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A New Procedure for the Preparation of β-Keto-δ-lactones from Sugars and Their Transformation into Glycosyl Acceptors in Disaccharides Synthesis

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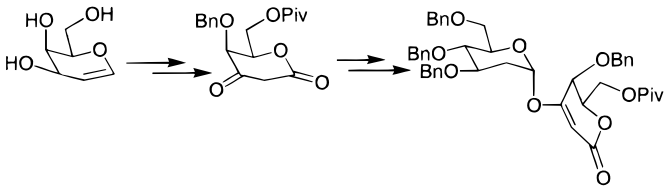
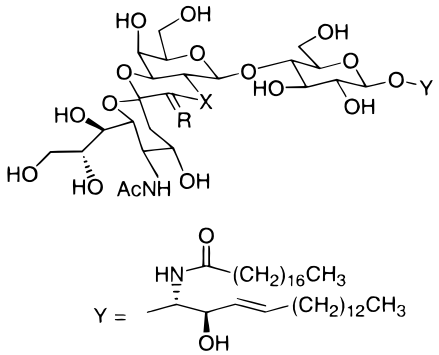
ABSTRACT



Glycals are effective starting materials for the synthesis of enantiopure β-ketone-δ-lactones. They are easily transformed, through a two-step, one-pot reaction, into the corresponding α,α′-dioxothiones which in turn can be quantitatively trapped with dienophiles in inverse electron-demand [4 + 2] cycloadditions. The reaction of dioxothione 8b with endo and exo glucals allowed the elaboration of a new protocol to prepare 2-thio- or 2-deoxydisaccharides stereoselectively.

β-Ketolactones are crucial compounds either as final products or as precursors in the synthesis of challenging targets.[1] Among the few procedures reported for their preparation, the most common rely on aldol condensations[2] or Dieckman cyclizations.[3] In the course of our research we had to face the problem of preparing β-keto-δ-lactones with two stereocenters in an enantiopure form, to be used as precursors of heterodienes in Diels−Alder reactions, toward the synthesis of an analogue of the GM_3 ganglioside lactone[4] (Figure 1).

Unfortunately, the drawbacks presented by known methods[2,3] to synthesize β-keto-δ-lactones (undesired side lactonizations or low selectivity in the formation of new stereocenters) made them unreliable for our purposes. In dealing with our target, carbohydrates are highly attractive



A: X = O, R = O
B: X = S, R = H_2

Figure 1. Structure of the GM_3 ganglioside lactone (**A**) and of the GM_3 ganglioside lactone analogue (**B**).

(1) (a) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 869−872. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678. (c) Seebach, D.; Meyer, H. *Angew. Chem.* **1974**, *40*, 86.

(2) (a) Sato, M.; Sugita, Y.; Abiko, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1157−1160. (b) Schlessinger, R. H.; Pettus, L. H. *J. Org. Chem.* **1998**, *63*, 9089−9094. (c) Kashihara, H.; Shinoki, H.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1986**, *34*, 4527−4532.

(3) Ge, P.; Kirk, K. L. *J. Org. Chem.* **1996**, *61*, 8671−8673.

(4) Regarding GM_3 lactone and its biological role, see: (a) Hamilton, W. B.; Helling, F.; Lloyd, K. O.; Livingston, P. O. *Int. J. Cancer* **1993**, *53*, 566. (b) Kojima, N.; Hakomori, S. *J. Biol.Chem.* **1991**, *266*, 17552−17558.

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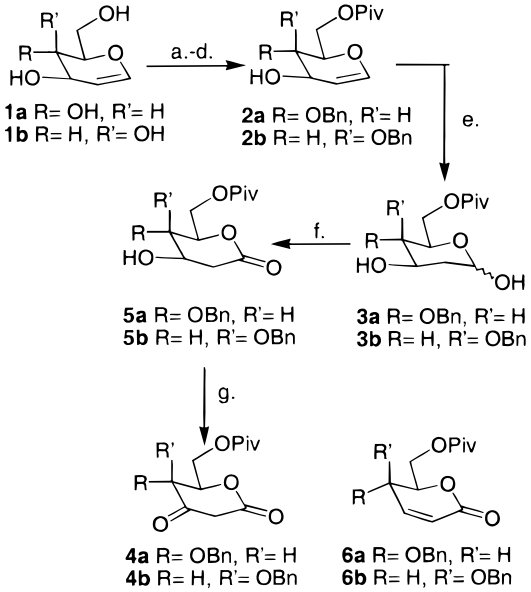
Scheme 1. Synthesis of β-Keto-δ-lactones from Glycals

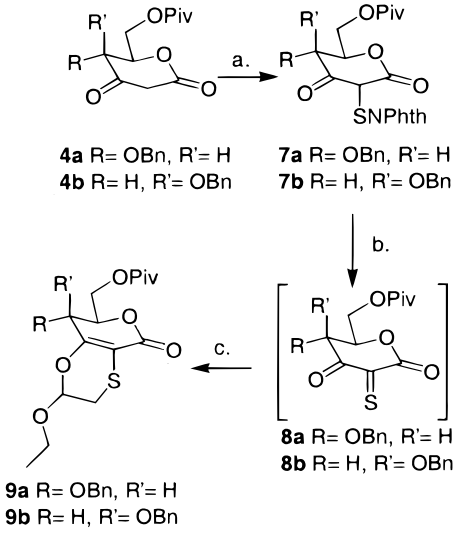


[a] *t*-BDMSOTf, py, 0 °C, 70% (*gluco*), >95% (*galacto*). [b] BnBr, NaH, DMF, rt, 3h. [c] TBAF, DMF, rt, 4 h, 98% (*gluco*), 97% (*galacto*) for two steps. [d] PivCl, py, CH_2Cl_2, rt., 8h, 74% (**2a**), 70% (**2b**). [e] **3a**: HCl, THF/H_2O, 40 °C, 6 h, 69%. **3b**: Bu_4NHSO_4, CH_3CN/H_2O, 65 °C, 15 h, 72%. [f] Ag_2CO_3−Celite, benzene, 80 °C, 3 h, 74% (**5a**), 97% (**5b**). [g] DMSO, Et_3N, $(CF_3CO)_2O$, −70 °C, 1 h, 86% (**4a**), 87% (**4b**).

chiral sources. To our knowledge there is only one literature method regarding the preparation of β-keto-δ-lactones using carbohydrates[3] as "chirons".[5]

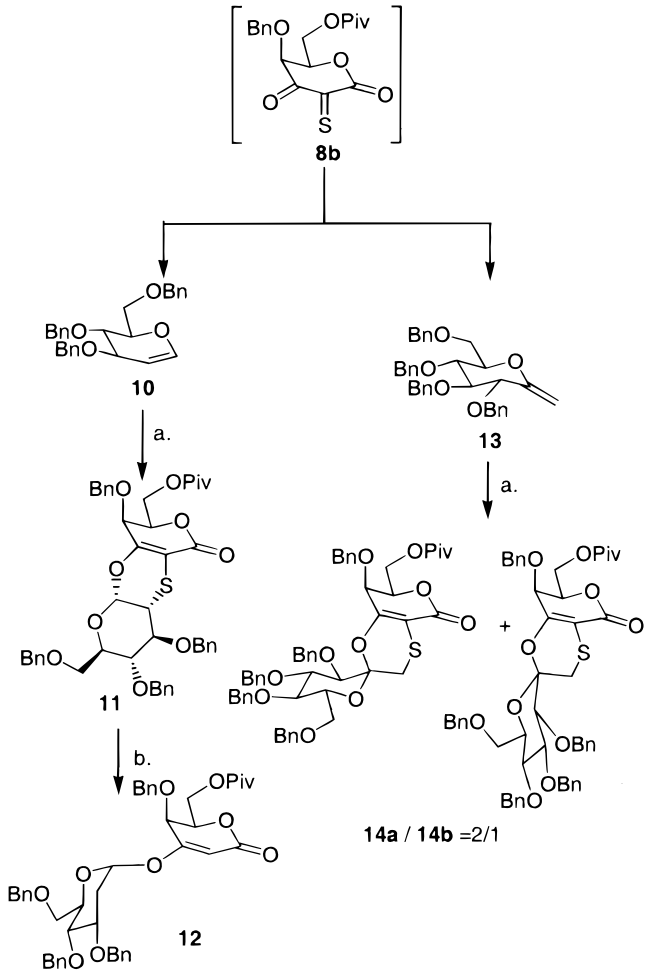
In this Letter we describe a new procedure for the preparation of β-keto-δ-lactones which takes advantage of carbohydrates as starting materials and is used to carry out

Scheme 2. Oxothione for Cycloadditions with Ethyl Vinyl Ether



[a] PhthNSCl, rt, $CHCl_3$, >95%. [b] Py, $CHCl_3$. [c] Ethyl vinyl ether, $CHCl_3$, rt, 8 h, (**9a**, 79%; **9b**, 88%).

Scheme 3. Transfer of Disaccharides Synthesis



[a] $CHCl_3$, rt, 5 h (**11**, 76%; **14**, 75%). [b] Ra/Ni, THF, rt, 1 h, 58%.

an easy and efficient transformation of the monosaccharide moiety. Glycals **1**[6] were selectively protected to give **2** which smoothly afforded **3**, the key intermediates to the desired β-keto-δ-lactones **4** (Scheme 1).

The oxidation sequence of the two hydroxyl groups of the lactols **3** was crucial for the successful formation of **4**. In fact, when **3** underwent oxidation under Swern conditions, to be directly transformed into **4**, the α,β-unsaturated lactones **6** were isolated as single products. On the other hand, when the same oxidation was performed with PCC, PDC, or SO_3.py, we only observed decomposition of the starting material.

To circumvent these problems, the two hydroxyl groups were oxidized independently, selecting in the first step an oxidant allowing the chemoselective transformation of the anomeric hydroxyl group in the presence of the unprotected OH at C-3. For this purpose the hydroxy lactols **3** were

(5) Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: Oxford, 1983.

(6) Glucal **1a** and galactal **1b** can be prepared from the corresponding triacetyl derivatives or from the pentaacetylglucose and pentaacetylgalactose, respectively.[7]

(7) Somsák, L.; Németh, I. *J. Carbohydr. Chem.* **1993**, *12*, 679−684.

treated with Ag_2CO_3 on Celite[8] to obtain the hydroxy lactones **5** in high yield (**5a**, 74%; **5b**, 97%). The subsequent oxidation of **5** using Swern's conditions gave the enantiomerically pure β-keto-δ-lactones **4**[9] (**4a**, 86%; **4b**, 87%).[10]

To test whether β-keto-δ-lactones could be employed as precursors of disaccharides through cycloaddition reactions, derivatives **4** were converted to 1,4-oxathiins **9** by means of ethyl vinyl ether. By following a previously described procedure,[11] treatment of **4** with phthalimidosulfenyl chloride afforded sulfenamides **7**; upon addition of pyridine the latter gave the transient α,α'-dioxothiones **8** which were directly trapped in situ by ethyl vinyl ether. The inverse electron-demand Diels−Alder reaction between **8** and ethyl vinyl ether allowed for isolation of the cycloadducts **9** as single regioisomers,[11,12] in a 1/1 diasteromeric ratio (Scheme 2). As depicted in Scheme 3, the cycloaddition of oxothione **8b** with tribenzyl glucal **10** afforded **11** as a single regio- and stereoisomer. Desulfurization of **11**, carried out with Raney/Ni at room temperature,[11] gave the corresponding 2-deoxy disaccharide **12**.

The procedure was also successfully employed with the exoglucal **13**,[13] affording the spiro derivatives **14a** and **14b**, which were obtained as a 2/1 mixture of stereoisomers.[14] It is readily apparent that **14b** constitutes the core structure of the GM_3 ganglioside lactone analogue **B**.[4,15]

In conclusion, we have devised a new procedure to prepare enantiopure β-keto-δ-lactones from carbohydrates which makes them available for use as new glycosyl acceptors for the synthesis of 2-thio- or 2-deoxydisaccharides.[16]

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Supporting Information Available: EA as well as ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Fetizon, M.; Golfier, M.; Mourgues, P. *Tetrahedron Lett.* **1972**, 4445−4448.

(9) No C-4 epimerization product was ever detected under the reported reaction conditions.

(10) **Representative Procedure. Oxidation of 4-*O*-Benzyl-2-deoxy-5-*O*-pivaloyl-D-galactopyranoside (3b) to the β-Ketolactone 4b.** To a solution of 3-hydroxylactol **3b** (0.41 mmol) in dry benzene (4 mL) was added 683 mg of silver carbonate on Celite. The mixture was refluxed under vigorous stirring for 2.5 h. After the reaction was completed, the reaction was cooled to room temperature and filtered through a pad of Celite. After removal of the solvent, the crude oil was chromatographed on silica gel (ethyl acetate/hexane 1/1) to yield the β-hydroxylactone **5b** (97%) which was fully characterized as the acetyl derivative: ^{1}H NMR ($CDCl_3$) δ 7.38−7.26 (m, 5H), 5.16 (td, J = 10.0, 2.0 Hz, 1H), 4.71 (AB system, J = 11.4 Hz, 2H), 4.50 (td, J = 6.0, 2.0 Hz, 1H), 4.39−4.19 (m, 2H), 4.08 (t, J = 2.0 Hz, 1H), 2.94 (d, J = 9.1 Hz, 2H), 2.05 (s, 3H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.0, 170.0, 167.4 (C-1), 137.0, 128.6, 128.3, 127.9, 76.8, 74.8, 71.1, 69.0, 62.3, 38.7, 31.9, 27.1, 20.9. Trifluoroacetic anhydride (1.03 mmol) was added dropwise to a mixure of DMSO (3.6 mmol) and dry CH_2Cl_2 (1.0 mL) previously cooled to −78 °C; a white precipitate formed. The suspension was warmed to −70 °C, stirred for 15 min, and then cooled again to −78 °C. A solution of **5b** (0.17 mmol) in dry CH_2Cl_2 (2.0 mL) was added and the reaction mixture stirred at −60 °C for 45 min. After this time Et_3N (1.36 mmol) was slowly added and the solution so obtained was gently warmed to room temperature, dissolved in dichloromethane, washed with brine, and dried over Na_2SO_4. The organic solvent was removed under reduced pressure, and the crude material was purified on a silica gel column (hexane/ethyl acetate 2/1) to yield **4b** (50 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 7.38−7.26 (m, 5H), 4.93−4.87 (A part of an AB system, J = 12.1 Hz, 1H), 4.68 (m, 1H), 4.61−4.54 (B part of an AB system, J = 12.1 Hz, 1H), 4.36 (AB part of an ABX system, J = 12.1 Hz, 2H), 4.09 (d, J = 4.4 Hz, 1H), 3.56 (AB system, J = 20.5 Hz, 2H), 1.14 (s, 9H); ^{1}H NMR (DMSO) δ 11.95 (s, 1H), 7.39−7.28 (m, 5H), 5.01 (s, 1H), 4.76−4.55 (m, 3H), 4.38−4.24 (m, 2H), 4.03 (d, J = 2.5 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 197.6 (C-3), 177.8, 165.8 (C-1), 135.9, 128.8, 128.7, 128.6, 128.4, 128.3, 74.8, 74.6, 72.9, 61.7, 44.7, 38.7, 26.9. Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.49; H, 8.30. Found: C, 63.80; H, 8.01.

(11) (a) Capozzi, G,; Franck, R. W.; Mattioli, M.; Menichetti, S.; Nativi, C.; Valle, G. *J. Org. Chem.* **1995**, *60*, 6416−6426. (b) Capozzi, G.; Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777−779.

(12) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Raffaelli, B. *Chem. Eur. J.* **1999**, *5*, 1748−1754.

(13) Bartolozzi, A.; Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Paolacci, B. A. *J. Org. Chem.* **1999**, *64*, 6490−6494.

(14) Compunds **14a** and **14b** were perfectly separated by chromatography on silica gel.

(15) For other examples of GM_3 ganglioside lactone analogues, see: (a) Ray, A. K.; Nilsson, U.; Magnusson, G. *J. Am. Chem. Soc.* **1992**, *114*, 2256−2257. (b) Tietze, L. F.; Keim, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1615−1617.

(16) All new compouds had EA and proton and carbon NMR data consistent with their structures.