A new route to 2,5-dihydrofurans and tetrahydrofuro[3,2-*b*]furans *via* ring contraction of pyranoid *C*-glycosides

Alphonse Tenaglia* and Jean-Yves Le Brazidec

Laboratoire de Réactivité en Synthèse Organique, associé au CNRS, Faculté de St-Jérôme, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

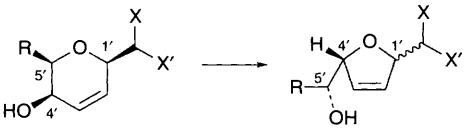
Hex-2-enopyranosides featuring a malonate-type *C*-glycosidic bond and a free hydroxy group at C-4′ undergo, under basic conditions [DBU (20 mol%) in trifluoroethanol], a ring contraction leading to either 2,5-dialkyl-2,5-dihydrofurans or 2-alkylfuro[3,2-*b*]furans depending on the substitution pattern of the glycosides.

Ring contraction reactions of pyranoid to furanoid derivatives are well established and especially useful in carbohydrate chemistry.[1] Such reactions generally require a suitable leaving group on the carbon atom β to the oxygen atom and intramolecular displacement with participation of the ring oxygen atom.[2] An alternative approach utilizes a Horner–Wadworth–Emmons type reaction of pyranoses[3] *via* an acyclic intermediate and *in situ* heteroatom conjugate addition across an α,β-unsaturated ester. The reaction sequence affords *C*-alkyl furanoses. During ongoing work on the use of pyranose β-*C*-glycosides as chiral building blocks,[4] we intended to synthesise the dihydrofurans and furo[3,2-*b*]furans. These compounds are present as substructures in numerous bioactive natural products such as pamamycins,[5] halichondrins,[6] nonactic acid,[7] goniofurfurone[8] and erythroskyrine.[9]

In the presence of base, malonate-type substituted *C*-glycosides epimerise[10] by a process involving a retro Michael–Michael sequence.[11,12] It was anticipated that such *C*-glycosides with a free C-4′ hydroxy group would be prone to ring contraction provided that trapping of the acyclic intermediate, which should form the tetrahydrofuran, occurs faster than the recombination leading to a tetrahydropyran. The transformation of a series of compounds **1** showed the feasibility of this concept.

Indeed, reaction of β-*C*-glycoside **1a**† in the presence of a base, yielded 2,5-dihydrofuran **2a**‡,§ as a mixture of diastereoisomers (1′α) and (1′β) roughly in a 1 : 1 ratio (Scheme 1 and Table 1). Weak bases (trifluoroethoxide) effect the transformation in higher yield than strong ones (methoxide) (entries 1 and 2). The ring contraction occurred with significantly increased yields, reaching effectively 60–65% with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or caesium carbonate in aprotic polar solvents, *e.g.* THF or acetone (entries 3 and 4). Finally, the best yield of **2a** was obtained by combining DBU (20 mol%) with trifluoroethanol (TFE) (entry 5). These optimized conditions were applied to β-*C*-glycosides **1b–e**† which afforded 2,5-dialkyl-2,5-dihydrofurans **2b–e**† respectively in fair to good yields (Table 2).

The hex-2-enopyranosides **1f–g**† under the above conditions lead to the 2-alkylfuro[3,2-*b*]furans **3a–c**‡ as a mixture of diastereoisomers (1′α) and (1′β) in a 3 : 7 ratio with moderate yields (Scheme 2). As depicted in Scheme 3, the formation of **3a** occurs with a *tert*-butyldimethylsilyl group transfer from primary to secondary oxygen (*e.g.* C-6′ → C-5′). With **1g**, the



1a R = H, X = X′ = COMe
b R = Me, X = X′ = COMe
c R = H, X = CO_2Me, X′ = NO_2
d R = Me, X = CO_2Et, X′ = NO_2
e R = $CH_2OTBDMS$, X = CO_2Me, X′ = NO_2

2a–e

Scheme 1

Table 1 Optimization of the base promoted ring contraction process from **1a**

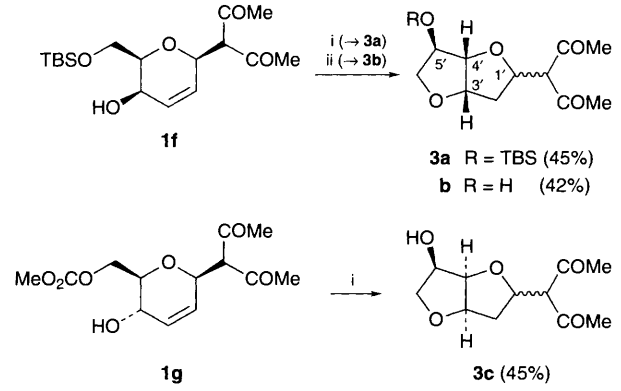
Entry[a]	Base	Solvent	t/h	Yield[b] of **2a**[c] (%)
1	MeONa	MeOH	40	35
2	CF_3CH_2ONa	TFE	1.5	32
3	Cs_2CO_3	acetone	1.5	65
4	DBU	THF	20	60
5	DBU	TFE	20	86

[a] The reactions were carried out at room temp. [b] Yields refer to pure isolated (flash chromatography, silica) products. [c] Mixture of epimers 1′α : 1′β in a 1 : 1 ratio estimated by ^{1}H NMR spectroscopy.

Table 2 Synthesis of 2,5-dialkyl-2,5-dihydrofurans **2a–e** from β-*C*-glycosides[a]

Entry	Glycoside **1**	*T*/°C	Product[b] **2**	Yield[c] (%)
1	**a**	25	**a**	86
2	**b**	55	**b**	60
3	**c**	25	**c**	82
4	**d**	55	**d**	75
5	**e**	55	**e**	77

[a] The reactions were carried out with DBU (20 mol%) in TFE. [b] Mixture of epimers 1′α : 1′β in a 1 : 1 ratio estimated by ^{1}H NMR spectroscopy. [c] Yields refer to pure isolated (flash chromatography, silica) products.



1f

3a R = TBS (45%)
b R = H (42%)

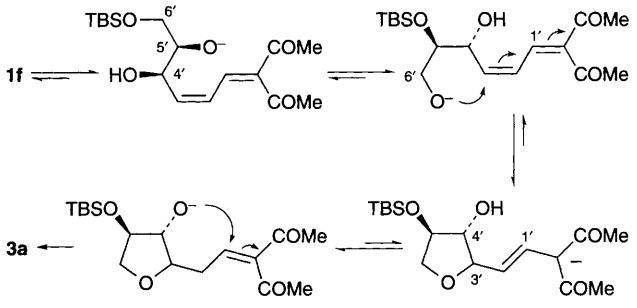
1g

3c (45%)

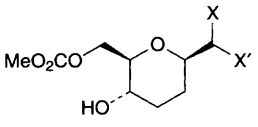
Scheme 2 *Reagents and conditions*: i, DBU (20 mol%), TFE, 55 °C; ii, Bu_4NF (1.1 equiv.), THF, room temp.

base sensitive methoxycarbonyl group was cleaved under these conditions. On the other hand, attempts to remove the *tert*-butyldimethylsilyl group in **1f** (Bu_4NF in THF) resulted in a rearrangement to the furofuran **3b**,§ most probably as a result of the more basic conditions.[13] From a mechanistic point of view, we assume that the formation of the furanofuran derivatives **3** proceeds through a double five-*exo*-trig[14] heterocyclization (Scheme 3). The configuration of the newly created chiral centre (C-3′) derives both from the C-4′ configuration and the necessity of the *cis* ring junction. Moreover, owing to the reversible steps of the skeletal rearrangement, no 1,2-*trans* disubstituted tetrahydrofuran derivatives are observed.

It is worth noting that this ring contraction proceeds satisfactorily in TFE as solvent. The higher efficiency of TFE is most likely due to its low p*K*a value (12)[15] which favours proton transfer equilibrations, leading to the five membered ring, owing to the proton acidity of this kind of *C*-glycosides. Moreover, the saturated β-*C*-glycosides **4a–b** (Scheme 4) did not lead to the respective ring contraction products but underwent partial epimerization on the anomeric carbon atom. Consequently, the *Z*-double bond in open-chain intermediates (Scheme 3) was crucial for ring contraction and presumably acts as a favourable entropic factor.[16] Finally, the importance of the *C*-aglycone functionalities (β-nitroacetate or 1,3-diketone) was highlighted by the difference of the β-*C*-glycosides **1e** and **1f**, with the latter favouring the formation of a bicyclic derivative.



Scheme 3 Proposed mechanism for the ring contraction of glycosides



4a X = X′ = COMe
b X = NO_2, X′ = CO_2Me

Scheme 4

Footnotes

† The β-*C*-glycosides were prepared using a palladium-catalysed alkylation of 3,4-dicarbonate glycals.

‡ All new compounds gave satisfactory analytical and/or spectral data.

§ *Spectroscopic data* for **2a** (two diastereoisomers): colourless oil, R_f = 0.13 (diethyl ether); IR (neat) ν/cm^{-1} 3382, 2960, 1707, 1364, 1261, 1089 and 800; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60 (3/2 H, s), 2.63 (3/2 H, s), 2.69 (3/2 H, s), 2.71 (3/2 H, s), 2.73 (1 H, br d, *J* 4.7 Hz), 3.52 (1 H, ddd, *J* 2.9, 4.7, 11.7 Hz), 3.68 (1 H, m), 3.69 (1 H, d, *J* 9.5 Hz), 4.87 (1 H, m), 5.23 (1 H, m), 5.76 (1 H, br d, *J* 6.0 Hz) and 5.91 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.37 (q), 30.09 (q), 30.63 (q), 30.76 (q), 64.22 (t), 64.55 (t), 73.59 (d), 75.13 (d), 84.42 (d), 84.82 (d), 86.85 (d), 87.30 (d), 128.52 (d), 129.54 (d), 129.66 (d), 201.90 (s), 202.06 (s), 202.40 (s) and 202.66 (s). For **3b** (two diastereoisomers): colourless oil, R_f = 0.35 (ethyl acetate); IR (neat) ν/cm^{-1} 3418, 2930, 1712, 1593, 1418, 1361, 1152, 1076, 973; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H *major diastereoisomer*: 1.56 (1 H, ddd, *J* 4.8, 10.0, 13.5 Hz), 2.00 (1 H, m), 2.16 (3 H, s), 2.24 (3 H, s), 2.32 (1 H, dd, *J* 5.2, 13.5 Hz), 3.69 (1 H, d, *J* 9.3 Hz), 3.77 (1 H, d, *J* 10.1 Hz), 3.92 (1 H, dd, *J* 3.9, 10.1 Hz), 4.26 (1 H, m), 4.40 (1 H, d, *J* 3.9 Hz), 4.53 (1 H, ddd, *J* 5.1, 9.3, 9.8 Hz), 4.78 (1 H, dd, *J* 4.2, 4.4 Hz); *minor diastereoisomer*: 1.58 (1 H, ddd, *J* 2.4, 6.6, 14.0 Hz), 2.15 (3 H, s), 2.22 (3 H, s), 2.42 (1 H, pseudo dt. *J* 7.0, 14.0 Hz), 3.75 (1 H, d, *J* 8.8 Hz), 3.85 (1 H, d, *J* 10.0 Hz), 4.01 (1 H, dd, *J* 3.7, 10.0 Hz), 4.23 (1 H, d, *J* 4.2 Hz), 4.54 (1 H, m) and 4.81 (1 H, m); ^{13}C NMR δ_C *major diastereoisomer*: 30.26 (2xq), 38.85 (t), 73.95 (d), 74.72 (t), 76.54 (d), 77.90 (d), 82.25 (d), 88.60 (d), 201.45 (s) and 202.38 (s).

References

1 H. Redlich, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1345.
2 C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs and F. Sirokman, *J. Am. Chem. Soc.*, 1966, **88**, 2073. P. W. Austin, J. G. Buchanan and R. M. Saunders, *J. Chem. Soc. C*, 1967, 372.
3 J. Rokach, C.-K. Lau, R. Zamboni and Y. Guindon, *Tetrahedron Lett.*, 1981, **22**, 2763; F. Nicotra, F. Ronchetti and G. Russo, *J. Org. Chem.*, 1982, **47**, 5381; A. H. Davidson, L. R. Hughes, S. S. Qureshi and B. Wright, *Tetrahedron Lett.*, 1988, **29**, 693.
4 A. Tenaglia, J.-Y. LeBrazidec and F. Souchon, *Tetrahedron Lett.*, 1995, **36**, 4241.
5 R. D. Walkup and S. W. Kim, *J. Org. Chem.*, 1994, **59**, 3433.
6 T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero and S. K. Yoon, *J. Am. Chem. Soc.*, 1992, **114**, 3162.
7 K. M. Sun and B. Fraser-Reid, *Can. J. Chem.*, 1980, **58**, 2732.
8 X.-P. Fang, J. E. Anderson, C.-J. Chang, P. E. Fanwick and J. L. McLaughlin, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1655.
9 R. C. F. Jones and M. Tankard, *J. Chem. Soc., Chem. Commun.*, 1990, 765.
10 M. Brakta, P. Lhoste and D. Sinou, *J. Org. Chem.*, 1989, **54**, 1890.
11 G. H. Engelbrecht and C. W. Holzapfel, *Heterocycles*, 1991, **32**, 1267.
12 B. Chaguir, M. Brakta, V. Bolitt, P. Lhoste and D. Sinou, *J. Carbohydr. Chem.*, 1992, **11**, 609.
13 J. Otera, Y. Niibo and H. Nozaki, *Tetrahedron Lett.*, 1992, **33**, 3655; L. A. Paquette, A. M. Doherty and C. M. Rayner, *J. Am. Chem. Soc.*, 1992, **114**, 3910.
14 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
15 A. L. Henne and W. C. Francis, *J. Am. Chem. Soc.*, 1953, **75**, 991.
16 M. A. Soler, J. M. Palazon and V. S. Martin, *Tetrahedron Lett.*, 1993, **34**, 5471.

Received, 10th April 1996; Com. 6/02521H