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Synthesis of potentially anti-inflammatory IPL576,092-contignasterol and IPL576,092-manoalide hybrids

Irene Izzo,[a,*] Elvira Avallone,[a] Carmela Della Monica,[a] Agostino Casapullo,[b] Maria Amigo[c] and Francesco De Riccardis[a,*]

[a]*Dipartimento di Chimica, University of Salerno, via S. Allende, Baronissi I-84081 (SA), Italy*
[b]*Dipartimento di Scienze Farmaceutiche, University of Salerno via Ponte Don Melillo, I-84084 Fisciano (SA), Italy*
[c]*Departamento de Farmacologia, Facultad de Farmacia, Universidad de Valencia, Av. Vicént Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain*

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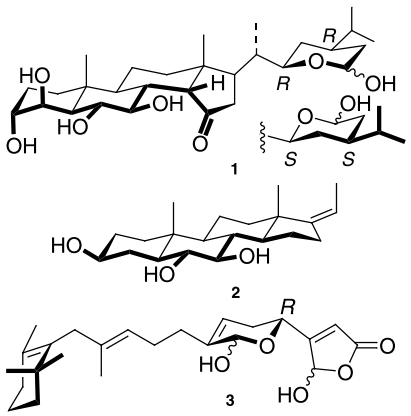
Abstract—The synthesis of two potentially anti-inflammatory steroidal hybrid compounds has been accomplished through a 16- and 17-step sequence, respectively, starting from commercially available androst-5-en-3β-ol-17-one. The synthetic strategies are based both on stereoselective side chains elaboration and high yielding functional group transformations.

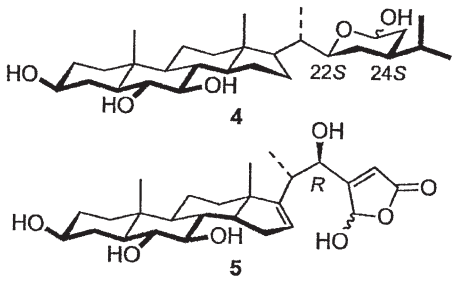
1. Introduction

Normal inflammation, a defense reaction caused by tissue damage or injury and characterized by redness, heat, swelling, and pain, is a highly regulated process. The inflammatory response, also involved in asthma and allergy, is induced by a localized release of histamine, leukotrienes, prostaglandins and cytokines.

With the recent discovery of the anti-inflammatory potential of contignasterol (**1**),[1] a polyhydroxysteroid isolated from the sponge *Petrosia contignata*, IPL576,092 (**2**),[2] a synthetic trihydroxypregnene, and manoalide (**3**), a marine sesterterpene isolated from the sponge *Luffariella variabilis*,[3] new perspectives have been opened in the treatment of inflammation-related pathological disorders.



Recently, a novel and promising approach in drug discovery, towards the development of new lead substances, has emerged. It consists in the combination of parts of structurally different naturally occurring bioactive products to yield hybrid structures that can, in principle, exceed the activities of their parent compounds.[4] From this perspective and as part of a broad program in the steroid area, we designed and synthesized the hybrid entities **4** and **5**, linking the IPL576,092 trihydroxylated tetracyclic nucleus to the contignasterol's (17*R*,20*S*,22*S*,24*S*)-lactol[5] and manoalide γ-hydroxybutenolide side chains, respectively. It is the preparation of these two new compounds that is reported here.



2. Results and discussion

Two important steps required to generate target compounds

Keywords: IPL576,092; Contignasterol; Manoalide; Steroids; Anti-inflammatory compounds.
* Corresponding authors. Tel.: +39089965230; fax: +39089965296; e-mail addresses: dericca@unisa.it; iizzo@unisa.it

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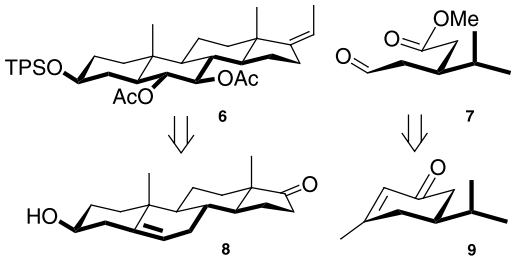
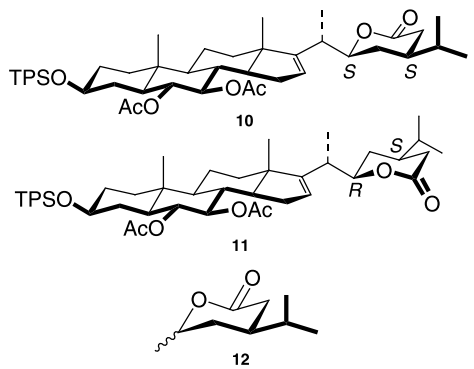
4 and **5** are: the synthesis of the fully protected common intermediate (*Z*)-6α,7β-(diacetoxy)-3β-[(*tert*-(butyldiphenysilyl)-oxy]-5α-pregn-17(20)-ene (**6**), and a highly reliable stereoselective method for the side chain precursor's introduction.

2.1. Synthesis of IPL576,092-contignasterol hybrid

Sterol **6** and preformed contignasterol's side chain intermediate **7** were conveniently prepared from commercially available androst-5-en-3β-ol-17-one (**8**), in 11 steps and 26% overall yield[6] and (*S*)-carvone (**9**), in five steps and 48% overall yield,[7] respectively.

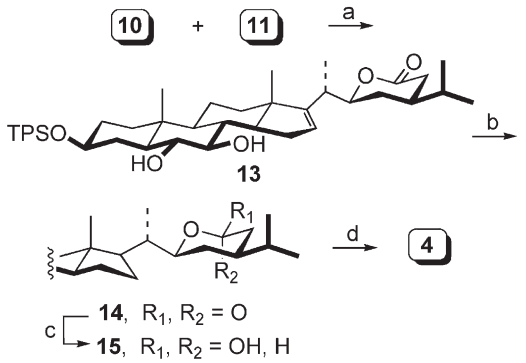


The two precursors **6** and **7** were linked through a stereochemically controlled Me_2AlCl-mediated carbonyl-ene reaction.[8] Although several ene reactions of linear aliphatic aldehydes have been reported,[8] we have encountered serious difficulties for the convergent coupling between **6** and **7**. The Lewis base character of the tetracyclic nucleus oxygenated substituents present in **6** and a probable 7β-acetoxy induced D ring unfavorable steric effect, could be the reasons of the low yields. The best results[9] were achieved using a two-fold excess of the Lewis acid relative to the aldehyde **7**[10] and afforded an inseparable mixture of diasteroimers **10** and **11**[11] (4:1 ratio in 66% overall yield, based on recovered starting material **6**). The excess of the Me_2AlCl acted as nucleophile, inducing the formation of the C-5 epimeric lactone **12**.



In order to suppress the formation of byproducts, we turned our attention to the non-alkylating $BF_3{\cdot}OEt_2$ Lewis acid.[12] Unfortunately, in this case, we observed the formation of a mixture of unidentified compounds, with no trace of the desired adduct **10**.

The next problem to be faced was transformation of precursor **10** to the requested target **4**. To this end the (20*S*,22*S*,24*S*)-Δ^{16}-lactone **10**, as a mixture with the (22*R*)-epimer **11**, was hydrolyzed and separated from its

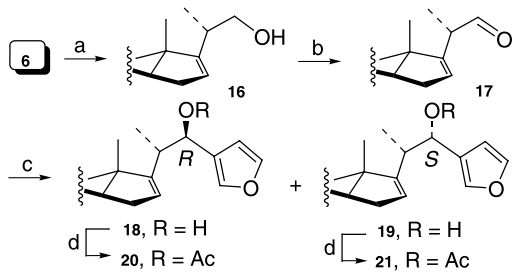


Scheme 1. (a) KOH, MeOH, 12 h, 70%; (b) H_2, Pt_2/C, AcOEt, 3 h, 90%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, quant.; (d) HF/pyridine, 0 °C, 3 days, 88%.

contaminant, to give pure **13** (Scheme 1). Highly stereoselective catalytic Δ^{16}-hydrogenation[7] and subsequent DIBAL-H mediated reduction, furnished the lactol **15**. Final HF-induced desilylation of the *tert*-(butyldiphenylsilyl) protecting group on C-3, provided the requested 3β,6α,7β-trihydroxy lactol **4** in good overall yield from intermediate **10**.[13]

2.2. Synthesis of IPL576,092-manoalide hybrid

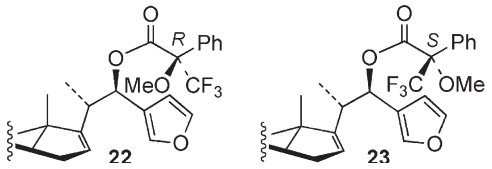
With the aim to combine IPL576,092 tetracyclic 3β,6α,7β-trihydroxylated nucleus with the γ-hydroxy butenolide manoalide[3]/luffariellolide[14] pharmacophore, we prepared the electrophilic aldehyde **17**, through a two-step sequence, from fully protected **6**, and exposed it to 3-furyllithium[15] (Scheme 2). The (*R*) stereochemistry of the major epimer **18** was assigned by comparison with the results observed for various alkyllithium or Grignard addition to this aldehyde, where the preferential formation of the Cram adduct is well documented.[16]



Scheme 2. (a) $BF_3{\cdot}OEt_2$, $(CH_2O)n$, CH_2Cl_2, −78 °C→−30 °C, 0.5 h, 90%;[6] (b) PDC, CH_2Cl_2, 2 h, 69%; (c) 3-bromofuran, *n*-BuLi, −78 °C, 15 min then **17**, −78 °C, 1 h, **18**: 57%, **19**: 28%; (d) Ac_2O, Py, 12 h, **20**: 95%, **21**: quant.

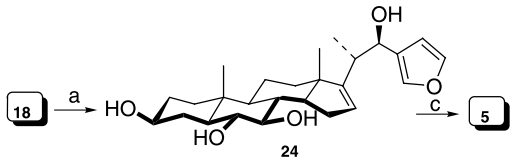
The stereochemical assignment was confirmed in two independent ways. It was empirically deduced by comparing the magnitude of the vicinal coupling of the $J_{H20-H22}$ in the acetylated derivatives **20** and **21**. It is known,[8] in fact, that the H-20/H-22 vicinal coupling constant should be smaller (~8 Hz) for the stereochemical arrangement present in **20** (20*S*,22*R*), and larger (~10 Hz) for that present in the epimer **21** (20*S*,22*S*). The observed $J_{H20-H22}$ coupling constants for **20** and **21** were 8.6 Hz and 10.7 Hz, respectively.

The (22*R*) configuration of **18** was also confirmed using the modified Mosher's esters method,[17] through comparison of the ^{1}H NMR spectra of α-methoxy-α-(trifluoromethyl)-phenylacetic (MTPA) derivatives **22** and **23**, easily achieved from (+)-(*S*)-MTPA-Cl and (−)-(*R*)-MTPA-Cl, respectively.[18]



Once ascertained the C-22 configuration of adducts **18** and **19**, we first desilylated at C-3 (Scheme 3) and then at C-6, C-7 deacetylated furyl alcohol **18**. Fully deprotected tetrol **24** was then submitted to a rose Bengal mediated photoxidation to give target γ-hydroxy butenolide **5**.[19]

The activity of hybrid **5** has been tested on human synovial $sPLA_2$-IIA, exerting a 63% of inhibition at 100 μM.[20] Additionally, this compound on lipopolysaccharide stimulated human monocytes was able to reduce nitric oxide and PGE_2 (two important mediators of the inflammatory process) at 10 μM (64 and 72%, respectively).[21]



Scheme 3. (a) (i) TBAF (1 M in THF), THF, 3 h; (ii) K_2CO_3, MeOH 12 h, 69% (two steps); (b) O_2/hν, rose Bengal, *i*-Pr_2EtN, CH_2Cl_2, −78 °C, 2 h, 40%.

3. Conclusions

In conclusion, we have reported the synthesis of two new IPL576,092-contignasterol and IPL576,092-manoalide analogs in 29 and 10% overall yields, respectively, starting from easily available (*Z*)-6α,7β-(diacetoxy)-3β-[(*tert*-(butyl-diphenysilyl)-oxy]-5α-pregn-17(20)-ene (**6**).

4. Experimental

4.1. General methods

The NMR spectra were recorded at room temperature on a Bruker DRX 400 spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz) or on Bruker DRX 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ=7.26, $^{13}CDCl_3$: δ=77.0, CD_2HOD: δ=3.31, $^{13}CD_3OD$: δ=49.0). Instruments used to obtain physical data and experimental conditions for the reactions and chromatography were the same as described in the preceding paper.[7]

4.2. Procedures for the synthesis of compounds 4, 10–15, described in paragraph 2.1

4.2.1. Compounds 10 and 11. To a solution of **6** (0.694 g, 1.05 mmol) and **7** (0.582 g, 3.38 mmol) in dry CH_2Cl_2 (15 mL), Me_2AlCl (1 M in hexane, 6.72 mL, 6.72 mmol) was added at −78 °C. The resulting mixture was warmed to −20 °C over 5 h and then stirred at −20 °C overnight. The reaction was quenched with MeOH/H_2O (18.0 mL, 1:1) at −78 °C. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic phases were successively washed with 1% aqueous HCl, saturated aqueous $NaHCO_3$, brine and then dried over Na_2SO_4. Removal of solvent in vacuo gave the crude containing **10** and **11** in a 4:1 ratio [^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ: 5.34 (0.8H, bs, H-16), 5.41 (0.2H, bs, H′-16)], which was purified by flash chromatography (20–80% diethyl ether in petroleum ether) to furnish a mixture of **10** and **11** (0.168 g, 20% overall yield, 66%, based on recovered starting material), of **6** (0.483 g, 70%) and **12** (variable amounts).

Compounds **10**–**11**. R_f=0.47 (30% ethyl acetate in petroleum ether). HR-ESMS: *m*/*z* 797.4817 (calcd 797.4813 for $C_{49}H_{69}O_7Si$).

Compound **12**. R_f=0.65 (30% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.84 (6H, d overlapped, *J*=7.0 Hz, −CH(C*H*$_3$)$_2$), 1.30 (1.5H, d, *J*=6.2 Hz, −CHC*H*$_3$), 1.31 (1.5H, d, *J*=6.2 Hz, −CHC*H*$_3$), 1.41–1.90 (4H, m, CHC*H*$_2$CH−, CH_2CHCH_2−, $(CH_3)_2CH$−, overlapped), 2.07 (0.5H, dd, *J*=17.7, 10.5 Hz, −C*H*HCOO), 2.17 (0.5H, dd, *J*=15.8, 11.1 Hz, −C*H*HCOO), 2.45 (0.5H, dd, *J*=15.8, 5.5 Hz, −CH*H*COO), 2.58 (0.5H, dd, *J*=17.7, 6.3 Hz, −CH*H*COO), 4.32 (0.5H, m, −*CH*OCO), 4.41 (0.5H, m, −*CH*OCO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ:19.0, 19.1, 19.2 (×2), 21.0, 21.8, 32.1 (×2), 32.6, 33.0, 33.4, 34.0, 35.0, 37.8, 73.8, 76.7, 172.0, 173.3. HR-ESMS: *m*/*z* 157.1237 (calcd 157.1229 for $C_9H_{17}O_2$).

4.2.2. Compound 13. *Compounds* **10** and **11** (0.115 g, 0.144 mmol) were dissolved in a 5% solution of KOH in MeOH (5.0 mL) and allowed to react overnight at room temperature. The reaction mixture was acidified with 2 M HCl to pH=1 at 0 °C. The solvents were concentrated in vacuo, to remove the excess MeOH, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude, which was flash chromatographed (10–30% diethyl ether in chloroform) to give pure **13** (0.072 g, 70%) as a white amorphous solid and an inseparable mixture of **13** and its C-22 (*R*)-epimer (0.031 g).

Compound **13**. R_f=0.33 (30% diethyl ether in chloroform, double migration). IR ($CHCl_3$) ν_{max} (cm^{-1}) 3400, 2959, 2929, 2853, 1728, 1471, 1428, 1375, 1219, 1110, 1077, 772, 703. $[\alpha]_D$=+15.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (3H, s, CH_3-18), 0.872 (3H, s, CH_3-19), 0.873 (6H, d, *J*=6.3 Hz, (C*H*$_3$)$_2$CH−), 1.05 (9H, s, (C*H*$_3$)$_3$CSi−), 1.14 (3H, d, *J*=6.7 Hz, CH_3-21), 2.14 (1H, dd, *J*=17.7, 9.9 Hz, H-28), 2.64 (1H, dd, *J*=17.7, 6.6 Hz, H′-28), 3.04 (1H, dd, *J*=9.3, 8.9 Hz, H-6 or H-7), 3.21 (1H, dd, *J*=10.6, 8.9 Hz, H-7 or H-6), 3.56 (1H, m, H-3), 4.22 (1H, t-like, *J*=8.9 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) δ: 13.6, 16.1, 18.3, 18.9, 19.1, 19.3, 20.9, 27.0 (×3), 31.1, 31.3, 32.2, 32.4, 33.7, 34.0, 34.6, 35.9, 37.1, 37.7, 38.0, 39.7, 47.9,

48.0, 52.3, 56.0, 72.5, 74.8, 80.2, 83.5, 124.1, 127.4 (×2), 127.5 (×2), 129.4, 129.5, 134.6, 134.8, 135.8 (×4), 155.6, 172.3. HR-ESMS: *m*/*z* 713.4615 (calcd 713.4601 for $C_{45}H_{65}O_5Si$).

4.2.3. Compound 14. To a solution of **13** (0.042 g, 0.059 mmol) in ethyl acetate (3.0 mL), a catalytic amount of 5% Pt/C (0.008 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 at room temperature. It was filtered through a pad of Celite® and concentrated in vacuo to afford **14** (0.038 g, 90%) which was used in the next step without further purification.

Compound **14**. R_f=0.68 (50% ethyl acetate in petroleum ether). $[\alpha]_D$=+15.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, s, CH_3-18), 0.82 (3H, s, CH_3-19), 0.90 (6H, bd, *J*=6.3 Hz, $(CH_3)_2CH-$), 0.95 (3H, d, *J*=6.5 Hz, CH_3-21), 1.04 (9H, s, $(CH_3)_3CSi-$), 2.09 (1H, dd, *J*=17.7, 10.8 Hz, H-28), 2.64 (1H, dd, *J*=17.7, 6.6 Hz, H′-28), 3.01 (1H, dd, *J*=9.3, 8.9 Hz, H-6 or H-7), 3.18 (1H, dd, *J*=10.6, 8.9 Hz, H-7 or H-6), 3.54 (1H, m, H-3), 4.33 (1H, bd, *J*=11.2 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) δ: 12.0, 12.6, 13.6, 19.1, 19.2, 19.3, 21.2, 26.5, 27.0 (×3), 28.0, 30.2, 31.2, 32.2, 32.4, 34.1, 35.5, 37.2, 38.0, 39.5, 40.3, 40.8, 43.2, 47.5, 50.6, 51.8, 55.5, 72.5, 74.8, 80.5, 82.5, 127.4 (×4), 129.4 (×2), 134.5, 134.8, 135.7 (×4), 172.7. HR-ESMS: *m*/*z* 715.4747 (calcd 715.4758 for $C_{45}H_{67}O_5Si$).

4.2.4. Compound 15. To a solution of **14** (0.033 g, 0.046 mmol) in dry CH_2Cl_2 (2.0 mL), DIBAL-H (1 M in CH_2Cl_2, 0.230 mL, 0.230 mmol) was added at −78 °C. The reaction mixture was stirred at −78 °C for 90 min, then quenched with MeOH/H_2O (1.0 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 (30–50% ethyl acetate in petroleum ether) to give **15** (0.033 g, quant.) as a white amorphous solid.

Compound **15**. R_f=0.66 (50% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.64 (3H, s, CH_3-18), 0.83 (3H, s, CH_3-19), 0.86–0.96 (9H, m, $(CH_3)_2CH-$, CH_3-21 overlapped), 1.05 (9H, s, $(CH_3)_3CSi-$), 3.01 (1H, dd, *J*=9.3, 8.9 Hz, H-6 or H-7), 3.18 (1H, dd, *J*=10.6, 8.9 Hz, H-7 or H-6), 3.41 (0.6H, bd, *J*=10.3 Hz, H-22), 3.54 (1H, m, H-3), 3.99 (0.4H, bd, *J*=11.1 Hz, H-22), 4.62 (0.6H, bd, *J*=8.9 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* 717.4917 (calcd 717.4914 for $C_{45}H_{69}O_5Si$).

4.2.5. Compound 4. To a solution of **15** (0.044 g, 0.061 mmol) in dry pyridine (0.600 mL), 70% HF in pyridine (0.073 mL) was added at 0 °C. The reaction mixture was stirred for 3 days at 0 °C and then diluted with $CHCl_3$. The solvents were removed under a N_2 stream and the residue was flash-chromatographed (5–20% methanol in a 0.1% solution of triethylamine in dichloromethane) to afford **4** (0.026 g, 88%) as a white amorphous solid.

Compound **4**. R_f=0.17 (10% methanol in dichloromethane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, bs, CH_3-18), 0.83–0.96 (6H, m, CH_3-19, CH_3-21 and $(CH_3)_2CH-$ overlapped), 3.03 (1H, m, H-6 or H-7), 3.18 (1H, m, H-7 or H-6), 3.40 (0.5H, bd, *J*=8.3 Hz, H-22), 3.60 (1H, m, H-3), 4.01 (0.5H, bd, *J*=10 Hz, H_{ax}-29), 4.63 (0.5H, bd, *J*=8.0 Hz, H-22), 5.31 (0.5H, bs, H_{eq}-29). HR-ESMS: *m*/*z* 479.3749 (calcd 479.3736 for $C_{29}H_{51}O_5$).

4.3. Procedures for the synthesis of compounds 5, 17–24, described in paragraph 2.2

4.3.1. Compound 17. To a solution of **16**[6] (0.202 g, 0.29 mmol) in dry CH_2Cl_2 (10 mL), 4 Å molecular sieves (0.20 g) and PDC (0.22 g, 0.59 mmol) were added. The mixture was stirred at room temperature for 3 h, then diluted with diethyl ether (10 mL) and allowed to stir for additional 45 min. Filtration through 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 (10–20% ethyl acetate in petroleum ether) to afford **17** (0.140 g, 69%) as a pale yellow oil.

Compound **17**. R_f=0.44 (20% ethyl acetate in petroleum ether). $[\alpha]_D$=+17.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.75 (3H, s, CH_3-18), 0.95 (3H, s, CH_3-19), 1.02 (9H, s, $(CH_3)_3CSi-$), 1.15 (3H, d, *J*=6.7 Hz, CH_3-21), 1.87 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CO), 2.97 (1H, bq, *J*=5.4 Hz, H-20), 3.54 (1H, m, H-3), 4.68 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.77 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.42 (1H, bs, H-16), 7.37 (6H, m, C_6H_5-), 7.63 (4H, m, C_6H_5-), 9.39 (1H, d, *J*=2.3 Hz, H-22). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.0, 14.0, 15.5, 18.7, 20.3, 20.5, 21.1, 26.6 (×3), 30.7, 31.8 (×2), 31.9, 33.6, 35.6, 36.5, 37.6, 45.4, 46.0, 51.6, 54.3, 71.6, 73.8, 77.2, 126.9, 127.1 (×4), 129.2 (×2), 134.1, 134.2, 135.4 (×4), 150.3, 170.3, 170.4, 200.5. HR-ESMS: *m*/*z* 685.3931 (calcd 685.3924 for $C_{42}H_{57}O_6Si$).

4.3.2. Compounds 18 and 19. To a solution of 3-bromofuran (0.065 mL, 0.72 mmol) in dry THF (2.5 mL), *n*-BuLi (1.6 M in hexane, 0.32 mL, 0.51 mmol) was added at −78 °C. After being stirred for 30 min, to the resulting mixture was added a solution of **17** (0.071 g, 0.10 mmol) in dry THF (2.5 mL) and the mixture was stirred for 30 min at −78 °C. The mixture was neutralized with saturated aqueous NH_4Cl, concentrated in vacuo, to remove the excess THF, and extracted with diethyl ether. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was flash-chromatographed (15–40% of ethyl ether in petroleum ether) to give **18** (0.036 g, 57%) and **19** (0.018 g, 28%) as oils.

Compound **18**. R_f=0.50 (30% ethyl acetate in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2936, 2856, 1743, 1376, 1251, 1110, 1081, 1029, 703. $[\alpha]_D$=+8.4 (*c* 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, s, CH_3-18), 0.94 (3H, s, CH_3-19), 1.01 (3H, d, *J*=6.7 Hz, CH_3-21), 1.02 (9H, s, $(CH_3)_3CSi-$), 1.87 (3H, s, CH_3CO), 1.96 (3H, s, CH_3CO), 2.40 (1H, m, H-20), 3.52 (1H, m, H-3), 4.66 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.74 (1H, d, *J*=5.6 Hz, H-22), 4.78 (1H, dd, *J*=9.9, 9.4 Hz, H-6 or H-7), 5.46 (1H, bs, H-16), 6.31 (1H, bs, H-4′), 7.38, (8H, m, C_6H_5-, H-2′ and

H-5′ overlapped), 7.62 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 15.5, 15.9, 19.1, 20.7, 20.9, 21.4, 26.9 (×3), 31.1, 32.0, 32.1, 34.2, 36.0, 36.8, 37.8, 38.8, 46.4, 47.7, 52.0, 55.2, 69.3, 72.0, 74.3, 77.6, 108.7, 124.7, 127.5 (×4), 127.8, 129.5 (×2), 134.5, 134.6, 135.7 (×4), 139.4, 142.8, 156.0, 170.6, 170.8. HR-ESMS: *m/z* 753.4179 (calcd 753.4187 for $C_{46}H_{61}O_7Si$).

Compound **19**. R_f=0.35 (30% ethyl acetate in petroleum ether). $[\alpha]_D$=+40.7 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.37 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.15 (3H, d, *J*=6.7 Hz, CH_3-21), 1.86 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.74 (1H, m, H-20), 3.51 (1H, m, H-3), 4.65 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (2H, m, H-7 or H-6 and H-22 overlapped), 5.41 (1H, bs, H-16), 6.31 (1H, bs, H-4′), 7.27–7.40 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.62 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 15.0, 18.9, 19.0, 20.7, 20.9, 21.4, 26.9 (×3), 31.1, 32.0, 32.1, 34.2, 35.9, 36.8, 36.9, 37.0, 37.8, 46.3, 48.0, 52.0, 54.6, 68.9, 72.0, 74.2, 77.5, 113.7, 123.6, 127.5 (×4), 129.5 (×2), 134.4, 134.5, 135.7 (×4), 141.5, 152.0, 155.0, 170.6, 170.8. HR-ESMS: *m/z* 753.4191 (calcd 753.4187 for $C_{46}H_{61}O_7Si$).

4.3.3. Compounds 20 and 21. To a solution of **18** (or **19**) (0.010 g, 0.013 mmol) in dry pyridine (0.100 mL), Ac_2O (0.040 mL) was added. The resulting mixture was stirred overnight, concentrated under a N_2 stream and flash-chromatographed (10–20% of ethyl acetate in petroleum ether) to give **20** (0.010 g, 95%) or **21** (0.011 g, quant.) as oils.

Compound **20**. R_f=0.59 (50% diethyl ether in petroleum ether). $[\alpha]_D$=+4.8 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.45 (3H, s, CH_3-18), 0.92 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.06 (3H, d, *J*=6.7 Hz, CH_3-21), 1.86 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.47 (1H, m, H-20), 3.51 (1H, m, H-3), 4.64 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.76 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.33 (1H, bs, H-16), 5.78 (1H, d, *J*=8.6 Hz, H-22), 6.27 (1H, bs, H-4′), 7.27–7.40 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.62 (4H, m, –C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 15.3, 15.9, 19.1, 20.7, 20.9, 21.2, 27.0 (×3), 29.7, 31.2 (×2), 32.2 (×2), 34.4, 36.0, 36.9, 37.3, 37.9, 46.4, 48.0, 52.1, 54.8, 71.7, 72.0, 74.3, 109.2, 124.1, 124.5, 127.5 (×4), 129.5 (×2), 134.7 (×2), 135.7 (×4), 140.5, 142.6, 154.6, 170.3, 170.6, 170.8. HR-ESMS: *m/z* 795.4285 (calcd 795.4292 for $C_{48}H_{63}O_8Si$).

Compound **21**. R_f=0.69 (30% ethyl acetate in petroleum ether). $[\alpha]_D$=+34.8 (*c*=0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.30 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.08 (3H, d, *J*=6.7 Hz, CH_3-21), 1.85 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 2.79 (1H, m, H-20), 3.50 (1H, m, H-3), 4.63 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.47 (1H, bs, H-16), 5.89 (1H, d, *J*=10.7 Hz, H-22), 6.31 (1H, bs, H-4′), 7.34–7.41 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.62 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 14.9, 19.1, 19.4, 20.7, 20.8, 20.9, 21.4, 26.9 (×3), 29.8, 32.1 (×2), 34.2, 34.8, 35.9, 36.8, 37.8, 46.4, 48.1, 52.0, 54.4, 69.8, 72.0, 74.2, 77.5, 113.9, 124.0 (×2), 127.5 (×4), 129.5 (×2), 134.6 (×2), 135.7 (×4), 141.9, 149.0, 153.7, 170.0, 170.6, 170.8. HR-ESMS: *m/z* 795.4281 (calcd 795.4292 for $C_{48}H_{63}O_8Si$).

4.3.4. Compounds 22 and 23. To a solution of **18** (0.010 g, 0.013 mmol) in dry pyridine (0.150 mL), (*S*)-MTPA-Cl (or (*R*)-MTPA-Cl 0.007 mL) was added at 0 °C. The resulting mixture was stirred 1 h, concentrated under a N_2 stream and flash-chromatographed (30% of diethyl ether in petroleum ether) to give **22** (or **23**) in quantitative yield.

Compound **22**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.40 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 0.93 (3H, d, *J*=6.7 Hz, CH_3-21), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.86 (3H, s, CH_3CO), 1.94 (3H, s, CH_3CO), 2.53 (1H, m, H-20), 3.40 (4H, m, H-3 and CH_3O– overlapped), 4.62 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.28 (1H, bs, H-16), 5.95 (1H, d, *J*=9.6 Hz, H-22), 6.31 (1H, bs, H-4′), 7.31–7.41 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.63 (4H, m, C_6H_5–). LR-ESMS: *m/z* 969.9 (calcd 969.5 for $C_{56}H_{68}F_3O_9Si$).

Compound **23**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.40 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.09 (3H, d, *J*=6.7 Hz, CH_3-21), 1.85 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.53 (1H, m, H-20), 3.49 (4H, m, H-3 and CH_3O– overlapped), 4.63 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.33 (1H, bs, H-16), 5.90 (1H, d, *J*=8.8 Hz, H-22), 6.14 (1H, bs, H-4′), 7.31–7.41 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.63 (4H, m, C_6H_5–). LR-ESMS: *m/z* 969.1 (calcd 969.5 for $C_{56}H_{68}F_3O_9Si$).

4.3.5. Compound 24. To a solution of **18** (0.170 g, 0.23 mmol) in dry THF (3.0 mL), *tetra*-butylammonium fluoride (TBAF, 1 M in THF, 0.92 mL, 0.92 mmol) was added. The mixture was stirred at room temperature for 3 h, then diluted with H_2O, concentrated in vacuo, to remove the excess THF, and extracted with diethyl ether. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. To a solution of the residue in MeOH (2.0 mL), K_2CO_3 (0.010 g, 0.072 mmol) was added. The mixture was stirred at reflux overnight and then quenched with $CHCl_3$ (3.0 mL). Solvents were concentrated in vacuo to the half of their volume. The procedure ($CHCl_3$ addition and concentration) was repeated several times to precipitate the carbonate. The solution was then filtrate through a pad of Celite®, concentrated in vacuo and the residue was flash-chromatographed (2–30% MeOH in CH_2Cl_2) to give **24** (0.066 g; 69% for two steps) as a white amorphous solid.

Compound **24**. R_f=0.74 (25% methanol in chloroform). $[\alpha]_D$=+32.6 (*c* 0.8, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.70 (3H, s, CH_3-18), 0.89 (3H, s, CH_3-19), 1.04 (9H, s, (CH_3)$_3$CSi–), 1.06 (3H, d, *J*=6.7 Hz, CH_3-21), 2.46 (1H, m, H-20), 3.13 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 3.28 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6) 3.58 (1H, m, H-3), 4.79 (1H, d, *J*=5.6 Hz, H-22), 5.60 (1H, bs, H-16), 6.33 (1H, bs, H-4′), 7.35 (2H, bs, H-2′ and H-5′). ^{13}C NMR (CD_3OD, 100 MHz) δ: 14.0, 15.9, 18.5, 18.8, 22.4, 31.9, 33.3, 35.1, 36.2, 37.0, 38.5, 40.6, 41.2, 49.8, 54.0, 58.1, 71.0, 71.9, 75.9, 81.1, 110.4, 125.3, 130.3, 141.0, 143.7, 157.6. HR-ESMS: *m/z* 431.2787 (calcd 431.2797 for $C_{26}H_{39}O_5$).

4.3.6. Compound 5. To a solution of **24** (0.020 g, 0.048 mmol) in dry CH_2Cl_2 (2.0 mL) and THF (1.0 mL), diisopropylethylamine (0.85 mL) and rose Bengal (0.001 g) were added. The mixture was irradiated at −78 °C with a 200-W tungsten incandescent lamp for 2 h. The reaction mixture was allowed to warm to 20 °C and concentrated in vacuo. The crude residue was purified by HPLC (Vydac C_{18} analytical column; 10–95% of CH_3CN and 0.1% TFA in H_2O and 0.1% TFA) to give **5** in (0.009 g, 40%) as a white amorphous solid.

Compound **5**. R_f=0.60 (25% methanol in chloroform). $[\alpha]_D$=+46.9 (*c* 0.8, CH_3OH). ^1H NMR (CD_3OD, 400 MHz) δ: 0.89 (3H, s, CH_3-18), 0.94 (3H, s, CH_3-19), 1.06 (3H, d, *J*=6.7 Hz, CH_3-21), 2.49 (1H, m, H-20), 3.04 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 3.18 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6) 3.51 (1H, m, H-3), 4.60 (1H, bd, *J*=3.8 Hz, H-22), 5.69 (1H, bs, H-16), 6.12 (1H, bs, C=C*H*CO), 6.40 (1H, bs, HOC*H*O–). HR-ESMS: *m/z* 463.2690 (calcd 463.2696 for $C_{26}H_{39}O_7$).

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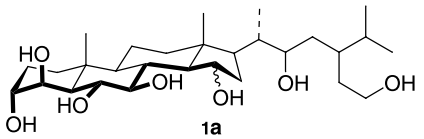

1a

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10. It is known that a lower ratio between Lewis acid and aldehyde induces an Oppenauer-type oxidation of the secondary alcohol present in the adduct (see Scheme II of Ref. 8).
11. The C-22 stereochemistries were assigned on strenght of comparative analysis with our previous results. See: Izzo, I.; Pironti, V.; Della Monica, C.; Sodano, G.; De Riccardis, F. *Tetrahedron Lett.* **2001**, *42*, 8977–8980.
12. A problem with $BF_3{\cdot}OEt_2$ catalyzed ene reaction is that the alcohol–Lewis acid complex, produced in the reaction, forms a strong protic acid capable of protonating the double bond of the ene adduct or the alkene. When Me_2AlCl is used as Lewis acid, the proton associated to the alcohol–Me_2AlCl adduct is quenched by the basic methyl aluminium substituent to yield methane and an inert aluminium alkoxide which does not undergo side reactions. See: (a) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555–563. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426–432.
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