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Synthesis and antiproliferative activity of (2*R*,3*R*)-disubstituted tetrahydropyrans. Part 2: Effect of side chain homologation☆

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Abstract—In this study, we synthesized a series of enantiomerically pure (2*R*,3*R*)- and (2*R*,3*S*)-disubstituted tetrahydropyrans bearing a CH_2O spacer group on the side chain at position 2 of the heterocyclic ring. The in vitro antiproliferative activities of the compounds were examined in the human solid tumor cell lines A2780 (ovarian cancer), SW1573 (non-small cell lung cancer), and WiDr (colon cancer). Overall, the results point out the relevance for antiproliferative activity of the distance between the heterocycle and the unsaturated group.

Marine drugs with cyclic ether scaffolds continue to attract considerably the attention of researchers in the search for novel antitumor compounds.[1] In our group, we have developed diverse methodologies for the synthesis of these structurally challenging molecules.[2]

We have reported on the antiproliferative activity of a series of (2*R*,3*S*)-disubstituted tetrahydropyrans (*trans*-THPs),[3] (2*R*,3*R*)-disubstituted tetrahydropyrans (*cis*-THPs),[4] and (2*R*,6*S*)-disubstituted tetrahydropyrans[5] against a representative panel of human solid tumor cell lines (Fig. 1). The structure–activity relationship (SAR) study revealed that in general *cis*-THPs are more active than *trans*-THPs. In addition, we found that an unsaturation (either α,β-unsaturated ester or vinyl group) on the side chain at position 2 of the THP ring appears relevant for the biological activity. The latter was observed also for 2,6-disubstituted THPs.

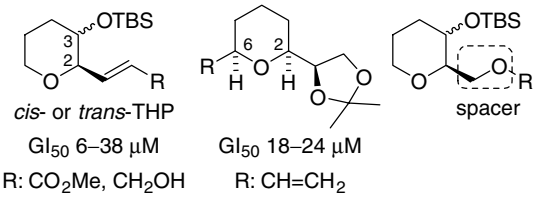

Figure 1. General structure of antiproliferative *cis*- and *trans*-THPs.

In this article, we explore the biological activity of a series of *cis*- and *trans*-THPs, which show a CH_2O spacer group between the heterocycle and the side chain at position 2 of said THP ring (Fig. 1). The choice of the CH_2O spacer group was done with two ideas in mind.

On the one hand, the synthesis of the novel *cis*- and *trans*-THPs could be achieved in a limited number of steps from the readily available THPs **1** and *trans*-**1**, respectively. On the other hand, the oxygen atom provides an additional point of diversity on the functional groups that can be prepared in order to perform a SAR study. The antiproliferative activity was assessed against the panel of three representative human solid tumor cell lines A2780 (ovarian cancer), SW1573 (non-small cell lung cancer), and WiDr (colon cancer).

Keywords: Marine products; Anticancer drugs; Cyclic ethers; Solid tumors; Structure–activity relationship.
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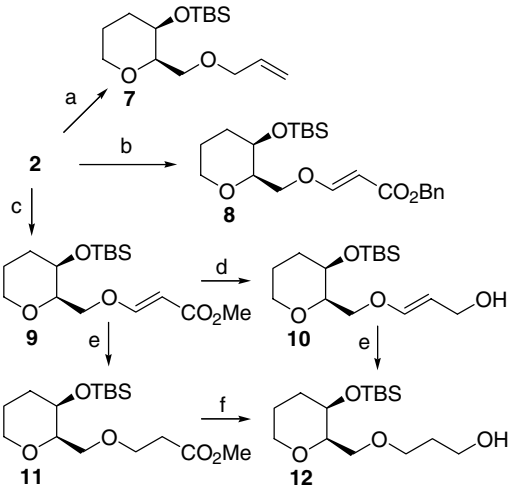
The results are compared to those obtained previously for *cis*- and *trans*-THPs bearing shorter side chains.

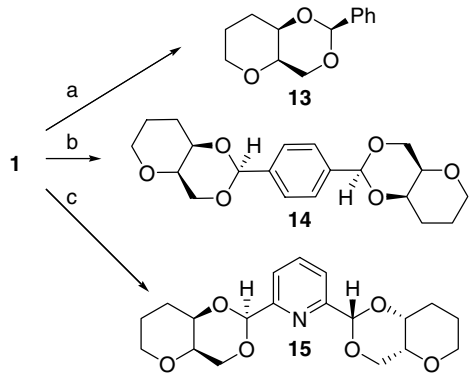
The synthesis of the *cis*-THP derivatives (Scheme 1) starts from diol **1**, which can be obtained from the commercially available tri-*O*-acetyl-D-galactal.[6] Silyl protection of **1** followed by selective cleavage of the exocyclic silyl ether leads to the *cis*-alcohol **2**.[7] Two-carbon homologation of the primary alcohol of compound **2** with sodium iodoacetate provides the carboxylic acid **3** in excellent yields. Esterification of the carboxylic acid **3** with benzyl alcohol gives the benzyl ester **4**. Further removal of the *tert*-butyl dimethylsilyl (TBS) ether affords the hydroxy ester **5**. Finally, the catalytic hydrogenation of compound **5** followed by lactonization using the 2-chloro-1,3-dimethylimidazolinium chloride, a commercially available dehydrating agent,[8] leads to the bicycle **6**. When applying the above-described synthetic methodology to the commercially available tri-*O*-acetyl-D-glucal,[9] the series of corresponding *trans*-THP derivatives is obtained (Scheme 1).

Further derivatization of compound **2** to obtain a variety of alkyloxy substituents with an unsaturation on the side chain is shown in Scheme 2. Thus, alkylation of the alcohol **2** with allyl bromide provides the allyl ether **7**. The hetero-Michael addition of alcohol **2** to the appropriate propiolate ester allows preparing benzyl ester **8** (from benzyl propiolate) and methyl ester **9** (from methyl propiolate). The reaction is catalyzed by tributylphosphine[10] and proceeds in high yields. The reduction of the methyl (*E*)-α,β-unsaturated ester **9** with DIBAL-H in THF at −20 °C provides the (*Z*) allylic alcohol **10** in low yields. The catalytic hydrogenation of the vinyl ether **10** gives the saturated alcohol **12** in modest yields (17% yield from **9**). On the contrary, the catalytic hydrogenation of compound **9** gives saturated methyl ester **11**, which after subsequent reduction with DIBAL-H in THF at 0 °C allows obtaining saturated alcohol **12** in 87% yield from **9**.

A final set of aromatic acetals is prepared from *cis*-alcohol **3** and it is shown in Scheme 3. Condensation of diol **1** with benzaldehydedimethyl acetal using catalytic amounts of CSA affords the benzylidene acetal **13** as

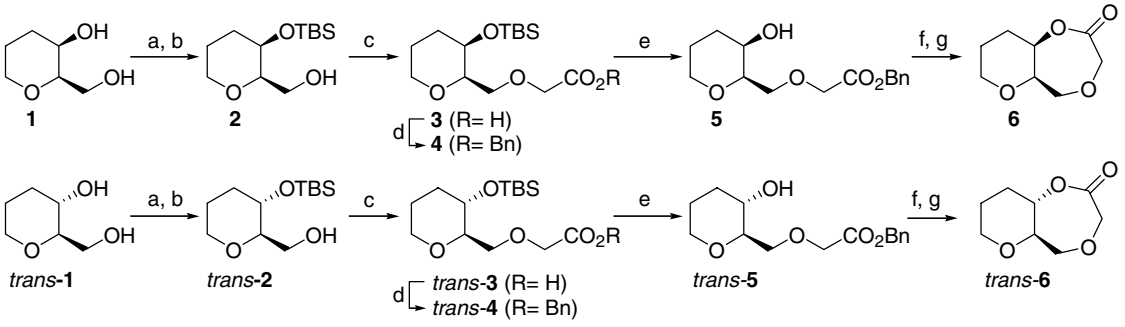


Scheme 2. Reagents and conditions: (a) NaH, allyl bromide, NBu_4I (cat.), THF, 97%; (b) benzyl propiolate, Bu_3P, CH_2Cl_2, rt, 89%; (c) methyl propiolate, Bu_3P, CH_2Cl_2, rt, 93%; (d) DIBAL-H, THF, –20 °C, 42%; (e) H_2, Pd(C) (cat.), AcOEt, 96% for **11**, 40% for **12**; (f) DIBAL-H, THF, 0 °C, 91%.



Scheme 3. Reagents and conditions: (a) $PhCH(OCH_3)_2$, CSA (cat.), CH_2Cl_2, 92%; (b) terephthalaldehyde, *p*-TsOH (cat.), CH_2Cl_2, 4 Å MS, Δ, 70%; (c) 2,6-pyridinedicarboxaldehyde, 2,2-dimethoxypropane, *p*-TsOH (cat.), toluene (0.25 M), Δ, 71%.

sole stereoisomer.[11] The *bis*-acetal **14** is obtained by a double condensation of two molecules of alcohol **1** with terephthalaldehyde. This reaction is catalyzed



Scheme 1. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2; (b) TFA/THF/H_2O (1:1:1), 76% yield from **1**, 78% yield from *trans*-**1**; (c) NaH, ICH_2CO_2Na, THF, 94% for **3**, 95% for *trans*-**3**; (d) BnOH, DMAP, CSA, DCC, CH_2Cl_2, 95% for **4**, 95% for *trans*-**4**; (e) HF, CH_3CN, 85% for **5**, 90% for *trans*-**5**; (f) H_2, $Pd(OH)_2$ (cat.), AcOEt; (g) 2-chloro-1,3-dimethylimidazolinium chloride, NaH, DMAP, CH_2Cl_2, 0 °C → rt, 83% yield from **6**, 87% yield from *trans*-**6**.

by *p*-TsOH. Finally, the condensation of diol **1** with 2,6-pyridinedicarboxaldehyde provides the *bis*-acetal **15**.[12]

The in vitro antiproliferative activity was evaluated using the National Cancer Institute (NCI) protocol.[13] We screened growth inhibition and cytotoxicity against the panel of human solid tumor cell lines A2780, SW1573, and WiDr after 48 h of drug exposure using the sulforhodamine B (SRB) assay.[4] In addition to the biological activity, for each compound the lipophilicity expressed as *C*log *P*[14] was calculated to correlate lipophilicity with antitumor activity.[15] The *C*log *P* values together with the growth inhibition data are listed in Table 1. From the results it is possible to divide the compounds in two groups. The group of active products comprises five products, which show *C*log *P* values in the range 3.5–5.3 and GI_{50} values in the range 15–50 μM. The remaining derivatives are not active against the panel of cell lines. This observation can be explained in part by the decreased lipophilicity that these THPs show (*C*log *P* < 3.3).

With the exception of compounds **7** and **9**, all active derivatives exhibit a similar antiproliferative activity against the three cell lines (GI_{50} values in the range 17–37 μM). Thus, WiDr colon cancer cells and SW1573 NSCLC cells were less sensitive to *cis*-THPs **7** and **9**, respectively. When considering TGI and LC_{50} values it is possible to observe that compounds *trans*-**4** and **7** are the most active of the series against the ovarian cancer and the NSCLC cells.

From the analysis of the growth inhibition parameters we obtain the following SAR. Consistently with our previous findings,[3,4] all active products bear a TBS ether group at position 3 of the THP ring, whilst the corresponding free hydroxyl derivatives were inactive (**4** vs **5**, and *trans*-**4** vs *trans*-**5**). In addition, the presence of the TBS ether group is not sufficient for antiproliferative activity as shown with inactive derivatives **2**, *trans*-**2**,**3**, *trans*-**3**, and **10**–**12**. Overall, saturated benzyl esters **4** and *trans*-**4** together with allylic ether **7** and α,β-unsaturated esters **8**–**9** induce growth inhibition. On the contrary, allylic alcohol **10**, saturated methyl ester **11**, saturated alcohol **12**, and acetals **13**–**15** are inactive in this assay.

A direct comparison of the growth inhibition parameters between THPs with (**4**, **8**–**9**) and without (**16**–**19**) the CH_2O spacer group reveals the following considerations. An improvement in antiproliferative activity is observed for the new β-alkoxy-α,β-unsaturated esters **8** and **9** when compared to the reported corresponding α,β-unsaturated esters **17** and **18**, respectively. This is particularly evident for the colon cancer cells WiDr (Table 1). A slight increase in biological activity evident from the TGI values happens to analog **4** when compared to its counterpart **19**. The preparation of β-alkoxy-α,β-unsaturated esters leads exclusively to compounds with (*E*) geometry of the double bond. Therefore, we were unable to perform SAR studies to determine the influence of the stereochemistry of the unsaturated functional group in this new type of derivatives.

Table 1. Lipophilicity and in vitro antiproliferative activity of THPs against human solid tumor cells[a]

Compound	*C*log *P*[b]	A2780			SW1573			WiDr		
		GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
2	2.34	>100			>100			>100		
3	2.76	>100			>100			>100		
4	4.68	28 (±7.3)	81 (±30)	94 (±11)	29 (±9.4)	85 (±26)		37 (±8.7)	88 (±23)	
5	1.29	>100			>100			>100		
6	–0.58	>100			>100			>100		
trans-**2**	2.34	>100			>100			>100		
trans-**4**	4.68	17 (±1.8)	36 (±2.6)	74 (±3.2)	17 (±4.2)	37 (±7.6)	79 (±13)	28 (±1.3)	91 (±13)	
trans-**5**	1.29	>100			>100			>100		
trans-**6**	–0.58	>100			>100			>100		
7	3.73	15 (±1.6)	32 (±1.8)	68 (±2.9)	18 (±1.8)	39 (±3.2)	85 (±6.4)	88 (±18)		
8	5.27	26 (±5.3)			26 (±7.0)			37 (±9.3)		
9	3.55	30 (±0.6)	82 (±4.7)		50 (±31)			36 (±3.7)		
10	2.59	>100			>100			>100		
11	3.30	>100			>100			>100		
12	2.72	>100			>100			>100		
13	1.32	>100			>100			>100		
14	0.56	>100			>100			>100		
15	–0.94	>100			>100			>100		
16	3.79	86 (±13)[c]			>100[c]			>100[c]		
17	5.26	32 (±2.7)[c]			37 (±5.7)[c]			90 (±14)[c]		
18	3.52	98 (±2.6)[c]			>100[c]			>100[c]		
19	4.97	23 (±4.5)[c]			30 (±2.9)[c]			19 (±1.6)[c]		
20	2.38	18 (±11)[d]			24 (±5.0)[c]			>100		

[a] Values are given in μM and are means of two to four experiments, standard deviation is given in parentheses. TGI and LC_{50} values are given only if they are less than 100 μM, which is the maximum concentration test.
[b] Ref. 15.
[c] Ref. 4.
[d] Ref. 2c.

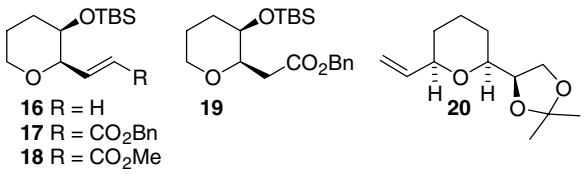


Figure 2. Structure of previously reported THPs without spacer group.

An interesting result is obtained for allylic ether **7**. The three-atom distance of the vinyl group from the THP ring induces a positive effect on the biological activity, when compared to the previously reported analog **16** (Fig. 2). We speculate on a steric hindrance effect of the TBS group to account for the loss of activity of the vinyl group in **16**. This assumption is made considering a previous result obtained for THP **20**,**5** which shows an antiproliferative effect due to the vinyl group, and similar to that observed for derivative **7**.

In summary, we have synthesized a series of enantiomerically pure *cis*- and *trans*-THPs bearing a CH_2O spacer group on the side chain at position 2 of the ring. The growth inhibition parameters were determined against a panel of three representative human solid tumor cell lines. Overall, the results show in these derivatives the relevance of the distance to the THP ring of the unsaturation located at the side chain.

Acknowledgments

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