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Totally Stereoselective Synthesis of 1,3-Disaccharides through Diels−Alder Reactions†

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A nonclassical, totally stereoselective synthesis of orthogonally protected 1,3-disaccharides is reported. Enantiomerically pure β-keto-δ-lactones, efficiently obtained from glucal and galactal, are transformed into electron-poor heterodienes and chemo-, regio-, and stereoselectively cycloadded to glycals as electron-rich dienophiles, to directly afford 2-thiodisaccharides. The reductive desulfurization of the latter smoothly gave the corresponding 2,2′-dideoxydisaccharides.

1. Introduction

The increased interest in glycobiology and the expansion of knowledge of the role of oligosaccharides[1] sets the stereocontrol in *O*-glycosylation as a central matter in carbohydrate chemistry.

The biological activity of entire classes of oligo- and polysaccharides are nowadays widely studied and complex oligosaccharide-containing molecules of considerable pharmaceutical interest are an important target for many research groups. Many of these active molecules, such as anthracyclines, aureolic acids, or cardiac glycosides, present deoxy oligosaccharide moieties as common and essential parts[2] (Figure 1).

Efficient and stereoselective methods affording disaccharides have often been reported.[3] Most of them concern the formation of 1,6-linked disaccharides and rely on the use of Lewis acids as promoters, while the stereochemical control is obtained making use of the anchimeric assistance of a neighboring group adjacent to the anomeric center.

In the synthesis of 2-deoxyglycosides (and 2-deoxydisaccharides) the most evident problems consist of the lack of a neighboring group and the associated lessened stability of suitable glycosyl donors. This explains well the few general and efficient methods existing for the direct stereoselective synthesis of this class of compounds. To circumvent these problems "tailored" transformations[4] are required.

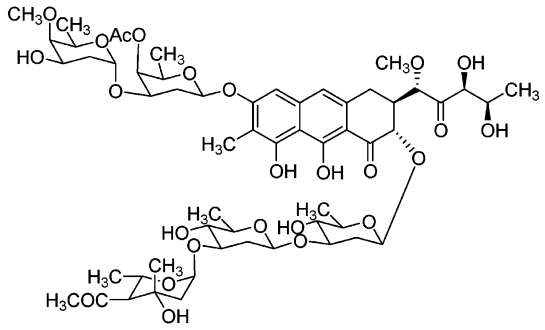

FIGURE 1. Structure of Chromomycin A_3 (a member of aureolic acid family).

A few years ago we published the effective synthesis for α- and β-*O*-glycosides based on the chemo-, regio-, and stereoselective [4+2] cycloadditions between "in situ" generated α,α'-dioxothiones **1**[5] (electron-poor dienes) and differently substituted or unsubstituted glycals **2** (electron-rich dienophiles)[6] (Scheme 1).

Taking advantage of the easily and selectively removable sulfur atom, the α- and β-2-deoxy-2-thio-*O*-glycosides **3** and **4** were transformed into the corre-

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† Dedicated to Prof. Giuseppe Capozzi on the occasion of his retirement.

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(1) (a) Yarema, K. J.; Bertozzi, C. R. *Curr. Op. Chem. Biol.* **1998**, *2*, 49. (b) Galli-Stampino, L.; Meinjohanns, E.; Frische, K.; Meldal, M.; Jensen, T.; Werdelin, O.; Mouritsen, S. *Cancer Res.* **1997**, *57*, 3214. (c) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (d) Varki, A. *Glycobiology* **1993**, *3*, 97.

(2) (a) Kirschning, A.; Bechtold, A. F. W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 2. (b) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285.

(3) (a) Capozzi, G.; Menichetti, S.; Nativi, C. In *New Trend in Synthetic Medicinal Chemistry. Methods and Principles in Medicinal Chemistry*; Gualtieri, Ed.; Wiley-VCH: Weinheim RFG, Germany, 2000; Vol. 7, pp 221−259. (b) Hanessian, S.; Lou, B. *Chem. Rev.* **2000**, *100*, 4443. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(4) (a) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385. (b) Hallis, T. M.; Liu, H. *Acc. Chem. Res.* **1999**, *32*, 579. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(5) For the synthesis of α,α'-dioxothiones see: Capozzi, G.; Franck, R. W.; Mattioli, M.; Menichetti, S.; Nativi, C.; Valle, G. *J. Org. Chem.* **1995**, *60*, 6416.

(6) (a) 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. (b) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Raffaelli, B. *Chem. Eur. J.* **1999**, *5*, 1748.

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SCHEME 1. Diels−Alder Reactions between α,α′-Dioxothiones 1 and Glycals 2

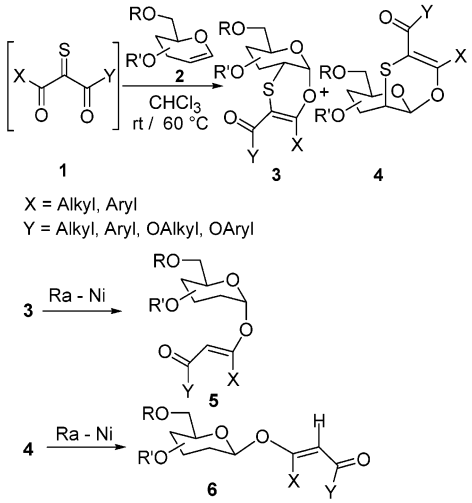
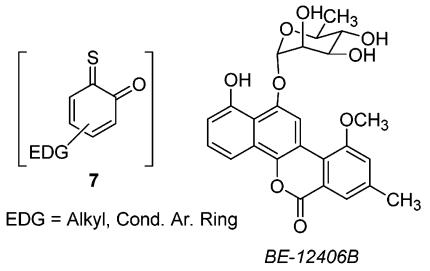


CHART 1. Structure of *o*-Thioquinones 7 and BE-12406B.



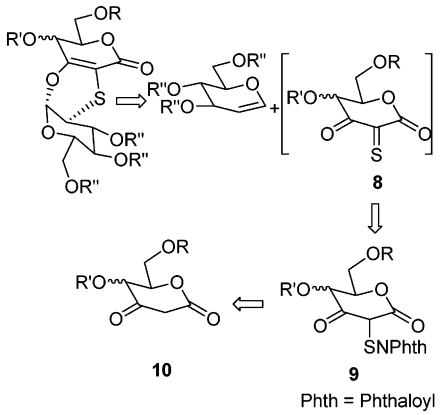
sponding α- and *β*-2-deoxy-*O*-glycosides **5** and **6** without affecting the absolute configuration of the anomeric center (Scheme 1).

The stereoselectivity of these cycloadditions can be adequately modulated and α- or *β*-isomers can be obtained as single stereoisomers if suitable glycals and solvent are employed.[6]

Cycloadducts **3** have also been successfully employed as glycosyl donors to prepare 2-deoxy-*β*-*O*-disaccharides. As a matter of fact, after "remote activation"[3b,7] **3** efficiently react with appropriate glycosyl acceptors to afford *β*-*O*-disaccharides with total stereoselectivity.[8]

Aryl α- or *β*-glycosides were analogously prepared employing *o*-thioquinones **7**[9] as electron-poor dienes (Chart 1). The cycloaddition occurs with the same chemo-, regio-, and stereoselectivity observed for α,α′-dioxothiones; moreover, as we reported[10] for the synthesis of the 2-deoxy analogue of the antitumor antibiotic BE-12406B[11] (Chart 1), the cycloaddition of *o*-thioquinones **7** to 6-deoxyglycals successfully affords aryl 2,6-dideoxy-*O*-glycosides, naturally occurring and synthetically challenging molecules.

SCHEME 2. Retrosynthesis for *β*-Keto-α-thiono-*δ*-lactones 8



We wish to report here on the extension of the efficient synthesis of alkyl- or aryl-*O*-glycosides, to prepare enantiomerically pure *O*-disaccharides directly through an inverse electron-demand Diels−Alder reaction between α,α′-dioxothiones deriving from monosaccharides and suitable glycals. This nonclassical approach to disaccharides stereoselectively affords *O*-glycosyl linkages under mild, neutral conditions.

2. Results and Discussion

Disaccharides can be obtained in a single step by cycloadding glycals to appropriately substituted α,α′-dioxothiones. A possible retrosynthetic scheme to achieve our target molecules, capitalizing on the chemo-, regio-, and stereochemical properties of the above-described inverse-electron demand Diels−Alder reactions, can be envisaged as depicted in Scheme 2. The α,α′-dioxothione **8** can be formed by the base treatment of the phthalimido derivative **9** obtained, in turn, from the enantiomerically pure *β*-keto-*δ*-lactones **10** (Scheme 2).

Looking in the literature for the synthesis of *β*-keto-*δ*-lactones such as **10**, we realized that the drawbacks presented by known methods[12] (undesired side lactonizations or low selectivity in the formation of new stereocenters) made them unreliable for our purposes.

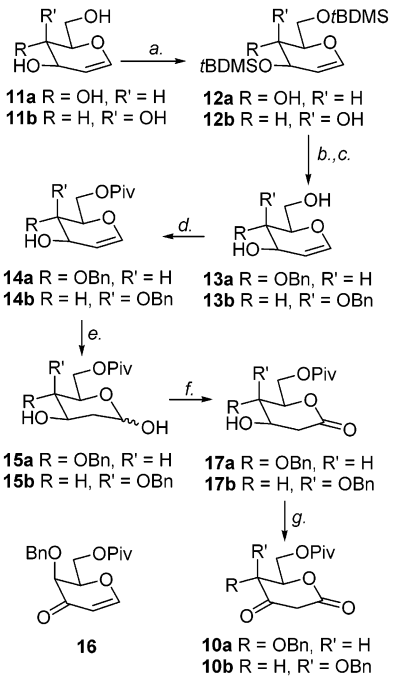
A new procedure for the preparation of enantiomerically pure *β*-keto-*δ*-lactones seemed to be advisable and dealing with our target, carbohydrates appeared highly attractive chiral sources.[13]

The stereoselective and efficient transformation of monosaccharides into *β*-keto-*δ*-lactones was realized[14] from glycals **11**, selectively protected to give **12**, which smoothly afforded **13**, the key intermediates to the desired *β*-keto-*δ*-lactones **10** (Scheme 3).

The oxidation sequence of the two hydroxyl groups of the lactols **15** was crucial for the successful formation of **10**. In fact, when **15b** was oxidized under Swern conditions, to be directly transformed into **10b**, the undesired

(7) Hanessian, S. In *Preparative Carbohydrate Chemistry*; Hanessian, Ed.; Marcel Dekker: New York, 1997; pp 381−388.
(8) Bartolozzi, A.; Capozzi, G.; Menichetti, S.; Nativi, C. *Eur. J. Org. Chem.* **2001**, 2083.
(9) For the synthesis of *o*-thioquinones see: Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **1997**, *62*, 2611.
(10) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Franck, R. W. *Tetrahedron Lett.* **1995**, *36*, 6755.
(11) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1994**, *35*, 4591.
(12) (a) Ge, P.; Kirk, K. L. *J. Org. Chem.* **1996**, *61*, 8671. (b) Sato, M.; Sugita, Y.; Abiko, Y.; Kaneko, C. *Tetrahedron*: *Asymmetry* **1992**, *3*, 1157. (c) Schlessinger, R. H.; Pettus, L. H. *J. Org. Chem.* **1998**, *63*, 9089. (d) Kashihara, H.; Shinoki, H.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1986**, *34*, 4527.
(13) For a described synthesis of *β*-keto-*δ*-lactones from carbohydrates see ref 12a.
(14) Previous communication: Bartolozzi, A.; Capozzi, G.; Menichetti, S.; Nativi, C. *Org. Lett.* **2000**, *2*, 251.

SCHEME 3. Synthesis of β-Keto-δ-lactones 10[a]



[a] Reagents and conditions: (a) *t*-BDMSOTf, py, CH_2Cl_2, 0 °C, 69% (**12a**), >98% (**12b**). (b) BnBr, NaH, DMF, rt, 3 h. (c) TBAF, DMF, rt, 4 h, 98% (**13a**), 97% (**13b**) for two steps. (d) PivCl, py, CH_2Cl_2, rt 20 h, 74% (**14a**), 70% (**14b**). (e) **15a**: HCl, THF/H_2O, 40 °C, 6 h, 69%. **15b**: Bu_4NHSO_4, CH_3CN/H_2O, 65 °C, 15 h, 72%. (f) Ag_2CO_3-Celite, benzene, 80 °C, 2.5-5 h, 74% (**17a**), 97% (**17b**). (g) DMSO, Et_3N, $(CF_3CO)_2O$, −70 °C, 1 h, 86% (**10a**), 87% (**10b**).

α,*β*-unsaturated lactone **16** was isolated as the sole product. 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 hydroxyl groups were transformed independently. In the first step, an oxidant allowing the chemoselective oxidation of the anomeric hydroxyl group in the presence of the unprotected OH at C-3 was chosen. The hydroxyl lactols **15** were thus treated with silver carbonate on Celite[15] to give the hydroxyl lactones **17** in high yield (**17a**, 74%; **17b**, 97%). The subsequent oxidation of **17** with Swern conditions gave the diasteromerically pure *β*-keto-*δ*-lactones **10** (**10a**, 86%; **10b**, 87%), without epimerization at C-4. The oxidation of **17** was attempted under Dess−Martin conditions[16] as well, but unreacted starting material was always recovered.

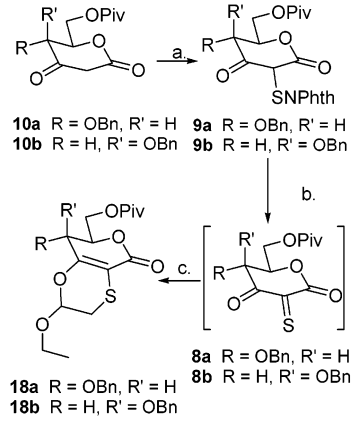
To test whether *β*-keto-*δ*-lactones could be employed as precursors of disaccharides through cycloaddition reactions, derivatives **10** were transformed into phthalimido derivatives **9**, which upon addition of pyridine gave the transient α,α′-dioxothiones **8**, directly trapped "in situ" by ethyl vinyl ether (Scheme 4).

The inverse electron-demand Diels−Alder reaction between **8** and ethyl vinyl ether allowed for isolation of the cycloadducts **18** as single chemo- and regioisomers[5,6] in a 1/1 diasteromeric ratio (Scheme 4).

The cycloaddition of α,α′-dioxothiones **8** was successfully performed with other, more appealing, dienophiles, as depicted in Scheme 5.

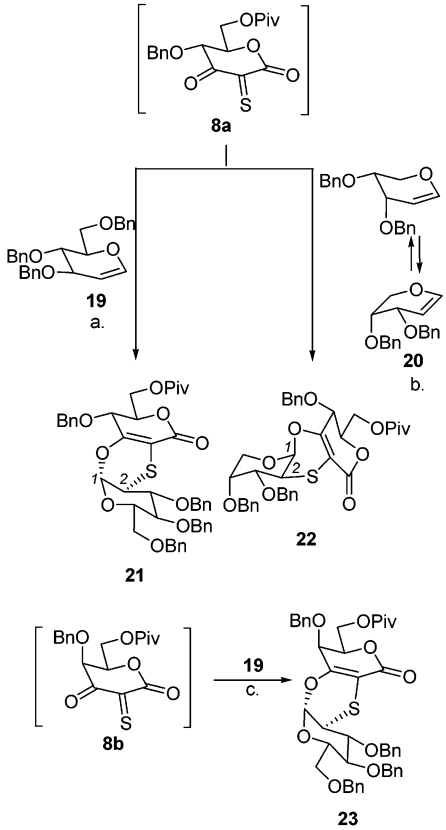
The 2-deoxy-2-thio-1,3-*O*-disaccharides **21** and **22** were obtained by reacting the glucothione **8a** with the tribenzyl-D-glucal **19** and the dibenzyl-L-arabinal **20**, respectively, while **23** was formed by cycloaddition of the galactothione **8b** with **19**. All cycloadducts were obtained as diasteromerically pure compounds.[17] The stereochemistry observed can be rationalized assuming that the attack of the oxothiones occurred from the bottom face

SCHEME 4. "In Situ" Generation of Oxothiones 8 and Their Trapping with Ethyl Vinyl Ether[a]



[a] Reagents and conditions: (a) PhthNSCl, rt, $CHCl_3$, >95%. (b) Py, $CHCl_3$. (c) Ethyl vinyl ether, $CHCl_3$, rt, 8 h, (**18a**, 79%; **18b**, 88%).

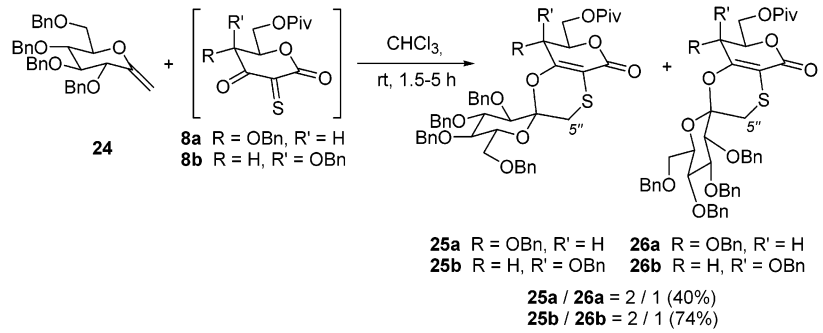
SCHEME 5. Synthesis of Cycloadducts 21−23[a]



[a] Reagents and conditions: (a) $CHCl_3$, rt, 1.5 h, 76%. (b) CHI_3, rt, 5 h, 52%. (c) $CHCl_3$, rt, 5 h 76%.

(15) Fetizon, M.; Golfier, M.; Morgues, P. *Tetrahedron Lett.* **1972**, 4445.
(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

SCHEME 6. Synthesis of Spirothioacetals 25 and 26



of the dienophiles for **21** and **23** and from the top face of the dienophile for **22**.[18]

The protocol was also successfully extended to the exoglycal **24**,[20] a product of interest for our research toward the synthesis of an analogue of the GM_3-ganglioside lactone.[14,21] Compound **24** reacted with **8a** affording the spiro derivatives **25a** and **26a** and with **8b**, affording the spiro derivatives **25b** and **26b**. Compounds **25a**/**26a** and **25b**/**26b** were obtained as 2/1 mixtures of diasteroisomers[22] (Scheme 6).

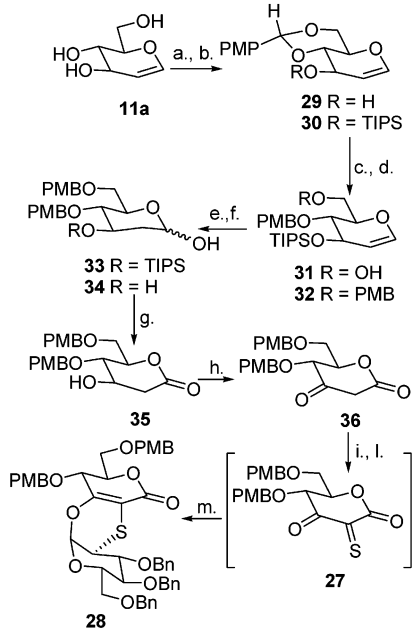
As extensively reported,[20] the preferred configuration of the spirocenters was determined by the anomeric effects and the structures **25a** and **25b** (i.e. the structures with two anomeric effects[23]) were assigned to the major isomers.[24]

To test the general applicability of the present procedure, the cycloaddition was also performed between the benzylglucal **19** and the bis-*p*-methoxybenzyl protected thiolactone **27**, which was prepared as reported in Scheme 7. The cycloadduct **28** was obtained as diastereomerically pure compound in 76% yield (Scheme 7).

The synthetic scheme for **27** presents some improvements with respect to that reported for **8a**, as a matter of fact (a) *p*-methoxybenzyl protecting groups can be selectively removed under mild conditions and (b) the same synthetic scheme can be followed to orthogonally protect hydroxyls at C-4 and C-6 (simply changing step d).

The removal of the two *p*-methoxybenzyl groups was realized by treating **28** with 2.5 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the diol **37** (68%), which was characterized as acetyl derivative **38** (Scheme 8).

SCHEME 7. Preparation of Thiolactone 27 and Synthesis of Disaccharide 28[a]



[a] Reagents and conditions: (a) $p(CH_3O)C_6H_4CH(OMe)_2$, PPTS, CH_3CN, rt, 4 h, 70% (**29**). (b) TIPSCl, IMI, DMAP, DMF, rt, 3 h, 95% (**30**). (c) DIBAL-H, CH_2Cl_2, −15 to 0 °C, 2 h, 73% (**31**). (d) PMBCl, *t*BuOK, DMSO, 0 °C to rt, 3 h, 84% (**32**). (e) HCl (8 N), dioxane−H_2O, 1.5 h, 59% (**33**). (f) HF (40% in H_2O), DMF, 93% (**34**). (g) Ag_2CO_3-Celite, benzene, 80 °C, 18 h , 89% (**35**). (h) DMSO, Et_3N, $(CF_3CO)_2O$, −70 °C, 1 h, 68% (**36**). (i) PhthNSCl, rt, $CHCl_3$. (l) Py, $CHCl_3$. (m) **19**, rt, 3 h, 76% (**28**).

Treatment of **28** with cerium(IV) ammonium nitrate (CAN) (3.5 equiv, CH_3CN/H_2O-9/1 rt, 9 h) did not afford the expected diol **37**, in fact the monodeprotected derivative **39** (20%) was isolated with undesired side products (Scheme 8).

The sulfur atom, regioselectively introduced by cycloaddition at C-2 and C-2′ of **21**−**23**, **25**, and **26**, can be reductively removed to afford the corresponding 2,2′-dideoxy derivatives. Desulfurization was carried out on **21**−**23** with Raney-Ni in tetrahydrofuran, at room temperature, giving the 2-deoxy disaccharides **41**−**43** (Scheme 9).

All reactions were performed in wet tetrahydrofuran, using commercially available activated Raney-Nickel, with yields comparable with those reported in the

(17) ^{1}H NMR analysis allowed the determination of the structures of cycloadducts **21**−**23** as reported below: indeed, **21** shows a doublet (J_{H1-2} = 2.6 Hz) at 5.75 ppm for H-1 and a doublet of doublets (J_{H2-3} = 10.4 Hz) at 3.31 ppm, **22** shows a doublet (J_{H1-2} = 2.5 Hz) at 5.70 ppm for H-1 and a doublet of doublets (J_{H2-3} = 11.0 Hz) at 3.71 ppm, while **23** shows a doublet (J_{H1-2} = 2.6 Hz) at 5.53 ppm for H-1 and a doublet of doublets (J_{H2-3} = 10.7 Hz) at 3.28 ppm.

(18) These results are perfectly in agreement with those previously reported.[6,10,19]

(19) (a) Li, B.; Franck, R. W.; Capozzi, G.; Menichetti, S.; Nativi, C. *Org. Lett.* **1999**, *1*, 111. (b) Dios, A.; Geer, A.; Marzabadi, C. H.; Franck, R. W. *J. Org. Chem.* **1998**, *63*, 6673.

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

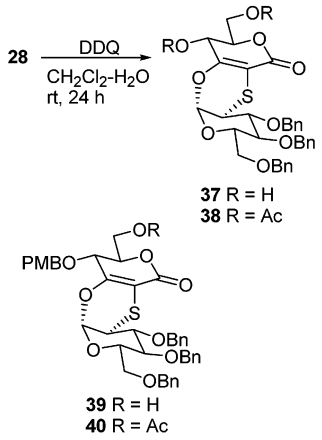
(21) Regarding GM_3 lactone and its biological role, see: (a) Hamilton, W. B.; Helling, F.; Lloyd, K. O.; Livingstone, P. O. *Int. J. Cancer* **1993**, *53*, 566. (b) Kojima, N.; Hakomori, S. *J. Biol. Chem.* **1991**, *266*, 17552.

(22) Compounds **25b** and **26b** were perfectly separated by column chromatography on silica gel.

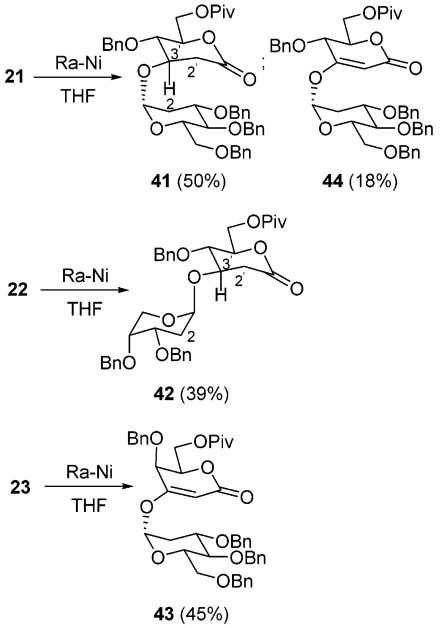
(23) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve', T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

(24) Structure assignment of **25a**, **25b**, **26a**, and **26b** was realized by ^{1}H NMR by comparison with reported data of related compounds.[20] More detailed investigations for the direct demonstration of the structure of the two couples of diasteroisomers are currently in progress in our labs.

SCHEME 8. Deprotection of *p*-Methoxybenzyldisaccharide 28



SCHEME 9. Synthesis of 2-Deoxy Disaccharides 41−43



literature.[4a,25] Generally, when using an aged Raney-Nickel sample, lower yields were observed.

Noteworthy, glucolactones **21** and **22** under standard desulfurizating conditions underwent the conjugated double bond reduction, affording the saturated 2,2′-dideoxydisaccharides **41** and **42**, respectively (Scheme 9). Depending on reaction conditions (low temperature and reduced amounts of Raney-Nickel), the disaccharide **41** was isolated with amounts of the unsaturated derivative **44** (18%); on the contrary, **42** was always formed as the major product with undesired side products. Attempts to improve the yield of **41** (prolonged reaction times or higher quantities of Raney-Nickel) failed, in fact the presence of decomposition products was observed.

The formation of the unsaturated deoxy derivatives **43** (*galacto* series) and of the saturated dideoxy derivative **42** (*arabino* series) (see Scheme 9) was tentatively explained considering a higher stability of **42** and **43** with respect to the corresponding unsaturated or saturated analogues.[26]

Compounds **41** and **42** were obtained as single stereoisomers and their stereochemistry, as depicted in Scheme 9, was unambiguously determined by ^{1}H NMR analysis: indeed, CH_2-2′, δ 2.69 (**41**), 2.79 (**42**) appeared as the AB part of ABX systems and H-3′ (**41** and **42**) is in the axial position.

3. Conclusions

In conclusion we have devised a new procedure to prepare enantiomerically pure carbohydrate β-keto-pyranolactones from carbohydrates and successfully employed them to achieve new glycosyl acceptors for the synthesis of 2-thio-2-deoxy- and 2-deoxy-*O*-disaccharides in an enantiomerically pure form. The general applicability of the present procedure together with the real possibility of using a variety of protecting groups on carbohydrate moieties make it a promising, general approach to the synthesis of complex deoxy oligosaccharides.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **10**, **12**−**18**, **21**−**23**, **25**, **26**, and **28**−**44**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034556R

(25) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem*. **1998**, *63*, 2197.

(26) Small amounts (5−10%) of starting glycals **19** and **20** (not shown) also can be isolated during the treatment of cycloadducts **21**−**23** with Ra−Ni. Studies on the elucidation of the desulfurization reactions mechanism are still in progress in our laboratories. For a related publication see: Tamarez, M. M.; Franck, R. W.; Geer, A. *Tetrahedron* **2003**, *59*, 4249.