in a sealed tube under an argon atmosphere was added trimethylorthoformate (8.0 mL, 73.1 mmol, 40 equiv) and pyridium *p*-toluenesulfonate (0.051 g, 0.20 mmol, 12% mole). The mixture was stirred at 70°C for 18 h. After cooling to 25°C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (6 mL). The volatiles were removed *in vacuo*, and the residue extracted with dichloromethane (4x10 mL). The combined extracts were dried (K_2CO_3), filtered and concentrated *in vacuo*. Chromatography over basic alumina eluting with 80% hexanes/EtOAc gave **33** (853 mg, 99.8%). $[\alpha]_D^{25}$ -10° (c = 1.0, $CHCl_3$). IR (thin film) 2947, 2882, 1729, 1446, 1306, 1140, 1097, 732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ , 0.95 (6H, s), 1.09 (3H, s), 1.75-0.83 (9H, m), 2.03-1.81 (3H, m), 2.31 (1H, s), 2.91 (3H, s), 3.30-3.10 (2H, m), 3.65-3.58 (1H, m), 3.65 (3H, s), 3.84 (1H, t, J = 7.7 Hz), 4.46 (1H, t, J = 8.0 Hz), 7.57-7.50 (3H, m), 7.90 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.7, 21.2, 21.3, 22.3, 29.5, 37.9, 38.8, 40.5, 42.0, 49.0, 50.2, 51.5, 55.1, 59.1, 62.8, 70.0, 74.2, 91.7, 111.7, 128.2, 129.2, 133.5, 138.9, 175.2. HRMS calcd for $C_{27}H_{38}O_7S$ (M^+) 506.2338. Found 506.2338.

2,4Hβ-13-Phenylsulfonyl-11,12-dihydro-3α,10α-oxido-2α,20α-oxido-2β-methoxy-12-nortaxane-12-one 34. A solution of **33** (817 mg, 1.61 mmol) in tetrahydrofuran (8 mL) in a 10 ml sealed tube was degassed with argon for 15 min. The mixture was stirred and heated to 70°C (external temperature) in an oil bath. Lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 4.2 mL, 4.2 mmol, 2.5 equiv) was added dropwise to the mixture over a period of 1.25 h *via* syringe pump. When the addition was complete, the mixture was stirred and heated for an additional 1.25 h. After cooling to 25°C, the reaction mixture was quenched with saturated aqueous NH_4Cl (5.0 mL). The volatiles were removed *in vacuo*, and the residue was partitioned between water and dichloromethane (4x15 mL). The combined extracts were dried (K_2CO_3), filtered, and concentrated *in vacuo* to give **34** as a yellowish colored foam that was used immediately (703 mg, 88%). IR (thin film) 2932, 2862, 1712, 1461, 1446, 1306, 1146, 1084, 1051 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H, s), 1.29 (3H, s), 1.42 (3H, s), 1.75-1.00 (6H, m), 1.85 (2H, m), 2.42-2.12 (6H, m), 2.75 (1H, m), 3.15 (3H, s), 3.43 (1H, dd, J = 7.5, 12.4 Hz), 3.94 (1H, t, J = 7.4 Hz), 4.28 (1H, ddd, J = 2.2, 5.2, 9.6 Hz), 4.63 (1H, m), 7.58-7.50 (3H, m), 8.03 (2H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 19.7, 21.2, 22.4, 24.6, 28.8, 32.7, 37.3, 41.5, 41.9, 44.0, 46.2, 47.0, 47.8, 65.0, 69.5, 70.4, 77.1, 93.4, 115.3, 128.7, 129.4, 133.5, 139.2, 204.2. HRMS(CI) calcd for $C_{26}H_{35}O_6S$ (M^+ + 1) 475.2154. Found 475.2143.

2,4Hβ-11,12-Dihydro-3α,10α-oxido-2α,20-oxido-2β-methoxy-12-nortaxane-12-one 35. Portions of sodium (~0.15 g, 6.5 mmol) were added to liquid ammonia (25 mL) at -40°C. To the resulting blue solution was added **34** (685 mg, 1.4 mmol) in tetrahydrofuran (8 mL) dropwise *via* syringe. The mixture was stirred for 20 min and quenched by the addition of isoprene (1 mL), followed by saturated aqueous NH_4Cl (4 mL). The ammonia was allowed to evaporate and the solvent evaporated *in vacuo*. The aqueous residue was extracted with dichloromethane (4x20 mL), and the combined extracts were dried (K_2CO_3), filtered and concentrated *in vacuo*. Chromatography over basic alumina eluting with 90% hexanes/EtOAc gave **35** as a white solid (354 mg, 64% for two steps). M.pt. 145–147°C. IR (thin film) 2938, 1705, 1458, 1097, 1049 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s) 1.31 (3H, s), 1.44 (3H, s), 1.68–1.20 (6H, m), 2.46–1.91 (8H, m), 2.67 (1H, m), 3.16 (3H, s), 3.52 (1H, dd, J = 7.3, 12.4 Hz), 3.95 (1H, t, J = 7.3 Hz), 4.28 (1H, ddd, J = 2.2, 5.2, 9.6 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 19.9, 21.2, 22.1, 22.5, 29.0, 33.7, 37.2, 38.2, 41.9, 42.0, 44.1, 45.8, 47.0, 47.7, 64.5, 70.3, 78.0, 93.0, 116.1, 215.9. HRMS (CI) calcd for $C_{20}H_{31}O_4$ ($M^+ + 1$) 335.2222. Found 335.2215.

11α-Cyano-1β-hydroxy-4α-(triisopropylsilyl)oxymethyl-1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecan-2-one 37. To a solution of **25** (2.70 g, 4.39 mmol) in dry tetrahydrofuran (80 mL) under an argon atmosphere at 24°C was added potassium *t*-butoxide (2.46 g, 21.98 mmol). After 0.1 h, the reaction mixture was cooled to -78°C, and triethylphosphite (1.88 mL, 10.99 mmol) added. Dry oxygen was bubbled beneath the reaction mixture surface for 0.75 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and poured into water (100 mL). The resulting mixture was extracted with dichloromethane (3x100 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was dried under high vacuum for 2.0 h to give **37** as a colorless foam (2.25 g, 81%). IR (thin film) 3422, 2940, 2866, 2239, 1694, 1153 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.90 (18H, m), 0.98-1.53 (17H, m), 1.75-2.30 (3H, m), 2.40-2.55 (1H, m), 2.72-2.93 (1H, m), 3.18 (1H, s), 3.19-3.36 (1H, m), 339-3.52 (4H, m), 4.27 (1H, s), 4.82-4.89 (1H, m), 7.52-7.67 (3H, m), 7.86-7.88 (2H, d, J = 7.2 Hz). HRMS (CI) calcd for $C_{34}H_{54}NO_6SiS$ ($M^+ + 1$) 632.3441. Found 632.3224.

11α-Cyano-1β-hydroxy-1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-2α,13α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecane 38. To a solution of **37** (2.25 g, 3.56 mmol) in dry trifluoroacetic acid (100 mL) at 0°C was added sodium cyanoborohydride (0.872 g, 13.19 mmol) (caused rapid gas evolution). After 0.25 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (500 mL), and extracted with dichloromethane (4x100 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was purified by chromatography over silica gel eluting under pressure with EtOAc/petroleum ether (1:3) to give **38** (1.63 g, 100%). M.pt. 237°C (from EtOAc/hexanes). IR (thin film) 3489, 2937, 2863, 2237, 1447, 1306, 1149, 737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, s), 1.11 (3H, s), 1.19-1.59 (6H, m), 1.36 (3H, s), 1.94-2.02 (5H, m), 2.30-2.40 (1H, m), 2.50 (1H, dd, J = 5.5, 12.2 Hz), 2.92 (1H, s), 3.23-3.34 (1H, m), 3.44 (1H, s), 3.46-3.49 (1H, m), 3.73 (1H, s), 4.66-4.69 (1H, m), 7.56-7.68 (3H, m), 7.88-7.91 (2H, d, J = 7.2 Hz). HRMS (CI) calcd for $C_{25}H_{34}NO_5S$ ($M^+ + 1$) 460.2157. Found 460.2144. Structure confirmed by single crystal X-ray analysis. ^1H NMR showed a mixture

of stereoisomers with the α-nitrile isomer being the predominant product, with only a trace of the β-nitrile isomer present.

Methyl-1β-hydroxy-1α-(2'-phenylsulfonylethyl)-3α,10α-oxido-2α,13α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodec-11α-oate 39. To a solution of **38** (0.50 g, 1.08 mmol) in dry dichloromethane (14 mL) under an argon atmosphere, at -78°C, was added 1M DIBAL-H in toluene (4.22 mL, 4.20 mmol). After 5.0 h, the reaction was quenched with 10M hydrochloric acid (10 mL), and saturated aqueous Rochelles salt added (10 mL). The resulting mixture was poured into water (100 mL), and extracted with dichloromethane (3x100 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was dried under high vacuum for 1.0 h. The residue was dissolved in *t*-butanol (15 mL) and 2-methyl-2-butene (2.15 mL). The resulting mixture was warmed to 60°C, and an aqueous solution of NaH_2PO_4 (0.38 g, 2.81 mmol), and sodium chlorite (0.98 g, 10.82 mmol) in water (15 mL) was added to the reaction mixture while stirring vigorously. After 3.0 h, the *t*-butanol was evaporated *in vacuo*, and the remaining solution diluted with water (100 mL). The resulting mixture was extracted with dichloromethane (3x50 mL), dried (Na_2SO_4), and the solvent removed *in vacuo*. The remaining residue was placed under high vacuum for 2.0 h to give a colorless foam. The foam was dissolved, under an argon atmosphere at 22°C, in dry acetone (10 mL). Potassium carbonate (4.33 g, 9.1 mmol) was added to the reaction solution, and the colorless solution turned yellow. After 0.25 h, iodomethane (0.674 mL, 10.82 mmol) was added to the reaction mixture. After 2.0 h, the reaction solution was poured into distilled water (100 mL), and extracted with dichloromethane (3x100 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was purified by chromatography over silica gel eluting under pressure with EtOAc/petroleum ether (1:1) to afford **39** as a colorless foam (0.35 g, 66%). IR (thin film) 3509, 2942, 2862, 1732, 1149 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.08 (3H, s), 1.21 (3H, s), 1.22-1.53 (3H, m), 1.84-2.02 (4H, m), 2.33-2.45 (3H, m), 2.63 (1H, s), 2.76 (1H, s), 3.33-3.54 (4H, m), 3.63 (1H, s), 3.67-3.72 (4H, m), 4.51-4.56 (1H, m), 7.54-7.66 (3H, m), 7.90-7.92 (2H, d, J = 7.1 Hz). HRMS (CI) calcd for $C_{26}H_{36}O_7S$ (M^+) 492.2181. Found 492.2185.

1β-Hydroxy-2,4Hβ-13-phenylsulfonyl-11,12-dihydro-3α,10α-oxido-2α,20α-oxido-12-nortaxane-12-one 40. To a solution of **39** (0.19 g, 0.38 mmol) in dry tetrahydrofuran (7.5 mL) under an argon atmosphere at 67°C was slowly added 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.22 mL, 1.22 mmol) *via* syringe pump over 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was poured into water (70 mL), and extracted with dichloromethane (3x50 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was purified over silica gel eluting under pressure with EtOAc/petroleum ether (1:3) to afford the product **40** as a colorless foam (0.17 g, 100%). IR (thin film) 3494, 2934, 2865, 1717, 1011, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, s), 1.21 (6H, s), 1.23-1.52 (5H, m), 1.73 (1H, dd, J = 9.5, 13.3 Hz), 1.96-2.26 (4H, m), 2.65 (1H, s), 2.73 (1H, dd, J = 9.2, 14.8 Hz), 3.42 (1H, dd, J = 8.0, 12.5 Hz), 3.90 (1H, t, J = 6.8 Hz), 4.08-4.11 (1H, m), 4.24 (1H, s), 4.26-4.31 (1H, m), 4.73 (1H, dd, J = 9.2, 11.4 Hz), 7.51-7.65 (3H, m), 8.25 (2H, d, J = 6.5 Hz). HRMS (CI) calcd for $C_{25}H_{32}O_6S$ (M^+) 460.1906. Found 460.1919.

1β-Hydroxy-2,4Hβ-11,12-dihydro-3α,10α-oxido-2α,20α-oxido-12-nortaxane-12-one 41. To a solution of **40** (0.14 g, 0.30 mmol) in dry tetrahydrofuran (15 mL) under an argon atmosphere, at -78°C, was slowly added anhydrous ammonia (excess) which was bubbled slowly beneath the reaction solution surface until the volume increased roughly by one third. Excess sodium was added (0.210 g, 9.13 mmol), and streaks of blue appeared in the reaction media. After a couple of minutes the reaction was quenched with water (5 mL). The resulting mixture was poured into water (20 mL), and extracted with dichloromethane (3x50 mL), and chloroform (3x50 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was placed under high vacuum for 2.0 h to give **41** as a colorless foam (0.095 g, 100%). The colorless solid product **41** was recrystallized from methanol to give thick colorless diamond shaped plates. M.pt. 139-140°C. IR (thin film) 3471, 2936, 2862, 1702, 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.23 (3H, s), 1.25 (3H, s), 1.32-1.61 (6H, m), 1.71-1.84 (2H, m), 1.98-2.02 (2H, m), 2.25-2.41 (3H, m), 2.47 (1H, s), 2.77-2.90 (1H, m), 3.50 (1H, dd, J = 7.5, 12.4 Hz), 3.89 (1H, t, J = 7.1 Hz), 4.29 (1H, s), 4.30-4.34 (1H, m). HRMS (CI) calcd for $C_{19}H_{28}O_4$ (M^+) 320.1980. Found 320.1987. Structure confirmed by single crystal X-ray analysis.

11α-Cyano-4α-(*tert*-butyldimethylsilyl)oxymethyl-1α-(2'-cyanoethyl)-3α,10α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecan-2-one 42. *n*-BuLi (8.0 mL, 2.0M solution in hexanes) was added drop wise to a stirred solution of diisopropylamine (1.7 g, 16.8 mmol) in tetrahydrofuran (20 mL) at 0°C. After 30 min the solution was cooled to -78°C and acetonitrile (0.6 mL; 18.6 mmol) was added. After 1 h a solution of **22** (410 mg, 1.0 mmol) in tetrahydrofuran (2 mL) was added *via* cannula. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), and extracted with dichloromethane (3x25 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. Chromatography over silica gel eluting with 20%→40% EtOAc/hexanes gave **42** (322 mg, 72%). M.pt. 149-151°C. IR (thin film) 2933, 2858, 2243, 1692, 1471, 1488, 1386, 1362, 1253, 1143, 1096 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (3H, s), -0.01 (3H, s), 0.82 (9H, s), 0.85 (3H, s), 1.00-1.20 (3H, m), 1.16 (3H, s), 1.20 (3H, s), 1.40 (1H, m), 1.50 (1H, m), 1.80-2.00 (2H, m), 2.10-2.30 (4H, m), 2.50 (1H, bd, J = 10.0 Hz), 2.50-2.60 (2H, m), 2.76 (1H, s), 3.27 (1H, t, J = 9.2 Hz), 3.37 (1H, dd, J = 9.2, 3.6 Hz), 4.89 (1H, dd, J = 9.4, 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.4, 17.6, 18.2, 19.3, 20.8, 22.0, 23.4, 24.8, 25.8 (3C), 31.0, 38.7, 38.9, 39.9, 43.2, 48.2, 49.5, 58.6, 65.3, 76.5, 94.7, 119.7, 120.6, 209.0. HRMS (CI) calcd for $C_{26}H_{43}N_2O_3Si$ (M^+ + 1) 459.3043. Found 459.3032.

11α-Formyl-4α-(*tert*-butyldimethylsilyl)oxymethyl-3α,10α-oxido-1α-(3'-propanal)-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecan-2-one 43. DIBAL-H (0.8 mL; 1.0M solution in dichloromethane) was added to a stirred solution of **42** (120 mg, 0.26 mmol) in dichloromethane (30 mL) at -78°C. After 20 min the cooling bath was removed and the reaction mixture was quenched by the addition of water (5 mL). The organic layer was washed with 2N HCl (5x30 mL) and the combined aqueous phases were re-extracted with dichloromethane (3x30 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated to afford **43** (100 mg, 82%, crude), which was used without further purification. IR (thin film) 2932, 2857, 2722, 2193, 1724, 1690, 1459, 1388, 1256 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.08 (3H, s), -0.02 (3H, s), 0.84 (12H, bs), 1.06 (3H, s), 1.10-1.20 (3H, m), 1.23 (3H, s), 1.40-1.50 (3H, m),

1.85-2.00 (3H, m), 2.10-2.20 (1H, m), 2.20 (1H, d, J = 3.3 Hz), 2.30-2.50 (2H, m), 2.55 (1H, bd, J = 8.1 Hz), 2.72 (1H, m), 3.27 (1H, t, J = 9.2 Hz), 3.42 (1H, dd, J = 9.2, 3.3 Hz), 4.93 (1H, dd, J = 9.4, 6.5 Hz), 9.76 (1H, s), 9.92 (1H, d, J = 3.3 Hz). HRMS (CI) calcd for $C_{26}H_{45}O_5Si$ (M^+ + 1) 465.3036. Found 465.3018.

2,4Hβ-11,12-dihydro-20-(*tert*-butyldimethylsilyloxy)-11β-formyl-12-hydroxy-3α,10α-oxido-12-nortaxane-2-one 44. Attempted purification of the crude product **43** (100 mg, 0.22 mmol) on neutral alumina resulted in the formation of **44** (35 mg, 30% from **42**). IR (thin film) 3472, 2929, 1721, 1687, 1463, 1258 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (6H, s), 0.84 (9H, s), 1.10-1.20 (2H, m), 1.11 (3H, s,), 1.19 (3H, s), 1.21 (3H, s), 1.30-1.50 (4H, m), 1.75-2.15 (6H, m), 2.20-2.40 (2H, m), 3.38 (1H, t, J = 9.3 Hz), 3.56 (1H, dd, J = 9.3, 4.7 Hz), 4.78 (1H, m), 5.09 (1H, dd, J = 10.2, 5.4 Hz), 9.79 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, 18.3, 19.2, 21.5, 22.1, 24.7, 25.9 (3C), 30.4, 31.4, 36.1, 41.5, 41.9, 44.2, 45.9, 49.8, 52.7, 61.7, 65.0, 67.4, 75.3, 92.1, 205.5, 219.6. HRMS (CI) calcd for $C_{26}H_{45}O_5Si$ (M^+ + 1) 465.3036. Found 465.3021.

2,4Hβ-11,12-dihydro-20-(*tert*-butyldimethylsilyloxy)-13-formyl-12-hydroxy-3α,10α-oxido-12-nortaxane-2-one 45. 1,1,3,3-tetramethylguanidine (160 mg, 1.40 mmol) was added to a solution of **43** (100 mg, 0.22 mmol) in dichloromethane (10 mL). After 24 h dichloromethane (20 mL) was added and the organic solution was washed with 2N aqueous HCl (20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to afford **45** as a single diastereoisomer (78 mg, 64% from **42**). IR (thin film) 3470, 3931, 2859, 1719, 1688, 1472, 1462, 1395, 1257, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (6H, s), 0.84 (9H, s), 0.97 (3H, s), 1.10-1.20 (2H, m), 1.14 (3H, s), 1.23 (3H, s), 1.30-1.50 (3H, m), 1.65 (2H, m), 1.80 (1H, m,), 2.10 (1H, m), 2.23 (1H, dd, J = 13.6, 5.3 Hz), 2.44 (1H, q, J = 7.1 Hz), 2.56 (1H, d, J = 4.5 Hz), 3.40 (2H, m), 3.61 (1H, dd, J = 9.6, 5.3 Hz), 4.60 (1H, m), 5.10 (1H, m), 9.79 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, 18.3, 19.2, 21.5, 22.1, 24.7, 25.9 (3C), 30.4, 31.4, 36.1, 41.5, 41.9, 44.2, 45.9, 49.8, 52.7, 61.7, 65.0, 67.4, 75.3, 92.1, 205.5, 219.6. HRMS (CI) calcd for $C_{26}H_{45}O_5Si$ (M^+ + 1) 465.3036. Found 465.3011.

11-Cyano-4α-(*tert*-butyldimethylsilyl)oxymethyl-1α-(2'-nitroethyl)-3α,10α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecan-2-one 46α/β. DBU (10.7 mL, 72 mmol) was added to a stirred solution of **22** (3:1) (6.0 g, 14.4 mmol) and nitromethane (7.8 mL, 144 mmol) in dichloromethane (150 mL) at -15°C. After 2 h 2N HCl (200 mL) was added, the layers were partitioned, and the acidic layer was extracted with dichloromethane (2x100 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. ^1H NMR indicated the presence of two diastereomers which were separated by chromatography over silica gel eluting with 20%→40% EtOAc/hexanes to give **46α** as a white solid (4.1 g, 60%) and **46β** (1.72 g, 25%) as a pale yellow oil. For epimer **46α**. M.pt. 134-135°C. $[\alpha]_D^{20}$ +11° (c = 1.0, $CHCl_3$). IR ($CHCl_3$) 2932, 2857, 2239, 1684, 1560, 1472, 1388, 1362, 1254, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.03 (3H, s), -0.02 (3H, s), 0.82 (12H, br s), 1.00-1.30 (3H, m), 1.18 (3H, s), 1.19 (3H, s), 1.40 (2H, bd, J = 8.7 Hz), 1.50 (1H, m), 1.78 (1H, dd, J = 13.9, 6.5 Hz), 1.93 (1H, bd, J = 9.8 Hz), 2.21 (1H, dd, J = 13.9, 9.7 Hz), 2.23 (2H, m), 2.52 (1H, bd, J = 8.4 Hz), 2.74 (1H, s), 3.27 (1H, t, J = 9.3 Hz), 3.37 (1H,

dd, J = 9.3, 3.6 Hz), 4.38 (1H, m), 4.63 (1H, m), 4.88 (1H, dd, J = 9.2, 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.4, 18.3, 19.3, 20.8, 21.9, 24.8, 25.4, 25.9 (3C), 30.9, 38.7, 38.8, 39.9, 43.2, 48.2, 49.6, 57.3, 65.3, 75.7, 76.5, 94.8, 120.6, 210.3. HRMS (CI) calcd for $C_{25}H_{43}N_2O_5Si$ (M^+ + 1) 479.2941. Found 479.2927.

11-Formyl-4α-(*tert*-butyldimethylsilyl)oxymethyl-1α-(2'-nitroethyl)-3α,10α-oxido-8β,12,12-trimethylbicyclo[6.4.0^{3,8}]dodecan-2-one 47α/β. DIBAL-H (2.0 mL, 1.0 M solution in dichloromethane) was added to a stirred solution of **46α** and **46β** (7:3) (740 mg, 1.55 mmol) in dichloromethane (50 mL) at -78°C. After 20 min the cooling bath was removed, and the reaction mixture quenched with water (20 mL). The organic layer was washed with 2N HCl (5x20 mL) followed by re-extraction of the combined acid layers with dichloromethane (3x30 mL). The combined extracts were dried ($MgSO_4$) and evaporated to afford a mixture of **47α** and **47β** as a white solid (7:3) (650 mg, 88%) which was used without further purification. For **47α**. $[\alpha]_D^{20}$ +3° (c = 3.0, $CHCl_3$). IR (thin film) 2931, 2857, 1722, 1688, 1555, 1471, 1446, 1386, 1257, 1144, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (3H, s), -0.01 (3H, s), 0.84 (9H, s), 0.85 (3H, s), 1.0-1.3 (3H, m), 1.10 (3H, s), 1.22 (3H, s), 1.40-1.60 (2H, m), 1.80-2.00 (2H, m), 1.86 (1H, dd, J = 13.3, 6.3 Hz), 2.16 (1H, dd, J = 13.3, 9.1 Hz), 2.21 (1H, d, J = 2.9 Hz), 2.35 (2H, m), 2.66 (1H, dd, J = 8.7, 2.6 Hz), 3.28 (1H, t, J = 8.9 Hz), 3.40 (1H, dd, J = 8.9, 2.8 Hz), 4.37 (1H, ddd, J = 19.2, 8.7, 5.9 Hz), 4.65 (1H, m), 4.95 (1H, dd, J = 8.8, 6.3 Hz), 9.91 (1H, d, J = 2.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, 18.3, 19.5, 20.9, 24.5, 24.9, 25.9 (3C), 30.1, 38.9, 40.0, 43.2, 47.4, 58.9, 65.5, 65.7, 73.1, 75.9, 94.3, 128.2, 129.0, 203.0, 211.2. HRMS (CI) calcd for $C_{25}H_{44}NO_6Si$ (M^+ + 1) 482.2940. Found 482.2916.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-12-hydroxy-13-nitro-3α,10α-oxido-12-nortaxane-2-one 48. Triethylamine (80 mg, 0.80 mmol) was added to a stirred solution of **47α** (140 mg, 0.29 mmol) in dichloromethane (10 mL). After 24 h the reaction was quenched by the addition of 2N HCl (20 mL). The acid layer was extracted with dichloromethane (2x30 mL), and the combined extracts dried ($MgSO_4$), and the solvent was evaporated *in vacuo* to give **48** as a single diastereomer (140 mg, 100%) which was used without further purification. IR (thin film) 3504, 2930, 2858, 1693, 1549, 1461, 1386, 1346, 1258, 1097 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (6H, s), 0.84 (9H, s), 1.10-1.20 (2H, m), 1.14 (3H, s), 1.18 (3H, s), 1.26 (3H, s), 1.30-1.50 (3H, m), 1.70 (2H, m), 1.81 (1H, bs,), 2.08 (1H, m), 2.24 (2H, m), 2.44 (1H, bd, J = 7.6 Hz), 2.73 (1H, bs), 2.90 (1H, dd, J = 15.5, 8.8 Hz), 3.41 (1H, dd, J = 9.7, 7.3 Hz), 3.61 (1H, dd, J = 9.7, 6.0 Hz), 4.93 (1H, dd, J = 8.2, 5.4 Hz), 5.12 (1H, m), 5.46 (1H, bq, J = 10.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5 (2C), 16.4, 19.2, 21.5, 24.7, 25.9 (3C), 27.1, 30.7, 30.9, 36.2, 41.1, 41.7, 44.3, 46.3, 51.3, 61.3, 64.9, 70.0, 74.7, 89.0, 92.1, 217.9. HRMS (CI) calcd for $C_{25}H_{44}NO_6Si$ (M^+ + 1) 482.2940. Found 482.2921.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-13-nitro-3α,10α-oxido-12-nortaxane-2,12-dione 49. Dess-Martin periodinane (400 mg, 0.94 mmol) was added to a stirred solution of **48** (140 mg, 0.29 mmol) in dichloromethane (10 mL). After 2 h water (10 mL) was added and the mixture stirred vigorously for 30 min. The aqueous layer was extracted with dichloromethane (3x20 mL), dried

($MgSO_4$) and the solvent was evaporated *in vacuo*. Trituration with 10% EtOAc/hexanes gave **49** (110 mg, 79%). $[\alpha]_D^{20}$ -79° (c = 3.0, $CHCl_3$). IR (thin film) 2931, 2858, 1736, 1698 , 1558 , 1462, 1388, 1253, 1108, 1062 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.01 (3H, s), 0.00 (3H, s), 0.81 (9H, s), 1.00-1.20 (3H, m), 1.11 (3H, s), 1.15 (3H, s), 1.25 (3H, s), 1.40-1.60 (3H, m), 1.74 (1H, dd, J = 13.8, 9.9 Hz), 2.07 (1H, m), 2.17 (1H, dd, J = 13.8, 5.5 Hz), 2.42 (1H, bs), 2.67 (1H, bd, J = 8.1 Hz), 2.75 (1H, m), 3.14 (1H, dd, J = 14.8, 9.8 Hz), 3.40 (1H, dd, J = 10.5, 5.3 Hz), 3.62 (1H, dd, J = 10.5, 6.4 Hz), 4.55 (1H, m), 6.00 (1H, t, J = 9.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4 (2C), 18.4, 19.3, 21.5, 24.8, 25.9 (3C), 26.8, 29.5, 30.5, 36.5, 40.8, 40.9, 44.1, 46.0, 60.2, 60.7, 62.5, 65.1, 91.2, 93.1, 200.4, 216.2. HRMS (CI) calcd for $C_{25}H_{42}NO_6Si$ (M^+ + 1) 480.2781. Found 480.2776.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-3α,10α-oxido-12-nortaxane-2,12-dione 50. AIBN (20 mg) was added to a solution of **49** (110 mg, 0.23 mmol) and tributyltin hydride (0.4 mL, 1.50 mmol) in benzene (15 mL) at 70°C. After 2 h the solvent was evaporated and the residue chromatographed over silica gel eluting with 20% EtOAc/hexanes to give **50** as a colorless oil (60 mg, 60%). $[\alpha]_D^{20}$ -114° (c = 1.0, $CHCl_3$). IR (thin film) 2928, 2863, 1708, 1691, 1464, 1389, 1254, 1097 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.11 (6H, s), 0.75 (9H, s), 0.84 (3H, s), 1.00-1.20 (3H, m), 1.04 (3H, s), 1.10 (3H, s), 1.20-1.50 (2H, m), 1.29 (1H, bs), 1.59 (1H, dd, J = 13.7, 10.0 Hz), 1.67 (1H, bd, J = 14.0 Hz), 1.90-2.10 (2H, m), 2.03 (1H, bs), 2.25 (2H, m), 2.42 (1H, bd, J = 8.5 Hz), 2.72 (1H, quin, J = 9.0 Hz), 3.29 (1H, dd, J = 9.5, 8.2 Hz), 3.52 (1H, dd, J = 9.5, 5.2 Hz), 4.39 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2, 18.3, 19.6, 20.6, 24.6, 25.8 (3C), 29.5, 31.1, 35.8, 37.4, 41.1, 41.3, 44.0, 45.6, 55.2, 61.8, 63.0, 64.8, 77.9, 92.8, 213.6, 219.2. HRMS (CI) calcd for $C_{25}H_{43}O_4Si$ (M^+ + 1) 435.2931. Found 435.2928.

4Hβ-11,12-Dihydro-20-hydroxy-3α,10α-oxido-12-nortaxane-2,12-dione 66. Hydrogen fluoride-pyridine complex (400 μL) was added dropwise to a stirred solution of **50** (18 mg, 0.04 mmol) in tetrahydrofuran (3 mL). After 2 h saturated aqueous $NaHCO_3$ (10 mL) was added cautiously and the product was extracted with dichloromethane (3x10 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated. Chromatography over silica gel eluting with 40% EtOAc/hexane gave **66** (12 mg, 90%). M.pt. 210-213°C. IR ($CHCl_3$) 3448, 2932, 1686, 1459, 1396, 1224, 1167, 1058 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 0.14 (3H, s), 1.21 (3H, s), 1.30-1.60 (5H, m), 1.70 (3H, m), 2.10-2.20 (2H, m), 2.15 (1H, s), 2.38 (1H, dd, J = 14.1, 10.4 Hz), 2.45 (1H, t, J = 9.6 Hz), 2.58 (1H, bd, J = 8.3 Hz), 2.76 (1H, m), 3.59 (2H, d, J = 4.8 Hz), 4.58 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 19.5, 20.3, 21.5, 24.9, 31.2, 35.9, 37.3, 41.0, 41.1, 43.5, 45.8, 61.8, 63.1, 65.5, 76.7, 94.2, 213.4, 219.8. HRMS (CI) calcd for $C_{19}H_{29}O_4$ (M^+ + 1) 321.2066. Found 321.2062.

4Hβ-11,12-Dihydro-20-[(1S)-(-)-camphanate]-3α,10α-oxido-12-nortaxane-2,12-dione 51. (S)-(-)-Camphanic acid chloride (13 mg, 0.06 mmol) was added to a stirred solution of **66** (12 mg, 0.38 mmol) and triethylamine (20 mg) in dichloromethane (1 mL). DMAP (2 mg) was added and stirring continued for 4 h. Water (10 mL) was added and the mixture extracted with dichloromethane (3x10 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography over silica gel eluting with 30% EtOAc/hexanes gave **51** (18 mg, 96%). Crystals suitable for X-ray analysis were obtained by

recrystallization from ethanol/hexanes. IR ($CHCl_3$) 2935, 1790, 1746, 1693, 1456, 1397, 1316, 1270, 1223, 1167, 1102 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, s), 0.95 (3H, s), 1.03 (3H, s), 1.08 (3H, s), 1.1-1.20 (3H, m), 1.14 (3H, s), 1.21 (3H, s), 1.30-1.60 (8H, m), 1.80-2.10 (2H, m), 2.15 (1H, bs), 2.20-2.50 (3H, m), 2.59 (1H, bd, J = 7.6 Hz), 2.80 (1H, m), 4.04 (1H, t, J = 10.4 Hz), 4.15 (1H, dd, J = 10.4, 5.6 Hz), 4.53 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 16.7 (2C), 19.3, 20.6, 21.1, 24.8, 28.9, 29.7, 30.7, 31.1, 35.8, 37.3, 40.3, 40.8, 41.0, 45.6, 54.2, 54.7, 61.7, 62.9, 66.9, 78.2, 90.9, 92.3, 167.4, 178.1, 213.1, 219.3. HRMS (CI) calcd for $C_{29}H_{41}O_7$ (M^+ + 1) 501.2852. Found 501.2849.

11Hβ-4Hβ-20-Dihydro-2α,20-oxido-3α,10α-oxido-12-trifluoromethanesulfonyl-12-nortaxane-12-ene 52. The ketone **30** (150 mg, 0.49 mmol) in tetrahydrofuran (1.5 mL) at 0°C was treated with sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.60 mL, 0.60 mmol, 1.2 equiv) and stirred for 1.5 h. 4-Chloropyridyl-bistriflimide (230.4 mg, 0.60 mmol, 1.2 equiv) was added in one portion. The reaction mixture was stirred at 25°C for 1.5 h, and quenched with saturated aqueous NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (10 mL) and dichloromethane (3x10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Purification by chromatography over silica gel eluting with 70% hexanes/Et_2O gave **52** (208 mg, 97%). IR (thin film) 2936, 1416, 1245, 1206, 1143, 1017, 881 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.21 (3H, s), 1.33 (3H, s), 1.60-0.70 (6H, m), 1.74 (1H, dd, J = 3.6, 13.5 Hz), 1.92 (1H, m), 2.05 (2H, m), 2.27 (2H, m), 2.57 (1H, dd, J = 4.0, 19.8 Hz), 3.51 (1H, dd, J = 7.5, 12.2 Hz), 3.83 (1H, t, J = 7.2 Hz), 4.24 (1H, d, J = 6.3 Hz), 4.39 (1H, ddd, J = 2.2, 4.3, 9.8 Hz), 5.73 (1H, t, J = 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 19.8, 22.0, 23.5, 28.1, 29.7, 32.3, 37.8, 41.4, 42.3, 44.3, 45.8, 46.1, 52.7, 70.7, 82.9, 91.7, 116.4, 118.7, 120.6, 148.9. HRMS (CI) calcd for $C_{20}H_{28}O_5F_3S$ (M^+ + 1) 437.1610. Found 437.1599.

11Hβ-4Hβ-20-Dihydro-2α,20-oxido-3α,10α-oxido-taxane-12-ene 53. To a slurry of CuI (1.5 g, 8.0 mmol, 10 equiv) in tetrahydrofuran (2 mL) at -10°C was added MeLi (1.4M in Et_2O, 4.6 mL, 6.4 mmol, 18 equiv) dropwise *via* syringe. This mixture was stirred for 30 min after which **52** (176 mg, 0.40 mmol) in tetrahydrofuran (4.5 mL) was added dropwise *via* syringe. The mixture was stirred at 0°C for 48 h, and quenched with saturated aqueous NH_4Cl (3 mL). The mixture was filtered through a short pad of Celite and washed with dichloromethane (25 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (4x30 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography over silica gel eluting with 90% hexanes/Et_2O gave **53** (107 mg, 88%). IR (thin film) 3018, 2927, 2859, 1455, 1388, 1140, 1051, 1013 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.20 (3H, s), 1.23 (3H, s), 1.66-1.10 (8H, m), 1.70 (3H, d, J = 1.9 Hz), 2.00-1.86 (1H, m) 2.20-2.00 (2H, m), 2.25 (1H, dd, J = 4.5, 13.1 Hz), 2.44-2.37 (1H, m), 3.61 (1H, dd, J = 7.4, 12.4 Hz), 3.81 (1H, t, J = 7.3 Hz), 4.32–4.24 (2H, m), 5.40 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 18.9, 19.9, 22.5, 22.9, 25.5, 28.7, 32.6, 36.2, 42.4, 42.3, 44.6, 45.9, 46.4, 54.1, 70.6, 78.2, 83.7, 91.3, 121.8, 134.4. HRMS (CI) calcd for $C_{20}H_{31}O_2$ (M^+ + 1) 303.2324. Found 303.2318.

4Hβ-11,12-Dihydro-2α,20-oxido-3α,10α-oxido-20-oxo-12-nortaxane-12-one 54. To a solution of **30** (62 mg, 0.20 mmol) in acetonitrile (0.42 mL), carbon tetrachloride (0.42 mL), and water (0.62

mL) was added $NaIO_4$ (0.18 g, 0.84 mmol, 4 equiv) and $RuO_2 \cdot xH_2O$ (0.006 mg, 0.004 mmol, 2% mole). The biphasic mixture was vigorously stirred for 20 h then diluted with Et_2O (10 mL). After filtration through Celite, the phases were separated and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **54** (64 mg, 98%). IR (thin film) 2939, 2872, 1778, 1704, 1464, 1396, 1235, 1190, 1141, 1088, 1013, 972, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.30 (3H, s), 1.32 (3H, s), 1.61-1.10 (6H, br m), 1.95-1.77 (2H, m), 2.04 (1H, s), 2.40-2.20 (4H, m), 2.50 (1H, dd, J = 4.2, 12.1 Hz), 2.64 (1H, m), 4.35 (1H, ddd, J = 2.2, 5.8, 9.3 Hz), 4.89 (1H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 18.2, 18.6, 19.2, 21.9, 28.3, 32.4, 36.8, 36.9, 41.1, 41.5, 43.8 45.3, 46.5, 63.8, 78.6, 84.7, 89.0, 174.7, 214.4. HRMS (CI) calcd for $C_{19}H_{27}O_4$ ($M^+ + 1$) 319.1909. Found 319.1903.

Diquinane 55. A solution of **54** (63 mg, 0.20 mmol) in toluene (1 mL) was treated with DBU (60 μL, 0.40 mmol, 2 equiv) and heated at 110°C in a sealed for 2 h. The solvent was evaporated *in vacuo* and the residue dissolved in Et_2O (20 mL). The ethereal solution was washed successively with 10% H_2SO_4 (5 mL) water (5 mL), and brine (5 mL). The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **55** as a white solid (63 mg, 100%). Crystals suitable for X-ray diffraction were grown from dichloromethane/hexanes by the vapor diffusion method. IR (thin film) 3440, 3001, 2928, 1775, 1683, 1163, 1017 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H,), 1.14 (3H, s), 1.17 (3H, s), 1.30-0.90 (2H, m), 1.54-1.35 (4H, m), 1.74 (1H, d, J = 14.6 Hz), 2.05-1.88 (3H, m), 2.55-2.10 (4H, m), 2.74-2.55 (2H, m), 4.28 (1H, d, J = 4.8 Hz), 5.15 (1H, d, J = 5.8 Hz), 5.56 (1H, d, J = 1.7 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 14.7, 18.1, 24.6, 24.6, 28.7, 37.4, 41.0, 41.8, 42.5, 44.7, 47.2, 50.6, 61.0, 66.8, 74.5, 75.9, 85.2, 179.3, 216.7. HRMS (CI) calcd for $C_{19}H_{27}O_4$ ($M^+ + 1$) 319.1909. Found 319.1901.

11Hβ-4Hβ-20-Dihydro-2β-methoxy-2α,20-oxido-3α,10α-oxido-12-trifluoromethane sulfonyl-12-nortaxane-12-ene 57. A solution of **35** (338 mg, 1.01 mmol) in tetrahydrofuran (4 mL) was treated as for **52**, gave **57** as a colorless oil (438 mg, 93%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s), 1.30 (3H, s), 1.50 (3H, s), 1.60-1.15 (6H, m), 1.65 (1H, dd, J = 10.0, 13.2 Hz), 2.20-2.00 (3H, m), 2.33 (1H, ddd, J = 3.5, 9.1, 20.0 Hz), 2.46 (1H, dd, J = 4.9, 13.1 Hz), 2.64 (1H, dd, J = 4.2, 20.0 Hz), 3.13 (3H, s), 3.48 (1H, dd, J = 7.3, 12.4 Hz), 3.92 (1H, t, J = 7.3 Hz), 4.42 (1H, ddd, J = 2.3, 5.00, 9.8 Hz), 5.70 (1H, t, J = 3.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 21.0, 22.4, 25.5, 28.5, 33.4, 37.9, 41.5, 41.8, 44.4, 44.8, 47.7, 48.2, 52.6, 70.5, 93.3, 104.3, 115.9, 118.9, 148.7. HRMS (CI) calcd for $C_{21}H_{30}O_6F_3S$ ($M^+ + 1$) 467.1715. Found 467.1712.

(-)-11Hβ-4Hβ-20-Dihydro-2β-methoxy-2α,20-oxido-3α,10α-oxido-taxane-12-ene 58. To a slurry of CuI (1.29 g, 6.8 mmol) in tetrahydrofuran (2 mL) at -4°C was added MeLi (1.6M in Et_2O, 7 mL, 11.2 mmol), dropwise *via* syringe. The reaction mixture was stirred for 30 min and **57** (0.31g, 0.66 mmol) in tetrahydrofuran (3 mL) was added. Treatment as for **53**, gave **58** (0.21g, 95%). $[\alpha]_D^{25}$ -119.6° (c = 0.6, $CHCl_3$). IR (thin film) 2933, 2856, 1096, 1054 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s), 1.32 (3H, s), 1.48 (3H, s), 1.68-1.20 (8H, m), 1.71 (3H, d, J = 1.8 Hz), 2.29-2.09 (3H, m), 2.52-2.39 (2H, m), 3.18 (3H, s), 3.57 (1H, dd, J = 7.2, 12.3 Hz), 3.94 (1H, t, J = 7.3 Hz), 4.33 (1H, ddd, J = 2.1, 4.9, 9.8 Hz),

5.38 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 20.0, 21.0, 22.7, 22.9, 27.4, 28.9, 29.7, 33.7, 36.3, 41.9, 42.6, 44.4, 44.8, 47.9, 54.3, 70.5, 78.7, 92.8, 116.6, 122.3, 134.2. HRMS (CI) calcd for $C_{21}H_{33}O_3$ ($M^+ + 1$) 333.2430. Found 333.2440.

(-)-11Hβ-4Hβ-20-Dihydro-20-hydroxy-3α,10α-oxido-taxane-12-ene-2-one 60. A solution of **58** (360 mg, 1.04 mmol) in dioxane (4 mL) and water (0.6 mL), was treated with glacial acetic acid (0.25 mL) and heated to 75°C (external temperature) in a sealed tube for 18 h. The mixture was cooled to 25°C, diluted with toluene (10 mL), and concentrated *in vacuo*. Chromatography over silica gel eluting with 85% hexanes/EtOAc gave **60** (290 mg, 93% yield at 94% conversion). M.pt. 133-135°C. $[\alpha]_D^{25}$ -120.0° (c = 1.0, $CHCl_3$). IR (thin film) 3492, 3424, 2928, 2862, 1684, 1064 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, s), 1.14 (3H, s), 1.24 (3H, s), 1.76 (3H, d, J = 1.6 Hz), 1.80-1.20 (8H, m), 2.05-1.95 (1H, m), 2.40-2.20 (2H, m), 2.60–2.50 (2H, m), 2.80 (1H, d, J = 10.7 Hz), 3.44 (1H, m), 3.70 (1H, dd, J = 1.9, 11.9 Hz), 4.52 (1H, ddd, J = 2.9, 4.8, 10.0 Hz), 5.46 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 19.4, 21.7, 22.7, 25.1, 25.4, 30.0, 31.6, 35.0, 40.5, 41.6, 42.3, 46.9, 53.0, 61.6, 66.0, 78.0, 94.7, 120.8, 135.6, 220.2. HRMS (CI) calcd for $C_{20}H_{31}O_3$ ($M^+ + 1$) 319.2273. Found 319.2274.

(-)-11Hβ-4Hβ-20-Dihydro-20-hydroxy-3α,10α-oxido-12α,13α-oxido-taxane-2-one 61 and 63. To a stirred solution of **60** (0.08 g, 0.25 mmol) in dichloromethane (2 mL) at 0°C was added 90% *m*-chloroperoxybenzoic acid (0.01g, 0.6 mmol). The reaction mixture was allowed to warm to 25°C over 3 h, and Et_2O (15 mL) was added. The organic phase was washed with a mixture of saturated aqueous $Na_2S_2O_3$ (2 mL) and 15% NaOH (2 mL). This procedure was repeated twice. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography over silica gel eluting with 40% EtOAc/hexane gave **61** (0.071 g, 87%). $[\alpha]_D^{25}$ -128° (c = 0.5, $CHCl_3$). IR (thin film) 2921, 2862, 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, s), 1.12 (3H, s), 1.20 (3H, s), 1.10-1.70 (6H, m), 1.67 (1H, dd, J = 14, 11 Hz), 2.06 (1H, dd, J =14, 6 Hz), 2.18 (1H, m), 2.40 (1H, bd, J = 11 Hz), 2.65 (1H, d, J = 17 Hz), 3.00 (1H, d, J = 6 Hz), 3.40 (2H, m), 3.69 (1H, bd, J = 11 Hz), 4.89 (1H, m). HRMS (CI) calcd for $C_{20}H_{31}O_4$ ($M^+ + 1$) 335.2222. Found 335.2217. Reduction of **61** (10 mg) with SmI_2 (3 mL, 0.1 M solution in THF) in methanol (0.25 mL) and tetrahydrofuran (0.5 mL) gave **63** (5 mg). IR (Thin film) 3361, 2864 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.9-1.3 (9H, m), 1.08 (3H, s), 1.25 (3H, s), 1.38 (3H, s), 1.44 (3H, s), 1.9-2.2 (3H, m), 2.38-2.47 (2H, m), 2.91 (1H, d, J = 5.6 Hz), 3.5 (1H, bd, J = 12 Hz), 4.42 (1H, d, J = 12 Hz), 4.6 (1H, bs), 4.68 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 18.8, 21.5, 21.9, 25.3, 25.8, 30.0, 31.3, 35.9, 41.7, 41.8, 42.2, 45.7, 49.9, 56.1, 59.5, 60.4, 65.3, 78.5, 94.8, 220.0. HRMS (CI) calcd for $C_{20}H_{33}O_4$ ($M^+ + 1$) 337.2379. Found 337.2382. Structure confirmed by single crystal X-ray analysis.

12Hβ-11Hβ-4Hβ-20-Tetrahydro-4α-(4-nitrobenzoyl)oxymethyl-3α,10α-oxido-taxane-2,13-dione 65. To a solution of **61** (10 mg) in dichloromethane (1 mL) was added Et_3N (0.013 mL), DMAP (1 crystal) and *p*-nitrobenzoyl chloride (10 mg, 1.5 equiv). The mixture was stirred at 25°C for 10 h and quenched with saturated aqueous NH_4Cl (5 mL) and extracted into EtOAc (5 mL). The dried (Na_2SO_4) was evaporated *in vacuo* to give **62** (9 mg). Treatment of crude **62** (8 mg) with TBSOTf (150 mg) in dichloromethane (0.5 mL) at 0°C for 1 h followed by hydrolysis with 10% aqueous HCl (0.1 mL) in dioxane

(0.4 mL) for 1.5 h gave **65** (6 mg). M.pt. 184-186°C. IR (thin film) 1729, 1703, 1528 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.27 (3H, d, J = 6.5 Hz), 1.38 (3H, s), 1.40 (3H, s), 1.77-1.30 (7H, m), 1.88 (1H, m), 2.44-2.35 (2H, m), 2.71-2.58 (2H, m), 3.02-2.88 (2H, m), 4.25 (2H, d, J = 6.5 Hz), 4.91-4.86 (1H, m), 8.29, 8.12 (4H, ABq, J = 9.0 Hz). HRMS (CI) calcd for $C_{27}H_{33}NO_7$ (M^+) 483.2257. Found 483.2253. Structure confirmed by single crystal X-ray analysis.

4Hβ-11,12-Dihydro-20-hydroxy-3α,10α-oxido-12-nortaxane-2,12-dione 66. To a solution of **35** (0.052 g) in dioxane (0.5 mL), in a thick walled glass tube was added glacial acetic acid (0.1 mL) and water (0.1 mL). The tube was sealed and the reaction mixture was heated at 80°C for 24 h. The reaction mixture was cooled to 25°C and concentrated *in vacuo*. Purification by chromatography over silica gel eluting with 20% EtOAc/hexane gave **66** (0.038g, 76%). See above for data for the conversion of **50** into **51**.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-3α,10α-oxido-12-nortaxane-2,12-dione 50. To a solution of **66** (0.036 g) in dimethylformamide (1 mL) was added imidazole (0.016 g), *t*-butyldimethylsilylchloride (0.02 g) and a catalytic amount of DMAP (2 crystals). The reaction mixture was stirred at 25°C for 16 hours. Water (5 mL) was added, and the solution was extracted with Et_2O (3x5 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography over silica gel eluting with 20% EtOAc/hexane gave **50** (0.039 g, 80%). See above for data for the conversion of **49** into **50**.

4Hβ-11,12-Dihydro-1β-hydroxy-3α,10α-oxido-2α,20-oxido-12-nortaxane-12,13-dione 67. To a solution of **41** (50 mg, 0.15 mmol) in dry tetrahydrofuran (4 mL) at 0°C was added *t*-BuOK (87 mg, 0.78 mmol). The reaction mixture turned from transparent to a white suspension within 0.25 h. The temperature was raised to 23°C, and dry oxygen bubbled slowly beneath the surface of the reaction mixture. The reaction mixture turned slightly yellow as it became transparent (0.25 h). Saturated aqueous NH_4Cl (3 mL), and water (10 mL) were added to the reaction mixture. The resulting mixture was separated, and the aqueous phase extracted with chloroform (3x40 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. to give **67** (51 mg, 100%). IR (thin film) 3449, 2935, 1722, 1677 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, s), 1.22 (3H, s), 1.34 (3H, s), 1.35-1.53 (7H, m), 1.79 (1H, dd, J = 9.8, 13.5 Hz), 1.84-1.96 (1H, m), 2.31 (1H, d, J = 2.5 Hz), 2.39 (1H, dd, J = 4.4, 13.4 Hz), 2.71 (1H, s), 3.45 (1H, dd, J = 7.4, 12.0 Hz), 3.82 (1H, t, J = 7.0 Hz), 4.27 (1H, s), 4.31-4.36 (1H, m), 5.83 (1H, s). HRMS (CI) calcd for $C_{19}H_{27}O_5$ ($M^+ + 1$) 335.1858. Found 335.1857.

4Hβ-11,12-Dihydro-1β-hydroxy-13-methoxy-3α,10α-oxido-2α,20-oxido-12-nortaxane-13-en-12-one 68. To a solution of **67** (50 mg, 0.15 mmol) in dry acetone (2.5 mL) at 23°C was added potassium carbonate (206 mg, 1.50 mmol). After 0.1 h, methyl iodide (1 mL, 16.05 mmol) was added to the reaction mixture. The reaction was stirred vigorously for 18 h and quenched with saturated aqueous NH_4Cl (5 mL), and resulting mixture extracted with chloroform (3x50 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo* to give **68** (51 mg, 100%). IR (thin film) 3492, 2937, 2864, 1715, 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, s), 1.21 (3H, s), 1.33 (3H, s), 1.37-1.53 (4H,

m), 1.78 (1H, dd, J = 9.7, 13.3 Hz), 1.91 (1H, m), 2.15 (1H, s), 2.27 (1H, d, J = 1.9 Hz), 2.35 (1H, dd, J = 4.4, 13.4 Hz), 2.61 (1H, s), 2.72 (1H, s), 3.45 (1H, dd, J = 7.2, 12.1 Hz), 3.63 (3H, s), 3.85 (1H, t, J = 6.8 Hz), 4.28 (1H, s), 4.32-4.37 (1H, m), 5.58 (1H, s). HRMS (CI) calcd for $C_{20}H_{29}O_5$ ($M^+ + 1$) 349.2014. Found 349.2003.

4Hβ-11,12-Dihydro-1β,12-dihydroxy-13-methoxy-3α,10α-oxido-2α,20-oxido-taxane-13-ene 69. To a solution of **68** (50 mg, 0.15 mmol)) in dry tetrahydrofuran (1 mL) at 0°C was added 1.4 M MeLi in Et_2O (0.5 mL, 0.69 mmol). After 0.25 h, saturated aqueous NH_4Cl (3 mL) was added to the reaction mixture, followed by water (20 mL). The resulting mixture was extracted with chloroform (3x50 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was purified over silica gel eluting under pressure with 40% EtOAc/petroleum ether. The C-12 epimers of product **69** were isolated as colorless foams (39 mg, 74%). IR (thin film) 3492, 2937, 2864, 1663 cm^{-1}. **69** C-12 epimer. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.27 (3H, s), 1.34 (3H, s), 1.21-1.51 (6H, m), 1.48 (3H, s), 1.62 (1H, m), 1.65-1.90 (1H, m), 2.02 (1H, d, J = 2.0 Hz), 2.36 (1H, s), 2.48 (1H, dd, J = 4.1, 13.4 Hz), 2.72 (1H, s), 3.43 (1H, dd, J = 7.1, 12.1 Hz), 3.56 (3H, s), 3.74 (1H, t, J = 6.6 Hz), 4.14 (1H, s), 4.61 (1H, s), 4.74-4.78 (1H, m). **69** C-12 epimer. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.19 (3H, s), 1.34 (3H, s), 1.23-1.64 (6H, m), 1.51 (3H, s), 1.64-1.67 (1H, m), 1.82-1.92 (1H, m), 2.03 (1H, s), 2.36 (1H, s), 2.50 (1H, dd, J = 4.7, 13.3 Hz), 2.72 (1H, s), 3.46 (1H, dd, J = 7.2, 12.2 Hz), 3.56 (3H, s), 3.76 (1H, t, J = 6.8 Hz), 4.18 (1H, s), 4.64 (1H, s), 5.12-5.18 (1H, m). Used directly in the next step.

4Hβ-11,12-Dihydro-1β-hydroxy-3α,10α-oxido-2α,20-oxido-taxane-12,18-en-13-one 70. To a solution of **69** (39 mg, 0.11 mmol) in dioxane (2 mL) at 23°C was added 6M HCl (1 mL). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with chloroform (3x50 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The product **70** was a colorless foam (34 mg, 100%). IR (thin film) 3460, 2934, 2863, 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, s), 1.21 (3H, s), 1.36 (3H, s), 1.24-1.49 (7H, m), 1.70 (1H, dd, J = 9.2, 12.8 Hz), 1.89-2.02 (1H, m), 2.32 (1H, d, J = 18.2 Hz), 2.29-2.36 (1H, m), 2.59 (1H, s), 3.00 (1H, d, J = 18.6 Hz), 3.49 (1H, dd, J = 7.7, 12.4 Hz), 3.86 (1H, t, J = 7.3 Hz), 4.20 (1H, s), 4.31-4.36 (1H, m), 5.06 (1H, s), 5.81 (1H, s). HRMS (CI) calcd for $C_{20}H_{28}O_4$ (M^+) 332.1987. Found 332.1982.

4Hβ-11,12-Dihydro-1β-hydroxy-18-(phenylthio)-3α,10α-oxido-2α,20-oxido-taxane-13-one 71. To a solution of **70** (15 mg, 0.04 mmol) in dry dichloromethane (1 mL) at 23°C was added thiophenol (0.1 mL, 0.90 mmol), and a catalytic amount of 1,1,3,3-tetramethylguanidine. After 3.0 h saturated aqueous NH_4Cl (2 mL) was added to the reaction mixture, and the resulting mixture extracted with chloroform (3x30 mL). The combined extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was purified over silica gel eluting under pressure with EtOAc in petroleum ether (1:3). The epimers of product **71** were isolated as colorless foams (19.9 mg, 100%). For C-12 α-epimer. IR (thin film) 3456, 1705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, s), 1.20 (3H, s), 1.33 (3H, s), 1.34-1.52 (6H, m), 1.69 (1H, dd, J = 10.5, 13.5 Hz), 1.94-2.02 (1H, m), 2.01 (1H, d, J = 1.98 Hz), 2.35 (1H, dd, J = 4.7, 13.6 Hz), 2.41 (1H, d, J = 18.3 Hz), 2.51 (1H, dd, J = 3.2, 11.2 Hz), 2.62 (1H, s), 2.73-2.82 (1H, m), 3.21 (1H, d, J =

18.2 Hz), 3.51 (1H, dd, J = 7.9, 12.5 Hz), 3.82-4.09 (2H, m), 4.11 (1H, s), 4.19-4.25 (1H, m), 7.15-7.49 (5H, m). For C-12 β-epimer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.19 (3H, s), 1.21-1.50 (7H, m), 1.39 (3H, s), 1.67 (1H, dd, J = 7.9, 13.5 Hz), 1.86-1.93 (1H, m), 2.03 (1H, s), 2.28 (1H, d, J = 16.9 Hz), 2.38 (1H, dd, J = 4.9, 13.2 Hz), 2.50 (1H, s), 2.85 (1H, d, J = 17.1 Hz), 2.95-2.97 (1H, m), 3.43 (1H, dd, J = 7.7, 12.2 Hz), 3.63 (1H, dd, J = 1.7, 9.9 Hz), 3.83 (1H, t, J = 7.2 Hz), 4.14 (1H, s), 4.44-4.49 (1H, m), 7.17-7.40 (5H, m). HRMS (CI) calcd for $C_{26}H_{34}O_4S$ (M^+) 442.2177. Found 442.2172.

4Hβ-11,12-Dihydro-1β-hydroxy-18-(phenylsulfonyl)-3α,10α-oxido-2α,20α-oxido-taxane-13,20-dione 72. To a solution of **71** (17 mg, 0.03 mmol) in carbon tetrachloride (1 mL) at 23°C, was added a catalytic amount of ruthenium (IV) oxide hydrate, followed by a solution of sodium periodate (206 mg, 0.96 mmol) in water (1 mL). The reaction mixture was stirred vigorously for 5 days, and then quenched with ethanol (2 mL). The resulting mixture was filtered through a short plug of Celite eluting with chloroform (150 mL). The organic phase was separated, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was dried under high vacuum for 2.0 h. to give **72** (18 mg, 100%). IR (thin film) 3489, 2937, 1781, 1704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.31 (3H, s), 1.33-1.49 (5H, m), 1.38 (3H, s), 1.57-1.78 (1H, m), 1.90 (1H, dd, J = 10.0, 13.9 Hz), 2.29 (1H, d, J = 2.03 Hz), 2.33 (1H, s), 2.35-2.41 (2H, m), 2.48-2.54 (1H, dd, J = 3.6, 11.8 Hz), 2.98-3.00 (1H, m), 3.17 (1H, d, J = 17.7 Hz), 4.06-4.14 (2H, m), 4.72 (1H, s), 4.75-4.90 (1H, m), 7.53-7.89 (3H, m), 7.90 (2H, d, J = 5.16 Hz). HRMS (CI) calcd for $C_{26}H_{33}O_4S$ (M^+ + 1) 489.1947. Found 489.1943.

4Hβ-11,12-Dihydro-1β-hydroxy-3α,10α-oxido-2α,20α-oxido-12-nortaxane-12,20-dione 73. To a solution of **41** (0.01 g, 0.03 mmol) in carbon tetrachloride (2 mL) at 23°C, was added a catalytic amount of ruthenium (IV) oxide hydrate, followed by a solution of sodium periodate (0.15 g, 0.69 mmol) in distilled water (2 ml). The reaction mixture was stirred vigorously for 20 h, and quenched with ethanol (3 mL). The resulting mixture was filtered through a short plug of Celite eluting with chloroform. The organic phase was separated , dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The remaining residue was dried under high vacuum for 2.0 h to give **73** (0.01 g, 100%). IR (thin film) 3470, 2926, 1779, 1709 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, s), 1.22 (3H, s), 1.31 (3H, s), 1.33 (3H, s), 1.35-1.98 (5H, m), 2.07 (1H, d, J = 1.9 Hz), 2.24-2.41 (3H, m), 2.50-2.59 (2H, m), 2.68-2.81 (1H, m), 4.40 (1H, ddd, J = 2.1, 4.4, 9.8 Hz), 4.88 (1H, s). HRMS (CI) calcd for $C_{19}H_{27}O_5$ (M^+ + 1) 335.1855. Found 335.1858.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-13-nitro-3α,10α-oxido-12-nortaxane-12-ene-2-one 74. 1,1,3,3-Tetramethylguanidine (50 mg, 0.43 mmol) was added to a stirred solution of **47α/β** (7:3) (640 mg, 1.33 mmol) in dichloromethane (50 mL). After 24 h tlc analysis indicated the formation of **48**. Methanesulfonylchloride (150 mL; 1.90 mmol) was added followed by DBU (0.60 mL, 4.06 mmol). After stirring for 30 min the reaction was quenched by the addition of 2N HCl. The acid layer was extracted with dichloromethane (2x30 mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography over silica gel eluting with 10% EtOAc/hexanes gave **74** as a pale yellow solid (410 mg, 64% from **46α/β**). M.pt.162-163°C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.02 (3H, s), 0.85 (9H, s), 1.00-1.20 (2H, m), 1.05 (3H, s), 1.15 (3H, s), 1.26 (3H, s), 1.30-1.50 (4H, m), 1.69 (1H, dd, J = 13.7,

10.0 Hz), 2.04 (1H, m), 2.28 (1H, dd, J = 13.7, 8.7 Hz), 2.30 (1H, m), 2.62 (1H, bs), 2.65 (1H, m), 3.27 (1H, dd, J = 9.9, 6.5 Hz), 3.43 (1H, m), 3.56 (1H, dd, J = 9.9, 6.9 Hz), 4.42 (1H, m), 7.39 (1H, d, J = 6.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6 (2C), 18.1, 19.3, 21.3, 23.8, 24.7, 25.8 (3C), 28.7, 31.9, 34.1, 41.1, 41.6, 44.1, 46.9, 48.7, 60.3, 64.7, 76.9, 91.9, 135.0, 150.3, 216.1. IR ($CHCl_3$) 2933, 2859, 1695, 1509, 1471, 1461, 1338, 1253, 1094 cm^{-1}. HRMS (CI) calcd for $C_{25}H_{42}NO_5Si$ (M^+ + 1) 464.2832. Found 464.2819.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-13-nitro-3α,10α-oxido-taxane-12-ene-2-one 75. Dimsyl lithium (1.8 mL, 0.5 M) was added to a stirred solution of **74** (190 mg, 0.41 mmol) in tetrahydrofuran (25 mL) at 0°C. After 16 h the reaction mixture was quenched by the addition of acetic acid (2 mL) and stirred for 30 min. Water (20 mL) was added and the organic components were extracted into dichloromethane (3x30 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. Chromatography over silica gel eluting with 10% EtOAc/hexanes gave **75** as a pale yellow solid (88 mg, 45%). IR ($CHCl_3$) 2930, 2857, 1697, 1510, 1463, 1328, 1256, 1169, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.00-1.20 (2H, m), 1.06 (3H, s), 1.15 (3H, s), 1.24 (3H, s), 1.30-1.50 (3H, m), 1.60 (1H, m), 1.70 (1H, dd, J = 13.7, 10.1 Hz), 1.95 (1H, bs), 2.05 (1H, m), 2.23 (1H, m), 2.23 (3H, s), 2.60 (1H, bs), 2.62 (1H, m), 3.32 (1H, dd, J = 9.7, 6.8 Hz), 3.42 (1H, bd, J = 18.1 Hz), 3.61 (1H, dd, J = 9.7, 6.8 Hz), 4.47 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6 (2C), 18.2, 19.4, 21.4, 21.6, 24.7, 25.8, 25.9 (3C), 28.8, 31.4, 34.4, 41.5, 41.6, 44.1, 46.8, 57.3, 60.5, 64.8, 76.9, 92.0, 142.3, 146.0, 216.4. HRMS (CI) calcd for $C_{26}H_{44}NO_5Si$ (M^+ + 1) 478.2989. Found 478.2992.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-3α,10α-oxido-12-nortaxane-2,13-dione 76. Sodium borohydride (200 mg, 5.26 mmol) was added portion wise with stirring to a solution of **74** (500 mg, 1.08 mmol) in methanol (20 mL) at 0°C. After 2 h hydrogen peroxide solution (6 mL, 30% in water) was added followed by potassium carbonate (2.0 g). After 16 h water was added and the product was extracted into dichloromethane (3x30 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography over silica gel eluting with 20% EtOAc/hexanes gave **76** as a colorless oil (280 mg, 60%). IR ($CHCl_3$) 2931, 1714, 1694, 1471, 1394, 1252, 1138 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.03 (6H, s), 0.84 (9H, s), 1.09 (3H, s), 1.20-1.30 (2H, m), 1.24 (3H, s), 1.25 (3H, s), 1.30-1.50 (4H, m), 1.50-1.65 (2H, m), 1.90 (1H, bs), 2.00 (1H, m), 2.18 (1H, dd, J = 13.6, 5.7 Hz), 2.35-2.50 (3H, m), 2.79 (1H, dd, J = 17.4, 5.7 Hz), 3.03 (1H, d, J = 17.4 Hz), 3.25 (1H, dd, J = 10.0, 7.1 Hz), 3.52 (1H, dd, J = 10.0, 6.9 Hz), 4.52 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3 (2C), 18.1, 19.6, 21.5, 24.6, 25.4 (3C), 25.9, 26.3, 29.9, 31.6, 34.7, 37.9, 41.6, 45.0, 46.6, 48.3, 62.6, 64.5, 83.2, 93.0, 206.5, 217.3. HRMS (CI) calcd for $C_{25}H_{43}O_4Si$ (M^+ + 1) 435.2931. Found 435.2924.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-13α-hydroxy-3α,10α-oxido-12-nortaxane-2-one 77. DIBAL-H (0.40 mL; 1.0*M* solution in dichloromethane) was added to a stirred solution of **76** (190 mg, 0.44 mmol) in dichloromethane (10 mL) at -78°C. After 20 min the cooling bath was removed and the reaction quenched by the addition of water (10 mL). The organic layer was washed with 2N HCl (20 mL) followed by extraction with dichloromethane (3x30 mL). The combined extracts were dried ($MgSO_4$) and

the solvent was evaporated *in vacuo*. Chromatography over silica gel gave **77** as a white solid (160 mg, 84%). IR ($CHCl_3$) 3493, 2929, 2858, 1690, 1462, 1394, 1257, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.02 (6H, s, 6H), 0.82 (9H, s), 1.20-1.40 (3H, m), 1.40-1.50 (4H, m), 1.60-1.75 (2H, m), 1.83 (1H, bd, J = 12.7 Hz), 2.05-2.20 (3H, m), 2.30 (1H, m), 2.64 (1H, m), 3.45 (1H, t, J = 10.7 Hz), 3.54 (1H, dd, J = 10.7, 4.9 Hz), 3.85 (1H, m), 4.63 (1H, m), 5.20 (1H, d, J = 12.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, -5.5, 18.2, 18.9, 19.2, 21.6, 24.3, 25.8 (3C), 26.0, 30.5, 30.8, 31.7, 34.1, 38.3, 41.6, 44.2, 46.2, 61.3, 61.9, 65.6, 83.3, 93.4, 219.3. HRMS (CI) calcd for $C_{25}H_{45}O_4Si$ (M^+ + 1) 437.3087. Found 437.3081.

4Hβ-11,12-Dihydro-13α,20-dihydroxy-3α,10α-oxido-12-nortaxane-2-one 78. Hydrogen fluoride-pyridine complex (400 μL) was added dropwise to a stirred solution of **77** (100 mg, 0.23 mmol) in tetrahydrofuran (5 mL). After 2 h saturated aqueous $NaHCO_3$ (10 mL) was added cautiously, and the product was extracted into dichloromethane (3x10 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography over silica gel eluting with 40% EtOAc/hexanes gave **78** as a white solid (67 mg, 91%). IR ($CHCl_3$) 33997, 2930, 1689, 1433, 1363, 1138 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, s), 1.14 (3H, s), 1.18 (3H, s), 1.25-1.55 (8H, m), 1.60-1.80 (3H, m), 2.00-2.20 (2H, m), 2.40 (1H, m), 2.68 (1H, m), 3.57 (1H, d, J = 5.3 Hz), 3.94 (1H, m), 4.68 (1H, m). HRMS (CI) calcd for $C_{19}H_{30}O_4$ (M^+ + 1) 323.2144. Found 323.2152.

4Hβ-11,12-Dihydro-20-(*tert*-butyldimethylsilyloxy)-3α,10α-oxido-12-nortaxane-2,12,13-trione 79. Sodium methoxide (8 mg, 0.15 mmol) was added to a stirred solution of **49** (46 mg, 0.1 mmol) in methanol (3 mL). After 10 min the solution was cooled to -78°C and ozone passed through the solution for 20 min. After a further 20 min at this temperature, dimethylsulfide (0.5 mL) was added, and the reaction mixture allowed to warm to room temperature overnight. The solvent was evaporated *in vacuo* and the residue purified by chromatography over silica gel eluting with 15% EtOAc/hexanes to give **79** as a pale yellow oil (22 mg, 51%). IR (thin film) 3444, 2932, 2857, 1693, 1677, 1464, 1386, 1253, 1229, 1198, 1096 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.0 (6H, s), 0.85 (9H, s), 1.1-1.2 (2H, m), 1.11 (3H, s), 1.14 (3H, s), 1.24 (3H, s), 1.3-1.4 (3H, m), 1.7 (1H, m), 1.75 (1H, dd, J = 13.9, 9.8 Hz, 2.1 (1H, m), 2.26 (1H, dd, J = 13.9, 5.0 Hz), 2.47 (1H, dd, J = 2.9, 1.4 Hz), 3.0 (1H, dd, J = 6.8, 1.4 Hz), 3.28 (1H, dd, J = 10.0, 8.1 Hz), 3.54 (1H, dd, J = 10.0, 5.8 Hz), 4.53 (1H, m), 5.93 (1H, d, J = 6.8 Hz), 6.00 (1H, s). HRMS (CI) calcd for $C_{25}H_{41}O_5Si$ (M^+ + 1) 449.2723. Found 449.2727.

11Hβ-4Hβ-4-Formyl-3α,10α-oxido-taxane-12-ene-2-one 80. A solution of **60** (50 mg, 0.15 mmol) in dichloromethane (2 mL) was treated with the Dess-Martin periodinane (320 mg, 0.75 mmol, 5 equiv) and stirred at 25°C for 2 h. The reaction mixture was quenched by the addition of a 10% aqueous solution of NaOH (2 mL) and a saturated aqueous NH_4Cl solution (1 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (4x10 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give **80** (50 mg, 100%, 9:1 mixture of aldehyde epimers) which was used immediately. IR (thin film) 2934, 1721, 1688 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, s), 1.17 (3H, s), 1.24 (3H, s), 1.70-1.10 (8H, m), 1.77 (3H, d, J = 1.4 Hz), 2.20 (2H, m), 2.29 (1H, dd, J = 4.9, 13.5 Hz), 2.50 (1H,

m), 2.87 (1H, m), 4.53 (1H, ddd, J = 2.6, 4.8, 10.1 Hz), 5.38 (1H, m), 9.63 (1H, d, J = 3.3 Hz). HRMS (CI) calcd for $C_{20}H_{29}O_3$ ($M^+ + 1$) 317.2117. Found 317.2108.

11Hβ-4Hβ-4-Carboxy-3α,10α-oxido-taxane-12-ene-2-one 81. A solution of **80** (50 mg, 0.15 mmol) in *tert*-butanol (2.5 mL), 2-methyl-2-butene (1.5 mL) and water (1.5 mL) was treated with NaH_2PO_4 (0.2 g, 1.5 mmol, 10 equiv) and $NaClO_2$ (0.14 g, 1.5 mmol, 10 equiv). The mixture was stirred vigorously at 25°C 4 h. The mixture was diluted with Et_2O (10 mL) and the phases were separated. The ethereal phase was washed with water followed by brine (2 mL each), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography over silica gel eluting with 60% hexanes/EtOAc and 0.5% AcOH gave **81** as a white solid (18 mg, 35% for two steps). IR (thin film) 3242, 2923, 1739, 1693, 1443, 1390, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.14 (3H, s), 1.23 (3H, s), 1.70 (3H, d, J = 1.8 Hz), 1.90-1.10 (8H, m), 2.38-2.20 (3H, m), 2.50 (1H, m), 3.09 (1H, dd, J = 4.5, 13.2 Hz), 4.63 (1H, ddd, J = 3.1, 4.6, 10.1 Hz), 5.41 (1H, m). HRMS (CI) calcd for $C_{20}H_{28}O_4$ (M^+) 332.1988. Found 332.1988.

4Hβ-11,12-Dihydro-2α,20-oxido-3α,10α-oxido-20-oxo-taxane-3,12-diene-10-one 83. A stock solution of lithium diisopropylamide was prepared as follows: a solution of diisopropylamine (0.2 mL, 1.5 mmol) in tetrahydrofuran (2.5 mL) at 0°C was treated with *n*-BuLi (2.5M in hexanes, 0.62 mL, 1.5 mmol), stirred for 15 min and used immediately. A solution of **81** (17.4 mg, 0.05 mmol) in tetrahydrofuran (0.3 mL) was treated with lithium diisopropylamide (0.52 mL, 0.26 mmol, 5 equiv). The mixture was stirred for 2 h at 25°C and quenched with saturated aqueous NH_4Cl (1 mL). The solvent was evaporated *in vacuo*, and the aqueous residue saturated with NaCl and extracted with dichloromethane (3x10mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by chromatography over silica gel eluting with 80% hexanes/EtOAc gave **83** as a white solid (11 mg, 69%). IR (thin film) 2928, 2852, 1757, 1692, 1675, 1437, 979 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, s), 1.18 (6H, s), 1.61 (3H, d, J = 1.7 Hz), 1.70-1.10 (5H, m), 1.83 (1H, dd, J = 1.7, 10.8 Hz), 2.35-2.15 (4H, m), 2.42 (1H, s), 3.19 (1H, d, J = 10.8 Hz), 5.07 (1H, m), 5.47 (1H, m). ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 18.5, 21.0, 21.7, 24.2, 26.2, 26.7, 33.7, 34.8, 37.9, 41.9, 44.4, 50.1, 63.9, 70.3, 82.1, 121.9, 130.9, 132.6, 165.3, 213.5. HRMS (CI) calcd for $C_{20}H_{27}O_3$ ($M^+ + 1$) 315.1960. Found 315.1950.

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†. Author for inquiries concerning the X-ray data.

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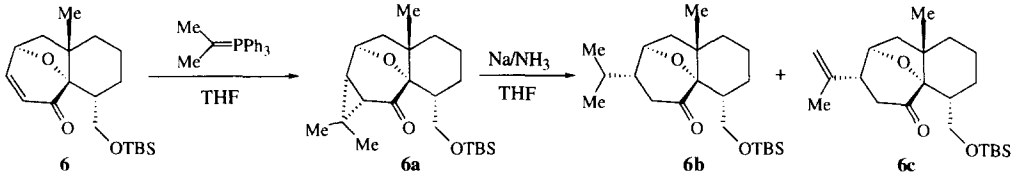

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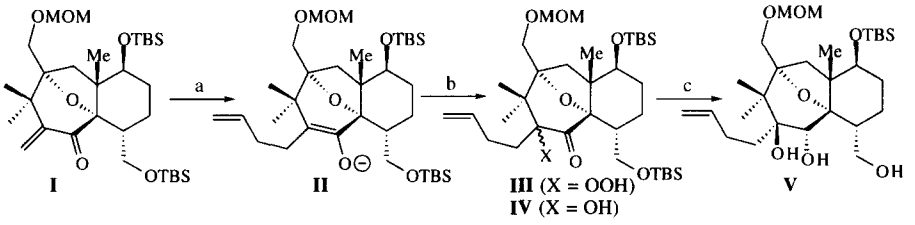
12. During studies that involved ring expansion using a semi-pinacol rearrangement we found that **I** underwent conjugate addition of allyl lithium to give **II**, which was directly treated with dry air to give **III** and **IV**. The structure of the major diastereoisomer was confirmed by conversion into **V** (X-ray). Dr. Melvyn Giles is thanked for carrying out these experiments.



Conditions:- a) Allyltri-*n*-butylstannane/MeLi/THF/-78°C. b) Dry air/-30°C, **III** (12%) and **IV** (66%, 4.5β:1α mixture of C-1 epimers). c) i. $LiAlH_4$/THF/0°C. ii. TBAF/THF (75% from **IV**).

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14. The reactions of enolates with triplet dioxygen is a SET process resulting in the enolate radical which couples with either triplet dioxygen or the radical anion of dioxygen. In approaching the transition state the enolate radical would undoubtedly prefer to orientate the large -$CH_2CH_2SO_2Ph$ side chain in an equatorial conformation thus leading to axial attack of dioxygen from the β-face.

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27. We have shown (7-oxy series) that the hydride migration is reversible (see reference 4).

28. Treatment of **82** with LDA/THF/60°C results in conversion to a mixture that does not contain **83**, but we were unable separate the compounds and it was not pursued further.

29. For reviews that outline the main strategies that have been used see:- Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15. Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. "*Recent Progress in the Synthesis of Taxanes*", Contemporary Organic Synthesis, **1994**, *1*, 47. Paquette, L. A. "*Studies Directed towards the Total Synthesis of Taxanes*". Studies in Natural Product Chemistry, Ed. Rahman, A-ur. **1992**, Vol 11, p. 3. Elsevier Science Publ. See also reference 11.

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