Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3721–3724
Tetrahedron Letters

Stereoselective iodine-induced cyclisation of alkene acetals. Application to the synthesis of 3-deoxy-*exo*-glycals and substituted tetrahydrofurans

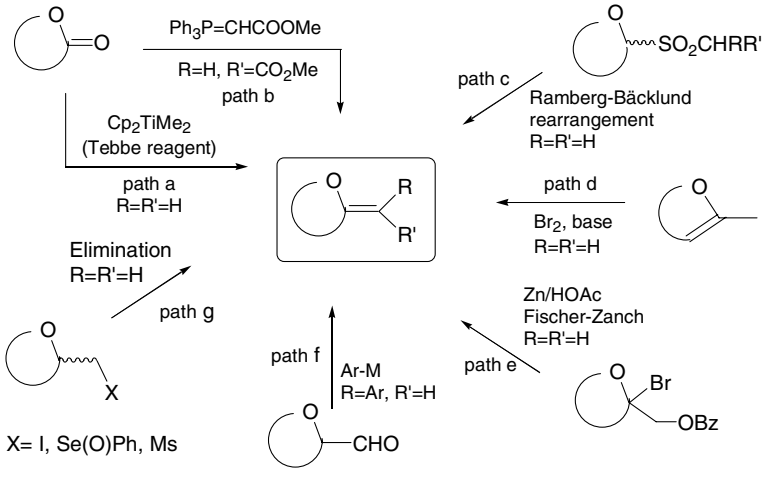
Pineda Molas, Mª Isabel Matheu* and Sergio Castillón*

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, Pl. Imperial Tarraco 1, 43005 Tarragona, Spain

Received 10 February 2004; revised 15 March 2004; accepted 16 March 2004

Abstract—2,5-Substituted tetrahydrofurans have been stereoselectively prepared by a iodine-induced cyclisation of alkene acetals, and the iodo derivatives obtained were transformed into 3-deoxy-*exo*-glycals and in polyhydroxy substituted tetrahydrofurans.

exo-Glycals[1] have not been studied as much as the corresponding *endo*-glycals, which are valuable intermediates in synthesis.[2,3] However, enol ether function of *exo*-glycals[1,4] also allows many interesting transformations, specially those directed to the synthesis of C-glycosides and C-disaccharides.[5] *exo*-Glycals have been obtained by reacting a sugar lactone with the Tebbe reagent[6] (Scheme 1, path a), by Wittig type olefination of glycosylphosphonium salts[7] or sugar lactones[8] (path b), by a Ramberg–Bäcklund rearrangement of S-glycosides[9] (path c), by reacting 1-methyl *endo*-glycals with bromine and elimination (path d),[10] by reductive elimination of bromoketoses in Fisher–Zanch conditions[11] (path e), by nucleophilic addition to sugar lactones[12] or C-formylglycosides and elimination[13] (path f) and by halogens,[14] sulfonate groups[15] or selenoxide



Scheme 1.

Keywords: Stereoselectivity; Cyclisation; *exo*-Glycals; Tetrahydrofurans.
* Corresponding authors. Tel.: +34-977559556; fax: +34-977559563; e-mail addresses: matheu@quimica.urv.es; castillon@quimica.urv.es

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.091

eliminations[16] (path g). Recently, we reported the preparation of 3,4-dideoxy-*exo*-glycals as intermediates in the synthesis of C′1-fluoromethyl-ddI.[17]

However, 3-deoxy-glycals have been studied considerably less, and there are only a few reports, which describe their synthesis based on the Wittig reaction starting from the glycosylphosphonium salts of 2-deoxy-carbohydrates.[18]

In this paper we report a short and stereoselective procedure for synthesising substituted tetrahydrofurans and 3-deoxy-furanoid glycals of *erythro* and *threo* configuration, based on a stereoselective iodine-induced cyclisation of alkene acetals.

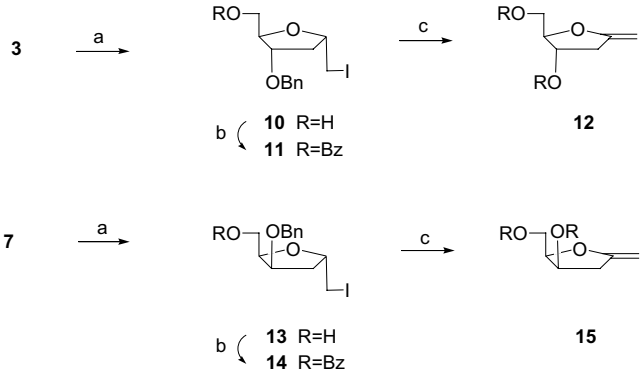
As it was mentioned before *exo*-glycals can be synthesised by an elimination reaction from iodomethyl-tetrahydrofuran derivatives, which in turn are commonly synthesised from pentoses by a Wittig olefination and subsequent iodine-induced cyclisation.[19] The stereoselectivity of this cyclisation is controlled by the allylic substituent,[20] but mixtures of diasteromers are usually obtained in their absence.

Stereoselective synthesis of alkenols **2** and **6** from glyceraldehyde (**1**) by using appropriate chiral allylborane reagents[21] and titanium reagents[22] has been reported (Scheme 2). Free hydroxyl groups of compounds **2** and **6** were protected by reaction with BnBr to give the benzyl ether derivatives **3** and **7**, respectively, in good yields.

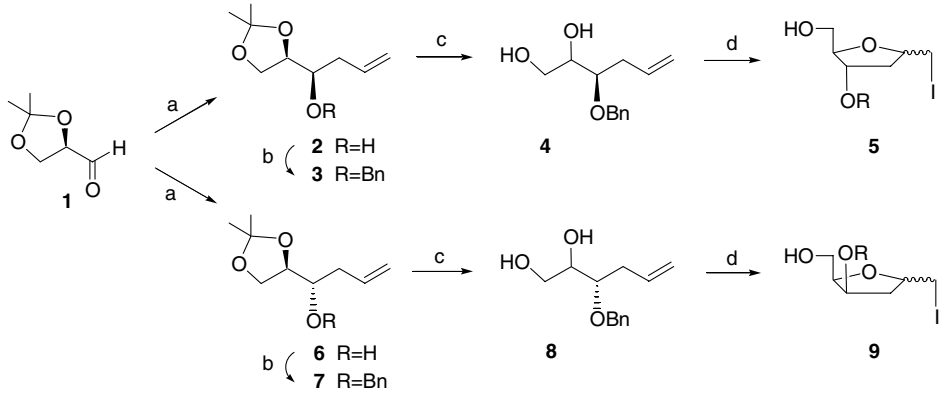
Initially, we deprotected the acetal group in compounds **3** and **7**, to give the alkenediols **4** and **8**, which were submitted to the iodine-induced cyclisation under kinetic control (Scheme 2). Labelle et al.[23] reported that electronegative homoallylic groups can control the stereoselectivity of the reaction. The resulting product has this group and the iodomethyl chain in a *trans* relative disposition. Cyclisation of **4** and **8** proceeded with good yields to give the iododerivatives **5** and **9**, respectively, but diastereoselectivities were very low. The relative stereochemistry of the resulting diastereomers was determined after carrying out NOE experiments.

In order to obtain tetrahdyrofuran derivatives with a defined stereochemistry, we focused in the Dabideen and Mootoo work[24] about the cyclisation of cyclic alkene-acetals induced by ($I(sym\text{-coll})_2ClO_4$).[25] Thus, compounds **3** and **7** were treated with ($I(sym\text{-coll})_2ClO_4$) in a mixture of CH_3CN and H_2O (Scheme 3) to give the tetrahydrofuran derivatives **10** and **13**[26,27] in a complete stereoselective way. Reaction of **10** and **13** with BzCl afforded compounds **11** and **14**, respectively, in quantitative yields.

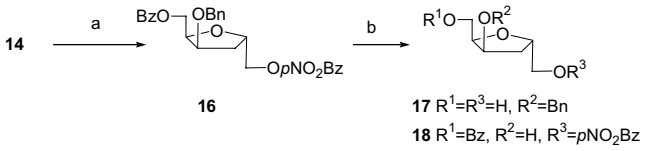
exo-Glycals were obtained by treating **11** and **14**, respectively, under basic conditions[14] (Scheme 3). The elimination was attempted with AgF and DBU, but the results where best with *t*-BuOK. In this case the starting material reacted to give the *exo*-cyclic glycals **12** and **15**,[28] of *threo* and *erythro* configuration, respectively, in good yields. The *exo*-glycals proved to be stable enough to be characterised by NMR techniques but slowly isomerised to *endo*-glycals when they were left to stand, particularly compound **12**. This was proved by the progressive appearance in the ^1H NMR spectra of a methyl group attached to position 1 of an *endo*-glycal.



Scheme 3. Reagents and conditions: (a) $Ag(sym\text{-coll})_2ClO_4$, I_2, CH_3CN, H_2O, rt, 1 h (**10**: 63%, **13**: 64%); (b) BzCl, Py, DMAP, rt, 2 h, 100%; (c) ^{t}BuOK, CH_2Cl_2, 1–6 h (**12**: 43%, **15**: 100%).



Scheme 2. Reagents and conditions: (a) Ref. 21. (b) NaH, BnBr, THF, 0 °C–rt, 16 h, 85%; (c) DOWEX/H^+, MeOH, rt, 6 h, 100%; (d) I_2, $NaHCO_3$, CH_3CN, 0 °C, 15 min, (**5**: 86%, **9**: 90%).



Scheme 4. Reagents and conditions: (a) KOCOPh*p*NO_2, 18-crown-6, DMSO, 90 °C, 2 h, 64%; (b) EtOAc, $NaBrO_3$, $Na_2S_2O_4$, H_2O, rt, 3 h, 62% (**18**).

Tetrahydrofuran rings are present in a broad spectrum of biological molecules.[29] Then, we considered the selective conversion of iodine derivative **14** in a differently protected polyhydroxylic derivative. For that, **14** was treated with KOCOPh*p*NO_2 in dimethylsufoxide to obtain compound **16** in 64% yield. Hydrolysis of compound **16** to give **17** is a straightforward process. However, when deprotection of benzyl group in **16** under hydrogenolytic conditions was tried, reduction of nitro group was exclusively produced. Finally, **18** could be obtained by using $NaBrO_3/Na_2S_2O_4$ (Scheme 4).[30]

In conclusion, we have developed a stereoselective protocol for the synthesis of 2,4,5-trisubstituted tetrahydrofurans, and of 3-deoxy-furanoid-*exo*-glycals, based on a iodine-induced stereoselective cyclisation of alkene acetals.

Acknowledgements

Financial support by DGESIC BQU2002-1155 (Ministerio de Educación y Cultura, Spain) is acknowledged. P.M. acknowledge Ministerio de Educación y Cultura for a grant. Technical assistance by the Servei de Recursos Cientifics (URV) is acknowledged.

References and notes

1. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263.
2. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.
3. (a) Somsak, L. *Chem. Rev.* **2001**, *101*, 81; (b) Postema, M. H. D. In *C-Glycoside Synthesis*; Rees, C. W., Ed.; CRC: Boca de Raton, FL, 1995.
4. Taylor, R. J. K. *Chem. Commun.* **1999**, 217.
5. (a) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183; (b) Gervay, J.; Flaherty, T. M.; Holmes, D. *Tetrahedron* **1997**, *53*, 16355; (c) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier: Exeter, 1995.
6. (a) Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406; (b) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458; (c) Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395.
7. Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903.
8. (a) Lakhrissi, Y.; Taillefumier, C.; Chrétien, F.; Chapleur, Y. *Tetrahedron Lett.* **2001**, *42*, 7265; (b) Lakhrissi, Y.; Chapleur, Y. *Angew. Chem., Int. Ed.* **1996**, *35*, 750; (c) Lakhrissi, Y.; Chapleur, Y. *J. Org. Chem.* **1994**, *59*, 5752; (d) Bandzouzi, M.; Lakhrissi, Y.; Chapleur, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1471; (e) Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 449.
9. (a) Campbell, A. D.; Paterson, D. E.; Raynham, T. M.; Taylor, R. K. J. *Chem. Commun.* **1999**, 1599; (b) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8179.
10. Gómez, A. M.; Pedregosa, A.; Valverde, S.; López, C. *Chem. Commun.* **2002**, 2022.
11. Lichtenthaler, F. W.; Hahn, S.; Flath, F.-J. *Liebigs Ann.* **1995**, 2081.
12. Yang, W. B.; Chang, C. F.; Wang, C. F.; Teo, C. F.; Lin, C. H. *Tetrahedron Lett.* **2001**, *42*, 4657.
13. Park, T. K.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 195.
14. (a) Tatibouët, A.; Rollin, P.; Martin, O. R. *J. Carbohydr. Chem.* **2000**, *19*, 641; (b) Hirota, K.; Takasu, H.; Tsuji, Y.; Sajiki, H. *Chem. Commun.* **1999**, 1827.
15. Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825.
16. Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 6501.
17. Molas, P.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Synlett* **2003**, 207.
18. (a) Jaouen, V.; Jégou, A.; Lemée, L.; Veyrières, A. *Tetrahedron* **1999**, *55*, 9245; (b) Lieberknecht, A.; Griesser, H.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1998**, *54*, 3159.
19. Pougny, J. R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375.
20. (a) Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, 507; (b) Bravo, F.; Díaz, Y.; Castillón, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1631, and references cited therein.
21. (a) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806; (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.
22. Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982.
23. Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533.
24. (a) Dabideen, D.; Mootoo, D. R. *Tetrahedron Lett.* **2003**, *44*, 8365; (b) Zhu, L.; Mootoo, D. R. *Org. Lett.* **2003**, *5*, 3475, and references cited therein.
25. (a) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862; (b) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956.
26. General method of cyclisation. A suspension formed with Ag(*sym*-coll)$_2ClO_4$ (1.23 g, 2.61 mmol), CH_3CN (7 mL) and I_2 (679 mg, 2.66 mmol) was stirred for 10 min at rt, and was added a solution of alkeneacetal (**3**, **7**) (500 mg, 1.91 mmol) in 6 mL of CH_3CN/H_2O (just two water drops). After 1 h the reaction mixture was filtered, diluted with 10%$Na_2S_2O_3$, and extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, dried over $MgSO_4$ and concentrated to dryness. Flash chromatography gave compounds **10** and **13** (63% and 64% yield) as foams. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ in ppm (numbered as tetrahydrofuran derivatives): 7.38–7.22 (m, 5H, H–Ar), 4.52 (d, 1H, $J = 11.5$ Hz, OCH_2Ph), 4.45 (d, 1H, OCH_2 Ph), 4.33–4.23 (m, 1H, H-5), 4.14 (dd, 1H, $J = 8.7$ Hz, H-2), 4.09–4.03 (m, 1H, H-3), 3.61 (dd, 1H, $J = 11.7$, 3.9 Hz, CH_2OH), 3.50 (dd, 1H, $J = 11.7$, 4.8 Hz, CH_2OH), 3.34–3.27 (m, 2H, CH_2I), 2.95 (s, 1H, OH), 2.27 (ddd, 1H, $J = 13.2$, 6.9, 6.9 Hz, H-4a), 2.03 (ddd, 1H, $J = 13.2$, 4.5, 4.5 Hz, H-4b). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm: 137.4, 128.3, 127.6, 127.5, 84.2, 79.6, 78.7, 71.4, 62.4, 37.0, 10.1. Compound **13**: ^{1}H NMR

(300 MHz, $CDCl_3$) δ in ppm: 7.38–7.22 (m, 5H, H–Ar), 4.56 (d, 1H, $J = 12.0$ Hz, OCH_2Ph), 4.35 (d, 1H, OCH_2Ph), 4.22–4.07 (m, 3H, H-2, H-3, H-5), 3.80 (dd, 1H, $J = 12.0$, 5.2 Hz, CH_2OH), 3.71 (dd, 1H, $J = 12.0$, 4.6 Hz, CH_2OH), 3.27–3.15 (m, 2H, CH_2I), 2.59 (s, 1H, OH), 2.29 (ddd, 1H, $J = 13.5$, 6.0, 1.5 Hz, H-4a), 1.71 (ddd, 1H, $J = 13.5$, 8.9, 5.0 Hz, H-4b). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm: 137.5, 128.4, 127.9, 128.4, 82.3, 80.2, 76.6 71.3, 61.8, 38.2, 10.7.

27. For the use of a related product in the synthesis of halichondrin see: Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193.
28. General method of synthesis of *exo*-glycals **12**, **15**. To a solution of **11**, **14** (1 mmol) in CH_2Cl_2 (0.18 mL) was added ^{t}BuOK (0.28 mmol) and let stir for 6 h. Afterwards the reaction mixture was diluted with 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2, the organic layer was dried over $MgSO_4$ and concentrated. Compounds **12** and **15** were obtained in 43% and 100% yield, respectively. **12**: ^1H NMR (300 MHz, $CDCl_3$) δ in ppm (numbered as 2,5-anhydro-hex-1-enitol derivatives): 7.97 (d, 2H, $J = 8.1$ Hz, H–Ar), 7.50–7.47 (m, 1H, H–Ar), 7.39–7.34 (m, 2H, H–Ar), 7.29–7.20 (m, 5H, H–Ar), 4.64–4.52 (m, 3H, H-5, H-6), 4.40 (d, 1H, $J = 9.9$ Hz, OCH_2Ph), 4.36 (d, 1H, OCH_2Ph), 4.30–4.25 (m, 1H, H-4), 3.86–3.84 (m, 2H, H-1), 2.72–2.66 (m, 2H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm: 166.5, 160.2, 137.5, 132.6, 129.6, 129.0, 128.5, 127.9, 127.6, 82.0, 80.4, 80.0, 71.5, 64.0, 37.0. Compound **15**: ^1H NMR (300 MHz, $CDCl_3$) δ in ppm: 7.98 (d, 2H, $J = 7.9$ Hz, H–Ar), 7.50–7.48 (m, 1H, H–Ar), 7.41–7.38 (m, 2H, H–Ar), 7.28–7.19 (m, 5H, H–Ar), 4.63–4.49, 4.40–4.19 (2m, 7H, H-1a, H-4, H-5, H-6, OCH_2Ph), 3.85–3.84 (m, 1H, H-1b), 2.71–2.66 (m, 2H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ in ppm: 166.2, 160.0, 137.4, 132.8, 130.0, 129.5, 128.2, 128.0, 127.6, 81.5, 80.9, 80.8, 71.2, 63.5, 36.6.
29. Faulkner, D. J. *Nat. Prod. Rep.* **1992**, *9*, 323.
30. Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **1999**, *40*, 8439.