Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5389-5392, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01085-4

First Total Synthesis and Structural Elucidation of (-)-Goniofupyrone

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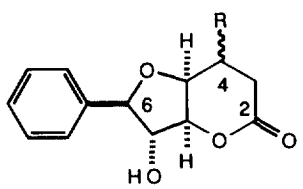
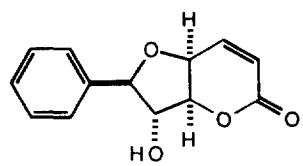
Abstract: The first total synthesis of (-)-goniofupyrone, isolated from *Goniothalamus giganteus*, was accomplished in a stereoselective manner from (+)-tricarbonyl(η^6-2-trimethylsilylbenzaldehyde)-chromium(0) complex. This synthesis unambiguously established the relative and absolute stereochemistry of (-)-goniofupyrone. Copyright © 1996 Elsevier Science Ltd

In 1991 (-)-goniofupyrone was isolated with several other antitumor styryllactones from the stem bark of *Goniothalamus giganteus*.[1] The gross structure of goniofupyrone was determined as (4R*,4aR*,6S*,7S*, 7aR*)-4,7-dihydroxy-6-phenyl-1,5-dioxabicyclo[4.3.0]nonan-2-one (**1**) based on its spectral evidence, especially by analysis of NMR spectra as well as by comparison with those of the related compounds, (+)-altholactone (**3**)[2] and its stereocongeners.[3] However, no information on its absolute configuration has so far been available. We describe herein the first total synthesis of **1**, the originally proposed structure for goniofupyrone, and its C-4 epimer **2** in optically active form, thereby unambiguously establishing the relative as well as absolute configuration of (-)-goniofupyrone.



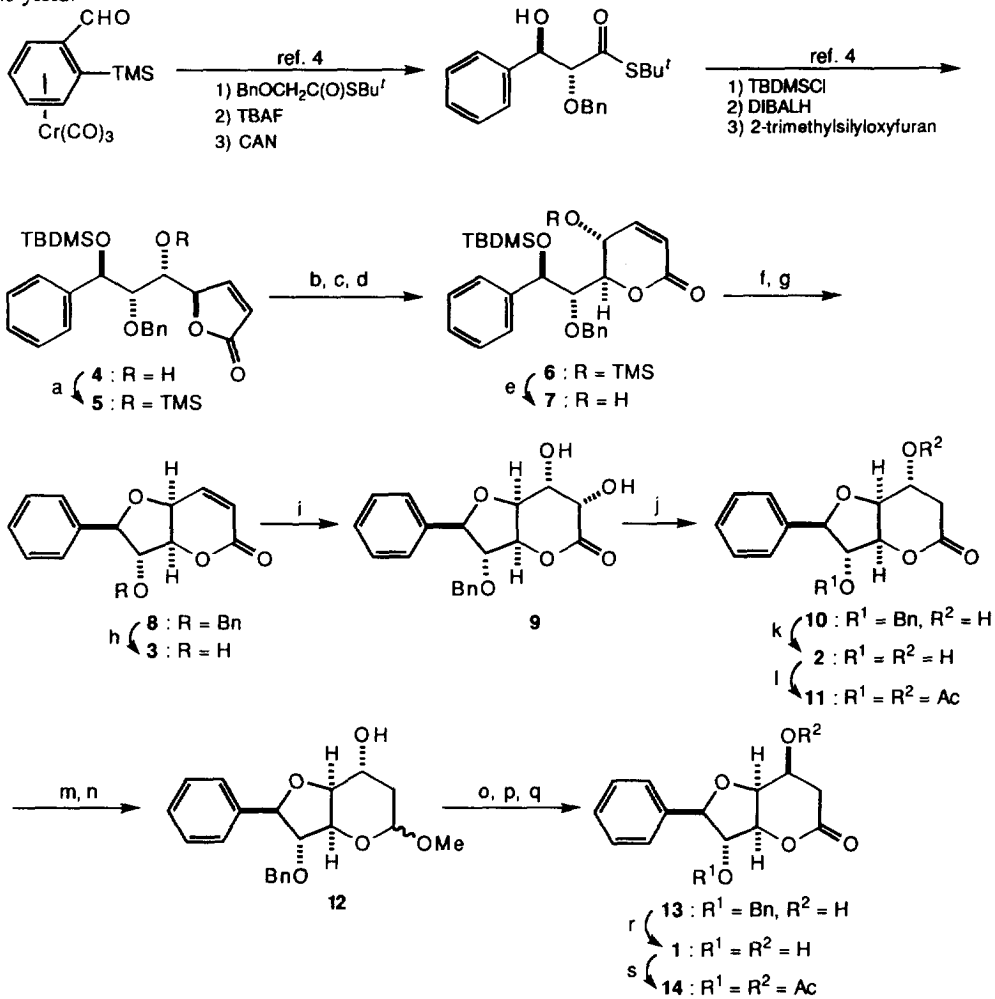
1 : R = ━━ OH (proposed structure)
2 : R = ┅┅ OH



3 : altholactone

Recently we have completed stereoselective total syntheses of goniofufurone,[4a,b] goniobutenolide A and B,[4b] antitumor styryllactones possessing the γ-lactone skeleton as a common structural feature, from (+)-tricarbonyl(η^6-2-trimethylsilylbenzaldehyde)chromium(0) complex[5] *via* the γ-butenolide intermediate **4**. Therefore our first concern and most significant requirement for our stereocontrolled synthesis of **1** and **2** in this paper was efficient transformation of the γ-lactone moiety of **4** into the δ-lactone framework.[6] The hydroxy group of (-)-**4**,[4] prepared from the chiral benzaldehyde-chromium(0) complex by six steps, was protected with TMS group to give **5** (97%), which was subsequently exposed to the following conditions,[6] (i) reduction with

DIBALH, (ii) treatment with potassium *tert*-butoxide at -60°C, (iii) oxidation with PDC, selectively giving rise to the ring transformed product **6** accompanied with migration of TMS group. Acid treatment of the crude products consising of **6** and a small amount of **5** provided the desired δ-lactone (-)-**7**,[7] in 67% overall yield from **5** along with (-)-**4** (7%). Construction of the dioxabicyclo[4.3.0]nonenone skeleton was achieved by tosylation of the allylic hydroxy group of **7** (92%), followed by exposure to tetrabutylammonium fluoride and hydrofluoric acid to afford (+)-**8** in 89% yield. Debenzylation of **8** with $SnCl_4$ gave (+)-altholactone (**3**)[7,8] in 98% yield.



Reaction Conditions : (a) TMS-imidazole, CH_2Cl_2, rt, 97%; (b) DIBALH, Et_2O, -78°C; (c) ^tBuOK, THF, -60°C; (d) PDC, AcONa, CH_2Cl_2, rt; (e) 10% HCl, MeOH, rt, 67% from **5**; (f) TsCl, DMAP, rt, 92%; (g) TBAF-HF, THF, rt, 89%; (h) $SnCl_4$, CH_2Cl_2, 40°C, 98%; (i) OsO_4, NMO, Me_2CO-H_2O, rt, 75%; (j) SmI_2, ethylene glycol, THF, rt, 62%; (k) $SnCl_4$, CH_2Cl_2, 40°C, 76%; (l) Ac_2O, DMAP, CH_2Cl_2, 90%; (m) DIBALH, Et_2O,-78°C; (n) TsOH, MeOH, rt, 77% (*ca.* 1 : 1 mixture) from **10**; (o) TPAP, NMO, CH_3CN, rt; (p) $LiAlH_4$, THF, -20°C; (q) *m*-CPBA, BF_3•OEt_2, CH_2Cl_2, rt, 60% from **12**; (r) $SnCl_4$, CH_2Cl_2, 40°C, 74%; (s) Ac_2O, DMAP, CH_2Cl_2, rt, 85%.

With the dioxabicyclo[4.3.0]nonen-2-one derivative (+)-**8** in hand, next phase of our program is faced to introduction of a hydroxy functionality at C-4 position from a concave face. Since direct and stereoselective hydroxylation at C-4 position of **8** from the *si*-face seemed to be difficult, we alternatively took the stepwise procedure. *cis*-Dihydroxylation of **8** from the *re*-face proceeded in a highly stereoselective manner when exposed to osmium tetraoxide[9] yielding (+)-**9**[10] in 75% yield. The hydroxy group at C-3 position of **9** was then removed by samarium diiodide[11] to furnish (+)-**10** (62%), which was subsequently converted into (-)-**2** ($[\alpha]_D^{18}$ -6.9° (*c* 0.15, $CHCl_3$)),[12] the C-4 epimer of **1**. Unexpectedly and surprisingly ^{1}H-NMR and ^{13}C-NMR data of (-)-**2**[13,14] and its diacetate **11**[13] were in good agreement with those[15,16] of natural (-)-goniofupyrone and its diacetate, respectively.

In order to confirm the structure of (-)-goniofupyrone, the synthesis of **1**, the proposed structure for goniofupyrone,[1] was completed. The Mitsunobu reaction[17] of **10** under several conditions was unfortunately fruitless, presumably due in large part to the β-hydroxy carbonyl structure leading to easy dehydration. The lactone moiety of **10** was therefore reduced with DIBALH to give **12** as a *ca.* 1 : 1 mixture of two stereoisomers in 77% yield. The acetal **12** was successively oxidized with tetrapropylammonium perruthenate[18] and reduced with $LiAlH_4$. Regeneration of the lactone moiety of the resulting C-4 epimers of **12** was achieved by treatment with *m*-CPBA in the presence of BF_3•OEt_2[19] producing **13** in 60% overall yield from **12** along with **10** (14%). Finally debenzylation of **13** with $SnCl_4$ gave (-)-**1**($[\alpha]_D^{18}$ -59.2° (*c* 0.10, $CHCl_3$)).[12] ^{1}H-NMR and ^{13}C-NMR data of synthetic (-)-**1**,[20,21] however, were not in accordance with those[15,16] of natural goniofupyrone. Furthermore, the diacetate **14** showed the different ^{1}H-NMR spectrum[20] from that[15] of the diacetate of natural goniofupyrone.

Thus we have accomplished the first total synthesis of (-)-goniofupyrone (**2**) from (+)-tricarbonyl(η^6-2-trimethylsilylbenzaldehyde)chromium(0) complex in a highly stereocontrolled manner. This synthesis concluded that natural (-)-goniofupyrone possesses (4R,4aS,6R,7R,7aS)-4,7-dihydroxy-6-phenyl-1,5-dioxabicyclo[4.3.0]nonan-2-one structure and should be depicted as **2**.

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(7) The structure of (-)-**7** was elucidated by its spectral evidence. Furthermore, conversion of (-)-**7** into the related styryllactones, (+)-goniotriol and (+)-8-acetylgoniotriol *via* inversion of the allylic hydroxy group

unambiguously confirmed its structure. These results combined with the detail of syntheses of (-)-goniofupyrone (**2**) and (+)-altholactone (**3**) will appear as a full paper in due course.

(8) Synthetic (+)-altholactone shows mp 108-109°C(lit.[2a] mp 110°C) and $[\alpha]_D^{25}$ +182.0° (*c* 0.05, EtOH)(lit.[2a] $[\alpha]_D^{25}$ +184.7° (EtOH)).

(9) For example; (a) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358-1364. (b) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083-6089. (c) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170-1172.

(10) The relative stereochemistry of two hydroxy groups at C-3 and C-4 positions was determined by X-ray crystallographic analysis of the diacetate derivative of racemic **9**. This result will also be reported with the detail of this manuscript.

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(12) The reported specific rotation for (-)-goniofupyrone is $[\alpha]_D^{25}$ -5.0° (*c* 0.10, $CHCl_3$).[1]

(13) Diagnostically selected ^{1}H-NMR data: **2**; 4.44 (dt, *J* =5.9, 3.9 Hz, C_4-H), 4.36 (ddd, *J* =5.4, 3.9, 1.0 Hz, C_{4a}-H), 2.91(dd, *J* =16.6, 3.9 Hz, C_3-H), 2.68 (ddd, *J* =16.6, 5.9, 1.0 Hz, C_3-H). **11**; 5.49 (q, *J* =3.9 Hz, C_4-H), 4.36 (br-t, *J* =3.9 Hz, C_{4a}-H), 3.03 (dd, *J* =17.6, 3.9 Hz, C_3-H), 2.75 (ddd, *J* =17.6, 3.9, 1.0 Hz, C_3-H).

(14) ^{13}C-NMR data of **2**; 169.29, 137.93, 128.72, 128.46, 126.00, 86.76, 85.72, 83.65, 76.37, 65.82, 35.08.

(15) Diagnostically selected ^{1}H-NMR data[1]: Goniofupyrone; 4.43 (ddd, *J* = 5.6, 3.9, 3.6 Hz, C_4-H), 4.32 (br-t, *J* =5.2, 3.9 Hz, C_{4a}-H), 2.89 (dd, *J* = 16.9, 3.6 Hz, C_3-H), 2.67 (dd, *J* =16.9, 5.6 Hz, C_3-H). Diacetate of goniofupyrone; 5.47 (q, *J* =4.2, 3.8, 3.5 Hz, C_4-H), 4.34 (br-t, *J* =3.5 Hz, C_{4a}-H), 3.10 (dd, *J* =17.5, 4.2 Hz, C_3-H), 2.73 (dd, *J* =17.5, 3.8 Hz, C_3-H).

(16) ^{13}C-NMR data[1] of goniofupyrone; 169.18, 137.90, 128.77, 128.52, 126.04, 86.67, 85.68, 83.68, 76.43, 65.85, 35.07.

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(20) Diagnostically selected ^{1}H-NMR data: **1**; 4.49 (dd, *J* =6.4, 3.9 Hz, C_{4a}-H), 4.37 (m, C_4-H), 2.91(dd, *J* =16.6, 7.8 Hz, C_3-H), 2.63 (dd, *J* =16.6, 3.4 Hz, C_3-H). **14**; 5.40 (ddd, *J* =11.2, 5.9, 2.9 Hz, C_4-H), 4.63 (t, *J* =2.9 Hz, C_{4a}-H), 3.03 (dd, *J* =17.1, 11.2 Hz, C_3-H), 2.91 (dd, *J* =17.1, 5.9 Hz, C_3-H).

(21) ^{13}C-NMR data of **1**; 168.88, 137.43, 128.79, 128.72, 126.25, 85.93, 84.57, 83.31, 74.11, 63.67, 34.83.

(*Received in Japan* 10 *May* 1996; *revised* 30 *May* 1996; *accepted* 3 *June* 1996)