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# Studies towards the total synthesis of contignasterol

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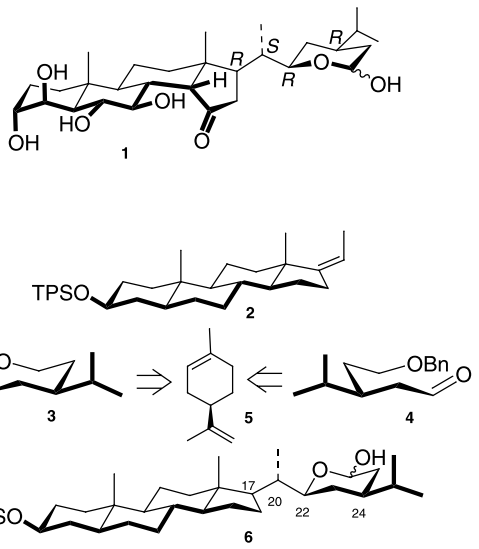
**Abstract**—The (17*R*,20*S*,22*S*,24*S*) $C_{20}-C_{29}$ segment of contignasterol has been stereoselectively prepared in 8 steps and 40% overall yield from (*S*)-carvone. Synthetic studies towards contignasterol's C/D ring functionalization/isomerization are also reported.


## 1. Introduction

Marine sponges have proven to be a rich source of novel steroids showing potent biological activities and unusual structural features.[1] Contignasterol[2] (**1**), 15-dehydro-14β-anosmagenin,[3] xestobergsterols A–C,[4] haliclostanone sulfate,[5] 14β-tamosterone sulfate[6] and clathriol[7] present common 15-keto, 3α(or β),6α,7β-trihydroxy functionalities and a rare *cis* C/D ring junction. This last feature is probably associated with potent antiiflammatory activity[8] as shown by Jung and Johnson's[9] brilliant synthesis of xestobergsterol A and its analogs.

In a previous work on the synthesis of contignasterol's side chain, we indicated as (*S*,*S*) the configuration for the C-22/C-24 stereogenic centres.[10] On the other side, 1 year after the publication of our results, Andersen and Yang[11] completed contignasterol's structural elucidation and, on the basis of a $^1$H NMR spectroscopic data analysis of C-22 (*R*/*S*)-MPA and (*R*/*S*)-MTPA esters, proposed a (22*R*,24*R*) configuration. In the authors' opinion the synthesis-based C22/24 antipodal assignment was due to the unfunctionalized *trans* C/D tetracyclic nucleus model, which is 'an unreliable predictor of the side chain stereochemistries'.[11]

As a prelude to the contignasterol total synthesis and with the aim of shedding light on this open question, herein we report a new, shorter and higher yielding route for the (17*R*,20*S*,22*S*,24*S*)-$C_{20}-C_{29}$ fragment and our studies towards the C/D ring functionalization/isomerization.




## 2. Results and discussion

### 2.1. New route to contignasterol's side chain

Our first synthesis of contignasterol's (17*R*,20*S*,22*S*,24*S*)-side chain[10] relied on a stereospecific pericyclic coupling between the protected (*Z*)-17(20)-ethylidene steroid **2** and partner pseudo-enantiomeric aldehydes **3** and **4**, both available from (*R*)-limonene (**5**). The synthesis of **6** was thus completed in 12 steps and 11% overall yield.

In this paper we wish to report full experimental details of a more convenient route towards **6**. This synthesis, based on intermediate **7**, gave the lactol **6** in 8 steps and 40% overall yield starting from (*S*)-carvone.[12]

*Keywords*: Contignasterol; Polyhydroxysteroids; Marine metabolite; *anti*-Inflammatory compounds; Ene reactions.
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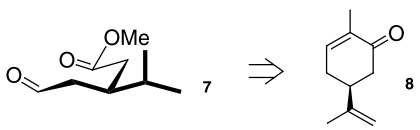
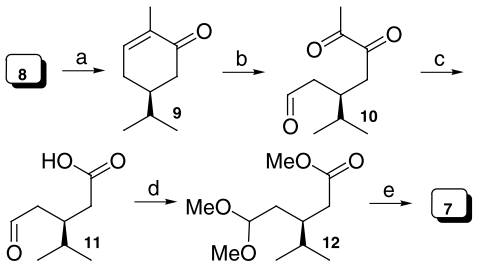
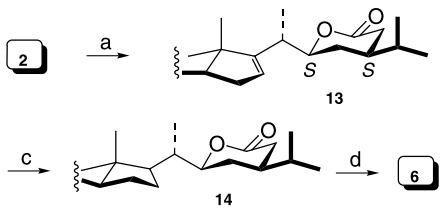


Elaboration of (*S*)-methyl 4-methyl-3-(2-oxo-ethyl)-pentanoate (**7**), reported in Scheme 1, began with a chemoselective reduction of (*S*)-carvone's isopropylidene double bond.[13] Carvotanacetone (**9**) was then converted, via ozonolysis,[13] $NaIO_4$-mediated oxidative cleavage,[13] and treatment with catalytic amount of *p*-TsOH in MeOH, into the air-stable acetal ester **12** (59% overall yield). When needed the aldehyde **7** was obtained through facile Pd(II)-mediated acetal hydrolysis.[14]



**Scheme 1.** (a) $H_2$, $Pt_2O$, MeOH; (b) $O_3$, MeOH, −60 °C then $Me_2S$, $H_2O$, MeOH; (c) $NaIO_4$, MeOH, $H_2O$; (d) MeOH, *p*-TsOH (59%, 4 steps); (e) $Pd(MeCN)_2Cl_2$, acetone/$H_2O$ (95:5), 82%.

The (17*R*,20*S*,22*S*,24*S*)-side chain stereogenic centres, present in **6**, were stereoselectively forged starting from Koreeda's coupling.[15] This pericyclic reaction gave, without detectable stereoisomeric contamination, the expected lactone **13**.[16] $\Delta^{16}$ stereoselective hydrogenation[17] and DIBAL-H mediated C-29 reduction, furnished known[10] lactol **6** (Scheme 2).



**Scheme 2.** (a) **7**, $Me_2AlCl$, $CH_2Cl_2$, −78 °C→−30 °C, 90%; (b) $H_2$, $Pt_2O$, EtOH, quant.; (c) DIBAL-H, $CH_2Cl_2$, −78 °C, 93%.

### 2.2. Studies towards C/D ring functionalization

A number of synthetic methods useful for allylic oxidation of unsaturated steroids have been reported.[18] Among these the chromium trioxide 3,5-dimethylpyrazole-complex ($CrO_3$-DMP) mediated[19] C-15 allylic oxidation gave good results. This reaction, when applied to **13**, afforded the $\Delta^{16}$-15-ketosteroid **15** in a satisfying yield (60%), along with the 16α,17α-epoxide **16**[20] (11% yield).

The *trans* C/D ring junction present in steroid **15** showed a slow but irreversible C-14 inversion ($t_{1/2}\approx$5 h, $CDCl_3$) to give the *cis* C/D steroid **17**.[21] Assignment of the C/D ring junction was made on the basis of the H-7 and C-18 NMR spectroscopy chemical shifts values ($^1$H NMR: $\delta_{H\text{-}18}$=0.98 for **15** versus $\delta_{H\text{-}18}$=1.18 for **17**, $\delta_{H\text{-}7\beta}$=2.63 for **15**, $\delta_{H\text{-}7\alpha}$=2.17 for **17**; $^{13}$C NMR: $\delta_{C\text{-}18}$=23.5 for **15** versus $\delta_{C\text{-}18}$=24.4 for **17**).[22] Semiempirical calculations at the AM1 level, using the Gaussian 98W software package,[23] on compounds **15** and **17**, in which the TPS group was replaced by a methyl, provided the two minimum energy conformers **18a** and **18b** respectively (Fig. 1). In particular, the *cis* C/D ketone **18b** was shown to be more stable than the *trans* C/D ketone **18a** by approximately 5.1 kcal/mol, a value which is in full accordance with the irreversible C-14 inversion.

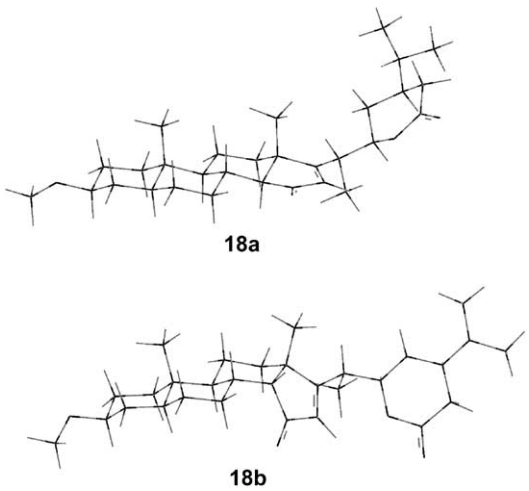


**Figure 1.** Minimum energy conformation for **18a** and **18b**, as determined by AM1 calculations.

Experimentally, the C-14 epimerization was complete in 24–30 h and served as point of departure for projected $\Delta^{16}$ reduction. Unfortunately, as a consequence of the conformation assumed by the unsaturated D ring,[17b,24] the hydrogenation gave quantitative yields of **19**, which, as clarified by a ROESY[25] experiment (Fig. 2), showed an unnatural C-17α (17*S*) side chain. Indeed, ROE cross-peaks

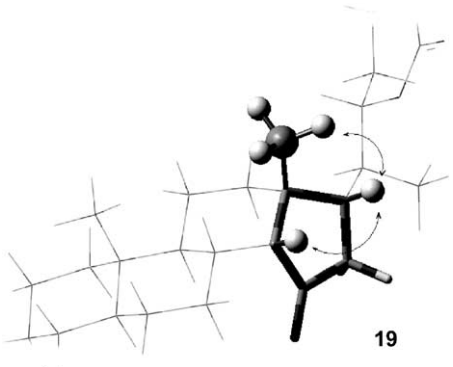
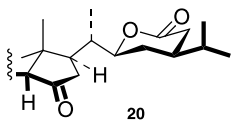


**Figure 2.** AM1 minimum energy conformation for **19**, in agreement with ROE cross-peaks between the H-17 with both $H_3$-18 and H-14.

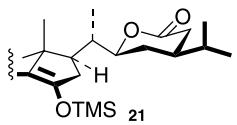
between the H-17 ($\delta$=1.80) with both $H_3$-18 ($\delta$=1.02) and H-14 ($\delta$=1.54), are in accordance with the distances of 2.98 and 2.70 Å, respectively, which were in turn measured in the AM1 minimum energy conformer of **19**.

In order to ensure a β-selective $\Delta^{16}$-hydrogenation, we subjected the *trans* C/D α,β-unsaturated ketone steroid **15** to an acid-free hydrogenation, immediately after its oxidative formation. This time the reduction furnished, in excellent yield (95%), a *trans* C/D ring ($^{13}$C NMR: $\delta_{C\text{-}18}$=12.9, $^1$H NMR: $\delta_{H\text{-}18}$=0.79) (17*R*)-steroid **20**.



**20**

With (17*R*,20*S*,22*S*,24*S*)-**20** in hand, we were ready for the required C/D ring junction inversion.[26] The lability of the lactone excluded a base-induced isomerization. On the other side, the attempted acid catalyzed (HCl) C-14 inversion proved unsuccessful. Alternatively, we planned the formation of silyl enol ether **21**, in the presence of 1,1,1,3,3,3-hexamethyldisilazane and LiI, under thermodynamic control, and its protonation with trifluoroacetic acid, but, when we performed the acid-mediated hydrolysis of the silyl enol ether **21**, no trace of the 14β-H 15-ketosteroid was observed in the crude reaction mixture.



**21**

At this point, considering the base-mediated C-14 inversion to be inevitable, we decided to transform the lactone moiety, into the base-stable C-29 acetal. Preliminary calculations (Fig. 3) on two steroid models, with an equatorial *O*-methyl acetal, showed contrasting results with regard to the relative stability of *trans* C/D ring steroid **22a** and the corresponding *cis* 15-ketosteroid **22b**. In fact, while AM1 calculations indicated the *cis* 15-ketosteroid **22b** to be more stable by about 2.5 kcal/mol with respect to the *trans* C/D ring steroid **22a**, PM3 calculation suggested a comparable stability.

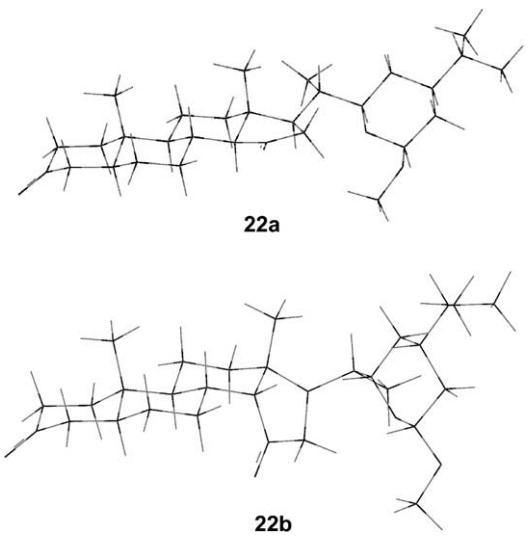
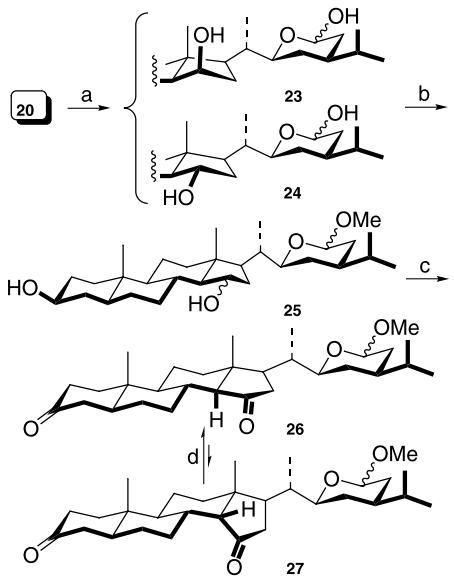


**Figure 3.** Minimum energy conformation for **22a** and **22b**, as determined by molecular mechanics calculation.

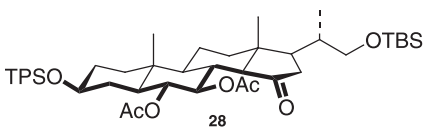
We thus reduced both the C-15 and C-29 carbonyls of **20** with DIBAL-H and separated (only for analytical purposes) the two epimeric C-15 alcohols **23** and **24**[27] (Scheme 3). Acid-mediated *O*-methylation of the mixture containing the C-15/C-29 epimers, furnished the four acetals **25** (the acid conditions deprotected the C-3 hydroxy group). Oxidation with PDC gave the expected 3,15-diketone **26** which, after treatment with different bases (MeONa, NaH, NaOH) at different temperatures and reaction times[28] did not show any C-14 isomerization.



**Scheme 3.** (a) DIBAL-H, $CH_2Cl_2$, −78 °C (**23**: 48%; **24**: 38%); (b) HCl in MeOH; (c) PDC, $CH_2Cl_2$, 55%, for 2 steps; (d) MeONa, MeOH, rt→reflux or NaH, THF, rt→reflux or NaOH, THF/EtOH, rt→reflux.

Having verified the difficulties in obtaining the required *cis* C/D ring junction with simpler model steroids, we decided to 'invest' in the known destabilizing influence exerted by the 7β-oxysubstituents on *trans* C/D ring junction.[9a] We thus projected the synthesis of 6α,7β-(diacetoxy)-22-[(*tert*-butyldimethylsilyl)oxy]-3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorcholan-15-one (**28**) with the aim to obtain a suitable substrate for the necessary C-14 inversion.

AM1 energy calculations on 7β-acetoxy *trans* C/D model steroid **28a** and 7β-acetoxy *cis* C/D **28b** showed that the former is less stable than the latter of about 5.5 kcal/mol, thus indicating the unfavourable steric interaction between the 7β-substituent and the C-15 keto group in *trans* C/D steroids, also accompanied, for structure **28a**, by a distortion of ring B from a pure chair conformation. This strain could be alleviated once the C-14/C-15 bond assumes the quasi-axial orientation present in *cis* C/D steroids (Fig. 4).



**28**

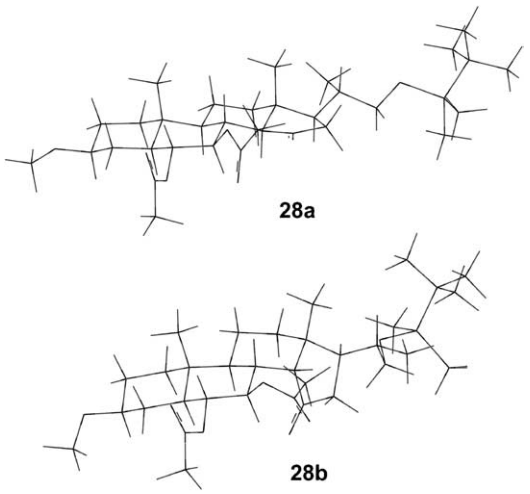
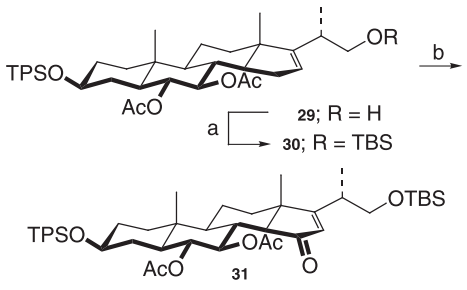



**Figure 4.** AM1 minimum energy conformations for **28a** and **28b**.

We thus embarked in the synthesis of the previously reported[29] 6α,7β-(diacetoxy)-3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-22-ol (**29**). Its construction was complete in 13 steps and 21% overall yield, starting from commercially available androst-5-en-3β-ol-17-one. Silylation of the primary C-22 alcohol with *tert*-butyldimethylsilyl chloride, gave the fully protected tetrol **30** (Scheme 4). This was subjected to both chromium,[19] copper,[18e] and selenium-mediated[18a] oxidation reactions (see Section 4) but, even forcing the reaction conditions, we did not observe the desired C-15 oxidation.[30]




**Scheme 4.** (a) TBSCl, DBU, $CH_2Cl_2$, 82%. (b) $CrO_3$-DMP, $CH_2Cl_2$ or $SeO_2$, *t*-BuOOH, $CH_2Cl_2$ or CuI, *t*-BuOOH, $CH_3CN$.

The analysis of the AM1 minimum energy conformer of **30a** (Fig. 5), in which the TPS group of **30** was replaced by a methyl, may suggest a steric hindrance of the 7β-acetoxy towards the access to C-15 which could prevent the oxidation reaction.

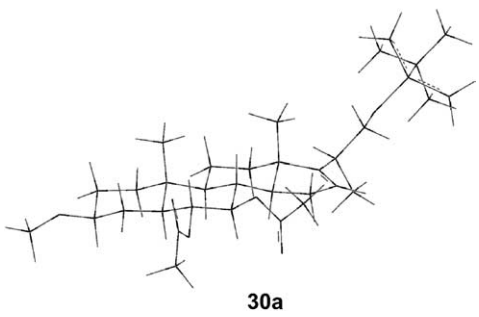



**Figure 5.** AM1 minimum energy conformations for **30a**.

At the end of this synthetic effort we assumed that the C-15 oxidation was incompatible with the presence of a 7β-oxysubstituent[31] and that, the only possible C-15 functionalization/C-14 isomerization route could be that starting from the Breslow remote functionalization (compatible with a 7β-oxysubstituent).[9a]

## 3. Conclusions

In conclusion, we have reported full experimental details of a new and more convenient route towards contignasterol's side chain and a synthetic and theoretical contribution for the C-15 oxidation/C-14 isomerization of contignasterol.

## 4. Experimental

### 4.1. General methods

All reactions were carried out under a dry argon atmosphere using freshly distilled and dried solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Toluene, methylene chloride and diethyl ether were distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried in vacuo over $P_2O_5$ or by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and sprying with $H_2SO_4$–$Ce(SO_4)_2$, *p*-anysaldeyde–EtOH–$H_2SO_4$–AcOH solutions and drying.

Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically ($^1H$ and $^{13}C$ NMR) pure materials. The NMR spectra were recorded at room temperature on a Bruker DRX 400 spectrometer (400 MHz) and $^1H$ NMR and ROESY spectra for compound **17** were recorded on a a Bruker DRX 600 spectrometer (600 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: $\delta$=7.26, $^{13}CDCl_3$: $\delta$=77.0). HR ESMS were performed on a Q-Star Applied Biosystem mass spectrometer. Infrared spectra were obtained at a resolution of 2.0 $cm^{-1}$ with a Vector 22 Bruker spectrometer. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

### 4.2. Procedures for the synthesis of compounds 6–7, 9–14, described in paragraph 2.1

**4.2.1. Compound 12.** To a vigorously stirred mixture of (*S*)-carvone (**8**) (5.0 g, 33.3 mmol) and $PtO_2$ (0.013 g) in MeOH (40 mL), hydrogen was introduced, at room temperature. Hydrogenation was monitored by $^1H$ NMR. After disappearance of starting material, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo to give 5.1 g of crude carvotanacetone (**9**). Ozone was bubbled into a stirred solution of crude **9** in MeOH (63.5 mL) at −60 °C for 4 h. After

flushing off the excess ozone with $N_2$ for 30 min, to the reaction mixture was slowly added, at −60 °C, a mixture of $Me_2S$ (4.40 mL), water (4.90 mL) and MeOH (14.8 mL) and the mixture was stirred overnight at room temperature. The reaction mixture, containing **10**, was then concentrated in vacuo to a half volume and to the residue was slowly added a solution of $NaIO_4$ (7.06 g, 33.3 mmol) in water (50 mL). The mixture was stirred vigorously for 4 h at room temperature. The white precipitate was filtered and repeatedly washed with ethyl acetate. The filtrate was extracted with ethyl acetate (3×100 mL) and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give crude **11**. To this was added MeOH (50 mL) and a catalytic amount of *p*-TsOH. The resultant mixture was stirred overnight at room temperature and then diluted with water and neutralized with a saturated solution of $NaHCO_3$. The mixture was concentrated in vacuo to remove the excess MeOH and the aqueous layer was extracted with $CH_2Cl_2$ (3×50 mL). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in vacuo. The crude residue was flash chromatographed (10–30% diethyl ether in petroleum ether) to afford **12** (4.29 g, 59% over four steps) as an oil.

*Compound* **12**. $R_f$=0.65 (50% diethyl ether in petroleum ether). IR ($CHCl_3$) $\nu_{max}$ ($cm^{-1}$) 2958, 2831, 1738, 1440, 1370, 1126. $[\alpha]_D^{21}$=+2.1 (*c* 1.2, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 0.84 (6H, d, *J*=6.9 Hz, $-CH(CH_3)_2$), 1.45 (1H, dddd, *J*=14.2, 8.4, 6.0 Hz, $-CHHCH(OCH_3)_2$), 1.62 (1H, dddd, *J*=14.2, 5.4, 5.4 Hz, $-CHHCH(OCH_3)_2$), 1.72 (1H, m, $-CH(CH_3)_2$), 1.93 (1H, m, $-CHCH(CH_3)_2$), 2.23 (1H, dd, *J*=15.3, 7.0 Hz, $MeO_2CCHH-$), 2.28 (1H, dd, *J*=15.3, 6.5 Hz, $MeO_2CCHH-$), 3.27 (3H, s, $CH_3OCH-$), 3.28 (3H, s, $CH_3'OCH-$), 3.64 (3H, s, $-COOCH_3$), 4.40 (1H, dd, *J*=6.0, 5.4 Hz, $(CH_3O)_2CH-$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 18.6, 18.8, 30.3, 33.7, 35.8, 36.7, 51.4, 52.4, 52.6, 103.4, 174.0. HR-ESMS: *m*/*z* 219.1587 (Calcd 219.1596 for $C_{11}H_{23}O_4$).

**4.2.2. Compound 7.** To a solution of the dimethyl acetal **12** (1.14 g, 5.2 mmol) in acetone and water (18.0 mL, 95:5), $Pd(MeCN)_2Cl_2$ (0.095 g, 0.366 mmol) was added at room temperature. The mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was dissolved in diethyl ether and filtered through a short pad of silica gel (particle size 0.040–0.063 mm). The filtrate was concentrated in vacuo to afford the desired aldehyde **7** (0.734 g, 82%) as a yellow oil, which was used in the next step without further purification.

*Compound* **7**. $R_f$=0.61 (50% diethyl ether in petroleum ether). IR ($CHCl_3$) $\nu_{max}$ ($cm^{-1}$) 2960, 2725, 1725, 1437, 1372, 1167, 1011. $[\alpha]_D^{25}$=−15.3 (*c* 1.4, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 0.86 (3H, d, *J*=6.9 Hz, $-CH(CH_3)$-$CH_3$), 0.87 (3H, d, *J*=6.9 Hz, $-CH(CH_3)CH_3$), 1.73 (1H, m, $-CH(CH_3)_2$), 2.23 (1H, m, $-CHCH(CH_3)_2$), 2.35–2.49 (4H, m, $MeO_2CCH_2-$ and $CH_2CHO$ overlapped), 3.68 (3H, s, $-COOCH_3$), 9.73 (1H, bs, $-CHO$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 18.9 (×2), 30.7, 35.3, 35.9, 45.5, 51.6, 173.3, 202.0. HR-ESMS: *m*/*z* 173.1184 (Calcd 173.1178 for $C_9H_{17}O_3$).

**4.2.3. Compound 13.** To a solution of **2** (0.738 g, 1.39 mmol) and **7** (0.764 g, 4.43 mmol) in dry $CH_2Cl_2$ (24 mL), $Me_2AlCl$ (1 M in hexane, 8.9 mL, 8.90 mmol) was added at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 6 h and at −20 °C overnight and then quenched with a solution of MeOH/$H_2O$ (20 mL, 1:1) at −78 °C. The aqueous layer was extracted with $CH_2Cl_2$ (3×20 mL) and the combined organic layers were successively washed with 1% aqueous HCl, saturated aqueous $NaHCO_3$ and brine and then dried over $MgSO_4$. Removal of solvent in vacuo gave the crude reaction mixture which was purified by flash chromatography (10–40% diethyl ether in petroleum ether) to furnish pure **13** (0.853 g, 90%) as a white amorphous solid.

*Compound* **13**. $R_f$=0.56 (50% diethyl ether in petroleum ether). IR ($CHCl_3$) $\nu_{max}$ ($cm^{-1}$) 2958, 2930, 2854, 1735, 1471, 1428, 1373, 1242, 1111, 1087, 702. $[\alpha]_D^{23}$=−0.7 (*c* 1.0, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 0.75 (3H, s, $CH_3$-18), 0.83 (3H, s, $CH_3$-19), 0.88 (6H, d, *J*=6.7 Hz, $(CH_3)_2CH-$), 1.05 (9H, s, $(CH_3)_3CSi-$), 1.14 (3H, d, *J*=6.8 Hz, $CH_3$-21), 1.79 (1H, dd, *J*=16.8, 11.2 Hz, H-15), 2.00–2.06 (2H, m, H′-15 and H-23 overlapped), 2.15 (1H, dd, *J*=17.7, 9.9 Hz, H-28), 2.25 (1H, m, H-20), 2.64 (1H, dd, *J*=17.7, 6.2 Hz, H′-28), 3.58 (1H, m, H-3), 4.23 (1H, ddd, *J*=11.0, 8.1, 2.1 Hz, H-22), 5.38 (1H, bs, H-16), 7.34–7.43 (6H, m, $C_6H_5-$), 7.68 (4H, m, $C_6H_5-$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 12.3, 16.3, 18.2, 18.9, 19.1, 19.4, 20.9, 27.0 (×3), 28.6, 31.1, 31.2, 31.7, 31.8, 32.4, 33.6, 34.1, 34.8, 35.6, 36.8, 37.7, 38.3 (×2), 45.0, 47.4, 54.9, 57.1, 72.7, 83.4, 123.4, 127.4 (×4), 129.4 (×2), 134.8, 134.9, 135.7 (×4), 156.8, 172.4. HR-ESMS: *m*/*z* 681.4717 (Calcd 681.4703 for $C_{45}H_{65}O_3Si$).

**4.2.4. Compound 14.** To a solution of **13** (0.006 g, 0.009 mmol) in ethanol (1.5 mL), a catalytic amount of $PtO_2$ was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred overnight under hydrogen. It was then filtered through a pad of Celite® and concentrated in vacuo. Flash chromatography of the residue (30–40% diethyl ether in petroleum ether) gave pure **14** (0.006 g, quant.) as a white amorphous solid.

*Compound* **14**. $R_f$=0.72 (50% diethyl ether in petroleum ether). $[\alpha]_D^{25}$=+3.0 (*c* 1.0, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 0.63 (3H, s, $CH_3$-18), 0.78 (3H, s, $CH_3$-19), 0.89 (3H, d, *J*=7.0 Hz, $-CH(CH_3)CH_3$), 0.90 (3H, d, *J*=7.0 Hz, $-CH(CH_3)CH_3$), 0.95 (3H, d, *J*=6.9 Hz, $CH_3$-21), 1.04 (9H, s, $(CH_3)_3CSi-$), 2.12 (1H, dd, *J*=17.8, 10.7 Hz, H-28), 2.64 (1H, ddd, *J*=17.8, 4.5, 1.5 Hz, H′-28), 3.58 (1H, m, H-3), 4.32 (1H, bd, H-22), 7.34–7.43 (6H, m, $C_6H_5-$), 7.67 (4H, m, $C_6H_5-$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 11.9, 12.3, 12.6, 19.2 (×2), 19.3, 21.2, 24.0, 27.0 (×3), 27.6, 28.6, 30.2, 31.7, 31.9, 32.4, 34.1, 35.3, 35.5, 36.9, 38.0, 38.3, 39.7, 40.4, 42.4, 44.6, 51.6, 54.1, 56.1, 72.8, 82.5, 127.4 (×4), 129.3 (×2), 134.9 (×2), 135.7 (×4), 172.5. HR-ESMS: *m*/*z* 683.4867 (Calcd 683.4859 for $C_{45}H_{67}O_3Si$).

**4.2.5. Compound 6.** To a solution of **14** (0.044 g, 0.064 mmol) in dry $CH_2Cl_2$ (2.0 mL), DIBAL-H (1 M in THF, 0.193 mL, 0.193 mmol) was added at −78 °C. After 2 h at −78 °C, MeOH (0.5 mL) and $H_2O$ (0.5 mL) were

sequentially added. After being warmed to room temperature, the mixture was diluted with diethyl ether (10 mL) and dried over $MgSO_4$. After stirring vigorously for 30 min, the mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo to give **6** (0.041 g, 93%) as a white amorphous solid.

*Compound* **6**. $R_f$=0.84 (50% diethyl ether in petroleum ether). $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 0.58 (3H, s, $CH_3$-18), 0.73 (3H, s, $CH_3$-19), 0.81 (6H, d overlapped, $J$=7.0 Hz, $(CH_3)_2CH-$), 0.86 (3H, d, $J$=6.7 Hz, $CH_3$-21), 0.99 (9H, s, $(CH_3)_3CSi-$), 3.26 (0.5H, bd, $J$=10.8 Hz, H-22), 3.57 (1H, m, H-3), 3.84 (0.5H, bd, $J$=11.3 Hz, H′-22), 4.44 (0.5H, bt, $J$=7.5 Hz, H-29), 5.11 (0.5H, bs, H′-29), 5.68 (0.5H, d, $J$=3.8 Hz, $-OH$), 6.19 (0.5H, d, $J$=6.5 Hz, $-OH$), 7.42 (6H, m, $C_6H_5-$), 7.59 (4H, m, $C_6H_5-$). HR-ESMS: $m/z$ 685.5027 (Calcd 685.5016 for $C_{45}H_{69}O_3Si$).

### 4.3. Procedures for the synthesis of compounds 15-17, 19-21, 23-26, 30, described in paragraph 2.2

**4.3.1. Compounds 15 and 16.** $CrO_3$ (0.882 g, 8.82 mmol) was finely ground with a mortar and pestle and dried in vacuo for 6 h. In an argon-purged flask, $CrO_3$ was suspended in dry $CH_2Cl_2$ (8.0 mL) and the resultant suspension was stirred for 15 min at room temperature. It was then cooled to −40 °C and the DMP (0.848 g, 8.82 mmol) was added in one portion. The dark red mixture was stirred at −40 °C for 30 min and then a solution of **13** (0.200 g, 0.294 mmol) in dry $CH_2Cl_2$ (15 mL) was added via cannula. The resultant thick, dark reaction mixture was allowed to warm to room temperature and stirred under argon overnight. NaOH solution (3 N, 9.5 mL) was subsequently added at 0 °C and the mixture was stirred for 45 min at room temperature. It was then diluted with diethyl ether (30 mL) and allowed to stir for additional 30 min. The organic phase was separated and the aqueous layer, containing a green precipitate, was washed with diethyl ether (3×30 mL). Filtration of the combined organic phases through a path of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded to a solution, which was concentrated in vacuo. The residue was flash chromatographed (40–70% diethyl ether in petroleum ether) to afford **15** (0.123 g, 60%) and **16** (0.023 g, 11%) as white amorphous solids.

*Compound* **15**. $R_f$=0.53 (60% diethyl ether in petroleum ether). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.85 (3H, s, $CH_3$-19), 0.87 (6H, d, $J$=6.8 Hz, $(CH_3)_2CH-$), 0.98 (3H, s, $CH_3$-18), 1.05 (9H, s, $(CH_3)_3CSi-$), 1.25 (3H, d, $J$=6.8 Hz, $CH_3$-21), 1.95 (1H, bd, $J$=13.7 Hz, H-23), 2.18 (1H, dd, $J$=17.7, 9.9 Hz, H-28), 2.57 (1H, m, H-20), 2.63 (1H, m, H-7β), 2.70 (1H, dd, $J$=17.8, 6.5 Hz, H′-28), 3.58 (1H, m, H-3), 4.28 (1H, ddd, $J$=11.0, 8.1, 2.1 Hz, H-22), 5.70 (1H, s, H-16), 7.33–7.41 (6H, m, $C_6H_5-$), 7.67 (4H, m, $C_6H_5-$). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 12.3, 17.5, 18.8, 19.1, 19.3, 20.3, 23.5, 26.9 (×3), 28.1, 30.2, 30.8, 31.6, 32.3 (×2), 33.4, 35.7, 36.7, 37.4, 38.1 (×2), 38.7, 44.8, 47.1, 54.8, 63.7, 72.5, 81.9, 125.9, 127.4 (×4), 129.4 (×2), 134.6, 134.8, 135.7 (×4), 171.6, 183.1, 207.1. HR-ESMS: $m/z$ 695.4499 (Calcd 695.4496 for $C_{45}H_{63}O_4Si$).

*Compound* **16**. $R_f$=0.28 (60% diethyl ether in petroleum ether). IR ($CHCl_3$) $\nu_{max}$ ($cm^{-1}$) 2960, 2931, 2856, 1728, 1471, 1427, 1242, 1217, 1111, 1087, 702. $[\alpha]_D^{23}$=+2.2 ($c$ 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.78 (3H, s, $CH_3$-18), 0.79 (3H, s, $CH_3$-19), 0.88 (3H, d, $J$=6.7 Hz, $(CH_3)CH_3CH-$), 0.89 (3H, d, $J$=6.7 Hz, $CH_3(CH_3)CH-$), 1.03 (9H, s, $(CH_3)_3CSi-$), 1.11 (3H, d, $J$=6.9 Hz, $CH_3$-21), 1.92 (1H, bd, $J$=13.9 Hz, H-23), 2.15 (1H, dd, $J$=17.8, 9.7 Hz, H-28), 2.29 (1H, m, H-20), 2.64 (1H, dd, $J$=17.8, 6.5 Hz, H′-28), 3.36 (1H, s, H-16), 3.57 (1H, m, H-3), 3.97 (1H, ddd, $J$=11.0, 8.1, 2.1 Hz, H-22), 7.34–7.43 (6H, m, $C_6H_5-$), 7.67 (4H, m, $C_6H_5-$). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 12.2, 12.5, 15.1, 15.9, 18.9, 19.0, 19.2, 20.6, 26.9 (×3), 27.3, 28.4, 30.6, 31.5, 32.2, 32.3, 33.6, 34.8, 35.4, 36.7, 37.7, 38.1, 43.0, 44.2, 44.6, 54.4, 60.0, 65.7, 71.3, 72.5, 81.4, 127.3 (×4), 129.3 (×2), 134.7 (×2), 135.6 (×4), 171.9. HR-ESMS: $m/z$ 697.4646 (Calcd 697.4652 for $C_{45}H_{65}O_4Si$).

**4.3.2. Compound 17.** *Compound* **15** (0.030 g, 0.043 mmol) was dissolved in 0.5 mL of a $CDCl_3$ solution and converted into **17** over 30 h at room temperature. The solution was concentrated in vacuo to give **17** (0.030 g, quant.) as a white amorphous solid.

*Compound* **17**. $R_f$=0.28 (60% diethyl ether in petroleum ether). $[\alpha]_D^{26}$=−0.9 ($c$ 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.74 (3H, s, $CH_3$-19), 0.86 (6H, d, $J$=6.7 Hz, $(CH_3)_2CH-$), 1.04 (9H, s, $(CH_3)_3CSi-$), 1.18 (3H, s, $CH_3$-18), 1.23 (3H, d, $J$=6.7 Hz, $CH_3$-21), 1.90 (1H, d, $J$=4.4 Hz, H-14), 2.15 (1H, dd, $J$=17.7, 9.9 Hz, H-28), 2.17 (1H, m, H-7α), 2.57 (1H, m, H-20), 2.65 (1H, dd, $J$=17.7, 6.4 Hz, H′-28), 3.53 (1H, m, H-3), 4.16 (1H, ddd, $J$=11.0, 8.1, 2.1 Hz, H-22), 5.98 (1H, s, H-16), 7.33–7.41 (6H, m, $C_6H_5-$), 7.65 (4H, m, $C_6H_5-$). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 10.9, 17.8, 18.9 (×2), 19.0, 19.3, 24.4, 26.9 (×3), 28.8, 30.8, 31.1, 32.3, 32.5, 33.6, 33.7 (×2), 36.2, 36.6, 37.6, 37.8, 38.1, 44.0, 44.5, 48.4, 57.0, 72.7, 82.6, 127.4 (×4), 129.4 (×2), 130.5, 134.6, 134.7, 135.7 (×4), 171.4, 185.4, 210.1. HR-ESMS: $m/z$ 695.4511 (Calcd 695.4496 for $C_{45}H_{63}O_4Si$).

**4.3.3. Compound 19.** To a solution of **17** (0.054 g, 0.078 mmol) in ethyl acetate (4.5 mL), a catalytic amount of 5% Pt/C (0.007 g) was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred under hydrogen for 3 h. It was filtered through a pad of Celite® and concentrated in vacuo. Flash chromatography of the residue (40–50% diethyl ether in petroleum ether) gave **19** (0.054 g, quant.) as a white amorphous solid.

*Compound* **19**. $R_f$=0.55 (70% diethyl ether in petroleum ether). IR ($CHCl_3$) $\nu_{max}$ ($cm^{-1}$) 2959, 2932, 2857, 1731, 1471, 1427, 1386, 1249, 1216, 1110, 1078, 702. $[\alpha]_D^{23}$=−9.2 ($c$ 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$+20% $C_6D_6$, 600 MHz): $\delta$ 0.63 (3H, s, $CH_3$-19), 0.66 (3H, d, $J$=6.9 Hz, $CH_3$-21), 0.70 (3H, d, $J$=6.8 Hz, $(CH_3)CH_3CH-$), 0.71 (3H, d, $J$=6.8 Hz, $(CH_3)CH_3CH-$), 1.02 (3H, s, $CH_3$-18), 1.05 (9H, s, $(CH_3)_3CSi-$), 1.54 (1H, bs, H-14), 1.72 (1H, m, H-20), 1.80 (1H, m, H-17), 1.93–1.84 (2H, m, H-16 and H-28 overlapped), 2.09 (1H, dd, $J$=18.8, 8.8 Hz, H′-16), 2.37–2.45 (2H, m, H′-28 and H-7 overlapped), 3.55 (1H, m, H-3), 4.01 (1H, bd, $J$=11.7 Hz, H-22), 7.23–7.30 (6H, m, $C_6H_5-$), 7.65 (4H, m, $C_6H_5-$). $^{13}$C NMR ($CDCl_3$,

100 MHz): δ 12.1, 12.2, 19.1 (×2), 19.3, 21.0, 23.1, 27.0 (×3), 28.7 (×2), 29.2 (×2), 31.4, 32.4, 33.3, 33.9, 35.4 (×2), 36.8, 38.0, 38.3, 39.5, 43.0, 43.8, 45.0, 47.7, 61.4, 72.7, 83.7, 127.4 (×4), 129.4 (×2), 134.7, 134.9, 135.7 (×4), 172.0, 217.8. HR-ESMS: *m/z* 697.4661 (Calcd 697.4652 for $C_{45}H_{65}O_4Si$).

**4.3.4. Compound 20.** To a solution of **15** (0.125 g, 0.180 mmol) in ethyl acetate (10 mL), previously neutralized with basic $Al_2O_3$, a catalytic amount of 5% Pt/C (0.010 g) was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred under hydrogen for 3 h. It was filtered through a pad of Celite® and concentrated in vacuo. Flash chromatography of the residue (40–50% diethyl ether in petroleum ether) gave **20** (0.119 g, 95%) as a white amorphous solid.

*Compound* **20**. $R_f$=0.45 (70% diethyl ether in petroleum ether). $[\alpha]_D^{23}$=+10.6 (*c* 1.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.72 (3H, s, $CH_3$-19), 0.79 (3H, s, $CH_3$-18), 0.906 (3H, d, *J*=6.8 Hz, ($CH_3$)$CH_3$CH–), 0.911 (3H, d, *J*=6.8 Hz, ($CH_3$)$CH_3$CH–), 1.03 (3H, d, *J*=6.8 Hz, $CH_3$-21), 1.04 (9H, s, ($CH_3$)$_3$CSi–), 1.76 (1H, dd, *J*=18.3, 9.7 Hz, H-16), 2.04 (1H, bd, *J*=12.5 Hz), 2.08–2.16 (2H, m, H-28 and H-17 overlapped), 2.48 (1H, dd, *J*=18.3, 8.8 Hz, H′-16), 2.58 (1H, bd, *J*=12.5 Hz), 2.66 (1H, dd, *J*=17.7, 6.2 Hz, H′-28), 3.57 (1H, m, H-3), 4.21 (1H, bd, *J*=11.1 Hz, H-22), 7.34–7.41 (6H, m, $C_6H_5$), 7.67 (4H, m, $C_6H_5$–). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 12.2, 12.8, 12.9, 19.2, 19.3, 20.7, 27.0 (×3), 28.2, 30.1, 30.3, 30.5, 31.6, 31.8, 32.3, 34.1, 35.4, 36.9, 38.0, 38.1, 39.7, 40.0, 41.1, 42.1, 44.5, 47.0, 53.7, 65.7, 72.6, 81.9, 127.4 (×4), 129.4 (×2), 134.7, 134.8, 135.7 (×4), 172.1, 214.8. HR-ESMS: *m/z* 697.4659 (Calcd 697.4652 for $C_{45}H_{65}O_4Si$).

### 4.4. C/D ring junction attempted isomerization of 20

To a solution of **20** (0.015 g, 0.021 mmol), in $CHCl_3$ (1.0 mL) was added 12 N HCl (0.050 mL) at room temperature. The reaction mixture was stirred at room temperature overnight then quenched with a saturated solution of $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic phases were washed with $H_2O$, dried over $MgSO_4$ and concentrated in vacuo to give a residue containing the starting material **20** (0.015 g).

**4.4.1. Compound 21.** To a solution of **20** (0.078 g, 0.112 mmol) and hexamethyldisilazane (0.236 mL, 1.12 mmol) in dry $CH_2Cl_2$ (1.5 mL), lithium iodide (0.039 g, 0.291 mmol) and trimethylchlorosilane (TMS-Cl, 0.114 mL, 0.896 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 3 h and then quenched by addition of triethylamine (0.400 mL) and of a saturated solution of $NaHCO_3$ (0.600 mL) at 0 °C and diluted with diethyl ether. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo to give crude **21**, which was used in the next step without further purification.

*Compound* **21**. $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.14 (9H, s, ($CH_3$)$_3$Si–), 0.78 (3H, s, $CH_3$-18), 0.87 (3H, s, $CH_3$-19), 0.90–0.96 (9H, m, ($CH_3$)$_2$CH– and $CH_3$-21 overlapped), 1.05 (9H, s, ($CH_3$)$_3$CSi–), 2.67 (1H, dd, *J*=17.8, 6.2 Hz, H-28), 3.60 (1H, m, H-3), 4.24 (1H, bd, *J*=11.4 Hz, H-22), 7.34–7.43 (6H, m, $C_6H_5$–), 7.68 (4H, m, $C_6H_5$–). LR-ESMS: *m/z* 769.1 (Calcd 769.5 for $C_{48}H_{73}O_4Si_2$).

### 4.5. C/D ring junction attempted isomerization of 21

To a solution of crude **21** (0.025 g, 0.032 mmol) in THF (1.0 mL), TFA (0.150 mL) was slowly added at room temperature. The reaction mixture was stirred for 10 min at room temperature and then quenched with a saturated solution of $NaHCO_3$, concentrated in vacuo, to remove the excess THF, and extracted with diethyl ether. The organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. No trace of the *cis* C/D isomer was observed by $^1$H NMR analysis of the crude residue, which was purified by flash chromatography (50–70% diethyl ether in petroleum ether) to give **20** (0.024 g).

**4.5.1. Compounds 23 and 24.** To a solution of **20** (0.058 g, 0.083 mmol) in dry $CH_2Cl_2$ (4.0 mL), DIBAL-H (1 M in $CH_2Cl_2$, 0.332 mL, 0.332 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, then quenched with a solution of MeOH/water (2.0 mL, 1:1) at −78 °C and stirred at room temperature for 20 min. Filtration through a pad of Celite® and concentration in vacuo afforded to a residue which was purified by flash chromatography (50ndash;90% diethyl ether in petroleum ether) to give **23** (0.028 g, 48%) and **24** (0.022 g, 38%) as white amorphous solids.

*Compound* **23**. $R_f$=0.60 (70% diethyl ether in petroleum ether). $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.82 (3H, s, $CH_3$-19), 0.85–0.97 (12H, m, $CH_3$-18, ($CH_3$)$_2$CH–, $CH_3$-21 overlapped), 1.04 (9H, s, ($CH_3$)$_3$CSi–), 3.39 (0.6H, bd, *J*=10.7 Hz, H-22), 3.58 (1H, m, H-3), 3.98 (0.4H, bd, *J*=11.3 Hz, H-22), 4.16 (1H, bt, *J*=6.0 Hz, H-15), 4.61 (0.6H, bd, *J*=8.7 Hz, $H_{ax}$-29), 5.34 (0.4H, bs, $H_{eq}$-29), 7.34–7.41 (6H, m, $C_6H_5$–), 7.67 (4H, m, $C_6H_5$–). HR-ESMS: *m/z* 701.4973 (Calcd 701.4965 for $C_{45}H_{69}O_4Si$).

*Compound* **24**. $R_f$=0.25 (70% diethyl ether in petroleum ether). $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.64 (3H, s, $CH_3$-18), 0.79 (3H, s, $CH_3$-19), 0.84–0.90 (7.5H, m, ($CH_3$)$_2$CH– and $CH_3$-21 overlapped), 0.94 (1.5H, d, *J*=6.7 Hz, $CH_3$-21), 1.04 (9H, s, ($CH_3$)$_3$CSi–), 3.32 (0.5H, bd, *J*=10.6 Hz, H-22), 3.56 (1H, m, H-3), 3.89–3.95 (1.5H, m, H-15 and H-22 overlapped), 4.62 (0.5H, bd, *J*=8.7 Hz, $H_{ax}$-29), 5.36 (0.5H, bs, $H_{eq}$-29), 7.34–7.41 (6H, m, $C_6H_5$–), 7.66 (4H, m, $C_6H_5$–). HR-ESMS: *m/z* 701.4960 (Calcd 701.4965 for $C_{45}H_{69}O_4Si$).

**4.5.2. Compound 26.** To a solution of a mixture of **23** and **24** (0.028 g, 0.040 mmol) in $CH_2Cl_2$ (1.0 mL), HCl in MeOH (1 N, 2.0 mL) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with $Ag_2CO_3$, stirred for 1 h, filtered and concentrated in vacuo to give **23** as a white amorphous solid which was used in the next step without further purification. To a solution of crude **23** in dry $CH_2Cl_2$ (2.0 mL), 4 Å molecular sieves (0.060 g) and PDC (0.030 g, 0.040 mmol) were added. The mixture was stirred at room temperature for 1 h, then diluted with diethyl ether (5.0 mL) and allowed to stir for additional

30 min. Filtration through a short pad of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution, which was concentrated in vacuo. The residue was flash chromatographed (30–70% diethyl ether in petroleum ether) to afford **26** (0.010 g, 55% on two steps) as a white amorphous solid.

*Compound* **26**. $R_f$=0.35 (50% diethyl ether in petroleum ether). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.77 (3H, s, $CH_3$-19), 0.86 (3H, d, $J$=6.9 Hz, ($CH_3$)$CH_3$CH–), 0.87 (3H, d, $J$=6.9 Hz, ($CH_3$)$CH_3$CH–), 1.01 (3H, s, $CH_3$-18), 1.02 (1.8H, d, $J$=6.8 Hz, $CH_3$-21), 1.07 (1.2H, d, $J$=6.8 Hz, $CH_3$-21), 3.26 (0.4H, bd, $J$=10.8 Hz, H-22), 3.34 (1.8H, s, $CH_3$O), 3.47 (1.2H, s, $CH_3$O), 3.70 (0.6H, bd, $J$=11.2 Hz, H-22), 4.19 (0.4H, bd, $J$=8.7 Hz, $H_{ax}$-29), 4.76 (0.6H, bs, $H_{eq}$-29). HR-ESMS: $m/z$ 473.3635 (Calcd 473.3631 for $C_{30}H_{49}O_4$).

### 4.6. C/D ring junction attempted isomerization of 26 with MeONa

To a solution of **26** (0.008 g, 0.017 mmol) in dry THF (0.500 mL), a solution of MeONa in dry methanol (1 M, 2.5 mL) was added. After 3 h at room temperature, the reaction mixture was refluxed for 2 days and then cooling at room temperature and diluted with diethyl ether. Filtration through a short pad of silica gel afforded a solution, which was concentrated in vacuo to give a residue containing starting material **26** (0.008 g).

### 4.7. C/D ring junction attempted isomerization of 26 with NaH

To a solution of **26** (0.008 g, 0.017 mmol) in dry THF (0.500 mL), was added NaH (0.010 mg, 0. 417 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and then refluxed for 3 days. It was then quenched by addition of water at 0 °C. The mixture was concentrated in vacuo to remove the excess THF and the aqueous layer was extracted with $CH_2Cl_2$. The organic phase was dried over $Na_2SO_4$, filtered and evaporated in vacuo to give a complex mixture of unidentified compounds.

### 4.8. C/D ring junction attempted isomerization of 26 with NaOH

To a solution of **26** (0.008 g, 0.017 mmol) in 1:1 THF/EtOH (0.500 mL), was added 10% NaOH (0.100 mL) and the reaction mixture was stirred for 4 h at room temperature and then refluxed for 2 days. It was then quenched by addition of water at 0 °C. The mixture was concentrated in vacuo to remove the excess THF and the aqueous layer was extracted with $CH_2Cl_2$. The organic phase was dried over $Na_2SO_4$, filtered and evaporated in vacuo to give a residue containing only the starting material **26** (0.008 g).

**4.8.1. Compound 30.** To a solution of **29** (0.300 g, 0.437 mmol) in dry $CH_2Cl_2$ (1.2 mL), DBU (0.120 g, 0.787 mmol) and TBSCl (0.105 g, 0.699 mmol) were added. The reaction mixture was stirred overnight at room temperature and then quenched with a saturated solution of $NH_4Cl$. The aqueous layer was extracted with $CH_2Cl_2$ (3×3.0 mL) and the combined organic phases were dried over $Na_2SO_4$, filtered and evaporated in vacuo. The crude product was flash-chromatographed (10% diethyl ether in petroleum ether) to afford **30** (0.289 g, 84%) as a white amorphous solid.

*Compound* **30**. $R_f$=0.71 (40% diethyl ether in petroleum ether). $[\alpha]_D^{20}$=+17.4 ($c$ 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.03 (6H, s, ($CH_3$)$_2$Si–), 0.73 (3H, s, $CH_3$-18), 0.88 (9H, s, ($CH_3$)$_3$CSi–), 0.96 (3H, s, $CH_3$-19), 0.99 (3H, d, $J$=6.8 Hz, $CH_3$-21), 1.04 (9H, s, ($CH_3$)$_3$CSi–), 1.87 (3H, s, OCC$H_3$), 1.96 (3H, s, OCC$H_3$), 3.39 (1H, dd, $J$=9.3, 9.3 Hz, H-22), 3.56 (2H, m, H-3 and H′-22 overlapped), 4.67 (1H, dd, $J$=9.4, 9.4 Hz, H-6 or H-7), 4.80 (1H, dd, $J$=11.2, 9.4 Hz, H-7 or H-6), 5.26 (1H, m, H-16), 7.34–7.43 (6H, m, $C_6H_5$–), 7.64 (4H, m, $C_6H_5$–). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ −5.3 (×2), 13.3, 15.9, 18.7, 19.1, 20.7, 21.0, 21.4, 25.6, 25.9 (×3), 26.9 (×3), 31.1, 32.0, 32.1, 34.3, 34.6, 36.0, 36.9, 38.0, 46.4, 47.9, 52.1, 54.7, 67.9, 72.0, 74.3, 77.7, 121.9, 127.4 (×4), 129.5 (×2), 134.5 (×2), 135.7 (×4), 156.8, 170.6, 170.8. HR-ESMS: $m/z$ 801.4935 (Calcd 801.4946 for $C_{48}H_{73}O_6Si_2$).

### 4.9. C-15 attempted allylic oxidation with $CrO_3$-DMP

$CrO_3$ (0.080 g, 0.80 mmol) was finely ground with a mortar and pestle and dried in vacuo for 6 h. In an argon-purged flask, $CrO_3$ was suspended in dry $CH_2Cl_2$ (0.5 mL) and the resultant suspension was stirred for 15 min at room temperature. Then it was cooled to −40 °C and the DMP (0.077 g, 0.80 mmol) was added in one portion. The dark red mixture was stirred at −40 °C for 30 min and then a solution of **30** (0.032 g, 0.04 mmol) in dry $CH_2Cl_2$ (1.0 mL) was added via cannula. The resultant thick, dark reaction mixture was allowed to warm at room temperature and stirred under argon overnight. NaOH solution (3 N, 0.5 mL) was subsequently added at 0 °C and the mixture was stirred for 45 min at room temperature. Then it was diluted with diethyl ether (2.0 mL) and allowed to stir for additional 30 min. The organic phase was separated and the aqueous layer, containing a green precipitate, was washed with diethyl ether (3×2.0 mL). Filtration of the combined organic phases through a path of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution, which was concentrated in vacuo. The residue was flash chromatographed (10% diethyl ether in petroleum ether) to afford starting material **30** (0.080 g).

### 4.10. C-15 attempted allylic oxidation with $SeO_2$, *t*-BuOOH

To a suspension of $SeO_2$ (0.005 g, 0.050 mmol) in $CH_2Cl_2$, (0.800 mL) a solution of TBHP (5.5 M in nonane, 0.018 mL, 0.100 mmol) was added at 0 °C. After 0.5 h a solution of **30** (0.040 g, 0.050 mmol) in $CH_2Cl_2$ (0.800 mL) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 10% NaOH aqueous solution and extracted with $CH_2Cl_2$, affording a complex mixture of unidentified compounds.

### 4.11. C-15 attempted allylic oxidation with CuI, *t*-BuOOH

To a solution of **30** (0.040 g, 0.050 mmol) in acetonitrile

(1.0 mL), copper iodide (1 mg) and TBHP (5.5 M in nonane, 0.054 mL, 0.300 mmol) were added. After one night, under magnetic stirring at 55 °C, the solution was poured into 10% sodium sulfite solution and extracted with diethyl ether. The residue contained only starting material **30** (0.038 g).

### 4.12. Computational details

Preliminary molecular mechanics/dynamics calculations on each of the compounds under examination were performed on Silicon Graphics Indigo2 using the CVFF force field[31] and the INSIGHT II/Discover package.[32] MD calculations (500 K, 50 ps) were executed in order to allow a full exploration of the conformational space. This led to the selection of the lowest energy minimum conformers. Subsequently, QM calculations were carried out using the Gaussian 98W program package; structures and energies of the considered species were optimized at AM1[33] and/or PM3[34] level.

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