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# A synthetic approach toward taxol analogs: studies on the construction of the CD ring

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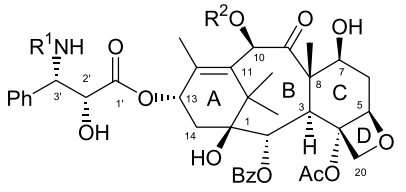
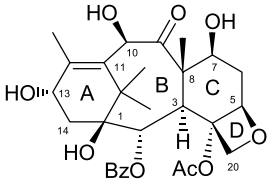
**Abstract**—Tricycle **6**, containing the CD ring of taxol, is constructed from (*S*)-(+)-carvone in 21 steps involving a Diels–Alder reaction with isoprene, a Baeyer–Villiger oxidation, an Oppenaurer oxidation and Meerwein–Ponndorf–Verley reduction, a stereospecific Grignard addition, and an intramolecular $S_N2$ reaction as the key steps.


## 1. Introduction

Paclitaxel (taxol®)[1] (**1**), the first member of a new group of anticancer drugs termed taxanes,[2] is a naturally occurring tetracyclic diterpenoid isolated[3] from the stem bark of Pacific Yew *Taxus brevifolia*. Taxol is recommended, in combination with *cis*-platin, for the treatment of primary ovarian cancer where standard platinum-containing therapy has failed, of metastatic breast cancer where anthracycline-containing thereapy has been unsuccessful or is inappropriate, and of nonsmall cell lung cancer when surgery and radiation therapy inappropriate.[4] The outstanding cytotoxic activity of taxol is believed to arise from its unique function as a mitotic inhibitor, hindering cell replication by preventing microtubules from depolymerization back to tubulin.[2] Docetaxel (taxotere®)[5] (**2**), a synthetic analog[6] of taxol (**1**), is recommended for use in advanced or metastatic breast cancer where adjutant cytotoxic chemotherapy (anthracycline or alkylation agent) has failed and in advanced nonsmall cell lung cancer where first line chemotherapy has failed.[4] Docetaxel (**2**) is twice as active as taxol (**1**) with regard to promoting the assembly and stability of microtubules.[7] Initially, the natural scarcity of taxol, the inefficient methods available for its isolation and its complex, strained framework attracted considerable attention from synthetic chemists. To date, 6 total syntheses of taxol have been published.[8–13] The shortest route is that reported by Wender et al.[11] starting from (1*R*)-(+)-verbenone and involving 37 steps in an overall yield of about 0.37%. Consequently, an industrial-scale production of taxol by total synthesis is unlikely to be economical. Fortunately, the supply problem of taxol has been adequately alleviated via semisynthesis from the naturally occurring 10-deacetylbaccatin III (**3**),[14] a renewable resource readily extractable in relatively high yield from the needles of the European Yew *Taxus baccata*. On the other hand, syntheses of structural analogs which might exhibit similar or improved biological activity has been an area of intense research.[2,15]



**1** Taxol $R^1 = C_6H_5CO$, $R^2$ = Ac (Paclitaxel)
**2** Taxotere $R^1$ = *t*-BuOCO, $R^2$ = H (docetaxel)



**3** 10-*O*-deacetylbaccatin III (10-DAB)

In our quest for the discovery of a structurally simplified, synthetically accessible taxol analog which possesses a comparable biological profile, we started a project to investigate a facile and flexible construction of the CD ring of taxol. The oxetane D ring is indispensable for

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*anti*-cancer properties.[16] Our preliminary experiments have shown that the $EtAlCl_2$ catalyzed Diels–Alder reaction between (*R*)-(−)-carvone and isoprene occurred preponderantly in an *anti* orientation with respect to the isopropylene group to give decalin **4** (Scheme 1).[17] Such a decalin system **4**, containing a stereo-defined angular methyl group at C-9, would be a valuable synthetic precursor for the taxane C ring system. Regioselective dihydroxylation at the endocyclic double bond of the cycloadduct **4** followed by acetonation gave a crystalline acetonide **5**, the structure and stereochemistry of which were confirmed by an X-ray crystallographic analysis.[17] Hence the stereochemical outcome of the Diels–Alder reaction was established and to obtain the correct absolute configuration at the angular methyl group, (*S*)-carvone had to be employed in our synthesis. This paper describes in detail our effort in the stereocontrolled construction of the CD ring with functionalities suitable for elaboration into taxol analogs.[18]

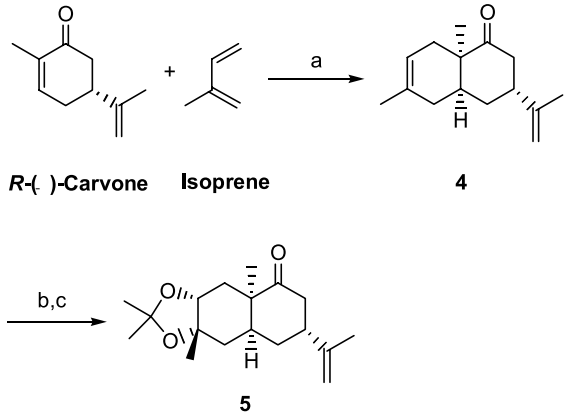
## 2. Results and discussion

### 2.1. Initial synthetic plan

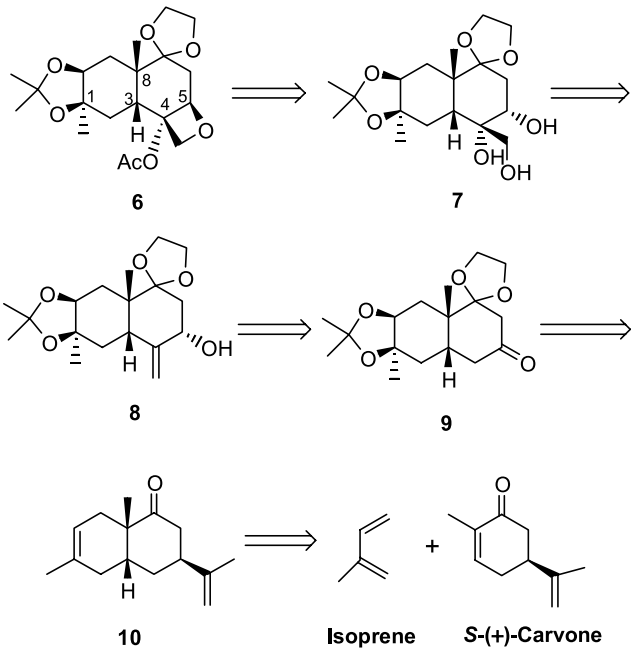
Retrosynthetic analysis of tricycle **6** containing a functionalized CD ring is shown in Scheme 2. We envisaged that the oxetane ring could be readily installed from the ring closure reaction between the hydroxyl groups at C-5 and C-11 in triol **7**. This triol could simply be obtained from dihydroxylation of the double bond in allylic alcohol **8** which would be transformed from ketone **9** via an aldol condensation with formaldehyde. The ketone **9** should be readily accessible from cycloadduct 10 through functional group manipulations. Finally intermolecular Diels–Alder reaction of *S*-(+)-carvone with isoprene should provide cycloadduct **10**.

### 2.2. Synthesis of ketone 9

The synthesis of the suitably protected ketone **9** is shown in Scheme 3. The intermolecular Diels–Alder reaction of *S*-(+)-carvone with isoprene using $EtAlCl_2$ as catalyst at room temperature afforded a mixture of major *anti*- and minor *syn*-cycloadducts, **10** and **11** respectively, in 92% combined

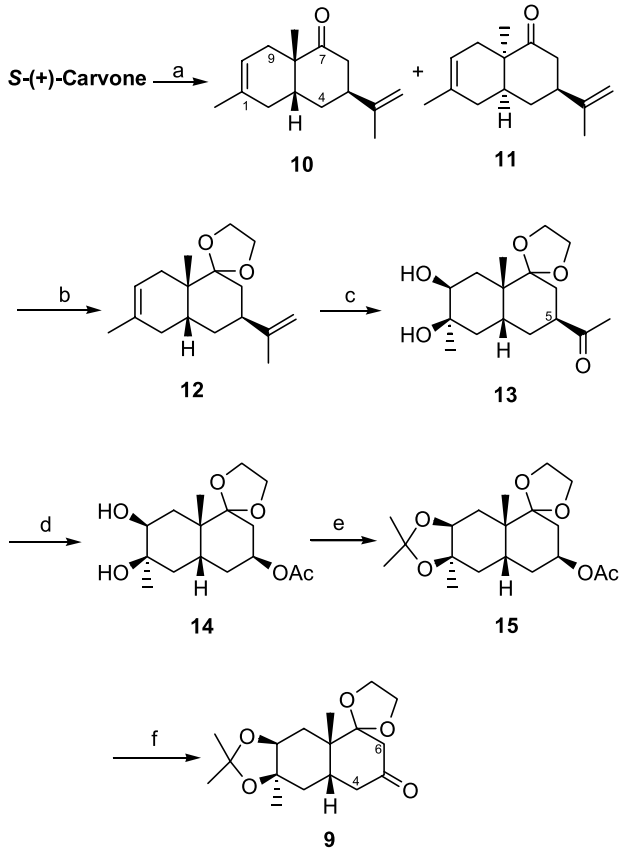



**Scheme 1.** Reaction conditions: (a) $EtAlCl_2$, rt, 48 h (100%); (b) $OsO_4$ (cat.), NMO, rt, 24 h (80%); (c) acetone, *p*-TsOH, reflux, 5 h (70%).




**Scheme 2.**

yield. The ratio of **10** to **11** was determined as 11.6:1 by GC-MS. This mixture which could not be separated by flash column chromatography on silica gel was directly put to the next step. Protection of the carbonyl group in octalones **10**




**Scheme 3.** Reaction conditions: (a) isoprene, $EtAlCl_2$, toluene (92%); (b) ethylene glycol, *p*-TsOH, PhH, reflux (89%); (c) $OsO_4$, NMO, acetone–$H_2O$ (4:1) then $NaIO_4$ (74%); (d) *m*CPBA, $CH_2Cl_2$, rt (93%); (e) DMP, *p*-TsOH, $CH_2Cl_2$ (92%); (f) (i) $K_2CO_3$, MeOH; (ii) PCC, $CH_2Cl_2$ (90%).

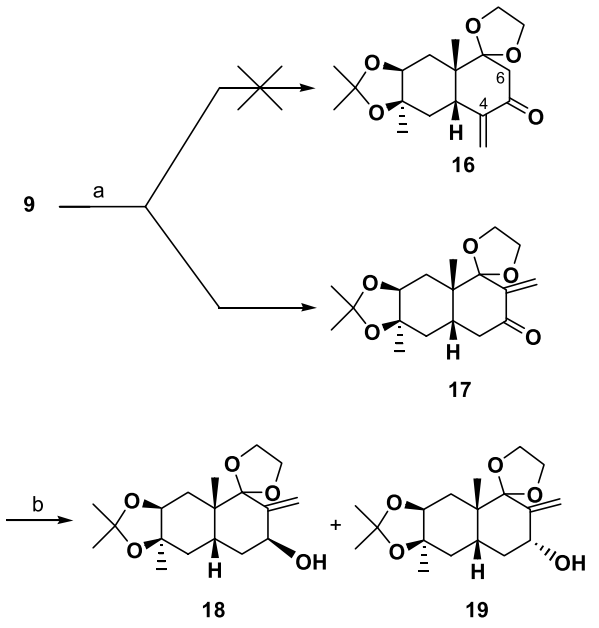
and **11** with ethylene glycol gave acetal **12** together with its diastereomer in 89% yield, which could not be fractionated on column chromatography either. Stereoselective dihydroxylation of the acetal **12** with a catalytic amount of osmium tetraoxide and *N*-methylmorpholine-*N*-oxide[19] furnished a tetraol in which the more reactive (containing a primary alcohol) exocyclic diol was selectively cleaved with 1 equiv of sodium metaperiodate,[20] and methyl ketone **13** could be isolated enantiopure in 74% overall yield from acetal **12**. Attack of $OsO_4$ was expected to occur at the less hindered convex face (β-face) of the bicyclic skeleton **12** to give, exclusively, the endocyclic β-diol as indicated in ketone **13**.

Installing an oxygen functionality at C-5 was effected with Baeyer–Villiger oxidation[21] of methyl ketone **13** using *meta*-chloroperbenzoic acid to give acetate **14** in 93% yield. At this point, protection of the free diol unit was necessary since manipulation of both alcohols would not be carried out in the present synthetic adventure. Thus, standard acidic acetonation of the diol moiety in **14** furnished acetonide **15** in 92% yield. Removal of the acetyl blocking group in acetate **15** with basic methanol followed by PCC oxidation of the liberated alcohol gave the desired ketone **9** in 90% overall yield.

### 2.3. Attempted aldol condensation of ketone 9

Since the D ring is situated across C-4 and C-5, homologation at C-4 was our next mission and the keto group in **9** should be assisting the elaboration. Initially, the obvious aldol condensation with formaldehyde,[22] following a regioselective deprotonation at C-4 of ketone **9**, was attempted in the hope to obtain enone **16**. Under kinetically controlled conditions, deprotonation of ketone **9** was speculated to take place at C-4 since the cyclic acetal blocking group should impose steric hinderance around C-6. Unfortunately, this step was found to be problematic. Our results (vide infra) indicated that standard strong base LDA reacted with ketone **9** to generate an enolate which attacked formaldehyde to yield enone **17** rather than the desired enone **16** (Scheme 4).

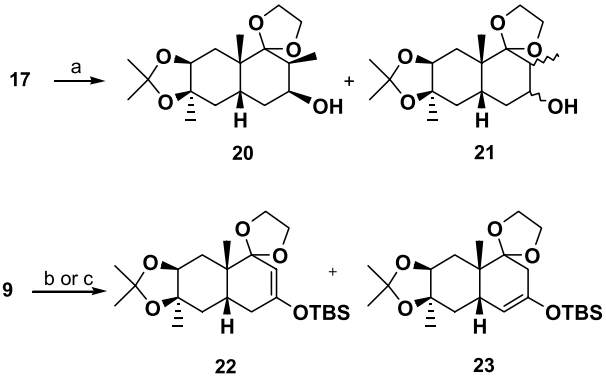
The enone **17** was found to be unstable at ambient conditions and a subsequent reduction was carried out in order to provide a stable compound. Thus Luche's reduction[23] of enone **17** immediately after the aldol condensation gave a mixture of diasteromeric allylic alcohols **18** and **19** in a respective ratio of 1:2. Since NMR spectral analysis could not confidently confirm the position of the methylene group inserted, two additional experiments were performed. As shown in Scheme 5, enone **17** was reduced with sodium borohyride in the absence of cerium chloride to give saturated alcohol **20** and its diastereomer **21** in 23% overall yield from **9**. An X-ray crystallographic analysis (CCDC-185889) of a single crystal from alcohol **20** confirmed its structure which proved that the aldol condensation had occurred at C-6. On the other hand, treatment of ketone **9** with LDA followed by trapping the resultant enolate with TBSOTf furnished silyl enol ethers **22** and **23** in a ratio of 2:1 and in a combined yield of 48%. Their structures were readily differentiated by $^1$H NMR spectroscopy as the olefinic proton in **22** appeared



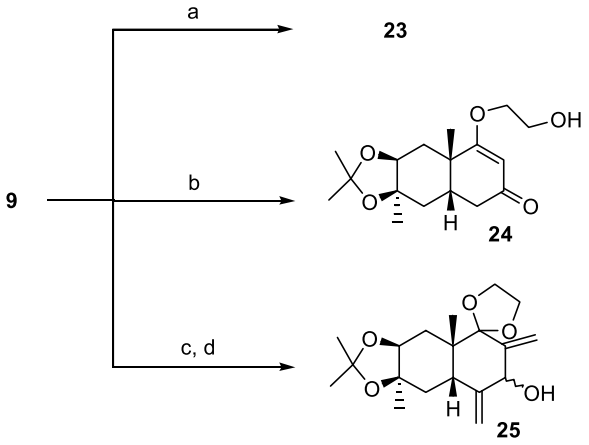

**Scheme 4.** Reaction conditions: (a) LDA, −78 °C gaseous HCHO, −30 °C; (b) $CeCl_3$, $NaBH_4$, MeOH, 0 °C (35%) (**18**:**19**=1:2).

as a singlet whereas that in **23** resonated as a doublet. Since enol ether **22** was the major product, deprotonation must have taken place at C-6 preponderantly. The regioselectivity of the deprotonation could be explained in terms of the interaction between the lithium ion and the oxygen atom of the cyclic acetal moiety. Hence, the methylene protons (H-6) closer to the cyclic acetal would be preferentially abstracted by LDA.

The setback with LDA was addressed with other bases and we turned to sodium *N*-hexamethyldisilazane (NaHMDS) first. However, only silyl enol ether **22** was produced in 50% yield when ketone **9** was treated with NaHMDS and TBSOTf. Since strong bases could not generate the desired C-4,5 enolate, weaker bases such as postassium carbonate, potassium *tert*-butoxide and sodium hydroxide were investigated. However, reactions with these bases afforded a stable enone **24** as the sole product, obtainable in high yields (Scheme 6). Again, deprotonation took place at C-6 rather than at C-4 to form an enolate which immediately caused β-elimination-opening of the cyclic acetal. Since all




**Scheme 5.** Reaction conditions: (a) $NaBH_4$, MeOH, 0 °C (23%); (b) LDA, −78 °C, TBSOTf (48%) (**22**:**23**=2:1); (c) NaHMDS, −78 °C, TBSOTf (50%) **22** only.



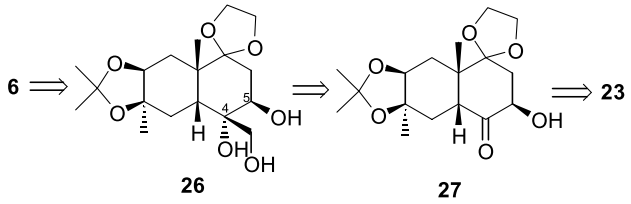

**Scheme 6.** Reaction conditions: (a) $Et_3N$, TBSOTf, −78 °C (88%); (b) NaOH, $K_2CO_3$ or BuOK, THF 0 °C (83%); (c) Eschensomer's salt, $Et_3N$, $CH_2Cl_2$, rt; (d) $CeCl_3$, $NaBH_4$, MeOH, 0 °C (40% from **9**).

metal bases could not furnish the desired enolate in good yields, organic bases might be suitable candidates to prevent the chelation effect of the cyclic acetal. Toward this end, ketone **9** was treated with $Et_3N$ and TBSOTf[24] at −78 °C and we were delighted to learn that the desired silyl enol ether **23** could be obtained pure in 88% yield as the sole product (Scheme 6). With the regio-correct masked enolate **23** in hand, reaction with formaldehyde or *S*-trioxane under the Mukaiyama conditions[25] should provide an aldol adduct. Unfortunately, after tremendous experimentations, the Mukaiyama reaction of **23** under various conditions (Lewis acids, solvents and temperatures) were all unsuccessful.

An alternative approach towards the addition of a methylene unit at the α-position of a carbonyl group could in principle be achieved with Eschenmoser's salt.[26] Ketone **9**, in the absence of base, gave no reaction with the Eschenmoser's salt in refluxing $CH_2Cl_2$ or THF. With the addition of $Et_3N$,[27] the α-methylenation did occur but was unbearably sluggish in THF. Interestingly, the reaction proceeded at a moderate rate in $CH_2Cl_2$. However, both C-4 and C-6 were aminomethylated and elimination occurred concommitantly to give an enone which was unstable upon isolation. Its stable derivative, amenable for characterization, was obtained by Luche's reduction[23] of the carbonyl group, giving dialkenyl alcohol **25** in 40% overall yield. However, careful control of the reaction conditions could not afford the desired enone **16**. On the other hand, silyl enol ether **23** was inert towards Eschenmoser's salt. Since diene alcohol **25** could not contribute to the synthesis of the CD ring of taxol, this approach of direct functionalization of C-4 was therefore abandoned and an alternative avenue had to be pursued.

## 2.4. Revised synthetic plan

The retrosynthesis of a new approach is summarized in Scheme 7. Oxetane **6** would be constructed form triol **26** in which the functionalities at C-4 could be installed by inserting a hydroxymethyl group to α-hydroxy ketone **27**. The ketone **27** would be derived from silyl enol ether **23** via a series of functional group manipulations. In this new




**Scheme 7.**

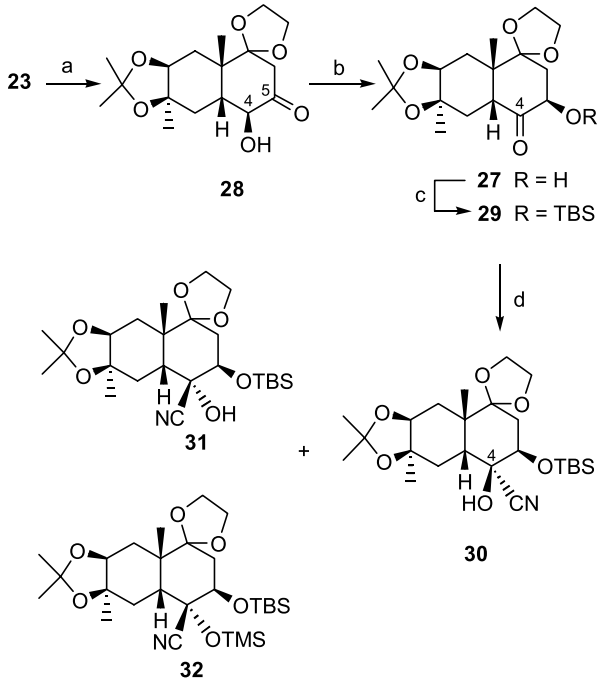
approach, the hydroxyl at C-5 would act as a nucleophile rather than a leaving group, which is different from the strategy reported [8-13] in the 6 total syntheses.

## 2.5. Synthesis of a highly functionalized precursor 33

The new approach started with silyl enol ether **23** which was hydroxylated using Oxone® and acetone[28] to give 4-hydroxy ketone **28** in 73% yield (Scheme 8). A 1-carbon homologation was required on C-4 and we planned to interconvert the ketone and hydroxy functionality between C-4 and C-5 so that the keto group at C-4 would be amenable for such elaboration.

This was accomplished by an intramolecular redox reaction: Oppenaurer oxidation and Meerwein–Ponndorf–Verley reduction[29] of 4-hydroxy ketone **28** using $Al(OiPr)_3$ as catalyst afforded 5-hydroxy ketone **27** in 79% yield. We believed that the transformation was thermodynamically controlled as the 1,3-diaxial interaction between the OH-4 and the angular methyl group was alleviated from **28** (Fig. 1).

To our knowledge, this is the first example of a direct interconversion between hydroxy and ketone groups intramolecularly in the presence of $Al(OiPr)_3$. It was reported that at least 1 equiv of $Al(OiPr)_3$ was required in




**Scheme 8.** Reaction conditions: (a) buffer, oxone, acetone, $CH_3CN$ (73%); (b) $Al(OiPr)_3$ toluene (79%); (c) imidazol, DMAP, TBSCl, $CH_2Cl_2$ (93%); (d) see Table 1.

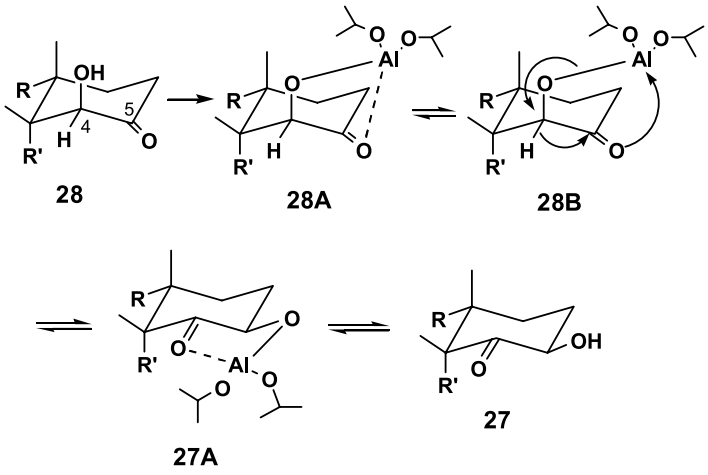



**Figure 1.** Proposed mechanism for the transformation of **28** into **27**. The cyclic acetal is not shown for clarity reason.

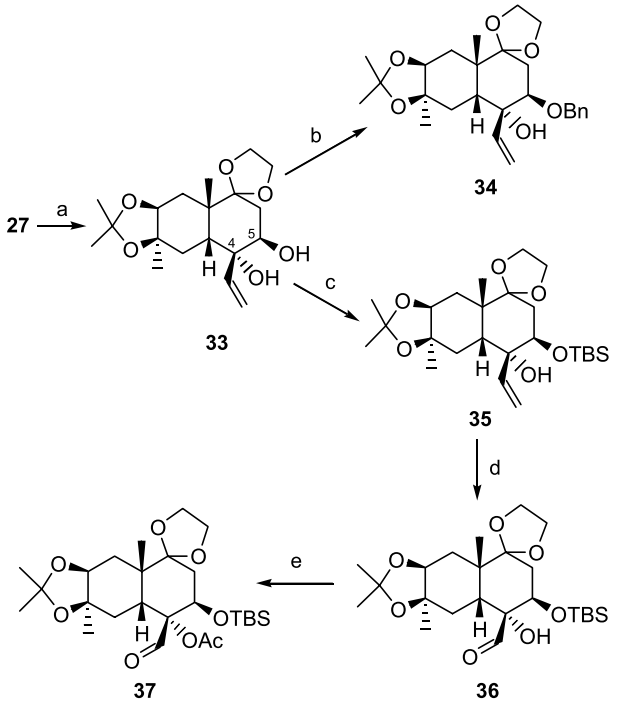
intermolecular reactions.[29] In our intramolecular case, the optimized yield was obtained with 0.5 equiv of $Al(OiPr)_3$ and the yield decreased dramatically with more than this amount. An X-ray crystallographic analysis (CCDC-185888) of a single crystal of **27** confirmed its structure and stereochemistry. Subsequent protection of the 5-hydroxy ketone **27** with TBSCl led to silyl ether ketone **29** in 93% yield. At this point, insertion of a hydroxymethyl group to the C-4 carbonyl group by nucleophilic addition became feasible. From a list of nucleophiles, TMSCN[30] should be a good choice since the nitrile moiety could be reduced to an aldehyde functionality by a number of reducing agents. Thus ketone **29** reacted with TMSCN at room temperature in the presence of 1.5 equiv (optimized) of $AlCl_3$ to give exclusively hydroxynitrile **30** in 66% yield whose stereochemistry at C-4 was confirmed undesirable by an X-ray crystallographic analysis (CCDC-185890). Interestingly, running the experiment at −35 °C afforded the desirable hydroxynitrile **31** and silyl ether nitrile **32** in 83% combined yield with a ratio of 3:1, respectively. These results revealed that at room temperature i.e. under thermodynamically controlled conditions, the bulkier nitrile group preferred to occupy the equatorial position and evaded the 1,3 diaxial interaction with the axial angular methyl group. On the other hand, under kinetically controlled conditions at −35 °C, the cyanide preferred to attack from the less hindered $\beta$-face due to the steric demand imposed by the *cis*-ring conformation. The yield of silyl ether nitrile **32** increased with the amount of $AlCl_3$ used and the best yield of **32** was achieved with 5 equiv of $AlCl_3$ (Table 1). It was clear that the hydroxy group of nitrile **31** could only be trimethylsilylated under forcing conditions.

The next step was the reduction of the nitrile group. To our disappointment, a number of reducing agents (DIBAL, LAH or Super hydride)[31a] or basic hydrolysis conditions[31b] could not reduce the nitrile group in **31** or **32** to an aldehyde or hydrolysed to the corresponding acid. For α-hydroxy nitrile **31**, the basic conditions caused retro-cyanohydrin formation to occur, affording the silyl ether ketone **29** in quantitative yield. The vicinity of the tertiary nitrile group might be sterically hindered by the angular methyl and the adjacent TBS group. This route was therefore abandoned and a Grignard reagent served as a hydroxymethyl equivalent was investigated. It has been well-known that Grignard reagent can attack a carbonyl group stereospecifically.[32] Vinyl magnesium bromide was chosen because the alkene moiety could be easily transformed into an aldehyde via a dihydroxylation-glycol cleavage protocol. However, α-silyl ether ketone **29** did not react the Grignard reagent attributable to the bulkiness of the TBS group. A straightforward method to alleviate this problem was to replace the TBS ether group with the less bulky TMS ether. Hence, transient protection of the free alcohol in 5-hydroxy ketone **27** as a TMS ether was followed by the addition of vinyl magnesium bromide, giving the corresponding allylic alcohol that was hydrolyzed with dilute HCl to give diol **33** in 90% overall yield (Scheme 9). It is noteworthy that the Grignard addition was stereospecific and only one stereoisomer was isolated in quantitative yield. The stereochemistry of the tertiary alcohol in diol **33** was confirmed desirable by an X-ray crystallographic analysis (CCDC-185891).

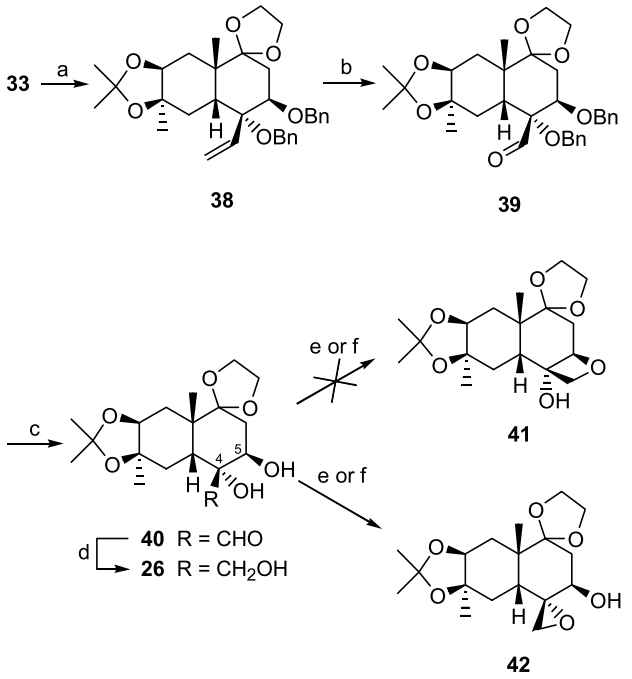
**Table 1.** Reactions of ketone **29** with TMSCN promoted by $AlCl_3$

| Conditions | Isolated yield (%) | Product ratio **30**:**31**:**32** |
|---|---|---|
| TMSCN, 1.5 equiv $AlCl_3$, rt, 10 min | 66 | 1:0:0 |
| TMSCN, 1.5 equiv $AlCl_3$, −35 °C, 2 h | 83 | 1:3:0 |
| TMSCN, 5 equiv $AlCl_3$, −35 °C, 2 h | 80 | 2:1:5 |

The onward steps were the selective protection of the secondary alcohol at C-5 followed by acetylation of the steric demanding tertiary hydroxy group at C-4. Thus, selective benzylation of the secondary alcohol in **33** afforded benzyl ether **34** in 86% yield without incident. To provide a variant for acetylation, selective silylation was also performed to furnish silyl ether **35** in 90% yield. To our regret, we could not acetylate the tertiary alcohol in **34** or **35** under various conditions and only unidentified decomposition products were isolated. Other research group[33] also encountered difficulty in carrying out acetylation in structurally similar systems. It was observed that the decomposition pattern of silyl ether **35** and benzyl ether **34** under various acetylation conditions were similar so only silyl ether **35** was selected for further studies. The reason for




**Scheme 9.** Reaction conditions: (a) (i) $Et_3N$, TMSCl, $CH_2Cl_2$; (ii) vinylMgBr, THF, −78 °C; (iii) 1 M HCl (90%); (b) NaH, BnBr, THF, 50 °C (86%); (c) imidazole, DMAP, TBSCl, $CH_2Cl_2$ (90%); (d) $OsO_4$, NMO, then $NaIO_4$ $CH_2Cl_2$:$H_2O$ (8:1) (78%); (e) Pyr, DMAP, $Ac_2O$, reflux (35%).

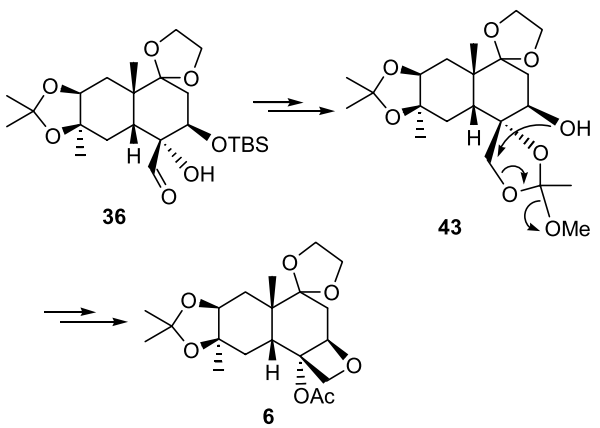



**Scheme 10.** Reaction conditions: (a) NaH, BnBr, THF, reflux (86%); (b) $OsO_4$, NMO, acetone–$H_2O$ (4:1), then $NaIO_4$ (78%); (c) 10% Pd/C, EtOH, $H_2$ (78%); (d) $NaBH_4$, MeOH, 0 °C (80%); (e) (i) $Et_3N$, MsCl, $CH_2Cl_2$, 0 °C; (ii) NaH, THF, reflux (92%); (f) (i) $Et_3N$, MsCl, $CH_2Cl_2$, 0 °C; (ii) DBU, toluene, reflux (92%).

the unsuccessful acetylation was attributed to steric hindrance. We therefore postponed the acetylation stage until a less bulky aldehyde was installed from oxidative cleavage of the double bond. Accordingly, we transformed silyl ether **35** into TBS aldehyde **36** by the conventional dihydroxylation-glycol cleavage protocol[34] in 78% yield. Acetylation of the tertiary alcohol in **36** under various conditions was then examined. Only the classical method ($Ac_2O$ and DMAP in refluxing pyridine) gave the desirable acetate aldehyde **37** in 35% yield accompanied by a number of unidentified side-products. The low yielding acetylation probably resulted from the steric factor and discouraged us to further investigate this route. Acetylation of the tertiary alcohol was scheduled to occur until the D-ring had been assembled.

As shown in Scheme 10, benzylation of the diol **33** in THF at reflux gave dibenzyl ether **38** in 86% yield. Dihydroxylation of the double bond in **38** followed by oxidative cleavage of the resulting diol afforded dibenzyl aldehyde **39** in 78% overall yield. Catalytic hydrogenolysis of dibenzyl ether **39** gave aldehyde diol **40** (78% yield) which underwent hydride reduction to generate triol **26** in 80% yield. To continue with our synthetic avenue, we allowed the tertiary hydroxyl unprotected in a hope that it would not participate in the intramolecular displacement during the oxetane ring formation. Thus selective mesylation of the primary alcohol in **26** gave the corresponding mesylate which would be attacked by the secondary C-5 alcohol to form oxetane **41** or by the tertiary alcohol at C-4 to produce epoxide **42**. Unluckily, the results indicated that the formation of the epoxide **42** was thermodynamically more stable. Even at prolonged reflux or with an excess amount of NaH or DBU, epoxide **42** could not be induced to undergo rearrangement to the desired oxetane **41**.[35] In principle, the rearrangement would occur if the C-5 hydroxyl and the leaving alkoxy group were arranged in an *anti*-periplanar fashion. However, it appeared that such alignment was not possible due to the ring strain of the C-ring. The formation of epoxide **42** as the sole product hinted at the importance of protecting the tertiary alcohol before the displacement reaction.

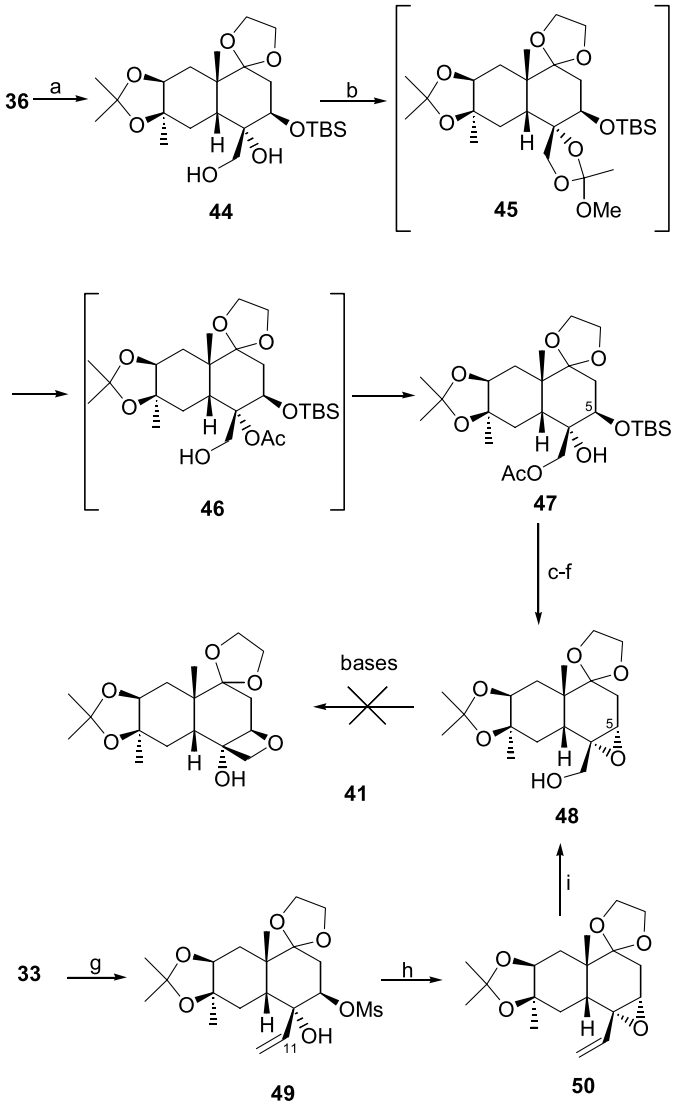
At this stage, we were tempted to make use of the trimethylorthroacetate[36] chemistry to construct the oxetane ring **6** (Scheme 11). Orthoester **43** would be assembled from the corresponding diol and it might serve the purpose of acetylation and oxetane formation since the C-5 hydroxyl could attack the orthoester to provide the oxetane and the C-4 acetate concomitantly.




**Scheme 11.**

As shown in Scheme 12, the aldehyde moiety in **36** was reduced to give diol **44** in 79% yield. Trimethylorthoacetate reacted with diol **44** in the presence of a stiochiometric amount of *p*-TsOH to give orthoester **45**. A catalytic amount of *p*-TsOH did not cause the reaction to take place. To our surprise, orthoester **45** was unstable even in the reaction mixture and the 5-membered ring readily hydrolyzed to form tertiary acetate **46**. Furthermore, another reaction was then involved which interfered with the isolation of the tertiary acetate **46**. Partial migration of the acetyl group from the tertiary position to the primary position took place readily in the reaction mixture to give a mixture of the tertiary acetate **46** and primary acetate **47**. The life time of the tertiary acetate **46** was too short for synthetic manipulation as facile rearrangement of tertiary acetate **46** to primary acetate **47** occurred quickly in weakly basic conditions ($Et_3N/CH_2Cl_2$). It was also found that **46** could be converted into **47** completely in silica gel so that the primary acetate **47** could be formed in 81% overall yield from diol **44**. Despite failure to obtain the desirable orthoester **45**, the acetate **47** could be a good candidate for a facile conversion into a CD ring precursor, i.e. oxirane **48**. Indeed, the TBS group in silyl ether **47** was smoothly erased with TBAF and the liberated C-5 hydroxyl was esterified with MsCl to give a mesylate. Intramolecular $S_N2$ displacement promoted by DBU in refluxing toluene followed by methanolysis of the acetate ester furnished epoxide **48** in 57% overall yield from silyl ether **47**.

The next hurdle to overcome was the isomerization of the oxirane moiety in **48** to an oxetane. Ideally, the freely rotating primary hydroxyl group in **48** should attack the epoxide at the less hindered C-5 in an *anti*-periplanar fashion to give oxetane **41**. However, attempts to isomerize the epoxide in **48** to the oxetane under different conditions failed. Bases such as $CsCO_3$ or $K_2CO_3$ in refluxing DMF or DBU in refluxing toluene gave no observable reactions. Reactions with $^t$BuOK, NaH and LDA gave unidentified side-products. At this stage, we considered the possibility to invert the C-5 stereocenter in diol **33** with a bromide so that the C-11 primary hydroxyl, accessible from a dihydroxylation-glycol cleavage-reduction sequence, could displace the



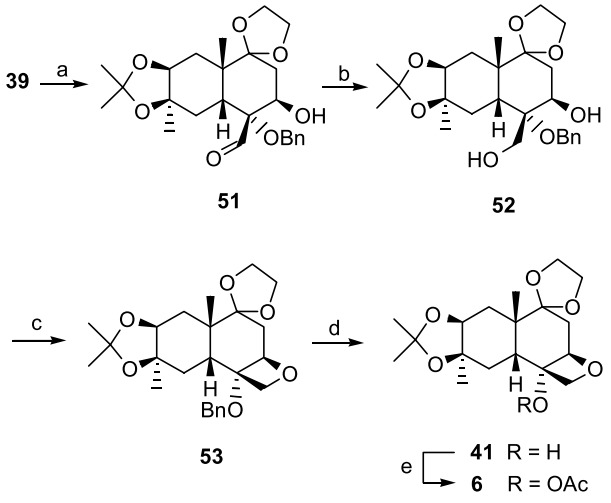

**Scheme 12.** Reaction conditions: (a) $NaBH_4$, MeOH, 0 °C (79%); (b) trimethylorthoacetate, *p*-TsOH, $CH_2Cl_2$, then $SiO_2$ (81%); (c) TBAF, THF; (d) $Et_3N$, MsCl, 0 °C; (e) DBU, toluene, reflux; (f) $K_2CO_3$, MeOh (57% from **47**); (g) $Et_3N$, MsCl, 0 °C (85%); (h) LiBr, $CH_3CN$ (74%); or $Bu_4NBr$, PhH, reflux (40%); (i) (i) $OsO_4$, NMO, then $NaIO_4$; (ii) $NaBH_4$, MeOH, 0 °C (72%).

bromide to give oxetane **41**. Thus, selective mesylation of diol **33** gave monomesylate **49** and unfortunately, bromide ion generated by LiBr in $CH_3CN$ or $^nBu_4NBr$ in benzene could not displace the mesylate group. Instead, the basic character of these reagents induced the tertiary hydroxyl to attack the mesylate group to form epoxide **50** in 74% and 40% yield, respectively. It was interesting to find that epoxide **50** could be transformed into oxirane **48** by a dihydroxylation-glycol cleavage-reduction sequence in 72% overall yield (Scheme 12).

### 2.6. Synthesis of the CD ring of taxol 6

The above results indicated that the tertiary alcohol had to be blocked before oxetane formation could be realized. After considering all the synthetic intermediates, we envisaged that retaining the tertiary benzyl group in dibenzyl ether **39** would be a good candidate for a successful venture.

Thus, catalytic and selective hydrogenolysis of the secondary benzyl group over the tertiary counterpart in dibenzyl ether **39** was investigated. After considerable efforts, it was observed that the choice of solvent could affect the rate and regioselectivity of the hydrogenolysis in our system. Only 5% palladium-on-charcoal in ethyl acetate could accomplish the task whereas the reaction in ethanol or THF showed very little selectivity. Under carefully controlled and monitored conditions, selective deprotection of the secondary benzyl group in **39** afforded, at best, aldehyde **51** in 70% yield, accompanied by the over-reduced diol **40** in 19% yield as shown in Scheme 13. Obviously, the selectivity was attributable to the less hindered secondary benzyl group. Subsequent reduction of the aldehyde in **51** with sodium borohydride in methanol furnished diol **52** in a quantitative yield. Selective mesylation of the primary C-11 hydroxyl group with MsCl and 2,4,6-collidine[37] at 0 °C gave a mesylate intermediate that was followed by an intramolecular $S_N2$ displacement[38] to give oxetane **53** for the first time in 83% yield. Hydrogenolysis of the tertiary benzyl ether in oxetane **53** with 10% palladium-on-charcoal in ethanol afforded alcohol **41** in 93% yield without incident. Finally, acetylation of the tertiary hydroxyl group was successfully achieved with $Ac_2O$ and DMAP in refluxing pyridine to give the CD ring of taxol **6** in 56% yield. Thus the tricycle **6** was constructed from (*S*)-(+)-carvone in 21 steps with an overall yield of 4%.




**Scheme 13.** Reaction conditions: (a) 5% Pd/C, ethyl acetate, $H_2$ (70% for **51**, 19% for **40**); (b) $NaBH_4$, MeOH, 0 °C (100%); (c) (i) 2,4,6-collidine, MsCl, 0 °C; (ii) NaH, THF, reflux (83%); (d) 10% Pd/C, EtOH, $H_2$ (93%); (e) Pyr, DMAP, $Ac_2O$ (56%).

In summary, we have presented a facile and stereocontrolled synthetic avenue for the construction of the functionalized CD ring in taxol. It is noteworthy that the BC ring in tricycle **6** or **41** is *cis*-fused and these tricycles may be versatile precursors for the preparation of taxol analogs with *cis*-fused BC rings and would provide excellent opportunities for structure-activity studies. The research in this direction is in progress.

## 3. Experimental

### 3.1. General

Melting points are reported in Celsius degrees and are uncorrected. Optical rotations were measured at 589 nm. GC-MS studies were performed on a GC with fused silica capillaries column and a GC/MS system with ion trap detector (ITD), injector temperature (250 °C), transfer line temperature (250 °C), oven temperature raised from 80 to 180 °C in a rate of 5 °C per min, EIMS by 70 eV electron beam. IR spectra were recorded on FT-IR spectrometer as a thin film or on a KBr disk. NMR spectra were measured at 300.13 MHz ($^1H$) or at 75.47 MHz ($^{13}C$) in $CDCl_3$ solutions, unless stated otherwise. All chemical shifts were recorded in ppm relative to tetramethylsilane ($\delta=0.0$). Spin–spin coupling constants (*J*) were measured directly from the spectra. MS and HRMS were performed at the Department of Chemistry, The Chinese University of Hong Kong, Hong Kong, China. Carbon and hydrogen elemental analyses were carried out by MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, U.K. All reactions were monitored by analytical TLC on aluminum precoated with silica gel $60F_{254}$ (E. Merck) and compounds were visualized with a spray of 5% w/v dodecamolybdophosphoric acid in EtOH and subsequent heating. E. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. All solvents were reagent grade unless otherwise stated. Toluene, benzene, and THF were freshly distilled from Na/benzophenone ketyl under nitrogen. $CH_2Cl_2$ was freshly distilled from $CaH_2$ under $N_2$. Diisopropylamine was freshly distilled from Na under $N_2$. Other reagents were purchased from commercial suppliers and used without purification. All hexanes used are *n*-hexane.

**3.1.1. Octalone 10 and 11.** A molar solution of $EtAlCl_2$ in hexane (1.5 mL, 1.5 mmol) was added to a solution of *S*-(+)-carvone (751 mg, 5.0 mmol) in dry toluene (20 mL). The solution was stirred at room temperature under $N_2$ for 20 min for complexation. Isoprene (2.0 mL, 15.0 mmol) was added and the resulting solution was stirred at room temperature under $N_2$ for 28 h. Ice water was added to the reaction mixture which was extracted with $Et_2O$ (3×). The combined organic extracts were dried ($MgSO_4$), filtered and

concentrated. The residue was fractionated by column chromatography (hexanes–$Et_2O$, 30:1) to give a mixture of octalones **10** and **11** as colorless oils (1.02 g, 92%, the ratio of **10**:**11** was determined by GC-MS to be 11.6:1): $[\alpha]_D^{20}=+3.7$ (*c* 0.27, $CHCl_3$); $R_f$ 0.63 (hexanes–$Et_2O$, 10:1); IR (thin film) 2926, 1703, 1637, 896 $cm^{-1}$; $^1H$ NMR $\delta$ 1.15 (s, 3H), 1.62 (s, 3H), 1.73 (s, 3H), 4.69 (brs, 1H), 4.81 (brs, 1H), 5.30 (brs, 1H); $^{13}C$ NMR $\delta$ 21.9, 23.5 24.2, 30.8, 32.8, 33.4, 38.1, 41.6, 41.9, 47.5, 111.7, 118.5, 131.8, 147.9, 215.6; MS (EI) *m/z* (relative intensity) 218 ($M^+$, 16.9), 91 (100). Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.38; H, 10.10.

**3.1.2. Acetal 12.** The aforedescribed mixture of octalones **10** and **11** (20.0 g, 0.092 mol), ethylene glycol (39.7 g, 0.64 mol) and *p*-TsOH (10 mg) were dissolved in benzene (350 mL) and the resulting solution was heated at reflux for 12 h with continuous azeotropic removal of water by means of a Dean–Stark trap. The cooled mixture was then washed with aqueous $NaHCO_3$, saturated brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was fractionated by column chromatography (hexanes–$Et_2O$, 30:1) to give acetal **12** as a colorless oil (21.5 g, 89%): $[\alpha]_D^{20}=+5.8$ (*c* 0.2, $CHCl_3$); $R_f$ 0.68 (hexanes–$Et_2O$, 10:1); IR (thin film) 2923, 2879, 1644, 886 $cm^{-1}$; $^1H$ NMR $\delta$ 0.84 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 3.89 (brs, 4H), 4.70 (brs, 2H), 5.32 (brs, 1H); $^{13}C$ NMR $\delta$ 17.9, 20.8, 23.7, 30.0, 33.8, 33.9, 35.2, 37.6, 39.8, 41.6, 64.9, 65.1, 108.5, 113.3, 117.8, 130.4, 149.5; MS (EI) *m/z* (relative intensity) 262 ($M^+$, 17), 91 (100); HRMS (EI) calcd for $C_{17}H_{26}O_2$ [M] 262.1927, found 262.1917.

**3.1.3. Methyl ketone 13.** A solution of acetal **12** (11.26 g, 43 mmol), NMO, (29 g, 215 mmol), and $OsO_4$ (50 mg) in 83% aqueous acetone (700 mL) was stirred at room temperature for 9 d. A solution of $NaIO_4$ (13.8 g, 64.5 mmol) in water (20 mL) was added at room temperature and precipitation occurred. The reaction mixture was stirred for 1 h and was then quenched with saturated aqueous $Na_2S_2O_3$. The resulting mixture was stirred for 24 h and was extracted with EtOAc (4×). The combined extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate under vacuum followed by flash column chromatography (hexanes–EtOAc, 1:1) afforded methyl ketone **13** as a white solid (9.5 g, 74%): mp 170–171 °C; $[\alpha]_D^{20}=+2.9$ (*c* 0.3, $CHCl_3$); $R_f$ 0.43 (EtOAc); IR (thin film) 3479, 2966, 1703, 1042 $cm^{-1}$; $^1H$ NMR $\delta$ 1.07 (s, 3H), 1.24 (s, 3H), 1.39 (d, $J=9.9$ Hz, 1H), 1.662 (m, 2H), 2.11 (s, 3H), 2.71 (m, 1H), 3.75 (dd, $J=5.7$, 14.2 Hz, 1H), 3.91 (brs, 4H); $^{13}C$ NMR $\delta$ 26.4, 27.2, 27.8, 28.3, 32.1, 36.4, 37.7, 40.1, 41.4, 44.8, 63.8, 64.3, 71.3, 71.9, 112.5, 211.3; MS (FAB) *m/z* (relative intensity) 299 ($[M+H]^+$, 4), 281 (3), 255 (100). Anal. calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.36; H, 8.93.

**3.1.4. Acetate 14.** *m*-Chloroperbenzoic acid (9.1 g, 52 mmol) was added to a stirred solution of methyl ketone **13** (7.84 g, 26 mmol) in $CH_2Cl_2$ (150 mL). The solution was stirred at room temperature for 72 h. The milky solution was cooled with an ice bath and the precipitated *m*-chlorobenzoic acid was removed by filtration. The filtrate was concentrated and upon purification by flash chromatography (hexanes–EtOAc, 1:2) gave acetate **14** as a white solid (7.56 g, 93%): mp 179–180 °C; $[\alpha]_D^{20}=-15.1$(*c* 0.37, $CHCl_3$); $R_f$ 0.53 (EtOAc); IR (thin film) 3461, 2966, 1732, $cm^{-1}$; $^1H$ NMR $\delta$ 1.13 (s, 3H), 1.24 (s, 3H), 2.02 (S, 3H), 3.73 (dd, $J=5.4$, 11.1 Hz, 1H), 3.92 (m, 4H), 4.96 (m, 1H); $^{13}C$ NMR $\delta$ 21.4, 26.7, 27.4, 31.6, 36.2, 36.3, 37.8, 40.5, 41.6, 63.9, 64.6, 68.9, 71.4, 72.3, 112.9, 170.4; MS (EI) *m/z* (relative intensity) 314 ($M^+$, 4), 271 (7), 255 (100), 236 (41). Anal. calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.42; H, 8.41.

**3.1.5. Acetonide 15.** To a stirred solution of acetate **14** (14.4 g, 45.9 mmol) in dry $CH_2Cl_2$ (350 mL) was added 2,2-dimethoxypropane (20 mL, 161 mmol) and a catalytic amount of *p*-TsOH (10 mg). The reaction mixture was stirred for 24 h at room temperature under $N_2$ and was then diluted with $Et_2O$. The organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a residue that was fractionated by column chromatography (hexanes–$Et_2O$, 2:1) to afford the acetonide **15** as a colorless oil (15.1 g, 92%): $[\alpha]_D^{20}=+21.9$ (*c* 1.5, $CHCl_3$); $R_f$ 0.56 (hexanes–$Et_2O$, 1:2); IR (thin film) 2980, 1736 $cm^{-1}$; $^1H$ NMR $\delta$ 1.28 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H,), 1.45 (s, 3H), 1.84 (dd, $J=6.3$, 12.3 Hz, 1H), 1.91 (d, $J=3.3$ Hz, 1H), 1.96 (brs, 1H), 2.01 (s, 3H), 2.18 (m, 1H), 3.87 (m, 2H), 3.96 (m, 1H), 4.04 (m, 2H), 4.91 (m, 1H); $^{13}C$ NMR $\delta$ 21.3, 25.9, 26.3, 27.4, 27.6, 30.0, 32.7, 34.2, 34.9, 38.9, 39.8, 63.4, 65.1, 69.2, 79.8, 80.5, 106.6, 113.0, 170.3; MS (FAB) *m/z* (relative intensity) 354 ($[M]^+$, 5), 339 ($[M-CH_3]^+$, 25), 295 (100); HRMS (FAB) calcd for $C_{19}H_{31}O_6$ [M+H] 355.2120, found 355.2118.

**3.1.6. Ketone 9.** Deprotection of the acetyl group in acetonide **15** was effected by adding $K_2CO_3$ (29.4 g, 213 mmol) to a solution of **15** (15.1 g, 42.7 mmol) in MeOH (350 mL). The reaction mixture was stirred for 4 h at room temperature and then concentrated in vacuo. The residue was dissolved in $Et_2O$ and $H_2O$, followed by acidification with 4 N aq. HCl until neutral. The solution was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a white solid residue which was directly subjected to the next step.

To a stirred solution of the white residue in dry $CH_2Cl_2$ (400 mL) was added a mixture of 3 Å molecular sieves (70 g) and PCC (46 g, 213 mmol). The reaction mixture was stirred for 3 h at room temperature under $N_2$ and then filtered through a pad of Celite and silica gel. The residue was eluted with $Et_2O$. Concentration of the filtrate followed by flash column chromatography (hexanes–$Et_2O$, 1:1) gave ketone **9** as a white solid (153 mg, 90%): mp 69–70 °C; $[\alpha]_D^{20}=+40.5$ (*c* 0.4, $CHCl_3$); $R_f$ 0.53 (hexanes–$Et_2O$, 1:2); IR (thin film) 2976, 1720 $cm^{-1}$; $^1H$ NMR $\delta$ 1.27 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.61–1.70 (m, 2H), 1.77 (d, $J=4.2$ Hz, 1H), 1.84 (dd, $J=3.3$, 15.3, 1H), 2.12–2.20 (m, 2H), 2.45 (bd, $J=16.2$ Hz, 1H), 2.61 (dd, $J=7.5$, 15.0 Hz, 2H), 3.93 (m, 4H), 4.13 (t, $J=3.6$ Hz, 1H); $^{13}C$ NMR $\delta$ 25.9, 26.2, 27.5, 27.6, 30.0, 34.3, 39.3, 41.1, 44.0, 46.4, 64.3, 64.9, 79.4, 79.7, 106.8, 113.6, 208.5; MS (FAB) *m/z* (relative intensity) 311 ($[M+H]^+$, 3), 149 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_5$ [M+H] 311.1858, found

311.1854. Anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.89; H, 8.61.

**3.1.7. Allylic alcohols 18 and 19.** To a stirred solution of diisopropylamine (0.23 mL, 1.61 mmol) in dry THF (4 mL) was added a 1.6 M solution of *n*-butyllithium in *n*-hexane (1.0 mL, 1.61 mmol) under $N_2$ at −78 °C. The reaction mixture was stirred for 15 min and a solution of ketone **9** (100 mg, 0.323 mmol) in dry THF (4 mL) was then added dropwise. The reaction mixture was stirred for 30 min at −78 °C, warmed to −30 °C and an excess amount of HCHO (1 g) was added over a period of 20 min. The reaction was quenched with saturated $NH_4Cl$ and extracted with $CH_2Cl_2$ (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification with a short silica gel column chromatography (hexanes–$Et_2O$ 2:1) gave the enone **17** which was used in the next reaction immediately.

To a stirred solution of the enone **17** and $CeCl_3\cdot 7H_2O$ (91 mg, 0.24 mmol) in MeOH (8 mL) was added $NaBH_4$ (23 mg, 0.61 mmol) in small batches over a period of 15 min at 0 °C. The reaction mixture was stirred for an additional 30 min and was then quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash column chromatography (hexanes–$Et_2O$, 10:1) afforded the β-hydroxy alkene **18** as a colorless oil (12 mg, 11%) and the α-hydroxy alkene **19** as a white solid (26 mg, 24%).

Data for **18**. $[\alpha]_D^{20}=+47.8$ (*c* 1.6, $CHCl_3$); $R_f$ 0.40 (hexanes–$Et_2O$, 1:2); IR (thin film) 3420, 2930, 1072 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) $\delta$ 1.13 (s, 3H), 1.26 (s, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 1.59 (dd, $J=3.6$, 15.3 Hz, 1H), 1.67 (m, 2H), 2.01 (m, 3H), 3.75 (m, 2H), 3.89 (m, 1H), 3.99 (m, 1H), 4.11 (t, $J=3$ Hz, 1H), 4.27 (m, 1H), 5.04 (t, $J=1.8$ Hz, 1H), 5.18 (t, $J=2.1$ Hz, 1H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 24.1, 24.4, 25.8, 28.9, 33.0, 37.1, 39.2, 39.5, 63.2, 63.3, 66.1, 79.3, 79.9, 104.8, 105.9, 112.3, 147.5; MS (FAB) *m/z* (relative intensity) 324 ($[M]^+$, 32), 307 (52), 249 ($[M-C_2H_4O_2-CH_3]^+$, 100); HRMS (FAB) calcd for $C_{18}H_{29}O_5$ [M+H] 325.2015, found 325.2023.

Data for **19**: mp 124–125 °C; $[\alpha]_D^{20}=-14.9$ (*c* 1.7, $CHCl_3$); $R_f$ 0.36 (hexanes–$Et_2O$ 1:2); IR (thin film) 3497, 2979, 1066 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) $\delta$ 1.23 (s, 3H), 1.28 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.53 (m, 2H), 1.73 (m, 1H), 1.79 (d, $J=3$ Hz), 1.92 (m, 1H), 2.08 (bd, $J=10.8$ Hz), 3.85 (m, 4H), 3.99 (t, $J=3$ Hz, 1H), 4.21 (m, 1H), 5.10 (t, $J=2.1$ Hz, 1H), 5.20 (t, $J=2.1$ Hz, 1H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 24.6, 26.5, 26.6, 27.8, 35.7, 37.8, 39.5 63.1, 64.6, 68.4, 76.9, 78.1, 105.0, 106.1, 117.5, 147.5; MS (FAB) *m/z* (relative intensity) 324 ($[M]^+$, 9), 249 ($[M-C_2H_4O_2-CH_3]^+$, 100), 187 (64); HRMS (FAB) calcd for $C_{18}H_{29}O_5$ [M+H] 325.2015, found 325.2000. Anal. calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.90; H, 8.82.

**3.1.8. Alcohol 20.** Enone **17** was prepared as above. To a stirred solution of the enone **17** in MeOH (15 mL) at 0 °C was added $NaBH_4$ (61 mg, 1.61 mmol) in small batches over a period of 15 min. The reaction mixture was stirred for 30 min and was then quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by column chromatography (hexanes–$Et_2O$, 1:1) gave alcohol **20** as a white solid (24 mg, 23%). A single crystal for X-ray crystallography was obtained from hexanes–$Et_2O$, 10:1.

Data for alcohol **20**: mp 151–152 °C; $[\alpha]_D^{20}=31.9$ (*c* 0.3, $CHCl_3$); $R_f$ 0.32 (hexanes–$Et_2O$ 1:2); IR (thin film) 3514, 2936, 1210 $cm^{-1}$; $^1H$ NMR $\delta$ 1.27 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.65 (m, 2H), 1.77 (d, $J=4.2$ Hz, 1H), 1.84 (dd, $J=3.3$, 15.3 Hz, 1H), 2.18 (m, 2H), 2.45 (bd, $J=16.2$ Hz, 1H), 2.61 (dd, $J=7.5$, 15.0 Hz, 2H), 3.93 (m, 4H), 4.13 (t, $J=3.6$ Hz, 1H); $^{13}C$ NMR $\delta$ 11.8, 19.5, 26.4, 28.2, 29.6, 33.6, 36.1, 38.2, 42.2, 67.1, 67.6, 71.7, 78.9, 106.9, 116.4; MS (EI) *m/z* (relative intensity) 326 ($[M]^+$, 7), 311 ($[M-CH_3]^+$, 17), 251 (26), 205 (100); HRMS (EI) calcd for $C_{18}H_{30}O_5$ [M] 326.2088, found 326.2083.

**3.1.9. Silyl enol ether 22.** To a stirred solution of diisopropylamine (0.1 mL, 0.73 mmol) in dry THF (4 mL) was added a 1.6 M solution of *n*-butyllithium in *n*-hexane (0.45 mL, 0.73 mmol) under $N_2$ at −78 °C. The reaction mixture was stirred for 15 min and a solution of the ketone **9** (45 mg, 0.15 mmol) in dry THF (4 mL) was added dropwise. After 30 min, *t*-butyldimethylsilyl trifluoromethanesulfonate (0.1 mL, 0.44 mmol) was added and the reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with saturated $NH_4Cl$ and extracted with $CH_2Cl_2$ (3×). The combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate under vacuum followed by fractionation of the residue by column chromatography (hexanes–$Et_2O$, 10:1) gave the silyl enol ether **22** as a white solid (20 mg, 32%) and the silyl enol ether **23** as a colorless oil (10 mg, 16%).

Data for **22**: mp 62–63 °C; $[\alpha]_D^{20}=-31.5$ (*c* 1.0, $CHCl_3$); $R_f$ 0.53 (hexanes–$Et_2O$, 3:1); IR (thin film) 3743, 2959, 1368, 1220, 1087, 847 $cm^{-1}$; $^1H$ NMR $\delta$ 0.13 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.07 (s, 3H), 1.26 (s, 3H), 1.43 (s, 3H), 1.71 (m, 2H), 1.99 (m, 2H), 2.11 (dd, $J=7.8$, 14.7 Hz, 1H), 2.48 (ddd, $J=1.8$, 6.3, 17.8 Hz, 1H), 3.84 (m, 4H), 4.03 (t, $J=7.8$ Hz, 1H), 4.75 (d, $J=1.8$ Hz, 1H); $^{13}C$ NMR $\delta$ −4.5, −4.2, 17.9, 25.6, 25.8, 28.3, 29.5, 29.8, 33.1, 35.2, 36.9, 39.5, 40.6, 63.5, 64.4, 79.3, 80.9, 104.1, 107.7, 111.4, 152.5; MS (FAB) *m/z* (relative intensity) 425 ($[M+H]^+$, 100), 367 ($[M-C(CH_3)]^+$, 80), 305 (57); HRMS (FAB) calcd for $C_{23}H_{41}O_5Si$ [M+H] 425.2718, found 425.2726.

**3.1.10. Silyl enol ether 23.** Triethylamine (0.23 mL, 1.61 mmol) and TBDMSOTf (0.19 mL, 0.81 mmol) were added to a stirred solution of ketone **9** (100 mg, 0.32 mmol) in dry $CH_2Cl_2$ (8 mL) under $N_2$ at −78 °C. The reaction was stirred for 30 min −78 °C and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $Et_2O$ (3×) and the combined organic layers were dried ($MgSO_4$), and filtered. The filtrate was concentrated under vacuum and the residue was fractionated by flash column chromatography (hexanes–$Et_2O$, 6:1) to give silyl enol ether **23** as a colorless oil (120 mg, 88%): $[\alpha]_D^{20}=+31.3$ (*c* 0.8, $CHCl_3$); $R_f$ 0.63

(hexanes–$Et_2O$, 3:1); IR (thin film) 2954, 1203, 1086, 841 $cm^{-1}$; $^1H$ NMR $\delta$ 0.109 (s, 3H), 0.123 (s, 3H), 0.90 (s, 9H), 1.24 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.64 (t, $J=12.6$ Hz, 2H), 1.73 (d, $J=2.7$ Hz, 2H), 2.06 (d, $J=16.5$ Hz, 1H), 2.32 (m, 2H), 3.97 (m, 4H), 4.11 (t, $J=3$ Hz, 1H), 4.70 (dd, $J=1.5$, 4.5 Hz, 1H); $^{13}C$ NMR $\delta$ −4.6, −4.3, 17.9, 25.5, 25.6, 27.2, 27.3, 28.3, 36.1, 26.4, 37.4, 39.5, 64.2, 65.1, 76.5, 76.9, 77.4, 79.8, 79.9, 106.6, 107.4, 112.7, 145.6; MS (FAB) *m/z* (relative intensity) 425 ($[M+H]^+$, 25), 365 ($[M+H\text{-}C_2H_4O_2]^+$, 100), 305 (90); HRMS (FAB) calcd for $C_{23}H_{41}O_5Si$ [M+H] 425.2718, found 425.2710. Anal. calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.33; H, 9.67.

**3.1.11. Enone 24.** The experimental procedures for NaOH, $^t$BuOK and $K_2CO_3$ were the same so that only the typical one was described. To a stirred solution of ketone **9** (40 mg, 0.13 mmol) in THF (4 mL) at 0 °C was added $^t$BuOK (22 mg, 0.19 mmol). The reaction was warmed to room temperature slowly and stirred for 1 h. The reaction was quenched with $NH_4Cl$ and the aqueous phase was extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash column chromatography (hexanes–EtOAc, 1:3) allowed the isolation of enone **24** as a white solid (33 mg, 83%): mp 110–111 °C; $[\alpha]_D^{20}=+92.3$ (*c* 0.6, $CHCl_3$); $R_f$ 0.57 ($CHCl_3$M–MeOH, 10:1); IR (thin film) 3743, 3430, 1648, 1208 $cm^{-1}$; $^1H$ NMR $\delta$ 1.264 (s, 3H), 1.350 (s, 3H), 1.40 (d, $J=8.1$ Hz, 2H), 1.470 (s, 3H), 1.475 (s, 3H), 1.63 (m, 1H), 1.89 (s, 1H), 2.10 (dd, $J=1.8$, 16.5 Hz, 1H), 2.19 (dd, $J=3.6$, 15.9 Hz, 1H), 2.37 (m, 2H), 2.72 (dd, $J=6.3$, 16.5 Hz, 1H), 3.89 (m, 4H), 4.07 (t, $J=3$ Hz, 1H), 5.24 (s, 1H); $^{13}C$ NMR $\delta$ 25.3, 26.7, 26.9, 27.08, 33.2, 33.6. 37.5, 39.6, 39.6, 60.5, 69.7, 79.0, 79.7, 100.4, 107.0, 180.4, 198.7; MS (FAB) *m/z* (relative intensity) 310 ($[M]^+$, 20), 309 (100), 252 (17); HRMS (FAB) calcd for $C_{17}H_{27}O_5$ [M+H] 311.1858, found 311.1842. Anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.81; H, 8.62.

**3.1.12. Diene alcohol 25.** $Et_3N$ (0.045 mL, 0.32 mmol) was added to a stirred solution of ketone **9** (50 mg, 0.16 mmol) in dry $CH_2Cl_2$ (4 mL) at room temperature under $N_2$. The reaction mixture was stirred for 15 min and Eschensomer's salt (89 mg, 0.49 mmol) was added to the reaction mixture which was stirred for 96 h. The reaction was quenched with $NH_4Cl$ and extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated under vacuum. The residue was directly subjected to the next step. $NaBH_4$ (30 mg, 0.98 mmol) was added to a stirred solution of the residue and $CeCl_3\cdot 7H_2O$ (120 mg, 0.31 mmol) in MeOH (5 mL) at 0 °C. The reaction mixture was stirred for 30 min and then quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $Et_2O$ (3×). The combined extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was fractionated by flash column chromatography (hexanes–$Et_2O$, 2:1) to furnish diene alcohol **25** as a colorless oil (22 mg, 40%): $[\alpha]_D^{20}=+46.7$ (*c* 0.9, $CHCl_3$); $R_f$ 0.63 (hexanes–$Et_2O$, 1:2); IR (thin film) 3490, 2932, 1080 $cm^{-1}$; $^1H$ NMR $\delta$ 1.07 (s, 3H), 1.31 (s, 3H), 1.38 (s, 3H), 1.51 (s, 3H), 1.69 (dd, $J=3.6$, 15.6 Hz, 1H), 1.88 (bd, $J=15.6$ Hz, 1H), 2.07 (m, 2H), 2.75 (dd, $J=2.1$, 13.8 Hz, 1H), 3.94 (m, 4H), 4.13 (t, $J=3$ Hz, 1H), 4.84 (brs, 2H), 5.06 (d, $J=6$ Hz, 2H), 5.19 (brs, 1H); $^{13}C$ NMR $\delta$ 25.7, 26.1, 27.3, 27.4, 28.8, 39.8, 41.2, 44.2, 64.2, 64.4, 70.4, 79.8, 80.3, 106.3, 106.7, 106.9, 112.7, 146.2, 151.1; MS (FAB) *m/z* (relative intensity) 336 ($[M+H]^+$, 15), 261 ($[M-C_2H_4O_2\text{–}CH_3]^+$, 42), 207 (100); HRMS (FAB) calcd for $C_{19}H_{28}O_5$ [M] calcd 336.1931, found 336.1943.

**3.1.13. 4-Hydroxy ketone 28.** Buffer solution [$4\times10^{-4}$ M aqueous $Na_2(EDTA)$] (2 mL), acetone (0.1 mL, excess), Oxone (215 mg, 0.35 mmol) and $NaHCO_3$ (61 mg, 1 mmol) were sequentially introduced to a solution of silyl enol ether **23** (30 mg, 0.07 mmol) in $CH_3CN$ (10 mL). The solution was stirred at room temperature for 4 h after which the reaction mixture was diluted with water and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. Flash column chromatography (hexanes–$Et_2O$, 2:1) of the residue gave 4-hydroxy ketone **28** as a colorless oil (16 mg, 73%): $[\alpha]_D^{20}=+82.8$ (*c* 0.6, $CHCl_3$); $R_f$ 0.42 (hexanes–$Et_2O$, 1:2); IR (thin film) 3477, 2977, 1718, 1102 $cm^{-1}$; $^1H$ NMR $\delta$ 1.21 (s, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.84 (m, 2H), 2.06 (m, 2H), 2.64 (dd, $J=18.3$, 42.9 Hz, 2H), 3.37 (d, $J=4.2$ Hz, 1H), 3.91 (m, 3H), 4.16 (m, 3H); $^{13}C$ NMR $\delta$ 26.0, 26.6, 27.6, 28.4, 28.9, 39.8, 40.2, 44.6, 45.3, 65.3, 65.6, 77.6, 107.4, 113.1, 209.9; MS (FAB) *m/z* (relative intensity) 327 ($[M+H]^+$, 26), 269 (30), 144 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_6$ [M+H] 327.1805, found 327.1814. Anal. calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.33; H, 7.96.

**3.1.14. 5-Hydroxy ketone 27.** $Al(O\textit{i}Pr)_3$ (10 mg, 0.05 mmol) was added to a stirred solution of 4-hydroxy ketone **28** (33 mg, 0.1 mmol) in dry toluene (2 mL) under $N_2$. The mixture was stirred at room temperature for 1 h, then was quenched with saturated $NH_4Cl$ solution, and extracted with EtOAc (3×). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was fractionated by column chromatography (hexanes–EtOAc, 3:1 to 1:1) to furnish 5-hydroxy ketone **27** as a white solid (15 mg, 79%) and recover starting material **28** (14 mg). A single crystal for X-ray crystallography was obtained from hexanes–$Et_2O$, 10:1.

Data for 5-hydroxy ketone **27**: mp 107–108 °C; $[\alpha]_D^{20}=+82.8$ (*c* 0.6, $CHCl_3$); $R_f$ 0.47 (hexanes–$Et_2O$, 1:2); IR (thin film) 3742, 2975, 1708, 1080 $cm^{-1}$; $^1H$ NMR $\delta$ 1.26 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.51 (s, 3H), 1.68 (dd, $J=3.3$, 15.3 Hz, 1H), 1.94 (m, 3H), 2.34 (dd, $J=6.9$, 12.9 Hz, 1H), 2.87 (dd, $J=2.4$, 13.8 Hz, 1H), 3.49 (d, $J=3.3$ Hz, 1H), 3.93 (m, 5H), 4.38 (ddd, $J=3.3$, 6.9, 12.6 Hz, 1H); $^{13}C$ NMR $\delta$ 25.3, 27.0, 27.2, 27.4, 28.2, 29.7, 36.8, 37.7, 41.9, 49.9, 63.8, 65.7, 71.1, 79.0, 79.2, 107.1, 111.6, 213.2; MS (FAB) *m/z* (relative intensity) 327 ($[M+H]^+$, 11), 311 ($[M+H\text{-}OH]^+$, 10), 269 (8), 115 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_6$ [M+H] 327.1805, found 327.1804. Anal. calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.29; H, 8.03.

**3.1.15. Silyl ether ketone 29.** Imidazol (25 mg, 0.368 mmol), dimethylaminopyridine (1 mg) and *tert*-butyldimethylsilyl chloride (27 mg, 0.184 mmol) were added to a solution of 5-hydroxy ketone **27** (12 mg, 0.037 mmol) in $CH_2Cl_2$ (3 mL) at room temperature under

$N_2$. The solution was stirred for 3 h and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $Et_2O$ (2×) and the combined organic layers were dried over $MgSO_4$. After filtration and concentration of the filtrate under vacuum, the residue was subjected to flash column chromatography (hexanes–$Et_2O$, 4:1) to give silyl ether ketone **29** as a white solid (15 mg, 93%): mp 98–99 °C; $[\alpha]_D^{20}=11.7$ (*c* 0.4, $CHCl_3$); $R_f$ 0.78 (hexanes–$Et_2O$, 3:1); IR (thin film) 2933, 1721, 1116 $cm^{-1}$; $^1H$ NMR $\delta$ 0.02 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.26 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.49 (s, 3H), 1.65 (dd, $J=3.3$, 15.3 Hz, 1H), 1.92 (m, 3H), 2.09 (d, $J=2.1$ Hz, 1H), 2.12 (s, 1H), 2.74 (dd, $J=2.4$, 13.8 Hz, 1H), 4.04 (m, 5H), 4.43 (dd, $J=8.7$, 10.5 Hz, 1H); $^{13}C$ NMR $\delta$ −5.7, −4.7, 25.4, 25.6, 25.7, 27.1, 27.2, 28.2, 37.8, 41.5, 50.8, 63.8, 65.6, 72.7, 79.1, 79.3, 107.1, 112.1, 210.9; MS (FAB) *m/z* (relative intensity) 440 ($[M]^{\cdot+}$, 2), 426 ($[M+H\text{-}CH]_3)^+$, 16), 382 (100), 325 ($[M-C(CH)_3Si]^+$, 32), 263 (34); HRMS (FAB) calcd for $C_{23}H_{41}O_6$ [M+H] 441.2667, found 441.2679.

**3.1.16. β-Hydroxy nitrile 30.** $AlCl_3$ (5 mg, 0.035 mmol) and trimethylsilyl cyanide (9 μL, 0.069 mmol) were added to a solution of silyl ether ketone **29** (10 mg, 0.023 mmol) in dry toluene (2 mL) under $N_2$. The solution was stirred for 5 min at room temperature and quenched with saturated $NaHCO_3$. The solution was extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate concentrated. The oil residue was purified by flash column chromatography (hexanes–$Et_2O$, 5:1) to give β-hydroxy nitrile **30** as a white solid (7 mg, 66%). A single crystal for X-ray crystallography was obtained from hexanes–$Et_2O$, 10:1.

Data for β-hydroxy nitrile **30**: mp 192–193 °C; $[\alpha]_D^{20}=+11.2$ (*c* 1.3, $CHCl_3$); $R_f$ 0.28 (hexanes–$Et_2O$, 3:1); IR (thin film) 3445, 2927, 1078, 779 $cm^{-1}$; $^1H$ NMR $\delta$ 0.14 (s, 3H), 0.19 (s, 3H), 0.93 (s, 9H), 1.33 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.53 (s, 3H), 1.63 (m, 1H), 1.71 (m, 1H), 1.90 (m, 2H), 2.01 (m, 1H), 2.51 (dd, $J=2.1$, 14.1 Hz, 1H), 3.44 (brs, 1H), 3.96 (m, 5H), 4.10 (t, $J=3$ Hz, 1H); $^{13}C$ NMR $\delta$ −4.8, −4.5, 25.4, 25.7, 27.1, 27.2, 28.1, 29.7, 30.6, 33.0, 37.3, 39.1, 41.9, 63.7, 65.4, 71.3, 76.9, 79.2, 80.2, 107.2, 112.6, 120.6; MS (FAB) *m/z* (relative intensity) 452 ($[M-CH_3]^+$, 35), 383 ($[M+H\text{-}SiC(CH_3)_3]^+$, 100); HRMS (EI) calcd for $C_{23}H_{38}NO_6Si$ [M−$CH_3$] 452.2463, found 452.2463.

**3.1.17. α-Hydroxy nitrile 31.** Trimethylsilyl cyanide (56 μL, 0.42 mmol) was added to a solution of α-silyl ether ketone **29** (37 mg, 0.084 mmol) in dry toluene (6 mL) at −35 °C under $N_2$. The solution was stirred for 5 min and $AlCl_3$ (20 mg, 0.151 mmol) was introduced intermittently throughout 2 h. The mixture was stirred for a further 0.5 h and quenched with saturated $NaHCO_3$ and extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (hexanes–$Et_2O$, 6:1) to give the starting ketone **29** (6 mg), α-hydroxy nitrile **31** as a colorless oil (20 mg, 61% based on starting ketone consumed) and β-hydroxy nitrile **30** as a white solid (7 mg, 22%).

Data for α-hydroxy nitrile **31**. $[\alpha]_D^{20}=-5.6$ (*c* 0.25, $CHCl_3$); $R_f$ 0.20 (hexanes–$Et_2O$, 3:1); IR (thin film) 3340, 2930, 2357, 1107 $cm^{-1}$; $^1H$ NMR $\delta$ 0.12 (s, 6H), 0.93 (s, 9H), 1.31 (s, 3H), 1.36 (s, 3H), 1.52 (s, 3H), 1.59 (s, 3H), 1.65 (d. $J=3.3$ Hz, 1H), 1.83 (dd, $J=4.2$, 13.5 Hz, 1H), 1.96 (m, 2H), 2.09 (m, 1H), 2.66 (dd, $J=2.1$, 13.5 Hz, 1H), 3.24 (s, 1H), 3.76 (dd, $J=4.2$, 12.0 Hz, 1H), 3.96 (m, 4H), 4.09 (t, $J=3$ Hz, 1H); $^{13}C$ NMR $\delta$ −4.7, −4.4, 18.5, 25.9, 26.3, 27.8, 28.2, 31.5, 32.7, 36.4, 41.5, 43.6, 64.3, 66.1, 72.1, 74.6, 79.6, 80.8, 107.7, 113.1, 122.6; MS (FAB) *m/z* (relative intensity) 468 ($[M+H]^+$, <1), 442 ($[M+H\text{-}CN]^+$, 20), 382 ($[M-SiC(CH_3)_3]^+$, 18), 229 (100); HRMS (FAB) calcd for $C_{24}H_{42}NO_6Si$ [M+H] 468.2776, found 468.2792.

**3.1.18. TMS nitrile 32.** Trimethylsilyl cyanide (14 μL, 0.1 mmol) was added to a solution of α-silyl ether ketone **29** (9 mg, 0.02 mmol) in dry toluene (3 mL) under $N_2$ at −35 °C. The solution was stirred for 5 min and $AlCl_3$ (11 mg, 0.08 mmol) was added intermittently throughout 20 min. The mixture was led to stir for further 2 h at −35 °C and then quenched with saturated $NaHCO_3$. The mixture was extracted with $Et_2O$ (3×). The combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was separated by flash column chromatography (hexanes–$Et_2O$, 9:1 to 5:1) to provide TMS nitrile **32** as a white solid (5 mg, 47%), α-hydroxy nitrile **31** (1 mg, 11%) and β-hydroxy nitrile **30** (2 mg, 22%).

Data for TMS nitrile **32**: mp 136–137 °C; $[\alpha]_D^{20}=+6.4$ (*c* 0.2, $CHCl_3$); $R_f$ 0.44 (hexanes–$Et_2O$, 2:1); IR (thin film) 3734, 1517, 1127 $cm^{-1}$; $^1H$ NMR $\delta$ 0.064 (s, 3H), 0.081 (s, 3H), 0.29 (s, 6H), 0.91 (s, 9H), 1.26 (s, 3H), 1.38 (s, 3H), 1.50 (s, 3H), 1.59 (s, 3H), 1.76 (dd, $J=4.2$, 13.8 Hz, 1H), 1.90 (m, 2H), 2.09 (m, 1H), 2.51 (dd, $J=2.1$, 13.5 Hz, 1H), 3.68 (dd, $J=3.9$, 12.0 Hz, 1H), 3.93 (m, 4H), 4.10 (t, $J=3$ Hz, 1H); $^{13}C$ NMR $\delta$ −5.07, −4.13, 1.47, 25.2, 25.8, 27.2, 27.6, 27.7, 31.2, 33.0, 35.9, 41.0, 45.6, 63.7, 65.3, 71.9, 75.2, 78.9, 80.3, 107.0, 112.4, 121.8; MS (FAB) *m/z* (relative intensity) 540 ($[M+H]^+$, 11), 514 ($[M+H\text{-}CN]^+$, 25), 482 (18), 319 (100); HRMS (FAB) calcd for $C_{27}H_{50}NO_6Si_2$ [M+H] 540.3171, found 540.3150. Anal. calcd for $C_{27}H_{49}NO_6Si_2$: C, 60.07; H, 9.15; N, 2.59. Found: C, 60.07; H, 8.96; N, 2.45.

**3.1.19. Diol 33.** $Et_3N$ (0.38 mL, 2.76 mmol), DMAP (3 mg) and TMS chloride (0.17 mL, 1.38 mmol) were added to a solution of 5-hydroxy ketone **27** (180 mg, 0.55 mmol) in $CH_2Cl_2$ (8 mL). The mixture was stirred for 20 min at room temperature under $N_2$. The reaction mixture was quenched with saturated $NH_4Cl$ and filtered through a short pad of silica gel which was eluted with $Et_2O$. The filtrate was removed under vacuum and the residue was put to the next step.

To a vigorously stirred suspension of magnesium powder (200 mg, 8.3 mmol) in dry THF (6 mL) under $N_2$ at −78 °C, was added dropwise vinyl bromide (2 mL, excess) by means of condensation with a cold finger containing dry ice and acetone. The suspension was stirred at room temperature and 1,2-dibromomethane (5 μL) was added as an initiator. When the solution started to boil, it was allowed to stir for further 30 min. The crude product from the previous step was dissolved in dry THF (4 mL) and the

solution was injected into the suspension at −78 °C. The reaction was complete within 10 min and saturated $NH_4Cl$ was added. The resulting mixture was extracted with $Et_2O$ (3×) and the combined organic layers were dried, filtered and the filtrate was concentrated under reduced pressure. The residue was redissolved in THF (4 mL) and 1 M HCl (1 mL) was added to the mixture. The reaction mixture was stirred for 30 min at room temperature and saturated $NaHCO_3$ was added for neutralization. The aqueous phase was extracted with EtOAc (3×). The combined extracts were dried ($MgSO_4$), filtered and the filtrate concentrated. Flash chromatography of the residue (hexanes–$Et_2O$, 2:1) provided diol **33** as a white solid (175 mg, 90%). A single crystal for X-ray crystallography was obtained from hexanes–$Et_2O$, 10:1.

Data for diol **33**: mp 150–151 °C; $[\alpha]_D^{20}=+24.1$ (*c* 0.3, $CHCl_3$); $R_f$ 0.22 (hexanes–$Et_2O$, 1:2); IR (thin film) 3442, 2982, 1372, 1075 $cm^{-1}$; $^1H$ NMR $\delta$ 1.36 (s, 9H), 1.46 (s, 3H), 1.96 (m, 6H), 2.28 (m, 2H), 2.61 (m, 1H), 4.91 (m, 5H), 4.12 (t, $J=3.0$ Hz, 1H), 5.30 (d, $J=10.8$ Hz, 1H), 5.51 (d, $J=16.5$ Hz, 1H), 6.47 (m, 1H); $^{13}C$ NMR $\delta$ 25.5, 27.1, 29.1, 30.9, 34.0, 34.5, 40.7, 44.9, 63.7, 65.1, 71.7, 75.2, 79.2, 80.6, 106.1, 113.2, 116.0, 143.1; HRMS (FAB) calcd for $C_{19}H_{31}O_6$ [M+H] 355.2115, found 355.2112. Anal. calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.68; H, 8.67.

**3.1.20. Benzyl ether 34.** A solution of the diol **33** (15 mg, 0.041 mol) in dry THF (2mL) was slowly added to a stirring suspension of 60% NaH (17 mg, 0.042 mmol) in dry THF (2 mL) under $N_2$ at 0 °C. The mixture was subsequently stirred at room temperature for 15 min and then 0 °C for 1 min. BnBr (6.2 μL, 0.05 mmol) was added to the mixture and the resulting mixture was stirred at 50 °C for 12 h. Saturated $NH_4Cl$ was added and the mixture was extracted with $Et_2O$ (3×), dried ($MgSO_4$), filtered and the filtrate was concentrated. The crude product was purified by column chromatography (hexanes–$Et_2O$, 6:1) to give benzyl ether **34** as a colorless oil (16 mg, 86%): $[\alpha]_D^{20}=+1.8$ (*c* 0.35, $CHCl_3$); $R_f$ 0.58 (hexanes–$Et_2O$, 1:2); IR (thin film) 3595, 2982, 1075 $cm^{-1}$; $^1H$ NMR $\delta$ 1.33 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.59 (dd, $J=3.3$, 15 Hz, 1H), 1.93 (m, 5H), 2.24 (dd, $J=2.4$, 13.8 Hz, 1H), 3.05 (brs, 1H), 3.59 (dd, $J=5.7$, 8.4 Hz, 1H), 3.94 (m, 4H), 4.11 (t, $J=3$ Hz, 1H), 5.19 (d, $J=10.8$ Hz, 1H), 5.50 (dd, $J=1.2$, 17.4 Hz, 1H), 6.42 (dd, $J=11.1$, 17.4 Hz, 1H); $^{13}C$ NMR $\delta$ 25.6, 27.2, 27.8, 28.6, 30.8, 32.9, 33.9, 40.1, 44.9, 63.7, 65.0, 72.2, 74.2, 79.4, 80.3, 80.7, 106.8, 113.5, 114.9, 127.6, 128.3, 138.7, 144.0; MS (EI) *m/z* (relative intensity) 444 ($[M]^+$, 1), 429 ($[M-CH_3]^+$, 13), 353 ($[M-OBn]^+$, 8), 309 ($[M-OBn\text{-}OH\text{-}vinyl]^+$, 81), 263 (100); HRMS (EI) calcd for $C_{26}H_{36}O_6$ [M] 444.2506, found 444.2494.

**3.1.21. Silyl ether 35.** Imidazol (46 mg, 0.68 mmol), DMAP (2 mg) and TBDMSCl (51 mg, 0.339 mmol) were added to a mixture of diol **33** (40 mg, 0.113 mmol) in $CH_2Cl_2$ (6 mL) at room temperature under $N_2$. The mixture was stirred for 96 h and quenched with saturated $NH_4Cl$, extracted with $Et_2O$ (3×). The organic layers were combined, dried ($MgSO_4$) and filtered. Removal of the solvent in vacuo gave the residue which was fractionated by column chromatography (hexanes–$Et_2O$, 7:1) to give silyl ether **35** as a white solid (48 mg, 90%): mp 84–85 °C; $[\alpha]_D^{20}=+2.01$ (*c* 0.85, $CHCl_3$); $R_f$ 0.45 (hexanes–$Et_2O$, 2:1); IR (thin film) 3460, 2953, 1108 $cm^{-1}$; $^1H$ NMR $\delta$ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.33 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 1.64 (d, $J=3.6$ Hz, 1H) 1.95 (m, 4H), 2.22 (dd, $J=2.1$, 13.5 Hz, 1H), 3.31 (brs, 1H), 3.88 (m, 5H), 4.12 (t, $J=2.7$ Hz, 1H), 5.14 (d, $J=10.8$ Hz, 1H), 5.43 (d, $J=16.2$ Hz, 1H), 6.23 (dd, $J=11.1$, 17.1 Hz, 1H); $^{13}C$ NMR $\delta$ −4.8, −4.7, 25.6, 25.7, 17.1, 27.9, 28.5, 30.6, 34.0, 37.3, 39.6, 43.4, 63.9, 64.9, 73.6, 74.4, 79.4, 80.1, 106.8, 113.7, 114.4, 144.1; MS (FAB) *m/z* (relative intensity) 491 ($[M+Na]^+$, 18), 451 ($[M-OH]^+$, 65), 229 (100); HRMS (FAB) calcd for $C_{25}H_{44}O_6SiNa$ [M+Na] 491.2799, found 491.2762. Anal. calcd for $C_{25}H_{44}O_6Si$: C, 64.06; H, 9.46. Found: C, 64.18; H, 9.49.

**3.1.22. TBS aldehyde 36.** NMO (50 mg, 0.41 mmol) and $OsO_4$ (2 mg) were introduced into a stirring mixture of silyl ether **35** (48 mg, 0.01 mmol) in acetone–$H_2O$ (4:1) (5 mL) at room temperature. The reaction mixture was stirred for 100 h and quenched with saturated aqueous $Na_2S_2O_3$ and stirred for a further 24 h. The resulting mixture was extracted with $Et_2O$ (3×), dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The crude product was dissolved in $CH_2Cl_2$–$H_2O$ (8:1) (4 mL) and sodium metaperiodate (157 mg, 0.72 mmol) was added. The mixture was stirred at room temperature for 48 h followed by quenching with saturated $Na_2S_2O_3$ and was stirred for a further 2 h. The aqueous phase was extracted with $Et_2O$ (3×), dried ($MgSO_4$) and filtered. The organic solvents were evaporated from the filtrate under vacuum and the residue was fractionated by flash column chromatography (hexanes–$Et_2O$, 3:1) to furnish TBS aldehyde **36** as a white solid (38 mg, 78%): mp 108–109 °C; $[\alpha]_D^{20}=+2.8$ (*c* 0.3, $CHCl_3$); $R_f$ 0.75 (hexanes–$Et_2O$, 1:2); IR (thin film) 3437, 2933, 1721, 1094 $cm^{-1}$; $^1H$ NMR $\delta$ 0.02 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.32 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.99 (m, 4H), 2.10 (dd, $J=11.7$, 13.8 Hz, 1H), 3.47 (s, 1H), 3.99 (m, 5H), 4.09 (t, $J=3$ Hz, 1H), 10.09 (s, 1H); $^{13}C$ NMR $\delta$ −4.9, −4.8, 17.9, 25.5, 25.6, 25.8, 27.1, 27.3, 28.2, 29.1, 30.7, 34.0, 35.9, 37.9, 40.2, 42.7, 63.8, 65.4, 65.6, 71.9, 79.1, 79.6, 80.2, 106.9, 112.6, 203.7; MS (EI) *m/z* (relative intensity) 470 ($[M]^+$, 4), 441 ($[M-CHO]^+$, 35), 425 ($[M-3CH_3]^+$, 98), 384 (100); HRMS (EI) calcd for $C_{24}H_{42}O_7Si$ [M] 470.2694, found 470.2695.

**3.1.23. Acetate aldehyde 37.** Acetic anhydride (0.1 mL, excess) and DMAP (1 mg) were added to a stirring mixture of tertiary alcohol **36** (10 mg, 0.021 mmol) in pyridine (2 mL) under $N_2$. It was heated under reflux for 100 h and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $Et_2O$ (3×) and the combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated under vacuum and the crude residue was subjected to column chromatography (hexanes–EtOAc, 6:1) to give starting material **36** (2 mg) and acetate aldehyde **37** as a colorless oil (3 mg, 35% based on consumed starting material): $[\alpha]_D^{20}=+8.9$ (*c* 0.9, $CHCl_3$); $R_f$ 0.57 (hexanes–$Et_2O$ 2:1); IR (thin film) 2953, 1765, 1200 $cm^{-1}$; $^1H$ NMR $\delta$ 0.07 (s, 3H), 0.12 (s, 3H), 0.87 (s, 9H), 1.29 (s, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 1.68 (m, 2H), 1.98 (m, 2H), 2.14 (s, 3H), 2.99 (dd, $J=1.8$, 13.5 Hz, 1H), 3.94 (m, 4H), 4.09 (t, $J=3$ Hz, 1H), 4.21 (dd, $J=4.5$, 12.3 Hz, 1H), 9.67 (s, 1H); $^{13}C$ NMR $\delta$ −5.4, −5.0, 25.4, 27.1, 27.3, 29.1,

29.2, 29.7, 31.2, 35.4, 36.9, 40.9, 43.5, 63.8, 65.5, 69.4, 78.8, 80.1, 90.2, 106.9, 112.2, 163.5, 192.6; MS (FAB) *m/z* (relative intensity) 513 ($[M+H]^+$, 2), 441 ($[M+H-C(CH_3)_3-CH_3]^+$, 24), 425 (30), 399 (26), 383 (100); HRMS (FAB) calcd for $C_{26}H_{45}O_8Si$ [M+H] 513.2878, found 513.2850.

**3.1.24. Dibenzyl ether 38.** A solution of the diol **33** (93 mg, 0.263 mmol) in dry THF (3 mL) was slowly added to a stirring suspension of 60% NaH (44 mg, 1.05 mmol) in dry THF (4 mL) under $N_2$ which had been cooled for 5 min at 0 °C. The mixture was kept to stir at room temperature for 15 min and then 0 °C for 1 min. BnBr (0.1 mL, 0.79 mmol) was added to the mixture and the resulting solution was heated under reflux for 12 h. The reaction was quenched with saturated $NH_4Cl$ and extracted with $Et_2O$ (3×). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated under vacuum. The residue was subjected to flash chromatography (hexanes–$Et_2O$, 5:1) to furnish dibenzyl ether **38** as a white solid (121 mg, 86%): mp 91–92 °C; $[\alpha]_D^{20}=+6.5$ (*c* 0.9, $CHCl_3$); $R_f$ 0.31 (hexanes–$Et_2O$, 4:1); IR (thin film) 3741, 2981, 1457, 1076 $cm^{-1}$; $^1H$ NMR $\delta$ 1.32 (s, 6H), 1.40 (s, 3H), 1.57 (s, 3H), 1.80 (m, 3H), 1.99 (dd, $J=2.4$, 12.6 Hz, 1H), 2.72 (d, $J=11.7$ Hz, 1H), 3.85 (m, 5H), 4.12 (t, $J=3$ Hz, 1H), 4.35 (dd, $J=11.4$, 33.3 Hz, 2H), 4.72 (dd, $J=11.7$, 82.8 Hz, 2H), 5.62 (m, 2H), 6.31 (dd, $J=11.4$, 18.3 Hz, 1H), 7.27 (m, 10H); $^{13}C$ NMR $\delta$ 25.4, 27.3, 29.9, 31.4, 33.4, 33.9, 39.1, 41.3, 63.3, 63.5, 65.2, 73.7, 79.3, 79.5, 80.7, 81.0, 106.7, 112.9, 120.3, 126.7, 127.1, 127.4, 127.6, 128.1, 128.2, 135.9, 139.5, 139.9; MS (FAB) *m/z* (relative intensity) 535 ($[M+H]^+$, 7), 427 ($[M-OBn]^+$, 78), 369 (36), 307 (100); HRMS (FAB) calcd for $C_{33}H_{43}O_6$ [M+H] 535.3054, found 535.3055. Anal. calcd for $C_{33}H_{42}O_6$: C, 74.13; H, 7.92. Found: C, 74.22; H, 7.96.

**3.1.25. Dibenzyl aldehyde 39.** NMO (53 mg, 0.45 mmol) and $OsO_4$ (2 mg) were introduced into a stirring solution of dibenzyl ether **38** (120 mg, 0.23 mmol) in acetone–$H_2O$ (4:1) (4 mL) at room temperature. The reaction was stirred for 96 h followed by quenched with saturated aqueous $Na_2S_2O_3$. The mixture was stirred for a further 24 h and extracted with $Et_2O$ (3×). The combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes–$Et_2O$, 5:1 then 1:1) to give the starting dibenzyl ether **38** (20 mg) and a mixture of diasteromeric diols as a colorless oil (90 mg, 88%). The diols were dissolved in acetone–$H_2O$ (5:1, 4 mL) and sodium metaperiodate (105 mg, 0.48 mmol) was added. The mixture was stirred at room temperature for 48 h and quenched with saturated $Na_2S_2O_3$ and stirred for a further 2 h. The aqueous phase was extracted with $Et_2O$ (3×). The combined extracts were dried ($MgSO_4$) and filtered. The filtrate was concentrated under vacuum and the residue was fractionated by column chromatography (hexanes–$Et_2O$, 3:1) to provide dibenzyl aldehyde **39** as a colorless oil (76 mg, 89%): $[\alpha]_D^{20}=+11.4$ (*c* 0.4, $CHCl_3$); $R_f$ 0.69 (hexanes–$Et_2O$, 1:2); IR (thin film) 2982, 1719, 1079 $cm^{-1}$; $^1H$ NMR $\delta$ 1.14 (s, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 1.63 (s, 3H), 1.65 (m, 2H), 1.82 (t, $J=12.9$ Hz, 1H), 1.97 (m, 2H), 2.95 (dd, $J=6.6$, 8.7 Hz, 1H), 3.88 (m, 5H), 4.12 (t, $J=3$ Hz, 1H), 4.39 (dd, $J=11.7$, 91.5 Hz, 2H), 4.79 (dd, $J=11.7$, 84.3 Hz, 2H), 7.29 (m, 10H), 10.16 (s, 1H); $^{13}C$ NMR $\delta$ 25.6, 26.9, 27.2, 28.9, 30.9, 32.7, 33.9, 34.6, 40.7, 63.4, 65.1, 65.3, 74.3, 79.5, 80.7, 82.2, 107.3, 112.2, 127.3, 127.4, 127.6, 127.7, 128.3, 138.5, 138.9, 200.4; MS (FAB) *m/z* (relative intensity) 537 ($[M+H]^+$, 24), 391 (99), 373 (41), 307 ($[M-2\ OBn\text{-}CH_3]^+$, 100); HRMS (FAB) calcd for $C_{32}H_{41}O_7$ [M+H] 537.2847, found 537.2862.

**3.1.26. Aldehyde diol 40.** 10% Palladium-on-charcoal (10 mg) was suspended in EtOH (2 mL). The mixture was degassed and refilled with hydrogen three times and then stirred for 10 min. A solution of the dibenzyl aldehyde **39** (32 mg, 0.059 mmol) in EtOH (2 mL) was added and the degas process was repeated and the mixture was stirred for 30 min under $H_2$ atmosphere (ballon). The resulting mixture was filtered and the filtrate was concentrated under vacuum. The residue was passed through a short pad of silica gel (hexanes–$Et_2O$, 1:1) to give aldehyde diol **40** as a white solid (17 mg, 78%): mp 188–189 °C; $[\alpha]_D^{20}=9.8$ (*c* 0.3, $CHCl_3$); $R_f$ 0.29 (hexanes–$Et_2O$, 1:2); IR (thin film) 3442, 2979, 1709, 1070 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) $\delta$ 1.13 (s, 3H), 1.21 (s, 3H), 1.24 (s, 3H), 1.33 (s, 3H), 1.47 (m, 3H), 1.89 (m, 3H), 2.06 (m, 1H), 2.16 (dd, $J=2.1$, 13.2 Hz), 3.85 (m, 5H), 4.03 (t, $J=3$ Hz, 1H), 9.85 (d, $J=0.9$ Hz, 1H); $^{13}C$ NMR $\delta$ 23.7, 25.4, 25.7, 26.8, 29.9, 32.2, 33.5, 39.8, 40.6, 62.8, 64.5, 69.4, 72.2, 78.6, 79.7, 106.1, 111.7, 202.7; MS (EI) *m/z* (relative intensity) 341 ($[M-CH_3]^+$, 5), 427 ($[M-CHO]^+$, 7), 205 (13), 122 (89), 105 (100); HRMS (EI) calcd for $C_{17}H_{25}O_7$ [M−$CH_3$] 341.1595, found 341.1599. Anal. calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.39; H, 7.86.

**3.1.27. Triol 26.** To a stirred solution of the aldehyde diol **40** (16 mg, 0.045 mmol) in MeOH (3 mL) at 0 °C was added $NaBH_4$ (5 mg, 0.13 mmol). The reaction mixture was stirred for 30 min and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate followed by column chromatography (hexanes–EtOAc, 1:2) gave the triol **26** as a colorless oil (13 mg, 80%): $[\alpha]_D^{20}=+14.5$ (c 0.25, $CHCl_3$); $R_f$ 0.33 ($CHCl_3$–MeOH, 15:1); IR (thin film) 3418, 2976, 1071 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) $\delta$ 1.29 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.47 (s, 3H), 1.54 (m, 2H), 1.80 (m, 2H), 1.92 (dd, $J=2.1$, 14.1 Hz, 1H), 1.74 (m, 2H), 2.02 (bd, $J=12.9$ Hz, 1H), 2.38 (dd, $J=1.8$, 13.2 Hz, 1H), 3.62 (d, $J=11.7$ Hz, 1H), 3.94 (m, 6H), 4.09 (t, $J=3$ Hz, 1H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 24.9, 26.4, 26.9, 28.1, 29.8, 31.8, 33.9, 35.2, 39.8, 40.8, 63.7, 65.3, 65.9, 72.2, 74.9, 79.6, 81.1, 107.2, 113.2; MS (EI) *m/z* (relative intensity) 343 ($[M-CH_3]^+$, 2); HRMS (EI) calcd for $C_{17}H_{27}O_7$ [M−$CH_3$] 343.1751, found 343.1756.

**3.1.28. Epoxide 42.** DMAP (13 mg, 0.11 mmol) was added to a stirred solution of triol **41** (13 mg, 0.036 mmol) in dry $CH_2Cl_2$ (3 mL) under $N_2$ at 0 °C. The mixture was stirred for 15 min and MsCl (3 μL, mmol) was introduced and stirred at 0 °C for 12 h. The resulting solution was quenched with saturated $NH_4Cl$ and the aqueous phase was extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated. The crude product was dissolved in THF (1 mL) and the resulting solution was added to a stirred suspension of

60% NaH (10 mg, 0.176 mmol) in THF (2 mL) under $N_2$. The mixture was heated under reflux for 5 h and saturated $NH_4Cl$ was added which was followed by extraction with $Et_2O$ (3×). The organic layers were combined, dried ($MgSO_4$), filtered and the filtrate was concentrated. Flash column chromatography of the residual oil (hexanes–$Et_2O$, 1:1 then $CHCl_3$–MeOH, 10:1) gave epoxide **42** as a colorless oil (7 mg, 92%) and recovered some unreacted triol **26** (5 mg).

Data for epoxide **42**. $[\alpha]_D^{20}=-8.3$ (*c* 0.3, $CHCl_3$); $R_f$ 0.42 (hexanes–$Et_2O$ 1:2); IR (thin film) 3448, 2976, 1372, 1077 $cm^{-1}$; $^1H$ NMR $\delta$ 1.32 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.79 (m, 4H), 1.97 (dd, $J=3.3$, 15.6 Hz, 1H), 2.07 (dd, $J=4.8$, 12.9 Hz, 1H), 2.54 (d, $J=5.1$ Hz, 1H), 3.23 (d, $J=5.1$ Hz, 1H), 3.93 (m, 3H), 4.07 (m, 3H); $^{13}C$ NMR $\delta$ 25.6, 26.7, 27.3, 27.4, 29.5, 34.9, 35.9, 41.5, 41.7, 52.1, 61.7, 63.6, 63.9, 65.4, 79.5, 79.9, 106.7, 112.8; MS (FAB) *m/z* (relative intensity) 341 ($[M+H]^+$, 75), 283 ($[M-C(CH_3)_2-OH+H]^+$, 100), 265 (45); HRMS (FAB) calcd for $C_{18}H_{29}O_6$ [M+H] 341.1958, found 341.1953.

**3.1.29. Diol 44.** To a stirred solution of the silyl ether **36** (20 mg, 0.043 mmol) in MeOH (2 mL) at 0 °C was added with $NaBH_4$ (4 mg, 0.11 mmol) slowly. The reaction mixture was stirred for 30 min and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate in vacuo followed by flash column chromatography (hexanes–$Et_2O$, 4:1) gave diol **44** as a colorless oil (16 mg, 79%): $[\alpha]_D^{20}=+4.7$ (*c* 1.0, $CHCl_3$); $R_f$ 0.42 (hexanes–$Et_2O$, 1:1); IR (thin film) 3407, 2954, 1455, 1074 $cm^{-1}$; $^1H$ NMR $\delta$ 0.092 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.31 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.56 (dd, $J=3.6$, 15 Hz, 1H), 1.95 (m, 4H), 2.09 (dd, $J=2.1$, 11.4 Hz, 1H), 2.97 (dd, $J=2.7$, 9.6 Hz, 1H), 2.29 (t, $J=$ 10.5 Hz, 1H), 3.95 (m, 5H), 4.09 (t, $J=3$ Hz, 1H), 4.31 (dd, $J=2.7$, 11.4 Hz, 1H); $^{13}C$ NMR $\delta$ −4.9, −4.8, 17.9, 25.5, 25.7, 27.1, 27.5, 28.7, 31.1, 33.8, 36.5, 40.2, 42.8, 63.8, 65.2, 68.8, 72.9, 75.3, 79.1, 80.3, 106.8, 113.2; MS (FAB) *m/z* (relative intensity) 473 ($[M+H]^+$, 50), 455 ($[M+H-H_2O]^+$, 45), 423 ($[M-OTBDMS\ -H_2O]^+$, 100), 229 (97); HRMS (FAB) calcd for $C_{24}H_{45}O_7Si$ [M+H] 473.2929, found 473.2920. Anal. calcd for $C_{24}H_{44}O_7Si$: C, 60.98; H, 9.38. Found: C, 61.20; H, 9.50.

**3.1.30. Acetate 47.** Trimethylorthoacetate (0.25 mL, 1.8 mmol) and *p*-TsOH (12 mg, 0.06 mmol) were added to a solution of diol **44** (30 mg, 0.06 mmol) in dry $CH_2Cl_2$ (4 mL) at room temperature under $N_2$. The mixture was allowed to stir for 5 h and made neutral by adding a few drops of $Et_3N$ which was followed by concentration of the volatiles under vacuum. The residue was redissolved in $CH_2Cl_2$ (4 mL) and $SiO_2$ (200 mg) was added. The mixture was stirred at room temperature for 2 h and the $SiO_2$ was filtered. The filtrate was concentrated under vacuum and the crude product was subjected to flash column chromatography (hexanes–EtOAc, 6:1) to provide the acetate **47** as a white solid (25 mg, 81%): mp 114–115 °C; $[\alpha]_D^{20}=-1.6$ (*c* 1.0, $CHCl_3$); $R_f$ 0.31 (hexanes–EtOAc, 4:1); IR (thin film) 3482, 2952, 1739, 1248, 1082 $cm^{-1}$; $^1H$ NMR $\delta$ 0.065 (s, 3H), 0.067 (s, 3H), 0.88 (s, 9H), 1.33 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.50 (s, 3H), 1.83 (m, 3H), 1.98 (dd, $J=6$, 14.1 Hz, 1H), 2.08 (s, 3H), 2.29 (dd, $J=2.1$, 13.5 Hz, 1H), 3.18 (brs, 1H), 3.92 (m, 5H), 4.12 (t, $J=3$ Hz, 1H), 4.31 (dd, $J=12$, 13.8 Hz, 2H); $^{13}C$ NMR $\delta$ −5.0, −4.9, 21.1, 25.5, 25.7, 27.0, 27.8, 28.2, 31.0, 34.5, 36.7, 38.8, 39.6, 63.9, 64.9, 67.9, 71.3, 73.7, 79.1, 80.1, 106.8, 113.4, 171.3; MS (FAB) *m/z* (relative intensity) 515 ($[M+H]^+$, 5), 437 ($[M-OAc\text{-}H_2O]^+$, 45), 397 (40), 229 (100); HRMS (FAB) calcd for $C_{26}H_{47}O_8Si$ [M+H] 515.3035, found 515.3030. Anal. calcd for $C_{26}H_{46}O_8Si$: C, 60.67; H, 9.01. Found: C, 60.73; H, 9.03.

**3.1.31. Epoxide 48.** A molar solution TBAF in THF (0.04 mL, 0.04 mmol) was added to a stirred solution of the acetate **47** (16 mg, 0.031 mmol) in THF (2 mL) under $N_2$. After 30 min, the reaction mixture was filtered through a pad of silica gel and eluted with $Et_2O$. Concentration of the filtrate gave a crude oil which was put to the next step. $Et_3N$ (0.1 mL, 0.77 mmol) was added to a stirred solution of the crude oil in $CH_2Cl_2$ (3 mL) at 0 °C. MsCl (10 μL, 0.12 mmol) was then added to the mixture which was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated $NH_4Cl$ and extracted with $Et_2O$ (3×). The organic layers were combined, dried ($MgSO_4$), and filtered. A residue was obtained upon concentration of the filtrate under reduced pressure. The residue was then dissolved in toluene (2.5 mL) and DBU (12 μL, 0.08 mmol) was introduced into the solution that was heated under reflux for 30 min. The reaction mixture was quenched with saturated $NH_4Cl$ and extracted with $Et_2O$ (3×). The combined extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was dissolved in MeOH (2 mL) and $K_2CO_3$ (6 mg, 0.043 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and saturated $NH_4Cl$ was added for neutralization. The mixture was extracted with $CH_2Cl_2$ (3×), dried ($MgSO_4$), filtered and the filtrate was concentrated. Purification of the residue by column chromatography (hexanes–EtOAc, 1:2) gave epoxide **48** as a white solid (6 mg, 57%): mp 159–160 °C; $[\alpha]_D^{20}=-2.3$ (*c* 0.5, $CHCl_3$); $R_f$ 0.28 (hexanes–$Et_2O$ 1:2); IR (thin film) 3460, 2923, 1072 $cm^{-1}$; $^1H$ NMR $\delta$ 1.25 (s, 3H), 1.31 (s, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 1.54 (dd, $J=2.1$, 14.4 Hz, 1H), 1.69 (m, 3H), 2.02 (dd, $J=2.1$, 15.6 Hz, 1H), 2.16 (m, 2H), 3.39 (s, 1H), 3.62 (dd, $J=12.3$, 19.2 Hz, 2H), 3.81 (m, 2H), 4.03 (m, 2H), 4.11 (t, $J=3$ Hz, 1H); $^{13}C$ NMR $\delta$ 25.3, 26.5, 27.2, 27.8, 29.6, 35.6, 36.1, 36.9, 55.5, 59.5, 62.2, 63.7, 65.6, 79.6, 79.8, 106.7, 112.2; MS (EI) *m/z* (relative intensity) 340 ($[M]^+$, 11), 325 ($[M-CH_3]^+$, 18), 309 (16), 98 (100); HRMS (EI) calcd for $C_{18}H_{28}O_6$ $[M]^+$ 340.1880, found 340.1877. Anal. calcd for $C_{18}H_{28}O_6Si$: C, 63.51; H, 8.29. Found: C, 63.30; H, 8.25.

Another approach towards the epoxide **48** started with a dihydroxylation-glycol cleavage-reduction sequence from alkene epoxide **50**. NMO (23 mg, 0.19 mmol) and $OsO_4$ (2 mg) were introduced into a stirring solution of alkene epoxide **50** (22 mg, 0.065 mmol) in acetone–$H_2O$ (4:1) (3 mL) at room temperature. After 48 h, the mixture was quenched with saturated $Na_2S_2O_3$ and stirred for a further 24 h. The resulting solution was extracted with $Et_2O$ (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate in vacuo provided the residue which was dissolved in $CH_2Cl_2$–

$H_2O$ (7:1) (3 mL) and sodium metaperiodate (25 mg, 0.12 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturated aqueous $Na_2S_2O_3$ and stirred for a further 2 h. The resulting mixture was extracted with $Et_2O$ (3×), dried ($MgSO_4$) and filtered. The filtrate was concentrated under vaccum and a crude oil was obtained. Methanol (3 mL) was added to the crude which was stirred for 15 min at 0 °C. $NaBH_4$ (4 mg, 0.1 mmol) was slowly added to the reaction mixture which was subsequently stirred for 30 min. Saturated $NH_4Cl$ was added to quench the reaction and the resulting mixture was extracted with $CH_2Cl_2$ (3×), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash column chromatography as mentioned above gave the epoxide **48** (16 mg, 72%).

**3.1.32. Mesylate 49.** $Et_3N$ (0.1 mL, 0.77 mmol) was added to a stirred solution of diol **33** (40 mg, 0.11 mmol) in $CH_2Cl_2$ (4 mL) at 0 °C. It was kept stirring for 15 min and MsCl (9 μL, 0.12 mmol) was added to the mixture which was stirred for 3 h. The reaction mixture was quenched with saturated $NH_4Cl$ and extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$) and filtered. Evaporation of the solvent in vacuo followed by purification of the residue by column chromatography (hexanes–$Et_2O$, 2:1) gave mesylate **49** as a colorless oil (34 mg, 85% based on starting material **33** consumed) and recovered the starting material (6 mg).

Data for mesylate **49**. $[\alpha]_D^{20}=+2.3$ (*c* 1.0, $CHCl_3$); $R_f$ 0.32 (hexanes–$Et_2O$ 1:2); IR (thin film) 3505, 2987, 1349, 1172 $cm^{-1}$; $^1H$ NMR $\delta$ 1.32 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.59 (m, 2H), 1.91 (dd, $J=2.4$, 15 Hz, 1H), 2.02 (dd, $J=1.8$, 14.1 Hz, 1H), 2.19 (m, 2H), 2.31 (dd, $J=1.8$, 13.5 Hz, 1H), 3.04 (s, 3H), 3.89 (m, 2H), 4.01 (m, 2H), 4.10 (t, $J=3$ Hz, 1H), 4.67 (dd, $J=6.0$, 9.9 Hz, 1H), 5.28 (d, $J=10.8$ Hz, 1H), 5.53 (dd, $J=17.4$ Hz, 1H), 6.42 (dd, $J=10.8$, 17.4 Hz, 1H); $^{13}C$ NMR $\delta$ 25.4, 27.1, 27.5, 28.6, 30.8, 32.7, 34.2, 38.1, 40.3, 46.0, 63.8, 65.2, 73.3, 79.1, 80.4, 83.2, 106.9, 112.5, 116.3, 142.3; MS (EI) *m/z* (relative intensity) 417 ($[M-CH_3]^+$, 50), 321 ($[M-CH_3-SO_2CH_3-OH]^+$, 100); HRMS (EI) calcd for $C_{19}H_{27}O_8S$ $[M-CH_3]$ 417.1578, found 417.1581.

**3.1.33. Epoxide 50.** LiBr (66 mg, 0.76 mmol) was added to a mixture of mesylate **49** (33 mg, 0.076 mmol) in dry $CH_3CN$ (5 mL) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 12 h and saturated $NH_4Cl$ was added. The aqueous phase was extracted with $Et_2O$ (3×) and the combined organic layers were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and purification of the crude product was accomplished by flash column chromatography (hexanes–$Et_2O$, 2:1) to afford epoxide **50** as a white solid (15 mg, 74% based on starting material **49** consumed) and recover the starting material (7 mg).

Data for expoxide **50**: mp 62–63 °C; $[\alpha]_D^{20}=+17.7$ (*c* 0.5, $CHCl_3$); $R_f$ 0.56 (hexanes–$Et_2O$, 1:2); IR (thin film) 2978, 1204, 1066, 673 $cm^{-1}$; $^1H$ NMR $\delta$ 1.28 (s, 3H), 1.31 (s, 3H), 1.37 (s, 3H), 1.51 (s, 3H), 1.67 (m, 3H), 2.11 (m, 2H), 2.51 (dd, $J=3.6$, 11.7 Hz, 1H), 3.11 (t, $J=1.8$ Hz, 1H), 3.80 (m, 2H), 4.03 (m, 2H), 4.13 (t, $J=3$ Hz, 1H), 5.19 (dd, $J=1.2$, 10.5 Hz, 1H), 5.40 (dd, $J=1.2$, 17.4 Hz, 1H), 5.62 (dd, $J=10.5$, 17.1 Hz, 1H); $^{13}C$ NMR $\delta$ 25.3, 26.6, 27.2, 27.3, 27.9, 29.9, 35.5, 36.7, 36.9, 59.0, 61.3, 63.7, 65.6, 79.7, 79.9, 102.7, 106.6, 111.9, 116.4, 139.2; MS (FAB) *m/z* (relative intensity) 337 ($[M+H]^+$, 24), 277 ($[M+H-C_2H_4O_2]^+$, 20), 185 (90), 93 (100); HRMS (FAB) calcd for $C_{19}H_{29}O_5$ [M+H] 337.2010, found 337.1989.

**3.1.34. Alcohol 51.** 5% Palladium-on-charcoal (40 mg) was suspended in EtOAc (5 mL) and the mixture was degassed and then filled with hydrogen gas three times and was stirred for 10 min. A solution of the aldehyde **39** (80 mg, 0.15 mmol) in EtOAc (4 mL) was added and the mixture was continuously monitored by TLC so that the starting material was estimated to be about 80% consumed. The resulting mixture was filtered through filter paper and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (hexanes–$Et_2O$, 3:1 to 1:3) to afford the starting aldehyde **39** (7 mg), alcohol **51** as a colorless oil (43 mg, 70%) and the aldehyde diol **40** (9 mg, 19%).

Data for alcohol **51**. $[\alpha]_D^{20}=+9.4$ (*c* 0.25, $CHCl_3$); $R_f$ 0.42 (hexanes–$Et_2O$, 1:2); IR (thin film) 3737, 2981, 1715, 1074 $cm^{-1}$; $^1H$ NMR $\delta$ 1.15 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.60 (s, 3H), 1.98 (m, 4H), 2.63 (brs, 1H), 2.91 (dd, $J=3.3$, 11.4 Hz, 1H), 3.98 (m, 5H), 4.13 (t, $J=3$ Hz, 1H), 4.44 (dd, $J=11.4$, 82.8 Hz, 2H), 7.34 (m, 5H), 10.03 (s, 1H); $^{13}C$ NMR $\delta$ 25.5, 26.9, 27.2, 28.8, 30.9, 32.4, 33.7, 34.9, 41.1, 63.5, 65.4, 65.6, 70.1, 79.4, 80.5, 80.6, 107.2, 111.9, 127.7, 127.9, 128.4, 137.9, 200.2; MS (FAB) *m/z* (relative intensity) 447 ($[M+H]^+$, 14), 417 ($[M-CHO]^+$, 36), 309 (95), 281 (92); HRMS (FAB) calcd for $C_{25}H_{35}O_7$ [M+H] 447.2377, found 447.2344.

**3.1.35. Diol 52.** To a stirred solution of the alcohol **51** (8 mg, 0.017 mmol) in MeOH (4 mL) at 0 °C was added with $NaBH_4$ (5 mg, 0.13 mmol) in small batches over a period of 5 min. The reaction mixture was stirred for 30 min and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate followed by flash column chromatography (hexanes–$Et_2O$, 1:1) afforded diol **52** as a colorless oil (8 mg, 100%): $[\alpha]_D^{20}=+10.6$ (*c* 0.45, $CHCl_3$); $R_f$ 0.35 (hexanes–$Et_2O$, 1:2); IR (thin film) 3313, 1378 $cm^{-1}$; $^1H$ NMR $\delta$ 1.31 (s, 3H), 1.32 (s, 3H), 1.37 (s, 3H), 1.51 (s, 3H), 1.89 (m, 5H), 2.24 (m, 1H), 3.06 (brs, 1H), 3.22 (brd, $J=5.4$ Hz, 1H), 3.92 (m, 6H), 4.09 (brs, 1H), 4.46 (d, $J=12.6$ Hz, 1H), 4.61 (dd, $J=9.9$, 52.5 Hz, 2H), 7.36 (m, 5H); $^{13}C$ NMR $\delta$ 25.4, 27.0, 29.2, 31.6, 33.5, 34.5, 39.9, 40.8, 63.5, 65.3, 73.3, 79.1, 79.3, 80.7, 106.9, 112.6, 127.5, 128.3, 128.4, 138.6; MS (EI) *m/z* (relative intensity) 417 ($[M-CH_2OH]^+$, 88), 359 ($[M-CH_2OH-C(CH_3)_2-OH+H]^+$, 100); HRMS (EI) calcd for $C_{24}H_{33}O_6$ $[M-CH_2OH]$ calcd 417.2272, found 417.2270.

**3.1.36. Oxetane 53.** 2,4,6-Collidine (0.32 mol, 2.49 mol) was added to a stirred solution of the diol **52** (140 mg, 0.313 mmol) in dry $CH_2Cl_2$ (6 mL) at 0 °C under $N_2$. After 15 min, MsCl (0.028 mL, 0.36 mmol) was added to the reaction mixture which was kept stirring at 0 °C for 48 h. The mixture was quenched with $NH_4Cl$ and extracted with

$Et_2O$ (3×). The combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a crude oil which was put to the next step.

The crude oil was added to a suspension of NaH (24 mg, 0.62 mmol) in dry THF (5mL) and the resulting mixture was heated under reflux for 4 h under $N_2$. The reaction was quenched with $NH_4Cl$ and the aqueous phase was extracted with $Et_2O$ (3×). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was fractionated by flash column chromatography (hexanes–$Et_2O$, 2:1 to 1:2) to give pure oxetane **53** as a white solid (70 mg, 83%) and the starting diol **52** (52 mg).

Data for oxetane **53**: mp 173–174 °C; $[\alpha]_D^{20} = +16.4$ (*c* 0.65, $CHCl_3$); $R_f$ 0.56 (hexanes–$Et_2O$, 1:2); IR (thin film) 2880, 1516, 1078 $cm^{-1}$; $^1H$ NMR $\delta$ 1.29 (s, 3H), 1.36 (s, 3H), 1.48 (s, 3H), 1.57 (s, 3H), 1.74 (dd, $J=3.3$, 15.0 Hz, 1H), 1.84 (dd, $J=2.4$, 15.3 Hz, 1H), 1.96 (dd, $J=3.6$, 14.7 Hz, 1H), 2.18 (m, 2H), 2.38 (dd, $J=3.6$, 11.4 Hz, 1H), 3.94 (m, 4H), 4.11 (t, $J=3$ Hz, 1H), 4.54 (d, $J=7.2$ Hz, 1H), 4.66 (s, 2H), 4.77 (d, $J=7.2$ Hz, 1H), 4.96 (m, 1H); $^{13}C$ NMR $\delta$ 25.6, 26.9, 27.3, 27.6, 30.6, 34.5, 35.0, 38.8, 42.7, 64.4, 64.7, 65.9, 78.6, 79.1, 79.6, 79.8, 83.8, 106.7, 112.3, 127.1, 127.3, 128.3, 138.9; MS (FAB) *m/z* (relative intensity) 431 ($[M+H]^+$, 6), 323 ($[M-OBn]^+$, 100), 309 (37), 265 (47); HRMS (FAB) calcd for $C_{25}H_{35}O_6$ [M+H] 431.2428, found 431.2430. Anal. calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.68; H, 8.04.

**3.1.37. Alcohol 41.** 10% Palladium-on-charcoal (10 mg) was suspended in EtOH (3 mL). The mixture was degassed and then filled with hydrogen gas three times and was stirred for 10 min at room temperature. A solution of the oxetane **52** (27 mg, 0.063 mmol) in EtOH (2 mL) was added and the resulting mixture was stirred for 30 min under hydrogen (balloon). The mixture was filtered and the filtrate was concentrated under vacuum. The residue was eluted through a short pad of silica gel (hexanes–$Et_2O$, 2:1) to give alcohol **41** as a colorless oil (20 mg, 93%): $[\alpha]_D^{20} = -25.2$ (c 0.7, $CHCl_3$); $R_f$ 0.30 (hexanes–$Et_2O$, 1:2); IR (thin film) 1378 $cm^{-1}$; $^1H$ NMR $\delta$ 1.35 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H), 1.53 (s, 3H), 1.77 (d, $J=3$ Hz, 2H), 1.95 (dd, $J=5.4$, 14.4 Hz, 1H), 2.09 (m, 2H), 2.34 (dd, $J=5.4$, 9.3 Hz, 1H), 2.55 (brs, 1H), 3.94 (m, 4H), 4.10 (t, $J=3$ Hz, 1H), 4.43 (dd, $J=6.3$, 5.25 Hz, 2H), 4.74 (dd, $J=6$, 8.7 Hz, 1H); $^{13}C$ NMR $\delta$ 25.9, 26.5, 27.3, 27.5, 28.9, 32.8, 34.3, 38.1, 43.6, 64.6, 64.9, 72.5, 78.8, 78.9, 84.1, 88.3, 106.8, 113.3; MS (FAB) *m/z* (relative intensity) 341 ($[M+H]^+$, 3), 307 (70), 289 (24), 154 (100); HRMS (FAB) calcd for $C_{18}H_{29}O_6$ [M+H] 341.1958, found 341.1916.

**3.1.38. Acetate 6.** Acetic anhydride (0.1 mL, excess) and DMAP (2 mg) were added to a stirring solution of the alcohol **41** (19 mg, 0.056 mmol) in pyridine (5 mL). The resulting mixture was heated under reflux for 9 h and quenched with saturated $NH_4Cl$. The aqueous phase was extracted with $Et_2O$ (3×). The combined organic layers were dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a crude oil which was purified by flash chromatography (hexanes–$Et_2O$, 2:1 to 1:2) to give acetate **6** as a white solid (10 mg, 56% based on starting material **41** consumed) and unreacted alcohol **41** (3 mg).

Data for acetate **6**: mp 131–132 °C; $[\alpha]_D^{20} = +6.1$ (*c* 0.25, $CHCl_3$); $R_f$ 0.50 (hexanes–$Et_2O$, 1:2); IR (thin film) 3742, 2934, 1697, 1077 $cm^{-1}$; $^1H$ NMR $\delta$ 1.27 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 1.63 (s, 3H), 1.73 (m, 2H), 2.13 (s, 3H), 2.19 (m, 1H), 2.29 (dd, $J=9$, 14.7 Hz, 1H), 2.75 (dd, $J=2.7$, 13.5 Hz, 1H), 3.86 (m, 1H), 3.99 (m, 3H), 4.11 (t, $J=3$ Hz, 1H), 4.76 (dd, $J=8.4$, 10.8 Hz, 2H), 4.82 (dd, $J=5.1$, 9.3 Hz, 1H); $^{13}C$ NMR $\delta$ 21.3, 25.5, 26.9, 27.2, 27.3, 29.7, 30.7, 34.7, 36.5, 38.6, 40.9, 64.3, 64.9, 78.9, 79.8, 80.5, 82.0, 84.5, 107.0, 112.3, 169.8; MS (FAB) *m/z* (relative intensity) 383 ($[M+H]^+$, 5), 307 ($[M-C_2H_4O_2-CH_3]^+$, 100); HRMS (FAB) calcd for $C_{20}H_{31}O_7$ [M+H] 383.2064, found 383.2060. Anal. calcd for $C_{20}H_{30}O_6$: C, 62.81; H, 7.91. Found: C, 62.86; H, 8.00.

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## References and notes

1. Taxol® is the registered trademark of Bristol-Myers Squibb Company for Paclitaxel.
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