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 NCI60 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 isolated2 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, GI₅₀ = 1.63 x 10⁻⁷ M), TD-47 (breast cancer, GI₅₀ = 2.10 x 10⁻⁷ M), and SNB (CNS cancer, GI₅₀ = 2.44 x 10⁻⁷ M) cell lines and lower potency against the DU-145 (prostate cancer, GI₅₀ = 1.10 x 10⁻⁶ M), HL-60 (TB) (leukaemia, GI₅₀ = 2.52 x 10⁻⁵ M), CCRF-CEM (leukaemia, GI₅₀ = 2.60 x 10⁻⁵ M), OVCAR-5 (ovarian cancer, GI₅₀ = 6.82 x 10⁻⁵ M), SNB-19 (CNS cancer, GI₅₀ = 9.13 x 10⁻⁵ M), and COLO 205 (colon cancer, GI₅₀ = 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\(^7\text{c}\) 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-butylidimethylsilyl chloride followed by partial reduction of the lactone 12 using DIBAL (2 equiv) in THF at -50 °C, acetylation 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, Et3N, DMAP, DMF, rt, 8 h, 95%; (b) DIBAL, THF, -50 °C, 4 h; (c) Ac2O, DMAP, CH2Cl2, 0 °C to rt, 12 h; (d) Me3Al, CH2Cl2, -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, PPh3, DIAD, THF, 0 °C, 1 h, 16 (85%), 18 (94%); (g) Mo(VI)/H2O2, 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\textsuperscript{16,17} with PTSH (2 equiv), Ph\textsubscript{3}P (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\textsuperscript{18} with the aldehyde 9a\textsuperscript{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.\textsuperscript{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.

\begin{align*}
\text{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.}
\end{align*}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Aldehyde & 6/7 (% yield)\textsuperscript{a} & 6 (% yield)\textsuperscript{b} & 7 (% yield)\textsuperscript{b} \\
\hline
1 & 9a & 76 & 56 & 14 \\
2 & 9b & 88 & 53 & 26 \\
3 & 9c & 80 & 49 & 3 \\
4 & 9d & 59 & 41 & 18 \\
5 & 9e & 61 & 61 & - \\
\hline
\end{tabular}
\caption{Formation of olefins 6a-k and 7a-k by reaction of sulfone 8 with aldehydes 9a-k}
\end{table}
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\textsuperscript{7c} gave 2-epi-varitriol 5 as a mixture of E/Z-isomers in the ratio 5:4.

![Scheme 4]

\textbf{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).

\textbf{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\textsuperscript{+/+}, HCT116p53\textsuperscript{-/-}), 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 cells\textsuperscript{M}. The determined activities were expressed as IC\textsubscript{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) \textit{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

| Entry | Aldehyde | 6/7 (% yield)\textsuperscript{a} | 6 (% yield)\textsuperscript{b} | 7 (% yield)\textsuperscript{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                             |

\textsuperscript{a}Combined yield of isolated 6 and 7. \textsuperscript{b}Isolated yield of pure isomers.
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. 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 NCI60 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 GI50 when evaluated against NCI60 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. | 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 >166 153 >166 >166 >166 >166 |
| 7a    | 121      | 163  | 158  | >166     | 132          | 111          | >166       | >166  | >166|
| 6b    | 145      | >166 | >166 | >166     | 151          | >166         | >166       | >166  | >166|
| 7b    | 160      | >166 | >166 | >166     | 149          | >166         | >166       | >166  | >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. | 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 | >166 | >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 IC₅₀ 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 NCI₆₀ 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 °C. 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 F254 (ALUGRAM® SIL G/UV254, Macherey-Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H2SO4 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 cm² 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). 1H and 13C 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.

2,3-0-Isopropylidene-5-O-tert-butyldimethylsilyl-γ-D-ribohalactone (12). To a solution of γ-D-ribohalactone (1.5 g, 7.97 mmol) in dry DMF (25 mL) were successively added Et3N (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 MgSO4 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: Rf 0.4 (15% AcOEt in hexanes), [α]25° -48.8 (c 0.221, CHCl3); IR (ATR): ν 2954 (m), 2929 (m), 1772 (vs, CO), 1107 (vs), 1077 (vs), 837 (vs) cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 0.06, 0.08 (2 x s, 6H, Si(CH3)2), 0.88 (s, 9H, C(CH3)3), 1.39, 1.48 (2 x s, 6H, C(CH3)2), 3.80 (dd, 1H, A of ABX, J5,5B = 11.3, J5,4,4 = 1.4Hz, H-5A), 3.90 (dd, 1H, B of ABX, J5,4A = 11.3, J5B,4 = 2.1Hz, H-5B) 4.61 (dd, 1H, J5B,4 = 1.8, J5A,4 = 1.5 Hz, H-4) 4.71 (d, 1H, J2,3 = 5.6 Hz, H-2 or H-3), 4.74 (d, 1H, J2,3 = 5.6 Hz, H-2 or H-3); 13C NMR (75 MHz, CDCl3): δ - 5.8, -5.6 (all q, Si(CH3)2), 18.2 (s, C(CH3)3), 25.6, 25.7, 26.8 (all q, C(CH3)2 C(CH3)3), 63.0 (t, C-5), 75.8, 78.4, 82.3 (all d, C-2, C-3, C-4), 113.0 (s, C(CH3)2), 174.1 (s, C-1). HRMS m/z Calc. for C14H26NaO5Si+: 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 MgSO4 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 Ac2O (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, Me₃Al (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: Rf 0.6 (10% AcOEt in hexanes), [α]D° -5.5 (c 0.217, CHCl₃); IR (ATR): ν 2954 (m), 2929 (s), 2858 (m), 1381 (m), 1253 (s), 1073 (s), 833 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.06, 0.07 (2 x s, 6H, Si(CH₃)₂), 0.90 (s, 9H, C(CH₃)₃), 1.28 (d, 3H, J₅,₆ = 6.4 Hz, H-6), 1.34, 1.53 (2 x s, 6H, C(CH₃)₂), 3.72 (dd, 2H, J₁,₂ = 3.9, J = 0.8 Hz, H-1), 3.95-4.01 (m, 2H, H-2, H-5) 4.21 (dd, 1H, J₃,₄ = 6.6, J = 5.0 Hz, H-3 or H-4) 4.64 (dd, 1H, J₃,₄ = 6.7, J = 3.6 Hz, H-3 or H-4); ¹³C NMR (75 MHz, CDCl₃): δ -5.4, -5.3 (all q, Si(CH₃)₂), 18.4 (s, C(CH₃)₃), 19.1, 25.5, 25.9, 27.5 (all q, C-6, C(CH₂)₂, C(CH₃)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, C(CH₃)₂). HRMS m/z Calc. for C₁₅H₃₀NaO₄Si⁺: 325.1806, found 325.1703 [M+Na]⁺.

2,5-Anhydro-6-deoxy-3,4-O-isopropylidene-1-O-tertbutyldimethylsilyl-d-talitol (14).
Selected data: Rf 0.5 (10% AcOEt in hexanes), [α]D° -9.1 (c 0.219, CHCl₃); IR (ATR): ν 2954 (m), 2929 (s), 2856 (m), 1379 (m), 1254 (s), 1086 (s), 834 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.05, 0.06 (2 x s, 6H, Si(CH₃)₂), 0.89 (s, 9H, C(CH₃)₃), 1.27 (d, 3H, J₅,₆ = 6.4 Hz, H-6), 1.36, 1.51 (2 x s, 6H, C(CH₃)₂), 3.69 (d, 2H, J₁,₂ = 4.0 Hz, H-1), 4.04 (t, 1H, J₁,₂ = 4.0 Hz, H-2), 4.20 (dq, 1H, J₅,₆ = 6.4, J₄,₅ = 4.1 Hz, H-5), 4.58 (dd, 1H, J₃,₄ = 6.1, J₄,₅ = 4.0 Hz, H-4), 4.81 (dd, 1H, J₃,₄ = 6.1, J₂,₃ = 0.5 Hz, H-3); ¹³C NMR (75 MHz, CDCl₃): δ -5.6, -5.5 (all q, Si(CH₃)₂), 14.6 (q, C-6) 18.1 (s, C(CH₃)₃), 25.1, 25.8, 26.3 (all q, C(CH₂)₂, C(CH₃)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, C(CH₃)₂). HRMS m/z Calc. for C₁₅H₃₄NO₄Si⁺: 320.2252, found 320.2096 [M+NaH]⁺.

2,5-Anhydro-6-deoxy-3,4-O-isopropylidene-l-allitol (15).
Tetraethyl 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 then concentrated and purified by flash chromatography (15% EtOAc in hexanes), yielding 15 (482 mg, 89%) as a colourless oil. Selected data: Rf 0.1 (10% AcOEt in hexanes), [α]D° +8.5 (c 0.743, CHCl₃); IR (ATR): ν 3334 (s, OH), 2925 (m), 1456 (m), 1082 (s), 1035(s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.32 (d, 3H, J₅,₆ = 6.4 Hz, H-6), 1.34, 1.54 (2 x s, 6H, C(CH₃)₂), 2.20 (bs, 1H, OH), 3.67 (dd, 1H, A of ABX, J₁A,₁B = 11.7, J₁A,₂ = 3.1 Hz, H-1A), 3.82 (dd, 1H, B of ABX, J₁A,₁B = 11.9, J₁B,₂ = 3.1 Hz, H-1B), 3.94-4.04 (m, 2H, H-2, H-5), 4.23 (dd, 1H, J₃,₄ = 6.9, J = 5.2 Hz, H-3 or H-4) 4.62 (dd, 1H, J₃,₄ = 7.0, J = 4.5 Hz, H-3 or H-4); ¹³C NMR (75 MHz, CDCl₃): δ 18.8, 25.4, 27.3 (all q, C-6, C(CH₂)₃), 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, C(CH₃)₂). HRMS m/z Calc. for C₉H₁₇O₄⁺: 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 (605 g, 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: $R_t$ 0.1 (10% AcOEt in hexanes), $[a]_D^{25} +5.0$ (c 0.240, CHCl$_3$); IR (ATR): $\nu$ 3412 (m, OH), 2986 (m), 2936 (m), 1732 (m), 1374 (s), 1208 (vs), 1032 (vs), 872 (vs) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.32 (d, 3H, $J_{3,6} = 6.3$ Hz, H-6), 1.35, 1.52 (2 x s, 6H, C($CH_3)_2$), 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$_3$): $\delta$ 14.2 (q, C-6), 25.1, 26.3 (all q, C($CH_3)_2$), 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, C($CH_3)_2$). HRMS $m/z$ Calc. for C$_9$H$_{17}$O$_4$: 189.1121, found 189.1127 [M+H]$^+$. 

2,5-Anhydro-1,6-dideoxy-3,4-O-isopropylidene-1-(1-phenyl-1H-tetrazol-5-ylsulfanyl)-L-allitol (16). 1-Phenyl-1H-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$_4$NaO$_3$S$: 371.1148, found 371.1187 [M+Na]$^+$. The physical and spectral data of 16 were in accord with the literature.$^7c$

2,5-Anhydro-1,6-dideoxy-3,4-O-isopropylidene-1-(1-phenyl-1H-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: $R_t$ 0.6 (50% AcOEt in hexanes), $[a]_D^{25} +24.9$ (c 0.205, CHCl$_3$); IR (ATR): $\nu$ 2982 (m), 2934 (m), 1596 (m), 1499 (vs), 1382 (vs), 1084 (vs), 1012 (vs), 761 (vs) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.29 (d, 3H, $J_{3,6} = 6.3$ Hz, H-6), 1.34, 1.49 (2 x s, 6H, C($CH_3)_2$), 3.53 (d, 2H, $J_{1,2} = 7.6$ Hz, H-1), 4.07 (dq, 1H, $J_{1,6} = 6.3$, $J_{4,5} = 3.5$ 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$_3$): $\delta$ 13.7 (q, C-6), 25.2, 26.3 (all q, C($CH_3)_2$), 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, C($CH_3)_2$), 123.9, 129.8, 130.2 (all d), 135.5, 153.9 (all s, i-Ph, i-Tetr). HRMS $m/z$ Calc. for C$_{16}$H$_{20}$N$_4$NaO$_3$S$: 371.1148, found 371.1177 [M+Na]$^+$. 

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

2,5-Anhydro-1,6-dideoxy-3,4-O-isopropylidene-1-(1-phenyl-1H-tetrazol-5-ylsulfanyl)-d-talitol (19). Prepared by Mo(IV)/H$_2$O$_2$ 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; $R_t$ 0.6 (50% AcOEt in hexanes), $[a]_D^{25} +82.5$ (c 0.147, CHCl$_3$); IR (ATR): $\nu$ 2990 (m), 2971 (m), 2934 (m), 1496 (s), 1349 (vs), 1152 (vs), 1075 (vs), 772 (vs) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.07 (d, 3H, $J_{3,6} = 6.3$ Hz, H-6), 1.31, 1.45 (2 x s, 6H, C($CH_3)_2$), 3.48 (dd, 1H, A of ABX, $J_{1A,1B} = 15$, $J_{1A,2} = 3.5$ Hz, H-1A), 3.80 (dq, 1H, $J_{1,6} = 6.2$, $J_{4,5} = 3.1$ 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, CDCl3): δ 13.2 (q, C-6), 25.0, 26.1 (all q, C(CH3)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, C(CH3)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 C16H20NaO3S+: 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 Na2CO3 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, 6a, 7a 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); $R_t$ 0.3 (50% AcOEt in hexanes), $[a]_D^{25} +34.5$ (c 0.568, MeOH); IR (ATR): ν 3390 (m, OH), 2933 (m), 1722 (m), 1577 (s), 1262 (vs), 1000 (vs), 752 (s) cm$^{-1}$; $^1$H NMR (300 MHz, (CD3)$_2$CO): δ 1.53 (d, 3H, JMe$_{e,2}$ = 6.5 Hz, Me, minor), 2.12 (d, 3H, JMe$_{e,2}$ = 6.5 Hz, Me, major), 3.82 (s, 3H, OMe, major), 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$_{2,3}$ = 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, (CD3)$_2$CO): δ 16.4, 16.6 (all q, Me), 56.4 (t, CH$_2$OH), 56.9, 57.0 (all q, OMe), 57.0 (t, CH$_2$OH), 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 C13H20NaO3S+: 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.  

**Z-Varitriol (7a).** Yield: 11 mg (14%, white solid); m.p. 126-130 °C, $R_t$ 0.2 (50% AcOEt in hexanes), $[a]_D^{25} +22.5$ (c 0.129, MeOH); IR (ATR): ν 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$_3$)$_2$CO): δ 1.21 (d, 3H, 7c
**E-(2S,3R,4S,5R)-2-MethyI-5-styryltetrahydrofuran-3,4-diol (6b).** Yield: 34 mg (53%, white solid); m.p. 72-74 °C, Rf 0.2 (50% AcOEt in hexanes), $\left[a\right]_D^{\text{20}} +49.54$ (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, Me), 3.70 (“t”, 1H, $J = 5.7$ Hz, H-3 or H-4), 3.84 (“qi”, 2H, J$_{Me,2}$ = 6.3 Hz, Me), 3.90 (“t”, 1H, $J = 5.7$ Hz, H-3 or H-4), 4.26 (“bt”, 1H, J$_{1:1}$ = 6.3, J$_{4:5}$ = 5.7 Hz, H-5), 5.63 (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-(2S,3R,4S,5R)-2-MethyI-5-styryltetrahydrofuran-3,4-diol (7b).** Yield: 17 mg (26%, white solid); m.p. 62-64 °C, Rf 0.3 (50% AcOEt in hexanes), $\left[a\right]_D^{\text{20}} -42.77$ (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, Me), 3.70 (“t”, 1H, $J = 5.5$ 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 (dd, 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), 138.4 (s, i-Ph). HRMS m/z Calc. for C$_{13}$H$_{16}$NaO$_3$: 243.0992, found 243.0947 [M+Na]$^+$. 

**E-(2S,3R,4S,5R)-5-(2-Methoxy styryl)-2-methyltetrahydrofuran-3,4-diol (6c).** Yield: 35 mg (49%); m.p. 130-131 °C, Rf 0.1 (50% AcOEt in hexanes), $\left[a\right]_D^{\text{20}} +48.3$ (c 0.197, MeOH); IR (ATR): ν 3337 (m, OH), 2912 (m), 1596 (m), 1489 (s), 1244 (vs), 968 (vs), 764 (vs) cm$^{-1}$; $^1$H NMR (300 MHz, (CD$_3$)$_2$OD): δ 1.31 (d, 3H, 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, 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$_3$)$_2$OD): δ 19.6 (q, Me), 56.0 (OMe), 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$_{13}$H$_{18}$O$_4$: 273.1097, found 273.0922 [M+Na]$^+$. 

**E-(2S,3R,4S,5R)-5-(4-Methoxy styryl)-2-methyltetrahydrofuran-3,4-diol (6d).** Yield: 44 mg (41%); Rf 0.1 (50% AcOEt in hexanes), $\left[a\right]_D^{\text{20}} +30.5$ (c 0.203, MeOH); IR (ATR): ν 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$_3$)$_2$CO): $\delta$ 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$_3$)$_2$CO): $\delta$ 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-(2S,3R,4S,5R)-5-(4-Methoxystyryl)-2-methyltetrahydrofuran-3,4-diol (7d). Yield: 19 mg (18%); m.p. 124-126 °C, $R_f$ 0.2 (50% AcOEt in hexanes), $[\alpha]_D^{25}$ -42.9 (c 0.098, MeOH); IR (ATR): $\nu$ 3326 (m, OH), 2912 (m), 1605 (s), 1590 (s), 1053 (vs), 1008 (vs), 839 (vs) cm$^{-1}$; $^1$H NMR (300 MHz, (CD$_3$)$_2$CO): $\delta$ 1.26 (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$_{1,5}$ = 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 (dd, 1H, J$_{1,5}$ = 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$_3$)$_2$CO): $\delta$ 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-(2S,3R,4S,5R)-5-(4-Methoxystyryl)-2-methyltetrahydrofuran-3,4-diol (6e). Yield: 60 mg (61%); $R_f$ 0.2 (50% AcOEt in hexanes), $[\alpha]_D^{25}$ +12.4 (c 0.631, MeOH); IR (ATR): $\nu$ 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$_3$)$_2$CO): $\delta$ 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$_{4,5}$ = 6.2, J$_{5,2}$ = 0.9 Hz, H-5), 6.64 (dd, 1H, J$_{1,2}$ = 16.0, J$_{1,5}$ = 7.0 Hz, H-1’), 6.54 (dd, 1H, J = 8.4, J = 2.4 Hz, Ph), 6.54 (d, 1H, J = 2.3 Hz, Ph), 5.99 (d, 1H, J$_{1,2}$ = 16.1 Hz, H-2’), 7.44 (d, 1H, J = 8.4 Hz, Ph);$^{13}$C NMR (75 MHz, (CD$_3$)$_2$CO): $\delta$ 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’), 107.9 (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$_{14}$H$_{20}$NaO$_4$+: 303.1203, found 303.1262 [M+Na]$^+$. 

E-(2S,3R,4S,5R)-5-(2,5-Dimethoxystyryl)-2-methyltetrahydrofuran-3,4-diol (6f). Yield: 63 mg (53%); $R_f$ 0.2 (50% AcOEt in hexanes), $[\alpha]_D^{25}$ +36.0 (c 0.692, MeOH); IR (ATR): $\nu$ 3376 (m, OH), 2928 (m), 1494 (vs), 1219 (vs), 1043 (vs), 1023 (vs), 970 (s) cm$^{-1}$; $^1$H NMR (300 MHz, (CD$_3$)$_2$CO): $\delta$ 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 (“q’”, 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$_3$)$_2$CO): $\delta$ 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]$^+$. 

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E-(2S,3R,4S,5R)-5-(2-(Trifluoromethyl)styryl)-2-methyltetrahydrofuran-3,4-diol  (6g). Yield: 50 mg (41%); Rf 0.2 (50% AcOEt in hexanes), [a]D 25 +51.6 (c 0.486, MeOH); IR (ATR): ν 3376 (w, OH), 2931 (w), 1715 (m), 1312 (vs), 1104 (vs), 1034 (vs), 764 (vs) cm⁻¹; 1H NMR (300 MHz, (CD₃)₂CO): δ 1.28 (d, 3H, J₉,₂ = 6.3 Hz, Me), 3.70 (“t”, 1H, J = 5.7 Hz, H-3 or H-4), 3.90 (“q”, 1H, J₉,₂ = J₂,₃ = 6.2 Hz, H-2) 3.95 (“t”, 1H, J = 5.3 Hz, H-3 or H-4), 4.35 (“dt”, 1H, J₁,₂ = J₄,₅ = 5.3, J₅,₂ = 1.3 Hz, H-5), 6.43 (dd, 1H, J₁,₂ = 15.7, J₅,₁ = 5.7 Hz, H-1), 7.06 (dd, 1H, J₁,₂ = 15.7, J₅,₂ = 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); 13C NMR (75 MHz, (CD₃)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, JCF = 270.2 Hz, CF₃), 127.3 (q, JCF = 2.1 Hz), 127.5 (q, JCF = 5.8 Hz), 128.5 (q, JCF = 29.5 Hz, C-4'), 129.3, 129.4 (all d), 134.2 (q, JCF = 1.0 Hz), 135.9 (d) 137.8 (q, JCF = 1.6 Hz); HRMS m/z Calc. for C₁₄H₁₃F₃NaO₃⁺: 311.0866, found 311.0709 [M+Na]⁺

E-(2S,3R,4S,5R)-5-(3-(Trifluoromethyl)styryl)-2-methyltetrahydrofuran-3,4-diol  (6h). Yield: 46 mg (37%); Rf 0.2 (50% AcOEt in hexanes), [a]D 25 +35.6 (c 0.438, MeOH); IR (ATR): ν 3392 (w, OH), 2931 (w), 1705 (m), 1330 (vs), 1119 (vs), 1070 (vs), 978 (s) cm⁻¹; 1H NMR (300 MHz, (CDCl₃): δ 1.35 (d, 3H, J₉,₂ = 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-3 or H-4) 4.33 (“t”, 1H, J₁,₂ = 6.2, J₅,₁ = 6 Hz, H-5'), 6.29 (dd, 1H, J₁,₂ = 15.9, J₅,₁ = 6.6 Hz, H-1'), 6.72 (d, 1H, J₁,₂ = 15.9 Hz, H-2'), 7.34-7.54 (m, 3H, Ph), 7.62 (s, 1H, Ph); 13C NMR (75 MHz, (CDCl₃): 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, JCF = 3.8 Hz, C-4' or C-6'), 124.0 (q, JCF = 272.4 Hz, CF₃), 124.4 (q, JCF = 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, JCF = 1.1 Hz, C-7'), 130.9 (q, JCF = 32.2 Hz, C-5'), 137.0 (s, C-3'). HRMS m/z Calc. for C₁₄H₁₃F₃NaO₃⁺: 311.0866, found 311.0810 [M+Na]⁺

Z-(2S,3R,4S,5R)-5-(3-(Trifluoromethyl)styryl)-2-methyltetrahydrofuran-3,4-diol  (7h). Yield: 31 mg (25%); m.p. 82-83 °C, Rf 0.3 (50% AcOEt in hexanes), [a]D 25 -32.8 (c 0.345, MeOH); IR (ATR): ν 3371 (m, OH), 2929 (w), 1486 (w), 1443 (m), 1327 (vs), 1074 (vs), 806 (s) cm⁻¹; 1H NMR (300 MHz, (CDCl₃): δ 1.35 (d, 3H, J₉,₂ = 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, J₉,₂ = J₂,₃ = 6.1 Hz, H-2'), 3.96 (“t”, 1H, J = 6.0 Hz, H-3 or H-4) 4.46 (dd, 1H, J₁,₂ = 9.3, J₄,₅ = 5.9 Hz, H-5), 5.73 (dd, 1H, J₁,₂ = 11.6, J₃,₅ = 9.3 Hz, H-1'), 6.75 (d, 1H, J₁,₂ = 11.6 Hz, H-2'), 7.40-7.70 (m, 4H, Ph); 13C NMR (75 MHz, (CDCl₃): 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, JCF = 272.3 Hz, CF₃), 124.2 (q, JCF = 3.8 Hz, C-4' or C-6'), 125.7 (q, JCF = 3.8 Hz, C-4' or C-6'), 130.6 (q, JCF = 32.2 Hz, C-5') 132.1 (q, JCF = 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 C₁₄H₁₅F₃NaO₃⁺: 311.0866, found 311.0699 [M+Na]⁺

E-(2S,3R,4S,5R)-5-(4-Bromostyryl)-2-methyltetrahydrofuran-3,4-diol  (6i). Yield: 71 mg (56%, white solid); m.p. 139-140 °C, Rf 0.2 (50% AcOEt in hexanes), [a]D 25 +49.9 (c 0.593, MeOH); IR (ATR): ν 3348 (m, OH), 3287 (m, OH), 2918 (m), 1487 (m), 1125 (s), 1054 (vs), 971 (vs), 841 (vs) cm⁻¹; 1H NMR (300 MHz, (CD₃)₂CO): δ 1.26 (d, 3H, J₉,₂ = 6.3 Hz, Me), 3.70 (“t”, 1H, J = 5.7 Hz, H-3 or H-4), 3.84 (“qi”, 1H, J₉,₂ = J₂,₃ = 6.1 Hz, H-2) 3.89 (“t”, 1H, J = 5.7
Hz, H-3 or H-4), 4.25 (“t”, 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$_3$)$_2$CO): $\delta$ 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-(2S,3R,4S,5R)-5-(4-Bromostyryl)-2-methyltetrahydrofuran-3,4-diol (7i)** Yield: 45 mg (35%, white solid); m.p. 100-102 °C, $R_f$ 0.3 (50% AcOEt in hexanes), $[\alpha]_D^{25}$ -52.9 (c 0.413, MeOH); IR (ATR): $\nu$ 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$_3$)$_2$CO): $\delta$ 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$_3$)$_2$CO): $\delta$ 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-(2S,3R,4S,5R)-5-(2-Fluorostyryl)-2-methyltetrahydrofuran-3,4-diol (6j)** Yield: 44 mg (35%, white solid); m.p. 47-49 °C, $R_f$ 0.3 (50% AcOEt in hexanes), $[\alpha]_D^{25}$ +44.9 (c 0.274, MeOH); IR (ATR): $\nu$ 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$_3$)$_2$CO): $\delta$ 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 (“q”, 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$_3$)$_2$CO): $\delta$ 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, $J_{CF} = 22.2$ Hz, C-5´), 124.2 (d, $J_{CF} = 3.9$ Hz, C-7´), 126.3 (d, $J_{CF} = 3.5$ Hz, C-1´), 126.4 (d, $J_{CF} = 11.2$ Hz, C-3´), 129.4 (d, $J_{CF} = 3.7$ Hz, C-8´), 130.9 (d, $J_{CF} = 8.5$ Hz, C-6´), 134.0 (d, $J_{CF} = 4.6$ Hz, C-2´), 162.0 (d, $J_{CF} = 247.3$ Hz, C-4´) HRMS m/z Calc. for C$_{13}$H$_{16}$O$_3$: 239.1078, found 239.1034 [M+H]$^+$. 

**E-(2S,3R,4S,5R)-5-(4-Fluorostyryl)-2-methyltetrahydrofuran-3,4-diol (6k)** Yield: 42 mg (30%, white solid); m.p. 116-119°C, $R_f$ 0.2 (50% AcOEt in hexanes), $[\alpha]_D^{25}$ +47.7 (c 0.239, MeOH); IR (ATR): $\nu$ 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$_3$)$_2$CO): $\delta$ 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 (“q”, 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, 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$_3$)$_2$CO): $\delta$ 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, $J_{CF} = 21.7$ Hz, C-5´, C-7´), 130.0 (d, $J_{CF} = 8.1$ Hz, C-4´, C-8´), 131.0 (d, $J_{CF} = 2.2$ Hz, C-2´), 131.2 (d, C-1´), 135.3 (s, $J_{CF} = 3.2$ Hz, C-3´), 164.0 (d, $J_{CF} = 244.7$ Hz, C-6´). HRMS m/z Calc. for C$_{13}$H$_{15}$FNaO$_3$: 261.0897, found 261.0867 [M+Na]$^+$. 

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Z-(2S,3R,4S,5R)-5-(4-Fluorostyryl)-2-methyltetrahydrofuran-3,4-diol (7k). Yield: 11 mg (8%, white solid); m.p. 70-73 °C, Rf 0.3 (50% AcOEt in hexanes), [α]D -34.9 (c 0.126, MeOH);
IR (ATR): ν 3458 (m, OH), 3323 (m, OH), 2978 (m), 2903 (m), 1602 (m), 1505 (s), 1220 (vs), 1086 (vs), 982 (vs), 848 (vs), cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂CO): δ 1.24 (d, 3H, JMe₂ = 6.2 Hz, Me), 3.71 ("it", 1H, J = 5.8 Hz, H-3 or H-4), 3.77 ("qi", 1H, JMe₂= J₂, = 6.1 Hz, H-2), 3.95 ("it", 1H, J = 5.4 Hz, H-3 or H-4) 4.50 (dt, 1H, J₁,₅ = 9.3, J₄,₅ = 5.4 Hz, H-5), 5.67 (dd, 1H, J₁,₂ = 11.7, J₁,₅ = 9.3 Hz, H-1’), 6.65 (d, 1H, J₁,₂ = 11.7 Hz, H-2’), 7.08-7.16 (m, 2H, Ph), 7.40-7.55 (m, 2H, Ph); ¹³C NMR (75 MHz, (CD₃)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, JCF = 21.5 Hz, C-5’, C-7’), 132.8 (d, JCF = 8.0 Hz, C-4’, C-8’), 133.0 (d, C-1’), 133.3 (d, JCF = 1.2 Hz, C-2’), 134.7 (s, JCF = 3.3 Hz, C-3’) 163.9 (s, JCF = 244.8 Hz, C-6’). HRMS m/z Calc. for C₁₃H₁₅FNaO₃⁺: 261.0897, found 261.0813 [M+Na]⁺.

Cytotoxic MTT assay²¹,²²

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 MRPs 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 cm² 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 NaHCO₃).

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 % CO₂ 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 % CO₂ 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-exposed well} / mean OD_{control wells}) \times 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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References

1. (a) Fenical, W.; Jensen, P. R. In Marine Biotechnology, Attaway, D. H.; Zaborsky, O. K. Eds.; Plenum Press: New York, 1993, Vol. 1, p 419. (b) Dong, Y.; Shi, Q.; Pai, H.-C.; Peng, C.-Y.; Pan, S.-L.; Teng, C.-M.; Nakagawa-Goto, K.; Yu, D.; Liu, Y.-N.; Wu, P.-C.; Bastow, K.-F.; Morris-Natschke, S. L.; Brossi, A.; Lang, J.-Y.; Hsu, J. L.; Hung, M.-C.; Lee, E.-Y.; Lee, K.-H. J. Med. Chem. 2010, 53, 2299. (c) Faulkner, D. J. Nat. Prod. Rep. 2000, 17, 7.

2. Malmström, J.; Christoffersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. J. Nat. Prod. 2002, 65, 364.

3. Mayer, A. M. S.; Gustafson, K. R. Eur. J. Cancer. 2004, 40, 2676.

4. Clemens, R. T.; Jennings, M. P. Chem. Commun. 2006, 2720.

5. McAllister, G. D.; Robinson, J. E.; Taylor, R. J. K. Tetrahedron 2007, 63, 12123.

6. (a) Kumar, V.; Shaw, A. K. J. Org. Chem. 2008, 73, 7526. (b) Ghosal, P.; Sharma, D.; Kumar, B.; Meena, S.; Sinha, S.; Shaw, A. K. Org & Biomol. Chem. 2011, 9, 7372.

7. (a) Palík, M.; Karlbíková, O.; Láskiková, A.; Kozišek, J.; Gracza, T. Eur. J. Org. Chem. 2009, 709. (b) Palík, M.; Karlbíková, O.; Lackovičová, D.; Láskiková, A.; Gracza, T. Tetrahedron 2010, 66, 5244. (c) Karlbíková, O.; Palík, M.; Láskiková, A.; Gracza, T. Synthesis 2010, 3449.

8. Ghosh, S.; Pradhan, T. K. J. Org. Chem. 2010, 75, 2107.

9. Brichacek, M.; Batory, L. A.; McGrath, N. A.; Njardarson, J. T. Tetrahedron 2010, 66, 4832.

10. Srinivas, B.; Sridhar, R.; Rama Rao, K. Tetrahedron 2010, 66, 8527.
11. Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, 13, 42.
12. (a) Nagarapu, L.; Paparaju, V.; Satyender, A. *Bioorg. Med. Chem. Lett.* **2008**, 18, 2351. (b) Nagarapu, L.; Paparaju, V.; Satyender, A.; Bantu, R. *Tetrahedron Lett.* **2011**, 52, 7075.
13. Vamshikrishna, K.; Srihari, P. *Tetrahedron* **2012**, 68, 1540.
14. Senthilmurugan, A.; Aidhen, I. S. *Eur. J. Org. Chem.* **2010**, 555.
15. (a) Gracza, T.; Jäger, V. *Synlett* **1992**, 191. (b) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359. (c) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron Lett.* **2002**, 43, 6983. (d) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, 61, 2471.
16. Mitsunobu, O. *Synthesis* **1981**, 1.
17. Loibnen, H.; Zbiral, E. *Helv. Chim. Acta* **1981**, 59, 2100.
18. (a) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26. (b) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 14, 4833.
19. Box, V. G. S.; Yianikorous, G. P. *Heterocycles* **1990**, 31, 1261.
20. Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2563.
21. Noskova, V.; Dzubak, P.; Kuzmina, G.; Ludkova, A.; Stehlik, D.; Trojamec, R.; Janostakova, A.; Korinkova, G.; Mihal, V.; Hajduch, M. *Neoplasma* **2002**, 49, 418.
22. Hajduch, M.; Kolar, Z.; Novotny, R.; Hanus, J.; Mihal, V.; Hlobilkova, A.; Noskova, V.; Strnad, M. *Anti-Cancer Drugs* **1997**, 10, 1007.