DOI: 10.1002/cmdc.200500057

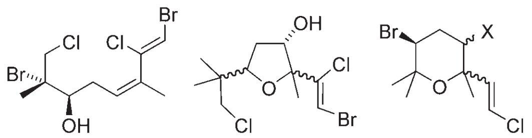
# Prins-Type Synthesis and SAR Study of Cytotoxic Alkyl Chloro Dihydropyrans

Pedro O. Miranda,[a, b] José M. Padrón,*[a, b, c] Juan I. Padrón,*[a, b] Jesús Villar,[c] and Víctor S. Martín*[a, b]

*A series of functionalized tetrahydropyran and dihydropyran derivatives was synthesized by means of a Prins-type cyclization between unsaturated alcohols and several aldehydes. An unprecedented dimer bearing two 4-chloro-5,6-dihydro-2*H*-pyran scaffolds was obtained in high yield. A panel of three representative human solid tumor cells from diverse origin was used to assess the cytotoxicity of the compounds. Overall, the results show the relevance of the chlorovinyl group in the biological activity, and 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans represent interesting leads for further chemical modifications and biological studies.*

## Introduction

The potential of marine organisms as a source of biologically active natural products, many of which contain halogen, has been reviewed extensively.[1] Red algae have proven to be an endless source of novel organohalogen secondary metabolites.[2] For instance, *Plocamium cartilagineum* is a rich source of halogenated monoterpenes of acyclic and oxacyclic skeletons, such as prefuroplocamioid[3] (**1**) and furoplocamioids A–C[4] (**2**), respectively (Scheme 1). A common feature of these compounds of particular interest to us is the presence of a chlorovinyl group. This functional group is found also in aplysiapyranoids A–D[5] (**3**), which were isolated from the sea slug *Aplysia kurodai*. Aplysiapyranoids A–D have shown modest in vitro cytotoxicity against diverse solid tumor cell lines with $IC_{50}$ values in the range 60–300 μM. Aplysiapyranoid D was the most active compound of the series against Moser cells (human colon cancer) with an $IC_{50}$ of 46 μM.[5]



**1** **2** **3** X = Br or Cl

**Scheme 1.** Structures of diverse marine natural products containing halovinyl groups.

We hypothesized that the chlorovinyl group is the moiety responsible for the activity exerted by aplysiapyranoids. This idea, together with our interest in the development of new selective cytotoxic agents,[6] encouraged us to explore the role of the chlorovinyl group in the biological activity of halogen containing oxacyclic derivatives.

We recently reported the synthesis of novel oxacycle systems through a Prins-type cyclization.[7] The Prins reaction allows the synthesis of functionalized tetrahydropyran derivatives by the coupling between unsaturated alcohols and aldehydes induced by Lewis acid.[8] Our approach to the Prins reaction is promoted by the inexpensive, stable, and environmentally friendly iron(III) chloride, and represents a way to obtain 2-alkyl-4-chloro-tetrahydropyrans and 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans in a single step. Overall, this process builds up one carbon–carbon bond, one oxygen–carbon bond, one chlorine–carbon bond, and a ring in a regioselective and efficient manner. In addition, the reaction times are very short (1 min), and the processing is extremely bench- and environmentally friendly.

In this paper, we present a systematic study on the synthesis and cytotoxicity of oxacyclic and linear derivatives obtained through iron(III) chloride catalysis. The compounds bear different functional groups covering a wide range of physicochemical properties. As a model system to study the biological activity, the representative human solid tumor cells A2780 (ovarian cancer), SW1573 (non-small cell lung cancer, NSCLC), and WiDr (colon cancer) were selected. The role of the chlorovinyl group in the biological activity is discussed.

[a] *P. O. Miranda, Dr. J. M. Padrón, Dr. J. I. Padrón, Prof. V. S. Martín*
*Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG)*
*Universidad de la Laguna*
*C/Astrofísico Francisco Sánchez, 2, 38206 La Laguna (Spain)*
*Fax: (+34) 922-318-571*
*E-mail: jmpadron@ull.es*

[b] *P. O. Miranda, Dr. J. M. Padrón, Dr. J. I. Padrón, Prof. V. S. Martín*
*Instituto Canario de Investigación del Cáncer (ICIC)*
*Red Temática de Investigación Cooperativa de Centros de Cáncer*
*Ctra. del Rosario s/n, 38010 S/C de Tenerife, (Spain)*

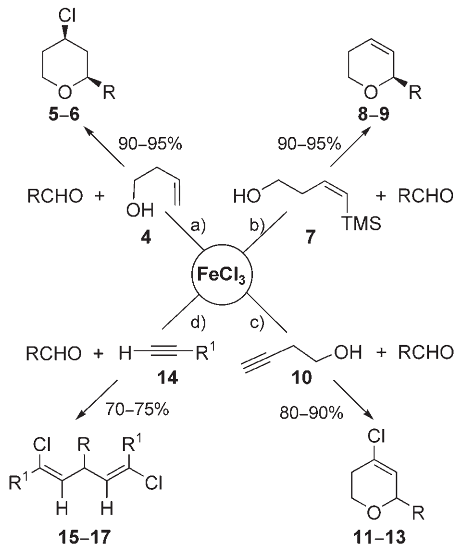
[c] *Dr. J. M. Padrón, Dr. J. Villar*
*Instituto Canario de Investigación Biomédica (ICIB)*
*Hospital Universitario NS de Candelaria*
*Ctra. del Rosario s/n, 38010 S/C de Tenerife, (Spain)*

*Supporting information for this article is available on the WWW under http://www.chemmedchem.org or from the author.*

## Results and Discussion

The first aim of our study was to design and synthesize a new series of halogen-containing di- and tetrahydropyran derivatives by a Prins-type cyclization reaction. Linear chlorovinyl compounds were investigated in addition to non-halogenated dihydropyran derivatives. The synthetic pathways are outlined in Scheme 2. Thus, the reaction of but-3-en-1-ol (**4**) with di-



**Scheme 2.** $FeCl_3$-promoted coupling between unsaturated compounds and aldehydes. a) **4**, $CH_2Cl_2$, RT, 1 min; b) **7**, $CH_2Cl_2$, RT, 1 min; c) **10**, $CH_2Cl_2$, RT, 1 min; d) **14**, $CH_2Cl_2$, RT, 1 min.

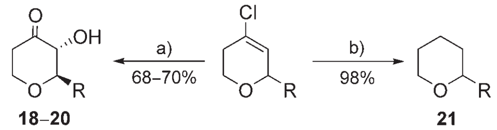
verse aldehydes (route a) afforded 2-alkyl-4-chloro-tetrahydropyrans (Table 1, **5**–**6**). The reaction proceeds with high regioselectivity, providing the oxacycle with the substituents in a *cis* configuration on the ring. Similarly, the reaction with olefin (*Z*)-4-trimethylsilanyl-but-3-en-1-ol (**7**)[9] led to 2-alkyl-5,6-dihydro-2*H*-pyran derivatives (Table 1, **8**–**9**). The silyl Prins reaction[10] worked well for cyclohexanecarbaldehyde and phenylacetaldehyde. However, pivalaldehyde (R=*t*Bu) did not react with olefin (**7**) to give the appropriate dihydropyran derivative, presumably due to steric hindrance. When but-3-yn-1-ol (**10**) was used (Scheme 2, route c), the corresponding unsaturated 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans (Table 1, **11**–**13**) were obtained. As proof of principle, we synthesized linear derivatives containing two chlorovinyl groups. These compounds were obtained through the coupling of terminal alkynes **14** and aldehydes catalyzed by anhydrous iron(III) chloride (route d). This stereoselective coupling of alkynes and aldehydes led to (*E*,*Z*)-1,5-dichloro-1,4-diene derivatives (Table 1, **15**–**17**).[11]

**Table 1.** Preliminary in vitro screening against human solid tumor cells.

| Compound | R | $R^1$ | A2780 | $GI_{50}$ [μM][a] SW1573 | WiDr |
|---|---|---|---|---|---|
| **5** | Ph | | >100 | >100 | >100 |
| **6** | *p*-$NO_2$-Ph | | >100 | >100 | >100 |
| **8** | *c*Hex | | n.p.[b] | >100 | >100 |
| **9** | Bn | | n.p.[b] | >100 | >100 |
| **11** | *c*Hex | | 20(±2.6) | 26(±3.6) | >100 |
| **12** | Bn | | 36(±13) | 58(±18) | >100 |
| **13** | *t*Bu | | 15(±8.6) | 12(±1.4) | >100 |
| **15** | *i*Bu | *n*Bu | >100 | >100 | >100 |
| **16** | *c*Hex | Ph | >100 | >100 | >100 |
| **17** | *n*Hex | Bn | >100 | >100 | >100 |
| **18** | *c*Hex | | >100 | >100 | >100 |
| **19** | Bn | | >100 | >100 | >100 |
| **20** | *i*Bu | | >100 | >100 | >100 |
| **21** | Bn | | >100 | >100 | >100 |

[a] Values are means of at least three experiments; standard deviation is given in parentheses. [b] n.p.=not performed.

An additional functional-diversity point on the oxacyclic framework was obtained by the ruthenium-catalyzed *cis*-hydroxylation of the chlorovinyl group. As shown in Scheme 3,



**Scheme 3.** Ruthenium-catalyzed *cis*-hydroxylation of 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans. a) $RuCl_3 \cdot H_2O$ (7 mol%), $NaIO_4$, EtOAc/$CH_3CN$/$H_2O$ (3:3:1), 0°C; b) $H_2$, Pd/C, EtOAc.

diverse 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans were stereoselectively transformed into the corresponding *trans*-2-alkyl-3-hydroxy-tetrahydropyran-4-ones (Table 1, **18**–**20**) as the sole stereoisomers.[11] The ruthenium methodology offers an improved alternative to the previously reported osmium-catalyzed *cis*-hydroxylation.[7] The major advantages of this new method include a) a reduction of reaction times from many hours to a few minutes; b) a decrease in reaction temperature from reflux to room temperature, c) an isolated-yield enhancement from 50% to 70%, and, last but not least, d) the avoidance of the use of osmium, a very toxic hazard. The palladium-catalyzed hydrogenation of 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans produces the corresponding dehalogenated and saturated derivative (Table 1, **21**).

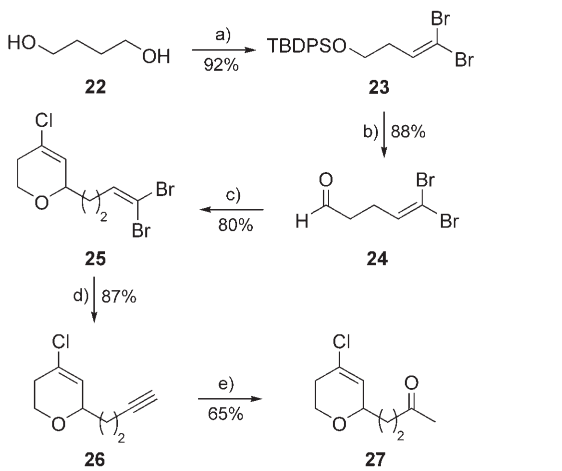
Thus, a first series of fourteen derivatives was submitted for biological assays. In vitro antiproliferative activity was evaluated by using the National Cancer Institute (NCI) protocol.[12] In this method, a dose-response curve is generated for each drug, and three levels of effect can be calculated. The effect is defined as percentage of growth (PG), where 50% growth inhibition ($GI_{50}$),[13] total growth inhibition (TGI), and 50% cell killing ($LC_{50}$) represent the concentration at which PG is +50, 0, and −50, respectively. With these calculations, a PG value of 0 corresponds to the amount of cells present at the start of drug exposure, while negative PG values denote net cell kill. The resulting sensitivities of the preliminary screening expressed as $GI_{50}$ are reported in Table 1.

The results show that those oxacyclic derivatives bearing a chlorovinyl group were the only products able to induce antiproliferative effects on the ovarian and lung cancer cell lines, with $GI_{50}$ values in the range 12–58 μM. The sensitivity of both cell lines to these drugs is similar; compound **13** is the most active derivative of the series. However, WiDr cells were not affected by these drugs. This result is consistent with a previous study in which colon cancer cells showed more drug resistance than ovarian cancer cells.[14]

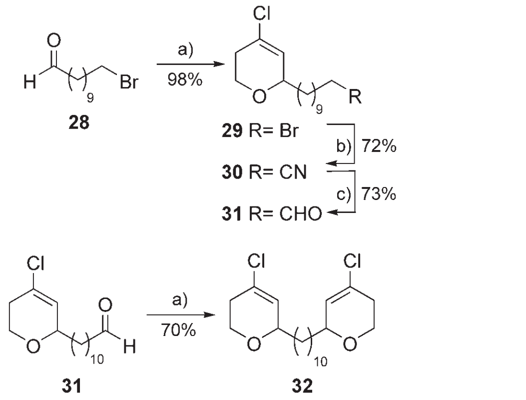
The preliminary screening identified derivatives **11**–**13** as the more active compounds. From the biological data, the presence of the chlorovinyl in the six-membered heterocyclic ring seems to play an essential role. According to this rationale, we decided to explore the activity of this class of compounds through modifications on the alkyl side chain.

To achieve this objective we prepared aldehyde **24** from readily available butane-1,4-diol (**22**) in excellent yield, as shown in Scheme 4. Thus, diol **22** was monoprotected as *tert*-butyldiphenylsilyl ether, and the free hydroxyl group was oxidized to the aldehyde by using the Parikh–Doering reaction.[15] The Corey–Fuchs olefination was then used to form the 1,1-dibromovinyl derivative **23**.[16] Cleavage of the silyl protecting group with HF followed by a Parikh–Doering oxidation led to the desired aldehyde **24**. Compound **24** was submitted to our $FeCl_3$-promoted coupling with homopropargylic alcohol **7** to afford the corresponding dihydropyran **25** in 80% yield.

Compound **25** contains a 1,1-dibromovinyl group at one end of the carbon backbone; this allows the introduction of diverse functional groups to perform additional structure–activity relationship (SAR) studies. The transformations reported in this article are shown in Scheme 4. Hence, treatment of dihydropyran **25** with *n*-butyllithium afforded the desired alkyne **26** in 87% yield. As an alternative to the classical oximercuration, derivative **26** was then subjected to the $FeBr_3$/CSA in-house methodology[11] to hydrate the triple bond. The corresponding methyl ketone **27** was obtained in 65% yield.




**Scheme 4.** Synthesis of chlorovinyl pyrans with diverse functional groups on the side chain. a) i. *n*BuLi, $Et_2O$, TBDPSCl, 0 °C; ii. $SO_3$·Py, DMSO, $Et_3N$; iii. $PPh_3$, $CBr_4$, $CH_2Cl_2$, 0 °C; b) i. HF/$CH_3CN$ (9:1); ii. $SO_3$·Py, DMSO, $Et_3N$; c) **7**, $CH_2Cl_2$, RT, 1 min; d) *n*BuLi, $Et_2O$, −78 °C; e) $FeBr_3$, CSA, $CH_2Cl_2$. TBDPSCl = *tert*-butyldiphenylsilyl chloride, CSA = camphorsulfonic acid.




**Scheme 5.** Synthesis of the chlorovinyl dimer. a) **7**, $CH_2Cl_2$, RT, 1 min; b) NaCN, DMSO, 4 Å MS, 80 °C; c) DIBAL-H, 0 °C, THF. MS = molecular sieves, DIBAL-H = diisobutylaluminium hydride.

An additional strategy, which we followed in order to obtain more derivatives with diverse functional groups, is depicted in Scheme 5. When aldehyde **28**[17] was treated with homopropargylic alcohol **10** under $FeCl_3$ catalysis, dihydropyran **29** was obtained in almost quantitative yield. Subsequent chemical modifications were performed on the aliphatic side chain of **29**. Chlorovinyl derivative **29** was treated with NaCN in DMSO to produce to the cyano derivative **30** in 72% yield. Reduction of the cyano group of compound **30** with DIBAL-H afforded the desired aldehyde **31** in 73% yield. With this aldehyde in hand, we carried out the Prins cyclization with but-3-yn-1-ol (**10**) under the aforementioned conditions. The unprecedented dimer **32** was obtained in 70% yield.

The antitumor activity of compounds **25**–**27** and **29**–**32** was evaluated against the three human solid tumor cell lines. The growth inhibition parameters $GI_{50}$, TGI, and $LC_{50}$ are given in Table 2 together with the values obtained for compounds **11**–

**Table 2.** Lipophilicity and growth-inhibition parameters for the in vitro screening of dihydropyrans against human solid tumor cells.

| | | A2780 | | | SW1573 | | | WiDr | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Compound | Clog *P*[b] | $GI_{50}$ | TGI[c] | $LC_{50}$[c] | $GI_{50}$ | TGI[c] | $LC_{50}$[c] | $GI_{50}$ | TGI[c] | $LC_{50}$[c] |
| **11** | 3.894 | 20(±2.6) | 90(±18) | | 26(±3.6) | 90(±17) | | >100 | | |
| **12** | 3.431 | 36(±13) | 93(±11) | | 58(±18) | | | >100 | | |
| **13** | 3.190 | 15(±8.6) | 50(±34) | 91(±15) | 12(±1.4) | 81(±33) | | >100 | | |
| **25** | 4.252 | 16(±5.5) | 53(±41) | 76(±23) | 30(±7.0) | 92(±16) | | 23(±3.5) | 57(±21) | 96(±5.9) |
| **26** | 2.242 | 37(±7.2) | | | 41(±6.4) | | | >100 | | |
| **27** | 1.499 | 74(±22) | | | 79(±29) | | | 64(±34) | | |
| **29** | 6.477 | 19(±0.9) | 55(±17) | 96(±7.7) | 18(±4.1) | 57(±27) | 86(±18) | 22(±3.9) | 75(±34) | 92(±14) |
| **30** | 5.007 | 19(±5.3) | 36(±6.0) | 69(±4.2) | 16(±4.2) | 38(±9.7) | 86(±24) | 25(±3.0) | 72(±27) | 97(±4.8) |
| **31** | 5.177 | 16(±1.1) | 36(±2.1) | 80(±5.2) | 17(±1.4) | 42(±5.1) | 97(±3.6) | 28(±1.8) | 76(±4.0) | 92(±11) |
| **32** | 7.264 | 8.6(±6.7) | 25(±6.1) | 65(±3.3) | 14(±6.2) | 36(±10) | 85(±17) | 20(±2.3) | 61(±5.6) | 89(±15) |

**13**, which were the only active products from the first screen. In addition to the antitumor activity, the lipophilicity (Clog *P*) of this series of compounds was evaluated by in silico calculation based on their chemical structure.[18] Clog *P* values were calculated to correlate lipophilicity with antitumor activity and are also shown in Table 2.

Taken as a whole, the results demonstrate that lipophilicity is an important feature for activity. This is especially true for WiDr cells. With the exception of compound **27,** the products that exerted activity against colon cancer cells have Clog *P* values larger than 4. The Clog *P* value for aplysiapyranoids A and B (**3**, X = Br) is 4.325, while for aplysiapyranoids C and D (**3**, X = Cl) it is 4.185. We cannot discard that possibility that the presence of the carbonyl group in derivative **27** accounts for the activity in WiDr cells. According to the results, we can classify the compounds into three groups. The first group comprises compounds **26** and **27**, with Clog *P* values lower than 3 and little activity. The second group includes compounds **11**–**13**, which show modest activity against ovarian and lung cancer cells and have Clog *P* values in the range 3–4. The largest group consists of those derivatives with Clog *P* values larger than 4, which are the most biologically active.

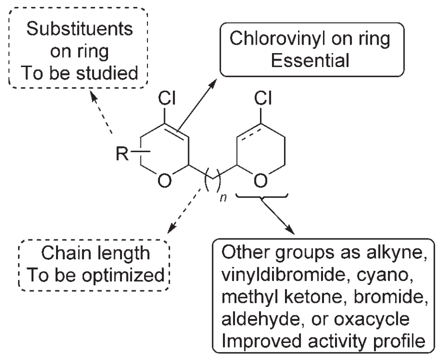
When considering growth-inhibition parameters, we find that compounds **25** and **29**–**32** are the only products that reach TGI and $LC_{50}$ values for all cell lines; that is, they are able to induce net cell kill, even in the resistant colon cancer cell line. It is noteworthy that all these synthetic derivatives show better activity profiles than the natural products, aplysiapyranoids (**3**). The natural compounds bear the chlorovinyl group in the side chain, whilst the synthetic products have that functional group in the oxacycle. We hypothesize that this difference might account for the observed differences in biological activity. In addition, the lack of activity of the linear derivatives **15**–**17**, which contain two chlorovinyl groups, might indicate the significance of the oxacycle ring for the activity.

The results also indicate that the nature of the functional group on the side chain is not relevant for the activity, as shown with compounds **25** and **29**–**31**. These findings suggest clearly that, at least in this series of compounds, the presence of the chlorovinyl group is essential for the antitumor effect.

Additional evidence is given by compound **32**. This dimer, bearing two 4-chloro-5,6-dihydro-2*H*-pyran fragments linked by an aliphatic chain, proved to be the most active compounds of the series. However, the presence of a second chlorovinyl group did not enhance the activity profile considerably.

## Conclusion

While the compounds reported herein are racemic, we think it is unlikely that enantiomerically pure derivatives would improve the activity profile considerably. Our assertion is based on the small differences reported for the diverse natural derivatives aplysiapyranoids A–D (**3**). On the other hand, modifications on the heterocyclic ring by the addition of diverse substituents might lead to new products with better activity profiles. The influence of the length of the linker chain on the activity of symmetric and asymmetric dimers is another point of interest for us (Scheme 6). At present, the mechanism of action of these compounds remains unclear. Ongoing studies will clarify this, and will be reported elsewhere.




**Scheme 6.** Structure–activity relationship parameters defined during this study and possible strategies for improvement.

In summary, we have constructed a series of 4-chloro-5,6-dihydro-2*H*-pyrans in a simple and direct way. The key step is a regioselective iron(III) chloride-catalyzed Prins-type cyclization. This general methodology allows the quick production of a variety of oxacyclic synthons that are useful for the combinatorial syntheses of novel bioactive compounds. Although the results are preliminary, we found that these synthetic derivatives considerably induced cytotoxicity in a panel of three human solid tumor cell lines of diverse origin. In addition, the synthetic analogues were more biologically active than the parent natural products, aplysiapyranoids A–D. On the basis of drug lipophilicity and growth inhibition parameters, a structure–activity relationship has been obtained.

## Experimental Section

**General remarks:** Dichloromethane and tetrahydrofuran were distilled from $CaH_2$ and Na/benzophenone, respectively, under $N_2$ immediately prior to use. All other chemicals were of reagent grade and were used without further purification. Thin-layer chromatography was carried out on aluminium sheets coated with silica gel 60F254. Plates were developed by using vanillin (6 g), AcOH (40 mL), $H_2SO_4$ (30 mL), and EtOH (450 mL). Flash chromatography was performed by using silica gel 0.25 mm Merck silica gel (60F-254). IR spectra were recorded on a Bruker IFS 55 spectrometer model. $^1$H NMR spectra were recorded at 400 and 300 MHz, $^{13}$C NMR spectra were recorded at 100 and 75 MHz, and chemical shifts are reported relative to internal $Me_4Si$. The samples were dissolved in $CDCl_3$ unless otherwise noted. Elemental analyses were obtained by using an EA 1108 CHNS-O FISONS-instruments.

Compounds **5**–**6**,[7] **11**–**13**,[7] **15**–**17**[11] were prepared according to literature procedures.

**General procedure for the $RuCl_3$-catalyzed oxidation of 4-chloro-5,6-dihydro-2*H*-pyrans**: $RuCl_3$·3 $H_2O$ (7 mol %) and a solution of $NaIO_4$ (1 mmol) in distilled water were added to a vigorously stirred solution of the alkene (1 mmol) in $CH_3CN$/EtOAc/$H_2O$ (3:3:1) at 0–5 °C (ice–water bath). The two-phase mixture was stirred vigorously for 1 min and quenched with a saturated aqueous solution of

$Na_2S_2O_3$. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica-gel column chromatography (EtOAc/*n*-hexane solvent systems) to give the corresponding 2-alkyl-3-hydroxy-tetrahydropyran-4-one.

Compounds **18**–**20**[11] were prepared according to this method and gave spectroscopic data consistent with that reported in the literature.

**General procedure for the Prins-type cyclization**: anhydrous $FeCl_3$ (1.40 mmol) was added in one portion and at room temperature to a stirred solution of the unsaturated alcohol (1.40 mmol) and the appropriate aldehyde (1.40 mmol) in dry $CH_2Cl_2$ (15 mL). The reaction was completed in approximately 1 min and quenched by the addition of water (10 mL). The solution was stirred for an additional 5 min and extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica-gel column chromatography (EtOAc/*n*-hexane solvent systems) to give the corresponding oxacyclic compound.

*2-Cyclohexyl-5,6-dihydro-2*H*-pyran (**8**)*: The general Prins-type cyclization procedure was applied to (*Z*)-4-trimethylsilanyl-but-3-en-1-ol (**7**) and cyclohexanecarbaldehyde on a 0.89 mmol scale. Compound **8** was obtained as an oil (104 mg, 0.62 mmol, 70%). $R_f=0.8$ (EtOAc/*n*-hexane 95:5); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.06$ (m, 5H), 1.40 (m, 1H),1.59–2.19 (m, 6H), 2.21 (m, 1H), 3.58 (ddd, $J=3.7$, 10.5, 14.19 Hz, 1H), 3.81 (brs, 1H), 3.91 (dd, $J=5.31$, 10.8 Hz, 1H), 5.61 (brd, $J=10.5$ Hz), 5.79 ppm (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=25.3$ ($CH_2$), 26.1 ($CH_2$), 26.3 ($CH_2$), 27.9 ($CH_2$), 28.5 ($CH_2$),42.5 (CH), 63.5 ($CH_2$),78.0 ($CH_2$), 124.9 (CH), 128.8 ppm (CH); IR (KBr): $\tilde{\nu}=2922$, 1730, 1659, 1603 cm$^{-1}$; elemental analysis calcd (%) for $C_{11}H_{18}O$ (166.26): C 79.46, H 10.91; found C 79.41, H 10.92.

*2-Benzyl-5,6-dihydro-2*H*-pyran (**9**)***:** The general Prins-type cyclization procedure was applied to (*Z*)-4-trimethylsilanyl-but-3-en-1-ol (**7**) and phenyl-acetaldehyde in a 0.89 mmol scale. Compound **9** was obtained (101 mg, 0.58 mmol, 65%) as an oil. $R_f=0.8$ (EtOAc/*n*-hexane 95:5); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.89$ (brd, $J=17.3$ Hz, 1H), 2.21 (m, 1H), 2.70 (dd, $J=6.6$, 13.5 Hz, 1H), 2.90 (dd, $J=7.4$, 13.5 Hz, 1H), 3.63 (ddd, $J=3.9$, 9.6, 15.0 Hz, 1H), 3.94 (m, 1H), 4.28 (brs, 1H), 5.61 (brd, $J=10.24$ Hz, 1H), 5.82 (m, 1H), 7.15–7.29 ppm (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=25.1$ ($CH_2$), 41.6 ($CH_2$), 63.2 ($CH_2$), 74.6 (CH), 124.9 (CH), 126.0 (CH), 128.0 (CH), 129.2 (CH), 129.3 (CH), 138.1 ppm (C); IR (KBr): $\tilde{\nu}=2922$, 1730, 1659, 1603 cm$^{-1}$; elemental analysis calcd (%) for $C_{12}H_{14}O$ (174.24): C 82.72, H 8.10; found C 82.73, H 8.15.

*2-Benzyl-tetrahydropyran (**21**)*: Pd/C (20 mg) was added to a stirred solution of **12** (83 mg, 0.40 mmol) in dry EtOAc (0.1 M). The mixture was stirred under a hydrogen atmosphere until TLC showed complete conversion, then filtered through a pad of Celite. The solvent was evaporated, and the crude product was purified by silica-gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford **21** (69 mg, 0.39 mmol, 98% yield) as an oil. $R_f=0.4$ (EtOAc/*n*-hexane 95:5); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.29$–1.71 (m, 5H), 1.86 (brs, 1H), 2.72 (dd, $J=6.2$, 13.5 Hz, 1H), 2.96 (dd, $J=6.5$, 13.5 Hz, 1H), 3.49 (m, 2H), 4.04 (brd, $J=11.2$ Hz, 1H), 7.33 ppm (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=23.6$ ($CH_2$), 26.1 ($CH_2$), 31.5 ($CH_2$), 43.3 ($CH_2$), 68.6 ($CH_2$), 78.8 ($CH_2$), 126.1 (CH), 128.3 (CH), 129.4 (CH), 138.9 ppm (C); IR (KBr): $\tilde{\nu}=2936$, 2843, 1088 cm$^{-1}$; elemental analysis calcd (%) for $C_{12}H_{16}O$ (176.25): C 81.77, H 9.15; found C 81.53, H 9.18.

*tert-Butyl(5,5-dibromopent-4-enyloxy)diphenylsilane (**23**) (three-step procedure)*: *n*BuLi (50 mL, 2.5 M, 0.110 mol) was added dropwise to a solution of butane-1,4-diol (10 g, 0.110 mol) in dry THF (300 mL) at 0 °C. The resulting thick, milky mixture was stirred vigorously while TBDPSCl (28 mL, 0.110 mol) was added dropwise. After being stirred overnight, the reaction mixture was quenched with pH 7 buffer and extracted with $Et_2O$. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the corresponding monoprotected alcohol. Without further purification, the crude product was dissolved in dry $CH_2Cl_2$ (250 mL) and DMSO (67 mL, 1.268 mol, 0.7 mL mmol$^{-1}$), $Et_3N$ (100 mL, 0.714 mol), and $SO_3$·Py (49 g, 0.306 mol) were sequentially added at RT. The mixture was stirred overnight. Then, 5% HCl aqueous solution (200 mL) was added to the reaction mixture, and the mixture was extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield the corresponding aldehyde, which was used without further purification. The crude product was dissolved in dry $CH_2Cl_2$ (500 mL) and cooled to 0 °C. Then $Ph_3P$ (147 g , 0.56 mol) and $CBr_4$ (90 g, 0.27 mol) were added. The resulting red–orange slurry was stirred at 0 °C for 30 min. Then, the reaction mixture was poured into an ice-cold saturated $NaHCO_3$ solution and extracted with $Et_2O$. The combined organic extract was washed with brine, dried over $MgSO_4$, concentrated, and filtered through a silica-gel short column to afford compound **23** (48 g, 92%) as an oil. $R_f=0.80$ (EtOAc/*n*-hexane, 5:95); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=1.03$ (s, 9H), 1.63 (quint, $J=6.8$ Hz, 2H), 2.18 (q, $J=7.4$ Hz, 2H), 3.64 (t, $J=6.0$ Hz, 2H), 6.35 (t, $J=7.2$ Hz, 1H), 7.37 (m, 6H,), 7.63 ppm (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=19.0$ (C), 26.6 (3$CH_3$), 29.5 ($CH_2$), 30.4 ($CH_2$), 62.7 ($CH_2$), 127.4 (4CH), 129.4 (2CH), 133.5 (2C), 135.3 (4CH), 138.2 ppm (CH).; IR (KBr): $\tilde{\nu}=3070$, 1589, 1110 cm$^{-1}$; elemental analysis calcd (%) for $C_{21}H_{26}Br_2OSi$ (468.30): C 52.29, H 5.43; found C 52.27, H 5.65.

*5,5-Dibromopent-4-enal (**24**) (2-step procedure)*: A solution of compound **23** (7 g, 0.015 mol) in aqueous $CH_3CN$ (14 mL) containing HF (40% HF/$CH_3CN$, 3:7) was stirred at room temperature for 48 h, after which time the reaction mixture was extracted with cold EtOAc. Saturated aqueous $NaHCO_3$ was added to the EtOAc extract with stirring at 0 °C until the water layer became neutral. The water layer was acidified to pH 5 with saturated aqueous $NH_4Cl$, and the organic layer was separated. After thorough extraction with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield the corresponding alcohol. Without further purification, this alcohol was dissolved in dry $CH_2Cl_2$ (200 mL) and DMSO (10.5 mL, 0.199 mol, 0.7 mL mmol$^{-1}$), $Et_3N$ (15 mL, 0.105 mol), and $SO_3$·Py (7.2 g, 0.105 mol) were added sequentially at room temperature. The mixture was stirred overnight, after which time 5% HCl aqueous solution (25 mL) was added. The crude product was extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield the corresponding aldehyde **24** (3.18 g, 0.013 mol, 88%) as an oil, that was purified by silica gel column chromatography (EtOAc/*n*-hexane solvent systems). $R_f=0.35$ (EtOAc/*n*-hexane, 10:90); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.35$ (t, $J=7.2$ Hz, 2H), 2.56 (t, 2H, $J=7.7$ Hz), 6.39 (t, 1H, $J=7.3$ Hz), 9.73 ppm (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=25.4$ ($CH_2$), 41.4 ($CH_2$), 90.3 (C), 136.0 (CH), 200.1 ppm (CH); IR (KBr): $\tilde{\nu}=2927$, 1598, 1130 cm$^{-1}$; elemental analysis calcd (%) for $C_5H_6Br_2O$ (241.91): C 24.82, H 2.50; found C 24.58, H 2.81.

*2-(4,4-Dibromobut-3-enyl)-4-chloro-5,6-dihydro-2*H*-pyran* (**25**): The general Prins-type cyclization procedure was applied to but-3-yn-1-ol (**10**) and aldehyde **24** on a 1.40 mmol scale. Compound **25** was obtained as a pale yellow oil (370 mg, 1.12 mmol, 80%). $R_f = 0.85$ (EtOAc/*n*-hexane, 5:95); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.64$ (q, $J = 7.4$ Hz, 2H,), 2.19 (m, 3H), 2.57 (m, 1H), 3.67 (ddd, $J = 3.92$, 10.0, 10.0 Hz, 1H,), 4.02 (ddd, $J = 2.0$, 5.8, 11.4 Hz,1H), 4.10 (brs, 1H), 5.73 (s, 1H), 6.41 ppm (t, $J = 7.3$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 28.5$ ($CH_2$), 32.6 ($CH_2$), 32.7 ($CH_2$), 63.6 ($CH_2$), 73.53(CH), 89.1 (C), 126.1 (CH), 130.1 (C), 137.7 ppm (CH); IR (KBr): $\tilde{\nu} = 2931$, 2858, 1656, 1342, 1124 cm$^{-1}$; elemental analysis calcd (%) for $C_9H_{11}Br_2ClO$ (330.44): C 32.71, H 3.36; found C 32.72, H 3.47.

*2-(But-3-ynyl)-4-chloro-5,6-dihydro-2*H*-pyran* (**26**): *n*BuLi (0.5 mL, 1.34 mmol; 1.67 M in cyclohexane) was added dropwise to a stirred solution of compound **25** (220 mg, 0.67 mmol) in dry $Et_2O$ (7 mL) at −78 °C. The reaction was completed in approximately 1 min, quenched with a saturated solution of $NH_4Cl$, and extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica-gel column chromatography (EtOAc/*n*-hexane solvent systems) to give compound **26** (100 mg, 0.58 mmol, 87%) as a pale yellow oil. $R_f = 0.80$ (EtOAc/*n*-hexane, 5:95); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.67$ (m, 2H), 1.89 (s, 1H), 2.25 (m. 2H), 2.44 (m, 2H), 3.63 (ddd, $J = 5.7$, 7.4, 7.4 Hz, 1H), 3.93 (m, 1H), 4.16 (brs, 1H), 5.69 ppm (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 14.1$ ($CH_2$), 32.6 ($CH_2$), 33.4 ($CH_2$), 63.4 ($CH_2$), 68.5 (CH), 72.9 (CH), 83.4 (C), 126.1(CH), 129.9 ppm (C); IR (KBr): $\tilde{\nu}$3298, 2925, 1657, 1606 cm$^{-1}$; elemental analysis calcd (%) for $C_9H_{11}ClO$ (170.64): C 63.35, H 6.50; found C 63.36, H 6.37.

*1-(4-Chloro-5,6-dihydro-2*H*-pyran-2-yl)propan-2-one* (**27**): Anhydrous camphorsulfonic acid (198 mg, 0.850 mmol) followed by anhydrous $FeBr_3$ (251 mg, 0.850 mmol) were added each in one portion to a stirred solution of compound **26** (145 mg, 0.850 mmol) in dry $CH_2Cl_2$ (10 mL) at room temperature. The reaction was monitored by TLC, then quenched with water. After the mixture had been stirred for 5 min, the crude product was extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica-gel column chromatography (*n*-hexane/EtOAc solvent systems) to afford compound **27** (104 mg, 0.552 mmol, 65%) as a pale yellow oil. $R_f = 0.30$ (EtOAc/*n*-hexane 5:95); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.75$ (m, 2H), 2.09 (s, 3H), 2.13 (m, 1H), 2.49 (t, $J = 7.2$ Hz, 3H), 3.60 (m, 1H), 3.93 (m, 1H), 4.06 (brs, 1H), 5.66 ppm (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 28.4$ ($CH_2$), 29.8 ($CH_3$), 32.6 ($CH_2$), 38.5 ($CH_2$), 63.4 ($CH_2$), 73.4 (CH), 126.3 (CH), 129.9 (C), 208.1 ppm (C); IR (KBr): $\tilde{\nu} = 2924$, 1713, 1343, 1120 cm$^{-1}$; elemental analysis calcd (%) for $C_9H_{13}ClO_2$ (188.65): C 57.30, H 6.95; found C 57.29, H 6.60.

*2-(10-Bromodecyl)-4-chloro-5,6-dihydro-2*H*-pyran* (**29**): The general Prins-type cyclization procedure was applied to but-3-yn-1-ol (**10**) and aldehyde **28**[17] on a 1.32 mmol scale. Compound **29** was obtained as a pale yellow oil (415 mg, 1.29 mmol, 98%). $R_f = 0.80$ (EtOAc/*n*-hexane 5:95); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.80$–1.44 (m, 16H), 1.76 (m, 2H), 2.08 (brd, $J = 16.9$ Hz, 1H), 2.48 (m, 1H), 3.32 (t, $J = 6.8$ Hz, 2H), 3.59 (ddd, $J = 6.3$, 7.4, 7.4 Hz, 1H), 3.95 (m, 2H), 5.74 ppm (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 25.1$ ($CH_2$), 28.2 ($CH_2$), 28.7 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 32.8 ($CH_2$), 33.0 ($CH_2$), 34.0 ($CH_2$), 35.1 ($CH_2$), 63.8 ($CH_2$), 74.8 (CH), 127.1 (CH), 129.4 ppm (C); IR (KBr): $\tilde{\nu} = 2928$, 2854, 1669, 1605 cm$^{-1}$; elemental analysis calcd (%) for $C_{15}H_{26}BrClO$ (337.72): C 53.35, H 7.76; found C 53.37, H 8.01.

*11-(4-Chloro-5,6-dihydro-2*H*-pyran-2-yl)undecanenitrile* (**30**): NaCN (392 mg, 8.0 mmol) was added to a stirred solution of the corresponding compound **29** (640 mg, 2.0 mmol) in dry DMSO (20 mL), and the reaction mixture was stirred at 80 °C for 3 h. Then it was allowed to cool down to room temperature, and water was added. The mixture was diluted with $Et_2O$, the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica-gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **30** as a pale yellow oil (409 mg, 1.44 mmol, 72%). $R_f = 0.40$ (EtOAc/*n*-hexane 10:90); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.39$ (m, 16H), 1.62 (m, 2H), 2.15 (brd, $J = 17.1$ Hz, 1H), 2.32 (t, $J = 6.9$ Hz, 2H), 2.55 (m, 1H), 3.67 (m, 1H), 4.01 (m, 2H), 5.75 ppm (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta =$ 16.9 ($CH_2$), 24.8 ($CH_2$), 25.1 ($CH_2$), 28.4 ($CH_2$), 28.5 ($CH_2$), 29.0 ($CH_2$), 29.1 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 32.7 ($CH_2$), 34.8 ($CH_2$), 63.6 ($CH_2$), 74.6 (CH), 119.6 (C), 126.9 (CH), 129.2 ppm (C); IR (KBr): $\tilde{\nu} = 2929$, 2855, 1670, 1602 cm$^{-1}$; elemental analysis calcd (%) for $C_{16}H_{26}ClNO$ (283.84): C 67.70, H 9.23; found C 67.71, H 9.28.

*11-(4-Chloro-5,6-dihydro-2*H*-pyran-2-yl)undecanal* (**31**): A solution of the corresponding nitrile **30** (385 mg, 1.36 mmol) in dry THF (20 mL) was cooled to 0 °C, and DIBAL-H (4.10 mL, 4.08 mmol, 1 M in cyclohexane) was added. The reaction mixture was stirred until TLC showed complete conversion of the substrate, then quenched by the addition of a 1 N HCl solution, and filtered through a Celite pad. The precipitate was thoroughly washed with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution. and dried over $MgSO_4$ The solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **31** as a pale yellow oil (285 mg, 0.99 mmol, 73%); $R_f = 0.45$ (EtOAc/*n*-hexane, 10:90). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.40$ (m, 17H), 2.13 (brd, $J = 16.9$ Hz, 1H), 2.35 (t, $J = 7.3$ Hz, 2H), 2.51 (m, 1H), 3.61 (m, 1H), 3.97 (m, 2H), 5.70 (s, 1H), 9.70 ppm (s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 21.8$ ($CH_2$), 24.8 ($CH_2$), 28.9 ($CH_2$), 29.1 ($2CH_2$), 29.2 ($2CH_2$), 29.3 ($CH_2$), 32.7 ($CH_2$), 34.8 ($CH_2$), 43.6 ($CH_2$), 63.6 ($CH_2$), 74.6 (CH), 126.9 (CH), 129.2 (C), 202.6 ppm (CH); IR (KBr): $\tilde{\nu} = 2926$, 2854, 1726, 1343 cm$^{-1}$; elemental analysis calcd (%) for $C_{16}H_{27}ClO_2$ (286.84): C 67.00, H 9.49; found C 67.01, H 9.88.

*4-Chloro-2-(10-(4-chloro-5,6-dihydro-2*H*-pyran-2-yl)decyl)-5,6-dihydro-2*H*-pyran* (**32**):The general Prins-type cyclization procedure was applied to but-3-yn-1-ol (**10**) and aldehyde **31** on a 0.216 mmol scale. Compound **32** was obtained as a pale yellow oil (56 mg, 0.155 mmol, 72%). $R_f = 0.40$ (EtOAc/*n*-hexane, 5:95); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.33$ (m, 18H), 2.11 (brd, $J = 16.9$ Hz, 2H), 2.51 (m, 2H), 3.62 (ddd, $J = 3.9$, 10.1, 10.1 Hz, 2H), 3.97 (m, 4H), 5.71 ppm (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 24.9$ ($2CH_2$), 29.3 ($6CH_2$), 32.7 ($2CH_2$), 34.8 ($2CH_2$), 63.6 ($2CH_2$), 74.6 (2CH), 126.9 (2CH), 129.2 ppm (2C); IR (KBr): $\tilde{\nu} = 2926$, 2854, 1656, 1343 1121 cm$^{-1}$; elemental analysis calcd (%) for $C_{20}H_{32}Cl_2O_2$ (375.37): C 63.99, H 8.59; found C 64.15, H 8.62.

### Biological tests

*Chemicals and reagents*: All starting materials were commercially available research-grade chemicals and were used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), fetal calf serum (FCS) was from Gibco (Grand Island, NY), trichloroacetic acid (TCA), glutamine, and gentamicin were from Merck (Darmstadt, Germany), and dimethyl sulfoxide (DMSO) and sulforhodamine B (SRB) were from Sigma (St Louis, MO).

*Cells, culture and plating:* The human solid tumor cell lines A2780, SW1573, and WiDr were used in this study. Cells were maintained in 25 $cm^2$ culture flasks in RPMI 1640 supplemented with 5% heat-inactivated fetal calf serum and L-glutamine (2 mM) in a 37°C, 5% $CO_2$, 95% humidified-air incubator. Exponentially growing cells were trypsinized and resuspended in antibiotic-containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 μL per well at densities of 7000 (A2780), 5000 (SW1573), and 10000 (WiDr) cells per well, based on their doubling times.

*Chemosensitivity testing:* Chemosensitivity tests were performed by using the SRB assay of the NCI[12] with slight modifications.[14] Pure compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (negative control). Each agent was tested in triplicate at different dilutions in the range 1–100 μM. The drug treatment was started on day 1 after plating. Drug incubation times were 48 h, after which time cells were precipitated with ice-cold trichloroacetic acid (50% *w/v*, 25 μL) and fixed for 60 min at 4°C. The SRB assay was then performed. The optical density (OD) of each well was measured at 490 nm by using BioTek's ELx800NB Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium. The percentage growth (PG) was calculated with respect to untreated control cells ($C$) at each of the drug-concentration levels based on the difference in OD at the start ($T_0$) and end ($T$) of drug exposure, according to NCI formulas.[13] Briefly, if $T$ is greater than or equal to $T_0$ the calculation is $100\times[(T-T_0)/(C-T_0)]$. If $T$ is less than $T_0$, which denotes cell killing, the calculation is $100\times[(T-T_0)/(T_0)]$. With these calculations, a PG value of 0 corresponds to the amount of cells present at the start of drug exposure, while negative PG values denote net cell kill.

## Acknowledgements

*We are indebted to Prof. Godefridus J. Peters (Free University Medical Center, Amsterdam) for providing us with the solid tumor cell lines. This research was supported by the Spanish MEC (PPQ2002-04361-C04-02) and the Canary Islands Government. J.M.P. is recipient of a postdoctoral fellowship from the ICIC. P.O.M. thanks the Spanish MEC for a FPI fellowship. J.I.P. thanks the Spanish MCYT-FSE for a Ramón y Cajal contract.*

**Keywords:** antitumor agents · iron(III) chloride · organohalogen drugs · Prins reaction · structure–activity relationships

[1] a) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–48, and earlier reviews in the same series; b) A. M. S. Mayer, K. R. Gustafson, *Eur. J. Cancer* **2004**, *40*, 2676–2704, and references therein.

[2] D. Iliopoulou, N. Mihopoulos, C. Vagias, P. Papazafiri, V. Roussis, *J. Org. Chem.* **2003**, *68*, 7667–7674, and references therein.

[3] A. R. Díaz-Marrero, M. Cueto, E. Dorta, J. Rovirosa, A. San-Martin, J. Darias, *Org. Lett.* **2002**, *4*, 2949–2952.

[4] J. Darias, J. Rovirosa, A. San Martin, A. R. Díaz, E. Dorta, M. Cueto, *J. Nat. Prod.* **2001**, *52*, 4597–4600.

[5] T. Kusumi, H. Uchida, Y. Inouye, M. Ishitsuka, H. Yamamoto, H. Kakisawa, *J. Org. Chem.* **1987**, *52*, 1383–1387.

[6] a) P. O. Miranda, F. Estévez, J. Quintana, C. I. García, I. Brouard, J. I. Padrón, J. P. Pivel, J. Bermejo, *J. Med. Chem.* **2004**, *47*, 292–295; b) A. G. González, M. Hernández Silva, J. I. Padrón, F. León, E. Reyes, M. Álvarez-Mon, J. P. Pivel, J. Quintana, F. Estévez, J. Bermejo, *J. Med. Chem.* **2002**, *45*, 2358–2361; c) O. J. Donadel, T. Martín, V. S. Martín, J. Villar, J. M. Padrón, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3536–3539; d) J. M. Padrón, D. Tejedor, A. Santos-Expósito, F. García-Tellado, V. S. Martín, J. Villar, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2487–2490.

[7] P. O. Miranda, D. D. Diaz, J. I. Padrón, J. Bermejo, V. S. Martín, *Org. Lett.* **2003**, *5*, 1979–1982.

[8] For recent advances in the Prins reaction, see: a) R. Jasti, C. D. Anderson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945; b) S. D. Rychnovsky, J. E. Dalgard, *J. Am. Chem. Soc.* **2004**, *126*, 15662–15663, and references therein; c) A. P. Dobbs, J. J. Guesné, S. Martinovic, S. J. Coles, M. B. Hursthouse, *J. Org. Chem.* **2003**, *68*, 7880–7883; d) V. K. Yadav, N. V. Kumar, *J. Am. Chem. Soc.* **2004**, *126*, 8652–8653; e) L. E. Overman, E. Velthuisen, *Org. Lett.* **2004**, *6*, 3853–3856; f) C.-M. Yu, S. K. Yoon, Y. T. Hong, J. Kim, *Chem. Commun.* **2004**, 1840–1841.

[9] C. Semeyn, R. H. Blaauw, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1997**, *62*, 3426–3427.

[10] Silyl-modified Prins cyclization: a) G. S. Viswanathan, J. Yang, C.-J. Li, *Org. Lett.* **1999**, *1*, 993–995; b) A. P. Dobbs, S. Martinovic, *Tetrahedron Lett.* **2002**, *43*, 7055–7057; c) K. Meilert, M. A. Brimble, *Org. Lett.* **2005**, *7*, 3497–3500.

[11] P. O. Miranda, D. D. Diaz, J. I. Padrón, M. A. Ramírez, V. S. Martín, *J. Org. Chem.* **2005**, *70*, 57–62.

[12] P. Skehan, P. Storeng, D. Scudeiro, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, M. R. Boyd, *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112.

[13] The NCI renamed the $IC_{50}$ value, the concentration that causes 50% growth inhibition, the $GI_{50}$ value so as to emphasize the correction for the cell count at time zero. A. Monks, D. A. Scudiero, P. Skehan, R. H. Shoemaker, K. D. Paull, D. T. Vistica, C. Hose, J. Langley, P. Cronice, M. Vaigro-Wolf, M. Gray-Goodrich, H. Campbell, M. R. Mayo, *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.

[14] P. E. Pizao, G. J. Peters, J. van Ark-Otte, L. A. Smets, E. Smitskamp-Wilms, B. Winograd, H. M. Pinedo, G. Giaccone, *Eur. J. Cancer* **1993**, *29A*, 1566–1573.

[15] J. R. Parikh, W. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[16] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

[17] J. E. Baldwin, R. M. Adlington, S. H. Ramcharitar, *Tetrahedron* **1992**, *48*, 3413–3428.

[18] The octanol/water partition coefficient expressed in logarithmic form (Clog *P*) is widely used for calculating drug lipophilicity. It is usually calculated from the sum of partition coefficients of the chemical fragments composing the molecule. Software-predicted lipophilicity of the compounds was calculated with the program Clog *P*, accessible from www.daylight.com/daycgi/clogp, working with Hansch–Leo's "fragment constant" method.

Received: October 5, 2005
Published online on January 30, 2006