Synthesis and antitumour activity of varitriol and its analogues

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Abstract

Novel analogues of (+)-varitriol have been synthesised via Julia-Kocienski olefination from γ-D-ribonolactone. Newly prepared compounds were screened for their in vitro cytotoxicity towards certain human tumours and NCI_{60} cancer cell line panel.

Keywords: Cytotoxic natural product, natural product analogues, varitriol, cytotoxic activity, Julia-Kocienski olefination

Introduction

Marine fungi are an important source of marine natural products.[1] Recently, the four new compounds, (+)-varitriol **1**, varioxirane **2**, dihydroterrein **3**, and varixanthone **4** have been isolated[2] from a marine-derived strain of the fungus *Emericella variecolor* (Figure 1). Amongst them, (+)-varitriol **1** demonstrated a more than 100-fold increased potency over the mean toxicity toward the RXF 393 (renal cancer, GI_{50} = 1.63 x 10^{-7} M), TD-47 (breast cancer, GI_{50} = 2.10 x 10^{-7} M), and SNB (CNS cancer, GI_{50} = 2.44 x 10^{-7} M) cell lines and lower potency against the DU-145 (prostate cancer, GI_{50} = 1.10 x 10^{-6} M), HL-60 (TB) (leukaemia, GI_{50} = 2.52 x 10^{-5} M), CCRF-CEM (leukaemia, GI_{50} = 2.60 x 10^{-5} M), OVCAR-5 (ovarian cancer, GI_{50} = 6.82 x 10^{-5} M), SNB-19 (CNS cancer, GI_{50} = 9.13 x 10^{-5} M), and COLO 205 (colon cancer, GI_{50} = 9.59 x 10^{-5} M) cell lines tested within the 60 cell lines panel of the National Cancer Institute (NCI).[2,3]
The combination of potent biological properties and a relatively straightforward molecular structure of (+)-**1** generated considerable synthetic interest directed toward the varitriol and its analogues. Since 2006, when Jennings *et al*.[4] established the absolute configuration of varitriol

by the total synthesis of unnatural enantiomer (-)-**1** from D-ribose, thirteen different syntheses of (+)- and (-)-varitriol have been reported.[4-13] In addition, the furanoside and pyranoside analogues of (+)-varitriol have been synthesised, but only a few were evaluated for their antitumour activity.[6b,12a,14]

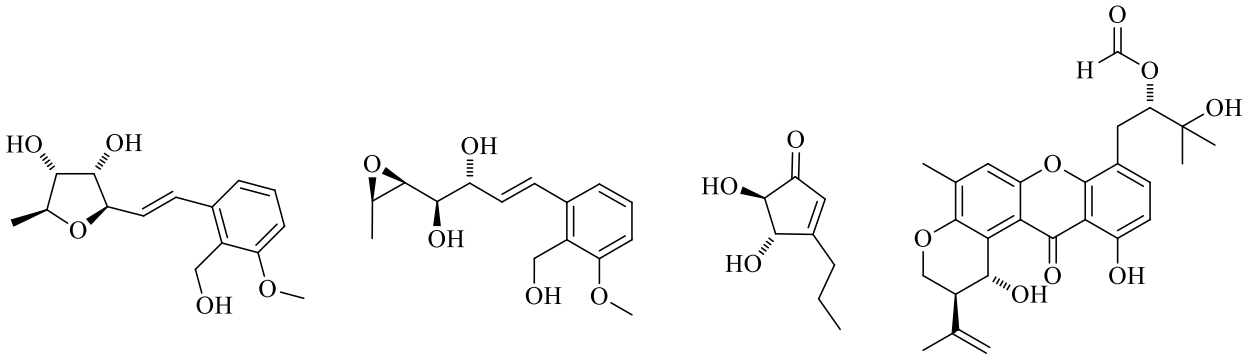


Figure 1. Chemical structures of the metabolites **1-4** from *E. variecolor*.

As a part of our ongoing project in the synthesis of new polyhydroxylated tetrahydrofurans as potential antitumour agents from monosaccharides,[15] we have recently developed a short and effective synthesis of varitriol from γ-D-ribonolactone.[7c] Herein, we wish to report the synthesis of varitriol analogues and their antitumour activity.

Results and Discussion

Chemistry

The array of interesting biological properties of (+)-**1** and the unknown mode of its action motivated us to synthesise a variety of analogues and to examine the bioactivity of structurally diverse „varitriol-like" compounds against set of tumour cell lines. New varitriol analogues have been designed by modification of the parent molecule (+)-**1** by substitution in aromatic ring **6**, configuration of furanoside part **5** as well as the geometry of the linker **7** (Figure 2).

All target compounds were prepared from γ-D-ribonolactone using our strategy for synthesis of (+)-varitriol.[7c] The synthesis represents a short and efficient approach to (+)-**1** in good overall yield (8 steps, 41% from D-ribonolactone and dimethylanisole). The key steps of the route include a highly stereoselective introduction of the methyl group at C-1 and Julia-Kocieński olefination with aromatic aldehyde at C-5 of the starting skeleton (Scheme 1). A rapid access to both key fragments, **8** and **9**, as well as the late stage of convergence of the synthesis, make the strategy suitable for the synthesis of the large library of substances for investigation of structure-activity relationship (SAR).

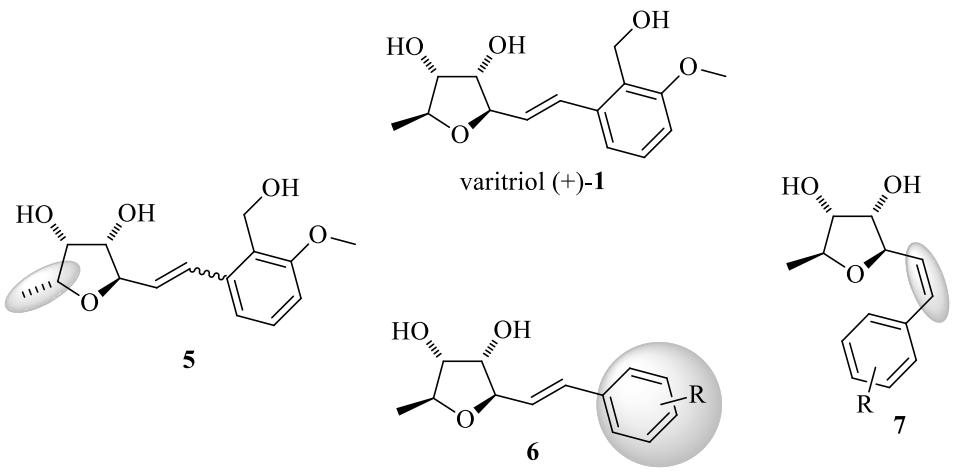
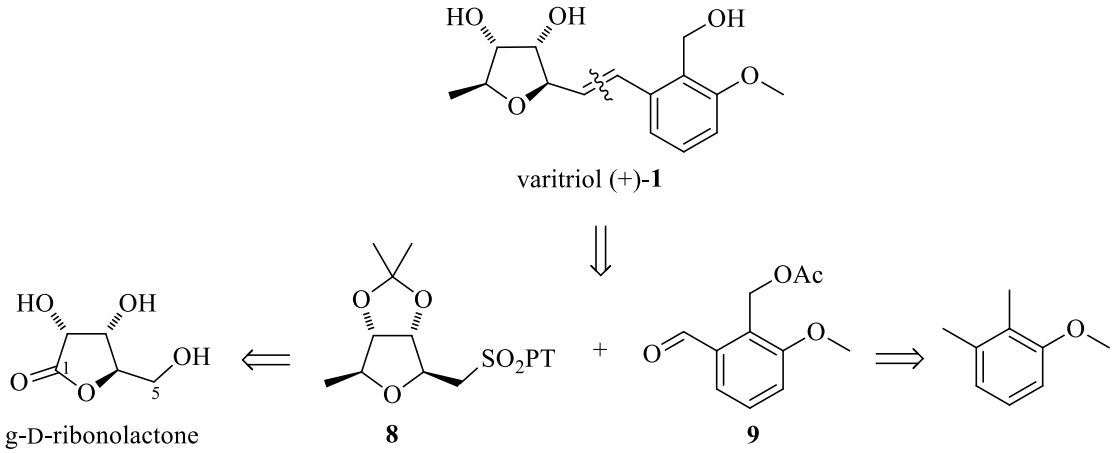


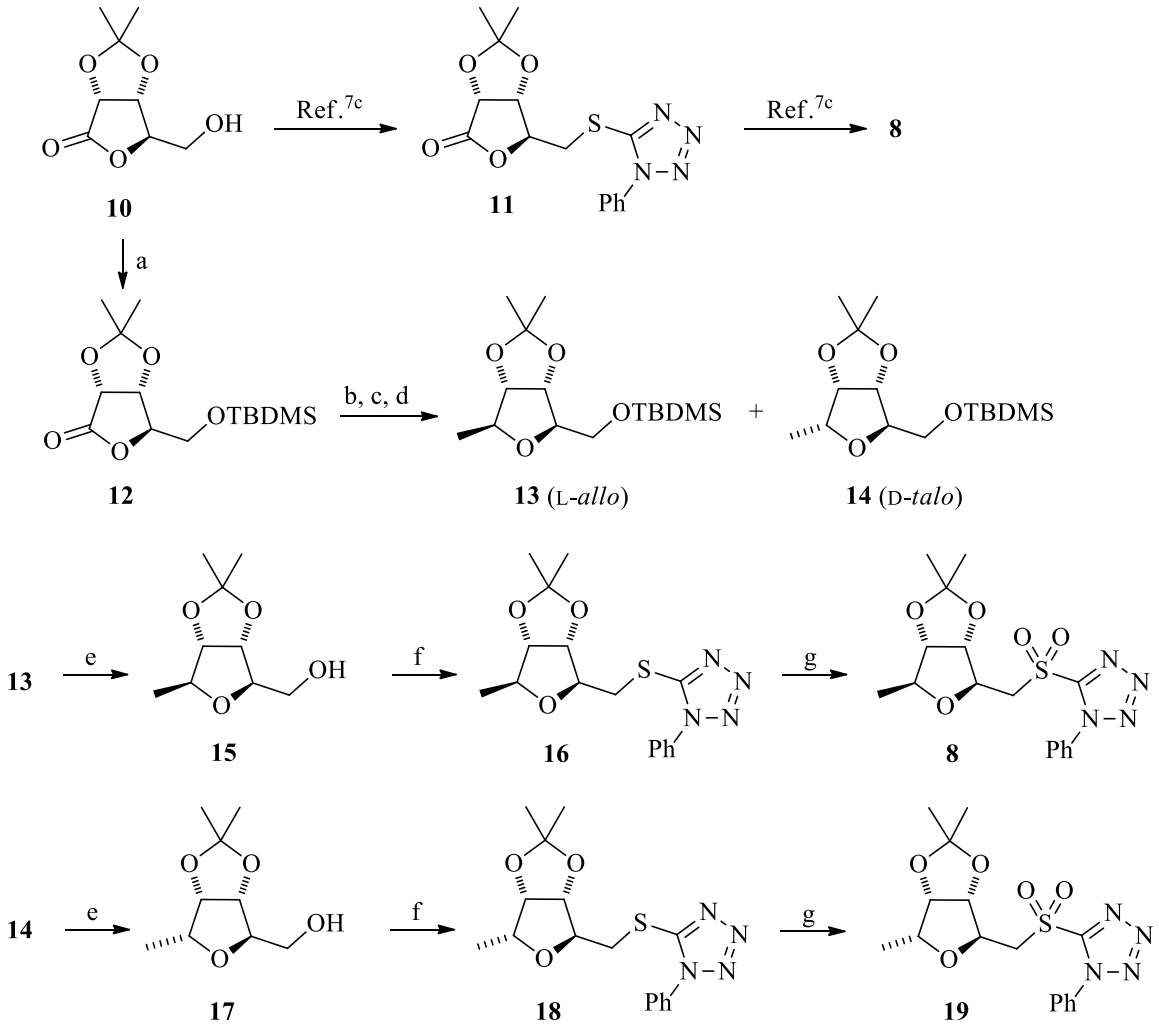
Figure 2. Structure of natural varitriol (+)-**1** and its analogues **5**, **6**, **7**.



Scheme 1. Retrosynthetic analysis of varitriol (+)-**1**.

The key furanoside fragments for coupling, protected diastereomeric sulfones **8** and **19**, were prepared from γ-D-ribonolactone adopting our synthesis[7c] of (+)-**1** (Scheme 2). In order to obtain both L-*allo* and D-*talo* diastereomers of methylated tetrahydrofuran derivatives **13** and **14**, we changed the reaction sequence of the original synthesis. At first, methyl was introduced at a carbonyl group of the lactone followed by installation of the phenyltetrazole sulfide moiety at C-5. In fact, since methylation of the lactone **11** proceeded with high *exo*-selectivity to produce a sole L-*allo* configured sulfone **8**, silyl protected lactone **12** provided both diastereomers **13**, **14** in the same reaction conditions. Thus, following the reaction sequence, primary hydroxyl group of **10** was protected with *tert*-butyldimethylsilyl chloride followed by partial reduction of the lactone **12** using DIBAL (2 equiv) in THF at -50 °C, acetylating with acetic anhydride (2 equiv) and 4-dimethylaminopyridine (3 equiv) and subsequent treatment of these acetates with trimethylaluminium (3 equiv) in dichloromethane at low temperature. The methylated

tetrahydrofurans **13** and **14** were prepared in 94% overall yield. The diastereomers could be readily separated by preparative MPLC to provide **13** and **14** in 70% and 15% yield, respectively.

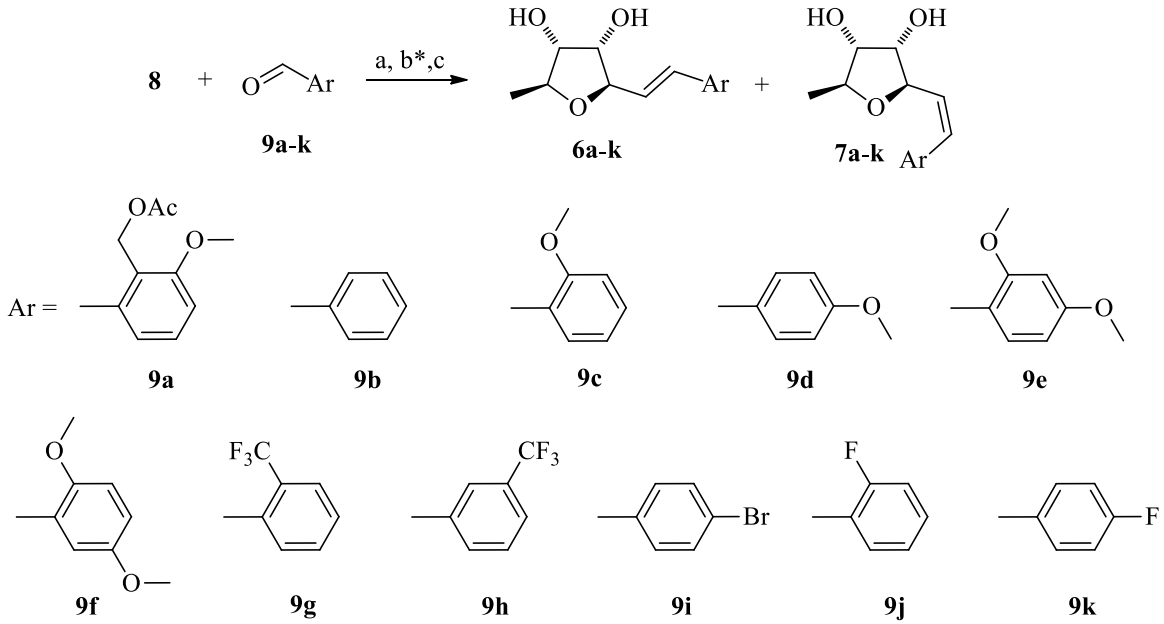


Scheme 2. *Reagents and conditions*: (a) TBDMSCl, Et_3N, DMAP, DMF, rt, 8 h, 95%; (b) DIBAL, THF, -50 °C, 4 h; (c) Ac_2O, DMAP, CH_2Cl_2, 0 °C to rt, 12 h; (d) Me_3Al, CH_2Cl_2, -30 to -18 °C, 6 d, 94% from **12** over 3 steps, preparative MPLC, **13** (70%) and **14** (15%); (e) TBAF, THF, rt, 12 h, **15** (89%), **17** (93%); (f) PTSH, PPh_3, DIAD, THF, 0 °C, 1 h, **16** (85%), **18** (94%); (g) Mo(VI)/H_2O_2, THF, EtOH, rt, 24 h, **8** (91%), **19** (91%).

The second crucial step of both syntheses, which were run in parallel with the pure diastereomers **13** (L-*allo*) and **14** (D-*talo*) is installation of the phenyltetrazole sulfide moiety. Firstly, silyl group was removed with tetrabutylammonium fluoride (2 equiv) in THF and alcohols **15** and **17** were exposed to Mitsunobu protocol for displacement of the primary hydroxyl group with phenyltetrazolylthiol. The reaction was carried out under standard reaction

conditions[16,17] with PTSH (2 equiv), Ph_3P (1.5 equiv) and DIAD (1.8 equiv) in THF to give the corresponding sulfides **16** (85%) and **18** (94%). The syntheses continued with oxidation of sulfides using hydrogen peroxide/ammonium molybdate in THF and EtOH affording the required sulfones **8** and **19** in good yields (91%).

Next, the sulfone **8** was used in the Kocieński-Julia olefination[18] with the aldehyde **9a**[19] leading to the protected (+)-**1** (**6a**), and with the set of commercially available aromatic aldehydes **9b-9k** (Scheme 3). The couplings were performed under so-called Barbier reaction conditions.[20] The potassium hexamethyldisilazane (1.8 equiv) was added to the mixture of sulfone **8**, and an excess amount of aldehyde **9** (5 equiv) in dimethoxyethane at -30 °C; the mixture was stirred at room temperature for 10 h. Final removal of the acetonide and acetyl protecting group with 1M aqueous HCl in THF and NaOMe in MeOH, respectively, furnished target compounds **6a-k**, **7a-k** as the mixtures of *E*/*Z*-isomers (Table 1), which were separated by preparative MPLC.



Scheme 3. *Reagents and conditions*: (a) KHDMS, DME, -30 °C to rt, 10 h; (b*) used for **6a, 7a**: NaOMe, MeOH, rt, 4 h; (c) HCl, THF, rt, 3-12 h; see Table 1.

Table 1. Formation of olefins **6a-k** and **7a-k** by reaction of sulfone **8** with aldehydes **9a-k**

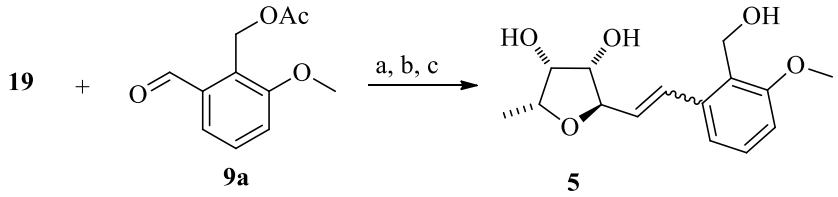
Entry	Aldehyde	6/7 (% yield)[a]	6 (% yield)[b]	7 (% yield)[b]
1	**9a**	76	56	14
2	**9b**	88	53	26
3	**9c**	80	49	3
4	**9d**	59	41	18
5	**9e**	61	61	-

Table 1 (continued)

Entry	Aldehyde	6/7 (% yield)[a]	6 (% yield)[b]	7 (% yield)[b]
6	**9f**	59	53	2
7	**9g**	41	41	-
8	**9h**	77	37	25
9	**9i**	98	56	35
10	**9j**	43	35	-
11	**9k**	42	30	8

[a]Combined yield of isolated **6** and **7.** [b]Isolated yield of pure isomers.

In the synthesis of 2-*epi*-varitriol **5**, D-*talo* configurated sulfone **19** reacted with the corresponding aldehyde **9a** under the same reaction conditions as above (Scheme 4). Global deprotection of all hydroxyl groups using the previously described conditions[7c] gave 2-*epi*-varitriol **5** as a mixture of *E*/*Z*-isomers in the ratio 5:4.



Scheme 4. *Reagents and conditions*: (a) KHDMS, DME, -30 °C to rt, 10 h; (b) NaOMe, MeOH, rt, 4 h; HCl, THF, rt, 5 h, 78% overall yield (*E*/*Z*- mixture in the ratio 5:4).

In vitro cytotoxic activity

Compounds **5, 6** and **7** were evaluated for their in vitro cytotoxicity against human drug sensitive (CCRF-CEM, K562) versus multidrug resistant leukaemia cell lines (K562-Tax, CEM-DNR-BULK), colon cancer cells with normal (+/+) or inactive (-/-) p53 oncosuppressor (HCT116p53$^{+/+}$, HCT116p53$^{-/-}$), lung adenocarcinoma (A549), normal foetal lung (MRC-5) and foreskin (BJ) fibroblasts. Cytotoxic activity was evaluated after 72 hrs of treatments using a cytotoxic MTT assay, based on reduction of yellow tetrazolium salt on blue formazan in mitochondria of living cellsM. The determined activities were expressed as IC_{50} values (concentrations leading to 50% decrease in cell survival).

As outlined in Table 2, compounds displayed only a mild activity against the above mentioned cell lines. The configurationally modified varitriol **5** as a mixture of *E*/*Z*-isomers (in the ratio 5:4) showed the most significant activities against the all tested cell lines, whereas varitriol **6a (***E*-isomer) and its *Z*-analogue **7a** showed much lower activities or were inactive. Interestingly, the difference in the geometry of the linker **6a, 6h, 6k** (*E*-isomers) *vs* **7a, 7h, 7k,** caused in general a slightly higher cytotoxic activities of *Z*-isomers (**7a, 7h, 7k**). The widest spectrum of activities from the set of analogues with differently substituted aromatic part, were

displayed by compounds **6e** (2,4-dimethoxy), **6f** (2,5-dimethoxy), **6i** (4-bromo). Majority of the tested compounds demonstrated the highest activities against human T-lymphoblastic leukaemia cell line CCRF-CEM and its multidrug resistant subline CEM-DNR-BULK overexpressing the multidrug resistant protein 1 (MRP-1), thus showing compounds activity in multidrug resistant cancers. Unexpectedly, the in vitro anticancer activity of synthetic varitriol and its analogues was dramatically lower than that reported for natural varitriol by Barrero *et al*., obtained from the tests against RXF 393, TD-47, SNB, DU-145, HL-60, CCRF-CEM, OVCAR-5, SNB-19 and COLO 205 cell lines.[2] Thus, in order to prevent bias in methodology of testing or cell line selection, we decided to submit all prepared compounds **5**, **6**, **7** for further testing against the NCI_{60} cancer cell line panel at the developmental therapeutics program, Division of Cancer Treatment and Diagnosis, National Cancer Institute (DTP, Bethesda, USA). Surprisingly, neither synthetic (+)-varitriol nor the analogues **5**, **6** and **7** exhibited expected GI_{50} when evaluated against NCI_{60} panel at a single 10 μM concentration (see supporting information), thus confirming our primary data from MTT cytotoxic activity evaluation.

Table 2. Antiproliferative activities of synthesised varitriol analogues **5**, **6a-k** and **7a**,**b**,**d**,**h**,**i**,**k**

Comp.	IC_{50} μM[a]								
	CCRF-CEM	A549	K562	K562-Tax	CEM-DNR-BULK	HCT116p53 +/+	HCT116p53 -/-	MRC 5	BJ
5	45.3	67.1	107	84.8	115	76.3	104	>166	150
6a [(+)-**1**]	161	>166	>166	>166	153	>166	>166	166	>166
7a	121	163	158	>166	132	111	>166	>166	>166
6b	145	>166	>166	>166	151	>166	>166	154	>166
7b	160	>166	>166	>166	149	>166	>166	152	>166
6c	142	>166	>166	>166	154	>166	>166	152	>166
6d	144	>166	>166	147	164	>166	>166	>166	>166
7d	157	>166	>166	153	>166	>166	>166	156	>166
6e	132	>166	149	159	133	140	155	>166	>166
6f	130	>166	155	>166	123	151	160	>166	>166
6g	147	>166	>166	>166	149	>166	>166	152	>166
6h	145	>166	>166	149	>166	154	>166	>166	>166
7h	147	>166	>166	151	135	>166	157	148	>166

Table 2 (continued)

Comp.	IC_{50} μM[a]								
	CCRF-CEM	A549	K562	K562-Tax	CEM-DNR-BULK	HCT116p53 +/+	HCT116p53 -/-	MRC 5	BJ
6i	146	>166	>166	136	>166	162	150	154	>166
7i	147	>166	>166	148	>166	>166	>166	>166	>166
6j	138	>166	153	>166	141	153	>166	>166	>166
6k	136	>166	>166	>166	143	>166	>166	>166	>166
7k	131	143	142	155	121	158	136	>166	156

[a] IC_{50} values in a 3-day MTT assay. Presented values are averages of at least three independent experiments, where standard deviations were typically within 25% of the average.

Conclusions

In summary, the varitriol analogues with modified aromatic part **6a-k**, geometry of the C-C double bond **7a-c**, **7e,f**, **7h** and **7k**, as well as a new 2-epimer **5** have been synthesised and evaluated for their in vitro antitumour activities against a number of selected human neoplastic cell lines and NCI_{60} cancer cell line panel at the Developmental Therapeutics Program, National Cancer Institute. All the compounds showed only mild activity, and compound **5** was the most active among the screened compounds. Though the compounds showed mild activity, the synthesis and screening of more analogues of varitriol with higher structural diversity or synthesis and exploration of bioactivity the other compounds (varioxirane **2**, dihydroterrein **3**, and varixanthone **4**) isolated from a marine-derived strain of the fungus *Emericella variecolor*, would give scope for further work in this area.

Finally, the synthetic strategy has been proven to apply for rapid construction of varitriol analogues with variable side chain, linker and configuration of furanoside portion of the target molecule.

Experimental Section

General. Commercial reagents were used without further purification. All solvents were distilled before use. Hexanes refer to the fraction boiling at 60-65 ºC. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40-63 μm, 230-400 mesh) using Buchi Sepacore® preparative MPLC system and analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with either 0.2 mm (DC-Alufolien, Merck)

or 0.25 mm silica gel 60 F_{254} (ALUGRAM® SIL G/UV_{254}, Macherey-Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulphate/ammonium molybdate followed by charring with a heat-gun. Melting points were determined on a Büchi 540 apparatus and were not corrected. Optical rotations were measured with a JASCO P-2000 polarimeter and are given in units of 10^{-1} deg·cm^2·g^{-1}. High resolution mass spectra (HRMS) were recorded on a Q-Tof PremierTM mass spectrometer with nanoACQUITY UPLCTM (Waters), and are accurate to ± 3 ppm. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory, using the reflectance technique (4000-400 cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on either 300 (75) MHz MercuryPlus or 600 (150) MHz Unity Inova spectrometers from Varian. Chemical shifts (δ) are quoted in ppm and are referenced to the tetramethylsilane (TMS) as internal standard.

2,3-*O*-Isopropylidene-5-*O*-tert-butyldimethylsilyl-γ-D-ribonolactone (12). To a solution of γ-D-ribonolactone (1.5 g, 7.97 mmol) in dry DMF (25 mL) were successively added Et_3N (2.22 mL, 15.94 mmol), TBDMSCl (1.92 g, 12.75 mmol) and DMAP (52 mg, 0.426 mmol). The resulting mixture was stirred at room temperature for 8 h than diluted with ether (75 mL) and extracted with water (50 mL). Aqueous phase was extracted with ether (4 x 30 mL), combined extracts were washed with water (3 x 30 mL), dried over $MgSO_4$ and concentrated. Purification by flash chromatography (5% EtOAc in hexanes) afforded the title compound **12** (2.29 g, 95%) as a white solid. Selected data: R_f 0.4 (15% AcOEt in hexanes), $[a]_D^{25}$ -48.8 (*c* 0.221, $CHCl_3$); IR (ATR): *v* 2954 (m), 2929 (m), 1772 (vs, CO), 1107 (vs), 1077 (vs), 837 (vs) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 0.06, 0.08 (2 x s, 6H, Si(C<u>H</u>$_3$)$_2$), 0.88 (s, 9H, C(C<u>H</u>$_3$)$_3$, 1.39, 1.48 (2 x s, 6H, C(C<u>H</u>$_3$)$_2$), 3.80 (dd, 1H, A of ABX, $J_{5A,5B}$ = 11.3, $J_{5A,4}$ = 1.4Hz, H-5A), 3.90 (dd, 1H, B of ABX, $J_{5A,5B}$ = 11.3, $J_{5B,4}$ = 2.1Hz, H-5B) 4.61 (dd, 1H, $J_{5B,4}$ = 1.8, $J_{5A,4}$ = 1.5 Hz, H-4) 4.71 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2 or H-3), 4.74 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2 or H-3); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* -5.8, -5.6 (all q, Si(C<u>H</u>$_3$)$_2$), 18.2(s, <u>C</u>(CH$_3$)$_3$), 25.6, 25.7, 26.8 (all q, C(<u>C</u>H$_3$)$_2$ C(<u>C</u>H$_3$)$_3$), 63.0 (t, C-5), 75.8, 78.4, 82.3 (all d, C-2, C-3, C-4), 113.0 (s, <u>C</u>(CH$_3$)$_2$), 174.1(s, C-1). HRMS *m/z* Calc. for $C_{14}H_{26}NaO_5Si^+$: 325.1442, found 325.1393 $[M+Na]^+$.

2,5-Anhydro-6-deoxy-3,4-*O*-isopropylidene-1-*O*-tertbutyldimethylsilyl-L-allitol (13) and 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-1-*O*-tertbutyldimethylsilyl-D-talitol (14). The lactone **12** (1.9 g, 6.29 mmol) was dissolved in dry toluene (120 mL), cooled to -78 °C under argon atmosphere and 10% w/w solution of DIBAL in hexanes (13 mmol, 28 mL) was added dropwise. Reaction mixture was allowed to warm to -50 °C and after 4 h was quenched with HCl 3M, 10 mL). After warming to room temperature reaction was extracted between water (100 mL) and ether (3 x 30 mL), combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was dissolved in dry dichloromethane (60 mL), cooled to 0 °C, than DMAP (2.3 g, 18.8 mmol) and Ac_2O (1.2 ml, 12.6 mmol) were added and the mixture was stirred for 12 h. Resulting mixture was diluted with DCM (100 mL), washed with water (50 mL) and brine (50 mL), concentrated and used for subsequent methylation without further

purification. Thus, Me_3Al (2M in hexanes, 10 mL, 20 mmol, 3 equiv) was added dropwise to the crude oil in dry DCM (35 mL) at -30 °C. Reaction mixture was allowed to warm to -18 °C and stirred overnight at this temperature. Resulting mixture was quenched with 5% w/w solution of citric acid (100 mL) extracted with ether (3 x 30 mL), dried and concentrated. Separation using flash chromatography (2% ether in hexanes) afforded 1.32 g (70%) of L-*allo*-diastereomer **13**, 270 mg of D-*talo*-diastereomer **14** (15%) and 140 mg (9%) of the mixture of both diastereomers (all were isolated as colourless liquids.)

2,5-Anhydro-6-deoxy-3,4-*O*-isopropylidene-1-*O*-tertbutyldimethylsilyl-L-allitol (13). Selected data: R_f 0.6 (10% AcOEt in hexanes), $[a]_D^{25}$ -5.5 (*c* 0.217, $CHCl_3$); IR (ATR): *v* 2954 (m), 2929 (s), 2858 (m), 1381 (m), 1253 (s), 1073 (s), 833 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.06, 0.07 (2 x s, 6H, Si($C\underline{H}_3$)$_2$), 0.90 (s, 9H, C($C\underline{H}_3$)$_3$, 1.28 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6), 1.34, 1.53 (2 x s, 6H, C($C\underline{H}_3$)$_2$), 3.72 (dd, 2H, $J_{1,2}$ = 3.9, *J* = 0.8 Hz, H-1), 3.95-4.01 (m, 2H, H-2, H-5) 4.21 (dd, 1H, $J_{3,4}$ = 6.6, *J* = 5.0 Hz, H-3 or H-4) 4.64 (dd, 1H, $J_{3,4}$ = 6.7, *J* = 3.6 Hz, H-3 or H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4, -5.3 (all q, Si($C\underline{H}_3$)$_2$), 18.4(s, $\underline{C}(CH_3)_3$), 19.1, 25.5, 25.9, 27.5 (all q, C-6, C($\underline{C}H_3$)$_2$ C($\underline{C}H_3$)$_3$), 63.7 (t, C-1), 80.6, 82.2, 84.4, 86.1 (all d, C-2, C-3, C-4, C-5), 113.9 (s, $\underline{C}(CH_3)_2$). HRMS *m/z* Calc. for $C_{15}H_{30}NaO_4Si^+$: 325.1806, found 325.1703 $[M+Na]^+$.

2,5-Anhydro-6-deoxy-3,4-*O*-isopropylidene-1-*O*-tertbutyldimethylsilyl-D-talitol (14). Selected data: R_f 0.5 (10% AcOEt in hexanes), $[a]_D^{25}$ -9.1 (*c* 0.219, $CHCl_3$); IR (ATR): *v* 2954 (m), 2929 (s), 2856 (m), 1379 (m), 1254 (s), 1086 (s), 834 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.05, 0.06 (2 x s, 6H, Si($C\underline{H}_3$)$_2$), 0.89 (s, 9H, C($C\underline{H}_3$)$_3$), 1.27 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6), 1.36, 1.51 (2 x s, 6H, C($C\underline{H}_3$)$_2$), 3.69 (d, 2H, $J_{1,2}$ = 4.0 Hz, H-1), 4.04 (t, 1H, $J_{1,2}$ = 4.0 Hz, H-2), 4.20 (dq, 1H, $J_{5,6}$ = 6.4, $J_{4,5}$ = 4.1 Hz, H-5), 4.58 (dd, 1H, $J_{3.4}$ = 6.1, $J_{4,5}$ = 4.0 Hz, H-4), 4.81 (dd, 1H, $J_{3,4}$ = 6.1, $J_{2,3}$ = 0.5 Hz, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.6, -5.5 (all q, Si($\underline{C}H_3$)$_2$), 14.6 (q, C-6) 18.1 (s, $\underline{C}(CH_3)_3$), 25.1, 25.8, 26.3 (all q, C($\underline{C}H_3$)$_2$ C($\underline{C}H_3$)$_3$), 64.7 (t, C-1), 78.2, 82.8, 83.5, 84.1 (all d, C-2, C-3, C-4, C-5), 112.0 (s, $\underline{C}(CH_3)_2$). HRMS m/z Calc. for $C_{15}H_{34}NO_4Si^+$: 320.2252, found 320.2096 $[M+NH_4]^+$.

2,5-Anhydro-6-deoxy-3,4-*O*-isopropylidene-L-allitol (15). Tetrabutyl ammonium fluoride trihydrate (1.815g, 5.76 mmol) was added to the solution of the silyl ether **13** (870 mg, 2.88 mmol) in THF (30 mL) and stirred for 12 h at room temperature. Resulting mixture was than concentrated and purified by flash chromatography (15% EtOAc in hexanes), yielding **15** (482 mg, 89%) as a colourless oil. Selected data: R_f 0.1 (10% AcOEt in hexanes), $[a]_D^{25}$ +8.5 (*c* 0.743, $CHCl_3$); IR (ATR): *v* 3334 (s, OH), 2925 (m), 1456 (m), 1082 (s), 1035(s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6), 1.34, 1.54 (2 x s, 6H, C($C\underline{H}_3$)$_2$), 2.20 (bs, 1H, OH), 3.67 (dd, 1H, A of ABX, $J_{1A,1B}$ = 11.7, $J_{1A,2}$ = 3.1Hz, H-1A), 3.82 (dd, 1H, B of ABX, $J_{1A,1B}$ = 11.9, $J_{1B,2}$ = 3.1 Hz, H-1B), 3.94-4.04 (m, 2H, H-2, H-5), 4.23 (dd, 1H, $J_{3,4}$ = 6.9, *J* = 5.2 Hz, H-3 or H-4) 4.62 (dd, 1H, $J_{3,4}$ = 7.0, *J* = 4.5 Hz, H-3 or H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.8, 25.4, 27.3 (all q, C-6, C($\underline{C}H_3$)$_2$), 62.7 (t, C-1), 80.5, 81.6, 84.1, 86.1 (all d, C-2, C-3, C-4, C-5), 114.7 (s, $\underline{C}(CH_3)_2$). HRMS *m/z* Calc. for $C_9H_{17}O_4^+$: 189.1121, found 189.1109 $[M+H]^+$.

2,5-Anhydro-6-deoxy-3,4-*O*-isopropylidene-D-talitol (17). A solution of **14** (290 mg, 0.96 mmol) and tetrabutyl ammonium fluoride trihydrate (605g, 1.92 mmol) in THF (10 mL) was stirred for 12 h at room temperature. Resulting mixture was concentrated and purified by flash chromatography (15% EtOAc in hexanes), providing title compound **17** (168 mg, 93%) as a colourless oil. Selected data: R_f 0.1 (10% AcOEt in hexanes), $[a]_D^{25}$ +5.0 (*c* 0.240, $CHCl_3$); IR (ATR): *v* 3412 (m, OH), 2986 (m), 2936 (m), 1732 (m), 1374 (s), 1208 (vs), 1032 (vs), 872 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6), 1.35, 1.52 (2 x s, 6H, $C(C\underline{H}_3)_2$), 2.12 (bs, 1H, OH), 3.60 (bs, 2H, H-1), 4.04-4.16 (m, 2H), 4.57-4.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (q, C-6), 25.1, 26.3 (all q, $C(\underline{C}H_3)_2$), 61.7 (t, C-1), 76.6, 82.3, 82.7, 84.1 (all d, C-2, C-3, C-4, C-5), 112.5 (s, $\underline{C}(CH_3)_2$). HRMS *m/z* Calc. for $C_9H_{17}O_4^+$: 189.1121, found 189.1127 $[M+H]^+$.

2,5-Anhydro-1,6-dideoxy-3,4-*O*-isopropylidene-1-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)-L-allitol (16). 1-Phenyl-1*H*-tetrazol-5-thiol (3.28 g, 18.41 mmol, 2.1 equiv) was added to the solution of **15** (1.65 g, 8.77 mmol) in THF (80 mL) and mixture was cooled to 0 °C. Then PPh_3 (3.45 mg, 13.15 mmol, 1.5 equiv) and DIAD (3.11 mL, 15.79 mmol, 1.8 equiv) were consecutively added. After stirring for 1 h, the reaction mixture was extracted between ether (2 x 50 mL) and brine (50 mL). Combined organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (10% EtOAc in hexanes). Sulfide **16** was obtained as a colourless oil (2.6 g, 85%). HRMS *m/z* Calc. for $C_{16}H_{20}N_4NaO_3S^+$: 371.1148, found 371.1187 [M+Na]+. The physical and spectral data of 16 were in accord with the literature.[7c]

2,5-Anhydro-1,6-dideoxy-3,4-*O*-isopropylidene-1-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)-D-talitol (18). Prepared as above from **17** (140 mg, 0.75 mmol), PTSH (279 mg, 1.56 mmol), DIAD (264 μl, 1.34 mmol). Yield: 256 mg (94%, colourless oil). Selected data: R_f 0.6 (50% AcOEt in hexanes), $[a]_D^{25}$ +24.9 (*c* 0.205, $CHCl_3$); IR (ATR): *v* 2982 (m), 2934 (m), 1596 (m), 1499 (vs), 1382 (vs), 1084 (vs), 1012 (vs), 761 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6), 1.34, 1.49 (2 x s, 6H, $C(C\underline{H}_3)_2$), 3.53 (d, 2H, $J_{1,2}$ = 7.6 Hz, H-1), 4.07 (dq, 1H, $J_{5,6}$ = 6.3, $J_{4,5}$ = 3.5 Hz, H-5), 4.35 (t, 1H, $J_{1,2}$ = 7.7 Hz, H-2), 4.65 (dd, 1H, $J_{3,4}$ = 6.0, $J_{4,5}$ = 3.4 Hz, H-4), 4.70 (dd, 1H, $J_{3,4}$ = 6.1, $J_{2,3}$ = 0.5 Hz, H-3), 7.53-7.60 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (q, C-6), 25.2, 26.3 (all q, $C(\underline{C}H_3)_2$), 33.7 (t, C-1), 76.3, 82.1, 82.2, 84.8 (all d, C-2, C-3, C-4, C-5), 112.8 (s, $\underline{C}(CH_3)_2$), 123.9, 129.8, 130.2 (all d, Ph), 133.5, 153.9 (all s, *i*-Ph, *i*-Tetr). HRMS *m/z* Calc. for $C_{16}H_{20}N_4NaO_3S^+$: 371.1148, found 371.1177 $[M+Na]^+$.

2,5-Anhydro-1,6-dideoxy-3,4-*O*-isopropylidene-1-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-L-allitol (**8**) was prepared from sulfide **16** as described.[7c]

2,5-Anhydro-1,6-dideoxy-3,4-*O*-isopropylidene-1-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-D-talitol (19). Prepared by Mo(IV)/H_2O_2 oxidation of sulfide **18** (50 mg, 0.137 mmol) according to the described procedure.*7c* Yield: 49 mg (91%, white solid). Selected data: m.p. 132-134 °C; R_f 0.6 (50% AcOEt in hexanes), $[a]_D^{25}$ +82.3 (*c* 0.147, $CHCl_3$); IR (ATR): *v* 2990 (m), 2971 (m), 2934 (m), 1496 (s), 1349 (vs), 1152 (vs), 1075 (vs), 772 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6), 1.31, 1.45 (2 x s, 6H, $C(C\underline{H}_3)_2$), 3.48 (dd, 1H, A of ABX, $J_{1A,1B}$ = 15, $J_{1A,2}$ = 3.5 Hz, H-1A), 3.80 (dq, 1H, $J_{5,6}$ = 6.2, $J_{4,5}$ = 3.1 Hz, H-5), 4.18 (dd, 1H, B of ABX,

$J_{1A,1B}$ = 15, $J_{1B,2}$ = 10.8 Hz, H-1B), 4.55-4.63 (m, 3H, H-2, H-3, H-4), 7.54-7.66 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2 (q, C-6), 25.0, 26.1 (all q, C($\underline{C}H_3)_2$), 55.9 (t, C-1), 76.2, 78.4, 81.8, 84.8 (all d, C-2, C-3, C-4, C-5), 113.1 (s, $\underline{C}(CH_3)_2$), 125.7, 129.4, 131.4 (all d, Ph), 133.0, 153.8 (all s, *i*-Ph, *i*-Tetr). HRMS *m/z* Calc. for $C_{16}H_{20}N_4NaO_5S^+$: 403.1047, found 403.1063 $[M+Na]^+$.

General procedure for the preparation of varitriol analogues

The solution of sulfone (**8** or **19**, 1 equiv) and aldehyde (**9**, 5 equiv) in dry DME (10 mL/100 mg of sulfone) was cooled to -30 °C under argon atmosphere. Potassium hexamethyldisilazane (0.5 M in toluene, 1.6 equiv) was added dropwise and the resulting mixture was allowed to warm slowly to rt and stirred overnight. The reaction was then quenched by addition of water (0.5 mL) and concentrated *in vacuo*. The crude product of the olefination was dissolved in THF (20 mL/100 mg of sulfone) and 1M aqueous HCl (20 mL/100 mg of sulfone) was added. The reaction mixture was stirred at rt until full conversion (TLC control, 3-12h). Mixture was neutralised with solid Na_2CO_3 and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel. Combined yields of olefins **5**, **6**, **7** as well as the yields of isolated pure isomers **6**, **7** are given in the Table 1. Deprotection of hydroxyl groups in the compounds **5**, **6a**, **7a** was carried out as follows: the crude product was dissolved in MeOH (6 mL) and freshly prepared sodium methoxide (0.6 M in MeOH, 2.1 mL) was added. The mixture was allowed to stir for 4 h, by which time TLC (EtOAc/hexanes, 3:7) showed complete conversion of the starting material. The residue was dissolved in THF (20 mL) and 1M aqueous HCl (20 mL) and stirred at rt for 5 h. The work-up followed as above.

2-Epi-varitriol (5). Yield: 62 mg (78%, *E*/*Z*-mixture in the ratio 5:4 by ^{1}H NMR as a slightly yellow oil); R_f 0.3 (50% AcOEt in hexanes), $[a]_D^{25}$ +34.5 (*c* 0.568, MeOH); IR (ATR): *v* 3390 (m, OH), 2933 (m), 1722 (m), 1577 (s), 1262 (vs), 1000 (vs), 752 (s) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.13 (d, 3H, $J_{Me,2}$ = 6.5 Hz, Me, minor), 1.22 (d, 3H, $J_{Me,2}$ = 6.5 Hz, Me, major), 3.82 (s, 3H, OMe, major), 3.83 (s, 3H, OMe, minor), 3.83-4.73 (m, 6H, H-2, H-3, H-4, H-5, OCH_2), 5.78 (dd, 1H, $J_{1´,2´}$ = 11.4, $J_{1´,5}$ = 9.7 Hz, H-1´ minor), 6.21 (dd, 1H, $J_{1´,2´}$ = 15.7, $J_{1´,5}$ = 6.8 Hz, H-1´, major), 6.86-7.26 (m, 4H, Ph, H-2´) ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 16.4, 16.6 (all q, Me), 56.4 (t, CH_2OH), 56.9, 57.0 (all q, OMe), 57.0 (t, CH_2OH), 74.9, 75.0, 77.9, 78.1, 78.7, 79.7, 80.0, 84.0 (all d, C-2, C-3, C-4, C-5), 111.5, 111.7 (d, C-6'), 128.8, 129.2 (s, C-4´), 120.3, 123.8, 130.0, 130.1, 130.3, 132.9, 134.1, 135.0 (all d, C-1´, C-2´, C-7', C-8'), 139.7, 140.1 (s, C-3´), 159.8, 159.9 (s, C-5´). HRMS *m/z* Calc. for $C_{15}H_{20}NaO_5^+$: 303.1203, found 303.1002 $[M+Na]^+$.

***E*-Varitriol (6a)**. Yield: 45 mg (56%, white solid). The physical and spectral data of **6a** were in accord with the literature.[7c]

***Z*-Varitriol (7a)**. Yield: 11 mg (14%, white solid); m.p. 126-130 °C, R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +22.5 (*c* 0.129, MeOH); IR (ATR): *v* 3384 (m, OH), 2962 (m), 1745 (w), 1577 (s), 1262 (vs), 1072 (vs), 1014 (vs), 775 (s) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.21 (d, 3H,

$J_{Me,2}$ = 6.1 Hz, Me), 3.62-3.70 (m, 2H), 3.84-3.92 (m, 6 H), 4.28 (dd, 1H, $J_{1',5}$ = 9.6, $J_{4,5}$ = 5.5 Hz, H-5), 4.59 (dd, 1H, $J_{A,B}$ = 11.4, $J_{A,OH}$ = 4.7 Hz, C$\underline{H}_A$H$_B$OH), 4.67 (dd, 1H, $J_{A,B}$ = 11.4, $J_{B,OH}$ = 4.5 Hz, CH$_A\underline{H}_B$OH), 5.74 (dd, 1H, $J_{1',2'}$ = 11.4, $J_{1',5}$ = 9.7 Hz, H-1′), 6.87-6.98 (m, 3H, H-2′, H-6′, H-8′), 7.23 (t, 1H, J = 8.0 Hz, H-7′); ^{13}C NMR (75 MHz, (CD,$_3$)$_2$CO): δ 20.6 (q, Me), 56.9 (q, OMe), 57.7 (t, CH$_2$OH), 77.7, 78.4, 81.2, 81.4 (all d, C-2, C-3, C-4, C-5), 111.8 (d, C-6'), 129.3 (s, C-4′), 123.7, 130.1, 132.9, 134.2 (all d, C-1′, C-2′, C-7', C-8'), 139.5 (s, C-3′), 159.9 (s, C-5′). HRMS *m/z* Calc. for $C_{15}H_{20}NaO_5^+$: 303.1203, found 303.1103 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-2-Methyl-5-styryltetrahydrofuran-3,4-diol (6b)**. Yield: 34 mg (53%, white solid); m.p. 72-74 ^{o}C, R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +49.54 (*c* 0.131, MeOH); IR (ATR): ν 3311(m, OH), 2976 (m), 1450 (m), 1123 (s), 1055 (vs), 964 (vs) cm^{-1}; ^{1}H NMR (300 MHz, (CD$_3$)$_2$CO): δ 1.27 (d, 3H, $J_{Me,2}$ = 6.3 Hz, Me), 3.70 ("t", 1H, J = 5.7 Hz, H-3 or H-4), 3.84 ("qi", 1H, $J_{Me,2}$ = 6.1, $J_{2,3}$ = 5.8 Hz, H-2) 3.90 ("t", 1H, J =5.7 Hz, H-3 or H-4), 4.26 ("bt", 1H, $J_{1',5}$ = 6.3, $J_{4,5}$ = 5.7 Hz, H-5), 6.33 (dd, 1H, $J_{1',2'}$ = 15.9, $J_{1',5}$ = 6.5 Hz, H-1′), 6.67 (d, 1H, $J_{1',2'}$ = 15.9 Hz, H-2′), 7.20-7.36 (m, 3H, Ph), 7.42-7.48 (m, 2H, Ph); ^{13}C NMR (75 MHz, (CD$_3$)$_2$CO): δ 20.5 (q, Me), 77.5, 78.1, 81.1, 86.1 (all d, C-2, C-3, C-4, C-5), 128.3, 129.3, 130.4, 131.1, 132.5 (all d, C-1′, C-2′, Ph), 138.9 (s, *i*-Ph). HRMS *m/z* Calc. for $C_{13}H_{16}NaO_3^+$: 243.0992, found 243.0871 $[M+Na]^+$.

***Z*-(2*S*,3*R*,4*S*,5*R*)-2-Methyl-5-styryltetrahydrofuran-3,4-diol (7b)**. Yield: 17 mg (26%, white solid); m.p. 62-64 ^{o}C, R_f 0.3 (50% AcOEt in hexanes), $[a]_D^{25}$ -42.771 (*c* 0.170, MeOH); IR (ATR): ν 3373 (m, OH), 2970 (m), 1446 (m), 1085 (vs), 979 (vs), 777 (vs) cm^{-1}; ^{1}H NMR (300 MHz, (CD$_3$)$_2$CO): δ 1.25 (d, 3H, $J_{Me,2}$ = 6.1 Hz, Me), 3.70 ("t", 1H, $J_{2,3}$ = 5.8, $J_{3,4}$ = 5.5 Hz, H-3), 3.77 ("qi", 1H, $J_{Me,2}$ = 6.1, $J_{2,3}$ = 5.8 Hz, H-2) 3.95 ("t", 1H, $J_{3,4}$ = 5.5, $J_{4,5}$ = 5.3 Hz, H-4), 4.56 (ddd, 1H, $J_{1',5}$ = 9.3, $J_{4,5}$ = 5.3, J = 0.7 Hz, H-5), 5.67 (dd, 1H, $J_{1',2'}$ = 11.7, $J_{1',5}$ = 9.3 Hz, H-1′), 6.67 (d, 1H, $J_{1',2'}$ = 11.7 Hz, H-2′), 7.22-7.39 (m, 3H, Ph), 7.44-7.50 (m, 2H, Ph); ^{13}C NMR (75 MHz, (CD$_3$)$_2$CO): δ 20.5 (q, Me), 78.1, 78.6, 80.9, 81.3 (all d, C-2, C-3, C-4, C-5), 129.1, 129.9, 130.9, 133.3, 134.1 (all d, C-1′, C-2′, Ph), 138.34 (s, *i*-Ph). HRMS *m/z* Calc. for $C_{13}H_{16}NaO_3^+$: 243.0992, found 243.0947 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(2-Methoxystyryl)-2-methyltetrahydrofuran-3,4-diol (6c)**. Yield: 35 mg (49%); m.p. 130-131 ^{o}C, R_f 0.1 (50% AcOEt in hexanes), $[a]_D^{25}$ +48.3 (*c* 0.197, MeOH); IR (ATR): *v* 3337 (m, OH), 2912 (m), 1596 (m), 1489 (s), 1244 (vs), 968 (vs), 764 (vs) cm^{-1}; ^{1}H NMR (300 MHz, (CD$_3$OD): δ 1.31 (d, 3H, $J_{Me,2}$ = 6.3 Hz, Me), 3.69 ("t", 1H, J = 5.6 Hz, H-3 or H-4), 3.83 (s, 3H, OMe) 3.85-3.95 (m, 2H, H-2, H-3 or H-4), 4.30 ("t", 1H, $J_{1',5}$ = 7.1, $J_{4,5}$ = 5.6 Hz, H-5), 4.61 (bs, 2H, 2 x OH), 6.22 (dd, 1H, $J_{1',2'}$ = 16, $J_{1',5}$ = 7.1 Hz, Hz, H-1′), 6.86-7.02 (m, 3H, H-2′, Ph), 7.22 (dt, 1H, J = 7.7, J = 1.6 Hz, Ph), 7.45 (dd, 1H, J = 7.6, J = 1.4 Hz, Ph); ^{13}C NMR (75 MHz, CD$_3$OD): δ 19.6 (q, Me), 56.0 (O$\underline{\text{Me}}$), 76.9, 77.6, 80.6, 86.2 (all d, C-2, C-3, C-4, C-5), 112.1, 121.7, 127.9, 128.3, 129.5, 130.1(all d, C-1′, C-2′, Ph), 126.7, 158.3 (all s, *i*-Ph). HRMS *m/z* Calc. for $C_{14}H_{18}NaO_4^+$: 273.1097, found 273.0922 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(4-Methoxystyryl)-2-methyltetrahydrofuran-3,4-diol (6d)**. Yield: 44 mg (41%); R_f 0.1 (50% AcOEt in hexanes), $[a]_D^{25}$ +30.5 (*c* 0.203, MeOH); IR (ATR): *v* 3367 (m, OH), 2968 (w), 2930 (w), 1705 (m), 1605 (s), 1511 (vs), 1245 (vs), 1027 (vs), 967 (s) cm^{-1}; ^{1}H

NMR (300 MHz, $(CD_3)_2CO$): δ 1.26 (d, 3H, $J_{Me,2}$ = 6.3 Hz, Me), 1.96 (s, 2H, 2 x OH) 3.68 ("t", 1H, J = 5.7 Hz, H-3 or H-4), 3.76-3.92 (m, 5H, H-2, H-3 or H-4, OMe), 4.22 ("bt", 1H, J = 6.1 Hz, H-5), 6.15 (dd, 1H, $J_{1',2'}$ = 15.9, $J_{1',5}$ =6.8 Hz, H-1´), 6.59 (d, 1H, $J_{1',2'}$= 15.9 Hz, H-2´), 6.89 (d, 2H, J = 8.8Hz, Ph), 7.38 (d, 2H, J = 8.7 Hz, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 56.5 (q, OMe), 77.5, 78.1, 81.0, 86.3 (all d, C-2, C-3, C-4, C-5), 115.8 (d, C-5´, C-7´), 128.6 (d, C-1´or C-2´), 129.5 (d, C-4´, C-8´), 131.4 (s, C-3´), 132.3 (d, C-1´or C-2´), 161.3 (s, C-6´). HRMS *m/z* Calc. for $C_{14}H_{18}NaO_4^+$: 273.1097, found 273.1056 $[M+Na]^+$.

***Z*-(2*S*,3*R*,4*S*,5*R*)-5-(4-Methoxystyryl)-2-methyltetrahydrofuran-3,4-diol (7d)**. Yield: 19 mg (18%); m.p. 124-126 ºC, R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ -45.9 (*c* 0.098, MeOH); IR (ATR): *v* 3326 (m, OH), 2912 (m), 1605 (s), 1509 (s), 1053 (vs), 1008 (vs), 839 (vs) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.24 (d, 3H, $J_{Me,2}$ = 6.1 Hz, Me), 3.65-3.82 (m, 5H, H-2, H-3 or H-4, OMe), 3.93 ("q", 1H, J = 5.3 Hz, H-3 or H-4), 4.12 (d, 1H, J = 5.5 Hz, OH), 4.24 (d, 1H, J = 5.5 Hz, OH), 4.56 (ddd, 1H, $J_{1',5}$ = 9.2, $J_{4,5}$ = 5.1, J = 0.6 Hz, H-5), 5.56 (dd, 1H, $J_{1',2'}$ = 11.6, $J_{1',5}$ = 9.2 Hz, H-1´), 6.58 (d, 1H, $J_{1',2'}$ =11.7 Hz, H-2´), 6.92 (d, 2H, J = 8.8 Hz, Ph), 7.43 (d, 2H, J = 8.7 Hz, Ph);^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 56.5 (q, OMe), 78.1, 78.6, 80.9, 81.5 (all d, C-2, C-3, C-4, C-5), 115.3 (d, C-5´ C-7´), 130.9 (s, C-3´), 131.5, 132.2, 133.7 (all d, C-1´, C-2´, C-4´, C-8´), 161.0 (s, C-6´). HRMS *m/z* Calc. for $C_{14}H_{18}NaO_4^+$: 273.1097, found 273.0960 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(2,4-Dimethoxystyryl)-2-methyltetrahydrofuran-3,4-diol (6e)**. Yield: 60 mg (61%); R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +12.4 (*c* 0.631, MeOH); IR (ATR): *v* 3382 (m, OH), 2966 (m), 2920 (m), 1611 (s), 1499 (s), 1154 (vs), 1030 (vs), 763 (s) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.26 (d, 3H, $J_{Me,2}$ = 6.3 Hz, Me), 3.63-3.71 (m, 1H), 3.74-3.85 (m, 8H, H-2, H-3, H-4, 2 x OMe), 4.21 (dt, 1H, $J_{4,5}$ = $J_{1',5}$ = 6.2, $J_{5,2'}$ = 0.9 Hz, H-5), 6.15 (dd, 1H, $J_{1',2'}$ = 16.0, $J_{1',5}$ = 7.0 Hz, H-1´), 6.50 (dd, 1H, J = 8.4, J = 2.4 Hz, Ph), 6.54 (d, 1H, J = 2.3 Hz, Ph), 6.85 (d, 1H, $J_{1',2'}$ = 16.1 Hz, H-2´), 7.40 (d, 1H, J = 8.4 Hz, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 56.6, 56.8 (2 x q, 2 x OMe), 77.9, 78.1, 80.9, 86.5 (all d, C-2, C-3, C-4, C-5), 99.9 (d, C-5´), 107.0 (d, C-7´), 120.3 (s, C-3´), 127.4, 128.8, 129.3 (all d, C-1´, C-2´, C-8´), 159.8, 162.6 (all s, C-4´, C-6´). HRMS *m/z* Calc. for $C_{15}H_{20}NaO_5^+$: 303.1203, found 303.1262 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(2,5-Dimethoxystyryl)-2-methyltetrahydrofuran-3,4-diol (6f)**. Yield: 63 mg (53%); R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +36.0 (*c* 0.692, MeOH); IR (ATR): *v* 3376 (m, OH), 2928 (m), 1494 (vs), 1219 (vs), 1043 (vs), 1023 (vs), 970 (s) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.27 (d, 3H, $J_{Me,2}$ =6.3 Hz, Me), 3.69 ("t", 1H, J = 5.7 Hz, H-3 or H-4), 3.76, 3.79 (2 x s, 6H, 2 x OMe), 3.83 ("qi", 1H, $J_{Me,2}$ = $J_{2,3}$ = 6.1 Hz, H-2), 3.89 ("t", 1H, J =5.7 Hz, H-3 or H-4), 4.25 (dt, 1H, $J_{1',5}$ = 6.5, $J_{4,5}$ = 5.5, $J_{5,2'}$ = 0.9 Hz, H-5), 6.31 (dd, 1H, $J_{1',2'}$ = 16.1, $J_{1',5}$ = 6.7 Hz, H-1´), 6.80 (dd, 1H, $J_{5'6'}$ = 8.9, $J_{6'8'}$ = 3.0 Hz, C-6´), 6.91 (d, 1H, $J_{5'6'}$ = 8.9 Hz, C-5´), 6.94 (dd, 1H, $J_{1',2'}$ = 15.8, $J_{5,2'}$ = 0.9 Hz, H-2´), 7.08 (d, 1H, $J_{6'8'}$ = 3.0 Hz, C-8´); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 56.8, 57.4 (2 x q, 2 x OMe), 77.4, 78.1, 81.0, 86.5 (all d, C-2, C-3, C-4, C-5), 113.5, 114.2, 115.6 (all d, C-5´, C-6´, C-8´), 127.2 (d, C-1´ or C-2´), 128.2 (s, C-3´), 131.5 (d, C-1´ or C-2´), 153.0, 155.6 (all s, C-4´, C-7´). HRMS *m/z* Calc. for $C_{15}H_{20}NaO_5^+$: 303.1203, found 303.1078 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(2-(Trifluoromethyl)styryl)-2-methyltetrahydrofuran-3,4-diol (6g)**. Yield: 50 mg (41%); R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +51.6 (*c* 0.486, MeOH); IR (ATR): *v* 3376 (w, OH), 2931 (w), 1715 (m), 1312 (vs), 1104 (vs), 1034 (vs), 764 (vs) cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 1.28 (d, 3H, $J_{Me,2}$ = 6.3 Hz, Me), 3.70 ("t", 1H, J = 5.7 Hz, H-3 or H-4), 3.90 ("qi", 1H, $J_{Me,2} = J_{2,3}$ = 6.2 Hz, H-2) 3.95 ("t", 1H, J = 5.3 Hz, H-3 or H-4), 4.35 ("dt", 1H, $J_{1',5} = J_{4,5}$ =5.3, $J_{5,2'}$ =1.3 Hz, H-5), 6.43 (dd, 1H, $J_{1',2'}$ = 15.7, $J_{5,1'}$ = 5.7 Hz, H-1´), 7.06 (dd, 1H, $J_{1',2'}$ = 15.7, $J_{5,2'}$ =1.7 Hz, H-2´), 7.45 (t, 1H, J = 7.6 Hz, Ph), 7.62 (t, 1H, J =7.6 Hz, Ph), 7.70 (d, 1H, J = 7.9 Hz, Ph), 7.81 (d, 1H, J = 7.9 Hz, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.4, (q, Me), 77.5, 78.1, 81.0, 85.6 (all d, C-2, C-3, C-4, C-5), 126.5 (q, $J_{C,F}$ = 272.0 Hz, $\underline{C}F_3$), 127.3 (q, $J_{C,F}$ = 2.1 Hz), 127.5 (q, $J_{C,F}$ = 5.8 Hz), 128.5 (q, $J_{C,F}$ =29.5 Hz, C-4´), 129.3, 129.4 (all d), 134.2 (q, $J_{C,F}$ = 1.0 Hz), 135.9 (d) 137.8 (q, $J_{C,F}$ = 1.6 Hz); HRMS *m/z* Calc. for $C_{14}H_{15}F_3NaO_3^+$: 311.0866, found 311.0709 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(3-(Trifluoromethyl)styryl)-2-methyltetrahydrofuran-3,4-diol (6h)**. Yield: 46 mg (37%); R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +35.6 (*c* 0.438, MeOH); IR (ATR): *v* 3392 (w, OH), 2931 (w), 1705 (m), 1330 (vs), 1119 (vs), 1070 (vs), 978 (s) cm^{-1}; ^1H NMR (300 MHz, $(CDCl_3)$: δ 1.35 (d, 3H, $J_{Me,2}$ = 6.4 Hz, Me), 3.24 (bs, 2H, 2 x OH) 3.78 ("t", 1H, J = 5.6 Hz, H-3 or H-4), 3.89-3.99 (m, 2H, H-2, H-3 or H-4) 4.33 ("t", 1H, $J_{1',5}$ = 6.2, $J_{4,5}$ = 6.0 Hz, H-5),), 6.29 (dd, 1H, $J_{1',2'}$ = 15.9, $J_{1',5}$ = 6.6 Hz, H-1´), 6.72 (d, 1H, $J_{1',2'}$ = 15.9 Hz, H-2´), 7.34-7.54 (m, 3H, Ph), 7.62 (s, 1H, Ph); ^{13}C NMR (75 MHz, $(CDCl_3)$: δ 19.0 (q, Me), 75.5, 76.2, 79.8, 83.8 (all d, C-2, C-3, C-4, C-5), 123.1 (q, $J_{C,F}$ = 3.8 Hz, C-4´ or C-6´), 124.0 (q, $J_{C,F}$ = 272.4 Hz, $\underline{C}F_3$), 124.4 (q, $J_{C,F}$ = 3.8 Hz, C-4´ or C-6´), 129.0, 129.3, 130.9 (all d, C-1´, C-2´, C-8´), 129.7 (q, $J_{C,F}$ = 1.1 Hz, C-7´), 130.9 (q, $J_{C,F}$ = 32.2 Hz, C-5´), 137.0 (s, C-3´). HRMS *m/z* Calc. for $C_{14}H_{15}F_3NaO_3^+$: 311.0866, found 311.0810 $[M+Na]^+$.

***Z*-(2*S*,3*R*,4*S*,5*R*)-5-(3-(Trifluoromethyl)styryl)-2-methyltetrahydrofuran-3,4-diol (7h)**. Yield: 31 mg (25%); m.p. 82-83 ºC, R_f 0.3 (50% AcOEt in hexanes), $[a]_D^{25}$ -32.8 (*c* 0.345, MeOH); IR (ATR): *v* 3371 (m, OH), 2929 (w), 1486 (w), 1443 (m), 1327 (vs), 1118 (vs), 1074 (vs), 806 (s) cm^{-1}; ^1H NMR (300 MHz, $(CDCl_3)$: δ 1.35 (d, 3H, $J_{Me,2}$ = 6.4 Hz, Me), 2.92 (bs, 2H, 2 x OH) 3.74 ("t", 1H, J = 5.8 Hz, H-3 or H-4), 3.81 ("qi", 1H, $J_{Me,2} = J_{2,3}$ = 6.1 Hz, H-2), 3.96 ("t", 1H, J = 6.0 Hz, H-3 or H-4) 4.46 (dd, 1H, $J_{1',5}$ = 9.3, $J_{4,5}$ = 5.9 Hz, H-5), 5.73 (dd, 1H, $J_{1',2'}$ = 11.6, $J_{1',5}$ = 9.3 Hz, H-1´), 6.75 (d, 1H, $J_{1',2'}$ = 11.6 Hz, H-2´), 7.40-7.70 (m, 4H, Ph); ^{13}C NMR (75 MHz, $(CDCl_3)$: δ 18.9 (q, Me), 75.8, 76.3, 79.0, 79.7 (all d, C-2, C-3, C-4, C-5), 124.0 (q, $J_{C,F}$ = 272.3 Hz, $\underline{C}F_3$), 124.2 (q, $J_{C,F}$ = 3.8 Hz, C-4´ or C-6´), 125.7 (q, $J_{C,F}$ = 3.8 Hz, C-4´ or C-6´), 130.6 (q, $J_{C,F}$ = 32.2 Hz, C-5´) 132.1 (q, $J_{C,F}$ = 1.1 Hz, C-7´), 128.7, 131.1, 132.9 (all d, C-1´, C-2´, C-8´), 136.6 (s, C-3´). HRMS *m/z* Calc. for $C_{14}H_{15}F_3NaO_3^+$: 311.0866, found 311.0699 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(4-Bromostyryl)-2-methyltetrahydrofuran-3,4-diol (6i)**. Yield: 71 mg (56%, white solid); m.p. 139-140 ºC, R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +49.9 (*c* 0.593, MeOH); IR (ATR): *v* 3348 (m, OH), 3287 (m, OH), 2918 (m), 1487 (m), 1125 (s), 1054 (vs), 971 (vs), 841 (vs) cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 1.26 (d, 3H, $J_{Me,2}$ = 6.3 Hz, Me), 3.70 ("t", 1H, J = 5.7 Hz, H-3 or H-4), 3.84 ("qi", 1H, $J_{Me,2} = J_{2,3}$ = 6.1Hz, H-2) 3.89 ("t", 1H, J = 5.7

Hz, H-3 or H-4), 4.25("bt", 1H, $J_{1',5} = J_{4,5} = 6.4$ Hz, H-5), 6.37 (dd, 1H, $J_{1',2'} = 15.9$, $J_{1',5} = 6.4$ Hz, H-1´), 6.64 (d, 1H, $J_{1',2'} = 16.0$ Hz, H-2´), 7.41 (d, 2H, $J = 8.5$ Hz, Ph), 7.50 (d, 2H, $J = 8.6$ Hz, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 77.4, 78.1, 81.2, 85.9 (all d, C-2, C-3, C-4, C-5), 122.5 (s, C-6´), 130.1 (d, C-4´, C-8´), 131.1, 132.2 (all d, C-1´, C-2´), 133.4 (d, C-5´, C-7´), 138.1 (s, C-3´). HRMS *m/z* Calc. for $C_{13}H_{15}BrNaO_3^+$: 321.0097, found 321.0057 $[M+Na]^+$.

***Z*-(2*S*,3*R*,4*S*,5*R*)-5-(4-Bromostyryl)-2-methyltetrahydrofuran-3,4-diol (7i)**. Yield: 45 mg (35%, white solid); m.p. 100-102 ºC, R_f 0.3 (50% AcOEt in hexanes), $[a]_D^{25}$ -52.9 (*c* 0.413, MeOH); IR (ATR): *v* 3375 (m, OH), 2917 (m), 1585 (w), 1486 (s), 1070 (vs), 1006 (vs), 836 (vs), 717 (s) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.24 (d, 3H, $J_{Me,2} = 6.1$ Hz, Me), 3.71 ("t", 1H, $J_{2,3} = J_{3,4} = 5.7$ Hz, H-3), 3.79 (dq, 1H, $J_{Me,2} = 6.1$, $J_{2,3} = 5.7$ Hz, H-2), 3.95 (dd, 1H, $J_{3,4} = 5.7$, $J_{4,5} = 5.4$ Hz, H-4), 4.50 (ddd, 1H, $J_{1',5} = 9.3$, $J_{4,5} = 5.4$, $J_{2',5} = 0.6$ Hz, H-5), 5.72 (dd, 1H, $J_{1',2'} = 11.7$, $J_{1',5,} = 9.3$ Hz, H-1´), 6.63 (bd, 1H, $J_{1',2'} = 11.7$ Hz, H-2´), 7.43 (d, 2H, $J = 8.5$ Hz, Ph), 7.53 (d, 2H, $J = 8.5$ Hz, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 78.0, 78.4, 81.0, 81.1 (all d, C-2, C-3, C-4, C-5), 122.7 (s, C-6´), 132.8, 132.9, 133.0, 134.2 (all d, C-1´, C-2´, C-4´, C-5´, C-7´, C-8´), 137.5 (s, C-3´). HRMS *m/z* Calc. for $C_{13}H_{15}BrNaO_3^+$: 321.0097, found 321.0095 $[M+Na]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(2-Fluorostyryl)-2-methyltetrahydrofuran-3,4-diol (6j)**. Yield: 44 mg (35%, white solid); m.p. 47-49 ºC, R_f 0.3 (50% AcOEt in hexanes), $[a]_D^{25}$ +44.9 (*c* 0.274, MeOH); IR (ATR): *v* 3327 (m, OH), 2980 (m), 2921(m), 1658 (w), 1487 (s), 1453 (s), 1231 (s), 1055 (vs), 967 (vs), 764 (vs) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.28 (d, 3H, $J_{Me,2} = 6.3$ Hz, Me), 3.70 ("t", 1H, $J = 5.6$ Hz, H-3 or H-4), 3.86 ("qi", 1H, $J_{Me,2} = J_{2,3} = 6.2$ Hz, H-2), 3.91 ("t", 1H, $J = 5.7$ Hz, H-3 or H-4) 4.29 (bt, 1H, $J_{1',5} = J_{4,5} = 5.8$ Hz, H-5), 6.45 (dd, 1H, $J_{1',2'} = 16.1$, $J_{1',5} = 6.2$ Hz, H-1´), 6.81 (bd, 1H, $J_{1',2'} = 16.1$ Hz, H-2´), 7.04-7.20 (m, 2H, Ph), 7.24-7.34 (m, 1H, Ph), 7.61 (dt, 1H, $J = 7.8$, $J = 1.6$ Hz, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 77.4, 78.1, 81.2, 86.0 (all d, C-2, C-3, C-4, C-5), 117.4 (d, $J_{C,F} = 22.2$ Hz, C-5´), 124.2 (d, $J_{C,F} = 3.9$ Hz, C-7´), 126.3 (d, $J_{C,F} = 3.5$ Hz, C-1´), 126.4 (d, $J_{C,F} = 11.2$ Hz, C-3´), 129.4 (d, $J_{C,F} = 3.7$ Hz, C-8´), 130.9 (d, $J_{C,F} = 8.5$ Hz, C-6´), 134.0 (d, $J_{C,F} = 4.6$ Hz, C-2´), 162.0 (d, $J_{C,F} = 247.3$ Hz, C-4´) HRMS *m/z* Calc. for $C_{13}H_{16}FO_3^+$: 239.1078, found 239.1034 $[M+H]^+$.

***E*-(2*S*,3*R*,4*S*,5*R*)-5-(4-Fluorostyryl)-2-methyltetrahydrofuran-3,4-diol (6k)**. Yield: 42 mg (30%, white solid); m.p. 116-119ºC, R_f 0.2 (50% AcOEt in hexanes), $[a]_D^{25}$ +47.7 (*c* 0.239, MeOH); IR (ATR): *v* 3288 (m, OH), 2924 (m), 1657 (w), 1603 (s), 1508 (vs), 1230 (vs), 1055 (vs), 970 (vs), 832 (vs) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.26 (d, 3H, $J_{Me,2} = 6.3$ Hz, Me), 3.67 ("t", 1H, $J = 5.7$ Hz, H-3 or H-4), 3.83 ("qi", 1H, $J_{Me,2} = J_{2,3} = 6.0$ Hz, H-2), 3.89 ("t", 1H, $J = 5.6$ Hz, H-3 or H-4) 4.20 (dt, 1H, $J_{1',5} = J_{4,5} = 6.0$, $J_{2',5} = 0.9$ Hz, H-5), 6.27 (dd, 1H, $J_{1',2'} = 15.9$, $J_{1',5} = 6.5$ Hz, Hz, H-1´), 6.66 (bd, 1H, $J_{1',2'} = 15.9$ Hz, H-2´), 7.05-7.14 (m, 2H, Ph), 7.46-7.53 (m, 2H, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 20.5 (q, Me), 77.4, 78.1, 81.1, 86.0 (all d, C-2, C-3, C-4, C-5), 117.1 (d, $J_{C,F} = 21.7$ Hz, C-5´, C-7´), 130.0 (d, $J_{C,F} = 8.1$ Hz, C-4´, C-8´), 131.0 (d, $J_{C,F} = 2.2$ Hz, C-2´), 131.2 (d, C-1´), 135.3 (s, $J_{C,F} = 3.2$ Hz, C-3´), 164.0 (d, $J_{C,F} = 244.7$ Hz, C-6´). HRMS *m/z* Calc. for $C_{13}H_{15}FNaO_3^+$: 261.0897, found 261.0867 $[M+Na]^+$.

***Z*-(2*S*,3*R*,4*S*,5*R*)-5-(4-Fluorostyryl)-2-methyltetrahydrofuran-3,4-diol (7k)**. Yield: 11 mg (8%, white solid); m.p. 70-73 °C, R_f 0.3 (50% AcOEt in hexanes), $[a]_D^{25}$ -34.9 (*c* 0.126, MeOH); IR (ATR): *v* 3458 (m, OH), 3323 (m, OH), 2978 (m), 2903 (m), 1602 (m), 1505 (s), 1220 (vs), 1086 (vs), 982 (vs), 848 (vs), cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.24 (d, 3H, $J_{Me,2}$ = 6.2 Hz, Me), 3.71 ("t", 1H, *J* = 5.8 Hz, H-3 or H-4), 3.77 ("qi", 1H, $J_{Me,2}$= $J_{2,3}$ = 6.1 Hz, H-2), 3.95 ("t", 1H, *J* = 5.4 Hz, H-3 or H-4) 4.50 (dt, 1H, $J_{1',5}$ = 9.3, $J_{4,5}$ = 5.4 Hz, H-5), 5.67 (dd, 1H, $J_{1',2'}$ = 11.7, $J_{1',5}$ = 9.3 Hz, H-1´), 6.65 (d, 1H, $J_{1',2'}$ = 11.7 Hz, H-2´), 7.08-7.16 (m, 2H, Ph), 7.40-7.55 (m, 2H, Ph); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): *δ* 20.5 (q, Me), 78.0, 78.4, 81.0, 81.1 (all d, C-2, C-3, C-4, C-5), 116.7 (d, $J_{C,F}$ = 21.5 Hz, C-5´, C-7´), 132.8 (d, $J_{C,F}$ = 8.0 Hz, C-4´, C-8´), 133.0 (d, C-1´), 133.3 (d, $J_{C,F}$ = 1.2 Hz, C-2´), 134.7 (s, $J_{C,F}$ = 3.3 Hz, C-3´) 163.9 (s, $J_{C,F}$ = 244.8 Hz, C-6´). HRMS *m/z* Calc. for $C_{13}H_{15}FNaO_3^+$: 261.0897, found 261.0813 $[M+Na]^+$.

Cytotoxic MTT assay[21,22]

1. All cells were purchased from the American Tissue Culture Collection (ATCC), unless otherwise indicated: the CCRF-CEM line are highly chemosensitive T-lymphoblastic leukemia cells, K562 cells were derived from patient with acute myeloid leukemia with bcr-abl translocation, A549 line is lung adenocarcinoma, HCT116 is colorectal tumor cell line and its p53 gene knock-down counterpart (HCT116p53-/-, Horizon Discovery, UK) is a model of human cancers with p53 mutation frequently associated with poor prognosis. The daunorubicin resistant subline of CCRF-CEM cells (CEM-DNR bulk) and paclitaxel resistant subline K562-tax were selected in our laboratory by the cultivation of maternal cell lines in increasing concentrations of daunorubicine or paclitaxel, respectively.[22] The CEM-DNR bulk cells overexpress MRP-1 protein, while K562-tax cells overexpress P-glycoprotein, both proteins belong to family of ABC transporters and are involved in primary and/or acquired multidrug resistance phenomenon.[22] The cells were maintained in Nunc/Corning 80 cm^2 plastic tissue culture flasks and cultured in cell culture medium (DMEM/RPMI 1640 with 5 g/L glucose, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, 10 % fetal calf serum, and $NaHCO_3$).

2. Cell suspensions were prepared and diluted according to the particular cell type and the expected target cell density (2 500–30 000 cells/well based on cell growth characteristics). Cells were added by pipette (80 μL) into 96-well microtiter plates. Inoculates were allowed a pre-incubation period of 24 h at 37 °C and 5 % CO_2 for stabilisation. Four-fold dilutions, in 20-μL aliquots, of the intended test concentration were added to the microtiter plate wells at time zero. All test compound concentrations were examined in duplicate. Incubation of the cells with the test compounds lasted for 72 h at 37 °C, in a 5 % CO_2 atmosphere at 100 % humidity. At the end of the incubation period, the cells were assayed using MTT. Aliquots (10 μL) of the MTT stock solution were pipetted into each well and incubated for a further 1–4 h. After this incubation period the formazan produced was dissolved by the addition of 100 μL/well of 10 % aq SDS (pH = 5.5), followed by a further incubation at 37 °C overnight. The optical density (OD) was measured at 540 nm with a Labsystem iEMS Reader MF. Tumour cell survival (TCS) was

calculated using the following equation: TCS = ($OD_{drug\text{-}exposed\ well}$ / mean $OD_{control\ wells}$) x 100 %. The TCS_{50} value, the drug concentration lethal to 50 % of the tumour cells, was calculated from appropriate dose-response curves.

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