Stereoselective Synthesis of the Naturally Occurring Styryllactones (+)-Goniofufurone and (+)-Cardiobutanolide

Purificación Ruiz,[†] Juan Murga,^{*,†} Miguel Carda,[†] and J. Alberto Marco*,‡

Departamento de Química Inorgánica y Orgánica, Universidad Jaume I, E-12071 Castellón, Spain, and Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain

alberto.marco@uv.es; jmurga@qio.uji.es

Received September 22, 2004



(+)-Goniofufurone

The naturally occurring γ -lactones (+)-goniofuturone **1** and (+)-cardiobutanolide 2, two pharmacologically active products from Goniothalamus species (Annonaceae), have been synthesized in enantiopure form using L-erythrulose as the chiral starting material. Key steps of these syntheses were a stereoselective anti boron aldol reaction and an asymmetric allylboration.

Introduction

The plant family Annonaceae, with its about 128 genera and over 2000 species, has for a long time aroused a considerable interest from a pharmacological point of view, most particularly because of its polyketide constituents.¹ One of its most notorious representatives, the Indomalayan genus Goniothalamus has given rise to the isolation of a range of compounds endowed with cytotoxic, pesticidal, teratogenic, and other various biological properties.² Two of these compounds are (+)-goniofufurone 1 and (+)-cardiobutanolide 2 (Figure 1). The former was isolated in 1990 from Goniothalamus giganteus and found to display significant cytotoxic properties.^{3,4} Not surprisingly, it has been the object of numerous synthetic efforts,

(2) Blazquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortés, D. Phytochem. Anal. 1999, 10, 161–170.



FIGURE 1. Structures of (+)-goniofufurone 1 and (+)cardiobutanolide 2.

not only toward the natural product but also toward several stereoisomers thereof.⁵ Cardiobutanolide has very recently been isolated from Goniothalamus cardiopetalus.⁶ No synthesis has been reported so far for this compound. Within our general interest in the application of aldol reactions to the stereoselective synthesis of bioactive natural compounds,7 we have now achieved a synthesis of these two natural styryllactones in enantiopure form.

Lactones 1 and 2 contain five contiguous stereocenters and display a clear structural similarity. In fact, 1 may be formally derived from **2** through dehydration between the hydroxyl groups at C-3 and C-6 with cyclic ether formation and configurational retention at both ends. We thus wanted to design a divergent synthesis for both compounds from a common intermediate. Among other methods,⁸ a tetrahydrofuran system can be formed through internal 5-exo-tet nucleophilic displacement of a suitable leaving group by a hydroxyl function with subsequent configurational inversion. Accordingly, we envisaged the retrosynthetic concept depicted in Scheme

 (5) (a) Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H. Tetrahedron 1992,
 48, 8659–8666. (b) Prakash, K. R. C.; Rao, S. P. Tetrahedron 1993,
 49, 1505–1510. (c) Murphy, P. J.; Dennison, S. T. Tetrahedron 1993, 49, 6695-6700. (d) Ye, J.; Bhatt, R. K.; Falck, J. R. Tetrahedron Lett. (a) 1993, 34, 8007–8010. (a) Te, 5., Bhate, R. R. Falck, S. R. Fetruhetton Internation Jates.
(b) 1993, 34, 8007–8010. (c) Gracza, T.; Jäger, V. Synthesis 1994, 1359–1367. (f) Yang, Z.-C.; Zhou, W.-S.; Tetrahedron 1995, 51, 1429–1436. (g) Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H. J. Org. Chem. 1996, 60, 3121–3130. (h) Mukai, C.; Hirai, S.; Kim, I. J.; Kido, M.; Hanaoka, M. Tetrahedron 1996, 52, 6547–6560. (i) Cagnolini, C.; Ferri, M.; Jones, D. D. M. (1997). P. R.; Murphy, P. J.; Ayres, B.; Cox, B. Tetrahedron 1997, 53, 4815-4820. (j) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. J. Org. Chem. **1998**, 63, 7472–7480. (k) Chen, W.-P.; Roberts, S. M. J. Chem. Soc., Perkin Trans. 1 1999, 103-105. (l) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. Tetrahedron 1999, 55, 2493-2514. (m) Bruns, R.; Wernicke, A.; Köll, P. Tetrahedron 1999, 55, 9793-9800. (n) Mereyala, H. B.; Gadikota, R. R.; Joe, M.; Arora, S. K.; Datidar, S. G.; Agarwal, S. Bioorg. Med. Chem. 1999, 7, 2095–2103. (o) Surivet, J.-P.; Vatèle, J.-M. Tetrahedron **1999**, 55, 13011–13028. (p) Su, Y.-L.; Yang, C.-S.; Teng, S.-J.; Zhao, G.; Ding, Y. *Tetrahedron* **2001**, 57, 2147–2153.

(6) Hisham, A.; Toubi, M.; Shuaily, W.; Bai, M. D. A.; Fujimoto, Y. Phytochemistry 2003, 62, 597-600.

(7) (a) Carda, M.; González, F.; Sánchez, R.; Marco, J. A. Tetrahe-dron: Asymmetry **2002**, 13, 1005–1010. (b) Carda, M.; Rodríguez, S.; Segovia, B.; Marco, J. A. J. Org. Chem. **2002**, 67, 6560–6563. (c) Díaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. Tetrahedron Ohra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Herandedron* **2004**, 60, 2979–2985. (d) Murga, J.; Ruiz, P.; Falomir, E.; Carda, M.;
 Peris, G.; Marco, J. A. J. Org. Chem. **2004**, 69, 1987–1992.
 (8) (a) Boivin, T. L. B. *Tetrahedron* **1987**, 43, 3309–3362. (b)
 Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, 4, 1711–
 Marco, J. K. J. Scherf, M. & Scherf, M.

1754. (c) Koert, U. Synthesis **1995**, 115–132. (d) Hoppe, R.; Scharf, H.-D. Synthesis **1995**, 1447–1464.

^{*} Corresponding Authors: (J.A.M.) Phone: 34-96-3544337. Fax: 34-96-3544328. (J.M.) Phone: 34-964-728174.

Universidad Jaume I.

[‡] Universidad de Valencia.

^{(1) (}a) Cavé, A.; Figadère, B.; Laurens, A.; Cortés, D. Prog. Chem. Org. Nat. Prod. **1997**, 70, 81–288. (b) Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortés, D. Phytochemistry **1998**, 48, 1087– 1117. (c) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. J. Nat. Prod. 1999, 62, 504 - 540.

⁽³⁾ Fang, X. P.; Anderson, J. E.; Chang, C. J.; Fanwick, P. E.; McLaughlin, J. L. J. Chem. Soc., Perkin Trans. 1 **1990**, 1655–1661. For some compounds, these cytotoxic properties have been related to damage of topoisomerase I: López-Lázaro, M.; Martín-Cordero, C.; Bermejo, A.; Cortés, D.; Ayuso, M. J. Anticancer Res. 2001, 21, 3493-3497

⁽⁴⁾ The 8-acetate (Zhang, Y. J.; Zhou, G. X.; Chen, R. Y.; Yu, D. Q. J. Asian Nat. Prod. Res. 1999, I, 189–197) and the 7-epimer of goniofufurone (Fang, X. P.; Anderson, J. E.; Chang, C. J.; McLaughlin, J. L.; Fanwick, P. E. J. Nat. Prod. 1991, 54, 1034-1043) are the only other reported natural representatives of the rare furanofurone class within styryllactones. Due to differences in numbering system, the latter compound is named as 7-epi-goniofufurone in some cases (see above), as 8-epi-goniofufurone in others (see ref 2), and even with both forms in others (see ref 5p).



SCHEME 1. Retrosynthetic Plan for Compounds 1 and 2

1. For both compounds, lactone ring-opening and, in the case of 1, intramolecular displacement would give rise via, respectively, **A** and **B**, to the two epimeric homoallyl alcohols **C** and **D**. These can be prepared from the same precursor aldehyde **E** by means of asymmetric allylation. Compound **E** in turn can be referred to β -hydroxy ketone **F** via standard functional manipulations. The structural features of **F** suggest that it can be obtained by means of an *anti*-aldol addition with a suitably protected L-erythrulose derivative^{7d} as the chiral starting material.

Results and Discussion

The synthesis of 1 and 2 is shown in Scheme 2. The common starting material was acetonide 4, obtained via an *anti* boron aldol reaction of L-erythrulose derivative 3 with benzaldehyde,^{7d} followed by functional manipulation.⁹ Interchange of protecting groups in compound 4 gave 6, which was then selectively desily-lated with the HF-pyridine complex¹⁰ to primary alcohol 7. Swern oxidation of the latter gave aldehyde 8, which was used in crude form in either of the two following allylation steps. The chiral allylborane generated from

(-)-DIP-Cl and allymagnesium bromide¹¹ reacted with 8 to yield homoally alcohol 9. The epimeric alcohol 13 (see below) was not present in the reaction mixture as judged by means of NMR detection. The free hydroxyl group of 9 was then mesylated, and mesylate 10 was treated with TBAF (Scheme 2). This treatment not only caused desilvlation but also intramolecular nucleophilic attack of the generated alkoxide anion to the mesylatebearing carbon, with configurational inversion at the latter and formation of the tetrahydrofuran ring. Compound 11 was then subjected to ozonolytic cleavage of the olefinic double bond in alkaline medium¹² to yield methyl ester 12. Treatment of the latter with boron trifluoride etherate and dimethyl sulfide¹³ caused complete elimination of the two acetal protecting groups and, in addition, in situ lactonization to give (+)-goniofufurone 1.

Aldehyde 8 was also a key intermediate in the synthesis of cardiobutanolide. Thus, allylation of 8 with (+)-DIP-Cl and allymagnesium bromide¹¹ exclusively provided homoallyl alcohol 13. Silylation of the hydroxyl group and oxidative cleavage of the olefinic bond furnished methyl ester 15. Finally, cleavage of all protecting groups in 15 and subsequent lactonization yielded (+)-cardiobutanolide 2, with spectral properties identical to those reported in the literature.⁶

Conclusion

We have performed a divergent, stereoselective synthesis of the natural γ -lactones (+)-goniofufurone **1** and (+)-cardiobutanolide **2**. The chiral starting material was the protected L-erythrulose derivative **3**,^{7d} which has again been shown to be a useful chiral d⁴ synthon that maximizes atom economy.¹⁴ Furthermore, this is the first synthesis of cardiobutanolide reported so far.

Experimental Section

(1S)-2-(*tert*-Butyldimethylsilyloxy)-1-[(4R,5R,6R)-5-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-6-phenyl-[1,3]dioxan-4-yl]ethanol (5). Oil; $[\alpha]_D + 4$ (c 1.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 4.54 (d, 1H, J = 7.3 Hz), 4.27 (dd, 1H, J = 4.5, 2 Hz), 4.23 (dd, 1H, J = 7.3, 4.5 Hz), 3.95 (m, 1H), 3.75 (dd, 1H, J = 9.4, 8.4 Hz), 3.66 (dd, 1H, J = 9.4, 4.6 Hz), 3.40 (br s, 1H, OH), 1.52 (s, 3H), 1.40 (s, 3H), 0.93 (s, 9H), 0.83 (s, 9H), 0.10 (s, 6H), 0.00 (s, 3H), -0.62 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 139.3, 101.3, 18.2, 17.8 (C), 128.5 (x 2), 128.4 (x 3), 78.3, 77.0, 71.5, 69.1 (CH), 62.3 (CH₂), 25.9 (x 3), 25.8 (x 4), 24.4, -4.7, -5.5 (x 2), -5.6 (CH₃). IR ν_{max} 3550 (br, OH) cm⁻¹. HR FAB MS m/z 519.2942 (M + Na)⁺; calcd for C₂₆H₄₈NaO₅Si₂, 519.2938.

(4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(1*S*)-2-(*tert*-butyldimethylsilyloxy)-1-(methoxymethoxy)ethyl]-2,2-di-methyl-6-phenyl-[1,3]dioxane (6). Solid, mp 51–52 °C (from hexanes–Et₂O); $[\alpha]_D$ –12.2 (*c* 1.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 4.84 (d, 1H, *J* = 6.5 Hz), 4.78 (d, 1H, *J* = 6.5 Hz), 4.60 (d, 1H, *J* = 5.5 Hz), 4.20 (m, 2H), 3.89 (m,

⁽⁹⁾ Acetonide 4 corresponds to compound **9b** in ref 7d.

⁽¹⁰⁾ See, for example: Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. J. Org. Chem. **2001**, *66*, 2382–2393.

^{(11) (}a) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1997**, 2417–2420. (b) For a recent review on asymmetric allylborations, see: Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23–35.

⁽¹²⁾ Marshall, J. A.; Garofalo, A. W. J. Org. Chem. **1993**, 58, 3675–3680.

⁽¹³⁾ Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. J. Org. Chem. **1995**, 60, 4419–4427. See also: Fuji, K.; Kawabata, T.; Fujita, E. Chem. Pharm. Bull. **1980**, 28, 3662–3664.

^{(14) (}a) Trost, B. M. Angew. Chem., Int. Ed. Engl. **1995**, 34, 259–281. (b) Trost, B. M. Acc. Chem. Res. **2002**, 35, 695–705.

SCHEME 2. Stereoselective Synthesis of Goniofufurone 1 and Cardiobutanolide 2^{a}



^a Reagents and conditions: (a) Excess K₂CO₃, MeOH, rt, 24 h. (b) MOMCl, EtN*i*Pr₂, CH₂Cl₂, Δ, 12 h. (c) HF-py, py/THF, rt, 12 h. (d) Swern oxidation, the crude aldehyde **8** is used in the subsequent allylation step (overall yields are given for the two consecutive steps). (e) AllylBIpc₂ from (-)-DIP-Cl and allylmagnesium bromide, Et₂O, -90 °C, 1 h. (f) MsCl, Et₃N, DMAP, CH₂Cl₂, rt, 1 h. (g) TBAF, THF, rt, 24 h (overall yield given for the two consecutive steps). (h) O₃, CH₂Cl₂, 2.5 M NaOH/MeOH, -78 °C. (i) BF₃·Et₂O, SMe₂, -10 °C, 40 min. (j) AllylBIpc₂ from (+)-DIP-Cl, Et₂O, -90 °C, 1 h. (k) TBDMSOTf, 2,6-lutidine, rt, CH₂Cl₂, 4 h. (l) (1) BF₃·Et₂O, SMe₂, -10 °C, 5 min; (2) aq TFA, rt, 24 h; (3) CSA (cat.), toluene, 80 °C, 4 h. Abbreviations and acronyms: DIP-Cl = diisopinocampheylboron chloride; TBAF = tetra-*n*-butylammonium fluoride hydrate; CSA = camphorsulfonic acid.

1H), 3.83 (dd, 1H, J= 10.8, 3 Hz), 3.78 (dd, 1H, J= 10.8, 4.7 Hz), 3.43 (s, 3H), 1.52 (s, 3H), 1.39 (s, 3H), 0.91 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), -0.14 (s, 3H), -0.32 (s, 3H). $^{13}\mathrm{C}$ NMR (125 MHz, CDCl₃) δ 140.0, 100.9, 18.3, 18.2 (C), 128.5 (x 2), 128.4 (x 2), 128.3, 77.8, 77.0, 74.5, 72.0 (CH), 97.3, 63.4 (CH₂), 55.5, 26.0 (x 3), 25.9 (x 3), 25.8, 24.4, -4.0, -4.8, -5.4, -5.5 (CH₃). HR EIMS m/z (% rel intensity) 525.3003 (M⁺ – Me, 1), 363 (100), 319 (45), 279 (90); calcd for C_{28}H_{52}O_6Si_2 – Me, 525.3067.

(2S)-2-[(4R,5R,6R)-5-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6-phenyl-[1,3]dioxan-4-yl]-2-(methoxymethoxy)-ethanol (7). Oil; $[\alpha]_D - 37.4$ (c 1.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 4.82 (d, 1H, J = 6.5 Hz), 4.77 (d, 1H, J = 6.5 Hz), 4.56 (d, 1H, J = 6 Hz), 4.22 (dd, 1H, J = 6, 3.5 Hz), 4.14 (dd, 1H, J = 8.3, 3.5 Hz), 3.92 (ddd, 1H, J = Hz), 3.79 (dd, 1H, J = 11.7, 2.5 Hz), 3.65 (dd, 1H, J = 11.7, 5.4 Hz), 3.44 (s, 3H), 2.90 (br s, 1H, OH), 1.52 (s, 3H), 1.38 (s, 3H), 0.84 (s, 9H), -0.15 (s, 3H), -0.36 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 139.5, 101.1, 18.2 (C), 128.6 (x 2), 128.5 (x 2), 128.4, 78.7, 77.8, 74.4, 72.2 (CH), 97.6, 62.6 (CH₂), 55.8, 26.0 (x 3), 25.6, 24.1, -4.0, -4.8 (CH₃). IR ν_{max} 3470 (br, OH) cm⁻¹. HR EIMS *m/z* (% rel intensity) 411.2231 (M⁺ - Me, 8), 231 (100), 177 (25); calcd for C₂₂H₃₈O₆Si - Me, 411.2197.

(15,2S)-1-[(4R,5R,6R)-5-(*tert*-Butyldimethylsilyloxy)-2,2dimethyl-6-phenyl-[1,3]dioxan-4-yl]-1-(methoxymethoxy)pent-4-en-2-ol (9). Oil; $[\alpha]_D - 43.2 (c \ 0.7, CHCl_3)$.¹H NMR (500 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 5.95 (m, 1H), 5.15 (dd, 1H, J = 17.2, 1.8 Hz), 5.11 (dd, 1H, J = 10.2, 1.8 Hz), 4.80 (d, 1H, J = 6.5 Hz), 4.78 (d, 1H, J = 6.5 Hz), 4.60 (d, 1H, J = 5.6 Hz), 4.17 (dd, 1H, J = 5.6, 3.2 Hz), 4.10 (dd, 1H, J = 7.5, 3.2 Hz), 3.93 (m, 2H), 3.44 (s, 3H), 3.10 (d, 1H, J = 7 Hz, OH), 2.35 (t, 2H, J = 6.5 Hz), 1.53 (s, 3H), 1.38 (s, 3H), 0.85 (s, 9H), -0.10 (s, 3H), -0.34 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 139.6, 101.2, 18.2 (C), 135.6, 128.6 (x 2), 128.5, 128.4 (x 2), 81.9, 78.1, 74.3, 72.7, 70.0 (CH), 117.1, 98.9, 37.4 (CH₂), 56.1, 26.0 (x 3), 25.8, 24.1, -4.0, -4.8 (CH₃). IR ν_{max} 3460 (br, OH) cm⁻¹. HR FAB MS m/z 489.2724 (M + Na)+; calcd for C₂₅H₄₂NaO₆Si, 489.2649. (4*R*,4*aR*,6*R*,7*S*,7*aS*)-6-Allyl-7-methoxymethoxy-2,2-dimethyl-4-phenyl-tetrahydrofuro[3,2-*d*][1,3]dioxine (11). Oil; $[\alpha]_D$ +0.7 (*c* 0.75, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, 2H, *J* = 8 Hz), 7.32 (t, 2H, *J* = 8 Hz), 7.23 (t, 1H, *J* = 8 Hz), 5.85 (m, 1H), 5.15 (dd, 1H, *J* = 17.2, 1.8 Hz), 5.07 (dd, 1H, *J* = 10.2, 1.8 Hz), 4.76 (d, 1H, *J* = 6.8 Hz), 4.66 (d, 1H, *J* = 6.8 Hz), 4.55 (d, 1H, *J* = 8.5 Hz), 4.42 (d, 1H, *J* = 5 Hz), 4.33 (dd, 1H, *J* = 8.5, 5 Hz), 4.25 (dt, 1H, *J* = 7, 3 Hz), 4.07 (d, 1H, *J* = 3 Hz), 3.38 (s, 3H), 2.47 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 140.3, 100.8 (C), 134.8, 128.4 (x 2), 127.6, 126.4 (x 2), 82.5, 81.6, 80.1, 75.4, 71.0 (CH), 116.9, 96.3, 32.8 (CH₂), 56.0, 24.8, 24.0 (CH₃). HR EIMS *m/z* (% rel intensity) 319.1511 (M⁺ - Me, 1), 363 (100), 319 (45), 279 (90); calcd for C₁₉H₂₆O₅ - Me, 319.1545.

Methyl (4*R*,4a*R*,6*R*,7*S*,7a*S*)-2-(7-Methoxymethoxy-2,2-dimethyl-4-phenyltetrahydrofuro[3,2-*d*][1,3]dioxin-6-yl)-acetate (12). Oil; $[\alpha]_D - 17.3$ (*c* 1.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.44 (d, 2H, *J* = 8 Hz), 7.34 (t, 2H, *J* = 8 Hz), 7.27 (t, 1H, *J* = 8 Hz), 4.75 (d, 1H, *J* = 6.8 Hz), 4.65 (dt, 1H, *J* = 7, 3.3 Hz), 4.62 (d, 1H, *J* = 6.8 Hz), 4.57 (d, 1H, *J* = 8.5 Hz), 4.44 (d, 1H, *J* = 5 Hz), 4.33 (dd, 1H, *J* = 8.5, 5 Hz), 4.23 (d, 1H, *J* = 3.3 Hz), 3.70 (s, 3H), 3.38 (s, 3H), 2.76 (d, 2H, *J* = 7 Hz), 1.45 (s, 3H), 1.45 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 140.1, 100.8 (C), 128.4 (x 2), 127.6, 126.4 (x 2), 82.7, 81.7, 76.7, 75.5, 71.0 (CH), 96.3, 33.6 (CH₂), 55.9, 51.7, 24.8, 24.0 (CH₃). IR ν_{max} 1740 (C=O) cm⁻¹. HR FAB MS *m*/z 367.1779 (M + H⁺); calcd for C₁₉H₂₇O₇, 367.1757.

(+)-Goniofufurone (1). Colorless crystals, mp 154–156 °C (from hexanes–EtOAc), lit.³ mp 152–154 °C); $[\alpha]_D$ +39.5 (*c* 1, CHCl₃), lit.^{5m} $[\alpha]_D$ +44.9 (*c* 1.12, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.30 (m, 5H), 5.19 (d, 1H, *J* = 4.8 Hz), 5.10 (dd, 1H, *J* = 5.7, 4.2 Hz), 4.86 (d, 1H, *J* = 4.2 Hz), 4.40 (d, 1H, *J* = 2.7 Hz), 4.10 (dd, 1H, *J* = 4.8, 2.7 Hz), 2.74 (dd, 1H, *J* = 18.8, 5.7 Hz), 2.68 (d, 1H, *J* = 18.8 Hz). ¹³C NMR (125 MHz, CDCl₃) δ 175.3, 139.1 (C), 128.8 (x 2), 128.4, 126.0 (x 2), 87.5, 83.1, 77.4, 74.6, 73.5 (CH), 36.1 (CH₂). IR ν_{max} 3340 (br, OH), 1755 (C=O) cm⁻¹. EIMS *mlz* (% rel intensity) 251 (M + H⁺, 1), 233 (M + H⁺)

- H2O, 11), 126 (60), 107 (100), 79 (64). The spectral features of synthetic 1 were identical to those of the natural compound. 3,5m

(1*S*,2*R*)-1-[(*4R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,2dimethyl-6-phenyl-[1,3]dioxan-4-yl]-1-(methoxymethoxy)pent-4-en-2-ol (13). Colorless solid, mp 71–72 °C (from hexanes– Et₂O); [α]_D –46 (*c* 1.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 5.93 (m, 1H), 5.15 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.12 (dd, 1H, *J* = 10.2, 1.5 Hz), 4.96 (d, 1H, *J* = 6.6 Hz), 4.76 (d, 1H, *J* = 6.6 Hz), 4.58 (d, 1H, *J* = 5.5 Hz), 4.36–4.30 (m, 2H), 3.80–3.74 (m, 2H), 3.46 (s, 3H), 2.47 (m, 1H), 2.33 (m, 1H), 2.20 (d, 1H, *J* = 8 Hz, OH), 1.52 (s, 3H), 1.38 (s, 3H), 0.84 (s, 9H), -0.17 (s, 3H), -0.34 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 139.6, 101.0, 18.2 (C), 135.0, 128.6 (x 2), 128.5 (x 2), 128.4, 78.8, 78.0, 76.8, 73.2, 70.0 (CH), 117.7, 98.3, 39.5 (CH₂), 56.4, 26.0 (x 3), 25.7, 24.2, -3.8, -4.7 (CH₃). IR ν_{max} 3460 (br, OH) cm⁻¹. HR EIMS *m/z* (rel intensity) 451.2430 (M⁺ – Me, 1), 231 (88), 177 (100), 105 (90); calcd for C₂₅H₄₂O₆Si – Me, 451.2515.

(10), 100, (00), (01),

Methyl (3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-[(4*R*,5*R*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-6phenyl-[1,3]dioxan-4-yl]-(4-methoxymethoxy)butyrate (15). Oil; $[\alpha]_D$ -26.8 (c 2; CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.30 (m, 5H), 4.95 (d, 1H, J = 6.6 Hz), 4.72 (d, 1H, J = 6.6 Hz), 4.59 (d, 1H, J = 6.5 Hz), 4.52 (m, 1H), 4.43 (dd, 1H, J = 5.5, 4 Hz), 4.22 (dd, 1H, J = 6.5, 4 Hz), 3.73 (dd, 1H, J = 5.5, 3.3 Hz), 3.68 (s, 3H), 3.44 (s, 3H), 2.72 (m, 2H), 1.51 (s, 3H), 1.41 (s, 3H), 0.91 (s, 9H), 0.82 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H), -0.06 (s, 3H), -0.50 (s, 3H). $^{13}\mathrm{C}$ NMR (125 MHz, CDCl₃) δ 172.8, 139.7, 101.1, 18.2 (x 2) (C), 128.6 (x 2), 128.5 (x 2), 128.4, 78.7, 77.6, 75.4, 71.0, 69.9 (CH), 98.4, 39.5 (CH₂), 56.2, 51.4, 26.1 (x 3), 26.0 (x 3), 25.4, 24.6, -4.1, -4.2, -4.3, -4.5 (CH₃). IR ν_{max} 1742 (C=O) cm⁻¹. HR EIMS m/z (rel intensity) 597.3313 (M⁺ – Me, 1), 555 (M⁺ – tBu, 2), 231 (100), 177 (26), 73 (60); calcd for C₃₁H₅₆O₈Si₂ – Me, 597.3279.

Cardiobutanolide (2). Colorless crystals, mp 196–198 °C (from acetone), lit.⁶ mp 189–190 °C; $[\alpha]_D +5.5$ (*c* 0.3; MeOH), lit.⁶ $[\alpha]_D +6.4$ (*c* 0.28; MeOH). ¹H NMR (500 MHz, Me₂CO-*d*₆) δ 7.44 (br d, 1H, J = 7.5 Hz), 7.30 (br t, 7.5 Hz, 1H), 7.23 (br t, 1H, J = 7.5 Hz), 4.80 (dd, 1H, J = 7.3, 5 Hz), 4.70 (d, 1H, J = 5 Hz, OH), 4.62 (br s, 2H), 4.55 (dd, 1H, J = 7.5, 3 Hz), 4.39 (m, 1H), 4.30 (d, 1H, J = 5 Hz, OH), 3.92 (td, 1H, J = 8, 1.5 Hz), 3.80 (d, 1H, J = 17 Hz). ¹³C NMR (125 MHz, Me₂CO-*d*₆) δ 176.1, 144.2 (C), 128.6, 128.0, 127.8, 86.6, 75.6, 74.2, 70.4, 68.7 (CH), 40.4 (CH₂). IR ν_{max} 3380 (br, OH), 1759 (C=O) cm⁻¹. The spectral features of synthetic **2** were identical to those of the natural compound.⁶

Acknowledgment. Financial support has been granted by the Spanish Ministry of Science and Technology (Project BQU2002-00468), by the AVCyT (Project Grupos03/180), and by the BANCAJA-UJI foundation (Project PI-1B2002-06). J.M. thanks the Spanish Ministry of Education and Science for a Ramón y Cajal fellowship. The authors further thank Prof. D. Cortés, from the Department of Pharmacology at the University of Valencia, and Prof. A. Hisham, from the Sultan Qaboos University, Oman, for providing spectra of goniofufurone and cardiobutanolide, respectively.

Supporting Information Available: General information about spectral measurements and experimental procedures and graphical NMR spectra of compounds 1, 2, 5–7, 9, and 11–15. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0483116