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Recent aspects of glycoconjugate synthesis: A synthetic approach to the linkage region of proteoglycans*

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Abstract - A versatile synthetic route to nonsulfated, as well as mono and disulfated glycohexaosyl serines that correspond to the linkage region of proteoglycans is developed by employing a glycotriaosyl donor and a glycotriaosyl acceptor Chemoselective removal of levuloyl groups among other ester groups without causing any acyl migration was carried out and subsequent regiospecific introduction of sulfate groups was achieved successfully.

INTRODUCTION

Different repeating dissaccharides of glycosaminoglycans are linked to core proteins through a common tetrasaccharide sequence "GlcAβ-(1→3)-Galβ-(1→3)-Galβ-(1→4)-Xylβ-(1→3)-Ser" (ref. 1), the presence of phosphate group at O-2 of β-Xyl[1] residue in both chondroitin sulfate from the Swarm Rat Sarcoma and heparan sulfate from bovine lung was demonstrated by Oegema, Jr. and co-workers (ref. 2) in 1984 and by L.-A. Fransson and co-workers (ref. 3) in 1985, respectively.

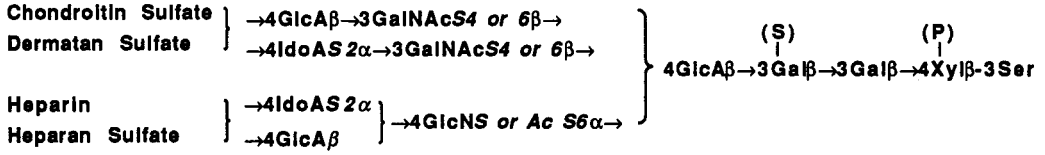


Fig. 1 Proteoglycans : Glycosaminoglycans and Linkage Regions

In 1988, Sugahara and co-workers isolated and chemically characterized neutral as well as sulfated glycohexaosylserines (**1**, **2** and **3**) as carbohydrate-protein linkage regions of chondroitin 4-sulfate of Swarm Rat Chondrosarcoma after exhaustive enzymic digestions (ref. 4). Discovery of the presence of sulfate group at the linkage region particularly at O-4 of Gal[3] of chondrotin 4-sulfate is of significant interest. The biological role played by these anionic phosphate and sulfate present in the linkage region of proteoglycans is not clear at the moment but could be the recognition signals for the transportation of the biosynthetic precursor molecules to a specific subcellular multienzymic compartment in the Golgi apparatus where specified repeating disaccharides schould be assembled.

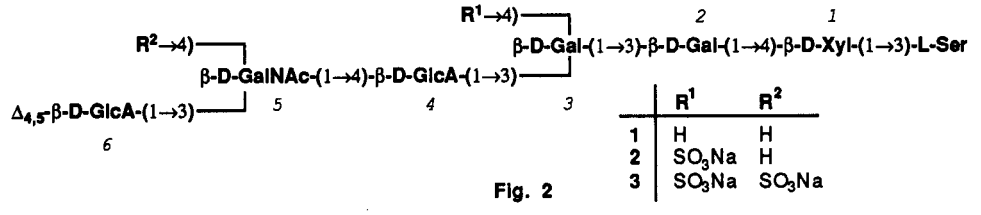


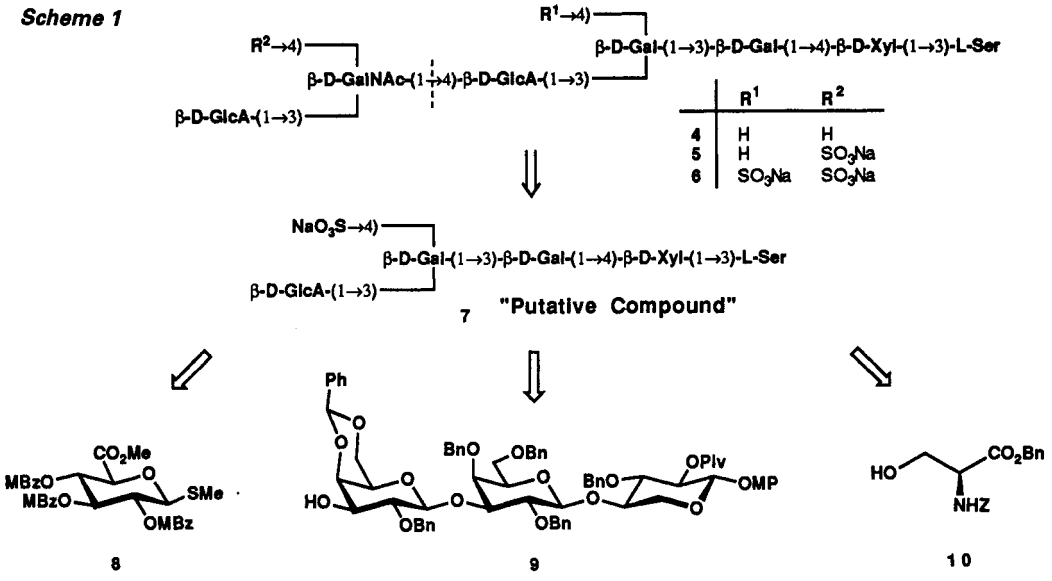
Fig. 2

* Part 90 in the series "Synthetic Studies on Cell-Surface Glycans". For part 89, see F. Goto, and T. Ogawa, *Tetrahedron Lett.*, submitted.

As part of our on-going project on the synthesis of glycosaminoglycan fragments (ref. 5), we describe here a versatile approach to the synthesis of glycohexaosyl serine **4**, **5**, and **6**, which may be expected to function as molecular probes for the clarification of biosynthetic pathways of proteoglycans. In relevant synthetic studies elegant routes to glycotriaosyl serin have been successfully developed (ref. 6). We first describe here a synthetic route to a glycotetraosyl serine **7**, a part structure of **6**.

STEREOSELECTIVE SYNTHESIS OF MONOSULFATED GLYCOTETRAOSYL SERINE

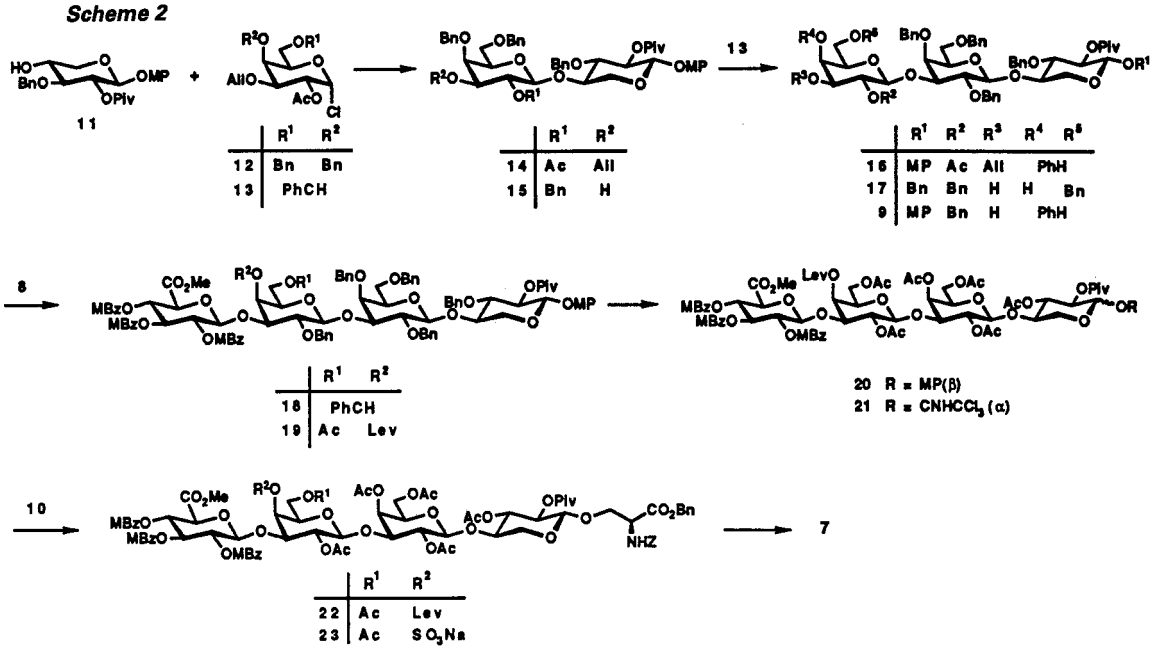
Scheme 1



Based upon a retrosynthetic analysis, we disconnected **7** into 3 parts and designed a GlcA donor **8**, glycotriaosyl acceptor **9** and serine derivative **10**. Thioglycoside **8** is readily available (ref. 7). Synthesis of **9** is carried out as follows. Xylopyranosyl derivative **11** (ref. 8) was coupled with 1.1 equivalents of Gal donor **12** (ref. 8) in the presence of AgOTf(ref. 9)-molecular sieves 4A (MS4A) in 5:2 toluene-CH_2Cl_2 at 20° to afford 70% of the desired β-D linked **14** (ref. 10) and 15% of the undesired α-anomer (ref. 10). **14** was converted into **15** (ref. 10) in 3 steps (*1* LiOH-H_2O_2 (ref. 11), *2* BnBr, KI, Ag_2O, *3* $[Ir(COD)(Ph_2MeP)_2]PF_6$(ref. 12) (Ir^+), H_2 in THF, then I_2-H_2O, in 89% overall). Glycosylation of **15** with 1.1 equivalents of Gal donor **13** (ref. 13) in the presence of AgOTf-MS4A in CH_2Cl_2 at -23° gave 94% of β-linked trisaccharide **16** (ref. 10) which was then converted into the designed intermediate **9** (ref. 10) in 3 steps (*1* LiOH, H_2O_2, *2* BnBr, Bu_4NI, NaH, *3* Ir^+, H_2 in THF, then I_2-H_2O-$NaHCO_3$, 87% overall). $CuBr_2$-Bu_4NBr-AgOTf-MS4A (ref. 14) promoted glycosylation of **9** with **8** (1.3 equivalents) in CH_2Cl_2 at -20°~20° afforded 80% of the β-linked product **18** (ref. 10). It is to be noted that in this highly efficient glycosylation the presence of 4,6-O-benzylidene group at galactose residue(Gal)-*3* is crucial to yield (1→3)-β-linked tetrasaccharide. Under the same condition, a glycosyl acceptor **17** (ref. 15) with 3,4-diol system at Gal-*3* gave only 15% of the desired β-(1→3)-linked tetrasaccharide in spite of the seemingly favorable steric environment around OH-3. **18** was then converted in 3 steps (*1* CSA in MeOH-CH_2Cl_2, *2* AcCl-Py, *3* Lev_2O-DMAP in Py, 86% overall) into **19** (ref. 10) which is armed with a selectively removable (ref. 16) levuloyl group at O-4 of Gal-3. Benzyl groups of **19** was replaced by acetyl groups in 2 steps (*1* 10% Pd-C, H_2 in EtOAc-MeOH, *2* Ac_2O-DMAP in Py, 49% overall) to afford **20** (ref. 10) which was further converted into the imidate **21** (ref. 10) in 2 steps (*1* CAN (ref. 17) in MeCN-H_2O, *2* Cl_3CCN, DBU (ref. 18), 78% overall). BF_3•OEt_2 promoted glycosylation of **10** (10 equivalents) with **21** in CH_2Cl_2 at -23° gave 75% of the β-linked product **22** (ref. 10). Chemoselective removal of levuloyl group of **22** and introduction of sulfate group could be carried out efficiently to yield **23** (ref. 10) in 2 steps (*1* NH_2NH_2•AcOH in toluene-EtOH (ref. 16), *2* Et_3NSO_3 (ref. 19) in DMF, 88% overall). Finally **23** was deprotected

to give the target molecule, glycotetraosyl serine **7** (ref. 10), in 3 steps (*1* Pd-black, H_2 in EtOAc, *2* LiOH in 10:3 THF-H_2O, *3* NaOH in 5:1 MeOH-H_2O, 97% overall).

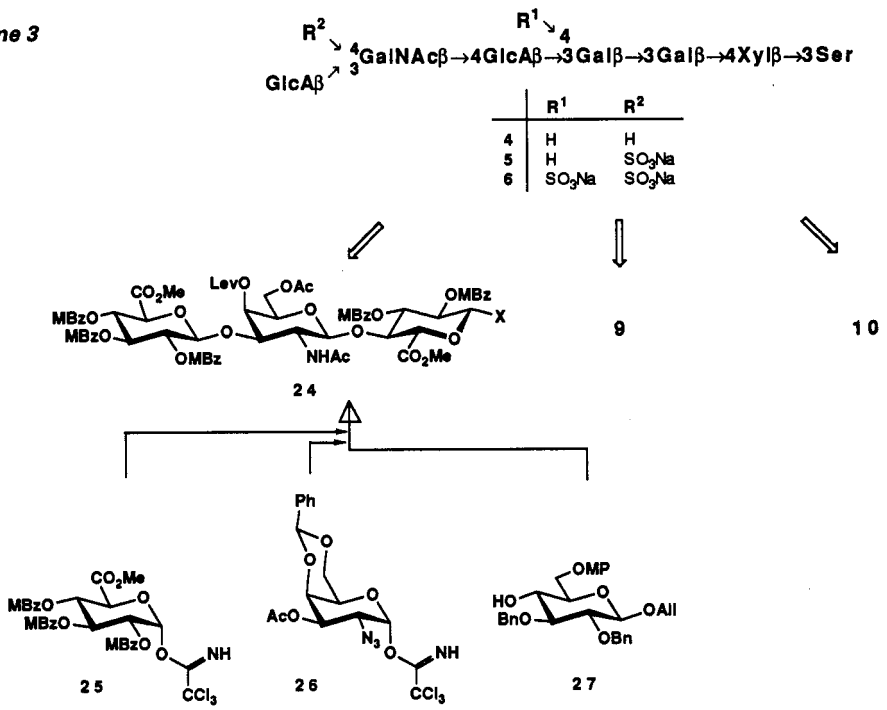
Scheme 2



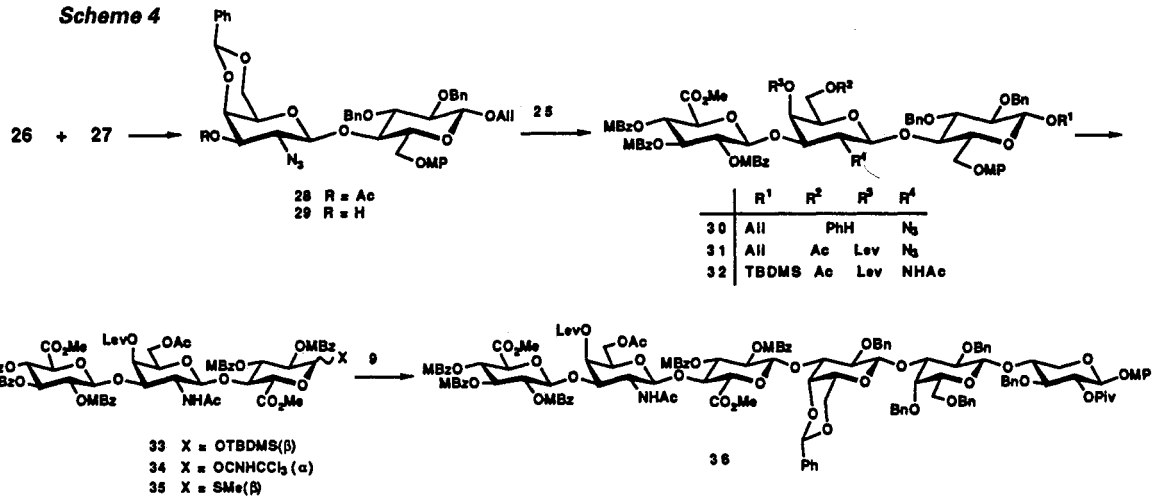
STEREOSELECTIVE SYNTHESIS OF MONO AND DISULFATED GLYCOHEXAOSYL SERINES

Having synthesized monosulfated glycotetraosyl serine **7** by employing a key glycotriaosyl acceptor **9**, now we have turned our attention to the use of **9** in the synthesis of glycohexaosyl serines **4**, **5**, and **6** as shown in scheme 3. Glycotriaosyl donor **24** may be obtained by successive glycosylation of **27** (ref. 20) with the imidates **26** (ref. 21) and **25** (ref. 22).

Scheme 3

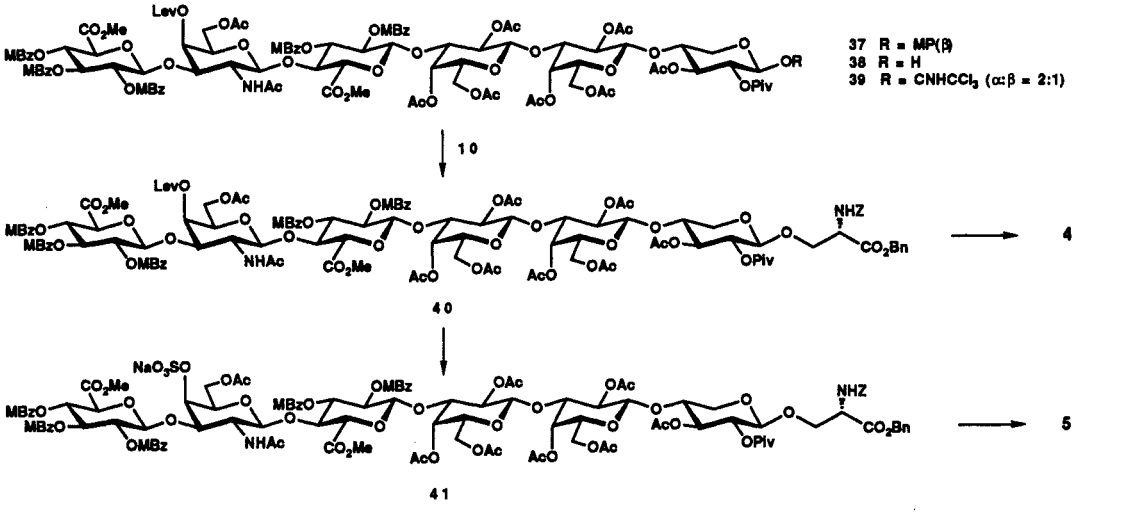


Scheme 4



TMSOTf-MS4A promoted glycosylation of **27** with **26** (1.7 equivalents) in toluene at -78° afforded 68% of β-linked product **28** (ref. 10) and 28% of the a-anomer (ref. 10). Saponification of **28** in MeONa in 1:1 MeOH-THF to give 97% of **29** (ref. 10) which was glycosylated with **25** (1.2 equivalents) in the presence of BF_3•OEt_2-MSAW300 in 30:1 toluene-$(ClCH_2)_2$ at -25° to give stereoselectively 60% of **30** (ref. 10). No α-anomer of **30** was detected in the reaction mixture. However, the coupling between **25** and **29** (1.3 equivalents) in the presence of TMSOTf-MS4A in 200:1 toluene-$(CH_2Cl)_2$ at -23° gave 70% of a mixture of **30** and the α-anomer in a ratio of 2:5. This dramatic change of stereochemical outcome remains to be rationalized. Conversion of **30** into **31** was carried out in 3 steps (*1* CSA in 1:1 MeOH-CH_2Cl_2, 20°, *2* AcCl in Py, -5°, *3* Lev_2O, DMAP in 4:1 Py-$(CH_2Cl)_2$, 20°, 83% overall). Now we have to study further transformation of **31** into glycotriaosyl donor **24**. **31** was submitted to the series of reactions, *1* $HS(CH_2)_3SH$ (ref. 22), Et_3N in MeOH, 20°, *2* Ac_2O, DMAP in Py, *3* $[Ir(COD)(Ph_2MeP)_2]PF_6$, H_2 in THF; then I_2-H_2O, *4* $^tBuMe_2SiCl$, imidazole in DMF, to give **32** in 86% overall. Oxidative transformation of **32** was performed in 6 steps (*1* 10% Pd-C, H_2 in 1:1 MeOH-EtOAc, *2* MBzCl, DMAP in Py, 20°, *3* CAN in 4:1 MeCN-H_2O at 0°, *4* $(COCl)_2$, DMSO in CH_2Cl_2 for 5 min at -78°, then iPr_2EtN for 10 min at -20°~-15°, *5* $NaClO_2$ (ref. 23), NaH_2PO_4 in 2:1:1 ^tBuOH-H_2O-2methyl-2-butene 22h at 20°, *6* CH_2N_2 in EtOAc-Et_2O at 20°, 68% overall) to give **33** which was then converted into imidate **34** in 2 steps (*1* Bu_4NF, AcOH in THF (ref. 24), *2* Cl_3CCN-DBU in CH_2Cl_2, 93% overall). Thioglycoside **35** was readily prepared in 79% by treatment of **34** with Bu_3SnSMe (ref. 25) and BF_3•OEt_2 in CH_2Cl_2 at -25°.

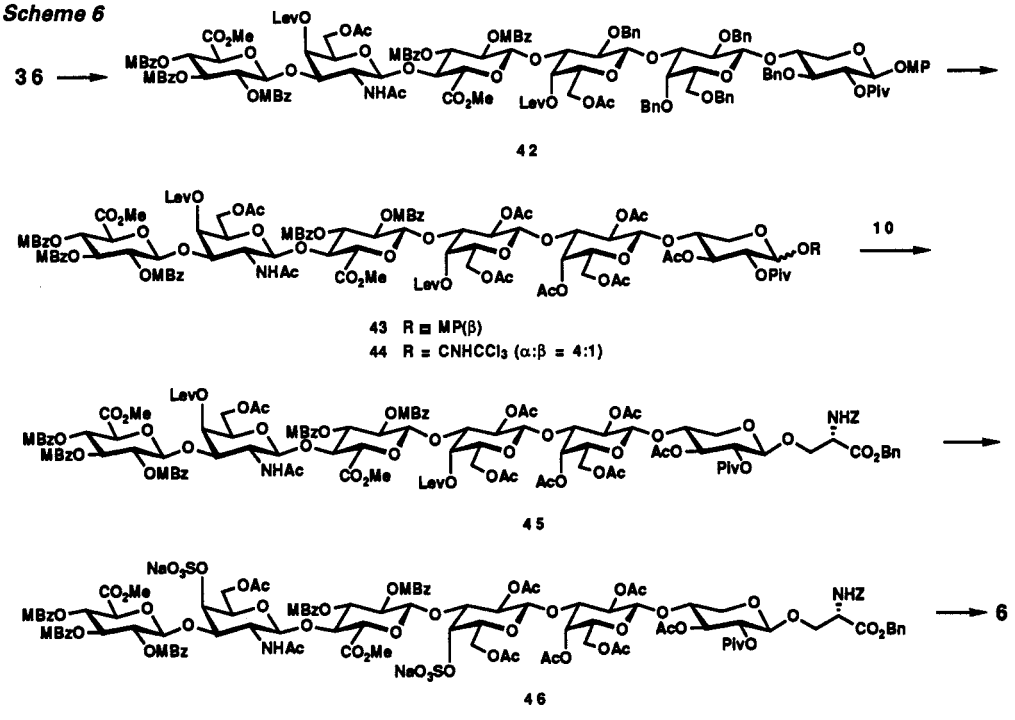
Scheme 5



Since the imidate **34** was found to give in the relevant glycosylations only low yield of the desired product upon reaction with related glycosyl acceptors, crucial coupling of glycotriaosyl acceptor **9** was examined with thioglycoside **35** (ref. 10) (0.7 equivalents) in the presence of $CuBr_2$-Bu_4NBr-AgOTf-MS4A in CH_2Cl_2 at -25° to afford 75% of the desired glycohexaosyl product **36** (ref. 10). Catalytic hydrogenolysis of **36** in the presence of 20% $Pd(OH)_2$-C in 2:1 EtOAc-MeOH and subsequent acetylation with Ac_2O-DMAP in pyridine gave 81% of **37** (ref. 10) which was further transformed into glycohexaosyl imidate **39** (ref. 10) via **38** (ref. 10) in 2 steps (*1* CAN in 4:1 MeCN-H_2O at 0°, *2* Cl_3CCN, DBU in CH_2Cl_2 at 0°, 90% overall). Coupling of the imidate **39** with serine derivative **10** (10 equivalents) in the presence of BF_3•OEt_2-MSAW300 at -23° afforded 64% of **40**. The structure of **40** was confirmed by complete deprotection that gave **4** in 3 steps (*1* Pd-black H_2 in 1:1 EtOAc-MeOH, *2* LiOH in 5:1 THF-H_2O at -10°, *3* NaOH in 4:1 MeOH-H_2O, 69% overall). ^{1}H-NMR data of **4** (Fig.3) are in good agreement with the structure of **4**. Introduction of sulfate into **40** was executed in 2 steps to give **41** (*1* NH_2NH_2•AcOH in 1:5 toluene-EtOH at 20°, *2* Et_3N•SO_3 in DMF at 50°, 43% overall). **41** was completely deprotected in 3 steps to give monosulfated glycohexaosyl serine **5** (*1* Pd-black, H_2 in 1:1 MeOH-EtOAc, *2* LiOH in 5:1 THF-H_2O at -8°, *3* NaOH in 4:1 MeOH-H_2O 88% overall) which gave a reasonable ^{1}H NMR as shown in Fig. 3.

To establish a route to disulfated target **6**, the key intermediate **36** was first converted in to **42** in 3 steps (*1* CSA in 1:1 CH_2Cl_2-MeOH at 20°, *2* AcCl in 9:4 Py-CH_2Cl_2 at -78°, *3* Lev_2O, DMAP in 3:1 Py-$(CH_2Cl)_2$ at 20°, 66% overall). **42** was converted into **44** via **43** in 4 steps (*1* 20% $Pd(OH)_2$-C, H_2 in 2:1 EtOAc-MeOH, *2* Ac_2O-DMAP in Py, *3* CAN in 2:1 MeCN-H_2O at 0°, *4* Cl_3CCN; DBU in CH_2Cl_2 at 0°, 72% overall). Coupling of **44** with **10** (10 equivalents) in the presence of BF_3•OEt_2-MSAW300 in CH_2Cl_2 at -23° gave 64% of **45**. Simultaneous introduction of two sulfate groups in **45** was performed in 2 steps to give **46** (*1* NH_2NH_2•AcOH in 1:5 toluene-EtOH, *2* Et_3NSO_3 in DMF at 50°, 43% overall). Finally deprotection of **46** into **6** was achieved in 3 steps (*1* Pd-black, H_2 in 1:1 EtOAc-MeOH, *2* LiOH in THF-H_2O at -8°, *3* NaOH in 4:1 MeOH-H_2O, 88% overall). ^{1}H-NMR of **6** (Fig.3) confirmed the structure.

Scheme 6



CONCLUSION

An efficient, stereocontrolled, and convergent synthetic route to the target glycohexaosyl serines **4**, **5**, and **6** was developed for the first time by employing key glycotriaosyl acceptor **9** and glycotriaosyl donor **35**. Sulfate groups could be introduced regioselectively to the specific hydroxyl groups that were temporarily protected with chemoselectively removable

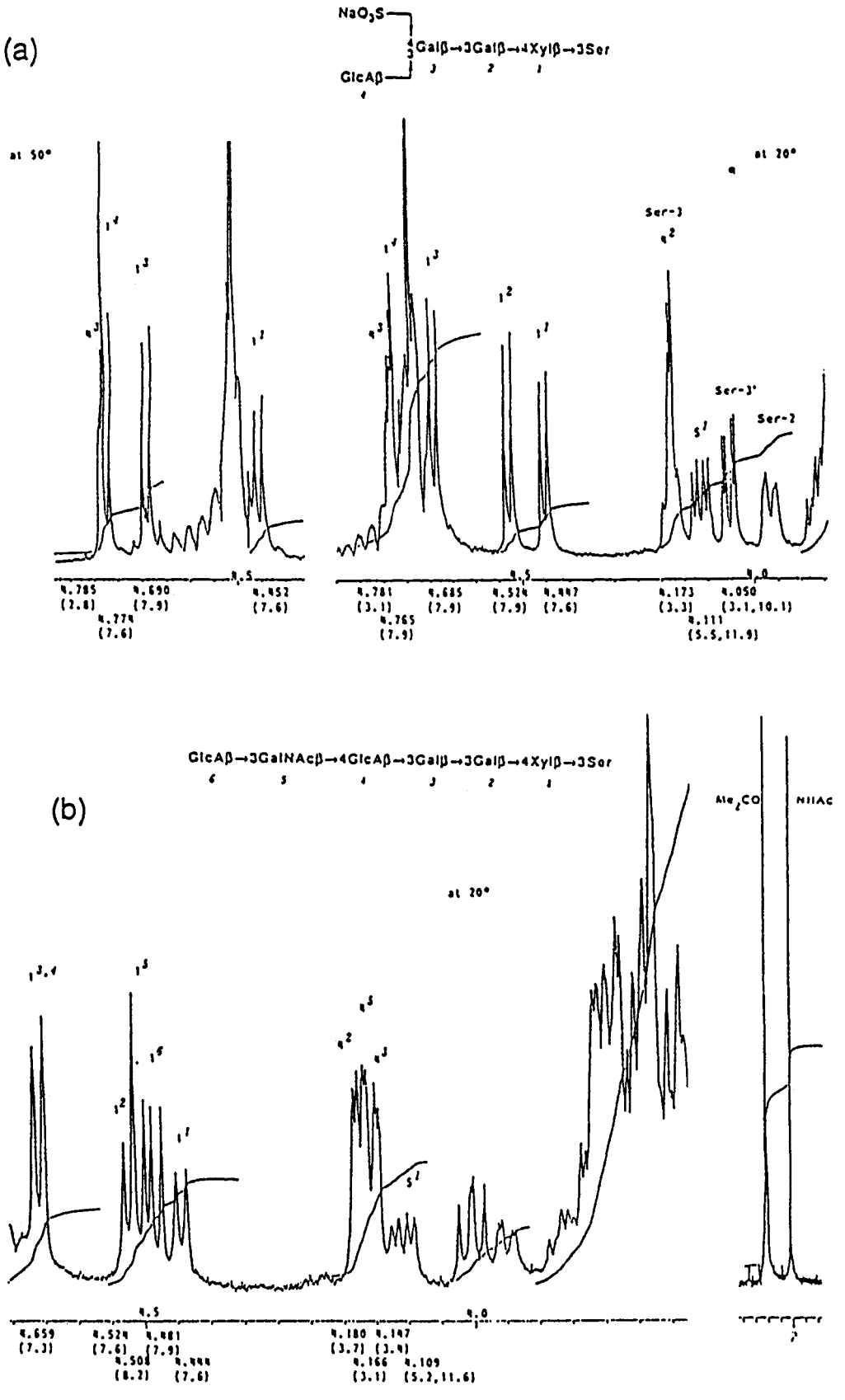


Fig. 3 500MHz ^{1}H NMR spectra in D_2O for compounds 7(a), and 4(b).

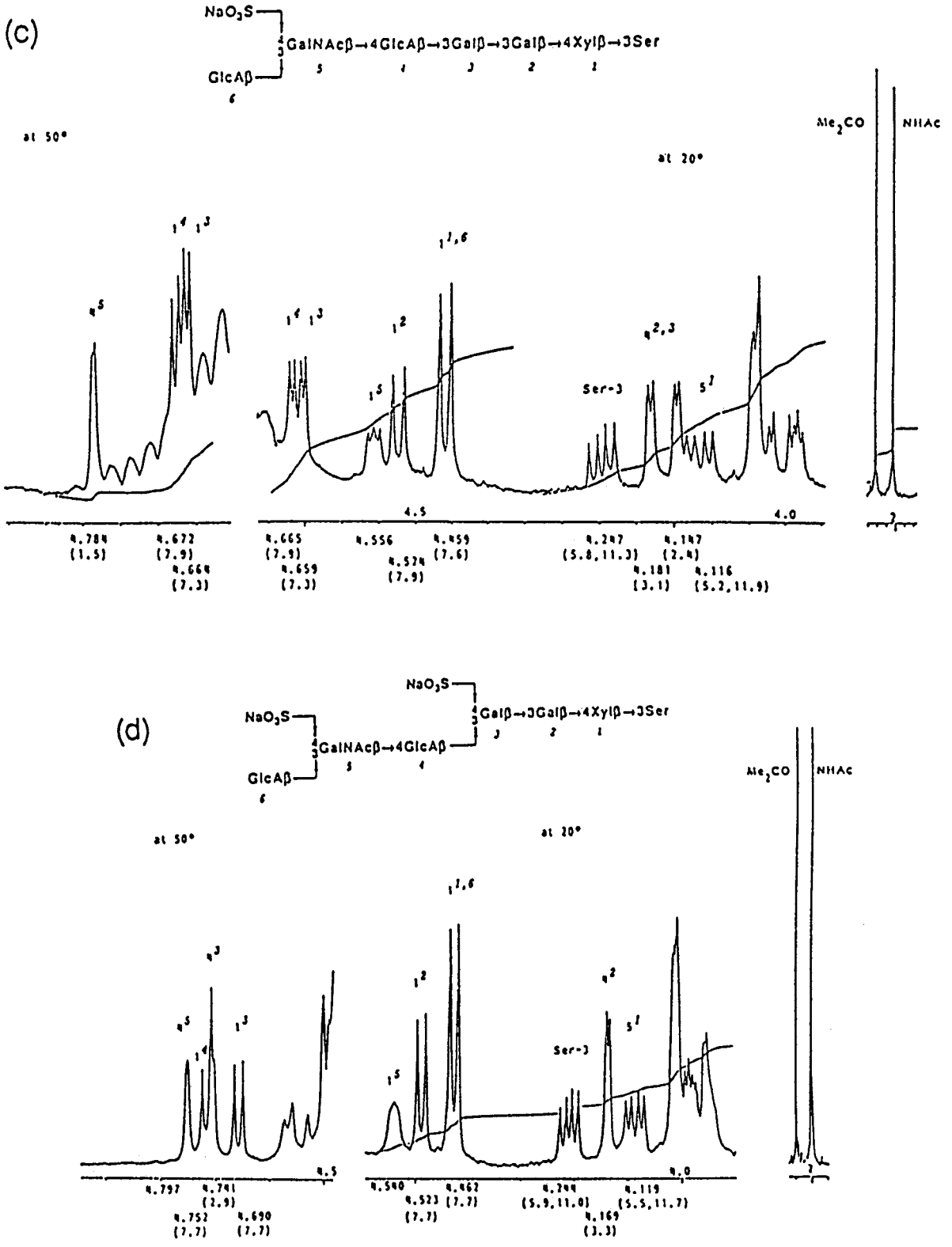


Fig. 3 (continued). 500MHz ^{1}H NMR spectra in D_2O for compounds 5(c), and 6(d).

levuloyl group in the presence of other ester groups. It should be noted that under the mildly basic condition employed for the removal of the levuloyl group and for the introduction of sulfate group no acetyl migration from O-6 to O-4 of Gal residue was observed.

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10. Physical data for new compounds are given below, values of $[\alpha]_D$ and $\delta_{H,C}$ were measured at 25°±3° for solutions in $CHCl_3$ and $CDCl_3$, respectively, unless noted otherwise. Signal assignment such as 1^3 stands for a proton at C-1 of sugar residue *3*. **14**: $[\alpha]_D$ -16.4° (c 3.8); R_F 0.37 in 7:3 hexane-EtOAc; δ_H 4.868 (d, 7.0Hz, 1^1), 4.452 (d, 7.9Hz, 1^2); The a-anomer of **14**: $[\alpha]_D$ +42.9° (c 1.3); R_F 0.52 in 7:3 hexane-EtOAc; δ_H 5.268 (d, 4.0Hz, 1^2), 4.800 (d, 7.6Hz, 1^2). **15**: $[\alpha]_D$ -22.8° (c 0.4); R_F 0.25 in 7:3 hexane-EtOAc; δ_H 4.973 (d, 6.1Hz, 1^2), 4.416 (d, 7.6Hz, 1^2), 1.179 (s, Piv). **16**: $[\alpha]_D$ -27.3° (c 0.2); R_F 0.52 in 1:1 toluene-EtOAc; δ_H 5.545 (s, PhCH), 4.943 (d, 6.1Hz, 1^1), 4.901 (d, 7.9Hz, 1^3), 4.407 (d, 7.3Hz, 1^2), 1.168 (s, Piv). **9**: $[\alpha]_D$ -19.1° (c 0.9); R_F 0.40 in 1:1 toluene-EtOAc; δ_H 5.475 (s, PhCH), 4.910 (d, 6.3Hz, 1^1), 4.680 (d, 8.3Hz, 1^3), 4.361 (d, 6.9Hz, 1^2), 1.114 (s, Piv). **18**: $[\alpha]_D$ -4.7° (c 1.7); R_F 0.50 in 2:1 toluene-EtOAc; δ_H 5.631 (s, PhCH), 5.381 (d, 6.9Hz, 1^4), 4.941 (d, 5.9Hz, 1^1), 4.856 (d, 7.6Hz, 1^3), 4.370 (d, 7.3Hz, 1^2), 3.759 and 3.644 (2s, 2 OMe), 1.169 (s, Piv). **19**: $[\alpha]_D$ -1.3° (c 0.5); R_F 0.17 in 3:1 toluene-EtOAc; δ_H 5.429 (d, 4.0Hz, 4^3), 4.954 (d, 5.9Hz, 1^1), 4.820 (d, 7.9Hz, 1^3), 4.391 (d, 7.3Hz, 1^2), 3.761 and 3.704 (2s, 2 OMe), 2.202 (s, Lev), 2.003 (s, Ac), 1.166 (s, Piv). **20**: $[\alpha]_D$ +2.4° (c 1.6); R_F 0.37 in 1:2 toluene-EtOAc; δ_H 5.488 (d, 3.3Hz, 4^3), 4.908 (d, 7.3Hz, 1^4), 4.895 (d, 6.9Hz, 1^1), 4.383 (d, 8.3Hz, 1^2 and 1^3), 2.204 (s, Lev). **21**: $[\alpha]_D$ +27.2° (c 0.9); R_F 0.47 in 1:2 toluene-EtOAc; δ_H 8.630 (d, C=NH), 6.418 (d, 3.7Hz, 1^1), 5.482 (d, 3.3Hz, 4^3), 2.204 (s, Lev), 1.128 (s, Piv). **22**: $[\alpha]_D$ +2.5° (c 0.7); R_F 0.40 in 1:1 toluene-EtOAc; δ_H 5.483 (d, 3.4Hz, 4^3), 4.905 (d, 7.3Hz, 1^4), 4.377 (d, 7.9Hz, 1^3), 4.334 (d, 7.0Hz, 1^1), 4.319 (d, 7.9Hz, 1^2), 2.202 (s, Lev), 1.117 (s, Piv). **23**: $[\alpha]_D$ -14.8° (c 0.4, MeOH); R_F 0.55 in 15:1 $CHCl_3$-MeOH; $\delta_H(CD_3OD)$ 5.307 (d, 3.4Hz, 4^3), 5.206 (d, 7.6Hz, 1^4), 4.486 (d, 7.0Hz, 1^1), 3.657 (s, OMe), 1.115 (s, Piv). **7**: R_F 0.28 in 5:2:2:2 Me_2CO-AcOH-MeOH-H_2O; $\delta_H(D_2O)$ 4.781 (d, 3.1Hz, 4^3), 4.765 (d, 7.9Hz, 1^4), 4.685 (d, 7.9Hz, 1^3), 4.524 (d, 7.9Hz, 1^2), 4.447 (d, 7.6Hz, 1^1), 4.173 (d, 3.4Hz, 4^2). **28**: $[\alpha]_D$ +33.5° (c 1.3); R_F 0.23 in 3:1 hexane-EtOAc; δ_H 5.446 (s, PhCH), 4.511 (d, 7.6Hz, 1^1), 4.477 (dd, 3.7 and 11.0Hz, 3^2), 4.377 (d, 8.2Hz, 1^2), 3.776 (s, OMe). α-anomer of **28**: $[\alpha]_D$ +99.1° (C 1.2); R_F 0.34 in 3:1 hexane-EtOAc; δ_H 5.349 (s, PhCH), 5.900 (d, 3.7Hz, 1^2), 4.534 (d, 7.6Hz,

1^1), 3.770 (s, OMe). **29**: $[\alpha]_D$ +5.5° (c 0.7); R_F 0.28 in 3:1 toluene-EtOAc; δ_H 5.516 (s, PhCH), 4.518 (d, 7.9Hz, 1^1), 4.268 (d, 8.2Hz, 1^2), 3.771 (s, OMe). **30**: $[\alpha]_D$ -6.2° (c 1.1); R_F 0.52 in 2:1 toluene-EtOAc; δ_H 5.415 (d, 7.3Hz, 1^3), 4.472 (d, 7.6Hz, 1^1), 4.293 (d, 8.2Hz, 1^2), 3.781 and 3.618 (2s, 2 OMe). The a-anomer of **30**: $[\alpha]_D$ +8.7° (c 1.6); R_F 0.59 in 2:1 toluene-EtOAc; δ_H 6.033 (d, 4.9Hz, 1^3), 4.478 (d, 7.6Hz, 1^1), 4.176 (d, 8.2Hz, 1^2), 3.709 and 3.629 (2s, 2 OMe). **31**: $[\alpha]_D$ -8.0° (c 0.1); R_F 0.32 in 3:1 toluene-EtOAc; δ_H 5.307 (d, 3.4Hz, 4^2), 5.028 (d, 7.6Hz, 1^3), 4.467 (d, 7.6Hz, 1^1), 4.284 (d, 7.9Hz, 1^2), 2.171 (s, Lev), 2.005 (s, Ac). **32**: $[\alpha]_D$ +15.4° (c 0.2); R_F 0.52 in 1:1 toluene-EtOAc; δ_H 5.404 (d, 3.7Hz, 4^2), 5.402 (dd, 8.2 and 9.5Hz, 2^3), 5.187 (d, 8.2Hz, 1^3), 4.869 (d, 7.6Hz, 1^2), 4.649 (d, 7.3Hz, 1^1), 3.779 and 3.672 (2s, 2 OMe), 2.174 (s, Lev), 1.966 (s, OAc), 1.370 (s, NAc). **33**: $[\alpha]_D$ +11.2° (c 0.3); R_F 0.41 in 1:1 toluene-EtOAc; δ_H 3.805 and 3.644 (2s, 2 OMe), 2.220 (s, Lev), 2.049 (s, OAc), 1.548 (s, NAc). **34**: $[\alpha]_D$ +21.6° (c 0.8); R_F 0.64 in 1:2 toluene-EtOAc; δ_H 6.720 (d, 3.7Hz, 1^1), 4.938 (d, 7.9Hz, 1^2), 4.790 (d, 7.6Hz, 1^3), 3.799 and 3.646 (2s, 2 OMe), 2.225 (s, Lev), 2.054 (s, OAc), 1.576 (s, NAc). **35**: $[\alpha]_D$ +22.7° (c 0.5); R_F 0.47 in 1:2 toluene-EtOAc; δ_H 4.571 (d, 9.8Hz, 1^1), 3.806 and 3.642 (2s, 2 OMe), 2.222 and 2.202 (2s, SMe and Lev), 2.047 (s, OAc), 1.560 (s, NAc). **36**: $[\alpha]_D$ -4.1° (c 0.7); R_F 0.48 in 1:3 hexane-EtOAc; δ_H 5.550 (s, PhCH), 5.274 (d, 6.7Hz, 1^4), 3.770, 3.765, and 3.646 (3s, 3 OMe), 2.213 (s, Lev), 2.015 (s, OAc), 1.566 (s, NAc), 1.165 (s, Piv). **37**: $[\alpha]_D$ +18.0° (c 0.2); R_F 0.45 in 1:4 toluene-EtOAc; δ_H 3.820, 3.764, and 3.639 (3s, 3 OMe), 2.208 (s, Lev), 1.166 (s, Piv). **38**: R_F 0.20 in 1:4 toluene-EtOAc; δ_H 3.821 and 3.640 (2s, 2 OMe). **39**: R_F 0.32 in 1:4 toluene-EtOAc; δ_H 8.669 (s, 0.34 H, (=NHβ), 8.626 (s, 0.66H, C=NHα), 6.410 (d, 3.3Hz, 0.66H, 1^1α), 3.820 and 3.639 (2s, 2 OMe). **40**: $[\alpha]_D$ +11.9° (c 0.7); R_F 0.18 in 1:2 toluene-EtOAc; δ_H 3.820 and 3.639 (2s, 2 OMe), 2.206 (s, Lev), 1.112 (s, Piv). **41**: $[\alpha]_D$ +4.8° (c 0.3, MeOH); R_F 0.39 in 10:1 $CHCl_3$-MeOH; δ_H(CD_3OD) 5.399 (d, 3.3Hz, 4^4), 3.819 and 3.628 (2s, 2 OMe), 1.108 (s, Piv). **4**: R_F 0.40 in 4:4:5:3 Me_2CO-MeOH-AcOH-H_2O; FAB MS m/z 1159 $[M\text{-}Na]^-$, 1137 $(M+1\text{-}2Na)^-$, 1115 $[M+2H\text{-}3Na]^-$. **5**: R_F 0.35 in 4:4:5:3 Me_2CO-MeOH-AcOH-H_2O; δ_H (D_2O, 50°), 4.784 (d, 1.5Hz, 4^5); δ_H(D_2O, 20°), 4.665 (d, 7.9Hz, 1^4), 4.524 (d, 7.9Hz, 1^2), 4.459 (d, 7.6Hz, 1^1 and 1^6). **42**: $[\alpha]_D$ +1.7° (c 1.5); R_F 0.63 in 1:4 hexane-EtOAc; δ_H 5.331 (d, 3.0Hz, 4^3), 5.247 (d, 3.3Hz, 4^5), 2.223 and 2.191 (2s, 2Lev), 1.165 (s, Piv). **43**: $[\alpha]_D$ +13.8° (c 0.9); R_F 0.20 in 1:4 toluene-EtOAc; δ_H 3.821, 3.766, and 3.643 (3s, 3 OMe), 2.209 and 2.203 (2s, 2Lev), 1.167 (s, Piv). **44**: R_F 0.29 in 1:6 toluene-EtOAc; δ_H 8.670 (s, 0.2H, C=NHβ), 8.628 (s, 0.8H, C=NHα), 6.413 (d, 3.6Hz, 0.8H, 1^1α), 3.819 and 3.640 (2s, 2 OMe). **45**: $[\alpha]_D$ +6.8° (c 0.4); R_F 0.25 in 1:4 toluene-EtOAc; δ_H 3.820 and 3.641 (2s, 2 OMe), 2.208 and 2.198 (2s, 2Lev), 1.112 (s, Piv). **46**: $[\alpha]_D$ +6.5° (c 0.5, MeOH); R_F 0.49 in 7:1 $CHCl_3$-MeOH; δ_H(CD_3OD) 3.730 and 3.671 (2s, 2 OMe), 1.111 (s, Piv). **6**: R_F 0.32 in 4:4:5:3 Me_2CO-MeOH-AcOH-H_2O.

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13. **13** was prepared from 4-methoxyphenyl β-D-galactopyranoside in 7 steps (*1* Bu_2SnO in 1:1 toluene-THF, then AllBr an Bu_4NBr reflux, *2* α,α-dimethoxytoluene, $TsOH{\cdot}H_2O$ in THF, *3* Ac_2O, DMAP in Py, *4* CAN in 4:1 MeCN-H_2O, *5* Ac_2O, DMAP in Py, *6* $NH_2NH_2{\cdot}AcOH$ in DMF, *7* CCl_4, $(Me_2N)_3P$ in THF, 29% overall). **13**: R_F 0.66 in 2:1 toluene-EtOAc; δ_H 6.505 (d, 3.7Hz, H-1), 5.585 (s, PhCH), 5.381 (dd, 3.7 and 10.4Hz, H-2).
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