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Synthesis of a Norsesquiterpene Spirolactone/Steroidal Hybrid by Using an Environmentally Friendly Domino Reaction as a Key Step

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A new class of hybrid molecules is accessed by elaborating testosterone's AB ring into the norsesquiterpene spirolactone A′B′ ring. The cyclic ene-acetal **6b**, obtained by a PhI-$(OAc)_2$-mediated domino process from vicinal unsaturated diol **5**, is used for the synthesis of a norsesquiterpene spirolactone/testosterone hybrid. The route presented combines the advantages of domino reactions with the ease of functional group interchange on steroidal frameworks.

Introduction

A plethora of elegant approaches towards both naturally occurring and synthetic hybrid constructs[1] have been studied, and numerous natural and unnatural analogues have been prepared. Among various approaches, those with a steroid substructure are the best suited for studies towards new therapeutic compounds due to the broad spectrum of biological activity profile and wide occurrence of steroids. Tietze et al.[2] focused on the synthesis of a natural-product hybrid **I**, possessing the structural features of steroid estrone and mycotoxin talaromycin to design a new class of cytotoxic compounds. Danishefsky et al.[3] synthesized a baccatin III/cholesterol hybrid **II**, De Ricardis et al.[4] prepared a steroid/anthraquinone hybrid **III**, while De Clercq et al.[5] synthesized estramycin **IV**, by installing an enediyne moiety on the D ring of estrone (Figure 1).

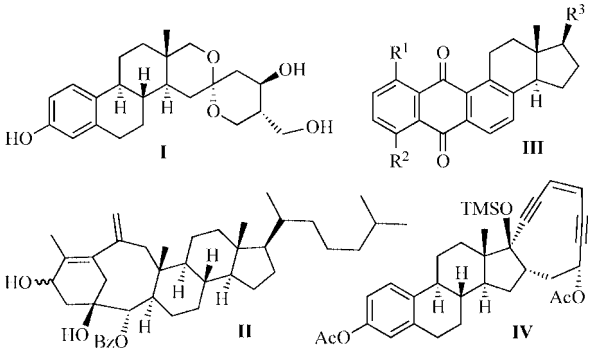

Figure 1. Representative examples of hybrids based on the steroid framework.

Methodology towards modified steroids that allows for the easy incorporation of oxygen or nitrogen into the steroid A ring could be useful for the synthesis of substrates that could affect metabolism.[6] We have previously reported on a straightforward preparation of skeleton-modified steroids using a domino reaction[7] developed in our laboratories.[8] Following these promising achievements, our subsequent goal was to combine pathylactone (**1a**)[9] and napalilactone (**1b**),[10] two rare norsesquiterpenes, with testosterone (**2**) to design a new class of hybrid molecules, which could exhibit an interesting biological profile. Isolated from marine sources, these two norsesquiterpene spirolactones differ only in the C1 substitution,[11] which is hydroxy and chloro, respectively (Figure 2). The cyclohexane core of **1** exhibits an impressive array of functionalities that include four heteroatom-substituted carbon atoms, four contiguous stereocentres (two of them quaternary) and a spiro-fused γ-lactone ring. Pathylactone A (**1a**, isolated from the soft coral *Paralemnalia thyrsoides*), reported to be a Ca^{2+} antagonist, is the first γ-spirolactone norsesquiterpenoid from a marine organism, while napalilactone (**1b**, isolated from *Lemnalia africana*) is the first halogenated norsesquiterpenoid from a soft coral. To the best of our knowledge, steroid/norsesquiterpene spirolactone hybrid constructs are not known, while the norsesquiterpene spirolactone framework itself remains scarce, even for the purpose of relatively small-scale research and tests. There is thus a need for syntheses of such hybrids that would employ readily available starting materials and that would be accomplished in a reasonable number of steps.

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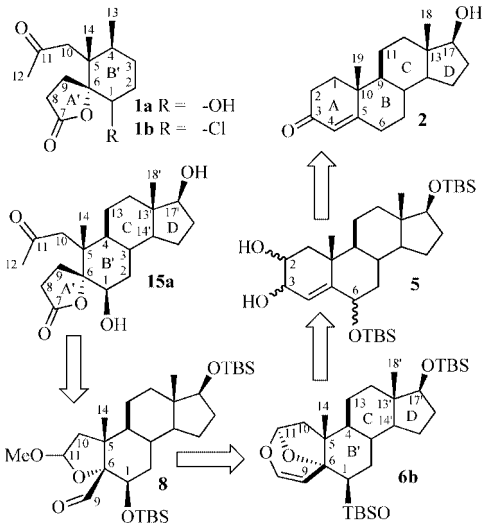


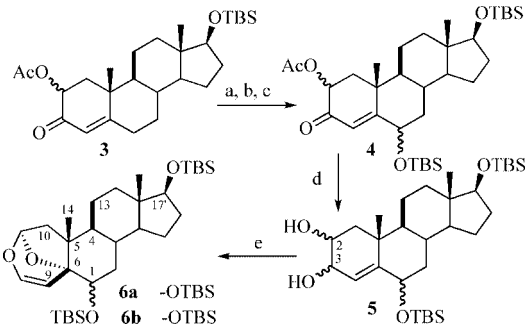
Figure 2. Retrosynthetic analysis based upon the key building block **6b**, derived from a domino reaction.

The route we propose (Figure 2) allows for a versatile entry into the hybrid spirolactone/testosterone skeleton, where the key A′B′CD ring system is assembled in nine steps from the domino product **6b**. Reported in this paper are the details of our approach, which culminated in an efficient synthesis of the main hybrid construct **15a** and allows access for several diversely substituted analogues.

Results and Discussion

The elaboration of the A′B′ part of the norsesquiterpene spirolactone framework formed most of the chemistry in this synthesis. This has been possible because of the easy access to the key building block **6**, obtained in multi-gram quantities via **3** (Scheme 1). The roughly 1:1 epimeric mixture of the latter was prepared from commercially available testosterone by the TBS protection of the C17 hydroxy group and subsequent acetoxylation, proceeding as in ref.[8] The α-acetoxyenone **3** thus obtained was first converted into its corresponding dienol diacetate and then was subjected to epoxidation[12] followed by TBS protection leading to a mixture of stereoisomeric allylic alcohols **4**, which in turn afforded the requisite 1,2-unsaturated diols **5** in good yields upon reduction.[13]

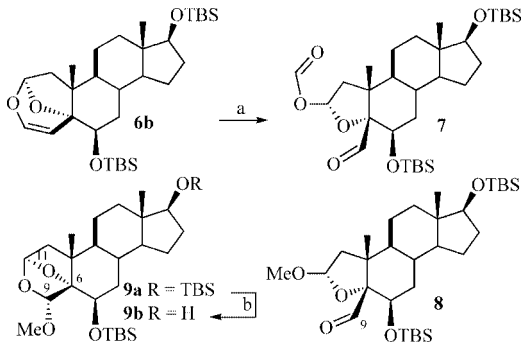
The initial problem to be addressed in the retrosynthetic analysis of Figure 2 was the conversion of the steroidal *vic*-unsaturated diol **5** to a spirolactone precursor **8**, already containing the two quaternary centres at C5 and C6 in their desired configuration.[14] Thus, to achieve the oxidative cleavage of **5**, initially we used 1 equiv. of $Pb(OAc)_4$ as the domino promoter in a stoichiometry-controlled domino reaction (PhMe, 25 °C, ca. 2–5 h, TLC monitoring).[15] With ever-growing environmental concern, we later developed a green protocol[16] using $PhI(OAc)_2$ as the oxidant,[17] which shows a reactivity pattern similar to that of $Pb(OAc)_4$. Under these conditions (Scheme 1) the oxidative pericyclic domino reaction allowed for easy access of the target A-



Scheme 1. (a) Ac_2O, py, DMAP, reflux, 24 h (98%); (b) MTO, 30% H_2O_2, py, CH_2Cl_2, 25 °C, 36 h (67% + 14% SM); (c) TBSCl, imidazole, DMF, 60 °C, 24 h (87% + 10% SM); (d) $LiAlH_4$, Et_2O, 0 °C, 30 min (96%); (e) $PhI(OAc)_2$, CH_3CN, 25 °C, 14 h (90%).

norsteroid **6** on large scale and in high isolated yields as an epimeric mixture (**6b**/**6a** = 4:1, 90% combined yield). The only necessary chromatographic separation of stereoisomers was carried out at this stage, and the pure major isomer **6b** was taken into the synthetic scheme. Our main effort was then directed at the problem of converting it into the fused methyl furanoside **8**. A convenient procedure was the ozonolytic cleavage of the glycal **6b**, which was initially carried out in CH_2Cl_2 followed by an Me_2S workup giving the expected **7** (unstable on standing even after chromatographic purification) but none of **8** (desired) or **9a**.

By performing the ozonolysis in methanol (–78 °C, 20 min) and the reductive workup as described above, a mixture of **7**, **8** and **9a** was produced, in a 74% combined yield and 6:2:1 ratio (Scheme 2). Finally, the best conversion was obtained by stirring the reaction mixture thus obtained at room temperature for 22 h before workup. Under these conditions a 98% overall yield of only two compounds, **8** and **9a**, was reproducibly obtained in a 2.3:1 ratio. The methyl furanoside **8** was obtained and characterized as an anomeric mixture (β/α = 10:0.7), as the anomeric carbon atom has no long-term significance since it is programmed to be destroyed in later steps.[18] The bond connectivity and relative stereochemistry in **9a** were unambiguously confirmed by extensive ^1H and ^{13}C NMR studies, while additional confirmation was provided by the X-ray analysis of its mono-deprotected derivative **9b** (Figure 3).



Scheme 2. (a) O_3, MeOH, –78 °C to 25 °C, Me_2S, 1 h (74%, **7**/**8**/**9a** = 6:2:1) or 22 h (98%, **7**/**8**/**9a** = 0:2.3:1); (b) TBAF, 25 °C–40 °C, 18 h (46% **9b** + 44% **9a**).

To this end, the bis(TBS)-protected **9a** was partially deprotected (Scheme 2, TLC monitoring) to give the crystalline **9b** (46% yield) along with **9a** remaining intact (44% yield).

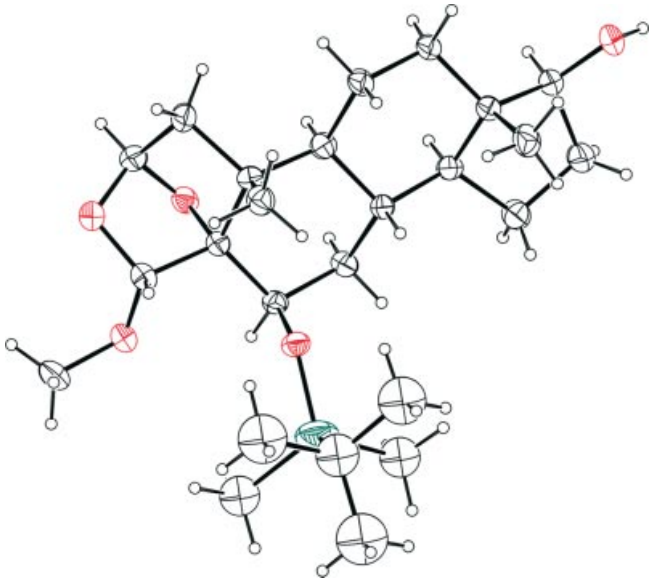
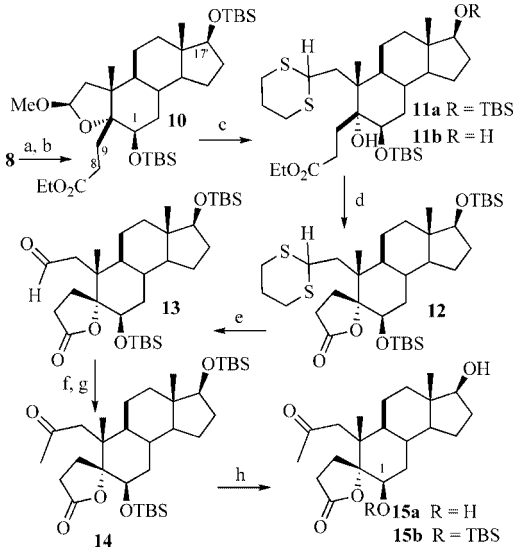


Figure 3. ORTEP view of the molecular structure of **9b** (O: red; Si: green).



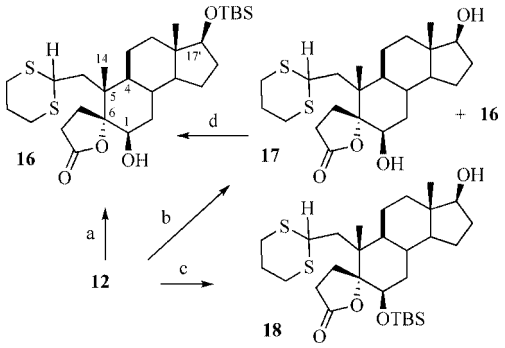
Scheme 3. (a) $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, THF, 25 °C, 14 h (97%); (b) H_2, Pd/C, MeOH, 25 °C, 16 h (99%); (c) $HS(CH_2)_3SH$, $TiCl_4$, –78 °C to –40 °C, 15 min (49% **11a** + 46% **11b**); (d) K_2CO_3, $MeOH/H_2O$ (10:1), 25 °C, 1.5 h (91%); (e) $HgCl_2$, $CaCO_3$, acetone/H_2O (10:1), reflux, 1 h (96%); (f) Me_3Al (2 M in hexanes), CH_2Cl_2, 0 °C, 20 min (94%); (g) DMP, py, CH_2Cl_2, 25 °C, 3 h (86%); (h) HF/CH_3CN (1:1), 25 °C, 2 d (58% **15a** + 38% **15b**).

From this point, the two-carbon-homologated derivative, hydroxy ester **11**, which would serve as the spirolactone precursor, was easily prepared as follows. The Wadsworth–Emmons coupling of aldehyde **8** with commercially available phosphonate $(EtO)_2P(O)CH_2CO_2Et$ (Scheme 3) proceeded smoothly affording cleanly the (*E*)-conjugated ester in 97% yield. The reduction of the C8–C9 olefin furnished the corresponding methyl furanoside **10** (99% isolated yield). Transthioacetalisation of the O,O-acetal **10** thus obtained was carried out under Lewis-acid catalysis. Accordingly, with $TiCl_4$ as the Lewis acid, in dichloromethane, methyl furanoside opening on **10** was realized, affording the requisite bis(TBS)-protected **11a** along with its mono-deprotected (at C17′) alcohol **11b** which could be recycled, in excellent combined yield (approximately 1:1 ratio, 95% yield).

With the dithiane derivative **11a** in hand, our main effort was then directed at the problem of converting it into the homologated methyl ketone **14** (Scheme 3). First, spirolactonisation of γ-hydroxy ester **11a** was carried out by its treatment with a mild base (K_2CO_3) affording cleanly the desired spirolactone **12** (91% yield).[19] The unveiling of the aldehyde function was then accomplished through the action of $HgCl_2$ in acetone/water, in the presence of $CaCO_3$ leading to **13** in 96% isolated yield. Conversion of the latter into the desired ketone **14** was accomplished by a simply executed sequence, which involved the treatment of **13** with Me_3Al in hexanes,[20] to provide the corresponding methyl carbinol as an epimeric mixture (94% yield) that was oxidized with Dess–Martin's periodinane to afford **14** (86% yield). This route proved superior to the alternative two-step procedure, consisting of a Wittig olefination of the aldehyde **13** followed by a Wacker oxidation, a route used in previous publications by Vyvyan et al.[9d] as well as Coelho et al.[9b,21]

To complete the synthesis of the targeted hybrid molecule **15a**, only the deprotection of the C1 and C17′ hydroxy groups remained. The initial attempts to remove the TBS groups using standard procedures such as tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 60 °C, 1 h) or camphorsulfonic acid (CSA, MeOH, 25 °C) resulted in either partial deprotection or formation of undesired side products.[22] These complications were bypassed by carrying out the cleavage of the silyl protecting groups with aqueous HF, used in ref.[9b] Accordingly, subjecting the bis(TBS)-protected precursor to these conditions (Scheme 3) provided a 91% yield of **15b** and a 9% yield of **15a** after 20 min. Prolonged reaction times (2 d) raised the yield of the target **15a** to 58%, obtained alongside the mono-deprotected **15b** (38% yield).

The overall efficiency of this process can be easily expanded to related ring systems with varying substitution at C1 and C17′. Subsequent to a chemoselective manipulation of the C1 and C17′ hydroxy groups (due to a marked steric differentiation), the synthesis of several hybrid molecules can be performed by the conversion of the free hydroxy group to a given functionality. As shown in Scheme 4, starting from **12**, fluoride-induced deprotection afforded cleanly the C1-mono-deprotected **16** as the sole product. However, by performing the same reaction at higher temperatures the fully deprotected **17** and the mono-deprotected **16** were obtained as a mixture (in a 1.8:1 ratio and a nearly quantitative yield). On the other hand, selective deprotection at C17′ can be carried out by using HF/MeCN to afford **18** in 92% isolated yield along with trace amounts of **17**.



Scheme 4. (a) TBAF, 25 °C, 3 h (85%); (b) TBAF, 50 °C, 2 h (67% **17** + 31% **16**; (c) HF/MeCN (1:1), 25 °C, 20 min (92%); (d) TBSCl, imidazole, DMF, 25 °C, 3 h (82%).

The mono-protected **16** can also be prepared from the fully deprotected **17** by TBS protection at C17′, since the C17′ hydroxy group is regioselectively protected as its corresponding TBS ether by its reaction with TBSCl (Scheme 4). The configurational assignments of the entire modified steroid-spirolactone core **17** were secured by spatial proximity studies using 1D NOEDIFF and NOESY techniques, and further corroborated by X-ray structure analysis (an ORTEP diagram is displayed in Figure 4).

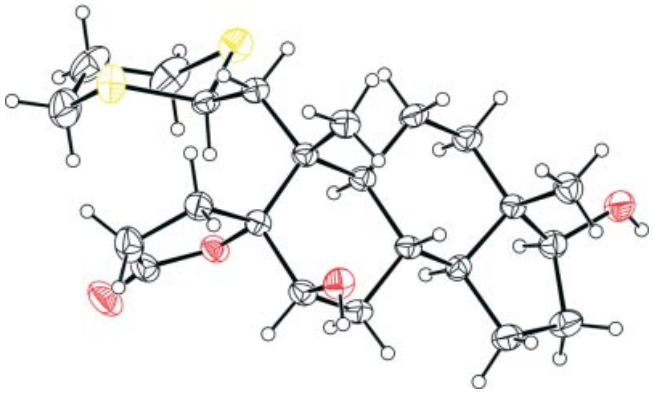


Figure 4. ORTEP view of the molecular structure of **17** (S: yellow; O: red).

Conclusions

The work reported here focused on the construction of the hybrid framework **15**, which belongs to the fourth class of Tietze's classification[1b] being a synthetic hybrid of partial structures of natural products. Its synthesis relied on previously reported methodology, an environmentally friendly domino reaction, developed in our laboratory, for elaborating the spirolactone moiety (A′B′ rings). The approach is flexible and should permit a range of substituents to be introduced on all rings, except the steroid C ring. The route followed is operationally simple and serves to further validate the synthetic utility of our domino methodology by allowing for practical access to a number of analogues for biological evaluation.

Experimental Section

General: "Usual workup" means washing of the organic layer with brine, drying with anhydrous $MgSO_4$, and concentrating in vacuo in a rotary evaporator at aspirator pressure. Melting points (uncorrected) were determined with the aid of a Büchi B-540 apparatus. IR spectra were recorded with a Perkin–Elmer Spectrum BX instrument with an FT-IR system. Absorptions are given in cm^{-1}. Optical rotations were measured with a JASCO-810 polarimeter using a cell of 1 dm path length. NMR spectra were performed in $CDCl_3$ unless otherwise noted. Experimental evidence favouring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR spectroscopic data (500 MHz and 125 MHz or 300 MHz and 75 MHz, respectively, 1D and 2D experiments) and corroborated by spatial proximity (NOE) studies using mainly the 1D NOEDIFF technique.[23] For all compounds investigated, the multiplicities of ^{13}C resonances were assigned by the SEFT technique.[24] ^1H chemical shifts are expressed in ppm downfield from TMS using the residual nondeuterated solvent as the internal standard ($CDCl_3$, ^1H: δ = 7.26 ppm). ^{13}C chemical shifts are reported relative to the $CDCl_3$ triplet centred at δ = 77.0 ppm. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^+) using a mobile phase of MeOH, are abbreviated as ESIMS (MeOH). HR is added for high-resolution mass measurements (HRESIMS). Full experimental details and product characterization (FT-IR, ^1H NMR, ^{13}C NMR, ESIMS, HRESIMS, elemental analysis, specific rotation, melting point, X-ray analysis for **9b** and **17**) for all compounds obtained in this work are given in the Supporting Information. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. CCDC-620323 (**9b**) and -620082 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Oxidative Cleavage of Unsaturated Diols 5. Preparation of the A-Ring-Modified Steroid 6 (Domino Product): A dry flask was charged with unsaturated diol **5** (11.00 g, 19.96 mmol) and $PhI(OAc)_2$ (7.74 g, 23.95 mmol), evacuated, flushed with argon and cooled to 0 °C. Acetonitrile (100 mL) was then added, and the cooling bath was removed soon after. The mixture was stirred at room temperature for 24 h (TLC monitoring), diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$, and subjected to the usual workup. The residue was purified by SiO_2 chromatography (heptane/EtOAc, 99:1) to give an epimeric mixture of the target A-nor-steroid **6** (9.87 g, **6a/6b** = 1:4, 90% isolated yield).

Faster-Eluting Isomer 6b (β-OTBS): White solid; m.p. 89–91 °C. $[\alpha]_D^{20}$ = 1 (c = 1.38, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2927, 2855, 1630, 1471, 1462, 1360, 1253, 1201, 1178, 1136, 1094, 1066, 1008, 954, 938, 903, 879, 833, 773, 734, 668 cm^{-1}. ^1H NMR (500 MHz): δ = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.06 (s, 3 H), 0.08 (s, 3 H), 0.72 (s, 3 H), 0.88 (s, 9 H), 0.89 (m, 1 H), 0.91 (s, 9 H), 0.97 (td, J = 4.2, 12.6 Hz, 1 H), 1.04 (ddd, J = 1.9, 4.7, 12.8 Hz, 1 H), 1.14 (s, 3 H), 1.21 (dd, J = 5.9, 12.2 Hz, 1 H), 1.34 (m, 2 H), 1.39 (dd, J = 2.4, 13.8 Hz, 1 H), 1.45 (m, 1 H), 1.57 (m, 1 H), 1.59 (dt, J = 3.1, 13.6 Hz, 1 H), 1.67 (qd, J = 3.1, 11.1 Hz, 1 H), 1.76 (dt, J = 3.1, 12.1 Hz, 1 H), 1.86 (dd, J = 1.2, 13.8 Hz, 1 H), 1.90 (dd, J = 5.2, 8.8 Hz, 1 H), 2.17 (dd, J = 5.8, 13.8 Hz, 1 H), 3.55 (t, J = 8.3 Hz, 1 H), 3.98 (t, J = 2.8 Hz, 1 H), 5.29 (d, J = 6.2 Hz, 1 H), 5.54 (d, J = 5.4 Hz, 1 H), 6.24 (d, J = 6.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.1, –4.8, –4.5, –4.3, 11.3, 15.2, 18.0, 18.1, 21.4, 23.4, 25.8 (3 C), 25.9 (3 C), 29.3, 31.0, 34.0, 37.3, 43.6, 47.8, 48.2, 49.8, 53.6, 69.3, 81.7, 83.2, 99.5, 108.6, 139.3 ppm. ESIMS (CH_2Cl_2

+ MeOH): *m/z* (%) = 571.3 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{31}H_{56}NaO_4Si_2$ 571.3615; found 571.3632. $C_{31}H_{56}O_4Si_2$ (548.94): calcd. C 67.83, H 10.28; found C 67.86, H 10.14.

Slower-Eluting Isomer 6a (α-OTBS): White solid; m.p. 164–167 °C. $[\alpha]_D^{20}$ = +11 (*c* = 0.87, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2927, 2855, 1639, 1472, 1462, 1389, 1360, 1254, 1203, 1131, 1111, 1089, 1033, 1007, 929, 883, 836, 774, 668 cm^{-1}. ^1H NMR (500 MHz): δ = 0.00 (2 s, 6 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.70 (s, 3 H), 0.87 (s, 9 H), 0.89 (s, 9 H), 0.98 (m, 2 H), 1.05 (s, 3 H), 1.06 (m, 1 H), 1.24 (dd, *J* = 5.9, 12.4 Hz, 1 H), 1.30 (m, 3 H), 1.43 (m, 2 H), 1.58 (m, 1 H), 1.62 (ddd, *J* = 3.3, 4.9, 12.4 Hz, 1 H), 1.74 (dt, *J* = 3.0, 12.3 Hz, 1 H), 1.89 (m, 1 H), 1.90 (d, *J* = 13.9 Hz, 1 H), 2.15 (dd, *J* = 5.9, 13.8 Hz, 1 H), 3.55 (t, *J* = 8.3 Hz, 1 H), 3.61 (dd, *J* = 4.7, 11.7 Hz, 1 H), 4.85 (d, *J* = 6.2 Hz, 1 H), 5.60 (d, *J* = 5.5 Hz, 1 H), 6.23 (d, *J* = 6.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –4.8, –4.6, –4.5, –3.8, 11.4, 14.1, 18.1, 18.3, 21.5, 23.5, 25.9 (3 C), 26.0 (3 C), 30.9, 34.9, 35.4, 37.1, 43.5, 47.2, 47.5, 49.9, 56.0, 71.2, 81.6, 85.7, 99.4, 109.6, 139.7 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 571.3 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{31}H_{56}NaO_4Si_2$ 571.3615; found 571.3623. $C_{31}H_{56}O_4Si_2 + 0.1H_2O$ (548.94): C 68.12, H 10.39; found: C 68.15, H 10.42.

Ozonolysis of the Major Domino Product 6b. Preparation of the Key Intermediate Methyl Furanoside 8: Ozone was passed into a stirred solution of **6b** (768 mg, 13.99 mmol) in MeOH (100 mL) at –78 °C until a purple-blue colour persisted. Me_2S (ca. 11 mL) was added. The reaction mixture was allowed to reach room temperature within 1 h, concentrated under reduced pressure, and the residue was flash-chromatographed on SiO_2. Elution with heptane/EtOAc (98:2) afforded a 74% yield of **7/8/9a** as a 6:2:1 mixture. Under the same reaction conditions, but stirring the reaction mixture for 22 h, transacetalisation was complete leading to a 2.3:1 mixture of **8** and **9a** (no more **7** was obtained). **7** was isolated pure for both characterization and test reactions for mechanistic purposes. The highest anomeric purity for **8** was 20:1 (β/α).

7: Colourless oil. $[\alpha]_D^{20}$ = –11 (*c* = 1.02, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2927, 2854, 1731, 1471, 1462, 1387, 1360, 1254, 1088, 1067, 960, 832, 774, 667 cm^{-1}. ^1H NMR (500 MHz): δ = –0.07 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.72 (s, 3 H), 0.85 (s, 9 H), 0.86 (s, 9 H), 0.98 (m, 1 H), 1.27 (m, 2 H), 1.31 (s, 3 H), 1.42 (m, 4 H), 1.63 (td, *J* = 3.2, 14.0 Hz, 1 H), 1.66 (m, 2 H), 1.70 (m, 2 H), 1.80 (td, *J* = 2.7, 12.7 Hz, 1 H), 1.89 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.41 (dd, *J* = 6.0, 13.7 Hz, 1 H), 3.55 (t, *J* = 8.2 Hz, 1 H), 4.21 (t, *J* = 2.7 Hz, 1 H), 6.31 (t, *J* = 5.5 Hz, 1 H), 8.02 (s, 1 H), 9.74 (s, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5, –4.2, 11.2, 14.4, 17.8, 17.9, 21.1, 23.3, 25.6 (3 C), 25.8 (3 C), 29.1, 30.9, 33.5, 37.0, 43.2, 43.4, 46.2, 47.3, 49.8, 68.0, 81.5, 88.2, 97.3, 160.3, 200.9 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 603.3 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{31}H_{56}NaO_6Si_2$ 603.3513; found 603.3471.

Methyl Furanoside 8 [20:1 (β/α) Mixture Described]: Colourless oil. IR (film): $\tilde{\nu}$ = 2954, 2856, 1727, 1471, 1381, 1256, 1088, 1065, 902, 834, 775, 668 cm^{-1}. ^1H NMR (500 MHz): δ = 0.00 (2 s, 6 H), 0.02 (s, 3 H), 0.08 (s, 3 H), 0.74 (s, 3 H), 0.87 (s, 9 H), 0.90 (s, 9 H), 1.01 (m, 1 H), 1.08 (dd, *J* = 4.6, 12.4 Hz, 1 H), 1.18 (s, 3 H), 1.24 (dd, *J* = 5.8, 12.2 Hz, 1 H), 1.44 (m, 4 H), 1.61 (m, 3 H), 1.77 (dd, *J* = 6.5, 13.4 Hz, 1 H), 1.77 (m, 1 H), 1.89 (m, 2 H), 1.91 (d, *J* = 13.7 Hz, 1 H), 3.36 (s, 3 H), 3.59 (t, *J* = 8.3 Hz, 1 H), 4.14 (s, 1 H), 5.16 (d, *J* = 6.7 Hz, 1 H), 10.04 (s, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5, –4.1, 11.2, 16.0, 18.0, 18.1, 21.0, 23.4, 25.7 (3 C), 25.9 (3 C), 29.3, 31.0, 33.8, 37.1, 43.4, 43.8, 43.9, 45.6, 49.8, 55.9, 69.2, 81.6, 89.6, 104.9, 206.2 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 589.4 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{31}H_{58}NaO_5Si_2$ 589.3721; found 589.3755.

9a: Orange oil. $[\alpha]_D^{20}$ = –40 (*c* = 1.59, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2928, 2855, 1471, 1462, 1387, 1360, 1251, 1094, 1078, 1066, 1019, 939, 881, 834, 774 cm^{-1}. ^1H NMR (500 MHz): δ = 0.00 (2 s, 6 H), 0.04 (s, 3 H), 0.07 (s, 3 H), 0.73 (s, 3 H), 0.87 (s, 9 H), 0.89 (s, 9 H), 0.92 (m, 2 H), 1.02 (ddd, *J* = 3.4, 10.1, 11.5 Hz, 1 H), 1.17 (s, 3 H), 1.22 (dd, *J* = 5.9, 12.1 Hz, 1 H), 1.29 (m, 2 H), 1.44 (d, *J* = 12.1 Hz, 2 H), 1.44 (m, 2 H), 1.58 (m, 1 H), 1.67 (dd, *J* = 2.6, 12.1 Hz, 1 H), 1.73 (dt, *J* = 3.3, 13.9 Hz, 1 H), 1.78 (m, 1 H), 1.88 (m, 1 H), 3.36 (s, 3 H), 3.53 (t, *J* = 8.3 Hz, 1 H), 4.46 (t, *J* = 2.6 Hz, 1 H), 4.95 (s, 1 H), 5.60 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5 (2 C), 11.2, 16.2, 18.0, 18.1, 21.1, 23.4, 25.8 (3 C), 25.9 (3 C), 30.1, 30.9, 35.5, 37.2, 41.0, 43.4, 48.7, 49.8, 50.5, 54.4, 66.1, 81.6, 89.2, 100.4, 102.5 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 589.4 (100) $[M + Na]^+$, 1155.8 (49) $[2 M + Na]^+$. HRESIMS: calcd. for $C_{31}H_{58}NaO_5Si_2$ 589.3721; found 589.3728. $C_{31}H_{58}O_5Si_2 + 0.3H_2O$ (566.96): calcd. C 65.54, H 10.42; found C 65.46, H 10.31.

Two-Carbon Homologation of 8: To a solution of $(EtO)_2P(O)CH_2CO_2Et$ (1.7 mL, 8.67 mmol) in dry THF (25 mL) was added at –78 °C under argon, NaHMDS (1.0 M in THF, 8.7 mL, 8.67 mmol). The resulting solution was stirred at –78 °C for 1 h before **8** (820 mg, 1.44 mmol) was added in dry THF (25 mL). The cooling bath was removed, and the solution was stirred at room temperature while the reaction progress was monitored by TLC. After 14 h of stirring, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aq. Na_2SO_3, saturated aq. $NaHCO_3$ and H_2O. The usual workup and chromatography on SiO_2 (heptane/EtOAc, 4:1) gave the conjugated ester (890 mg, 97% yield), characterized as an epimeric mixture (α,β-OMe): Yellow oil. IR (film): $\tilde{\nu}$ = 2953, 2928, 2856, 1720, 1471, 1388, 1362, 1305, 1256, 1174, 1087, 1065, 1027, 1007, 906, 834 cm^{-1}. ESIMS (MeOH): *m/z* (%) = 659.4 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{35}H_{64}NaO_6Si_2$ 659.4139; found 659.4122.

Reduction of the C8–C9 Olefin: The conjugated ester was hydrogenated by first placing palladium (10% w/w) on activated carbon (833 mg, 8.30 mmol) in a flask, followed by the conjugated ester (1.76 g, 2.76 mmol) dissolved in MeOH (150 mL). The mixture was allowed to react for 16 h. After removing the solvents without heating and dilution of the residue with EtOAc, the catalyst was removed by filtration through Celite, rinsing with EtOAc. The usual workup and chromatography on SiO_2 (heptane/EtOAc, 80:1) gave **10** (1.75 g, 99% yield). The stereochemistry was as depicted; the minor anomer (present in the 20:1 anomeric mixture of starting methyl furanoside **8**) could not be isolated pure.

10: White solid; m.p. 99–101 °C. $[\alpha]_D^{20}$ = +32 (*c* = 1.01, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2928, 2856, 1736, 1471, 1461, 1382, 1251, 1137, 1085, 1066, 1030, 1005, 972, 947, 903, 832, 773 cm^{-1}. ^1H NMR (500 MHz): δ = –0.01 (s, 3 H), 0.00 (s, 3 H), 0.05 (s, 3 H), 0.07 (s, 3 H), 0.71 (s, 3 H), 0.87 (s, 9 H), 0.88 (s, 9 H), 0.94 (s, 3 H), 0.98 (ddd, *J* = 4.3, 6.6, 11.0 Hz, 1 H), 1.04 (ddd, *J* = 7.3, 9.7, 12.3 Hz, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.25 (m, 1 H), 1.42 (m, 4 H), 1.54 (m, 3 H), 1.67 (m, 2 H), 1.74 (dt, *J* = 3.1, 12.3 Hz, 1 H), 1.86 (d, *J* = 13.6 Hz, 1 H), 1.87 (m, 1 H), 1.96 (dd, *J* = 6.9, 13.7 Hz, 1 H), 2.12 (ddd, *J* = 5.4, 9.8, 13.8 Hz, 1 H), 2.22 (ddd, *J* = 5.4, 9.9, 15.4 Hz, 1 H), 2.39 (ddd, *J* = 6.2, 9.7, 15.7 Hz, 1 H), 3.28 (s, 3 H), 3.57 (t, *J* = 3.6 Hz, 1 H), 3.89 (dd, *J* = 2.5, 3.3 Hz, 1 H), 4.12 (qd, *J* = 3.5, 7.1 Hz, 2 H), 4.80 (dd, *J* = 1.4, 6.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.4, –4.8, –4.5, –3.8, 11.2, 14.3, 15.3, 18.0, 18.1, 22.3, 23.3, 25.7 (3 C), 25.8 (3 C), 27.6, 28.4, 29.1, 31.0, 33.5, 37.4, 43.4, 44.5, 44.6, 46.3, 50.2, 55.6, 60.2, 67.8, 81.7, 86.4, 103.8,

174.5 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 661.4 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{35}H_{66}NaO_6Si_2$ 661.4296; found 661.4277. $C_{35}H_{66}O_6Si_2$ (639.07): calcd. C 65.78, H 10.41; found C 66.06, H 10.21.

Transthioketalisation. Preparation of Spirolactone Precursor 11a: A solution of **10** (300 mg, 0.47 mmol) and propanedithiol (0.19 mL, 1.87 mmol) in CH_2Cl_2 (10 mL) at –78 °C was treated with $TiCl_4$ (0.1 mL, 0.56 mmol). The resulting solution was then warmed slowly to –40 °C and maintained at –40 °C for 15 min. The reaction was then quenched by the addition of saturated aq. Na_2CO_3 and diluted with diethyl ether. The layers were separated, and the aq. layer was extracted with diethyl ether. The usual workup gave, after SiO_2 chromatography (heptane/EtOAc, 14:1), **11a** (165 mg, 49% yield) and **11b** (130 mg, 46% yield).

11a: Colourless oil. $[\alpha]_D^{20}$ = +27 (*c* = 0.81, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3415, 2951, 2929, 2897, 2855, 1734, 1471, 1250, 1098, 1085, 1066, 906, 833, 773, 733 cm^{-1}. ^{1}H NMR (500 MHz): δ = –0.01 (s, 3 H), 0.00 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 3 H), 0.69 (s, 3 H), 0.86 (2 s, 18 H), 0.97 (m, 2 H), 1.04 (s, 3 H), 1.18 (dd, *J* = 6.3, 12.3 Hz, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.42 (m, 3 H), 1.56 (m, 3 H), 1.67 (m, 3 H), 1.78 (m, 2 H), 1.87 (m, 2 H), 1.95 (ddd, *J* = 5.0, 9.8, 12.7 Hz, 1 H), 2.07 (m, 1 H), 2.21 (ddd, *J* = 4.6, 9.9, 15.8 Hz, 1 H), 2.28 (dt, *J* = 5.2, 15.6 Hz, 1 H), 2.44 (m, 1 H), 2.78 (m, 2 H), 2.93 (m, 2 H), 3.38 (s, 1 H), 3.55 (t, *J* = 8.3 Hz, 1 H), 3.65 (t, *J* = 2.9 Hz, 1 H), 4.11 (qd, *J* = 2.6, 7.1 Hz, 2 H), 4.15 (dd, *J* = 3.1, 6.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.5, –4.8, –4.5, –3.8, 11.1, 14.2, 18.0 (2 C), 18.1, 21.6, 23.5, 25.0, 25.8 (6 C), 26.8, 28.1, 29.9, 30.9, 31.3, 31.9, 34.0, 37.1, 43.1, 43.4, 43.5, 43.6, 45.5, 50.1, 60.3, 71.5, 76.8, 81.7, 174.5 ppm. ESIMS (MeOH): *m/z* (%) = 737.4 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{37}H_{70}NaO_5S_2Si_2$ 737.4101; found 737.4124. $C_{37}H_{70}O_5S_2Si_2$ + 0.1 heptane (715.25): calcd. C 62.43, H 9.95; found C 62.68, H 9.85.

11b: White solid; M.p. 63–65 °C. $[\alpha]_D^{20}$ = +23 (*c* = 1.05, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3410, 2950, 2929, 2900, 2856, 1725, 1470, 1376, 1308, 1251, 1184, 1093, 1074, 1057, 1025, 908, 833, 773, 729 cm^{-1}. ^{1}H NMR (500 MHz): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.73 (s, 3 H), 0.86 (s, 9 H), 1.05 (m, 1 H), 1.05 (s, 3 H), 1.13 (td, *J* = 4.2, 12.9 Hz, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.23 (m, 1 H), 1.43 (m, 2 H), 1.54 (dt, *J* = 2.9, 14.1 Hz, 1 H), 1.62 (m, 3 H), 1.70 (m, 4 H), 1.81 (m, 2 H), 1.91 (dd, *J* = 6.4, 16.9 Hz, 1 H), 1.97 (m, 1 H), 2.07 (m, 2 H), 2.21 (ddd, *J* = 5.0, 10.3, 15.8 Hz, 1 H), 2.28 (td, *J* = 5.3, 10.6 Hz, 1 H), 2.44 (ddd, *J* = 5.7, 10.6, 16.0 Hz, 1 H), 2.78 (m, 2 H), 2.93 (m, 2 H), 3.40 (s, 1 H), 3.65 (m, 2 H), 4.11 (m, 2 H), 4.15 (dd, *J* = 3.1, 6.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.4, –3.7, 10.9, 14.2, 18.0, 18.1, 21.6, 23.4, 25.0, 25.8 (3 C), 26.8, 28.2, 29.9, 30.5, 31.3, 31.8, 33.9, 36.7, 42.7, 43.4 (2 C), 43.5, 45.5, 50.5, 60.3, 71.4, 76.8, 81.9, 174.5 ppm. ESIMS (MeOH): *m/z* (%) = 623.3 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{31}H_{56}NaO_5S_2Si$ 623.3236; found 623.3235. $C_{31}H_{56}O_5S_2Si$ + 0.4H_2O (600.99): calcd. C 61.22, H 9.41; found C 61.17, H 9.35.

Preparation of Spirolactone 12: To a stirred solution of **11a** (165 mg, 0.23 mmol) in a mixture of MeOH (5 mL) and water (0.5 mL), was added potassium carbonate (96 mg, 0.69 mmol). The resulting mixture was stirred at room temperature for 1 h. After removing the solvents without heating and dilution of the residue with EtOAc, the usual workup and chromatography on SiO_2 (heptane/EtOAc, 9:1) gave **12** (140 mg, 91% yield).

12: Colourless oil. $[\alpha]_D^{20}$ = +23 (*c* = 1.29, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2951, 2928, 2855, 1773, 1470, 1249, 1193, 1131, 1099, 1083, 1015, 908, 834, 732 cm^{-1}. ^{1}H NMR (500 MHz): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.06 (2 s, 6 H), 0.72 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.02 (s, 3 H), 1.04 (m, 2 H), 1.20 (dd, *J* = 5.9, 12.1 Hz, 1 H), 1.38 (dd, *J* = 4.2, 12.7 Hz, 1 H), 1.44 (m, 1 H), 1.55 (m, 4 H), 1.70 (dd, *J* = 4.4, 6.9 Hz, 2 H), 1.76 (m, 4 H), 1.90 (m, 1 H), 2.05 (m, 1 H), 2.21 (dt, *J* = 10.6, 13.5 Hz, 1 H), 2.32 (ddd, *J* = 2.4, 10.1, 12.8 Hz, 1 H), 2.50 (dt, *J* = 10.4, 18.3 Hz, 1 H), 2.61 (ddd, *J* = 2.4, 10.5, 18.3 Hz, 1 H), 2.70 (m, 1 H), 2.76 (m, 1 H), 2.90 (m, 1 H), 2.98 (m, 1 H), 3.57 (t, *J* = 2.5 Hz, 1 H), 3.58 (t, *J* = 8.3 Hz, 1 H), 4.20 (t, *J* = 4.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5, –4.2, 11.3, 17.0, 17.9, 18.1, 22.0, 23.5, 23.9, 25.1, 25.7 (3 C), 25.8 (3 C), 28.0, 29.9, 30.9, 31.9 (2 C), 33.5, 36.8, 43.1, 43.4 (2 C), 43.8, 45.5, 49.6, 71.9, 81.6, 91.6, 176.6 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 691.3 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{35}H_{64}NaO_4S_2Si_2$ 691.3682; found 691.3707. $C_{35}H_{64}O_4S_2Si_2$ (669.18): calcd. C 62.82, H 9.64; found C 62.89, H 9.76.

Oxidative Dethioketalisation. Unveiling of the Aldehyde at C11: To a solution of **12** (129 mg, 0.19 mmol) in acetone (10 mL) and water (1 mL) was added $CaCO_3$ (365 mg, 3.65 mmol) and $HgCl_2$ (408 mg, 1.50 mmol). The mixture was stirred at reflux for 1 h, filtered through Celite, the acetone was then removed under reduced pressure, and the residue was diluted with water, extracted with CH_2Cl_2 and subjected to the usual workup. The residue was purified by flash chromatography on SiO_2 (heptane/EtOAc, 8:1) to afford the corresponding aldehyde **13** (108 mg, 96% yield).

13: White solid; m.p. 155–157 °C. $[\alpha]_D^{20}$ = +11 (*c* = 0.48, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2928, 2856, 1780, 1714, 1471, 1256, 1192, 1098, 1084, 1017, 907, 834, 806, 775 cm^{-1}. ^{1}H NMR (500 MHz): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.74 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.01 (td, *J* = 7.1, 11.9 Hz, 1 H), 1.08 (dd, *J* = 4.0, 12.7 Hz, 1 H), 1.13 (s, 3 H), 1.21 (dd, *J* = 5.9, 12.2 Hz, 1 H), 1.49 (m, 3 H), 1.58 (m, 1 H), 1.63 (dt, *J* = 3.2, 14.0 Hz, 1 H), 1.70 (m, 1 H), 1.72 (dd, *J* = 4.1, 12.4 Hz, 1 H), 1.82 (m, 2 H), 1.91 (m, 1 H), 2.13 (dt, *J* = 10.4, 13.7 Hz, 1 H), 2.35 (d, *J* = 3.3 Hz, 2 H), 2.27 (m, 1 H), 2.52 (m, 2 H), 3.58 (t, *J* = 8.3 Hz, 1 H), 3.64 (t, *J* = 2.6 Hz, 1 H), 9.77 (t, *J* = 3.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5, –4.2, 11.2, 17.7, 18.0, 18.1, 21.6, 23.4, 24.6, 25.7 (3 C), 25.8 (3 C), 27.6, 29.5, 30.8, 33.8, 36.9, 43.1, 45.1, 45.3, 49.5, 50.0, 71.9, 81.5, 90.5, 175.5, 201.6 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 601.3 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{32}H_{58}NaO_5Si_2$ 601.3721; found 601.3712.

Installation of the Last Carbon Atom and Preparation of the Hybrid Molecule 15a

Addition of Me_3Al onto a Carbonyl Group. One-Carbon (C12) Homologation: The aldehyde **13** (108 mg, 0.19 mmol) was dissolved in dry CH_2Cl_2 (5 mL), chilled to 0 °C and treated dropwise with Me_3Al (2.0 M in hexanes, 0.46 mL, 0.93 mmol) and stirring was continued at 0 °C for 20 min. The mixture was diluted with CH_2Cl_2 and quenched by the addition of saturated aq. NH_4Cl. The aq. layer was back-extracted with CH_2Cl_2, the extracts were subjected to the usual workup and chromatographed on SiO_2 (heptane/EtOAc, 9:1) to give the requisite methyl carbinol as a diastereomeric mixture (105 mg, 94% yield).

C11-Carbinol (One Major Isomer in the Mixture): Colourless oil. IR (film): $\tilde{\nu}$ = 3452, 2951, 2927, 2856, 1764, 1462, 1250, 1100, 1085, 1045, 1016, 908, 835, 775, 731 cm^{-1}. ^{1}H NMR (500 MHz): δ = 0.01 (2 s, 6 H), 0.06 (2 s, 6 H), 0.71 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 0.99 (s, 3 H), 1.01 (m, 2 H), 1.15 (d, *J* = 6.2 Hz, 1 H), 1.27 (m, 1 H), 1.20 (dd, *J* = 5.7, 12.0 Hz, 1 H), 1.36 (m, 2 H), 1.46 (m, 3 H), 1.58 (m, 4 H), 1.67 (dd, *J* = 7.2, 16.4 Hz, 1 H), 1.77 (m, 1 H), 1.89 (ddd, *J* = 3.4, 8.8, 12.4 Hz, 1 H), 2.67 (m, 2 H), 2.45 (dd, *J* = 9.9, 18.1 Hz, 1 H), 2.54 (ddd, *J* = 5.9, 7.8, 18.0 Hz, 1 H), 3.56 (t, *J* = 8.3 Hz, 1 H), 3.59 (t, *J* = 2.5 Hz, 1 H), 4.07 (t, *J* = 6.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5, –4.2, 11.2, 18.0, 18.1, 18.5, 21.7, 23.5, 23.7, 25.7 (3 C), 25.9 (3 C), 26.8, 28.1, 29.9,

30.9, 33.9, 37.1, 42.5, 43.1, 44.7, 46.7, 49.8, 63.5, 72.1, 81.7, 91.5, 178.0 ppm. ESIMS (MeOH): *m/z* (%) = 617.4 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{33}H_{62}NaO_5Si_2$ 617.4034; found 617.4061. $C_{33}H_{62}O_5Si_2$ (595.01): calcd. C 66.61, H 10.50; found C 66.82, H 10.63.

Dess–Martin Oxidation: The periodinane oxidation of the carbinol thus obtained was performed using standard conditions. To a solution of the alcohol (105 mg, 0.18 mmol) in dry CH_2Cl_2 (5 mL) and pyridine (0.1 mL, 0.88 mmol) was added DMP (225 mg, 0.53 mmol) and stirring was continued at room temperature for 3 h. The reaction mixture was then diluted with CH_2Cl_2, the reaction quenched with saturated aq. $NaHCO_3$ and the mixture washed with brine. The usual workup and chromatography (heptane/EtOAc, 9:1) afforded **14** (90 mg, 86% yield).

14: White solid; m.p. 155 °C. $[\alpha]_D^{20}$ = +6 (*c* = 0.64, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2952, 2928, 2856, 1779, 1700, 1471, 1251, 1183, 1100, 1083, 1017, 907, 835, 775 cm^{-1}. ^1H NMR (500 MHz): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.06 (2 s, 6 H), 0.73 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.02 (ddd, *J* = 5.2, 9.0, 12.5 Hz, 1 H), 1.09 (s, 3 H), 1.09 (m, 1 H), 1.20 (dd, *J* = 5.9, 12.2 Hz, 1 H), 1.46 (m, 3 H), 1.54 (m, 1 H), 1.58 (dt, *J* = 3.1, 13.6 Hz, 1 H), 1.68 (m, 2 H), 1.77 (dt, *J* = 2.6, 10.7 Hz, 1 H), 1.81 (ddd, *J* = 2.7, 3.9, 12.5 Hz, 1 H), 1.90 (m, 1 H), 2.15 (s, 3 H), 2.29 (dd, *J* = 3.9, 14.4 Hz, 1 H), 2.34 (dd, *J* = 4.1, 13.4 Hz, 1 H), 2.44 (d, *J* = 4.8 Hz, 2 H), 2.51 (m, 2 H), 3.58 (m, 2 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.8, –4.5, –4.2, 11.3, 17.8, 18.0, 18.1, 22.3, 23.4, 24.3, 25.7 (3 C), 25.9 (3 C), 27.7, 29.8, 30.9, 32.3, 33.5, 37.0, 42.2, 46.0, 46.1, 49.5, 49.7, 71.8, 81.5, 90.8, 176.2, 208.6 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 615.4 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{33}H_{60}NaO_5Si_2$ 615.3877; found 615.3901. $C_{33}H_{60}O_5Si_2$ (593.00): calcd. C 66.84, H 10.20; found C 67.01, H 10.33.

Completion of the Synthesis. Removal of TBS Protecting Groups: A solution of **14** (56 mg, 0.09 mmol) in a mixture of CH_3CN/HF (1:1, 4 mL, 48% w/v of HF in water), was stirred at room temperature for 2 d. After that, the reaction mixture was diluted with water, extracted with CH_2Cl_2 and washed with saturated aq. $NaHCO_3$. The usual workup and SiO_2 flash column chromatography (heptane/EtOAc, 1:1) afforded **15a** (19 mg, 58% yield) and **15b** (16.3 mg, 38% yield).

Hybrid Molecule 15a: White solid; m.p. 192–193 °C. $[\alpha]_D^{20}$ = +15 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3413, 2930, 2870, 2852, 1759, 1693, 1468, 1355, 1248, 1224, 1188, 1135, 1062, 1045, 999, 735 cm^{-1}. ^1H NMR (500 MHz): δ = 0.79 (s, 3 H), 1.09 (dd, *J* = 4.5, 7.9 Hz, 1 H), 1.12 (s, 3 H), 1.19 (td, *J* = 4.1, 13.1 Hz, 1 H), 1.28 (dd, *J* = 5.9, 12.3 Hz, 1 H), 1.50 (m, 3 H), 1.62 (m, 3 H), 1.72 (m, 2 H), 1.82 (m, 2 H), 1.88 (dt, *J* = 3.4, 12.6 Hz, 1 H), 2.09 (m, 1 H), 2.15 (s, 3 H), 2.33 (dt, *J* = 10.4, 13.4 Hz, 1 H), 2.46 (s, 2 H), 2.49 (dd, *J* = 4.8, 14.6 Hz, 1 H), 2.56 (m, 2 H), 3.69 (t, *J* = 3.4 Hz, 1 H), 3.69 (t, *J* = 8.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 11.2, 17.4, 22.2, 23.3, 24.2, 27.7, 29.7, 30.5, 32.4, 34.0, 36.5, 42.9, 45.8, 45.9, 49.2, 50.3, 71.8, 81.6, 90.3, 176.2, 208.4 ppm. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 387.2 (100) $[M + Na]^+$, 751.5 (4) $[2 M + Na]^+$. HRESIMS: calcd. for $C_{21}H_{32}NaO_5$ 387.2147; found 387.2145.

15b: White solid; m.p. 175–176 °C. $[\alpha]_D^{20}$ = +2 (*c* = 1.15, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3440, 2849, 2928, 2855, 1770, 1695, 1471, 1388, 1359, 1249, 1183, 1083, 1051, 1013, 926, 902, 831, 775, 733, 698 cm^{-1}. ^1H NMR (500 MHz): δ = 0.06 (2 s, 6 H), 0.78 (s, 3 H), 0.88 (m, 1 H), 0.90 (s, 9 H), 1.10 (s, 3 H), 1.21 (m, 2 H), 1.47 (m, 3 H), 1.59 (m, 3 H), 1.70 (m, 2 H), 1.79 (t, *J* = 11.3 Hz, 1 H), 1.88 (d, *J* = 12.4 Hz, 1 H), 2.08 (m, 1 H), 2.14 (s, 3 H), 2.30 (m, 2 H), 2.46 (s, 2 H), 2.52 (m, 2 H), 3.59 (t, *J* = 2.7 Hz, 1 H), 3.68 (t, *J* = 8.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = –5.3, –4.2, 11.0, 17.7, 17.9, 22.2, 23.3, 24.3, 25.7 (3 C), 27.6, 29.7, 30.5, 32.4, 33.5, 36.6, 42.9, 45.9, 46.0, 49.3, 50.1, 71.7, 81.6, 90.7, 176.2, 208.5 ppm. ^1H NMR (500 MHz, $[D_6]$DMSO): δ = 0.06 (s, 3 H), 0.08 (s, 3 H), 0.64 (s, 3 H), 0.87 (s, 9 H), 0.96 (m, 1 H), 1.01 (s, 3 H), 1.09 (m, 2 H), 1.11 (m, 1 H), 1.35 (m, 2 H), 1.53 (m, 2 H), 1.69 (m, 4 H), 1.85 (m, 1 H), 2.01 (s, 3 H), 2.22 (m, 2 H), 2.29 (d, *J* = 14.6 Hz, 1 H), 2.46 (m, 2 H), 2.65 (m, 1 H), 3.59 (dt, *J* = 4.7, 8.5 Hz, 1 H), 3.70 (s, 1 H), 4.46 (dd, *J* = 1.5, 4.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $[D_6]$DMSO): δ = –5.4, –4.7, 11.0, 17.4, 17.6, 21.5, 23.0, 23.8, 25.5 (3 C), 27.0, 29.1, 29.8, 32.4, 33.4, 36.4, 42.4, 44.9, 45.4, 47.7, 49.7, 70.7, 79.9, 90.0, 175.9, 207.4 ppm. HMBC (DMSO): correlations between C16 and C17-OH, C17 and C17-OH. ESIMS (CH_2Cl_2 + MeOH): *m/z* (%) = 501.3 (100) $[M + Na]^+$, 979.7 (88) $[2 M + Na]^+$. HRESIMS: calcd. for $C_{27}H_{46}NaO_5Si$ 501.3012; found 501.3014. $C_{27}H_{46}O_5Si$ (478.74): calcd. C 64.61, H 9.19; found C 64.69, H 9.13.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures for the synthesis, including those presented here, spectral characterization of all compounds investigated and X-ray crystallographic data for **9b** and **17**.

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[13] Since the overall process resulting in the introduction of new stereogenic centres proceeds through a rehybridisation of the two sp^3 centres, the C2 and C3 stereochemistry of the starting diols is not of concern, and hence, no chromatographic separation at this level is needed.

[14] We use norsesquiterpene spirolactone numbering for the left half (A′, B′ rings) while a marked steroid numbering (i.e. 17′) is applied for the right half (C, D rings) throughout the text, starting at **6**.

[15] This one-step conversion of unsaturated diols to cyclic eneacetals is operative in a wide range of solvents; Ö. Sesenoglu, J. I. Candela Lena, E. Altinel, N. Birlirakis, S. Arseniyadis, *Tetrahedron: Asymmetry* **2005**, *16*, 995–1015.

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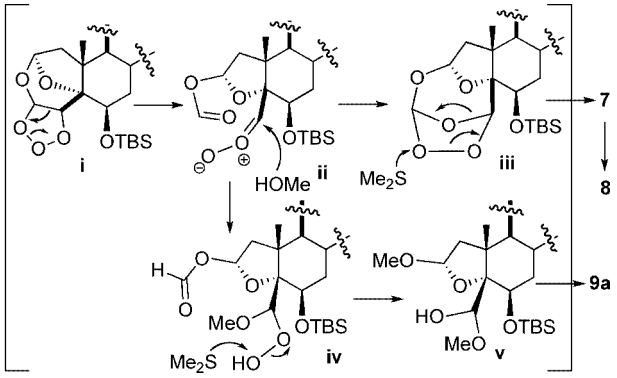

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[22] Coelho et al. observed a similar behaviour upon fluoride-induced desylilation in ref.[9b]

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