Tetrahedron Letters,Vol.30,No.39,pp 5325-5328,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF ENANTIOMERICALLY PURE 2,3-DIDEOXY-HEPT-2-ENONO-1,4-LACTONE DERIVATIVES VIA DIASTEREOSELECTIVE ADDITION OF 2-(TRIMETHYLSILOXY)FURAN TO D-GLYCERALDEHYDE AND D-SERINAL-BASED THREE-CARBON SYNTHONS

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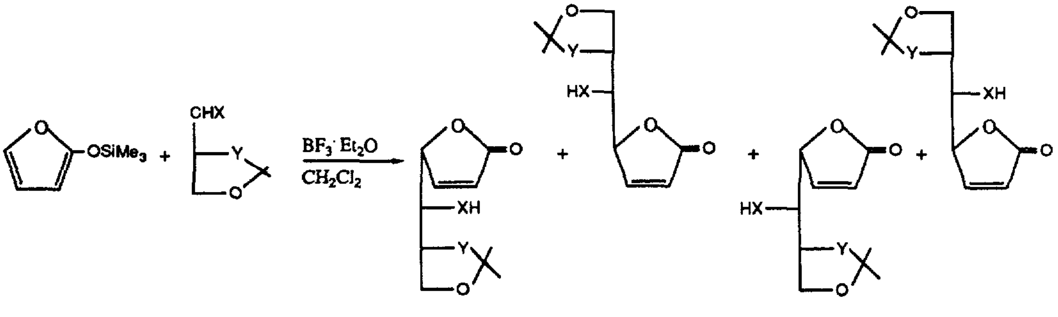
Summary: The BF_3-promoted addition of 2-(trimethylsiloxy)furan to 2,3-O-isopropylidene-D-glyceraldehyde and N-t-BOC-D-serinal, and the corresponding imine derivatives gives the title seven-carbon lactones with great preference for the D-arabino diastereoisomers.

The widespread occurence in Nature[1] and the utility as chiral building blocks[2] renders enantiomerically pure α,β-unsaturated γ- butyrolactones [2(5H)-butenolides] attractive and largely pursued synthetic objectives.[3].



1 **2** **3** **4** **5** **6**

a : X = Y = O **b** : X = O ; Y = N-t-BOC
c : X = N-p-anisyl : Y = O **d** : X = N-p-anisyl ; Y = N-t-BOC

What we now present is a novel versatile approach to highly functionalized seven-carbon representatives of this class of compounds which is based on stereocontrolled four-carbon elongation of D- glyceraldehyde and D-serinal based C_3 synthons by using 2-(trimethylsiloxy)furan.[4]

2,3-O-Isopropylidene -D-glyceraldehyde (**2a**), N-t-BOC-2,3-N,O-isopropylidene-D-serinal (**2b**) and the corresponding imines **2c** and **2d** were allowed to react with 2-(trimethylsiloxy)furan (**1**)[5] in CH_2Cl_2 in the presence of 1.0 molar equiv. of BF_3 etherate at -78°C. After quenching the reaction mixture with an aqueous $NaHCO_3$ solution, D-arabino- and D-ribo-hept-2-enono-1,4-lactone derivatives **3** and **4** were isolated in good yield along with trace amounts of D-lyxo- and D-xylo- stereoisomers **5** and **6**,[6] respectively.

Table. Synthesis of 2,3-dideoxy-D-hept-2-enono-1,4-lactones

Entry	Starting 2	Yield(%)[a]	Diatereoisomeric Composition[b]
1	**2a**	69	**3a**(82):**4a**(17):**5a+6a**(<1)
2	**2b**	70	**3b**(86):**4b**(10):**5b+6b**(4)[c]
3	**2c**	73	**3c**(85):**4c**(10):**5c+6c**(5)[c]
4	**2d**	80	**3d**(73):**4d**(15):**5d+6d**(12)[c]

[a] Overall yield of isolated products.
[b] Determined by HPLC analysis (μ-Bondapak C_{18}; MeCN:H_2O).
[c] 1:1 mixture, not separated.

As can be seen from the Table, in all experiments, lactones of the D-arabino series **3** (4,5-threo-5,6-erythro relationship) largely predominated over the corresponding D-ribo compounds **4** (4,5-erythro-5,6-erythro relationship), while the isomers having 5,6-threo stereodisposition **5** and **6** were only marginal products,[7] as a consequence of the nearly complete Cram-type erythro-selective[8] diastereofacial control of the nucleophilic addition of **1** to prochiral sp^2 carbon of **2**.

The assignment of D-arabino configuration (4R,5S,6R) to D-glyceraldehyde derived lactone **3a** is consistent with our ^{1}H-NMR spectral data,[9] and was confirmed by single crystal X-ray analysis of the corresponding unprotected derivative (80% AcOH-THF 9:1).[10] The D-ribo assignment to **4a** was mainly based on the clean Et_3N-catalyzed epimerization of **3a** into **4a** (35:65 equilibrium ratio at 25°C),[11] while the stereochemical assignment to the related structures **3b-d** and **4b-d** was proposed as shown, based upon ^{1}H-NMR spectral evidences and reasonable assumptions based upon mechanistic analogy.

We are now in a position to prepare significant quantity of enantiomerically pure 2,3-dideoxy-hept-2-enono-1,4-lactones of the D-series (and possibly of the L-series) which are endowed with multiple adjacent hydroxy or mixed hydroxy-amino functionalities. The major stereoisomers **3a-d** possess the 4R,5S,6R configuration, which makes them attractive materials for the synthesis of biologically important monosaccharides of the D-arabino series.[12]

We think that this simple procedure could prove extremely useful in future application and that transformation of the chiral synthons in our hand into interesting sugar-related molecules would be feasible.

ACKNOWLEDGEMENTS: We are grateful to Prof. G. Paglietti (Facoltà di Farmacia, Università di Sassari) for NMR facilities and to Mr. A. Carta for recording the spectra.

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5 Commercially available product (Fluka) was used through this work.

6 n-Bu_4NF and 2,4,6-trimethylphenoxymagnesium bromide are also helpful but somewhat less effective than BF_3 etherate. $SnCl_4$, $TiCl_4$, $TiCl(OPr^i)_3$, Et_2AlCl, and $EtAlCl_2$ did not give satisfactory results, however.

7 Using the reaction between **1** and **2a** as a typical example: 10 mmol of BF_3 etherate (1.23 mL) was added by syringe to a solution of **1** (10 mmol, 1.65 mL) and **2a** (10 mmol, 1.29 g) in 60 mL of CH_2Cl_2 at -78°C. After being stirred for 6h at -78°C, the reaction mixture was hydrolized with 1.44 mL of saturated $NaHCO_3$ followed by extraction of the aqueous portions with ethyl acetate (5x15 mL), and drying the combined organic fractions with $MgSO_4$. After removal of the solvent, the crude reaction mixture was

flash chromatographed on SiO_2 (petroleum ether-ethyl acetate eluant, 15:85) to afford **4a** (0.28 g, 13 %) and then **3a** (1.21 g, 56 %).

8 Ahn, N.T. *Top. Curr. Chem.* 1980, **88**, 145. Reetz, M.T. *Angew. Chem. Int. Ed. Engl.* 1984, **23**, 556.

9 The elemental analyses and spectral data for the new compounds were in accordance with the structures assigned, and only selected data for major isomers **3** are listed.

3a: m.p. 125 °C; $[\alpha]_D^{20}$ +69.6° (c 1, $CHCl_3$); ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.59 (dd, 1H, $J_{2,3}$ 5.84, $J_{3,4}$ 1.24 Hz, H-3), 6.17(dd, 1H, $J_{2,4}$ 1.53 Hz, H-2), 5.24(ddd, 1H, $J_{4,5}$ 3.55 Hz, H-4), 3.9-4.3(m, 3H, H-6 and H-7), 3.66(ddd, 1H, $J_{5,6}$, $J_{5,OH}$ 7.4 Hz, H-5), 2.7(d, 1H, OH), 1.42(s, 3H, Me), 1.31(s, 3H, Me).

3b: oil, $[\alpha]_D^{20}$ +79.1° (c 1.2, $CHCl_3$); ^{1}H-NMR(200MHz; $CDCl_3$) δ 7.42(dd, 1H, $J_{2,3}$ 5.66, $J_{3,4}$ 1.10 Hz, H-3), 6.19(dd, 1H, $J_{2,4}$ 1.76 Hz, H-2), 5.15(m, 1H, H-4), 4.4-3.9(m, 5H, H-5, H-6, H-7, and OH), 1.63(s, 3H, Me), 1.51(s, 12H, Bu^t and Me).

3c: oil, $[\alpha]_D^{20}$ +14.1° (c 3.34, $CHCl_3$); 1H-NMR(200MHz; $CDCl_3$) δ 7.53(dd, 1H, $J_{2,3}$ 5.76, $J_{3,4}$ 1.54, H-3), 6.7(AA'BB', 4H, arom.), 6.13(dd, 1H, $J_{2,4}$ 2.14 Hz, H-2), 5.31(ddd, 1H, $J_{4,5}$ 3.82 Hz, H-4), 3.9-4.2(m, 3H, H-6 and H-7), 3.73(s, 3H, OMe), 3.70(m, 1H, H-5), 3.45(d, 1H, $J_{5,NH}$ 10.44 Hz, NH), 1.45(s, 3H, Me), 1.32(s, 3H, Me).

3d: glass, $[\alpha]_D^{20}$ +35.7° (c 1.2, $CHCl_3$); ^{1}H-NMR(200MHz; $CDCl_3$);δ 7.57(dd, 1H, $J_{2,3}$ 5.78, $J_{3,4}$ 1.52Hz, H-3), 6.7(AA'BB', 4H, arom.) 6.18(dd, 1H, $J_{2,4}$ 2.0 Hz, H-2), 5.29(m, 1H, H-4), 3.9-4.2(m, 4H, H-5, H-6, and H-7), 3.76(s, 3H, OMe), 3.49(bd, NH), 1.51(s, 3H, Me), 1.47(s, 12H, Bu^t and Me).

10 2,3-Dideoxy-D-arabino-hept-2-enono-1,4-lactone: colorless prismatic crystals from CH_2Cl_2, m.p. 108°C; $[\alpha]_D^{20}$ +124° (c 1, 95% ethanol). The single crystal X-ray structure determination was performed by Prof. G. Gasparri Fava and M. Ferrari Belicchi, University of Parma, Italy.

11 Base-catalyzed C-4 epimerization of this type has been reported: Corey, E. J. ; Veukatesawarlu, A. *J. Am. Chem. Soc.* 1972, **94**, 6190.

12 Relevant examples: 3-deoxy-D-arabino-2-heptulosonic acid (Paerels, G. B. ; Geluk, H. W. *Nature* 1963, **197**, 379); 3-deoxy-D-manno-2-octulosonic acid (Vuger, F. M. *Adv. Carbohydr. Chem. Biochem.* 1981, **38**, 323-388).

(Received in UK 9 August 1989)