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Tetrahedron: *Asymmetry* 16 (2005) 3241–3255
Tetrahedron: *Asymmetry*

The aldol–annulation–fragmentation strategy toward the taxoid diterpene framework revisited. Instructive failures in the chemistry of medium ring containing systems

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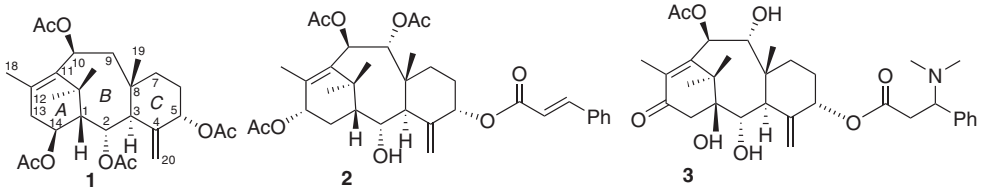
Received 3 August 2005; accepted 30 August 2005
Available online 28 September 2005

Abstract—Central intermediate **5** for the taxoid diterpene framework, prepared by the aldol–annulation sequence, permitted the construction of A-secotaxane frameworks incorporating differentiatable olefin and oxygen functionalities suitable for further elaboration. The key BC-subunits **9** and **8** have proven amenable to efficient conversion into both oxa-bridged **7** and its central eight-membered B-ring analogue **6**, providing two potential precursors for taxoid construction. Although their further elaboration into **4** was not progressed at this stage, **6** and **7** are potentially useful synthetic intermediates. Extensive structural studies that included 800 MHz ^{1}H (200 MHz ^{13}C) NMR as well as X-ray crystallographic analyses of **7**, **17**, and **20** have contributed to the unambiguous elucidation of all the complex structures synthesized.

1. Introduction

The search for the development of multi-drug resistance (MDR) reversing agents in cancer therapy resulted in the discovery of non-oncological properties of various lower oxygenated taxanes. Unlike taxol,[1] which lacks this activity, some low-oxygenated taxanes are powerful inhibitors of P-glycoprotein mediated transport and act as MDR reversing agents.[2] For example, taxoids related to taxuyunnanine C **1** have NGF-like activity and have been claimed to be useful for the treatment of Alzheimer's disease.[3] Naturally occurring taxane diterpenes, such as taxezopidine G **2**, have been reported to show inhibitory activities comparable to that of verapamyl.[4] Other non-oncological potential applications of low-oxygenated taxoids possessing neither a fused oxetane ring nor a C-13 (*N*-acyl)phenylisoserin and C-2 *O*-benzoyl moieties, which had been regarded as very important for binding of taxoids to tubulin, are psoriasis, malaria, arthritis, multiple sclerosis, polycystic kidney disease, and more likely to come.[5] Taxine B **3**, on the other hand, the most abundant precursor present in the needles of *Taxus Baccata* L., has been used as a starting material for the synthesis of various taxoid analogues (Scheme 1).[6]



Scheme 1.

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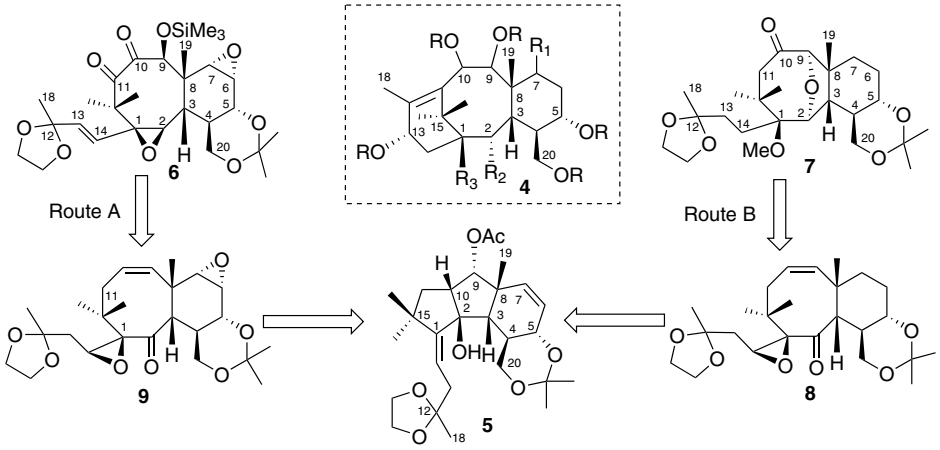
doi:10.1016/j.tetasy.2005.08.044



Scheme 2.

The above cited low-oxygenated taxanes, easier to synthesize compared to the parent drug taxol, number one in oncology along with its unnatural derivative taxotere, are likely to become major synthetic targets. Early studies from these laboratories, aimed at the construction of the taxoid diterpene skeleton **4**, have established the feasibility of producing the 20-carbon framework of the A-secotaxane diterpene **9** in 12 linear steps from inexpensive starting materials.[7] The sequence begins with two achiral aldol partners and leads to the *cis-syn-cis* tricyclic key intermediate **5** as a single diastereomer (Scheme 2). The central role played by the enolate geometry in the stereochemistry during the formation of C–C bonds secured an excellent diastereoselectivity meaning that the chromatographic separation of diastereomers was therefore avoided.

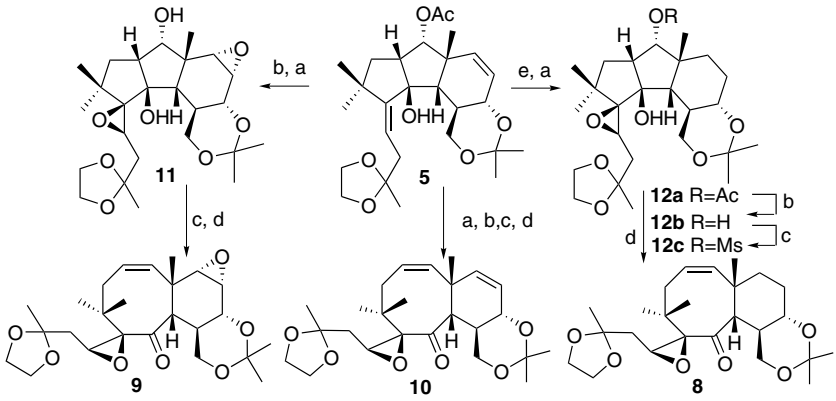
The advanced intermediate **5** thus obtained was fragmented into the BC-subunit **9**, but difficulties were encountered for the requisite C11 functionalization. This major drawback forced a change in strategy for the elaboration of the eight-membered B-ring moiety. We thus decided to use a temporary oxa-bridged structure, the C6–C7 unsaturated analogue of **7**, with the hope of avoiding difficulties inherent to an eight-membered ring system. The latter was A-ring annulated thus establishing the viability of this approach for taxoid synthesis.[8]

Based upon these precedents, it seemed likely that variously substituted A-secotaxanes **6** and **7** should be similarly accessible. It thus became our goal to demonstrate that the generalized BC-intermediates **9** and **8** could be transformed into the corresponding taxoid diterpene backbone of type **4**. Our retrosynthetic analysis for their construction is outlined in general terms in Scheme 2, and makes use of results detailed in our previously published work. With the aim to build up a dual plan for the synthesis of **6**, and its oxa-bridged surrogate **7**, we have developed two efficient routes (route A and route B, Scheme 2), which both target a variously elaborated analogue of **4** as a key intermediate for taxoid construction. The first option, route A, requires the conversion of **5** into **6**, containing the crucial eight-membered B-ring with complete oxygenation in the periphery, via **9**, through a continuation of a route, which was reported earlier.[7] The second option, route B, based on competing transannular processes that could be used to synthetic advantage, involves a temporary oxa-bridge formation through an in situ epoxide opening, and thus formation of **7** (Scheme 2).

Herein, we report the application of the aldol–annulation–fragmentation strategy to include a route, which would be amenable to a series of both high- and low-oxygenated taxoids, routes A and B, respectively, with minor structural modifications, along with a brief survey of the failures encountered en route to the target. Although all our previous work was achieved on optically homogeneous material starting from **5**, for convenience, we chose to restrict these probing experiments to report the conversion of **5** in the racemic series. Furthermore, the previous erroneous assignment of the C9–C10 olefin geometry[7] is corrected.

2. Results and discussion

To assemble the core ABC structure of taxoids, we required functionalization at C11. The source of this required functionality could have been either **9**, **10**, or **8** prepared in high yields from **5** as depicted in Scheme 3. In this context, we focused our work on the large scale synthesis of the above three BC-subunits, which contain the common structural fragment, the bicyclo[6.4.0]dodecane ring system, and allow for investigation of the effect of structural variation on reactivity in the eight-membered ring moiety. The observed difference in reactivity occurred exclusively in the cyclooctenyl moiety, suggesting a variation of hybridization at ring carbons as a potential contributor to reactivity change in this moiety. To assess the influence of hybridization in the B ring periphery on the reactivity, three sets of experiments were performed. In the first set, the C11 functionalization was attempted on **9**, **10**, **8**, and **16**, containing an sp^2 hybridized carbon at C2 (carbonyl down topology) while the second contained no sp^2 hybridized carbon at C2 (**24**, Scheme 6), and the third contained a C2–



Scheme 3. Reagents and conditions: (a) $VO(acac)_2$, *t*-BuOOH in decane, PhH, reflux; (b) 6 N NaOH, MeOH; (c) MsCl, pyridine, DMAP cat., 0 °C; (d) *t*-BuOK/*t*-BuOH–THF, 70 °C; (e) H_2, Ra-Ni, MeOH.

C9 oxa-bridge **18** and **7** (Scheme 5). These experiments provide an estimate of the combined effects of the substitution pattern and ring geometry induced changes in chemical reactivity. The reaction sequence leading from common precursor **5** to the C6–C7 differentiated A-secotaxanes **9**, **10**, and **8** is shown in Scheme 3. While the routes via **9** and **8** allow access to the above mentioned taxoid representatives specifically, we thought that it would be useful to maintain the C6–C7 olefin in **10** until later stages to allow for a switch at will to any of the two former routes by using the appropriate sequencing of the steps. This would ensure a route for taxoids with a higher/lower oxygenation pattern through **10**. Reduction of the C6–C7 double bond would provide access to 7-nor taxoids through **8** while a double Sharpless epoxidation, as described in our previous studies, would afford more oxygenated taxoids via **9**.

Preparation of the epoxides **9**, **10**, and **8** derived from the common precursor **5** required a selective epoxidation (92%), saponification of the C9 ester group (98%), installation of the mesylate leaving group and fragmentation (88% two steps).[9] The overall sequence, common for the three target molecules, provided a short and efficient route for 6 + 8 fused ring systems embodying the 20 carbons of the taxoid diterpene skeleton and a significant substitution pattern on the B-ring periphery.

Starting from **5**, a Raney nickel reduction (H_2, Ra-Ni, MeOH, rt) of the C6–C7 double bond (C1–C14 olefin remained intact) followed by a hydroxyl directed Sharpless epoxidation[10] [$VO(acac)_2$ cat., *t*-BuOOH in decane, PhH, reflux, 15 min, 92%] afforded **12a** (98%).[11] Transformation of the latter into fragmentation precursor **12c** involved the hydrolysis of the acetate functionality (6 M NaOH, MeOH, 0 °C to rt, 2 h, 98%), and mesylation (MsCl, pyridine, DMAP cat., 0 °C, 1 h.). Heating the mesylate in THF and *t*-BuOK (1 M in *t*-BuOH) for 45 min achieved the C2–C10 cleavage affording **8** in 88% yield (two steps).

2.1. The C11 functionalization

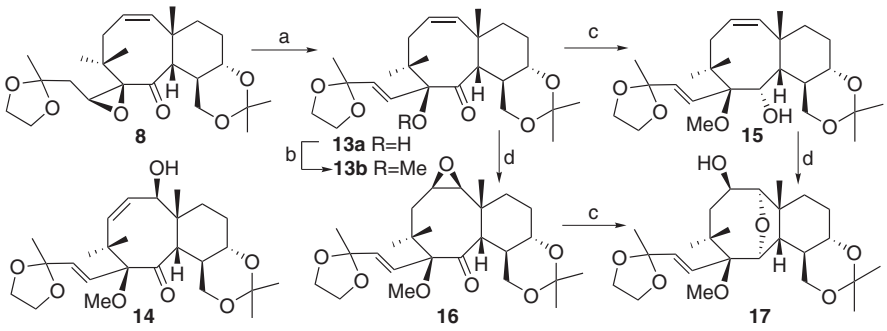
We then examined several possible routes to C11-functionalization, since, in theory, this could be efficiently accomplished by methodology typically employed for allylic oxidation.[12] Despite an extensive search for suitable reaction conditions that would accommodate the C11 functionality, directly onto the BC-subunits **9**, **10**, and **8**, none were found. Similarly, efforts to migrate the double bond into the C10–C11 position, using the Barton conditions ($RhCl_3$, EtOH, reflux), failed.[13] Several sets of conditions were screened in an attempt to overcome this problem, but all failed. Applying harsh conditions under standard allylic oxidations (prolonged heating at reflux for example) did not give the desired C11-hydroxylated derivative of **9**, **10** or **8**, but instead resulted in the formation of a partially C12 ketal-deprotected product along with unchanged starting material. The difficulties encountered in securing the functionalization at C11 forced a change in strategy for the elaboration of the eight-membered B-ring moiety.

2.2. The oxa-bridge construction

Since our attempts to functionalize the C11 position by direct allylic oxidation were unsuccessful, we opted for altering the central B-ring by imposing a form of structural constraint.

With the ultimate goal of producing a suitable precursor for a C11–C12 bond forming operation, leading to the taxoid ABC-core, we first investigated routes to **7** in analogy with those undertaken for its C6–C7 unsaturated analogue **10**, which was reported earlier.[8] We therefore used the route depicted in Scheme 4, which proved to be satisfactory. Starting from **8**, the epoxide opening was carried out by treatment with a 10-fold excess of lithium diethylamide and dry HMPA, at room temperature, for 20 min, leading to the target α-ketol **13a** in 98% isolated yield. The C1 tertiary alcohol of the α-ketol thus obtained was converted to its corresponding methyl ether **13b** by treatment with 12 equiv of powdered KOH, in DMSO (10 mL per mmol) and, immediately after, addition of excess, freshly distilled, MeI (30 min room temperature stirring) in 93% isolated yield.

Attention was then turned to the construction of the C2–C9 oxa-bridged portion of the BC-subunit **17**.



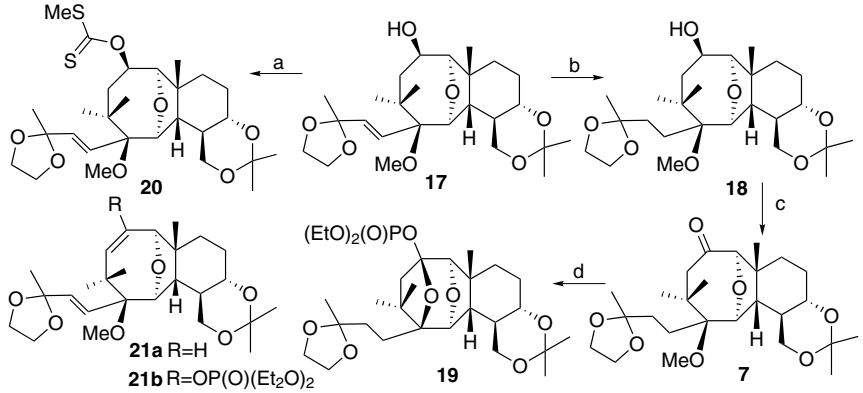
Scheme 4. Reagents and conditions: (a) $LiEt_2N$, THF, HMPA, rt; (b) KOH, DMSO, MeI, rt; (c) LAH, THF, reflux; (d) $MeReO_3$ cat., pyridine, H_2O_2, CH_2Cl_2.

Formation of the latter involved the transannular interaction of the C2 hydroxy group and the C9–C10 epoxide formed from the corresponding olefin upon subjection to the Sharpless modification of MTO catalyzed epoxidation.[14] This was achieved in two ways: first by the in situ transannular epoxide opening upon reduction at the C2 carbonyl or second, through an epoxidation of the C9–C10 olefin on an already reduced compound (paths d, c and c, d, respectively, Scheme 4). Upon reduction of **13b** with lithium aluminum hydride in dry THF, under an argon at 70 °C, a 68% isolated yield of **15** bearing a C2–αOH group was obtained. This stereochemical outcome is a direct consequence of the ''carbonyl-down'' conformation preferentially adopted by **13b**. Treatment of **15** with methyltrioxorhenium (MTO, 0.5 mol %) in the presence of 30% aq H_2O_2 and pyridine in CH_2Cl_2 under argon at room temperature for 12 h afforded the desired oxa-bridged **17** in 92% isolated yield. Following the d, c path, when **13b** was treated with methyltrioxorhenium at room temperature for 8 h, the corresponding epoxide **16** was obtained as a single isomer, assigned as depicted in Scheme 4, in 98% isolated yield. Following in situ epoxide opening by the C2 hydroxy group, upon refluxing with $LiAlH_4$ in THF for 6 h, the oxa-bridged **17**, whose structure was corroborated by single crystal X-ray analysis, was obtained in 80% yield. The C2-carbonyl topology and the epoxide stereochemistry in **16** account well for the observed ease of oxa-bridge formation. The exclusive formation of the required 2α-hydroxyl group in **15** results from convex face addition of the hydride to the C2 carbonyl. Depicted in Scheme 4 is a dual path for inserting the C2–C9 oxa-bridge into ring B.

2.3. The C11 functionalization on the oxa-bridged B-ring

In exploring approaches to C11 functionalization, introduction of a C10–C11 double bond was targeted en route toward one of the type **14** (Scheme 4) or **21a**,**b** (Scheme 5) A-seco taxoid frameworks for final ring closing (C11–C12 bonding). We reasoned that the Burgess reagent[15] ($MeO_2CNSO_2NEt_3$), which has been demonstrated to prefer a *cis*-elimination pathway, could achieve dehydration. Exposure of **17** to 3 equiv of Burgess reagent in benzene at room temperature (2 h), or in DMF at 100 °C (1 h) afforded only the starting material.

Williams[16] used the Burgess reagent, as did Holton in his taxol synthesis, to dehydrate a tertiary alcohol at C4 in order to form the exocyclic olefin C4–C20, while Paquette,[17] in his taxusin synthesis, generated (excellent yield) a double bond on ring B using either a Burgess reagent or Martin sulfurane.[18] Thus, the Martin sulfurane ($[Ph_2S[OC(CF_3)Ph]_2$), which is a more powerful dehydrating agent and performs dehydration at room temperature within hours, was our next choice. Treated with 4 equiv of this reagent in CH_2Cl_2, in the presence of cat. triethylamine, from 0 °C to reflux for 20 h, **17** was again recovered intact.



Scheme 5. Reagents and conditions: (a) CS_2, NaH, MeI, DMF, 0 °C; (b) H_2, Ra-Ni, MeOH, rt; (c) Dess–Martin periodinane, CH_2Cl_2, pyridine, rt; (d) LDA, $ClP(O)(OEt)_2$, THF, 0 °C to rt.

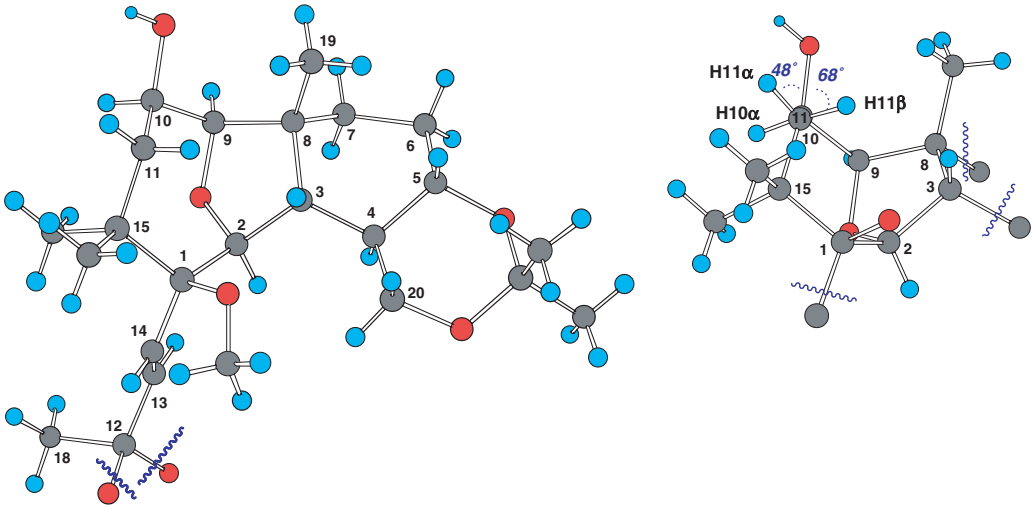


Figure 1. Crystal structure of **17** (Chem 3D from X-ray coordinates) and a Newman view down the C10–C11 bond. Non-relevant parts have been omitted to simplify matters.

Pursuing dehydration studies, **17** was subjected to acetate pyrolysis and mesylate displacement (DBU, pyridine) on the corresponding **17** 10-OAc (Ac_2O, py, DMAP) and **17** 10-OMs (MsCl, py, DMAP). Both attempts failed to produce the desired olefin. X-ray dihedral angle data on **17** were then used to clarify the structural origins of the observed lack in reactivity. Figure 1 shows a Chem 3D representation of **17** from the X-ray coordinates. For the reaction to occur from **17**, or its C10-mesylated/acetoxylated derivatives, the effectiveness of orbital overlap depends on the initial alignment of relevant bonds (CH11/C10=O). Inspection of the X-ray stuctures revealed that transient reactive intermediates derived from **17** could not attain the required transition state, as the oxa-bridged ring system is fairly rigid. From the inspection of the X-ray structure of **17**, evidence was acquired that the C10 hydroxyl group was in a gauche arrangement with both the C11Hα and C11Hβ, dihedral angles being 48° and 68°, respectively.

As an alternative approach, xanthate **20** was prepared from **17** (CS_2, NaH, 0 °C, 20 min, then MeI, DMF, 0 °C, 1 h, 91%) and subjected to pyrolysis (250 °C, in xylene, toluene, or PhOPh, sealed tube) without success. Employing extended heat (at the outset incrementally, then 24 h at 250 °C) as a means of populating better suited conformers of **20** did not induce conversion to **21a**, as required for the A-ring closure. Instead the xanthate derivative was recovered intact, with the only extra identified product being the C12-ketal deprotection.

Single-crystal X-ray diffraction analysis of the crystalline derivative **20** (Fig. 2) enabled unequivocal stereochemical assignment and further confirmed the correctness of previous assignments by NMR techniques. It is widely accepted that any factors, which disrupt the orbital alignment, will inhibit olefin formation. As it can be seen from X-ray derived structure, **20**, just like **17**, showed a pronounced tendency to minimize transannular non-bonded repulsions. As a consequence the *gem*-dimethyl group at C15 avoided proximity with the C8 angular methyl group. The C10–C11 olefin formation needs a more favorable, disposition of the C11 hydrogens. However, this would introduce unfavorable steric interaction especially among the methyl substituents at C8 and C15. Furthermore, only one H11 is available for the Chugaev elimination,[19] the one leading to a *Z*-olefin, in a seven-membered ring. When viewed via an adapted Newman projection down the C10/C11-methylene bond, the relevant dihedral angles are seen to be 47° for H11α and 69° for H11β, both values being far from those required for maximum overlap. H11β, the improbable removal of which would result in a high energy *trans*-cycloheptene, also has an unfavorable dihedral angle of 69°. Raney nickel reduction of **17** (H_2, Ra-Ni, MeOH, 6 h) provided **18** (72% yield along with deketalized starting material), while a subsequent Dess–Martin periodinane oxidation[20] (DMP, py, CH_2Cl_2, rt, 1 h) gave the target ketone **7** in a nearly quantitative yield. Following C13–C14 *E*-double bond reduction, attempted $ZnCl_2$[21] or $TiCl_4$[22] catalyzed intramolecular aldol in the presence of C12-ketal protecting group[23] failed. We reasoned that we could create the required olefin at C10–C11 via a Shapiro reaction[24] by a base promoted decomposition of *p*-toluenesulfonylhydrazone of C10-ketone. Unfortunately, in our case, the formation of the required tosylhydrazone ($TsNHNH_2$, EtOH abs.) failed, probably due to difficulties from forming the tetrahedral intermediate.

Enol diethyl phosphates were attractive to us due to their various reactivity patterns, particularly their lithium-amine reduction to the corresponding alkenes.[25] Furthermore, being considerably more stable than their silyl-enol ether analogs, they could resist a series of functional group transformations. However, upon attempted phosphorylation of the enolate anion derived from **7** (LDA, 0 °C, 20 min, then $ClP(O)(OEt)_2$, THF, 0 °C to rt, 1 h 20 min) the formation of **21b** failed, with the only identified product being **19** (46%). The latter is believed to occur through an intermediate oxonium ion formation, favored by the oxophilic character of phosphorus. We set as our next goal, the allylic alcohol **14** (Scheme 4). In practice, three protocols were pursued to convert

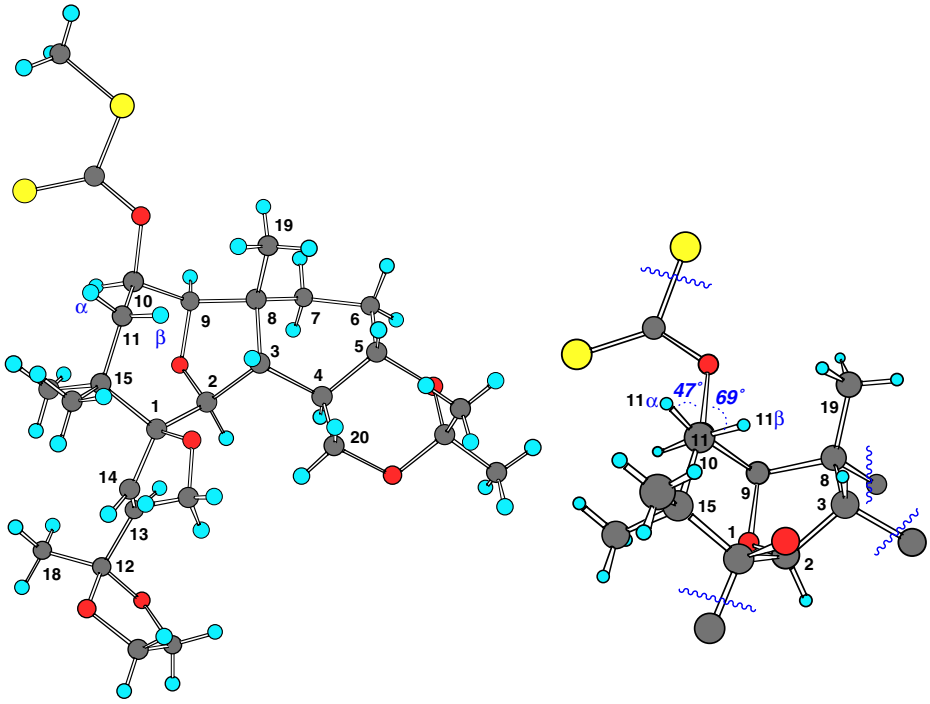


Figure 2. Crystal structure of **20** (Chem 3D from X-ray coordinates) and a Newman view down the C10–C11 bond. Non-relevant parts have been omitted to simplify matters.

epoxide **16** into the target system, allylic alcohol **14**, with all of them unrewarding. In the first protocol, Lewis acid induced epoxide opening ($Al(O\textit{i}\text{-}Pr)_3$, PhMe, reflux, 50 h)[26] gave only unchanged starting material. When **16** was found to be unreactive toward the lithium diethylamide ($LiEt_2N$, Et_2O–HMPA, rt) induced rearrangement of epoxides to allylic alcohols,[27] the second protocol, recourse was made instead to organoaluminum reagents such as diethyl aluminum 2,2,6,6-tetramethylpiperidide (DATMP, PhH, 0 °C) mediated epoxide opening following precedents.[28] All attempts remained fruitless.

While its precursor, **17**, proved to be resistant to acetate pyrolysis, mesylate elimination or Chugaev elimination, **7** should, by analogy to its C6–C7 epoxy derivative,[8] be readily enolizable to afford the required C11 functionalization. This comprises a formal synthesis of the taxoid ABC-diterpene framework, since the C-ring analogue (C6–C7 epoxide) of bridged ketone **7** was also a key intermediate in our original synthesis of C2–C9 oxa-bridged taxoid intermediate. Extensive NMR analysis of this advanced intermediate unambiguously confirmed its stereochemical assignments; the veracity of which was corroborated by X-ray analysis, which are shown in Figure 3. Changing from an sp^3 to sp^2 at the C10 position significantly modified the dihedral angles. The stereoelectronic requirement for kinetic deprotonation is optimal with a C11–H dihedral angle of 90° to the carbonyl sigma plane. From inspection of the X-ray structure of **7**, evidence was acquired that C10 carbonyl plane was in a coplanar arrangement with C11Hβ and nearly orthogonal to C11Hα, thus, basic abstraction of the latter could achieve enolate formation. The C11–H/C=O dihedral angle was found to be 115° by X-ray analysis, a value not very far from what was believed to be ideal for maximum stereoelectronic overlap. This conformation allows optimum orbital overlap, which is necessary for the formation of the enol.

When viewed via an adapted Newman projection down the C10–carbonyl/C11–methylene bond, the relevant dihedral angle was seen to be 115°, a value approaching what was believed to be ideal for maximum overlap. Furthermore, the removal of this proton generates a *Z*-enolate (a strained *E*-enolate seems unlikely).

In summary, attempts to manipulate the free C10–OH, OAc, OMs and xanthate functionality on **17** for the elaboration of the C10–C11 olefin did not lead to any useful advances. After several trials with various ways to install the C10–C11 olefin, we were unable to successfully accomplish this transformation. The epoxide opening on **16**, the enol-phosphate or the C10–tosylhydrazone and the Mukaiyama type intramolecular aldol directly on the C12-ketal protected **7** also proved unsuccessful. With the A-ring annulation successfully achieved,[8] the remaining challenge was a similar adjustment of the substitution pattern at C11. Proceeding as in our previous work, a four-step sequence would convert **7** into taxoid ABC system **30**, which would set the stage for analogue synthesis (Scheme 7).

2.4. Further elaboration of the central B-ring

With the efficient synthesis of the bicyclo[6.4.0]dodecane ring system **22** realized following our published procedure, we went on to prepare the more advanced intermediate represented by formula **6**. At this step, a set of conditions had to be devised to give the A-ring annula-

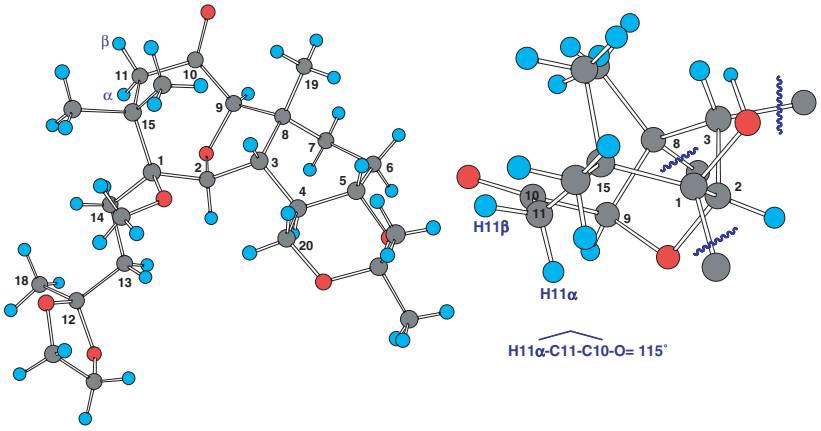
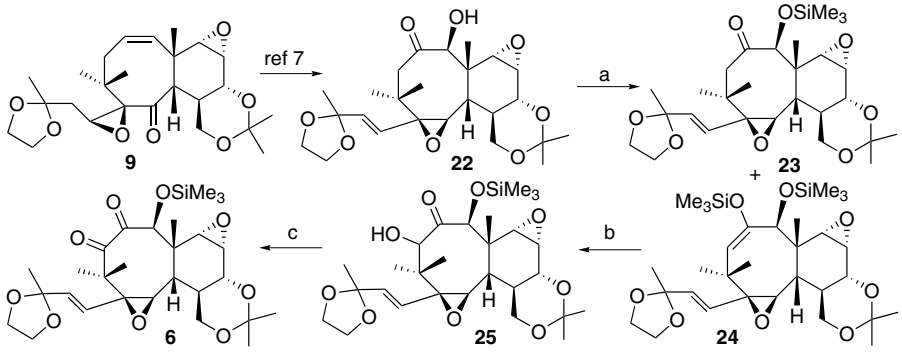


Figure 3. Crystal structure of **7** (Chem 3D from X-ray coordinates) and a Newman view down the C10–C11 bond. Non-relevant parts have been omitted to simplify matters.

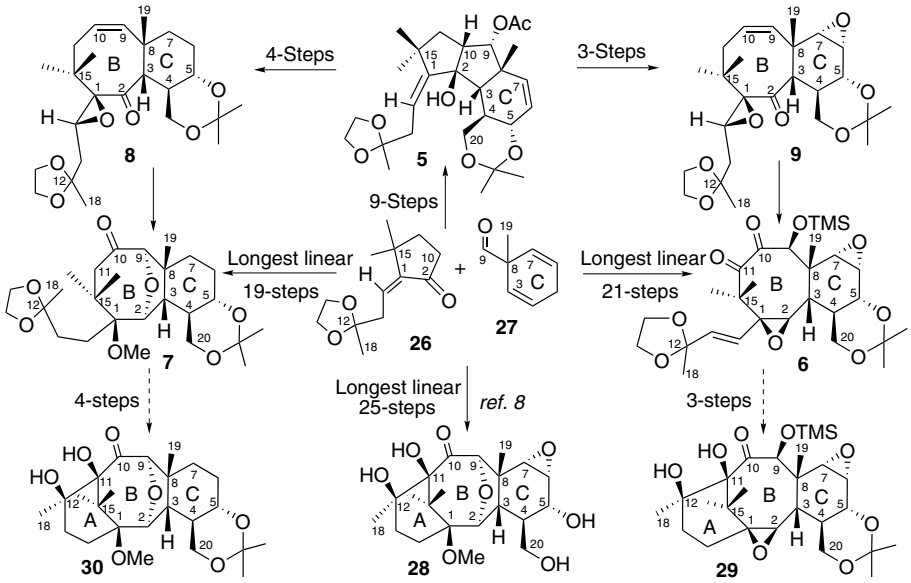
tion precursor. A prerequisite for the sequence of reactions outlined in Scheme 6 was, as for the first target **7**, the successful functionalization of the C11 position. Having experienced failures with templates containing C2 carbonyl functionality, we hypothesized that the eight-membered ring might be more amenable to further elaboration if the C2 carbonyl was replaced by an sp^3 functionality, and preferably with a sterically undemanding epoxide in the C1–C2 position. The objective now became to effect a C11 functionalization to construct the fully functional eight-membered B-ring. Methods for accomplishing this synthetic transformation at the carbon atoms adjacent to olefins, ketones, or alcohols do not seem to be easily applicable on an eight membered ring template heavily substituted on the periphery such as **9** or **22**.

In order to functionalize the B-ring at C11, it is important to be able to enolize the C10 carbonyl. This depends upon the substitution pattern around the B-ring periphery and the hybridization at the southern part of the molecule.[29] This was achieved using the two-step sequence, which led to a 1:1 mixture of **23** and **24** as shown in Scheme 6. Enol-ether formation, which proceeded under the standard, relatively mild conditions, smoothly converted the previously synthesized **22** into the cyclization precursor **6** in a three-step sequence and good yield.

We therefore used the route depicted in Scheme 6, which proved to be satisfactory. Thus, treatment of **22** with LDA in THF at −78 °C resulted in a smooth, regioselective conversion to an enolate anion, the capture of which with TMSCl led to **24** in 23% yield, along with the OTMS-protected acyloin **23** (74%). The same conversion was achieved using TMSIm–NaH in THF, at 0 °C still in low yields (42% of **24** together with 45% of **23**). The efficiency of this process was improved by recycling the silyl-ketone **23** after chromatographic separation. We found that alpha to carbonyl hydroxylation using Rubottom conditions (1.3 equiv of *m*-chloroperbenzoic acid under $NaHCO_3$-buffered conditions, at 0 °C in dichloromethane) resulted in very clean conversion into the desired mono-protected bis-acyloin **25**, which was isolated in quantitative yield. With this transformation successfully completed, we went on to prepare the most advanced intermediate **6**. Oxidation of **25** with IBX in DMSO at 50 °C for 1 h provided a 98% isolated yield of **6**. This result indicates that the A-ring construction can be secured through this route, by applying the same sequence as the one used for the successful samarium iodide mediated A-ring formation.[8] The highly elaborated polycyclic taxoid precursor **6** thus obtained, which contains nine stereogenic centers and can exist in 512 stereomeric forms, was synthesized, as a single isomer, from readily available achiral aldol



Scheme 6. Reagents and conditions: (a) TMSIm (15 min), NaH (30 min), THF, 0 °C; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 20 min; (c) IBX, DMSO, 50 °C, 1 h.



Scheme 7.

partners **26** and **27** (Scheme 7). Within the limits of detection by high field NMR spectroscopy, no stereoisomer was produced throughout this 21-step transformation.

The final task remaining in the construction of the ABC-taxoid diterpene by the second option involved the generation of triketone at C10–C11–C12 after a Raney-Nickel reduction of the C13–C14 double bond, thus creating conditions for a SmI_2 induced A-ring formation or appropriate functionalization of the C10–C11–C12 segment to allow for an aldolization–crotonization leading to the A-ring formation. By appropriate selection of the subsequent operations, various taxoid building blocks could be accessed.

3. Conclusion

The aldol–annulation–fragmentation strategy is indeed a general reaction scheme as evidenced by the successful synthesis of a structural variety of A-secotaxoid intermediates, since the A-ring closure was successfully achieved in our laboratories. By leaving the C2-OH group unprotected, we allowed the in situ transannular epoxide opening and this in turn furnished the desired C11 functionalization via silyl-enol ether formation and subsequent Rubottom hydroxylation. By changing hybridization on the B-ring periphery, on the other hand, we succeeded in C11-functionalization, thus opening avenues for the synthesis of the analogues.

These experiments provided two potential precursors **6** and **7** for the construction of the taxane framework, thus illustrating the synthetic utility of our approach (Scheme 7). Major advantages of the present strategy include the ease of preparing the key intermediate **5** containing structural features for further functional elaboration and the efficient use of control elements, which allow for single isomer transformation during the whole synthetic scheme. The route is general and broadens the scope of the aldol–annulation–fragmentation sequence as a tool for the preparation of various 6+8 bicyclic ring systems. The overall sequence can be readily modified to produce the required carbon/oxygen skeleton offering several distinct ways for further elaboration.

4. Experimental

4.1. General

Solvents and reagents used herein were purified according to standard literature techniques and stored under argon. Experiments, which required an inert atmosphere, were carried out under dry argon in a flame dried glass system. Flash chromatographies were run on silica gel (230–400 mesh) with the solvent mixture indicated. Thin layer chromatography was performed on commercial silica gel plates that were developed by immersion in 5% phosphomolybdic acid in 95% ethanol. 'Usual work-up' means washing of the organic layer with brine, drying on anhydrous $MgSO_4$, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Melting points were uncorrected. IR spectra were recorded with an FT-IR instrument through NaCl cell windows. NMR spectra were run in $CDCl_3$ unless otherwise noted. Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (400–300–250 and 100–75–69.5 MHz, respectively, 1D and 2D experiments) and corroborated by spatial proximity (NOE) studies using mainly the 1D NOEDIFF technique.[30] ^1H (800 MHz) and ^{13}C NMR (200 MHz) experiments were carried out on a spectrometer, equipped with triple resonance H/C/N probeheads and a three-axis pulsed field gradient modules. Gradients were used for the coherence transfer pathway selection in HMBC and HMQC exper-

iments. In the latter, broadband decoupling was performed by using adiabatic WURST-40 pulses. For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[31]

^{1}H chemical shifts are expressed in parts per million downfield from TMS using the residual non-deuterated solvent as internal standard ($CDCl_3$ ^{1}H, 7.27 ppm; C_6D_6 ^{1}H, 7.15). ^{13}C spectra were measured at 62.5 and 75 MHz and the chemical shifts are reported relative to $CDCl_3$ or C_6D_6 triplet centered, respectively, at 77.0 and 128.0 ppm. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^+) using a mobile phase of methanol will be abbreviated as ESIMS (MeOH).

4.2. C6–C7 hydrogenation—preparation of compound 12a

An aqueous suspension of Raney Nickel (1.3 g) was added to a stirred solution of the known[7] C1–C14 epoxy derivative of **5** (527 mg, 1.07 mmol), at room temperature in 60 mL of methanol and the mixture stirred for a further 4 h under a hydrogen atmosphere. The mixture was diluted with ethyl acetate and filtered through Celite, and the solvents were evaporated to yield 518 mg (98%) of the reduced compound **12a**: mp: 68 °C (heptane). IR (film): 3463, 2962, 1762, 1380, 1244, 1044, 737 cm^{-1}. ^{1}H NMR (300 MHz) δ 0.89 (s, 3H), 1.17 (s, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.36–1.55 (m, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 1.68 (m, 2H), 1.90 (m, 3H), 2.04 (m, 2H), 2.09 (s, 3H), 2.82 (m, 1H), 3.27 (dd, $J = 2.9$, 9.6 Hz, 1H), 3.28 (s, 1H), 3.56 (m, 1H), 3.60 (t, $J = 11.0$ Hz, 1H), 3.98 (m, 4H), 4.09 (dd, $J = 4.2$, 11.1 Hz, 1H), 5.04 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (62.5 MHz) δ 19.2, 21.0, 24.2, 26.2, 27.7, 28.4, 29.8, 32.2, 32.8, 37.1, 38.0, 38.3, 39.5, 46.2, 55.0, 55.4, 57.6, 64.6, 64.7, 65.7, 71.8, 73.2, 82.9, 89.3, 98.0, 109.3, 170.5. ESIMS (MeOH): 517.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{27}H_{42}O_8Na$ m/z 517.2777, found: 517.2757.

4.3. Hydrolysis of the C-9 acetate—preparation of compound 12b

Sodium hydroxide (20.4 mmol, 3.5 mL of a 6 M solution) was added dropwise to a stirring solution of **12a** (507 mg, 1.02 mmol) in methanol (20 mL) at 0 °C. After 1 h, the mixture was allowed to warm to room temperature and then stirred for an additional 1 h. Methanol was evaporated under reduced pressure and the residue taken up in ethyl acetate. The solution was washed with water, saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$, and concentrated. The crude obtained was purified on SiO_2 gel (heptane–EtOAc, 1:1) to give 452 mg (98%) of **12b**: mp: 170 °C (heptane). IR (film): 3480, 2961, 1381, 1266, 1201, 1054, 732 cm^{-1}. ^{1}H NMR (300 MHz) δ 0.90 (s, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 1.39 (s, 3H), 1.40 (m, 2H), 1.43 (s, 3H), 1.47 (s, 3H), 1.61 (m, 3H), 1.86 (t, $J = 13.2$ Hz, 1H), 1.99 (m, 5H), 2.59 (ddd, $J = 13.1$, 8.3, 5.7 Hz, 1H), 3.09 (s, 1H), 3.25 (dd, $J = 9.0$, 3.6 Hz, 1H), 3.59 (t, $J = 10.9$ Hz, 1H), 3.64 (m, 1H), 3.97 (m, 4H), 4.09 (dd, $J = 11.2$, 4.3 Hz, 1H), 4.15 (t, $J = 5.7$ Hz, 1H). Diagnostic NOEs: {Me-16}: Me17 (NOE *gem*), H11β, H10, H14; {Me17}: Me16 (NOE *gem*), H11α, H14. ^{13}C NMR (75 MHz) δ 19.2, 24.3, 26.3, 27.0, 27.5, 29.9, 30.1, 31.8, 37.2, 37.3, 38.4, 38.8, 46.0, 55.7, 57.1, 57.6, 64.6, 64.7, 65.9, 71.1, 73.4, 81.4, 88.1, 98.0, 109.4. ESIMS (MeOH): 475.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{25}H_{40}O_7Na$ m/z 475.2672, found: 475.2664.

4.4. Mesylation—preparation of compound 12c

To a stirred solution of **12b** (466 mg, 1.03 mmol) in pyridine (7 mL), in the presence of DMAP as catalyst (few crystals), methanesulfonyl chloride (MsCl, 1.1 mL, 13 mmol) was added at 0 °C and stirred for 1 h at this temperature. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate and extracted with methylene chloride. The combined extracts were washed with 1 M HCl, sodium bicarbonate and brine, and then dried over magnesium sulfate, and concentrated under reduced pressure to give 550 mg of the required mesylate as a crude material. Compound **12c** was taken into the next step without purification. A sample was purified for characterization (SiO_2, heptane–EtOAc, 1:1 as eluent). Compound **12c**: mp: 73 °C (dec, heptane). IR (film): 3465, 2965, 1462, 1357, 1267, 1176, 704 cm^{-1}. ^{1}H NMR (300 MHz) δ 0.91 (s, 3H), 1.19 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 1.49 (m, 2H), 1.59 (m, 1H), 1.71 (dd, $J = 14.0$, 9.0 Hz, 1H), 1.87 (m, 1H), 1.99 (m, 5H), 2.81 (m, 1H), 3.03 (s, 3H), 3.27 (dd, $J = 10.1$, 2.5 Hz, 1H), 3.30 (s, 1H), 3.58 (m, 1H), 3.59 (t, $J = 10.8$ Hz, 1H), 3.98 (m, 4H), 4.08 (dd, $J = 11.2$, 4.2 Hz, 1H), 4.94 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.2, 24.3, 26.2, 27.6 (2C), 29.8, 31.5, 32.0, 37.1, 38.0, 38.5 (2C), 39.2, 46.4, 54.7, 55.9, 57.6, 64.6, 64.7, 65.6, 71.2, 73.1, 88.9, 89.7, 98.1, 109.3. HRESIMS: calcd for $C_{26}H_{42}O_9SNa$ m/z 553.2447, found: 553.2457.

4.5. Fragmentation—preparation of compound 8

Mesylate **12c** (447 mg, 1.03 mmol) was dissolved in 15 mL of THF and *t*-BuOK (1 M in *t*-BuOH, 3.5 mL, 3.5 mmol) was then added at room temperature. The temperature was then raised to 70 °C (bath temp.) and the reaction mixture was stirred for 45 min. After cooling, then dilution with ether, water was added. Extraction with EtOAc, followed by usual workup and rapid filtration on SiO_2 (heptane–EtOAc, 2:1 to 1:1), gave pure **8** in 88% isolated yield for two steps. Compound **8**: mp: 122 °C (heptane). IR (film): 2988, 1696, 1458, 1382, 1199, 1053, 735 cm^{-1}. ^{1}H NMR (300 MHz) δ 0.85 (s, 3H), 1.17 (s, 3H), 1.31 (dd, $J = 14.7$, 7.5 Hz, 1H), 1.38 (s, 3H), 1.39 (s, 3H), 1.44 (s, 3H), 1.45 (m, 1H), 1.54 (m, 1H), 1.59 (s, 3H), 1.76 (dt, $J = 14.0$, 8.4 Hz, 1H), 1.77 (m, 2H), 2.02 (dt, $J = 13.6$, 5.4 Hz, 1H), 2.12 (qd, $J = 10.9$, 4.5 Hz, 1H), 2.74 (d, $J = 11.1$ Hz, 1H), 2.84 (dd, $J = 14.0$, 9.2 Hz, 1H), 3.16 (dd, $J = 7.4$, 3.7 Hz, 1H), 3.36 (t, $J = 10.9$ Hz, 1H), 3.69 (dd, $J = 11.2$, 4.4 Hz, 1H), 3.79 (ddd, $J = 11.1$, 9.4, 5.5 Hz, 1H), 3.95 (m, 4H), 5.47 (dt, $J = 8.7$, 11.8 Hz, 1H), 5.60 (d, $J = 11.8$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.3, 24.4, 24.6, 24.9, 26.6, 29.5, 29.8, 37.2, 37.9, 38.2, 38.2, 38.4, 38.7, 56.6, 57.0, 64.6, 64.7,

64.8, 70.0, 70.3, 98.3, 108.5, 126.3, 139.9, 207.0. ESIMS (MeOH): 457.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{25}H_{38}O_6Na$ *m/z* 457.2566, found: 457.2550.

4.6. C1–C14 epoxide opening—preparation of compound 13a

To a solution of $LiNEt_2$ (prepared at 0 °C from 10.3 mmol of Et_2NH and 8.5 mmol of *n*-BuLi, 1.6 M in hexanes) in 10 mL of dry THF, HMPA (2.13 mL, 12.2 mmol) was added and the reaction mixture allowed to reach room temperature. A solution of **8** (365.8 mg, 0.84 mmol) in 8 mL of dry THF was then added and stirring continued for 20 min at room temperature, under an argon atmosphere. After quenching with saturated aqueous solution of ammonium chloride and dilution with ether, the aqueous phase was extracted with EtOAc. Following the usual workup, the residue was filtered on SiO_2 (eluent heptane–EtOAc, 2:1) to give 358 mg (98%) of **13a**: mp: 198 °C (heptane). IR (film): 3509, 2954, 1700, 1459, 1374, 908, 732 cm^{-1}. ^1H NMR (300 MHz) δ 0.87 (s, 3H), 0.95 (s, 3H), 1.25 (s, 3H), 1.31 (m, 2H), 1.36 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 1.52 (m, 1H), 1.64 (dd, $J = 12.7$, 5.4 Hz, 1H), 1.85 (s, 1H), 2.06 (qd, $J = 11.2$, 4.8 Hz, 1H), 2.23 (m, 1H), 2.79 (t, $J = 12.7$ Hz, 1H), 3.34 (dd, $J = 11.5$, 4.8 Hz, 1H), 3.61 (t, $J = 11.2$ Hz, 1H), 3.67 (d, $J = 11.2$ Hz, 1H), 3.82 (m, 2H), 3.95 (m, 2H), 4.05 (m, 1H), 5.24 (m, 1H), 5.42 (d, $J = 11.7$ Hz, 1H), 5.50 (d, $J = 15.9$ Hz, 1H), 6.35 (d, $J = 16.1$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.1, 22.2, 24.1, 25.2, 25.6, 29.9, 30.0, 33.1, 34.9, 37.7, 39.6, 40.0, 51.1, 64.1 (2C), 64.7, 67.1, 83.3, 98.4, 107.3, 125.3, 129.5, 131.6, 143.5, 213.9. ESIMS (MeOH): 457.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{25}H_{38}O_6Na$ *m/z* 457.2566, found: 457.2556.

4.7. Protection of the C-1 hydroxyl group as its methyl ether—preparation of compound 13b

Freshly powdered KOH (739 mg, 13 mmol) was added to DMSO (8 mL) and the mixture stirred for 10 min at room temperature. A solution of **13a** (381 mg, 0.88 mmol) in DMSO (10 mL) was added, followed 2 min later by an excess of MeI (distilled and filtered through basic alumina, under an argon atmosphere, just before use). The reaction mixture was stirred for 30 min. After dilution with CH_2Cl_2, addition of water and extraction with CH_2Cl_2, the organic layer was washed with brine, dried over $MgSO_4$, concentrated, and purified on silica gel (eluent heptane–AcOEt, 2:1) to give 367 mg (93%) of **13b**: mp: 119 °C (heptane). IR (film): 2964, 1708, 1461, 1383, 1268, 1200, 1092, 1043, 911, 736 cm^{-1}. ^1H NMR (300 MHz) δ 0.80 (s, 3H), 1.03 (s, 3H), 1.28 (s, 3H), 1.30 (dd, $J = 13.1$, 6.8 Hz, 1H), 1.39 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 1.51 (dd, $J = 14.0$, 7.6 Hz, 1H), 1.53 (m, 1H), 2.06 (m, 1H), 2.21 (m, 2H), 2.88 (dd, $J = 13.8$, 10.9 Hz, 1H), 3.34 (s, 3H), 3.46 (dd, $J = 11.3$, 4.7 Hz, 1H), 3.50 (d, $J = 11.0$ Hz, 1H), 3.60 (t, $J = 11.1$ Hz, 1H), 3.83 (m, 2H), 3.96 (m, 2H), 4.04 (m, 1H), 5.20 (td, $J = 11.1$, 7.7 Hz, 1H), 5.34 (d, $J = 11.5$ Hz, 1H), 5.71 (d, $J = 16.3$ Hz, 1H), 5.81 (d, $J = 16.3$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.1, 21.3, 25.2, 25.5, 25.7, 29.7, 29.9, 33.8, 35.0, 37.8, 40.3, 40.6, 52.2, 54.3, 64.3, 64.6, 65.2, 67.5, 88.0, 98.3, 107.3, 124.3, 125.8, 136.8, 142.8, 214.5. ESIMS (MeOH): 471.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{26}H_{40}O_6Na$ *m/z* 471.2723, found: 471.2701.

4.8. Reduction of the C-2 carbonyl—preparation of compound 15

To an ice cold magnetically stirred solution of **13b** (447 mg, 1 mmol) in 10 mL of dry THF, under an argon atmosphere, $LiAlH_4$ (304 mg, 8 mmol) was added. The mixture was stirred at 70 °C (bath temperature) for 4 h (TLC monitoring). Upon disappearance of the starting material, the reaction mixture was cooled to 0 °C, diluted with ether, then a small amount of water, 6 M aq NaOH and water again were added successively (for each 1 g of $LiAlH_4$, 1 mL of water, 1 mL of 6 M NaOH and 3 mL more water were added), and stirring continued at room temperature for 45 min. Rapid filtration on SiO_2 (eluent: EtOAc) and removal of solvent gave a residue that was purified by silica gel chromatography (heptane–EtOAc, 1:1) to yield 306 mg (68%) of **15**: mp: 105 °C (heptane). IR (film): 3523, 2941, 1462, 1379, 1200, 1082, 736 cm^{-1}. ^1H NMR (800 MHz) δ 0.91 (s, 3H), 1.07 (s, 3H), 1.24 (s, 3H), 1.32 (dd, $J = 13.5$, 8.4 Hz, 1H), 1.41 (s, 3H), 1.49 (s, 3H), 1.50 (s, 3H), 1.54 (dt, $J = 13.8$, 8.1 Hz, 1H), 1.60 (dd, $J = 13.5$, 7.2 Hz, 1H), 1.87 (qd, $J = 11.0$, 4.2 Hz, 1H), 2.07 (m, 1H), 2.22 (m, 1H), 2.43 (d, $J = 10.6$ Hz, 1H), 2.84 (d, $J = 12.9$ Hz, 1H), 2.86 (t, $J = 13.1$, 11.6 Hz, 1H), 3.23 (s, 3H), 3.59 (t, $J = 11.3$ Hz, 1H), 3.85 (m, 3H), 3.92 (d, $J = 12.9$ Hz, 1H), 3.98 (m, 2H), 4.18 (td, $J = 11.6$, 8.6 Hz, 1H), 5.54 (td, $J = 11.1$, 7.3 Hz, 1H), 5.76 (d, $J = 11.1$ Hz, 1H), 6.02 (d, $J = 16.3$ Hz, 1H), 6.06 (d, $J = 16.3$, 1H). ^{13}C NMR (75 MHz) δ 19.1, 24.4, 25.2, 25.3, 28.5, 29.8, 30.2, 33.9, 35.7, 36.2, 43.0, 44.2, 44.7, 53.4, 64.4 (2C), 66.2, 67.9, 81.6, 81.7, 98.1, 107.5, 129.1, 130.0, 134.1, 143.5. ESIMS (MeOH): 473.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{26}H_{42}O_6Na$ *m/z* 473.2879, found: 473.2869.

4.9. Preparation of compound 16

To a stirred solution of **13b** (121 mg, 0.27 mmol) and pyridine (8 μL, 0.10 mmol) in 2 mL of CH_2Cl_2 at room temperature was added MTO (0.8 mg, 0.003 mmol) followed by 0.03 mL (0.45 mmol) of 30% aqueous H_2O_2. After 12 h, the solution was diluted with CH_2Cl_2, washed with a solution of $Na_2S_2O_3$ and, following the usual workup, purified through a short column of silica gel (heptane–EtOAc, 1:1) to yield 122 mg (98%) of **16**: mp: 146 °C (heptane). IR (film): 2940, 1694, 1460, 1382, 1271, 1199, 1088, 1042, 864 cm^{-1}. ^1H NMR (800 MHz) δ 1.02 (s, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.42 (s, 3H), 1.47 (s, 6H), 1.59 (m, 2H), 1.77 (dd, $J = 14.6$, 4.5 Hz, 1H), 1.90 (m, 1H), 2.06 (dd, $J = 14.4$, 11.5 Hz, 1H), 2.17 (m, 1H), 2.46 (qd, $J = 11.1$, 4.4 Hz, 1H), 2.80 (dt, $J = 11.3$, 4.5 Hz, 1H), 2.82 (d, $J = 12.0$ Hz, 1H), 2.84 (d, $J = 4.4$ Hz, 1H), 3.34 (s, 3H), 3.38 (t, $J = 10.7$ Hz, 1H), 3.44 (dd, $J = 10.9$, 4.4 Hz, 1H), 3.78 (m, 1H), 3.82 (m, 2H), 3.98 (m, 2H), 5,66 (d, $J = 16.2$ Hz, 1H), 5.80 (d, $J = 16.2$ Hz, 1H). ^{13}C NMR (62.5 MHz) δ 19.1, 22.8, 25.1, 26.4, 26.6

(2C), 29.7, 35.2, 36.5, 38.4, 39.0, 43.9, 54.0, 54.5, 55.6, 62.6, 64.4, 64.5, 64.6, 70.3, 89.9, 98.5, 107.1, 125.4, 135.7, 214.7. ESIMS (MeOH): 487.4 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{26}H_{40}O_7Na$ m/z 487.2672, found: 487.2679.

4.10. Transannular epoxide opening

4.10.1. Preparation of the oxa-bridged 17 starting from 15. Over a stirred solution of **15** (155 mg, 0.34 mmol) and pyridine (8 μL, 0.10 mmol) in 7 mL of CH_2Cl_2 at room temperature was added MTO (0.8 mg, 0.003 mmol) followed by 0.06 mL (0.68 mmol) of 30% aq H_2O_2. After 12 h, the solution was diluted with CH_2Cl_2 and washed with a solution of $Na_2S_2O_3$ and brine. The mixture was dried over $MgSO_4$, concentrated, and purified through a short column of silica gel (heptane–EtOAc, 1:1) to give 146 mg (92%) of **17**: mp: 212–213 °C (heptane). IR (film): 3467, 2948, 1462, 1380, 1268, 1199, 1090, 1050, 867, 732 cm^{-1}. ^1H NMR (800 MHz) δ 0.93 (s, 3H), 1.04 (s, 3H), 1.30 (d, $J = 14.1$ Hz, 1H), 1.34 (s, 3H), 1.37 (dd, $J = 13.0$, 7.8 Hz, 1H), 1.39 (s, 3H), 1.48 (s, 3H), 1.49 (s, 3H), 1.52 (dt, $J = 13.1$, 7.8 Hz, 1H), 1.62 (s, 1H), 1.65 (qd, $J = 11.1$, 5.0 Hz, 1H), 2.05 (m, 1H), 2.10 (dt, $J = 13.1$, 8.0 Hz, 1H), 2.23 (dd, $J = 10.1$, 4.1 Hz, 1H), 2.29 (t, $J = 13.4$ Hz, 1H), 3.24 (s, 3H), 3.58 (t, $J = 11.5$ Hz, 1H), 3.71 (dd, $J = 12.0$, 5.0 Hz, 1H), 3.74 (d, $J = 4.8$ Hz, 1H), 3.85 (m, 2H), 3.98 (m, 2H), 4.04 (dt, $J = 11.8$, 7.8 Hz, 1H), 4.10 (m, 1H), 4.29 (d, $J = 4.1$ Hz, 1H), 5.73 (d, $J = 16.1$ Hz, 1H), 6.15 (d, $J = 16.1$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.2, 21.5, 25.1, 25.4, 27.6, 28.5, 30.0, 31.2, 40.4, 43.4, 43.8, 43.9, 46.7, 53.4, 64.6, 64.7, 65.7, 67.0, 70.6, 81.3, 89.8, 92.6, 98.2, 107.6, 130.1, 132.9. HRESIMS: calcd for $C_{26}H_{42}O_7Na$ m/z 489.2828, found: 489.2815. Anal. Calcd for $C_{26}H_{42}O_7$ (466.61): C, 66.93; H, 9.07. Found: C, 66.87; H, 9.11.

4.10.2. Preparation of the oxa-bridged 17 starting from 16. To an ice cold stirred solution of **16** (116 mg, 0.25 mmol) in 8 mL of dry THF, under an argon atmosphere, $LiAlH_4$ (76 mg, 2 mmol) was added. The mixture was stirred at reflux for 6 h. The reaction mixture was cooled to 0 °C, diluted with ether, and a small amount of water, 6 M aqueous NaOH, and water again were added successively (for each 1 g of $LiAlH_4$, 1 mL of water, 1 mL of 6 M NaOH, and 3 mL more water were added), and stirring continued at room temperature for 45 min. Rapid filtration on SiO_2 (eluent: EtOAc) and removal of solvent gave a residue, which was purified by silica gel chromatography (heptane–EtOAc, 2:1) to yield **17** (93 mg, 80%).

4.10.2.1. X-ray structure analysis. $C_{26}H_{42}O_7$, $M_r = 466.60$, orthorhombic, $P212121$, $a = 9.9716(3)$, $b = 13.1891(4)$, $c = 18.9328(6)$ Å, $V = 2489.97(13)$ $Å^{-3}$, $Z = 4$, $D_x = 1.245$ Mg m^{-3}, $\lambda(MoK\alpha) = 0.71073$ Å, $\mu = 0.89$ cm^{-1}, $F(000) = 1016$, $T = 120$ K. The sample ($0.45 \times 0.38 \times 0.38$ mm) is studied on a NONIUS Kappa CCD with graphite monochromatized MoKα radiation. The cell parameters are obtained with Denzo and Scalepack[32] with 10 frames (psi rotation: 1° per frame). The data collection (Nonius, 1999)[33] ($2\theta_{max} = 54°$, 58 frames via 2.0° omega rotation and 34 s per frame, range *HKL*: *H* 0,12 *K* 0,17 *L* 0,24) gave 3230 reflections. The data reduction with Denzo and Scalepack leads to 3205 independent reflections from which 2735 with $I > 2.0\sigma(I)$. The structure was solved with SIR-97,[34] which reveals the non-hydrogen atoms of the structure. After anisotropic refinement, many hydrogen atoms could be found with a Fourier Difference. The whole structure was refined with SHELXL97[35] by the full-matrix least-square techniques (use of *F* square magnitude; *x*, *y*, *z*, β_{ij} for O and C atoms, *x*, *y*, *z* in riding mode for H atoms; 299 variables and 2735 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(Fo^2) + (0.127P)^2 + 2.36P]$ where $P = (Fo^2 + 2Fc^2)/3$ with the resulting $R = 0.068$, $R_w = 0.185$ and $S_w = 1.009$, $\Delta\rho < 0.90$ e $Å^{-3}$).

Crystallographic data (excluding structure factors) for the structures reported herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 229578 (compound **24**), CCDC 283210 (compound **7**) and CCDC 283200 (compound **21**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21 EZ, UK [fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

4.11. Preparation of xanthate 20

To a stirred solution of **17** (44 mg, 0.09 mmol) in DMF (2 mL) at 0 °C, CS_2 (0.15 mL, 2.5 mmol) was added followed 5 min later by the addition of NaH (1.13 mg, 0.47 mmol). After 20 min, an excess of MeI (0.15 mL, 2.3 mmol) was added and the solution stirred for 1 h at 0 °C. The mixture was diluted with Et_2O and the reaction quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O. The usual workup and purification on silica gel (eluent heptane–EtOAc, 2:1) gave 48 mg (91%) of **20**: mp: 177 °C (heptane). IR (film): 2947, 1463, 1380, 1217, 1056 cm^{-1}. ^1H NMR (800 MHz) δ 1.05 (s, 6H), 1.31 (s, 3H), 1.34 (dd, $J = 13.1$, 7.9 Hz, 1H), 1.40 (s, 3H), 1.49 (s, 3H), 1.50 (s, 3H), 1.50 (m, 1H), 1.53 (dt, $J = 13.2$, 8.5 Hz, 1H), 1.67 (qd, $J = 10.8$, 5.0 Hz, 1H), 2.05 (m, 1H), 2.10 (m, 1H), 2.27 (dd, $J = 10.0$, 4.1 Hz, 1H), 2.34 (t, $J = 13.4$ Hz, 1H), 2.55 (s, 3H), 3.25 (s, 3H), 3.59 (t, $J = 11.8$ Hz, 1H), 3.73 (dd, $J = 12.0$, 5.0 Hz, 1H), 3.86 (m, 2H), 3.95 (d, $J = 5.0$ Hz, 1H), 3.99 (m, 2H), 4.05 (dt, $J = 11.8$, 8.2 Hz, 1H), 4.35 (d, $J = 4.2$ Hz, 1H), 5.75 (d, $J = 16.1$ Hz, 1H), 5.95 (ddd, $J = 12.8$, 4.8, 3.1 Hz, 1H), 6.16 (d, $J = 16.1$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.0, 19.1, 21.5, 25.0, 25.4, 27.0, 28.1, 29.9, 30.7, 39.2, 40.8, 43.4, 44.0, 46.5, 53.4, 64.5, 64.7, 65.6, 66.8, 80.3, 81.3, 86.6, 92.9, 98.1, 107.5, 129.6, 133.3, 214.9. ESIMS (MeOH): 579.2 ($[MNa]^+$, 100). HRESIMS: calcd for $C_{28}H_{44}O_7S_2Na$ m/z 579.2426, found: 579.2424. Anal. Calcd for $C_{28}H_{44}O_7S_2$ (556.77): C, 60.40; H, 7.97; S, 11.52. Found: C, 60.54; H, 7.86; S, 11.72.

4.11.1. X-ray structure analysis. $C_{28}H_{44}O_7S_2$, $M_r = 556.75$, monoclinic, $P2_1/n$, $a = 13.4019(2)$, $b = 16.6011(3)$, $c = 13.7749(2)$ Å, $\beta = 106.689(1)°$, $V =$

2935.6(1) Å^{-3}, $Z = 4$, $D_x = 1.260$ Mg m^{-3}, λ(MoKα) = 0.71073 Å, $\mu = 2.24$ cm^{-1}, $F(000) = 1022$, $T = 150$ K. The sample ($0.40 \times 0.32 \times 0.25$ mm) is studied on a NONIUS Kappa CCD with graphite monochromatized MoKα radiation. The cell parameters are obtained with Denzo and Scalepack with 10 frames (psi rotation: 1° per frame). The data collection (Nonius, 1999) ($2\theta_{max} = 54°$, 160 frames via 2.0° omega rotation and 30 s per frame, range *HKL*: *H* 0,17 *K* 0,21 *L* −17,17) gives 40,024 reflections. The data reduction with Denzo and Scalepack leads to 6731 independent reflections from which 5013 with $I > 2.0\sigma(I)$. The structure was solved with SIR-97, which reveals the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined with SHELXL97 by the full-matrix least-square techniques (use of *F* square magnitude; *x*, *y*, *z*, β_{ij} for C, S and O atoms, *x*, *y*, *z* in riding mode for H atoms; 335 variables and 5013 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(Fo^2) + (0.09P)^2 + 1.05P]$ where $P = (Fo^2 + 2Fc^2)/3$ with the resulting $R = 0.052$, $R_w = 0.141$ and $S_w = 0.992$, $\Delta\rho < 0.55$ e Å^{-3}).

4.12. C13–C14 hydrogenation—preparation of compound 18

This compound was produced by the same procedure described for **5**, by treatment of **17** (40 mg, 0.09 mmol) with Raney Nickel under a hydrogen atmosphere (0.14 g, 7.28 mmol) for 6 h to yield 29 mg (72%) of the reduced compound **18**: mp: 179 °C (heptane). IR (film): 3449, 2947, 1460, 1380, 1198, 1089, 1052 cm^{-1}. ^{1}H NMR (800 MHz) δ 1.00 (s, 3H), 1.10 (s, 3H), 1.24 (dq, $J = 14.0$, 3.1, 1.5 Hz, 1H), 1.33 (s, 3H), 1.34 (s, 3H), 1.36 (dd, $J = 13.2$, 8.2 Hz, 1H), 1.41 (s, 3H), 1.49 (s, 3H), 1.52 (dt, $J = 13.4$, 8.2 Hz, 1H), 1.58 (m, 2H), 1.60 (qd, $J = 11.3$, 5.1 Hz, 1H), 1.77–1.88 (m, 3H), 2.01 (dt, $J = 12.8$, 9.0 Hz, 1H), 2.09 (m, 1H), 2.20 (dd, $J = 10.0$, 4.1 Hz, 1H), 2.28 (t, $J = 13.4$ Hz, 1H), 3.30 (s, 3H), 3.58 (t, $J = 11.5$ Hz, 1H), 3.73 (dd, $J = 5.0$, 1.2 Hz, 1H), 3.82 (dd, $J = 12.1$, 5.0 Hz, 1H), 3.88–3.98 (m, 4H), 4.05 (dt, $J = 11.7$, 8.1 Hz, 1H), 4.08 (d, $J = 4.3$ Hz, 1H), 4.14 (m, 1H). ^{13}C NMR (62.5 MHz) δ 19.1, 21.5, 24.0, 25.0, 26.2, 26.9, 29.9 (2C), 30.9, 33.3, 42.0, 43.2, 44.0, 44.1, 46.1, 52.8, 64.7 (2C), 65.7, 66.9, 70.4, 82.6, 89.4, 92.6, 98.1, 110.2. ESIMS (MeOH): 491.3 ([MNa]$^+$, 100). Anal. Calcd for $C_{26}H_{44}O_7$ (468.62): C, 66.64; H, 9.46, found C 66.62; H, 9.75.

4.13. Periodinane oxidation of 18

To a solution of **18** (90 mg, 0.19 mmol) in dry methylene chloride (10 mL) and pyridine (0.16 mL) was added 245 mg (0.57 mmol) of Dess–Martin periodinane and stirring continued at room temperature for 1 h. The reaction was then diluted with methylene chloride, quenched with a saturated aqueous solution of sodium bicarbonate and washed with brine. The solution was then dried over $MgSO_4$ and the solvents evaporated. The product obtained was purified by chromatography (heptane–EtOAc, 1:1) to afford 88 mg (98%) of **7**: mp: 145 °C (heptane). IR (film): 2957, 1704, 1461, 1379, 1197, 1104, 858 cm^{-1}. ^{1}H NMR (800 MHz) δ 1.10 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 1.38 (s, 3H), 1.39 (m, 1H), 1.40 (s, 3H), 1.48 (s, 3H), 1.54 (m, 1H), 1.62 (m, 2H), 1.86 (td, $J = 13.4$, 6.2 Hz, 1H), 1.97 (m, 2H), 2.05 (t, $J = 13.6$ Hz, 1H), 2.10 (m, 3H), 3.01 (d, $J = 13.2$ Hz, 1H), 3.36 (s, 3H), 3.50 (t, $J = 12.2$ Hz, 1H), 6.65 (s, 1H), 3.91 (dt, $J = 11.7$, 8.2 Hz, 1H), 3.93 (m, 2H), 3.94 (dd, $J = 12.6$, 4.9 Hz, 1H), 3.99 (m, 2H), 4.13 (d, $J = 3.8$ Hz, 1H). ^{13}C NMR (75 MHz) δ 19.1, 20.9, 23.6, 24.0, 25.0, 25.7, 29.9, 30.3, 31.2, 33.2, 41.3, 42.3, 44.8, 45.8, 51.6, 54.8, 64.7 (2C), 65.3, 66.8, 80.2, 91.5, 92.5, 98.2, 110.1, 214.6. ESIMS (MeOH): 489.2 ([MNa]$^+$, 100). Anal. Calcd for $C_{26}H_{42}O_7$ (466.61): C, 66.93; H, 9.07, found C 66.97; H, 9.26.

4.13.1. X-ray structure analysis. $C_{26}H_{42}O_7$, $M_r = 466.60$, monoclinic, *C*2/*c*, $a = 31.9077(5)$, $b = 7.8550(1)$, $c = 21.7940(4)$ Å, $\beta = 112.635(1)°$, $V = 5041.6(1)$ Å^{-3}, $Z = 8$, $D_x = 1.229$ Mg m^{-3}, λ(MoKα) = 0.71073 Å, $\mu = 0.88$ cm^{-1}, $F(000) = 2032$, $T = 293$ K. The sample ($0.45 \times 0.22 \times 0.22$ mm) was studied on a NONIUS Kappa CCD with graphite monochromatized MoKα radiation. The cell parameters were obtained with a Denzo and Scalepack with 10 frames (psi rotation: 1° per frame). The data collection (Nonius, 1999) ($2\theta_{max} = 54°$, 204 frames via 1.8° omega rotation and 39 s per frame, range *HKL*: *H* 0,41 *K* 0,10 *L* −28,28) gave 38599 reflections. The data reduction with Denzo and Scalepack led to 5778 independent reflections from which 3716 with $I > 2.0\sigma(I)$. The structure was solved with SIR-97, which reveals the non-hydrogen atoms of the structure. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined with SHELXL97 by the full-matrix least-square techniques (use of *F* square magnitude; *x*, *y*, *z*, β_{ij} for O and C atoms, *x*, *y*, *z* in riding mode for H atoms; 299 variables and 3716 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(Fo^2) + (0.105P)^2 + 0.65P]$ where $P = (Fo^2 + 2Fc^2)/3$ with the resulting $R = 0.057$, $R_w = 0.163$ and $S_w = 1.073$, $\Delta\rho < 0.27$ e Å^{-3}).

4.14. Formation of phosphate 19

A solution of ketone **7** (81 mg, 0.17 mmol) in THF (0.5 mL) was added dropwise to a stirred solution of LDA (0.52 mmol) in 0.5 mL of THF at 0 °C. After 20 min, diethylchlorophosphate (0.075 mL, 0.52 mmol) was added. The cooling bath was removed and the mixture allowed to stir at ambient temperature for 80 min. The solution was diluted with ether and water was added. After extraction with ethyl acetate and usual workup, chromatography of the residue on silica gel (heptane–EtOAc, 2:1) gave 47 mg (46%) of **19**: mp: 119 °C (heptane). IR (film): 2958, 1458, 1381, 1268, 1034 cm^{-1}. ^{1}H NMR (800 MHz) δ 1.18 (s, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.33 (q, $J = 7.2$ Hz, 6H), 1.35 (m, 1H), 1.36 (s, 3H), 1.39 (s, 3H), 1.43 (m, 2H), 1.48 (s, 3H), 1.50 (m, 1H), 1.55 (m, 1H), 1.61 (d, $J = 11.7$ Hz, 1H), 1.73 (m, 2H), 1.97 (dt, $J = 12.8$, 8.6 Hz, 1H), 2.11 (m, 1H), 2.19 (d, $J = 12.1$ Hz, 1H), 2.44 (d, $J = 12.1$ Hz, 1H), 3.38 (s, 1H), 3.58 (t, $J = 11.2$ Hz, 1H), 3.75 (s, 1H), 3.78 (dd, $J = 11.6$, 4.7 Hz, 1H), 3.85

(m, 1H), 3.87–3.99 (m, 4H), 4.11 (m, 4H). ^{13}C NMR (75 MHz) δ 16.1, 16.2, 19.2, 19.4, 22.8, 23.7, 24.5, 24.9, 28.6, 29.9, 30.3, 33.3, 37.3, 43.9, 45.1, 47.5, 51.2, 63.7 (d, ^{2}J(C–P) = 6.3 Hz), 63.9 (d, ^{2}J(C–P) = 5.3 Hz), 64.8 (2C), 65.7, 67.5, 83.7, 86.4 (d, J(C–P) = 7.3 Hz), 88.5, 98.8, 107.4 (d, ^{3}J(C–P) = 5.2 Hz), 109.3. ESIMS (MeOH): 611.2 ([MNa]$^{+}$, 100). HRESIMS: calcd for $C_{29}H_{49}O_{10}PNa$ m/z 611.2961, found: 611.2950.

4.15. Preparation of TMS-enol ether 24

4.15.1. Method a (with LDA, TMSCl). To a solution of diisopropylamine (0.03 mL, 0.21 mmol) in THF (0.5 mL) at −70 °C was added a solution of *n*-butyllithium in hexanes (1.6 M, 0.13 mL, 0.21 mmol). The mixture was stirred at −70 °C for 1 h, then chlorotrimethylsilane (0.07 mL, 0.52 mmol) was added followed 5 min later by the dropwise addition of **22** (23 mg, 0.04 mmol) in 0.5 mL of THF. The mixture was stirred at the same temperature for 30 min and then diluted with pentane. After a rapid filtration of the salts, the solution was concentrated under vacuum and the products separated by flash chromatography (SiO_2, heptane–EtOAc, 3:1) to give **24** (6 mg, 23%) and **23** (17 mg, 74%).

4.15.2. Method b (with TMSIm, NaH). To a stirred solution of **22** (40 mg, 0.09 mmol) in 2 mL of THF at 0 °C was added an excess of TMSIm (0.06 mL, 0.43 mmol) followed 15 min later by an addition of NaH (5 mg, 0.2 mmol). After 30 min, the mixture was diluted with Et_2O. Usual workup and purification on silica gel (heptane–EtOAc, 2:1) afforded **24** (22 mg, 42%) and **23** (21 mg, 45%).

Compound **24:** ^{1}H NMR (800 MHz) δ 0.15 (s, 9H), 0.22 (s, 9H), 0.98 (s, 3H), 0.99 (s, 3H), 1.13 (m, 1H), 1.14 (s, 3H), 1.45 (s, 6H), 1.48 (s, 3H), 2.23 (tt, J = 11.4, 5.5 Hz, 1H), 2.95 (d, J = 10.1 Hz, 1H), 3.20 (d, J = 5.2 Hz, 1H), 3.51 (d, J = 5.1 Hz, 1H), 3.62 (t, J = 10.9 Hz, 1H), 3.84 (m, 2H), 3.90 (dd, J = 10.7, 4.6 Hz, 1H), 3.95 (m, 2H), 4.36 (d, J = 10.9 Hz, 1H), 4.43 (s, 1H), 4.80 (s, 1H), 5.69 (d, J = 15.2 Hz, 1H), 6.11 (d, J = 15.2 Hz, 1H). ^{13}C NMR (75 MHz) δ −0.1 (3C), 0.4 (3C), 19.3, 20.1, 25.2, 29.8, 30.1, 32.3, 36.3, 38.8, 39.6, 42.6, 53.3, 55.6, 63.0, 64.5 (2C), 65.4, 70.0, 70.4, 72.3, 99.7, 107.3, 114.7, 128.7, 130.1, 146.2.

Compound **23**: mp: 123 °C (heptane). IR (film): 2927, 1709, 1370, 1254, 1197, 1079, 1039, 844 cm^{-1}. ^{1}H NMR (800 MHz) δ 0.18 (s, 9H), 0.97 (s, 3H), 1.02 (s, 3H), 1.08 (s, 3H), 1.31 (t, J = 8.9 Hz, 1H), 1.47 (s, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 2.25 (tdd, J = 11.1, 6.5, 4.6 Hz, 1H), 2.50 (d, J = 13.7 Hz, 1H), 2.59 (d, J = 13.6 Hz, 1H), 3.03 (d, J = 9.1 Hz, 1H), 3.26 (d, J = 5.1 Hz, 1H), 3.51 (d, J = 5.1 Hz, 1H), 3.66 (t, J = 11.3 Hz, 1H), 3.86 (m, 2H), 3.96 (dd, J = 10.8, 4.4 Hz, 1H), 3.99 (m, 2H), 4.38 (d, J = 10.8 Hz, 1H), 4.63 (s, 1H), 5.78 (d, J = 15.1 Hz, 1H), 6.20 (d, J = 15.1 Hz, 1H). ^{13}C NMR (75 MHz) δ 0.2 (3C), 19.2, 19.6, 25.1, 25.9, 29.1, 29.7, 34.9, 41.1, 41.8, 42.1, 53.3, 54.3, 55.9, 64.5, 64.6, 65.4, 65.5, 69.6, 72.8, 78.0, 99.8, 107.1, 128.4, 131.6, 208.8. ESIMS (MeOH): 559.2 ([MNa]$^{+}$, 100). HRESIMS: calcd for $C_{28}H_{44}O_8SiNa$ m/z 559.2703, found: 559.2686.

4.16. C-11 hydroxylation—preparation of compound 25

To a solution of **24** (8 mg, 0.013 mmol) in 1 mL of dichloromethane at 0 °C were added $NaHCO_3$ (8 mg, 0.09 mmol) and *m*-CPBA (3 mg, 0.017 mmol). The mixture was stirred for 20 min at 0 °C, diluted with dichloromethane and successively washed with a 5% $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution and brine. The solution was dried over $MgSO_4$ and concentrated. Chromatography (SiO_2, heptane–EtOAc, 2:1) gave 7 mg (99%) of pure **25** as a white powder. Compound **25**: mp: 79 °C (heptane). IR (film): 3463, 2989, 1707, 1384, 1370, 1253, 1032, 847, 733 cm^{-1}. ^{1}H NMR (800 MHz) δ 0.20 (s, 9H), 0.85 (s, 3H), 0.90 (s, 3H), 1.17 (s, 3H), 1.39 (t, J = 7.5 Hz, 1H), 1.48 (s, 6H), 1.50 (s, 3H), 2.25 (m, 1H), 3.03 (d, J = 8.6 Hz, 1H), 3.28 (d, J = 5.1 Hz, 1H), 3.54 (d, J = 5.0 Hz, 1H), 3.68 (t, J = 11.3 Hz, 1H), 3.85 (m, 2H), 3.98 (m, 3H), 4.01 (dd, J = 10.9, 4.5 Hz, 1H), 4.12 (s, 1H), 4.35 (d, J = 10.9 Hz, 1H), 4.79 (s, 1H), 5.80 (d, J = 15.1 Hz, 1H), 6.10 (d, J = 15.1 Hz, 1H). ^{13}C NMR (75 MHz) δ 0.3 (3C), 19.1, 20.2, 20.7, 23.3, 25.1, 29.7, 40.2, 40.7, 42.5, 43.6, 53.4, 55.7, 64.5, 64.7, 65.4 (2C), 69.4, 73.9, 78.2, 79.6, 99.9, 107.1, 128.4, 132.2, 209.4. ESIMS (MeOH): 575.2 ([MNa]$^{+}$, 100). HRESIMS: calcd for $C_{28}H_{44}O_9SiNa$ m/z 575.2652, found: 575.2644.

4.17. Preparation of α-diketone 6

IBX (10 mg, 0.036 mmol) was dissolved in 1 mL of DMSO. After 10 min, **25** (5 mg, 0.009 mmol) was added and the solution stirred at 50 °C for 1 h and diluted with dichloromethane. Usual workup and chromatography (SiO_2, heptane–EtOAc, 2:1) gave 5 mg (98%) of **6**: mp: 79 °C (heptane). IR (film): 2988, 1715, 1370, 1253, 1196, 1106, 1039, 859 cm^{-1}. ^{1}H NMR (300 MHz) δ 0.24 (s, 9H), 0.88 (dd, J = 10.1, 5.6 Hz, 1H), 1.07 (s, 3H), 1.15 (s, 3H), 1.24 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 2.28 (m, 1H), 3.19 (d, J = 9.9 Hz, 1H), 3.29 (d, J = 5.2 Hz, 1H), 3.47 (d, J = 5.1 Hz, 1H), 3.59 (t, J = 11.2 Hz, 1H), 3.84 (m, 2H), 3.89 (dd, J = 10.9, 4.4 Hz, 1H), 3.98 (m, 2H), 4.33 (d, J = 10.9 Hz, 1H), 4.68 (s, 1H), 5.82 (d, J = 15.1 Hz, 1H), 6.06 (d, J = 15.1 Hz, 1H). ^{13}C NMR (75 MHz) δ 0.2 (3C), 19.1, 19.5, 20.6, 25.1, 25.2, 29.7, 40.1 (2C), 40.3, 46.9, 53.3, 55.7, 62.7, 64.6, 64.7, 65.2, 69.2, 70.6, 80.9, 99.9, 106.9, 125.9, 133.4, 206.4, 208.2. ESIMS (MeOH): 573.3 ([MNa]$^{+}$, 100). HRESIMS: calcd for $C_{28}H_{42}O_9SiNa$ m/z 573.2496, found: 573.2485.

Acknowledgments

The authors wish to thank the European Commission for a Research Training Grant to J. I. Candela Lena, Ministerio de Educacion y Cultura (Spain) for fellowships to J. Quílez del Moral and J. I. Martín Hernando, A.R.C. (Association pour la Recherche sur le Cancer, France) for a fellowship to M. Rico Ferreira, and

Professor Jean-Yves Lallemand for his kind interest and constant encouragements.

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