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Novel and stereocontrolled asymmetric synthesis of a new naturally occurring styryllactone, (+)-cardiobutanolide

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Abstract—An efficient and stereodefined strategy is described for the asymmetric synthesis of a new styryllactone from the stem bark of *Goniothalamus cardiopetalus*, cardiobutanolide. The synthetic process is based on requisite manipulation of the functionalized bicyclic lactol–lactone intermediate incorporating the glucuronolactone-derived skeleton in a complete stereoselective manner.

Trees of genus *Goniothalamus* of the plant family Annonaceae have for a long time aroused considerable interest as a source of potent biologically active styryllactones[1] from a pharmacological point of view.[2] These styryl-types of natural products have been used as a traditional medicine in Asia to treat rheumatism, edema, as an abortifacient, and as a mosquito repellent.[3] Especially, lactones isolated can be mainly classified into two groups related to the size of the lactone ring. The first group consists of the five-membered lactones such as cardiobutanolide (**1**) and goniofufurone (**2**) as shown in Figure 1 and the second group consists of the six-membered lactone moiety, for example, goniotriol (**3**), etharvendiol (**4**), altholactone (**5**), and goniopyrone (**6**). Their unique and intriguing structures coupled with diverse and useful characteristics as well as their broad spectrum of activity have made them inviting targets for synthesis.[4] In addition, one of the most useful representatives of the plant family Annonaceae, the Indomalayan genus *Goniothalamus cardiopetalus*, has in 2003 given rise to the isolation of a new styryllactone, cardiobutanolide (**1**) described above, possessing potentially biological properties.[5] Herein, we wish to communicate a novel and stereocontrolled asymmetric synthesis of **1** based on nucleophilic Grignard addition to the bicyclic lactol–lactone elaborated from commercially available D-glucuronolactone followed by complete stereoselective reduction of the crucial hemiketal intermediate

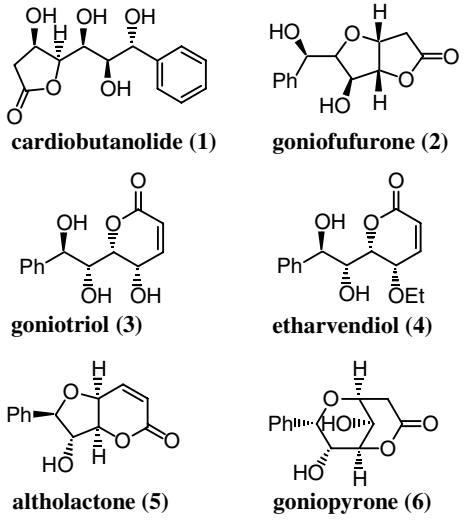

Figure 1. Styryllactones.

obtained in this sequence. To the best of our knowledge, only one approach to the synthesis of **1** has been reported[6] recently during the course of our synthetic studies.

In formulating the synthetic plan for **1**, we recognized that the absolute configurations at C(3), C(4), and C(5) are the same as the configurations at the corresponding centers C(3), C(4), and C(5) of readily available and inexpensive D-glucuronolactone (**7**) as shown in Figure 2. Further we envisioned that the stereogenic center of C(6) in **1** would be constructed through nucleophilic addition of organometallic reagent to a

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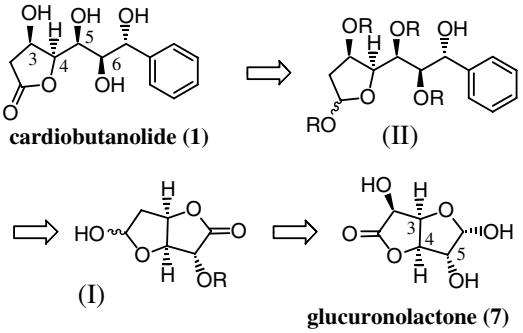
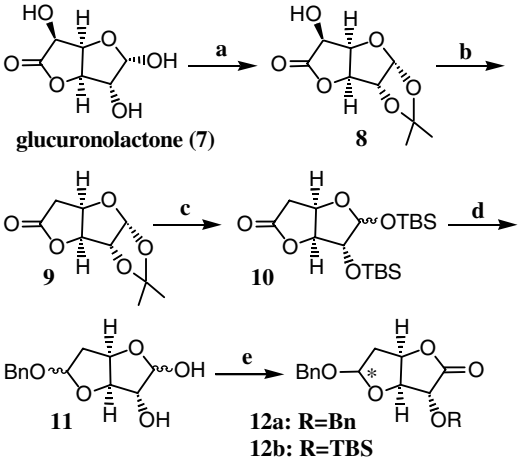


Figure 2. Retrosynthetic pathways.

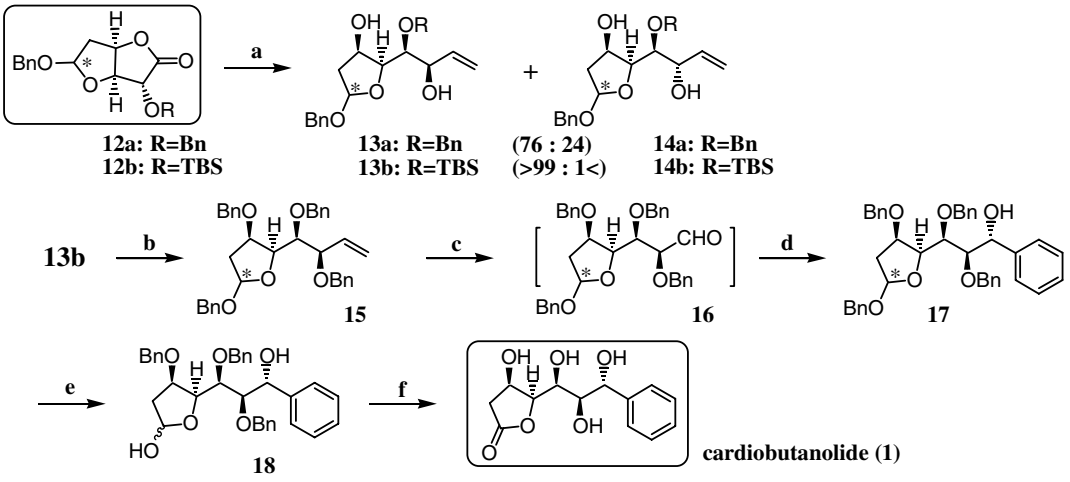
bicyclic lactol–lactone (**I**) followed by stereoselective reduction of its hemiketal intermediate, allowing the synthesis of the lactol derivative (**II**). Meanwhile, the construction of (**I**) would have to be independently set in chemo- and regioselective manipulation of the starting material **7**.

To begin with, an attempt to synthesize the important intermediate such as the type of lactol–lactone (**I**) was designed. The results are summarized in Scheme 1. α-Hydroxyl function of D-glucuronolactone (**7**) was effectively eliminated through successive acetonide[7] and phenylthiocarbonate formations, followed by deoxygenation under radical conditions[8] to give the lactone **9** in 89% yield (three steps).[4r] After exchange of the protecting groups of **9** to the bis-TBS ethers,[9] the lactonic segment of **10** thus obtained was protected as the lactol–benzyl ether through DIBAL-H reduction, which was, in turn, submitted to desilylation, leading to the diol–lactol derivative **11** as a mixture of four anomers. Then, **11** was effected by chemoselective Fetizon's oxidation with Ag_2CO_3 of the lactol function only and the following hydroxyl protection with two different groups to provide the desired bicyclic lactol–lactone intermediates **12** in high yield. Interestingly both **12a** and **12b** are obtained as a single anomer product, respectively.[10]



Scheme 1. Reagents and conditions: (a) acetone, H_2SO_4; 95%; (b) **1**, PhOC(S)Cl, DMPA, pyridine, CH_3CN; **2**, Bu_3SnH, AIBN, toluene, 110 °C; 94% (two steps); (c) **1**, TFA–H_2O (20:1), THF; 89%; **2**, TBSCl, imidazole, DMF; 98%; (d) **1**, DIBAL-H, THF, −78 °C; 98%; **2**, BnBr, Ag_2O, AcOEt; **3**, Bu_4NF, THF; 55% (two steps); (e) **1**, Ag_2CO_3, toluene, Celite, reflux; 88%; **2**, BnBr, Ag_2O, AcOEt; 96% (**12a**); TBSCl, imidazole, DMF; 92% (**12b**).

With the compounds **12** in hand, we next focused our research on the total synthesis of **1** as shown in Scheme 2. Thus, **12a** was initially effected with vinylmagnesium chloride in the presence of $CeCl_3$[11] at low temperature to afford the labile hemiketal intermediate, which was readily treated with $NaBH_4$ also in the presence of $CeCl_3$ at −40 °C, providing the corresponding allyl alcohol mixture of **13a** and **14a** with moderately diastereofacial differentiation (**13a**:**14a** = 76:24, determined by ^1H NMR). On the contrary, we were delighted to find that the use of TBS-protected **12b**, $[\alpha]_D^{27}$ +130.8 (*c* 0.96, $CHCl_3$), dramatically changed the results and fortunately brought about the desired isomer **13b**, $[\alpha]_D^{27.6}$ +60.65 (*c* 1.17, $CHCl_3$), as the single product (determined by ^1H and ^{13}C NMR)[12] in 68% isolated yield (two steps) under the same reaction conditions.[13] For



Scheme 2. Reagents and conditions: (a) **1**, vinylmagnesium chloride, $CeCl_3$, THF, −78 °C; **2**, $NaBH_4$, $CeCl_3$, MeOH, −40 °C; 55% (two steps) (**13a**+**14a**); 68% (two steps) (**13b**); (b) **1**, Bu_4NF, THF; 95%; **2**, NaH, BnBr, Bu_4NI, THF; 90%; (c) **1**, cat. OsO_4, NMO, acetone–H_2O (1:1); **2**, $NaIO_4$, THF–H_2O (1:1); (d) PhMgBr, $CeCl_3$, THF, −78 °C; 56% (three steps); (e) 70%-AcOH; 91%; (f) **1**, Ag_2CO_3, Celite, toluene, reflux; 97%; **2**, H_2, Pd/C, AcOEt; 80%.

the purpose of reducing the formation of by-products, the sily group in **13b** was next replaced with the benzyl function together with the same benzyl-protection of the resulting two hydroxyl moieties. The olefinic part in **15**, $[\alpha]_D^{25}$ +4.57 (*c* 1.05, $CHCl_3$), thus obtained was then cleaved via dihydroxylation to afford the aldehyde intermediate **16**, which was successively subjected to phenyl-Grignard addition at low temperature in the presence of $CeCl_3$ in expectation of higher stereoselective results. This effect resulted in the preparation of the fully functionalized alcohol **17**, $[\alpha]_D^{25}$ +4.18 (*c* 1.16, $CHCl_3$), as a sole product in 56% yield (three steps) with the desired configuration[14] as well as fortunately complete stereoselectivity.[15] Then, the use of 70% acetic acid underwent chemoselective reaction for hydrolysis to afford the corresponding lactol **18**. Finally, this compound was submitted to Fetizon's Ag_2CO_3-oxidation followed by deprotection of the tribenzyl groups with H_2 on Pd/C to complete the total synthesis of the natural type of **1**, $[\alpha]_D^{26}$ +9.72 (*c* 1.00, MeOH) {natural **1**; $[\alpha]_D^{24}$ +6.4 (*c* 0.28, MeOH)[5] and synthetic **1**, $[\alpha]_D$ +5.5 (*c* 0.3, MeOH)[6]} in 80% yield. The spectral data of synthetic **1** were identical to those of the reported natural and synthetic product.

In summary, this process involves no separation of stereoisomers and was substantially performed under mild conditions through the entire sequence. Further it constitutes a new synthetic strategy and, in addition, represents an easily accessible pathway to styryllactone natural products.

Acknowledgments

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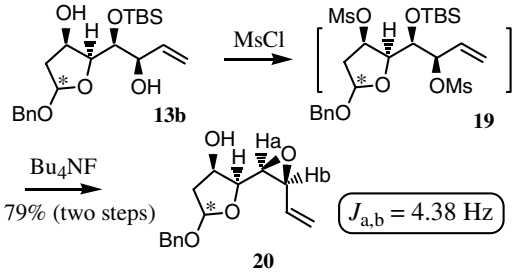
References and notes

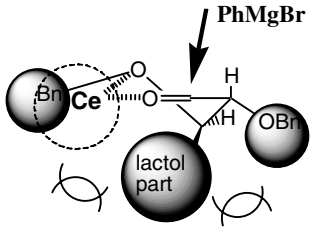
1. For a review on styryllactones from *Goniothalamus* species, see: Blàzquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161.
2. (a) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504; (b) Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortés, D. *Phytochemistry* **1998**, *48*, 1087; (c) Cavé, A.; Figadère, B.; Laurens, A.; Cortés, D. *Prog. Chem. Org. Nat. Prod.* **1997**, *70*, 81.
3. On the cytotoxic activity and other bioactivity of styryllactones, see: Mereyala, H. B.; Joe, M. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 293.
4. For some recent examples; (a) Prasad, K. R.; Gholap, S. L. *Synlett* **2005**, 2260; (b) Popsavin, V.; Grabež, S.; Popsavin, M.; Krstić, I.; Kojić, V.; Bogdanović, G.; Divjaković, V. *Tetrahedron Lett.* **2004**, *45*, 9409; (c) Peris, E.; Cavé, A.; Estornell, E.; Zafra-Polo, M. C.; Figadère, B.; Cortes, D.; Bermejo, A. *Tetrahedron* **2002**, *58*, 1335; (d) Srikanth, G. S. C.; Krishna, U. M.; Trivedi, G. K. *Tetrahedron Lett.* **2002**, *43*, 5471; (e) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161; (e) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161; (f) Su, Y.-L.; Yang, C.-S.; Teng, S.-J.; Zhao, G.; Ding, Y. *Tetrahedron* **2001**, *57*, 2147; (g) Surivet, J.-P.; Vatele, J.-M. *Tetrahedron* **1999**, *55*, 13011; (h) Mereyala, H. B.; Gadikota, R. R.; Joe, M.; Arora, S. K.; Datidar, S. G.; Agarwal, S. *Bioorg. Med. Chem.* **1999**, *7*, 2095; (i) Bruns, R.; Wenicke, A.; Köll, P. *Tetrahedron* **1999**, *55*, 9793; (j) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493; (k) Chen, W.-P.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 103; (l) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472; (m) Cagnolini, C.; Ferri, M.; Jones, P. R.; Murphy, P. J.; Ayres, B.; Cox, B. *Tetrahedron* **1997**, *53*, 4815; (n) Mukai, C.; Hirai, S.; Km, I. J.; Kido, M.; Hanaoka, M. *Tetrahedron* **1996**, *52*, 6547; (o) Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H. *J. Org. Chem.* **1995**, *60*, 3121; (p) Yang, Z.-C.; Zhou, W.-S. *Tetrahedron* **1995**, *51*, 1429; (q) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359; (r) Ye, J.; Bhatt, R. K.; Falck, R. J. R. *Tetrahedron Lett.* **1993**, *34*, 8007; (s) Murphy, P. J.; Dennison, S. T. *Tetrahedron* **1993**, *49*, 6695; Prakash, K. R. C.; Rao, S. P. *Tetrahedron* **1993**, *49*, 1505; (t) Shine, T. K. M.; Tsui, H. C.; Zhou, Z. H. *Tetrahedron* **1992**, *48*, 8659.
   Absolute configurations of these styryl groups are in accord with those of all suggested biogenetic precursors and allowed to propose the absolute configurations of related cytotoxic styryllactones and strucutures of potential biosynthetic intermediates not identified so far, see: Ref. 4q.
5. Hisham, A.; Toubi, M.; Shuaily, W.; Ajitha Bai, M. D.; Fujimoto, Y. *Phytochemistry* **2003**, *62*, 597.
6. Ruiz, P.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 713.
7. (a) Yoda, H.; Nakaseko, Y.; Takabe, K. *Tetrahedron Lett.* **2004**, *45*, 4217; (b) Yoda, H.; Nakaseko, Y.; Takabe, K. *Synlett* **2002**, 1532.
8. Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
9. Similar carbohydrate-derived starting materials were also applied to the total synthesis of related styryllactones. For example, see: Ref. 4o.
   Direct treatment of **9** according to the following reaction sequence cited in Scheme 1 yielded only intractable materials at the final step of acetonide-deprotection.
10. It is not necessarily to determine the absolute configuration at this anomer center, since the lactol function should be oxidized to the corresponding lactone at the final stage for the synthesis of **1**.
11. (a) Yoda, H.; Mizutani, M.; Takabe, K. *Heterocycles* **1998**, *48*, 479; (b) Yoda, H.; Mizutani, M.; Takabe, K. *Synlett* **1998**, 855.
12. The absolute configuration of the newly created stereogenic center of **13b** was easily characterized to be *R* after derivatization via the mesylate **19** to the corresponding *cis*-epoxide **20** as shown below.



The observed vicinal coupling constant ($J_{a,b}$) of protons (H_a, H_b) was 4.38 Hz, which indicates the epoxide in **20** occupy the cis-relation; see: Tanaka, K.; Horiuchi, H.; Yoda, H. *J. Org. Chem.* **1989**, *54*, 63; Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Mori, I.; Nakata, T.; Oishi, T.

Tetrahedron Lett. **1984**, *25*, 4775. Compound **13a** was also estimated to have the same configuration based on the similarity of its spectral data to those of **13b**.

13. When reduction of the labile hemiketal intermediate derived from **12b** was carried out under slightly different conditions (change of the reduction temperature from −40 to −20 °C), the reaction occurred with unsatisfactory stereoselectivity to give the mixture of the two diastereomers (**13b**:**14b** = 86:14). It is consequently apparent that stereochemical outcome in these reactions strongly depends on the two factors; (a) steric bulkiness of the protecting groups in **12** and (b) reduction temperature of the hemiketal intermediates. These results can be explained that the reaction would proceed simply in terms of the thermodynamically more stable Cram's non-chelation transition structure.
14. The absolute *R*-configuration of the generated stereogenic center was determined unambiguously based on its spectral data of synthetic (+)-**1**.
15. We also tried the same reaction in the absence of $CeCl_3$, leading, as we expected, to the mixture of stereoisomers of **1**. At present we postulate that this high stereoselective performance would be attributed to the steric demand of the $CeCl_3$-mediated six-membered metal–chelate structure due to the bottom-face shielding effect of the three large functional groups described below.



The same type of transition metal halide-promoted six-membered chelating reactions have already been demonstrated in this laboratory with high stereoselectivity; see: Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531.