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Divergent Synthesis of Cytotoxic Styryl Lactones from D-Xylose. The First Total Synthesis of (+)-Crassalactone C

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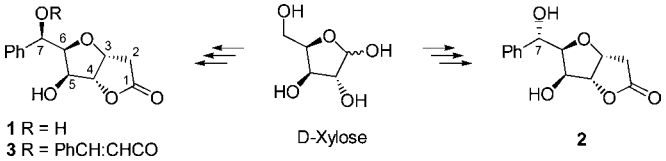
ABSTRACT



A new divergent approach to (+)-goniofufurone (1) and 7-*epi*-(+)-goniofufurone (2), as well as the first total synthesis of crassalactone C (3), has been achieved starting from D-xylose. In a preliminary bioassay, all three natural products 1, 2, and 3 showed remarkable in vitro antiproliferative activities against K562, Raji, and HeLa neoplastic cell lines.

Asian trees of the genus *Goniothalamus* of the plant family Annonaceae have long been recognized as a source of biologically active styryl lactones.[1] Many styryl lactones that have been isolated from *Goniothalamus* species or synthesized exhibited a notable cytotoxic activity against certain human tumor cell lines.[2] (+)-Goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone[3] (**2**) are naturally occurring styryl lactones that have attracted considerable attention since their isolation from the stem bark of *Goniothalamus giganteus* (Annonaceae).[4,5] Due to their unique structural features and promising antitumor activities, both natural products **1** and **2**, along with a number of their analogues, have been the targets of many total syntheses.[6,7] (+)-Crassalactone C (**3**) is a natural 7-*O*-cinnamoyl derivative of (+)-goniofufurone that was very recently isolated from the leaves and twigs of *Polyalthia crassa*.[8] Its structure was determined on the basis of spectroscopic methods. The absolute stereochemistry of **3** was established by treatment of the isolated (+)-**1** with cinnamoyl chloride. Apart from this nonselective and low-yielding single step route,[8] no total synthesis of **3** was hitherto reported. As a part of our continuing interest in the synthesis of natural products and analogues having γ-lactone rings,[9] we have planned the synthesis of **1**−**3**. We report herein their

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(1) For a review on chemistry, biogenesis, and biological activities of styryl lactones from *Goniothalamus* species, see: Blazquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161.

(2) For recent reviews on cytotoxicity of styryl lactones and their analogues, see: (a) de Fatima, A.; Modolo, L. V.; Conegero, L. S.; Pilli, R. A.; Ferreira, C. V.; Kohn, L. K.; de Carvalho, J. E. *Curr. Med. Chem.* **2006**, *13*, 3371. (b) Mereyala, H. B.; Joe, M. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 293. (c) See also ref. 1

(3) Due to differences in numbering systems, compound **2** is sometimes named as 8-*epi*-goniofufurone (e.g., see ref 8).

(4) Fang, X. P.; Anderson, J. E.; Chang, C. J.; Fanwick, P. E.; McLaughlin, J. L. J. *Chem. Soc., Perkin Trans. 1* **1990**, 1655.

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(8) Tuchinda, P.; Munyoo, B.; Pohmakotr, M.; Thinapong, P.; Sophasan, S.; Santisuk, T.; Reutrakul, V. *J. Nat. Prod.* **2006**, *69*, 1728.

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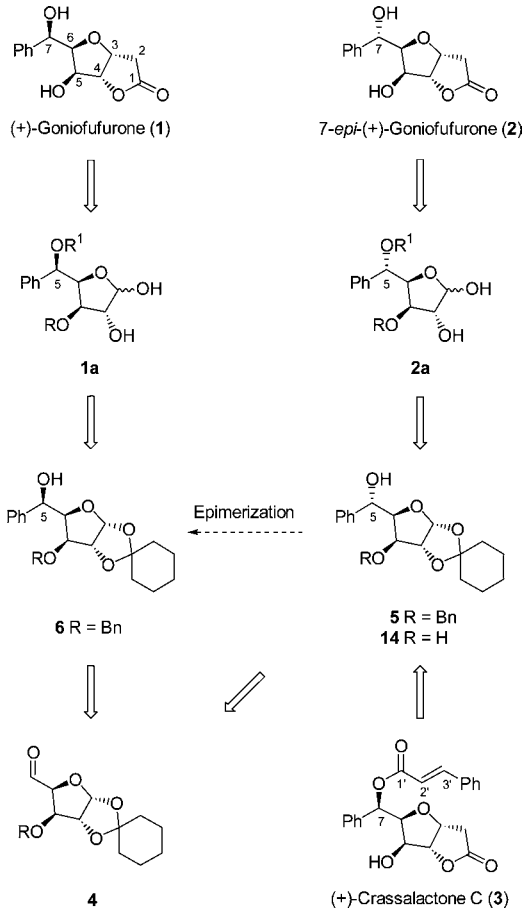
divergent synthesis using D-xylose as a chiral precursor and a preliminary bioassay against human K562, Raji, HeLa, and MRC-5 cell lines. The data related to cytotoxic activities of **1**−**3** against the mentioned cell lines are herein for the first time reported.

All three target compounds **1**−**3** contain five contiguous stereocenters and display a clear structural similarity. We thus wanted to design a divergent synthesis for all three compounds from a common intermediate. Among other methods, the required [3.3.0] bicyclic lactone core could be formed through condensation of Meldrum's acid with a protected sugar lactol derivative.[10] Accordingly, we envisaged the retrosynthetic concept depicted in Scheme 1. For both **1**

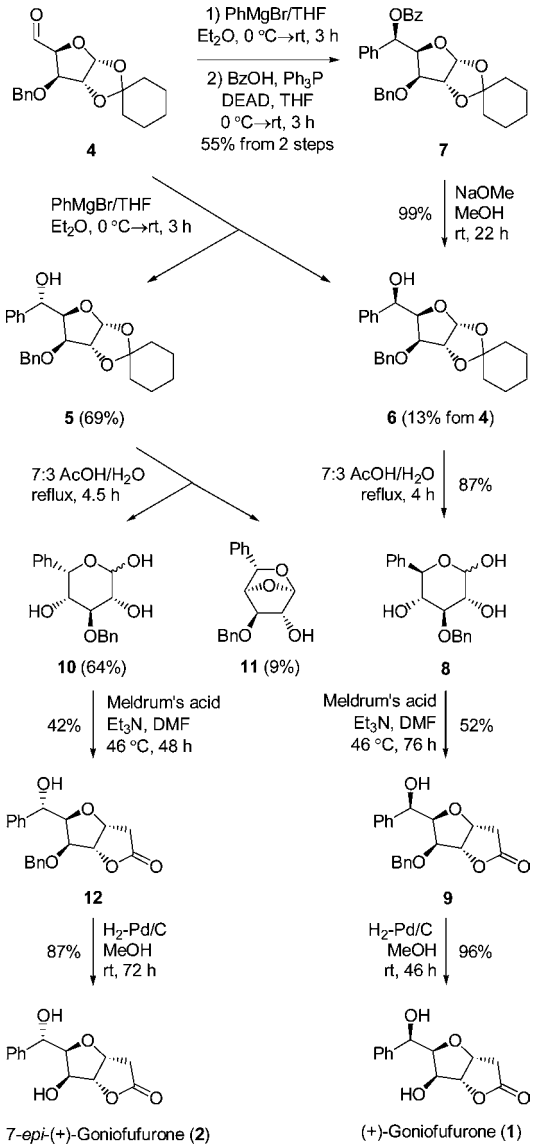
Scheme 1. Retrosynthetic Analysis of (+)-Goniofufurone (**1**), 7-*epi*-Goniofufurone (**2**), and (+)-Crassalactone C (**3**)



and **2**, lactone ring-removal would give rise via, respectively, **1a** and **2a** to the two epimeric alcohols **6** and **5**. These can be prepared from the same aldehyde **4** by means of stereoselective addition of PhMgBr. Synthesis of **4** itself is visualized from D-xylose by established chemical reactions.[9b]

Disconnection of **3** shows that it can be derived from the diol **14** by a number of successive transformations that involve regioselective Mitsunobu reaction in the presence of cinnamic acid and hydrolytic removal of the 1,2-*O*-cyclohexylidene protective group, followed by γ-lactone formation. Intermediate **14** in turn should be accessible from **5** by removal of benzyl protective group from C-3.

Scheme 2. Synthesis of (+)-Goniofufurone (**1**) and 7-*epi*-Goniofufurone (**2**)



The synthesis of **1** and **2** is presented in Scheme 2. Addition of phenylmagnesium bromide in ether to **4** led to two diastereomeric alcohols **5** and **6** in a 6:1 ratio and 82% combined yield. The observed diastereoselectivity may be explained as a result of the 1,2-chelation control.[11] The major L-ido isomer **5** has the same stereochemistry as target **2**, while the minor D-gluco stereoisomer **6** is of the same absolute

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(10) Bruns, R.; Wernicke, A.; Koll, P. *Tetrahedron* **1999**, *55*, 9793.

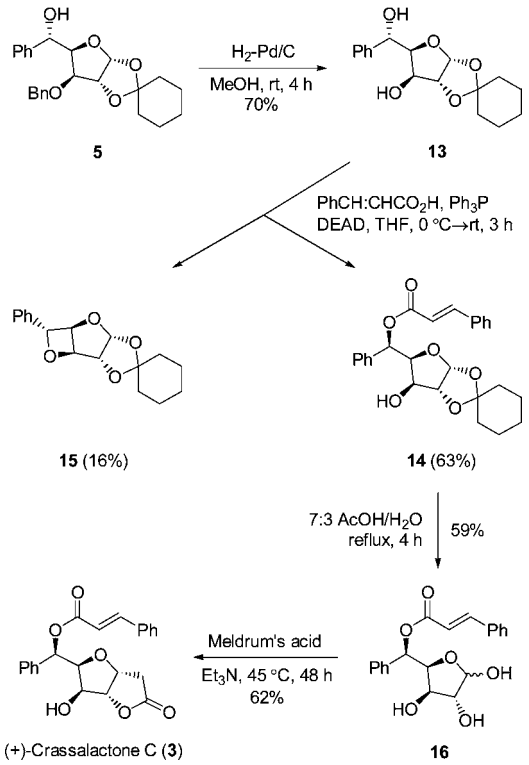
(11) Gracza, T.; Szolcsányi, P. *Molecules* **2000**, *5*, 1386.

configuration as both targets **1** and **3**. Efforts to change the isomeric ratio in favor of **6** were unsuccessful (e.g., use of phenylcerium dichloride[11] gave **5** and **6** in a 2:1 ratio, but in only 20% yield). To prepare compound **6**, an efficient two-step route was developed that involved configurational inversion at C-5 in **5** under the Mitsunobu conditions.[12] Accordingly, treatment of **5** with diethyl azodicarboxylate, triphenylphosphine, and benzoic acid gave the expected 5-*O*-benzoyl derivative **7** which upon deprotection with methanolic sodium methoxide formed **6** in 55% yield (from three steps). Hydrolytic removal of the cyclohexylidene protective group in **6** with aqueous acetic acid, gave the corresponding lactol **8**. Since the pyridine solution of **8** mutarotated to a more positive equilibrium value {$[\alpha]^{20}_D = +23.7 \rightarrow +39.6$ (77 h)}, the crystalline **8** was the β anomer (Hadson's rule). Attempted condensation of **8** with Meldrum's acid in the presence of *tert*-butylamine[10] failed to give the expected γ-lactone **9**. However, when the last reaction was carried out in the presence of triethylamine as a catalyst,[13] the desired γ-lactone **9** was obtained in 52% yield. Final cleavage of benzyl protecting group in **9** gave (+)-goniofufurone (**1**). The physical and spectral data of thus-obtained sample **1** were identical to those reported in the literature.[7e,10]

The stereoisomer **5** was converted to (+)-7-*epi*-goniofufurone (**2**) by using the same methodology as that already applied for the conversion of **6** to **1**. Treatment of **5** with aqueous acetic acid gave **10** (64%) along with a minor amount of **11** (9%).[14] Reaction of **10** with Meldrum's acid, followed by hydrogenolytic 5-*O*-deprotection gave (+)-7-*epi*-goniofufurone (**2**). All physical constants and spectral data of thus prepared natural product **2** were in good agreement with those reported in the literature.[10,15]

The synthesis of (+)-crassalactone C (**3**) is presented in Scheme 3. Removal of the benzyl protective group in **5** gave the corresponding diol **13** (70%) that was further allowed to react with cinnamic acid under the standard Mitsunobu conditions. The corresponding cinnamic ester **14** was thus obtained (63%) accompanied by a minor amount of 3,5-anhydro derivative **15** (16%). The side product **15** was presumably formed by a competitive intramolecular nucleophilic displacement process.[12] Indeed, when the last reaction was carried out in the absence of cinnamic acid (Ph_3P, DEAD, refluxing toluene, 1.5 h), the oxetane **15** was isolated as a main reaction product in 71% yield. The assignment of stereochemistry at the C-5 in product **15** was confirmed by an NOE interaction between H-1 and H-5, indicating that these protons are in close proximity on the same side of the ring. Compound **15** might be of use for a synthesis of a hitherto unknown conformationally constrained analogue of **1** (5,7-anhydrogoniofufurone). Hydrolytic removal of the cyclohexylidene protective group in **14** gave the expected lactol **16** (59%), which upon treatment with Meldrum's acid in the presence of triethylamine gave (+)-crassalactone C (**3**), with physical and spectral properties in reasonable agreement with those reported in the literature.[8]

Scheme 3. Synthesis of (+)-Crassalactone C (**3**)



Compounds **1**−**3** were evaluated for their in vitro antiproliferative activity toward human myelogenous leukemia (K562), Burkitt's lymphoma (Raji cells), cervix carcinoma (HeLa), and normal fetal lung (MRC-5) cell lines. Cytotoxic activities were evaluated by using standard MTT assay[16] after exposure of cells to the tested compounds for 72 h. The commercial cytotoxic agent doxorubicin (DOX) was used as a positive control in this bioassay. The results are shown in Table 1.

Table 1. In Vitro Cytotoxicity of **1**−**3** and DOX

	IC_{50}, μM[a]			
compd	K562	Raji	HeLa	MRC-5
1	0.41	18.45	8.32	>100
2	0.028	1.25	0.89	>100
3	3.56	15.46	11.25	>100
DOX	0.25	2.98	0.07	0.10

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

In general, all three natural products **1**−**3** exhibited antiproliferative activities against all of the malignant cell

(12) Mitsunobu, O. *Synthesis* **1981**, 1.
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(14) The side product **11** was presumably formed as a result of the competitive intramolecular dehydration of **10** (in furanose form), during removal of acetic acid by codistillation with toluene.
(15) Yang, M.; Li, H. M.; Zhao, G.; Yu, Q.-S.; Ding, Y. *Chin. J. Chem.* **2000**, *18*, 225.
(16) Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827.

lines (K562, Raji, and HeLa) but were devoid of any cytotoxicity against the normal fetal lung fibroblasts (MRC-5). 7-*epi*-(+)-Goniofufurone (**2**) was found to be the most efficient cytotoxic agent against all neoplastic cells, with IC_{50} values ranging from 0.028 to 1.25 μM. The most pronounced antiproliferative activity of compound **2** was recorded against the K562 cells, being ca. 9-fold more potent than the commercial cytotoxic agent doxorubicin. Against the Raji cells, 7-*epi*-(+)-goniofufurone (**2**) was over 2-fold more active with respect to the reference compound, doxorubicin. This compound was also active against HeLa cells, but it was almost 13-fold less potent than the reference compound (DOX). Remarkably, compound **2** exhibited 1 order of magnitude higher cytoxicity against all the malignant cell lines when compared to (+)-goniofufurone (**1**) and (+)-crassalactone C (**3**). The previous biological data[2] in different neoplastic cell lines suggested that (+)-goniofufurone (**1**) was more active than 7-*epi*-(+)-goniofufurone (**2**). It appears that K562, Raji, and HeLa represent the first neoplastic cell lines in which stereoisomer **2** shows a stronger in vitro antiproliferative activity with respect to (+)-goniofufurone (**1**).

In conclusion, by utilizing a chiral pool strategy based on D-xylose as the starting material, we have completed a new divergent synthesis of the natural styryl lactones (+)-goniofufurone (**1**) and (+)-7-*epi*-goniofufurone (**2**), as well as the first total synthesis of (+)-crassalactone C (**3**), a novel 7-*O*-cinnamoyl (+)-goniofufurone derivative that has been recently isolated from the tropical plant *Polyalthia crassa*.[8] In addition to providing a divergent access to the natural products **1**−**3**, this approach is flexible and straightforward. It uses nonexpensive reagents and a readily available starting material.[17] These advantages make the synthetic methodology suitable for easy preparation of a variety of 7-*O*-substituted (+)-goniofufurone analogues for biological evaluation. In a preliminary MTT bioassay, all three natural products **1**, **2**, and **3** showed remarkable in vitro antiproliferative activities against K562, Raji, and HeLa neoplastic cell lines. 7-*epi*-(+)-Goniofufurone (**2**) was found to be the most active compound, being at least 1 order of magnitude more cytotoxic than (+)-goniofufurone (**1**). To the best of our knowledge, the K562, Raji, and HeLa cells represent the first malignant cell lines, for the time being, in which 7-*epi*-(+)-goniofufurone (**2**) exhibits more potent in vitro antiproliferative activity with respect to (+)-goniofufurone (**1**). Finally, based upon observed antitumor activities of **1**−**3**, as well as their inactivity against the normal MRC-5 cells, we believe that these natural products may serve as important leads in the synthesis of more potent and selective antitumor agents derived from the parent compounds **1**−**3**.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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