Synthesis of Tetrahydrofurans through a Novel Pseudo-*meso*-trick

Matej Babjak, L'uboš Remeň, Ol'ga Karlubíková, Tibor Gracza*

Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovak Republic
E-mail: tibor.gracza@stuba.sk

Received 30 March 2005

Abstract: Diastereoselective synthesis of trisubstituted tetrahydrofuran (D-*lyxo*-**4**) from the equimolar diastereomeric mixture of D-*erythro*-/D-*threo*-1-pentenitols (**1**) is described. The synthesis exploits a sequence of two novel reactions: diastereospecific palladium(II)-catalyzed bicyclization of pentenitols **1** with degeneration of the allylic stereogenic center and subsequent regioselective ring-opening of bicyclic skeleton **2**.

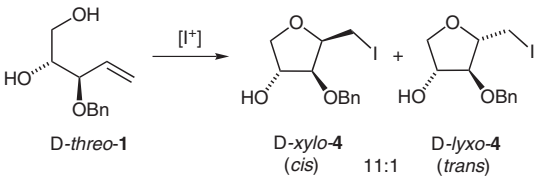
Key words: palladium, catalysis, stereoselective synthesis, cyclizations, diastereoselectivity

Methods for the preparation of substituted oxygen heterocycles have attracted considerable attention since furan and pyran substructures have been found in polyether antibiotics and other biologically active natural products.[1] As a part of our ongoing project aimed at the application of palladium(II)-catalyzed cyclizations in the natural product synthesis,[2] we required a versatile method for the stereoselective construction of substituted tetrahydrofurans with *trans*-relationship at C2–C3. Our previous work showed that unsaturated polyols undergo Pd(II)-catalyzed intramolecular oxycarbonylation with high chemo-, regio- and stereoselectivity.[3] The process is characterized by excellent *threo*-selectivity concerning the newly formed stereogenic center with respect to the configuration at the allylic carbon. Thus, the tetrahydrofuranyl lactones with *cis*-arrangement of C2–C3 substituents are served.

Herein, we present the stereoselective two-step synthesis of 3-*O*-benzyl-1-deoxy-1-iodo-2,5-anhydro-D-lyxitol [(3*R*,4*S*,5*S*)-4-benzyloxy)-5-iodomethyltetrahydrofuran-3-ol] (D-*lyxo*-**4**) from the equimolar diastereomeric mixture of D-*erythro*-/D-*threo*-1-pentenitols (**1**).

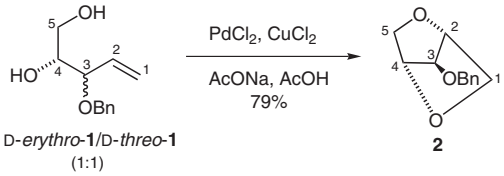
To the best of our knowledge, there is only one paper[4] in the literature, which describes the formation of D-*lyxo*-**4**. However, it has been reported as a minor product of the iodocyclization of diastereomerically pure D-*threo*-1-pentenitol (D-*threo*-**1**) along with the formation of major D-*xylo* diastereomer (D-*xylo*-**4**) in a ratio of 11:1 (Scheme 1).

Generally, halogen-induced cycloetherifications of alkenols with allylic-O functionality prefer 5-*exo* cyclization to form a tetrahydrofuran skeleton with *cis*-arrangement of C2–C3 substituents[5] due to the stereoelectronic effects.



Scheme 1

Our synthesis commences from the equimolar diastereomeric mixture of pentenetriols **1**, readily available from D-glyceraldehyde.[6] The first step is the palladium(II)-catalyzed bicyclization of **1**, see Scheme 2.



Scheme 2

The reaction was carried out using palladium(II) chloride as catalyst (0.1 equiv), copper(II) chloride as reoxidant (3 equiv) and sodium acetate (3 equiv) in acetic acid as buffer at room temperature. This new type of Pd(II)-initiated bicyclization of diastereomeric alkenols **1** furnished bicyclic anhydroalditol **2** as the sole product in 79% yield. The structure of 1,4:2,5-dianhydro-3-*O*-benzyl-D-lyxitol (**2**) was established by comparison of NMR data and specific rotation value $\{[\alpha]_D^{20}$ +48.5$\}$ with the reported data for **2**[4] $\{[\alpha]_D^{25}$ +50.5$\}$ and for its enantiomer[7] $\{[\alpha]_D^{20}$ –48.1$\}$, respectively, which were prepared by alkaline treatment of both D-*lyxo*-**4** and 1,4-anhydro-2-*O*-tosyl-3-*O*-benzyl-L-xylitol to confirm their absolute configurations.

Most intriguing features of this transformation are: (i) diastereospecific generation of a new stereocentre at C2 with *cis*-arrangement according to hydroxyl group at C4 and (ii) because of C_2-symmetry of skeleton **2** degeneration of the existing allylic stereogenic center of triols **1** at position C3 occurred (Figure 1).

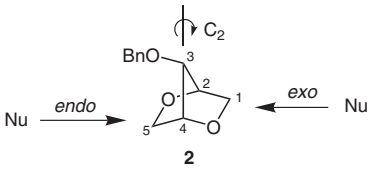


Figure 1

SYNLETT 2005, No. 10, pp 1609–1611
Advanced online publication: 12.05.2005
DOI: 10.1055/s-2005-869840; Art ID: G11005ST

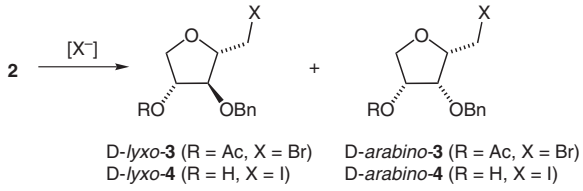
Table 1 Ring-Opening of 1,4:2,5-Dianhydro-3-*O*-benzyl-D-lyxitol (**2**)

Entry	Reaction conditions	Yield (product, %)	D-*lyxo*:D-*arabino*[a]
1	Sat. HBr, AcOH, Ac_2O, 0 °C, 30 min	42 (D-*lyxo*-**3**) 47 (D-*arabino*-**3**)	1:1
2	$BF_3{\cdot}OEt_2$ (1 equiv), TBAI (1 equiv), $CHCl_3$, r.t., 3 d	–	–
3	Concd HCl, TBAI (1 equiv), CH_2Cl_2, r.t., 7 d	24 (D-*lyxo*-**4**)	6:1
4	TMSCl (1 equiv), NaI (1.5 equiv), MeCN, 0 °C, 90 min	59 (D-*lyxo*-**4**)	8:1
5	TMSCl (1.1 equiv), TBAI (2.1 equiv), concd HCl, CH_2Cl_2, r.t., 28 h	74 (D-*lyxo*-**4**)	10:1

[a] Determined by HPLC analysis of crude reaction mixture.

Thus, the enantiomerically pure bicyclic compound **2** is formed by stereoconvergent reaction of diastereomeric mixture (1:1) of triols **1**.

Subsequent regioselective ring-opening of bicycle **2** should lead to one of both diastereomeric tetrahydrofurans. Firstly, the addition of sat. HBr in acetic acid[8] at different reaction temperatures was examined. In all cases both diastereomeric bromides D-*lyxo*-**3** and D-*arabino*-**3** as products of ring-opening were obtained in good yields (68–89%), albeit with no regioselectivity (Scheme 3, Table 1, entry 1). While the use of tetrabutylammonium iodide with $BF_3{\cdot}OEt_2$ failed (entry 2), the presence of concentrated HCl furnished both furan derivatives D-*lyxo*-**4** and D-*arabino*-**4** in a ratio 6:1, however, in a poor yield (24%, entry 3). Comparable selectivity but better yield of **4** (59%, entry 4) was obtained by treatment of **2** with trimethylsilyl chloride/NaI in acetonitrile at 0 °C. The best result in terms of yield and diastereoselectivity was achieved using TMSCl/TBAI/HCl in CH_2Cl_2 at r.t. (74%, 82% de, entry 5). In all cases (except entry 1), D-*lyxo*-**4** was formed as a major product via *exo*-attack of the nucleophile to **2** due to the steric hindrance between the bulky reagent and the benzyloxy group. The NMR data as well as specific rotation value {$[\alpha]_D^{20}$ +6.4} were in good agreement with the reported data[4] for D-*lyxo*-**4** {$[\alpha]_D^{25}$ +7.8}. No debenzylation was observed under this reaction conditions, although in situ generated TMSI is known as an efficient benzylether cleaving agent.[9]



Scheme 3

In conclusion, we have worked out a new two-step synthesis of 2,3,4-trisubstituted tetrahydrofurans with *trans*-relationship of C2–C3 substituents from the equimolar diastereomeric mixture of D-*erythro*-/D-*threo*-1-pentenitols (**1**) through a novel pseudo-*meso*-trick. The goal of the synthesis is a diastereospecific Pd(II)-catalyzed bicyclization of triols **1** to furnish enantiomerically pure **2**. The configuration at C4 of **1** introduces a new stereocenter in **2** in *threo* fashion along with concomitant degeneration of allylic stereogenic center of an alkene. Regioselective ring-opening of bicycle **2** provides a diastereomer D-*lyxo*-**4**, a useful chiron.

1,4:2,5-Dianhydro-3-*O*-benzyl-D-lyxitol [(1*R*,4*R*)-7-benzyloxy-2,5-dioxabicyclo[2.2.1]heptane] (2)

A 25 mL flask was charged with triols **1** (166 mg, 0.8 mmol), $PdCl_2$ (10 mg, 0.06 mmol), AcONa (196 mg, 2.4 mmol), $CuCl_2$ (320 mg, 2.4 mmol) and glacial acetic acid (8 mL) under argon atmosphere. The green mixture was stirred at r.t. for 12 h, then diluted with Et_2O (20 mL), filtered through Celite® 2 × 1 cm pad and washed several times with EtOAc (15 mL). Collected filtrates were concentrated in vacuo and the residue was partitioned between EtOAc (30 mL) and 10% aq $NaHCO_3$. After phase separation, the water layer was extracted with EtOAc, combined extracts were dried over anhyd K_2CO_3 and concentrated. Pale green crude oil was purified by Kugelrohr distillation under reduced pressure (180 °C, 0.05 Torr). Title compound was isolated as exclusive product of reaction as a colorless oil (130 mg, 79%).

Compound **2**: R_f = 0.55 (50% EtOAc in hexanes); $[\alpha]_D^{25}$ +48.5 (*c* 0.16, CH_2Cl_2) {lit.[5] $[\alpha]_D^{25}$ +50.5 (1.35, $CHCl_3$); for enantiomer of **2** lit.[7] $[\alpha]_D^{20}$ –48.1 (*c* 1.43, $CHCl_3$)}. IR (neat): ν = 3005 (m), 2947 (m), 2882 (m), 1726 (m), 1497 (m), 1454 (m), 1363 (m), 1334 (m), 1292 (m), 1275 (m), 1235 (m), 1211 (m), 1176 (m), 1128 (s), 1068 (s), 1030 (s), 1003 (m), 951 (m), 885 (m), 856 (s), 700 (m) cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$ (206.2): C, 69.88; H, 6.84. Found: C, 69.96; H, 6.94. NMR data of isolated **2** were in full accordance with lit.[5,7]

4-*O*-Acetyl-3-*O*-benzyl-1-deoxy-1-bromo-2,5-anhydro-D-lyxitol [(3*R*,4*S*,5*S*)-4-Benzyloxy-5-bromomethyltetrahydrofuran-3-yl Acetate] (D-*lyxo*-3) and 4-*O*-Acetyl-3-*O*-benzyl-1-deoxy-1-bromo-2,5-anhydro-D-arabitol [(3*R*,4*R*,5*S*)-4-Benzyloxy-5-bromomethyltetrahydrofuran-3-yl Acetate] (D-*arabino*-3)

The bicyclic derivative 2 (60 mg, 0.29 mmol) and Ac_2O (0.1 mL, 1 mmol) were cooled to 0 °C and sat. HBr in HOAc (1 mL) was added. The mixture was stirred for 30 min at 0 °C under TLC control, H_2O (5 mL) was added after full conversion of substrate and the solution was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated. The crude oil was purified by flash chromatography (9% EtOAc in hexanes). The fractions with R_f = 0.69 (33% EtOAc in hexanes) contained D-*lyxo*-**3** isomer, fractions with R_f = 0.60 (33% EtOAc in hexanes) contained D-*arabino*-**3**, and both isomers were isolated as colorless oils (D-*lyxo*-**3**: 40 mg, 42%; D-*arabino*-**3**: 45 mg, 47%).

D-*lyxo*-3: $[\alpha]_D^{25}$ +17.6 (*c* 0.29, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, Ac), 3.42 (dd, 1 H, $J_{1A,2}$ = 6.8 Hz, $J_{1A,1B}$ = 10.5 Hz, H-1A), 3.46 (dd, 1 H, $J_{1B,2}$ = 5.8 Hz, $J_{1A,1B}$ = 10.5 Hz, H-1B), 3.97 (ddd, 1 H, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 1.1 Hz, $J_{3,5A}$ = 0.9 Hz, H-3), 4.02 (br d, 1 H, $J_{5A,5B}$ = 10.5 Hz, H-5A), 4.11 (dd, 1 H, $J_{4,5B}$ = 4.0 Hz, $J_{5A,5B}$ = 10.5 Hz, H-5A), 4.11 (m, 1 H, $J_{1A,2}$ = 6.8 Hz, H-2), 4.63, 4.73 (2 × d, 2 H, $J_{A,B}$ = 11.7 Hz, Bn), 5.21 (ddd, 1 H, $J_{4,5B}$ = 4.0 Hz, $J_{4,5A}$ = 1.3 Hz, $J_{3,4}$ = 1.1 Hz, H-4), 7.29–7.38 (m, 5 H, Bn). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (Ac), 31.8 (C-1), 72.1 (Bn), 72.3 (C-5), 77.9 (C-4), 3.5 (C-2), 85.4 (C-3), 127.9, 128.0, 128.5 (Bn), 137.3 (Bn), 170.2 (Ac). Anal. Calcd for $C_{14}H_{17}BrO_4$ (329.2): C, 51.08; H, 5.21. Found: C, 50.96; H, 5.14.

D-*arabino*-3: ^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, Ac), 3.50 (dd, 1 H, $J_{1A,2}$ = 7.3 Hz, $J_{1A,1B}$ = 10.3 Hz, H-1A), 3.61 (dd, 1 H, $J_{1B,2}$ = 4.7 Hz, $J_{1A,1B}$ = 10.3 Hz, H-1B), 3.97 (br d, 1 H, $J_{4,5A}$ = 4.3 Hz, $J_{5A,5B}$ = 10.0 Hz, H-5A), 4.05 (dd, 1 H, $J_{4,5B}$ = 5.6 Hz, $J_{5A,5B}$ = 10.0 Hz, H-5B), 4.25 (m, 2 H, $J_{1B,2}$ = 4.7 Hz, $J_{1A,2}$ = 7.3 Hz, H-2, H-3), 4.56, 4.67 (2 × d, 2 H, $J_{A,B}$ = 11.3 Hz, Bn), 5.36 (dd, 1 H, $J_{4,5A}$ = 4.3 Hz, $J_{4,5B}$ = 5.6 Hz, H-4), 7.30–7.41 (m, 5 H, Bn). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (Ac), 31.0 (C-1), 69.6 (Bn), 72.3 (C-2), 74.0 (C-5), 78.1 (C-4), 79.8 (C-3), 127.8, 128.0, 128.5 (Bn), 137.4 (Bn), 170.4 (Ac). Anal. Calcd for $C_{14}H_{17}BrO_4$ (329.2): C, 51.08; H, 5.21. Found: C, 51.18; H, 5.17.

3-*O*-Benzyl-1-deoxy-1-iodo-2,5-anhydro-D-lyxitol [(3*R*,4*S*,5*S*)-4-Benzyloxy-5-iodomethyltetrahydrofuran-3-ol] (D-*lyxo*-4)

Bicyclic derivative **2** (100 mg, 0.49 mmol), TMSCl (58 mg, 0.53 mmol), tetrabutylamonium iodide (337 mg, 1.03 mmol) and aq concd HCl (150 μL) were stirred in CH_2Cl_2 (1.5 mL) at r.t. for 28 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (3 mL), then with aq solution of $Na_2S_2O_3$ (10%, 5 mL). Organic phase was dried over $MgSO_4$ and concentrated. Crude oil was purified by flash chromatography (17% EtOAc in hexanes). Pure D-*lyxo*-**4** was isolated as colorless oil (121 mg, 74%), along with inseparable mixture of **2** and D-*arabino*-**4** (10 mg). HPLC analysis of crude product mixture determined ratio D-*lyxo*-**4**/D-*arabino*-**4** 10:1 (Separon SGX Si 100 column, 1 mL/min, 50% EtOAc in *n*-hexane).

D-***lyxo*-4**: R_f = 0.58 (50% EtOAc in hexanes); $[\alpha]_D^{25}$ +6.4 (*c* 0.39, $CHCl_3$), {lit.[4] $[\alpha]_D^{25}$ +7.8 (*c* 1.46, $CHCl_3$)}. Anal. Calcd for $C_{12}H_{15}IO_3$ (334.2): C, 43.13; H, 4.52. Found: C, 43.26; H, 4.56. NMR data of isolated D-*lyxo*-**4** as well as of minor D-*arabino*-**4** were in full accordance with lit.[4]

Acknowledgment

We are grateful to Dr. Szolcsányi for the help with the manuscript preparation. This work was supported by Slovak Grant Agencies (VEGA, Slovak Academy of Sciences and Ministry of Education, Bratislava, project No. 1/7314/20, and APVT, Bratislava, project No. APVT-20-010702).

References

(1) (a) Barlett, P. A. In *Selectivity – A Goal for Synthetic Efficiency*; Bartmann, W.; Trost, B. M., Eds.; Verlag Chemie: Weinheim, **1984**, 1. (b) Boivin, T. L. *Tetrahedron* **1987**, *43*, 3309. (c) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470. (d) Nishiyma, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 6239. (e) McLaughlin, J. L.; Chang, C.-J.; Smith, D. L. *Studies in Natural Products Chemistry*, Vol. 9; Rahman, A.-U., Ed.; Elsevier: Amsterdam, **1991**, 383. (f) McLaughlin, J. L.; Chang, C.-J.; Smith, D.-L. In *Human Medicinal Agents From Plants*; Kinghorn, A. D.; Balandrin, M. F., Eds.; ACS: Washington DC, **1993**, 112. (g) Howard, B. H.; Raistrick, H. *Biochem. J.* **1949**, *44*, 227. (h) Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. K. H.; Pereira, J. T.; Goh, S.-H. *Tetrahedron* **1998**, *54*, 2143.

(2) (a) Gracza, T.; Jäger, V. *Synlett* **1992**, 191. (b) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359. (c) Dixon, D. J.; Ley, S. V.; Gracza, T.; Szolcsányi, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 839. (d) Szolcsányi, P.; Gracza, T.; Koman, M.; Pronayová, N.; Liptaj, T. *Chem. Commun.* **2000**, 471. (e) Szolcsányi, P.; Gracza, T.; Koman, M.; Pronayová, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, 2579. (f) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983. (g) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471.

(3) (a) Jäger, V.; Gracza, T.; Dubois, E.; Hasenöhrl, T.; Hümmer, W.; Kautz, U.; Kirschbaum, B.; Lieberknecht, A.; Remen, L.; Shaw, D.; Stahl, U.; Stephan, O. In *Organic Synthesis via Organometallics, OSM5*; Helmchen, G., Ed.; F. Vieweg & Sohn Verlagsgesellschaft: Braunschweig, Wiesbaden, **1997**, 321. (b) Gracza, T.; Hasenöhrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108.

(4) Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, 507.

(5) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Orena, M. In *Houben-Weyl*, 4th ed., Vol. E21e; Helmchen, G.; Hoffmann, R.; Mulzer, J., Eds.; Thieme: Stuttgart, **1995**, 4760.

(6) Babjak, M.; Zálupský, P.; Gracza, T. *ARKIVOC* **2005**, *v*, 45.

(7) Crotti, P.; Di Bussolo, V.; Favero, L.; Gozzi, C.; Pineschi, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1611.

(8) Kuszmann, J. *Carbohydr. Res.* **1985**, *142*, 71.

(9) Olah, G. A.; Narang, S. C.; Balaram Gupta, G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.