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Novel goniofufurone and 7-*epi*-goniofufurone mimics from an unexpected titanium-mediated displacement process

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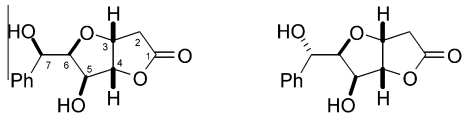
ABSTRACT

Treatment of 7-*O*-benzoyl-5-*O*-benzyl derivatives of (+)-goniofufurone or 7-*epi*-(+)-goniofufurone with titanium(IV) chloride or titanium(IV) bromide gave 7-chloro and 7-bromo-7-deoxy-goniofufurone mimics as the main reaction products along with minor amounts of the corresponding C-7 epimers. An unexpected cyclized product, benzoxepane **8** was isolated in some cases.

(+)-Goniofufurone and 7-*epi*-(+)-goniofufurone (**1** and **2**, Fig. 1) are naturally occurring styryl lactones that exhibit significant cytotoxic activities against several human tumour cell lines.[1] Their cytotoxicity appears to be specific to neoplastic cells since no effects of these compounds on the growth of normal cells were reported. Due to their unique structural features and promising antitumour activities, both natural products **1** and **2**, along with a number of their analogues have been the targets of many total syntheses.[2,3] We have also been involved in the synthesis of these natural products, their derivatives and analogues. Thus, during the synthesis of 7-*O*-benzoyl-(+)-goniofufurone (Scheme 1) we faced the problem of de-O-benzylation of **3** at C-5. Since it has been shown that the standard de-O-benzylation reaction catalysed with palladium on carbon always gives certain amounts of 7-deoxy derivatives,[4] we wanted to explore an alternative de-O-benzylation of **3**, by using Lewis acids ($TiCl_4$ or $TiBr_4$) and an adapted literature procedure.[5]

However, treatment of **3** with $TiCl_4$ in dry CH_2Cl_2 (Scheme 1) did not afford the expected O-debenzylated product, but resulted in the formation of 7-chloro-7-deoxy derivative **6** (33%), the corresponding C-7 epimer **7** (19%), and the benzoxepane **8** (17%).

Essentially the same product distribution (33% of **6**, 16% of **7** and 18% of **8**) was obtained after the treatment of compound **9** under the same reaction conditions ($TiCl_4$, CH_2Cl_2, 1 h at 0 °C, 3 h at rt). This points to a possible S_N1 mechanism for the reaction, presumably via the stabilized benzylic carbocation **3a** and 3-*O*-benzyl derivatives **4** or **5** (isolated in small quantities from some experiments). Preferential attack of the chloride from the less hindered *re*-face (path *b*) leads to (7*R*)-epimer **4** as the major reaction product, while the minor (7*S*)-epimer **5** is formed as a result of carbocation capture from the more hindered *si*-face (path *c*). Subsequent titanium-mediated 5-O-debenzylation of intermediates **4** and **5** gave the final products **6** and **7**. The cyclized product **8** was presumably formed by an intramolecular Friedel–Crafts alkylation process (path *d*).



(+)-goniofufurone (**1**) 7-*epi*-(+)-goniofufurone (**2**)

Figure 1. Structures of natural products **1** and **2**.

In order to gain a better insight into the mechanism of the process, we planned to synthesize the postulated intermediates **4** and **5**, and then to explore their chemical behaviour in the presence of $TiCl_4$ in dichloromethane. Benzylic alcohols **10** and **12** (Scheme 2), previously synthesized in our laboratory starting from D-xylose,[6] were used as convenient starting compounds for this work.

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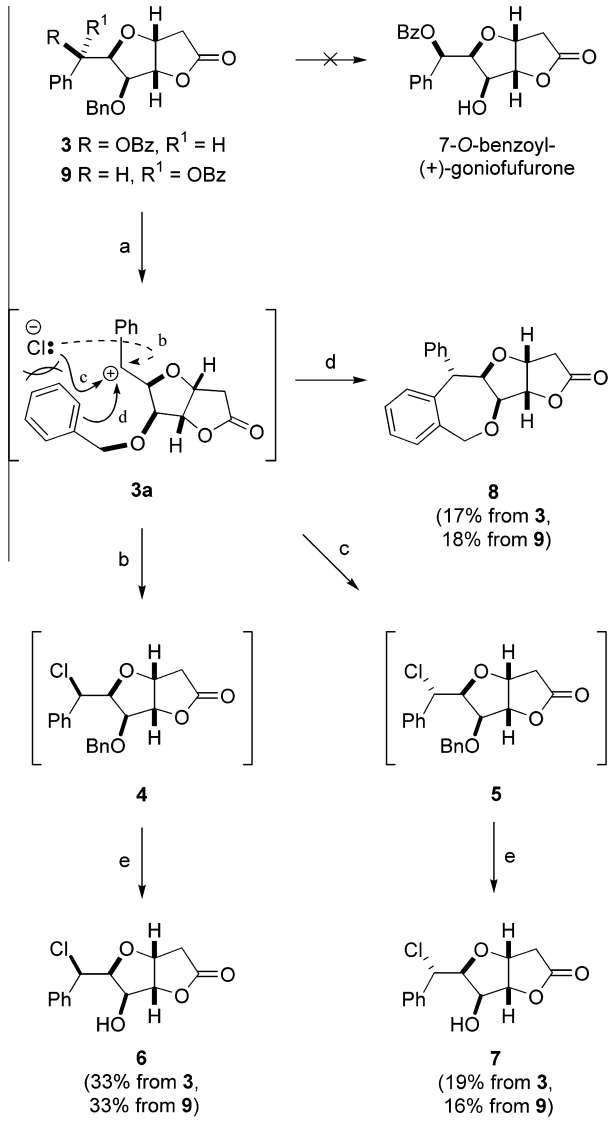
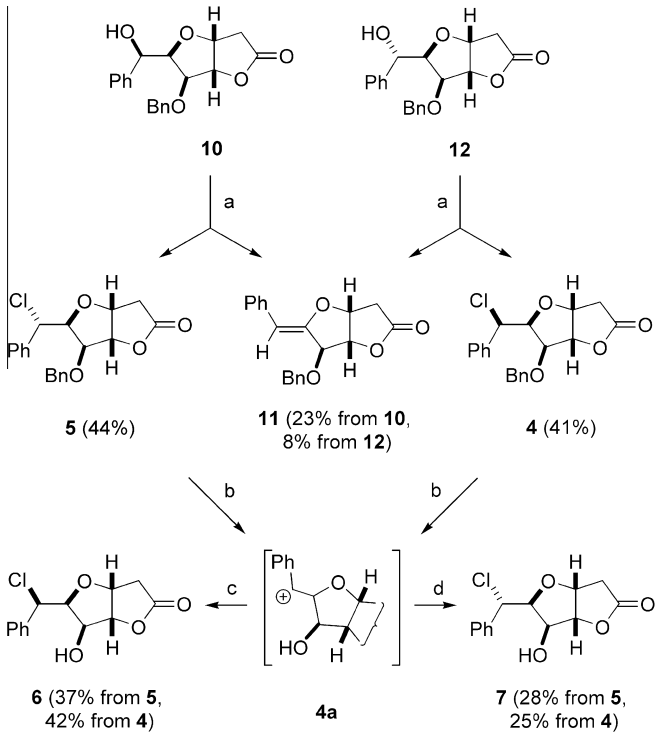


Scheme 1. Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, 0 °C, 1 h, then rt, 3 h; (b) attack from *re*-face (the less hindered); (c) attack from *si*-face (the more hindered); (d) intramolecular Friedel–Crafts alkylation; (e) de-O-benzylation.

Thus, alcohol **10** readily reacted with CCl_4 and Ph_3P, under the standard conditions of the Whistler–Anisuzzaman reaction,[7] to afford 7-chloro-7-deoxy derivative **5** (44%) as the main product, accompanied with a minor amount of olefin **11** (23%). Under the same reaction conditions, compound **12** gave the expected 7-chloro-7-deoxy derivative **4** in a 41% yield along with a minor amount of olefin **11** that was isolated in an 8% yield. The *Z*-geometry of **11** was confirmed by an NOE interaction between H-5 and H-7, indicating that these protons are in close proximity.

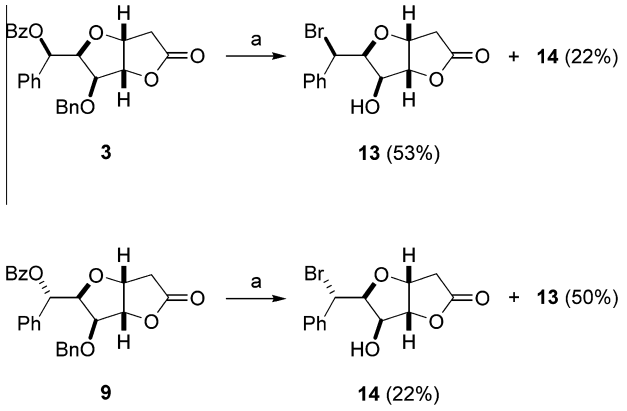
After chromatographic purification, the reactions of **4** and **5** with $TiCl_4$ in CH_2Cl_2 gave a mixture of **6** (42% from **4**, 37% from **5**) and **7** (25% from **4**, 28% from **5**). As in the previous de-O-benzylation reaction (Scheme 1), both starting compounds (**4** and **5**) on treatment with $TiCl_4$ gave approximately the same ratio of C-7 epimers **6** and **7**, thus indicating that the epimerization of **4** and **5** also occurs through an S_N1 mechanism, presumably via the stabilized benzylic carbocation **4a**. Since the product of the Friedel–Crafts alkylation process could not be detected in the reaction mixture it can be concluded that de-O-benzylation of **4** and **5** precedes the epimerization at C-7.



Scheme 2. Reagents and conditions: (a) CCl_4, Ph_3P, Py, 0 °C, 0.5 h, then rt (6 h for **10**, 27 h for **12**); (b) $TiCl_4$, CH_2Cl_2, 0 °C, (0.5 h for **5**, 1 h for **4**), then rt (6 h for **5**, 3 h for **4**); (c) attack from the *re*-face (less hindered); (d) attack from the *si*-face (more hindered).

Since molecules **6** and **7** represent direct isosteres of (+)-goniofufurone and 7-*epi*-(+)-goniofufurone, we expanded our study to the synthesis of the corresponding bromide analogues **13** and **14**, in order to explore their biological activity. Hence, this study was continued by investigating the reaction of **3** with titanium(IV) bromide in CH_2Cl_2 (Scheme 3).

We were pleased to find that 7-bromo derivative **13** was formed in a 53% yield accompanied by a minor amount of its C-7 epimer **14** (22%) as the only by-product. The intramolecular Friedel–Crafts alkylation process did not occur in the presence of this catalyst, as oxepane **8** was not detected in the reaction mixture. When the same reaction conditions were applied to epimer **9**, compounds **13** and **14** were obtained in 50% and 22% yields, respectively. Obviously, the major product **13** in this reaction is formed as a result of Walden inversion at C-7. Moreover, it seems that titanium(IV)



Scheme 3. Reagents and conditions: (a) $TiBr_4$, CH_2Cl_2, 0 °C, 1 h, then rt (2 h for **3**, 4 h for **9**).

bromide is not only a more selective catalyst, but also gives a moderate yield of (+)-goniofufurone isostere **13** (50–53%) compared with the poor chemoselectivity and low yield of **6** (33%) obtained with $TiCl_4$.

For the sake of further comparisons of both catalysts, we decided to prepare the bromide analogues of **4** and **5** (compounds **15** and **16**, Scheme 4), and to explore their reactivity in the presence of titanium(IV) bromide as the catalyst.

Whistler–Anisuzzaman reaction of **10** with CBr_4 and Ph_3P gave a mixture of the expected 7-bromo derivative **15** (49%) and olefin **11** (24%). However, when **12** was allowed to react under the same reaction conditions the expected product **16** was isolated in a 54% yield, accompanied with only a small amount of olefin **11** (8%).

To our pleasant surprise, a clean and smooth reaction of **16** occurred in the presence of $TiBr_4$ whereupon (+)-goniofufurone mimic **13** was obtained in an 86% yield, while the opposite 7-epimer **14** was isolated in only a 1% yield. Moreover, reaction of 5-*O*-benzyl derivative **15** with $TiBr_4$ under the same conditions gave a a 60% yield of 7-*epi*-(+)-goniofufurone mimic **14**, along with a minor amount of epimerized product **13** (14%). Accordingly, the epimerization at C-7 catalysed with $TiBr_4$ is considerably slower than that catalysed by $TiCl_4$. The structures of products **6**, **7**, **8**, **13**, and **14** were unambiguously confirmed by X-ray diffraction analyses.[8]

A side-by-side comparison of the antiproliferative activity of the synthesized styryl lactone mimics **6**, **7**, **13**, and **14** against a range of human tumour cell lines[9] is presented in Table 1. The commercial anti-tumour agent doxorubicin (DOX), as well as the naturally occurring styryl lactones (+)-goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone (**2**), served as reference compounds.

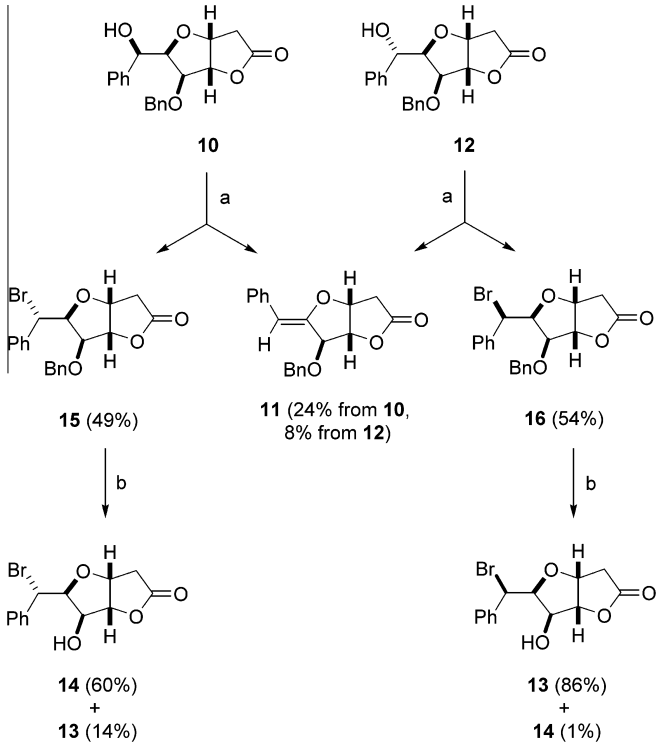
As the data from Table 1 reveal, both (+)-goniofufurone mimics **6** and **13** showed stronger in vitro antitumour activity compared to the parent compound **1** against all the malignant cells under evaluation. Analogue **6** exhibited the most powerful activity towards Raji cells being 654-fold more potent than the commercial cytotoxic agent doxorubicin. The bromide analogue **13** showed potent antiproliferative activity towards HL-60 cells, while the corresponding parent compound **1** was completely inactive against this cell line. Analogue **13** demonstrated over five and twofold greater cytotoxicity in HL-60 cells, when compared to the chloro derivative **6** and DOX, respectively. Finally, both 7-*epi*-(+)-goniofufurone mimics **7** and **14** showed stronger cytotoxicity compared to the lead **2** against the most tested malignant cell lines (with the exception of **14** against Raji cells). Analogue **7** exhibited a strong antiproliferative activity against the Jurkat cell line being 285-fold more potent than the parent compound **2**. At the same time, compound **7** demonstrated threefold higher potency than DOX in the same cell line. Analogue **14** showed the most potent cytotoxicity towards HL-60 cells. This molecule exhibited approximately 20- and 2-fold higher potency against this cell line with respect to lead **2** and DOX, respectively. Remarkably, both natural products **1** and **2** and analogues **6**, **7**, **13**, and **14** were inactive against normal foetal lung fibroblasts (MRC-5).

Table 1
In vitro cytotoxicity of **1**, **2**, **6**, **7**, **13**, **14**, and DOX

Compound	IC_{50}[a] (μM)					
	K562	HL-60	Jurkat	Raji	HeLa	MRC-5
1	7.29	>100	65.87	39.27	10.36	>100
6	4.78	10.34	50.51	0.06	7.38	>100
13	2.15	2.01	5.64	21.22	2.31	>100
2	3.62	38.61	34.21	5.93	5.99	>100
7	2.78	11.64	0.12	3.54	5.68	>100
14	3.52	1.95	7.61	16.73	3.33	>100
DOX	0.36	4.62	0.39	4.09	1.17	0.12

[a] IC_{50} is the concentration of compound required to inhibit cell growth by 50% compared to an untreated control.

The results of this bioassay are consistent with our previous findings,[10] which indicated that 7-*epi*-(+)-goniofufurone (**2**) represents a more potent cytotoxic agent than (+)-goniofufurone (**1**). In fact, it appears that **1** showed the weakest activity when compared to all the other lactones under evaluation. In order to address this issue, we first compared the structures of natural products **1** and **2**, determined previously by X-ray analysis,[11,12] with our X-ray data of analogues **6**, **7**, **13**, and **14**. As the superimposed structures reveal (Fig. 2), the geometries of the bicyclic cores in all the lactones were very similar. The torsion angle between H-6 and H-7 in the crystal structures of **2**, **6**, **7**, **13**, and **14** was in the range of 174.3–178.4°. These values correspond well with the ^1H NMR vicinal couplings ($J_{6,7}$ = 7.9–10.3 Hz), thus implying that all the compounds had similar conformations both in solution and in the solid state. However, the torsion angle between H-6 and H-7 in the crystal structure of **1** is 72.1° as a result of the intramolecular H-bond formed between the 5-OH and 7-OH.[11] The corresponding vicinal coupling ($J_{6,7}$ = 5.3 Hz) again indicates similar geometries of the acyclic moieties both in solution and in the solid state. The



Scheme 4. Reagents and conditions: (a) CBr_4, Ph_3P, Py, 0 °C, 0.5 h, then rt (26.5 h for **10**, 3.5 h for **12**); (b) $TiBr_4$, CH_2Cl_2, 0 °C, 1 h, then rt (5 h for **15**, 4 h for **16**).

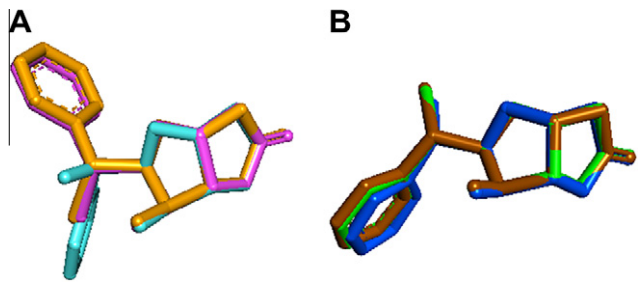


Figure 2. Superimposed structures of: (A) **1** (turquoise), **6** (pink), **13** (orange) and (B) **2** (blue), **7** (green), and **14** (brown).

structural difference between **1** and all the other molecules might be a reason for the different antiproliferative activities of compound **1**.

In summary, we have developed a new and facile route to (+)-goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone (**2**) mimics bearing chloro (**6** and **7**), or bromo functions (**13** and **14**) at C-7. Both titanium(IV) chloride and titanium(IV) bromide were found to catalyse rapid nucleophilic substitution of the benzylic ester functions at C-7 along with de-O-benzylation at C-5. However, these transformations were usually accompanied by epimerization at C-7, which was more pronounced in the presence of $TiCl_4$, but was much less evident when titanium(IV) bromide was used as the catalyst. All the synthesized styryl lactone mimics demonstrated potent to moderate growth-inhibitory effects against a panel of human malignant cell lines, but were devoid of any significant cytotoxicity towards normal foetal lung fibroblasts (MRC-5). Additionally, all of the synthesized analogues were broadly toxic against most of the cell lines under evaluation. Bromide isosteres **13** and **14** exhibited the most pronounced growth inhibitory effects when compared to leads **1** and **2**, respectively. These results confirm that the isosteric replacement of hydroxy functionalities at C-7 with Cl or Br groups improves the antiproliferative effects of the resulting mimics against some human neoplastic cells.

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Supplementary data

Supplementary data (general experimental procedures, full characterization data, detailed description of the crystallographic results and copies of NMR spectra of final products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.121. These data include MOL files and InChiKeys of the most important compounds described in this article.

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