Tetrahedron Letters, Vol. 34, No. 50, pp. 8007-8010, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Stereospecific α-Alkoxystannane Couplings With Acyl Chlorides: Total Synthesis of (+)-Goniofufurone

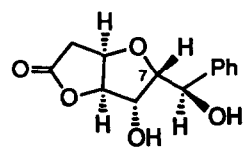
Jianhua Ye, Rama K. Bhatt, and J. R. Falck*

Departments of Molecular Genetics and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235

Key Words: C-glycoside, palladium, Stille coupling, anticancer, tin.

Abstract: Stereospecific C-glycoside formation via Pd/Cu mediated coupling of PhCOCl with cyclic α-alkoxystannane **6**, derived from D-glucurono-6,3-lactone, was the key transformation in a concise total synthesis of the anticancer agent (+)-goniofufurone.

Goniofufurone (**1**) is a highly functionalized oxygen heterocycle recently isolated from the stem bark of *Goniothalamus gigontens* Hook. f., Thomas (Annonoaceae) by McLaughlin and colleagues.[1] Its significant cytotoxicity towards several human tumor cell lines and novel structure have attracted considerable attention, resulting in total syntheses of **1**, its enantiomer, and 8-*epi*- isomer.[2,3] Most investigators, to date, have relied upon intramolecular Michael additions to an unsaturated ester/lactone to create the fully substituted tetrahydrofuran ring. None have attempted to directly create the crucial C-glycosidic center at C(7). Herein, we describe a novel C-glycoside synthesis[4] predicated on the stereospecific Pd/Cu assisted[5] coupling of cyclic α-alkoxystannanes with acyl chlorides and illustrate its utility in a concise route to **1** from commercial D-glucurono-6,3-lactone.



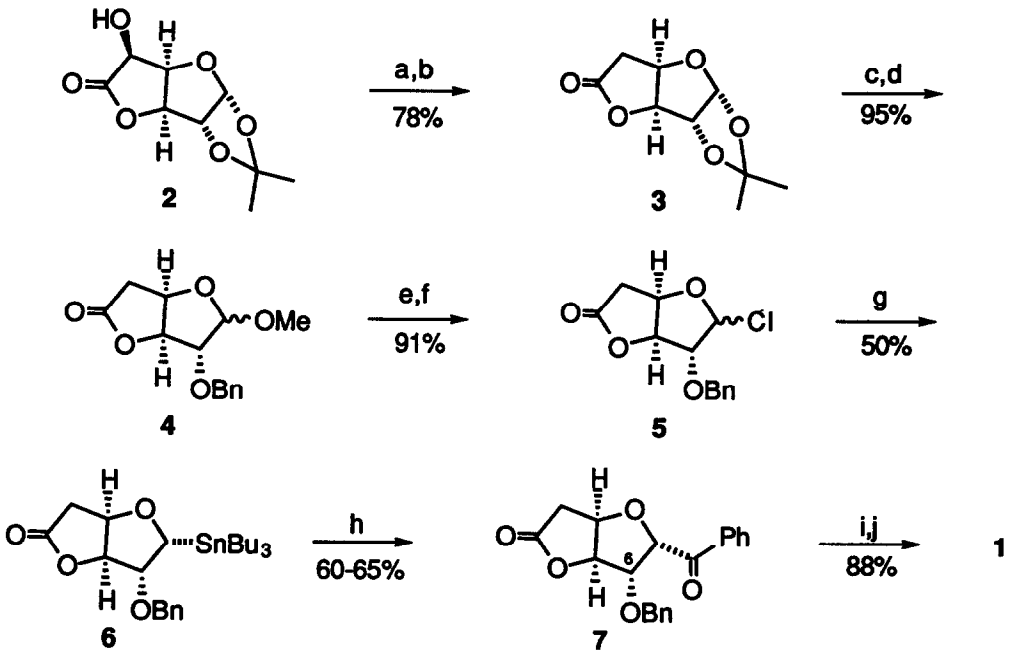
1

(+)-Goniofufurone

Acetonide **2**, readily available[6] (one-step, 90%) from D-glucurono-6,3-lactone, was smoothly converted to the deoxygenated lactone **3**[7,8], mp 90-92°C, using the Barton[9] procedure on the C(5)-phenyl thiocarbonate (Scheme 1). Acidic solvolysis of the isopropylidene and mild benzylation afforded methyl lactol **4** as a mixture of anomers from which the corresponding chlorides **5** were obtained in good yield by standard procedures. Low temperature S_N2 displacement of **5** with tributylstannyl anion, generated in DMF via desilylation using

scrupulously dried[10] Bu_4NF in the presence of activated 4Å molecular sieves, provided glycosylstannane **6** and its β-epimer (4:1), conveniently resolved by TLC [SiO_2, EtOAc/hexane (3:7), R_f~0.50 and 0.55, respectively].

SCHEME 1[a]



[a]Reaction conditions: (a) PhOC(S)Cl, DMAP, CH_3CN, 0→24 °C, 1 h. (b) Bu_3SnH, AIBN, $PhCH_3$, 110 °C, 3 h. (c) DOWEX 50X400, MeOH, 65 °C, 5 h. (d) $Ag_2O/PhCH_2Br$ (3 equiv each), PhH, 24 °C, 36 h. (e) 10% HCl/dioxane, 101 °C, 5 h. (f) Ph_3P, THF/CCl_4 (3:1), 65 °C, 3h. (g) $Bu_3SnSiMe_3/Bu_4NF$ (1.5 equiv each), 4Å MS, DMF, -45 °C, 4 h. (h) PhCOCl, $(Ph_3P)_2PdCl_2$ (4 mole %)/CuCN (8 mole %), $PhCH_3$, 95 °C, 18 h; DCC, DMAP, CH_2Cl_2, 24 °C, 8 h. (i) $LiAlH(^tBuO)_3$, THF, 0 °C, 45 min. (j) Pd/C, H_2 (1 atm), MeOH, 24 °C,16 h.

The key cross-coupling between **6** and benzoyl chloride required co-catalysis by Pd(II) and CuCN[11] in benzene for optimum results.[5] Either catalyst alone failed or gave greatly reduced yields as did reactions performed in polar (e.g., dioxane, DMF) or halogenated solvents. Filtration and treatment of the crude reaction mixture with 1,3-dicyclohexylcarbodiimide (DCC)/dimethylaminopyridine (DMAP) to re-lactonize a small amount of *seco*-acid afforded ketone **7**, mp 108-110°C, in a combined 60-65% yield. Significantly, the coupling proceeded with virtually complete *retention of configuration.*[13] This is in stark contrast with Stille[12] who observed inversion of configuration using tetra-alkylstannanes and benzoyl chloride. An almost completely stereoselective reduction of the ketone in **7** by lithium tri-*tert*-butoxyaluminohydride, possibly the consequence

of chelation control[14], and uneventful catalytic debenzylation completed the preparation of **1**, whose spectral and physical properties[8] were in accord with published data.[2]

Acknowledgment: Supported financially by the Robert A. Welch Foundation (I-782) and the USPHS NIH (DK38226).

References and Notes

1. Fang, X.-p.; Anderson, J.E.; Chang, C.-j.; Fanwick, P.E.; McLaughlin, J.L. *J. Chem Soc., Perkin Trans. 1* **1990**, 1655. Fang, X.-p.; Anderson, J.E.; McLaughlin, J.L.; Fanwick, P.E. *J. Nat. Prod.* **1991**, *54*, 1034.
2. (a) Shing, T.K.M.; Tsui, H.-C.; Zhou, Z.-H.*Tetrahedron* **1992**, *48*, 8659. (b) Prakash, K.R.C.; Rao, S.P. *ibid.* **1993**, *49*, 1505. (c) Murphy, P.J. *J. Chem Soc., Chem. Commun.* **1992**, 1096. (d) Shing, T.K.M.; Tsui, H.-c.; Zhou, Z.-h. *ibid.* **1992**, 810. (e) Shing, T.K.M.; Tsui, H.-c. *ibid.* **1992**, 432. (f) Prakash, K.R.C.; Rao, S.P. *Synlett* **1993**, 123. (g) Saito, S.; Harumari, T.; Shimamura, N.; Asahara, M.; Moriwake, T. *ibid.* **1992**, 325. (h) Gracza, T.; Jager, V. *ibid.* **1992**, 191.
3. Methodology: Gracza, T.; Hasenohrl, T.; Stahl, U.; Jager, V. *Synthesis* **1991**, 1108. Prakash, K.R.C.; Rao, S.P. *Tetrahedron Lett.* **1991**, *32*, 7473.
4. Reviews of C-glycoside synthesis: Postema, M. H. D. *Tetrahedron* **1992**,*48*, 8545-8599. Herscovici, J.; Antonakis, K. *Studies Nat. Prod. Chem.* **1992**, *10*, 337-403.
5. Bhatt, R.K.; Ye, J.; Falck, J.R. *205th ACS National Meeting*, Denver, Co., March, 1993; ORG 63.
6. Bashyal, B.P.; Chow, H.-F.; Fellows, L.E.; Fleet, G.W.J. *Tetrahedron* **1987**, *43*, 415.
7. Satisfactory NMR (^{1}H, ^{13}C) and mass spectral data were obtained for all new compounds using chromatographically homogeneous samples.
8. Spectral and physical data for **3**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.96 (d, J=3.8 Hz, 1H), 5.00 (dt, J=1.6, 3.4 Hz,1H), 4.82 (dd, J=3.6, 6.0 Hz, 2H) 2.64-2.80 (m, 2H), 1.50 (s, 3H), 1.38 (s, 3H); ^{13}C NMR: δ 174.17, 112.68, 106.18, 85.45, 82.41, 77.97, 35.83, 26.92, 26.44. **4**: ^{1}H NMR: δ 7.24-7.40 (m, 5H), 4.80-5.20 (m, 3H), 4.60-4.78 (m, 2H), 3.95-4.18 (m, 1H), 3.41 and 3.65 (s, anomeric methyls, 3H), 2.60-2.82 (m, 2H); ^{13}C NMR: δ 174.66, 136.55, 128.21, 127.91, 127.79, 127.51, 107.09, 83.96, 83.71, 77.50, 71.87, 59.93, 54.86, 36.40. **6**: ^{1}H NMR: δ 7.25-7.38 (m, 5H), 4.86 (dd, J= 0.4, 4.65 Hz, 1H), 4.70 (d, J=11.5 Hz, 1H), 4.55 (d, J=11.5 Hz, 1H), 4.53-4.48 (m, 1H), 4.24 (dd, J=0.4. 8.7 Hz, 1H), 3.78 (d, J=8.7 Hz, 1H), 2.58-2.77 (m, 2H), 1.39-1.48 (m, 6H), 1.20-1.37 (m, 6H), 0.80-1.00 (m, 15H); ^{13}C NMR: δ 175.30, 136.95, 128.54, 128.19, 128.12, 88.67, 87.39, 79.04, 75.73, 72.76, 35.37, 28.94, 27.31, 13.65, 8.78. **7**: ^{1}H NMR: δ 7.80-7.90 (m, 2H), 7.36-7.60 (m, 3H), 7.10 - 7.22 (m, 3H), 6.88-6.92 (m, 2H), 5.62 (d, J=5.2 Hz, 1H) 5.25-5.32 (m, 1H), 4.94 (d, J=5.2 Hz, 1H), 4.41 (d, J=11.8 Hz, 1H), 4.35 (d, J=11.8 Hz, 1H), 2.78-2.83 (m, 2H).1: mp 150-152°C (lit.[2b] mp 149-150°C); $[\alpha]_D^{24}$+8.69° (c 0.55, 95% EtOH) [lit.[2c] $[\alpha]_D^{24}$+8.5° (c 0.8, EtOH)].
9. Robins, M.J.; Wilson, J.S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
10. Majetich,G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* **1986** , *51*, 1745-1753.
11. The role of copper is obscure, but may involve facilitation of the transmetalation step. The beneficial effect of cocatalytic copper (I) in sluggish or otherwise unsuccessful Stille cross-couplings involving tin-sp_2 carbon bonds has been noted before: Liebeskind, L.S.; Foster, B.S. *J. Am. Chem. Soc.* **1990**, *112*,

8612-8613. Liebeskind, L.S.; Fengl, R.W. *J. Org. Chem.* **1990**, *55*, 5359-5364. Saa, J.M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963-1966. Palmisano, G.; Santagostino, M. *Tetrahedron* **1993**, *49*, 2533-2542. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127-2130. Ichikawa, J.; Minami, T.; Sonoda, T.; Kobayashi, H. *ibid.* **1992**, *33*, 3779-3782. Labaudiniere, L.; Normant, J.-F. *ibid.***1992**, *33*, 6139-6142. Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739-740. Gomez-Bengoa, E.; Echavarren, A.M. *J. Org. Chem.* **1991**, *56*, 3497-3501.

12. Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.
13. Stille-coupling of the β-glycosylstannane was also stereospecific and led exclusively to the β-C-glycosidic analog of **7**.
14. Consistent with this suggestion, reduction of the β-C-glycosidic analog of **7** under identical conditions, but where chelation with the C(6)-oxygen is not significant, resulted in a *ca.* 1:1 mixture of benzyl alcohols.

(Received in USA 14 September 1993; accepted 8 October 1993)