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Saponaceolides: Differential Cytotoxicity and Enantioselective Synthesis of the Right-hand Lactone Moiety

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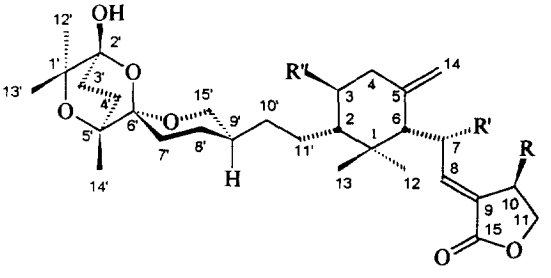
Abstract: The enantioselective synthesis of the right-hand lactone moiety **5** of saponaceolide B, **2**, is described. The mean graph profiles of **5** do not match the characteristic patterns of differential cytotoxicity of saponaceolides A, **1**, and B, **2**, in the NCI human disease-oriented tumor screening panel, pointing out the need of the entire saponaceolide structure for maintaining the specificity and potency of the antitumor activity. En route to **5** several useful chiral building blocks, such as compounds **6**, **10**, **19**, **27**, and **28** were prepared.

A small group of bioactive triterpenes, saponaceolides A-D, **1-4**, were first isolated from the fruiting bodies of *Tricholoma saponaceum*.[1,2] Subsequently, saponaceolide B, **2**, was also isolated from *T. terreum*[3] and *T. scalpturatum*.[4] Preliminary results indicated that saponaceolides have an interesting *in vitro* antitumor activity,[1-3] which in principle could be attributed to the presence of an α-alkylidene-γ-butyrolactone unit capable of undergoing a Michael reaction with biological nucleophiles such as L-cysteine or thiol-containing enzymes.[5]



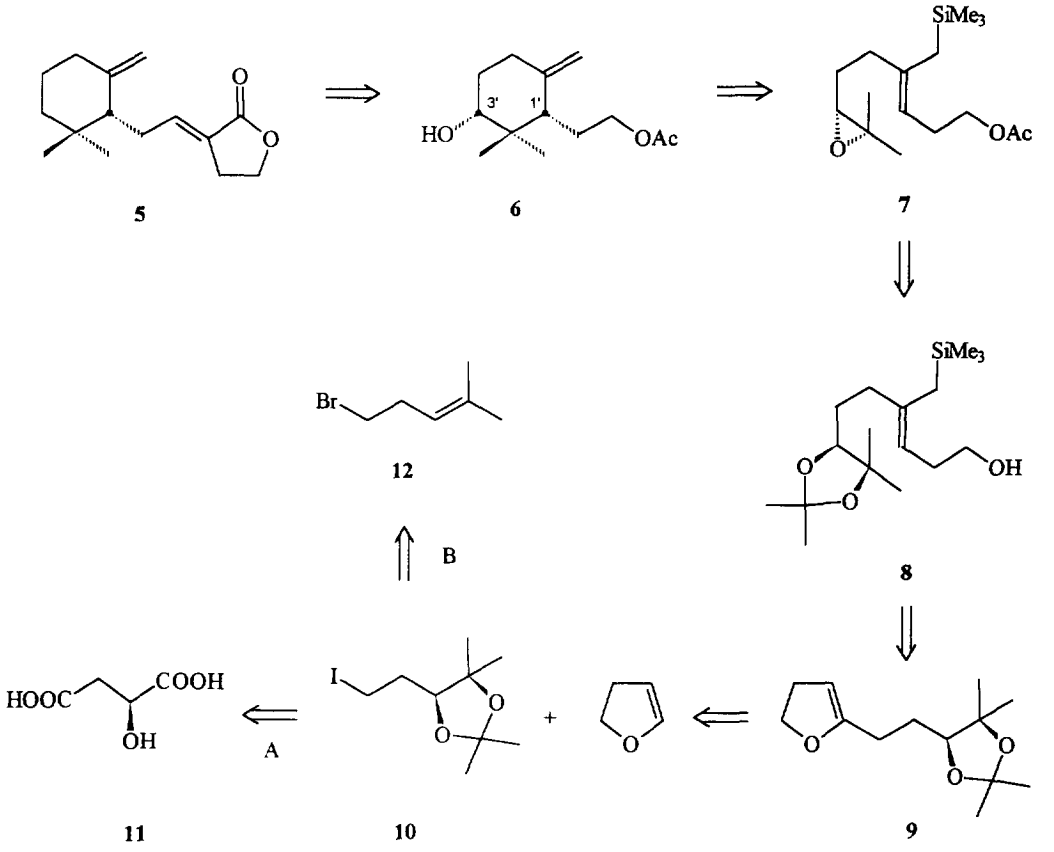
R = OH; R' = R" = H Saponaceolide A **1** R = R' = R" = H Saponaceolide B **2**

R = R' = OH; R" = H Saponaceolide C **3** R = R" = OH; R' = H Saponaceolide D **4**

The singularity of structures **1-4**, along with their unprecedented biosynthetic pathway and *in vitro* antitumor activity, prompted us to embark on a synthetic project aimed at the enantioselective construction

of the saponaceolide molecules.[6] Herein, we describe the stereoselective preparation of the model lactone **5**, corresponding to the right-hand fragment of saponaceolide B, **2**. With the availability of **5**, our aim was to examine whether the specificity and potency of the antitumor activity of saponaceolides could be preserved by the much simpler structure **5** or whether it would dramatically be affected by cutting away the dissymmetric tricyclospiroketal subunit. Therefore, the antitumor activities of compounds **1** and **2**, and the model compound **5**, were evaluated comparatively according to the standard procedures of the NCI,[7,8] on a cell line panel consisting of 60 lines. As an additional benefit, the synthesis of lactone **5** provided a highly stereoselective preparation of several useful enantiomerically pure building blocks such as **10**, **19**, **27**, **28**, and the alcohol **6** which we wish to use in the future for the synthesis of saponaceolides and other terpenoids.

The synthesis of lactone **5** is based on the retrosynthetic analysis illustrated in Scheme 1. A formal synthesis of the enantiomer of the key alcohol **6** starting from (S)-3-hydroxy-2,2-dimethylcyclohexanone was described previously.[9] However, this route is poorly diastereoselective, furnishing a 1:2,4 mixture of the *cis* and *trans* stereoisomers.[9] Therefore, we explored a completely different approach (Scheme 1) for constructing **6**, relying on a biomimetic electrophilic olefin cyclization.[10]



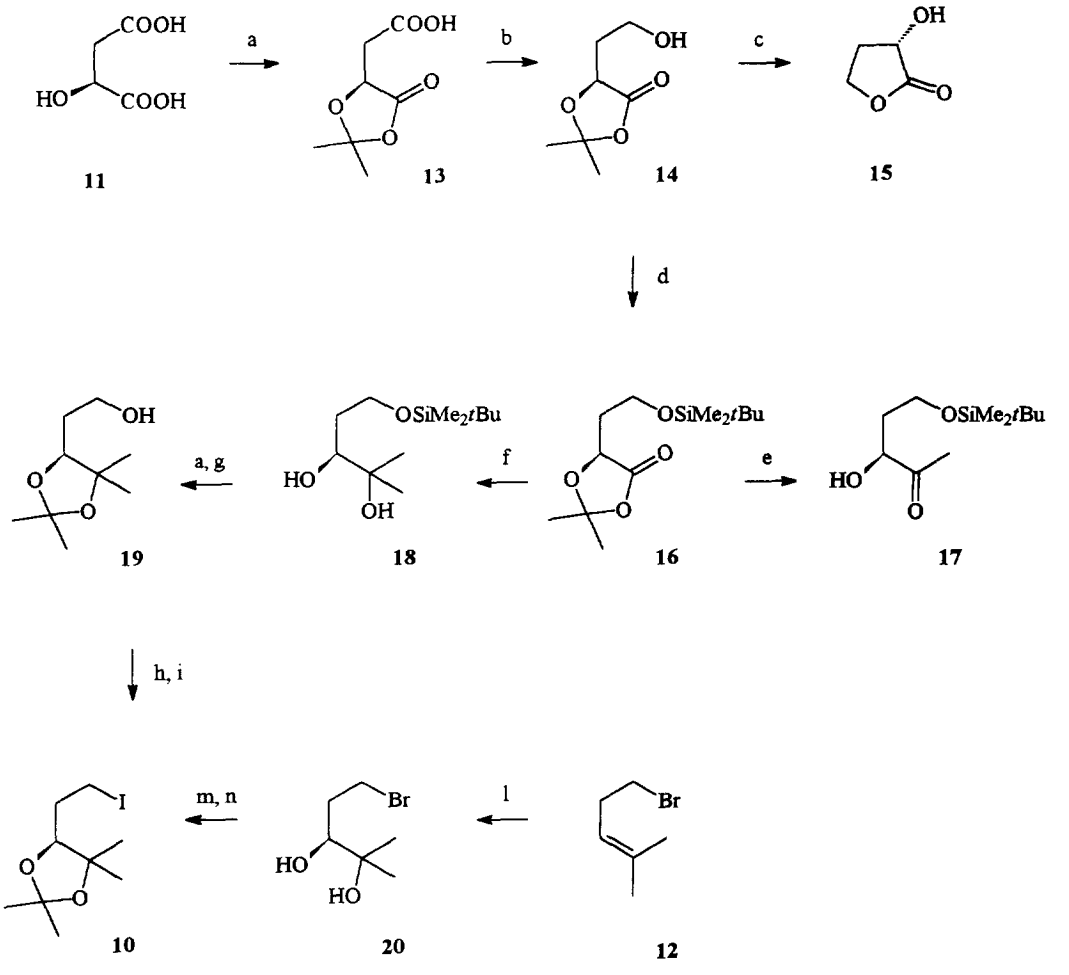
Scheme 1

Some years ago it was shown that epoxy-allylsilanes are particularly suitable for this type of intramolecular cyclization;[10] however, strangely enough, this strategy has seldom been employed for the enantiospecific synthesis of a simple chiral cyclohexanol,[11] in spite of the fact that it has been successful for the stereoselective preparation of various multiply fused carbocyclic structures.[10,12] Consideration of the conformational and stereoelectronic factors involved in this type of Lewis acid mediated ring closure led us to regard the optically active epoxy-allylsilane **7** as a suitable precursor of methylenecyclohexanol **6**. Compound **7** could be obtained from ketal **8** which in turn could be derived from the 5-alkyl-2,3-dihydrofuran **9** according to the procedure of Wenkert and Kocienski for the preparation of homoallylic alcohols containing stereodefined trisubstitued double bonds.[13] Eventually, 5-alkyldihydrofuran **9** could be obtained by alkylation of 2,3-dihydrofuran with the enantiomerically pure iodide **10**.

RESULTS AND DISCUSSION

We envisaged two possible routes (A and B, Scheme 1) leading towards the optically active fragment **10**: in the former the chiral information was already encoded in the starting material (S)-(-)-malic acid, **11**, while in the latter it would be introduced by a Sharpless asymmetric dihydroxylation[14] of olefin **12**. Scheme 2 illustrates the preparation of the key building block **10** by both routes. Differentiation between the two carboxy groups of malic acid **11** and reduction of the free carboxylic acid of ketal **13** was achieved using Still's procedure,[15] to afford the unstable primary alcohol **14** which slowly converted into hydroxybutyrolactone **15**. This transformation occurred rapidly and completely with traces of acid or on silica gel. Therefore, crude **14** was immediately protected as the volatile primary silyl ether **16** which was submitted to the reaction with methylmagnesium iodide for installing the 1,2 secondary-tertiary OH groups of diol **18**. This conversion stopped cleanly after the addition of 1 equivalent of reagent to afford methylketone **17**, while an excess of the Grignard reagent afforded diol **18** in poor yield (15%). Since intramolecular chelation was strongly suspected to reduce propensity of ketone **17** to undergo addition of the Grignard reagent, we examined the reaction of **16** with MeLi. In accordance with the weaker chelating power of lithium ion compared to magnesium, diol **18** was now produced in much better yield (55%). The ee of diol **18** was ≥95%, as determined by the Mosher method,[16] indicating that negligible racemisation occurred under the conditions of MeLi addition to ketone **17**. Conversion of silyl ether **18** to iodide **10** proceeded uneventfully by means of standard methods in satisfactory overall yield.[17]

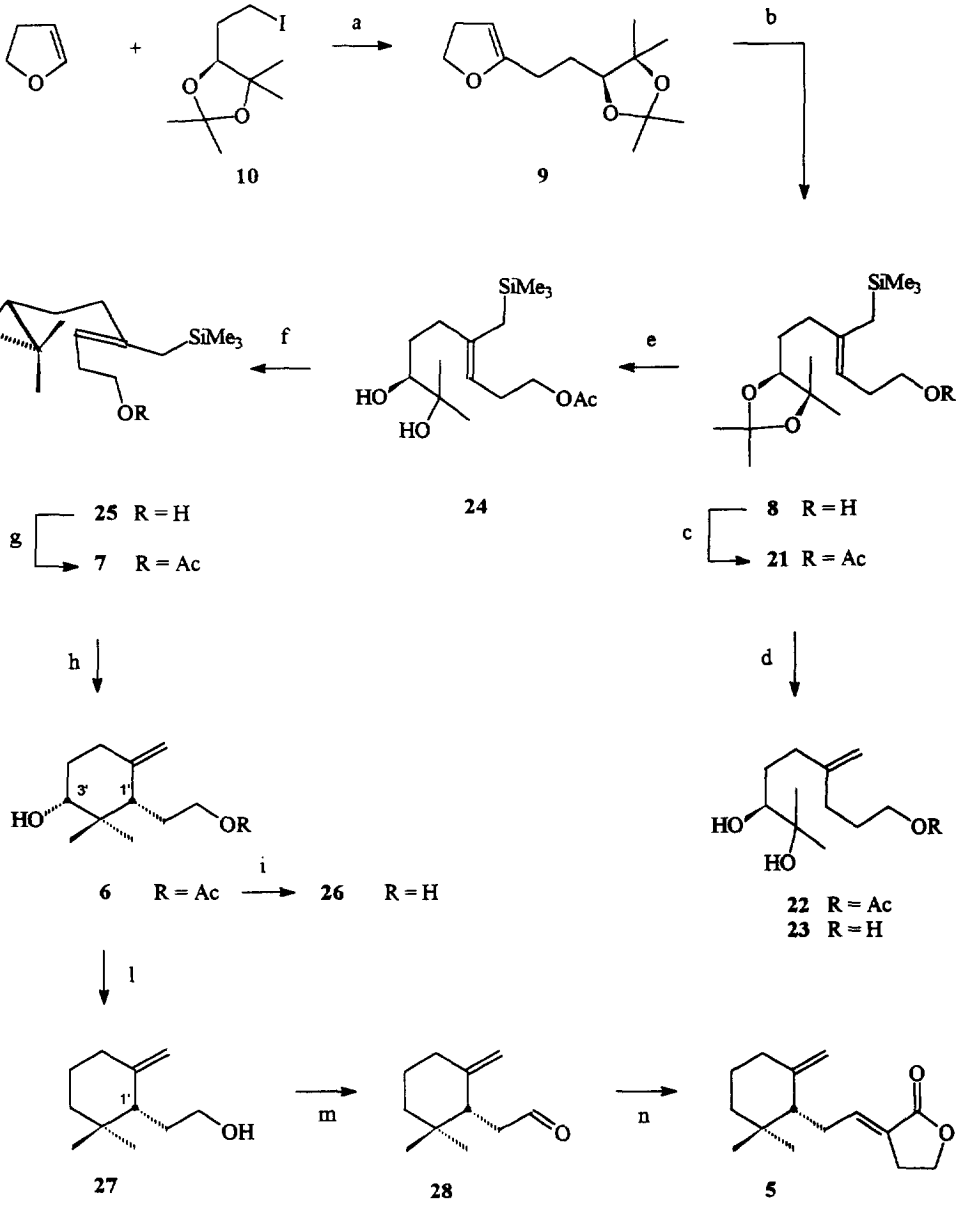
Synthesis of **10** could considerably be shortened by employing the commercially available bromide **12** as the starting material. A Sharpless catalytic asymmetric dihydroxylation of the trisubstituted olefin **12** with standard AD-mix-α[18] readily afforded the enantiomerically pure (≥95% ee by Mosher method[16]) (3S)-diol **20** which was converted to iodide **10**[19] in two simple steps. Efficient coupling of 5-lithio-2,3-dihydrofuran with iodide **10** was accomplished by using the Boeckman's methodology,[20] to afford the unstable cyclic α-alkylvinyl ether **9** (Scheme 3), which was submitted immediately to the Wenkert-Kocienski reaction.[13] Ni(0) catalyzed coupling of the dihydrofuran **9** with Me_3SiCH_2MgCl proceeded rapidly and cleanly to give the homoallylic alcohol **8** with satisfactory retention of stereochemistry (Z:E=10:1 by integration of the olefinic proton signals in the ^{1}H-NMR spectra of the crude mixture). Silica gel column chromatography afforded diastereomerically pure **8** in 66% overall yield from **10**.



Scheme 2

Reagents and conditions: a) 2-methoxypropene, pyridinium *p*-toluensulfonate, THF:CH_2Cl_2 (1.5:1), 0°→25°C, 4 h, 74%; b) BH_3SMe_2, THF, 0°→25°, 15 h, 80%; c) *p*-TsOH, CH_2Cl_2, 25°C, 1 h, 100%; d) TBDMS-Cl, imidazol, DMF, 70°C, 12 h, 65%; e) CH_3MgI, Et_2O, 25°C, 2 h, 15%; f) CH_3Li, Et_2O, 0°C, 30 min, 55%; g) Bu_4NF, THF, 25°C, 2 h, 98%; h) MsCl, NEt_3, CH_2Cl_2, 10°C, 20 min, 80%; i) NaI, acetone, reflux, 45 min, 66%; l) AD-mix-α, $CH_3SO_2NH_2$, $^tBuOH:H_2O$ (1:1), 0°C, 24 h, 55%; m) 2-methoxypropene, pyridinium *p*-toluensulfonate, CH_2Cl_2, 0°→25°, 4 h, 87%; n) KI, DMF, 50°C, 15 h, 89%.

Conversion of the acetate **21** of alcohol **8** to the epoxide **7** was more troublesome than that expected, since the allylsilane group turned out to be very sensitive to the acidic conditions needed for acetal hydrolysis. For example, exposure of acetal **21** to aqueous 1 N HCl in THF at 45°C afforded only the two protodesilylated products **22** and **23**. Finally, removal of the acetal protecting group was achieved, albeit in modest yield, by treating **21** with CF_3COOH in THF-H_2O (4:1) to afford diol **24**, which was converted to epoxide **7** using standard methodology (Scheme 3).



Scheme 3

Reagents and conditions: a) *t*BuLi, THF, -50°→0°C, 30 min; then **10**, THF, -30°→25°C, 3 h, 100% (crude); b) Me_3SiCH_2MgCl, [1,3-bis(diphenylphosphine)propane]nickel(II)cloride, C_6H_6, 25°C, 15 min; then **9**, C_6H_6, reflux, 6 h, 66% ; c) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 25°C, 2 h, 55%; d) HCl 1N, THF, 25°C, 7 h.; e) CF_3COOH, THF:H_2O (4:1), 0°→25°C, 6 h, 34%; f) MsCl, NEt_3, CH_2Cl_2, -10°C, 30 min; then MeONa, MeOH, -10°C, 30 min, 65%; g) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 25°C, 2 h, 100%; h) BF_3OEt_2, CH_2Cl_2, -78°C, 1 h, 83%; i) 10% MeONa, MeOH, 25°C, 1 h, 95%; l-1) PTC-Cl, Py, CH_2Cl_2, 25°C, 4 h; 2) Bu_3SnH, AIBN, toluene, 100°C, 3 h.; then Na_2CO_3, MeOH, 40°C, 5 h, 66% vs **6**; m) TPAP, 4-methylmorpholine-N-oxide, CH_2Cl_2, 25°C, 3 h, 70%; n) α-(Triphenylphosphoranylidene)-γ-butyrolactone, THF, 50°C, 24 h, 70%.

Cell line		Log GI50 1	2	5
I	1	-5,95	-4,99	-4,67
	2	-6,57	-5,95	-4,94
	3	-6,8	-7,45	-4,92
	4	-5,76	-5,74	-4,97
	5	-5,73	-5,84	-5,18
	6	-5,94	-5,61	-4,91
II	7	-5,71	-4,83	-4,86
	8	-6,09	-5,43	-4,8
	9	-5,34	-4,54	-4,75
	10	-5,74	-4,87	-4,92
	11	-5,8	-4,86	-5
	12	-6,57	-7,65	-4,85
	13	-5,62	-4,35	-4,77
	14	-5,61	-4,79	-4,93
	15	-5,97	-5,1	-4,74
III	16	-5,52	-4,82	-4,71
	17	-5,71	-4,61	-4,62
	18	-6,05	-5,33	-4,9
	19	-5,94	-4,97	-4,84
	20	n.t.	-5,21	-4,86
	21	-5,84	-4,67	-4,75
	22	-5,59	-4,4	-4,73
IV	23	-5,76	-4,39	-5,04
	24	-5,82	n.t.	-4,77
	25	-5,69	-4,79	-4,76
	26	-5,82	-4,28	-4,77
	27	-5,46	-4,57	n.t
	28	-5,94	-4,76	-4,77
V	29	-6,51	-7,43	-4,94
	30	-5,64	-4,76	-4,87
	31	-5,55	-4,53	-4,76
	32	-5,92	-4,69	-4,2
	33	-5,87	-4,54	-4,79
	34	-7,2	-7,29	-4,99
	35	-6,54	-6,17	-4,92
	36	-6	-4,57	-4,53
VI	37	-5,57	-4,48	-4,85
	38	-5,71	-4,74	-4,82
	39	-5,9	-4,89	-4,96
	40	-5,83	-4,5	-4,75
	41	-5,97	-4,69	n.t.
	42	-5,56	-4,69	-4,98
VII	43	-5,73	-4,91	-4,83
	44	-5,65	-4,88	-4,76
	45	-5,89	-5,13	-4,8
	46	n.t.	-4,48	-4,78
	47	-5,66	-4,54	n.t.
	48	-5,69	-4,83	-4,74
	49	-5,68	-4,44	-4,71
	50	-5,81	-4,71	-4,79
VIII	51	-5,74	-5,34	-4,77
	52	-5,61	-4,82	-4,88
IX	53	-5,97	-5,69	-4,89
	54	-6,11	-6,07	-4,98
	55	-5,8	-4,51	n.t.
	56	-5,42	-4,58	-4,77
	57	-5,82	-4,83	-4,99
	58	-5,84	-4,7	-4,75
	59	-5,95	-4,93	-4,85
	60	-5,99	-5,77	-4,27
MG_MID		-5,87	-5,08	-4,82

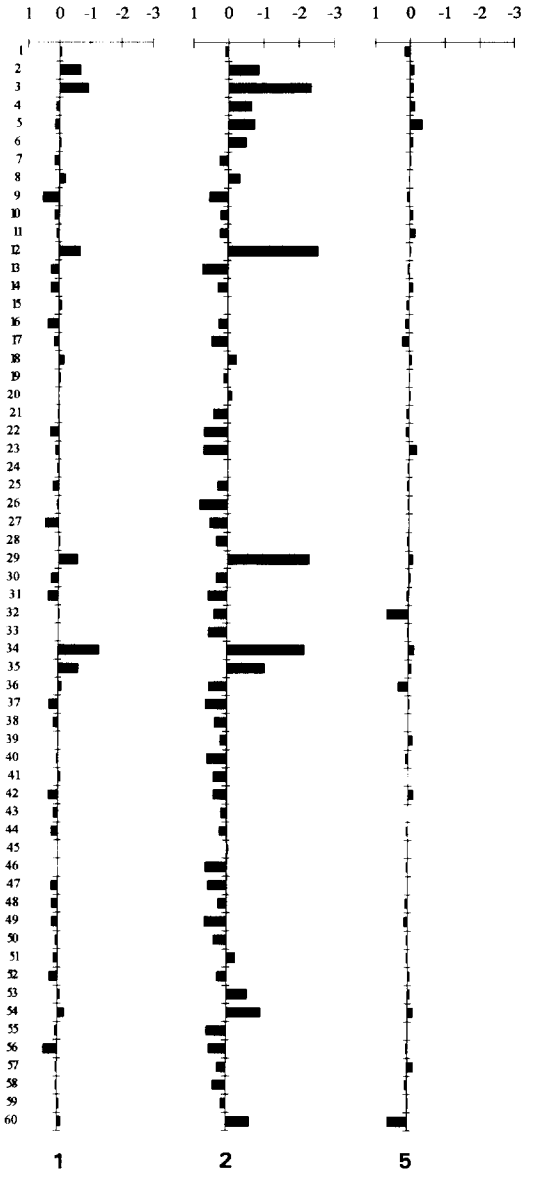


Figure 1. GI_{50} mean graph profiles of saponaceolide A, **1**, saponaceolide B, **2**, and lactone moiety **5** in the NCI in vitro screen. The individual $\log_{10}GI_{50}$ values for each cell line are provided in the table to the left of the mean graph. The last value in the column is MG-MID, calculated mean panel GI_{50}; values for **1**, **2** and **5** are -5.87, -5.08, and -4.82, respectively. The subpanel and individual cell line identifiers are presented top-to -bottom as follows: I (*Leukemia*) 1) CCRF-CEM, 2) HL-60(TB), 3) K-562, 4) MOLT-4, 5) RPMI-8226, 6) SR; II (*Non-Small Cell Lung C.*) 7) A549/ATCC, 8) EKVX, 9) HOP-62, 10) HOP-92, 11) NCI-H226, 12) NCI-H23, 13) NCI-H322M, 14) NCI-H460, 15) NCI-H522; III (*Colon C.*) 16) COLO 205, 17) HCC-2998, 18) HCT-116, 19) HCT-15, 20) HT29, 21) KM12, 22) SW-620; IV (*CNS*) 23) SF-268, 24) SF-295, 25) SF-539, 26) SNB-19, 27) SNB-75, 28) U251; V (*Melanoma*) 29) LOX IMVI, 30) MALME-3M, 31) M14, 32) SK-MEL-2, 33) SK-MEL-28, 34) SK-MEL-5, 35) UACC-257, 36) UACC-62; VI (*Ovarian C.*) 37) IGR-OV1, 38) OVCAR-3, 39) OVCAR-4, 40) OVCAR-5, 41) OVCAR-8, 42) SK-OV-3; VII (*Renal C.*) 43) 786-0, 44) A498, 45) ACHN, 46) CAKI-1, 47) RXF-393, 48) SN12C, 49) TK-10, 50) UO-31; VIII (*Prostate C.*) 51) PC-3, 52) DU-145; IX (*Breast C.*) 53) MCF7, 54) MCF7/ADR-RES, 55) MDA-MB-231/ATCC, 56) HS 578T, 57) MDA-MB-435, 58) MDA-N, 59) BT-549, 60) T-47D.

Treatment of **7** with BF_3OEt_2 in CH_2Cl_2 at -78° C cleanly afforded a single product, regioisomerically and diastereomerically pure on the basis of its ^1H and ^{13}C-NMR spectra. The 1'S, 3'R configuration was assigned to the cyclization product **6** on the basis of the configuration of starting epoxide **7** and on the assumption that such stereospecific cyclization proceeded via a transition state with a chair-like conformation.[10] Moreover, methanolysis of **6** gave the diol **26** whose IR and NMR data, and the absolute value of specific rotation nicely corresponded to the 1'R, 3'S stereoisomer synthesized by Mori, while the sign of optical rotation was opposite.[9]

To complete our synthesis, the secondary alcohol **6** was deoxygenated using the Robins procedure[21] to give, after basic work up, the expected alcohol **27** which was converted to lactone **5** in two steps using standard reactions. NOE experiments showed that lactone **5** was obtained as a single diastereomer possessing E configuration.

Saponaceolides A, **1**, and B, **2**, and lactone **5** were evaluated comparatively in the U.S. National Cancer Institute's human tumor cancer cell line panel.[7,8] Consistent with previous testing results,[1,2] saponaceolides A and B are of comparable potency in the NCI screen, while the synthetic lactone **5** is less active. The calculated mean panel Log_{10} GI_{50} values of **1**, **2** and **5** are -5.87, -5.08 and -4.82, respectively. More interesting are the characteristic GI_{50}-centered mean graph profiles of the three compounds (Figure 1), since they provide, for each compound, a visual representation of the individual cell lines that are proportionally more sensitive than average, and thus may facilitate the discovery of potential candidates for drug development with unprecedented antitumor profiles.[7,8] Saponaceolides A and B show similar fingerprints; however, the higher sensitivity to saponaceolide B displayed by a few individual cell lines points out the importance of subtle structural changes in a series of related compounds for determining the optimal antitumor activity. By contrast, the simplified structure **5**, devoid of the dissymmetric tricyclospiroketal moiety of saponaceolides, does not match the pattern of antitumor activities of the entire molecules **1** and **2**, thus justifying our efforts in achieving saponaceolides by total synthesis.

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EXPERIMENTAL

Melting points were determined on a Fisher Jones hot plate and are uncorrected. IR spectra were recorded (film or KBr pellets) with a Perkin-Elmer Model 257 spectrometer. ^1H-(300 MHz) and ^{13}C-NMR (75.47 MHz) spectra were recorded in $CDCl_3$ solution, using a Bruker CXP 300 spectrometer. Chemical shifts are reported in δ units with Me_4Si as internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad are used throughout. Coupling constants (J) are reported in Hz. Mass spectra were determined with a Finnigan MAT 8222 instrument at 70 eV (0.5 mA) using a direct inlet system (MS) or with an ITS40 apparatus, DB5 column, gas carrier helium (10 mL/min), injector temperature 250°C, source temperature 250°C, coupled with Finnigan MAT instrument (GC-MS). Merck Kieselgel 60 (0.043-0.060 mm) was used for column chromatography. Analytical GF_{254} TLC plates (250 nm) were obtained from Merck. The spots were visualized under UV light or by spraying the

plates with an EtOH sulphuric acid-vanillin solution and then heating to 120°C for few minutes. For GLC analysis a Perkin-Elmer Sigma 3B gas chromatograph with a FID and a WCOT CP-Sil-5CB, 1.09 μm film, 0.53 nm ID, 10 m column was used; the carrier gas (N_2) flow rate was 11 mL/min, the injector temperature was 250°C and the detector temperature was 300°C. Optical activity was measured with Perkin-Elmer 241 polarimeter. All solvents were purified and dried by standard techniques just before use. All reactions were routinely carried out under an inert atmosphere of dry, oxigen free, N_2 or argon. Yelds are reported for chromatographically and spectroscopically pure isolated compounds. Actually, the high volatility of **7**, **10**, **16**, **21**, **27**, **28**, gave rise to considerable losses of these compounds during evaporation of the organic solution containing them, even under atmospheric pressure.

(5S)-5-[2'-(*t*Butyldimethylsilyloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-one 16. A solution of *tert*-butyldimethylsilylchloride (0.75 g, 4.97 mmol) and imidazole (0.706 g, 1.038 mmol) in dry DMF (10 mL) was added to a solution in dry DMF (10 mL) of (5S)-5-(2'-hydroxyethyl)-2,2-dimethyl-[1,3]dioxolan-4-one, **14**, (0,75 g, 4.68 mmol), prepared from (S)-(-)-malic acid, **11**,[15] in 60% yield over two steps. 4-dimethylaminopyridine (catalytic amount) was then added and the mixture was stirred at 70°C for 12 h, monitoring the reaction by GC (program: T_i= 70°C for 0', rate=10 °C/min., T_f=250°C for 5'; t_{r16}=7'13" at T=140°C). The mixture was quenched with H_2O (20% excess vs DMF) and extracted with hexane. The organic layer was dried ($MgSO_4$) and concentrated under atmospheric pressure. The residue was purified by column chromatography on silica gel (hexane-AcOEt, 95:5) to afford **16** (0.84 g, 65%), $[\alpha]_D^{20}$=-7.16 (c=2.13, $CHCl_3$). IR ν (cm^{-1}): 2955, 2930, 2860, 1795, 1470, 1385, 1270, 1255, 1135, 1100, 835, 780. ^{1}H-NMR (300 MHz) δ: 0.05 (s, 6H, Si*Me*$_2$); 0.9 (s, 9H, Si*tBu*); 1.55 and 1.61 (2s, 2x3H, C(2)*Me*$_2$); 1.82-1.96 and 2.04-2.16 (2m, 2x1H, C(1')*H*$_2$); 3.69-3.79 and 3.79-3.88 (2m, 2x1H, C(2')*H*$_2$); 4.54 (dd, J's=8 and 4.5, 1H, C(5)*H*). CIMS (NH_3) *m/z*: 309 ($M+NH_3+NH_4^+$), 292 ($M+NH_4^+$), 275 ($M+H^+$).

(3S)-5-(*t*Butyldimethylsilyloxy)-2-methyl-pentane-2,3-diol 18. To a stirred solution of **16** (0.122 g, 0.45 mmol) in dry Et_2O (3.5 mL) at 0°C was added dropwise MeLi (1.6 M in Et_2O, 0.7 mL, 1.12 mmol) and stirring was continued at 0°C for 30 min. The mixture was then quenched with saturated aqueous NH_4Cl and extracted with AcOEt; the organic layer was dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane-AcOEt, 6:4) afforded **18** (0.062 g, 55%), $[\alpha]_D^{20}$=+7.95 (c=1, $CHCl_3$). IR ν (cm^{-1}): 3430, 2930, 2860, 1255, 1090, 835, 775. ^{1}H-NMR (300 MHz) δ: 0.1 (s, 6H, Si*Me*$_2$); 0.85 (s, 9H, Si*tBu*); 1.1 and 1.15 (2s, 2x3H, C(2)*Me*$_2$); 1.65 (m, 2H, C(4)*H*$_2$); 3.62 (X part of an ABX system, 1H, C(3)*H*); 3.82 (m, 2H, C(5)*H*$_2$).

(4'S)-2-(2',2',5',5'-Tetramethyl-[1',3']dioxolan-4'-yl)-ethanol 19. Pyridinium *p*-toluensulphonate (0.223 g, 0.89 mmol) and 2-methoxypropene (2.16 mL., 22.6 mmol) were added to a solution of diol **18** (2.79 g, 11.25 mmol) in dry CH_2Cl_2 (20 mL) at 0°C. The mixture was stirred at 25°C for 1 h., then neutralized with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2. Drying ($MgSO_4$) and evaporation of the organic solution followed by purification of the residue by column chromatography on silica gel (hexane-AcOEt, 95:5) gave the expected ketal (2.4 g, 74%). $[\alpha]_D^{20}$=-18.03 (c 1.09, $CHCl_3$). IR ν (cm^{-1}): 2960, 2935, 2860, 1470, 1370, 1255, 1115, 1085, 1010, 835, 775. ^{1}H-NMR (300 MHz) δ: 0.08 (s, 6H Si*Me*$_2$); 0.91 (s, 9H, Si*tBu*), 1.10 and 1.25 (2s, 2x3H, C(5')*Me*$_2$); 1.33 and 1.42 (2s, 2x3H, C(2')*Me*$_2$); 1.55-1.78 (m, 2H, C(2)*H*$_2$); 3.67-3.82 (m, 2H, C(1)*H*$_2$); 3.86 (dd, J's=9.5 and 3.5, C(4')*H*). CIMS (NH_3) *m/z*: 306 (M+18), 289 (M+1). EIMS *m/z* (% rel. int.) 273 (10), 173 (92), 155 (12), 129 (10), 99 (15), 89 (31), 75 (100), 57 (40). To a solution of this silylether (2.4 g, 8.33 mmol) in dry THF (25 mL) was added Bu_4NF (1 M in THF, 20.7 mL, 20.7 mmol), and the mixture was stirred at 25°C for 2 h, then filtered on silica gel to remove salts. Evaporation of solvent and purification of the residue by column chromatography

on silica gel (hexane-AcOEt, 7:3) gave compound **19** (1.42 g, 98%); $[\alpha]_D^{20}$=-19.2 (c 0.837, $CHCl_3$) [Lit.[17b] $[\alpha]_D^{22}$=-21.2 (EtOH)]. IR ν (cm^{-1}): 3280, 2960, 2360, 1465, 1375, 1235, 1115, 890. ^{1}H-NMR (300 MHz) δ: 1.13 and 1.28 (2s, 2x3H, C(5')*Me*$_2$); 1.35 and 1.42 (2s, 2x3H, C(2')*Me*$_2$); 1.60-1.70 and 1.75- 1.88 (2m, 2x1H, C(2)*H*$_2$); 2.30 (bs, 1H, O*H*); 3.82 (m, 2H, C(1)*H*$_2$); 3.88 (d, 3, C(4')*H*).

(3S)-5-Bromo-2-methyl-pentane-2,3-diol 20. AD-mix-α (0.86 g) was added to a stirred 1:1 mixture of *t*BuOH-H_2O (6 mL), and stirring was continued at 25°C until two bright yellow phases were obtained. $MeSO_2NH_2$ (0.058 g, 0.61 mmol) was then added, followed by 5-bromo-2-methyl-2-pentene, **12**, (0.1 g, 0.61 mmol) at 0°C. The heterogeneus mixture was stirred vigorously at 0°C for 24 h, then quenched with solid Na_2SO_3 (0.919 g, 7.3 mmol); stirring was continued for 30 min, until decoloration, allowing the mixture to warm to room temperature. AcOEt was added, and after separation of the layers the aqueous phase was further extracted with the same organic solvent. The combined organic layers were washed with 0.1N aqueous NaOH to remove $MeSO_2NH_2$, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (hexane-AcOEt, 7:3) to afford **20** as a colorless oil (0.065 g, 55%), $[\alpha]_D^{20}$=+16.8 (c=0.95, $CHCl_3$). IR ν (cm^{-1}): 3430, 2980, 2890, 1460, 1365, 1110, 1040. ^{1}H-NMR (300 MHz) δ: 1.15 and 1.24 (2s, 2x3H, C(2)*Me*$_2$); 1.84-1.96 and 2.26-2.38 (2m, 2x1H, C(4)*H*$_2$); 2.11 (bs, 1H, O*H*); 3.86 (td, J's=8.5 and 5, 1H, C(5)*H*H); 3.91-4.02 (m, 2H, C(5)H*H* and C(3)*H*). EIMS *m/z* (% rel. int.): 149 (28), 111 (11), 97 (20), 83 (20), 71 (42), 59 (100), 41 (43).

(5S)-5-(2'-Iodoethyl)-2,2,4,4-tetramethyl-[1,3]dioxolane 10. *Route A: from alcohol* **19**. Et_3N (280 μL, 2 mmol) and then MsCl (120 μL, 1.55 mmol) were added dropwise over 10 min to a solution of alcohol **19** (0.235 g, 1.35 mmol) in dry CH_2Cl_2 (4 mL), at 10°C The mixture was stirred for 20 min, then evaporated to remove solvent and excess MsCl. The residue was dissolved in CH_2Cl_2 and filtered to remove organic salts. Evaporation of the filtrate afforded the expected methanesulphonate of alcohol **19** (0.27 g, 80%). Without further purification this compound (0.102 g, 0.4 mmol) was added to a solution of NaI (0.086 g, 0.57 mmol) in dry acetone (1 mL) at 25°C and the mixture was stirred at 25°C for 30 min, then heated under reflux for 45 min, monitoring the reaction by GC (program: T_i=50°C for 5', rate 10°/min, T_f=150° for 0'; t_{r10}=10'15"). After cooling to 25°C, the mixture was filtered and evaporated to remove acetone, then diluted with CH_2Cl_2 and washed first with an aqueous $Na_2S_2O_3$ solution and then with brine. Drying ($MgSO_4$) and evaporation of the organic layer afforded **10** as a colorless oil (0.074 g, 66%); $[\alpha]_D^{20}$=-25.3 (c 0.97, $CHCl_3$) [Lit.[17c] $[\alpha]_D^{25}$=+30.2 ($CHCl_3$) for the (5R)-enantiomer]. IR ν (cm^{-1}): 2985, 2940, 2875 1370, 1235, 1215, 1200, 1105, 995, 845. ^{1}H-NMR (300 MHz) δ: 1.11 and 1.28 (2s, 2x3H, C(4)*Me*$_2$); 1.36 and 1.42 (2s, 2x3H, C(2)*Me*$_2$); 1.88 and 2.02 (2m, 2x1H, C(1')*H*$_2$); 3.23 and 3.38 (2m, 2x1H, C(2')*H*$_2$); 3.78 (dd, J's=10 and 2.6, 1H, C(5)*H*). GC-MS (program: T_1=40°C for 4 min, first rate 4°C/min, T_2=120°C, second rate 10°C/min, T_3=230°C) *m/z* (% rel. int.): 285 (M+1, 1), 269 (54), 227 (13), 99 (23), 43 (100).

Route B: from bromide **20**. Pyridinium *p*-toluensulphonate (0.064 g, 0.25 mmol) and 2-methoxypropene (0.2 mL, 2.09 mmol) were added to a solution of diol **20** (0.202 g, 1.03 mmol) in dry CH_2Cl_2 (2 mL) at 0°C. The mixture was allowed to warm to 25°C and stirred for 4 h, then neutralized with saturated aqueous Na_2CO_3. Extraction with CH_2Cl_2, drying ($MgSO_4$), and evaporation of the organic layer afforded the expected ketal (0.212 g, 87%). A solution of this bromide (0.106 g, 0.45 mmol) in dry DMF (0.5 mL) was added dropwise to a solution of anhydrous KI (0.45 g, 2.7 mmol) in dry DMF (1.8 mL) at 25°C and the mixture was stirred at 50°C for 15 h, monitoring the reaction by GC (program: T_i=50°C for 5', rate 10°/min, T_f=150° for 0'; t_{r10}=10'15"). The reaction was quenched by adding H_2O (20% excess vs DMF) at 0°C. Extraction with hexane, drying ($MgSO_4$), and evaporation of the organic layer gave a residue wich was purified by column chromatography on silica gel (hexane-AcOEt, 9:1) to afford **10** (0.113 g, 89%), $[\alpha]_D^{20}$=-23.9 (c=2.2, $CHCl_3$), identical to a sample obtained from **14**.

Determination of the enantiomeric excess of diols 18 and 20 A sample of (RS)-**18** was obtained from (RS)-malic acid following the same methodology described for the preparation of (3S)-**18**. A sample of (RS)-**20** was obtained from olefin **12** under standard osmilation conditions (OsO_4, Py, THF). (R)-MTPA esters of the optically active diols (3S)-**18** and (3S)-**20** and the corresponding racemates were prepared following standard procedures.[22] In both cases, the C(OH)Me_2 signals for each diastereoisomer were considered and their integration allowed us to calculate an e.e.≥95% for both the optically active diols. Diol **18**: 1.130 and 1.187 (2s, 2x3H, (S)-(+)-**18**-(R)-MTPA C(OH)Me_2); 1.175 and 1.225 (2s, 2x3H, (R)-(-)-**18**-(R)-MTPA C(OH)Me_2). Diol **20**: 1.127 and 1.222 (2s, 2x3H, (S)-(+)-**20**-(R)-MTPA C(OH)Me_2); 1.172 and 1.257 (2s, 2x3H, (R)-(-)-**20**-(R)-MTPA C(OH)Me_2).

(5S)-5-[2'-(4",5"-Dihydrofuran-2"-yl)-ethyl]-2,2,4,4-tetramethyl-[1,3]-dioxolane 9. A solution of *t*BuLi (1.6 M in pentane, 550 μL, 0.88 mmol) was added dropwise to a solution of 2,3 dihydrofuran (67 μL, 0.88 mmol) in dry THF (120 μL) at -50°C. The resulting pale yellow suspension was allowed to warm to 0°C and stirred for an additional 30 min. The mixture was then cooled to -30°C and a solution of **10** (0.103 g, 0.362 mmol) in dry THF (1 mL) was added. The mixture was allowed to warm to 25°C and stirred for 3 h. The resulting white suspension was poured into a mixture of 28% aqueous NH_4OH (1 mL) and saturated aqueous NH_4Cl (9 mL) under vigorous stirring, and the organic compounds were extracted exhaustively with Et_2O. The combined extracts were dried over K_2CO_3 and evaporated to leave a yellow oil (quantitative yield) that was submitted to the next step without further purification. IR ν (cm^{-1}): 2980, 2935, 2860, 1665, 1370, 1215, 1200, 1115, 1100, 1005, 935. ^{1}H-NMR (300 MHz) δ: 1.10 and 1.25 (2s, 2x3H, C(4)Me_2); 1.33 and 1.42 (2s, 2x3H, C(2)Me_2); 1.66-1.86 (m, 2H, C(1')H_2); 2.10-2.75 (m, 4H, C(2')H_2 and C(4")H_2); 3.69 (dd, J's=9.0 and 4.0, 1H, C(5)*H*); 4.31 (t, J=9.4, 2H, C(5")H_2); 4.63 (m, 1H, C(3'')*H*). GC-MS (program: T_1=40°C for 2 min, first rate 10°C/min, T_2=180°C, second rate 8°C/min, T_3=230°C for 10 min) *m/z* (% rel. int.): 227 (M+1, 1), 169 (100), 97 (50), 84 (31), 43 (76).

(3Z)-(4'S)-6-(2',2',5',5'-Tetramethyl-[1',3']dioxolan-4'-yl)-4-trimehylsilanylmethyl-hex-3-en-1-ol 8. A solution of MeMgBr (1 M in Et_2O, 1 mL. 1 mmol) was added to a stirred suspension of [1,3-bis(triphenylphosphine)propane]$NiCl_2$ (0.019 g, 0.035 mmol) in dry benzene (500 μL), and the resulting red solution was stirred at 25°C for 20 min until turned black. Et_2O was then removed under reduced pressure and dry benzene (500 μL) was added, followed by a solution of **9** (0.053 g, 0.23 mmol) in dry benzene (450 μL). The mixture was heated under reflux for 6 h, cooled to 0 °C, and poured into saturated aqueous NH_4Cl (5 mL) under vigorous stirring. The mixture was stirred until decolorized and extracted exhaustively with Et_2O. Drying ($MgSO_4$) and evaporation of the combined extracts left a residue that was purified by column chromatography (Et_2O-hexane, 1:4) to afford **8** (0.048 g, 66%). $[\alpha]_D^{20}$=+0.51 (c=3.1, $CHCl_3$). IR ν (cm^{-1}): 3430, 2960, 2880, 1655, 1370, 1245, 1115, 1050, 1000, 855. ^{1}H-NMR (300 MHz) δ: 0.03 (s, 9H, SiMe_3); 1.10 and 1.24 (2s, 2x3H, C(5')Me_2); 1.32 and 1.42 (2s, 2x3H, C(2')Me_2); 1.5-1.7 (m, 2H, C(6)H_2); 1.6 (s, 2H, CH_2Si); 1.98-2.35 (m, 4H, C(2)H_2 and C(5)H_2); 3.60 (dt, J's=1.5 and 6.5, 2H, C(1)H_2); 3.65 (dd, J's=9.4 and 3.2, 1H, C(4')*H*); 5.08 (t, J=7.3, 1H, C(3)*H*). GC-MS (program: T_1=60°C, rate 25°C/min, T_2=300°C for 25 min) *m/z* (% rel. int.): 299 (6), 286 (24), 239 (7), 215 (7), 149 (100), 121 (28), 107 (54), 93 (38), 73 (35).

(3Z)-(4'S)-6-(2',2',5',5'-Tetramethyl-[1',3']dioxolan-4'-yl)-4-trimehylsilanylmethyl-hex-3-en-1-yl acetate 21. Et_3N (22 μL, 0.158 mmol), 4-dimethylaminopyridine (0.009 g, 0.074 mmol) and Ac_2O (15 μL, 0.153 mmol) were added to a solution of **8** (0.024 g, 0.076 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred at 25°C for 2 h, then quenched by the sequential addition of MeOH and brine after 15 min. The mixture was extracted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (Et_2O-hexane, 1:9) gave **21** (0.015 g, 55%).

$[\alpha]_D^{20}$=+7.22 (c=3.2, $CHCl_3$). IR ν (cm^{-1}): 2980, 2960, 1740, 1655, 1370, 1250, 1115, 1030, 855. ^{1}H-NMR (300 MHz) δ: 0.02 (s, 9H, Si*Me$_3$*); 1.10 and 1.23 (2s, 2x3H, C(5')*Me$_2$*); 1.31 and 1.41 (2s, 2x3H, C(2')*Me$_2$*); 1.40-1.68 (m, 2H, C(6)*H$_2$*); 1.54 (ABq, J=13.0, 2H, C*H$_2$*Si); 1.90-2.18 (m, 2H, C(5)*H$_2$*); 2.04 (s, 3H, COC*H$_3$*); 2.27 (dq, J's=1.0 and 7.0, 2H, C(2)*H$_2$*); 3.65 (dd, J's=9.0 and 3.7, 1H, C(4')*H*); 4.02 (t, J=7, 2H, C(1)*H$_2$*); 4.91 (bt,J=7, 1H, C(3)*H*).

(3Z)-(7S)-7,8-Dihydroxy-8-methyl-4-trimethylsilanylmethyl-non-3-en-1-yl acetate 24. Trifluoro_ acetic acid (20 μL, 0.26 mmol) was added buy syringe to a solution of **21** (0.020 g, 0.056 mmol) in THF-H_2O (4:1, 1 mL) at 0°C. The mixture was stirred at 25°C for 6 h, then neutralized with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography on silica gel (hexane-AcOEt, 7:3) to give **24** (0.006 g, 34%). IR ν (cm^{-1}): 3445, 2955, 1735, 1655, 1370, 1250, 1160, 910, 855, 735. ^{1}H-NMR (300 MHz) δ: 0.03 (s, 9H, Si*Me$_3$*); 1.17 and 1.21 (2s, 2x3H, C(8)*Me$_2$*); 1.35-1.66 (m, 2H, C(6)*H$_2$*); 1.55 (ABq, J=13.0, 2H, C*H$_2$*Si); 1.66-1.99 (m, 2H, O*H*); 2.05 (s, 3H, COC*H$_3$*); 1.99-2.23 (m, 2H, C(5)*H$_2$*); 2.28 (q, J=7, 2H, C(2)*H$_2$*); 3.35 (dd, J's=10.0 and 1.6, 1H, C(7)*H*); 4.05 (td, J's=7.0 and 2.0, 2H, C(1)*H$_2$*); 5.05 (bt, J=7, 1H, C(3)*H*).

(3Z)-(7R)-7,8-Epoxy-8-methyl-4-trimethylsilanylmethyl-non-3-en-1-ol 25. Et_3N (120 μL, 0.86 mmol) and freshly distilled MsCl (16 μL, 0.207 mmol) were sequentially added to a solution of **24** (0.050 g, 0.16 mmol) in dry CH_2Cl_2 (1 mL) at -10°C The mixture was stirred for 30 min to complete the reaction, then diluted with MeOH (3 mL), treated with a solution of MeONa in MeOH (0.032 g of Na in 3 mL of MeOH) and stirred at -10°C. After 2 h the mixture was quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatograpy on silica gel (hexane-AcOEt, 95:5 → 1:2) to afford **25** as a colourless oil (0.027 g, 65%), $[\alpha]_D^{20}$=+17.6 (c=0.462, CH_2Cl_2). IR ν (cm^{-1}): 3440, 2960, 1420, 1380, 1250, 1180, 1120, 1050, 840, 690. ^{1}H-NMR (300 MHz) δ: 0.03 (s, 9H, Si*Me$_3$*); 1.25 and 1.29 (2s, 2x3H, C(8)*Me$_2$*); 1.57 (ABq, J=14.0, 2H, C*H$_2$*Si); 1.58-1.75 (m, 2H, C(6)*H$_2$*); 2.03-2.17 (m, 2H, C(2)*H$_2$*); 2.17-2.30 (m, 2H, C(5)*H$_2$*); 2.70 (dd, J's=7.0 and 5.0, 1H, C(7)*H*); 3.60 (dt, J's=6.5 and 1.0, 2H, C(1)*H$_2$*); 5.07 (t, J=7.0, 1H, C(3)*H*). ^{13}C-NMR δ: -0.84 (q) Si*Me$_3$*; 18.68 (q) and 24.72 (q) C(8)*Me$_2$*; 21.35 (t) *C*H$_2$Si; 27.32 (t) *C*(6); 31.89 (t) *C*(2); 36.00 (t) *C*(5); 58.09 (s) *C*(8); 62.47 (t) *C*(1); 64.23 (d) *C*(7); 117.59 (d) *C*(3); 139.52 (s) *C*(4).

(1'S)-(3'R)-2-(3'-Hydroxy-2',2'-dimethyl-6'-methylene-cyclohexyl)-ethyl acetate 6. Et_3N (50 μL, 0.36 mmol), 4-dimethylaminopyridine (catalytic amount) and Ac_2O (34 μL, 0.36 mmol) were added to a solution of **25** (0.036 g, 0.14 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred at 25°C for 1 h, then quenched by the sequential addition of MeOH and brine after 15 min. The mixture was extracted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$) and evaporated to give the expected acetate **7** (0.042 g, quantitative yield) which was immediately submitted to the following step. BF_3Et_2O (70 μl, 0.57 mmol) was added dropwise to a solution of **7** (0.042 g, 0.14 mmol) in dry CH_2Cl_2 (1 mL) at -78°C. The solution was stirred at -78°C for 1 h then quenched with 5% aqueous $NaHCO_3$ and allowed to warm to 25°C (~30 min). The mixture was extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (hexane-AcOEt, 5:1 → 1:1) to afford **6** (0.026g, 83%). $[\alpha]_D^{20}$=+12.7 (c=0.47, CH_2Cl_2). IR ν (cm^{-1}): 3460, 2940, 1740, 1645, 1440, 1390, 1255, 1040, 895, 850. ^{1}H-NMR (300 MHz) δ: 0.77 and 1.02 (2s, 2x3H, C(2')*Me$_2$*); 1.46-2.03 (m, 6H, C(2)*H$_2$*, C(4')*H$_2$*, C(1')*H*, and C(5')*H*H); 1.59 (bs, 1H, O*H*); 2.04 (s, 3H, COC*H$_3$*); 2.36 (dt, J's=13.5 and 5.3, 1H, C(5')H*H*); 3.45 (dd, 4, 9, 1H, C(3')*H*OH); 3.90 (dt, J=7.5 and 11.0, 1H, C(1)*H*H); 4.15 (m, 1H, C(1)H*H*); 4.64 (bs, 1H, C=C*H*H); 4.89 (bs, 1H, C=CH*H*). ^{13}C-NMR δ: 16.14 (q) and 25.88 (q)

C(2')*Me*$_2$; 20.92 (q) CO*C*H$_3$; 24.84 (t) *C*(5'); 31.79 (t) and 31.89 (t) *C*(4') and *C*(2); 40.01 (s) *C*(2'); 48.04 (d) *C*(1'); 63.95 (t) *C*(1); 76.73 (d) *C*(3'); 108.87 (t) C=*C*H$_2$; 146.54 (s) *C*(6'); 171.07 (s) *C*=O.

(1'S)-(3'R)-2-(3'-Hydroxy-2',2'-dimethyl-6'-methylene-cyclohexyl)-ethanol 26. To a solution of **6** (0.026 g, 0.115 mmol) in MeOH (0.5 mL) was added 10% NaOH in MeOH (1 mL) and the mixture was stirred at 25°C for 1 h. The reaction was quenched with H_2O and the mixture extracted with Et_2O; the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to afford **26** as a colorless oil (0.020 g, 95%), $[\alpha]_D^{20} = +14.5$ (c=0.5, CH_2Cl_2). IR and NMR data identical to those reported in the literature for the 1'R,3'S enantiomer.[9]

(1'R)-2-(2',2'-Dimethyl-6'-methylene-cyclohexyl)-ethanol 27. Dry pyridine (110 μL, 1.36 mmol) and phenoxythiocarbonylchloride (60 μL, 0.44 mmol) were added to a solution of **6** (0.081 g, 0.358 mmol) in dry CH_2Cl_2 (3 mL). The mixture was stirred at 25°C for 4 h, then quenched with H_2O, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated to afford a residue which was redissolved in dry toluene (6 mL) without purification. This solution was treated with AIBN (0.001g, 0.006 mmol) in dry toluene (0.5 mL) and *n*Bu$_3$SnH (150 μL, 0.55 mmol), and stirred at 100°C for 3 h. The reaction was quenched with MeOH and toluene was removed by azeotropic distillation. To the residue redissolved in MeOH was added solid Na_2CO_3 (0.380 g, 3,58 mmol) to carry out direct deacetylation of the primary acetoxy group. After stirring at 40°C for 5h, MeOH was evaporated and the residue diluted with CH_2Cl_2 and filtered. The solution was evaporated and the residue purified by column chromatography (hexane-AcOEt, 6:1) to give **27** as a colourless oil (0.040 g, 66%).$[\alpha]_D^{20} = -24.4$ (c=2, CH_2Cl_2) IR ν (cm^{-1}): 3340, 3070, 2935, 2870, 1645, 1450, 1385, 1365, 1050, 1030, 890, 750, 690, 630. ^{1}H-NMR (300 MHz) δ: 0.85 and 0.92 (2s, 3H, C(2')*Me*$_2$); 1.15-1.80 (m, 7H, C(2)*H*$_2$, C(3')*H*$_2$, C(4')*H*$_2$, and OH); 1.90 (bdd, J's=7.5 and 4.0, C(1')*H*); 2.05 (m, 2H, C(5')*H*$_2$); 3.6 (m, 2H, C(1)*H*$_2$); 4.64 (bd, J=2.5, 1H, C=C*H*H); 4.78 (m, J=1.3, 1H, C=CH*H*). EIMS *m/z* (% rel. int.): 168 (M^+, 10), 167 (57), 149 (33), 123 (100), 107 (90), 93 (82), 81 (82), 69 (96), 55 (63), 41 (97). CIMS (methane) *m/z* (% rel. int.): 169 (M^++1, 36), 151 (53), 135 (9), 125 (100), 113 (21).

(1'R)-(2,2-Dimethyl-6-methylene-cyclohexyl)-acetaldehyde 28. 4-methylmorpholine-N-oxide (0,061 g, 0.52 mmol), tetrapropylammonium perruthenate(VII) (catalytic amount), and powdered activated 4Å molecular sieves (0.150 g) were added to a solution of compound **27** (0.035 g, 0.208 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred at 25°C for 3 h, then diluted with Et_2O and washed with saturated aqueous Na_2SO_3 (5 mL) followed by saturated aqueous $CuSO_4$ (5 mL). The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography on silica gel (hexane-AcOEt, 9:1) to afford **28** as a colourless oil (0,024 g, 70%). IR ν (cm^{-1}): 3075, 2955, 2935, 2870, 2715, 1730, 1645, 1450, 1385, 1365, 1245, 1045, 900. ^{1}H-NMR (300 MHz) δ: 0.80 and 0.98 (2s, 2x3H, C*Me*$_2$); 1.15-2.05 (m, 9H,); 4.52 (bs, 1H, C=C*H*H), 4.80 (bm, 1H,C=CH*H*), 9.65 (t, J=2.5 1H, C*H*O). EIMS *m/z* (% rel. int.): 150 (52), 135 (48), 123 (28), 107 (47), 95 (68), 81 (68), 69 (100), 55 (58), 41 (96). CIMS (isobutane) *m/z* (% rel. int.): 183 (50), 167 (M^++1, 55), 149 (65), 131 (81).

(1"R)-(1'E)-3-[2'-(2",2"-Dimethyl-6"-methylene-cyclohexyl)-ethylidene]-dihydrofuran-2-one 5. Aldehyde **28** (0.018 g, 0.108 mmol) and α-(triphenylphosphoranylidene)-γ-butyrolactone[23] (0.050 g, 0.145 mmol) in dry THF (3 mL) were stirred at 50°C for 24 h, then the mixture was diluted with CH_2Cl_2 (15 mL) and filtered to remove insoluble excess ylide and triphenylphosphine oxide. The organic layer was evaporated and the residue was purified by column chromatography on silica gel (hexane-AcOEt, 5:1) to afford **5** as a colorless oil (0,018 g, 70%). $[\alpha]_D^{20} = -20.1$ (c=0.7, CH_2Cl_2). IR ν (cm^{-1}): 3070, 2960, 2925, 2865, 1763, 1680, 1645, 1465, 1378, 1365, 1220, 1180, 1030, 1010, 890. ^{1}H-NMR (300 MHz) δ: 0.87

and 0.99 (2s, 2x3H, C(2")Me_2); 1.2-1.6 (m, 4H, C(3")H_2 and C(4")H_2); 1.9-2.45 (m, 5H, C(2')H_2, C(1")H, and C(5")H_2); 2.85 (m, 2H, C(4)H_2); 4.37 (t, J=7.5, 2H, C(5)H_2); 4.51 (bs, 1H, C=CHH); 4.78 (bs, 1H, C=CHH); 6.69 (m, 1H, C(1')H). ^{13}C-NMR δ: 15.15 (q) and 24.76 (q) C(2")Me_2; 23.42 (t), 25.08 (t), 27.68 (t), 33.25 (t), and 37.23 (t) CH_2; 52.98 (d) C(1"); 65.15 (t) C(5); 109.54 (t) C=CH_2; 124.61 (s) C(3); 141.27 (d) C(1'); 147.89 (s) C(6"); 171.11 (s) C=O. EIMS *m/z* (% rel. int.): 234 (M^+,18), 219 (16), 148 (22), 133 (19), 123 (100), 112 (57), 105 (17), 91 (28), 81 (82), 69 (37), 55 (33), 41 (62).

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